Anesthesiology
1999; 91:796–803

Combining Partial Liquid Ventilation and Prone Position in Experimental Acute Lung Injury

Martin Max, M.D., Ralf Kuhlen, M.D.,* Frank López, B.A.,† Stefan Matthias Reyle-Hahn, M.D.,* Jan Hinrich Baumert, M.D.,* Rolf Rossaint, M.D., Ph.D.‡*

Background: **Partial liquid ventilation (PLV) and prone position can improve arterial oxygen tension (Pa_{O_2}) in acute lung injury (ALI). The authors evaluated additive effects of these techniques in a saline lung lavage model of ALI.**

Methods: **ALI was induced in 20 medium-sized pigs (29.2 ± 2.5 kg body weight). Gas exchange and hemodynamic parameters were determined in both supine and prone position in all animals. Thereafter, one group was assigned to PLV with two sequential doses of 15 ml/kg of perfluorocarbon (n = 10); the second group was assigned to gaseous ventilation (n = 10). Gas-exchange and hemodynamic parameters were determined at corresponding time points in both groups in prone and supine position.**

Results: **In the PLV group, positioning the animals prone resulted in an increase of Pa_{O_2} prior to PLV and during PLV with both doses of perfluorocarbon when compared to ALI. PLV in supine position was only effective if 30 ml/kg of perfluorocarbon was applied. In the gaseous ventilation group, Pa_{O_2} increased reproducibly compared with ALI when the animals were turned prone. A significant additive improvement of arterial oxygenation was observed during combined therapy with 30 ml/kg of perfluorocarbon and prone position in the PLV group compared with either therapy alone.**

Conclusions: **The authors conclude that combining PLV with prone position exerts additive effects on pulmonary gas exchange in a saline lung lavage model of ALI in medium-sized pigs. (Key words: Perfluorocarbon; positioning; respiratory failure.)**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

*Assistant Professor.

†Technician.

‡Professor and Head, Department of Anesthesiology.

Received from the Klinik für Anaesthesie, Rheinisch-Westfaelische Technische Hochschule Aachen, Aachen, Germany. Submitted for publication July 24, 1998. Accepted for publication April 26, 1999. Supported by grant no. DFG Ro 2000/1–2 from Deutsche Forschungsgemeinschaft, Bonn, Germany.

Address reprint requests to Dr. Max: Klinik für Anaesthesie, Medizinische Einrichtungen der RWTH Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany. Address electronic mail to: Martin.Max2@post.rwth-aachen.de

ALTHOUGH several new therapeutical techniques have been introduced in the treatment of the acute respiratory distress syndrome (ARDS) during the past 25 years, none has been shown to improve mortality or morbidity statistics for this lung disorder. One of the latest strategies being evaluated for its use in improving hypoxemia in ARDS is partial liquid ventilation (PLV), combining the intrapulmonary administration of perfluorocarbons in volumes up to the functional residual capacity with superimposed conventional mechanical ventilation with gaseous tidal volumes.[1] Perfluorocarbons are inert, radiopaque liquids with high densities, low surface tensions, and the capacity to dissolve large amounts of oxygen and carbon dioxide. During PLV perfluorocarbons have been shown to increase the functional residual capacity,[2] suggesting a recruitment of otherwise atelectatic, consolidated lung segments. Furthermore, it is hypothesized that pooling of perfluorocarbons in the dependent lung regions along a gravitational gradient results in a redistribution of pulmonary blood flow to ventral, better ventilated lung segments, thereby improving the ventilation/perfusion mismatch.[3,4] Several animal studies and clinical applications of the technique revealed its efficacy in increasing arterial oxygenation in acute lung injury[5–7]; however, not all patients responded to the treatment.[8]

Improvements in arterial oxygenation after turning patients with ARDS from supine to prone position were reported by 1976[9] and have been confirmed since then by several short-term[10,11] and long-term trials.[12] Animal studies showed that prone position results in a more uniform gravitational distribution of pleural pressure than supine position, without affecting the regional lung perfusion or lung volumes.[13–15] In acute lung injury, pleural pressures are increased because of the stiffness and weight of the edematous lung and can become positive in the dependent segments of the lung.[13] Consequently, the transpulmonary pressures achieved during mechanical ventilation in supine position may not be sufficient to exceed airway opening pressure, and de-

pendent lung regions might be below closing volume.[16] The decrease of pleural pressure in the dorsal lung segments together with a more homogenous vertical pleural pressure gradient in prone position can facilitate the recruitment of atelectatic dorsal lung areas and result in a more homogenous ventilation of the whole lung, thereby improving ventilation/perfusion mismatch.[15] However, for unknown reasons there are patients who do not respond to prone position.[10,11]

The successful clinical treatment of ARDS usually requires the combined application of several therapeutical strategies. Both prone position and PLV have been shown to improve hypoxemia in some patients. To evaluate possible additive effects of these techniques, each acting by a different mechanism to increase arterial oxygenation, we investigated the combined application of PLV and prone position in an animal model of acute lung injury.

Materials and Methods

Animal Preparation

The experimental protocol was approved by the appropriate governmental institution, and the study was performed according to the Helsinki convention for the use and care of animals.

Twenty female pigs (Deutsches Hausschwein) with body weight of 29.2 ± 2.5 kg (PLV group 29.9 ± 3.2 kg body weight, gaseous ventilation [GV] group 28.5 ± 1.5 kg body weight) were included in the study after confirming the absence of any clinical sign of infection by the responsible veterinary surgeon.

Premedication was performed with azaperon (5 mg/kg intramuscularly) followed by ketamine (10 mg/kg intramuscularly) and atropine (0.01 mg/kg intramuscularly). After venous access *via* an auricular vein, anesthesia was induced with a bolus of thiopental (3 mg/kg intravenously) and maintained with a continuous infusion of thiopental (6–10 mg · kg^{-1} · h^{-1}) and fentanyl (0.1 μg · kg^{-1} · min^{-1}). Muscle relaxation was achieved with pancuronium bromide (3 μg · kg^{-1} · min^{-1}). All animals were orotracheally intubated with a 7.5–8.5-mm internal diameter endotracheal tube and submitted to pressure-controlled mechanical ventilation (Servo 300 NO-A; Siemens Elema, Lund, Sweden). Peak inspiratory pressure was limited to 40 cm H_2O at a respiratory rate of 20 per minute, an inspiration:expiration time ratio of 1:2, and a positive end-expiratory pressure of 5 cm H_2O. The inspiratory pressure was set to achieve tidal volumes of 8–10 ml/kg; the fraction of inspiratory oxygen ($F_{I_{O_2}}$) was maintained at 1.0 throughout the experiment. Prior to the induction of lung injury, the inspiratory pressure was adjusted to keep the animals normocapnic, as determined by two sequential blood gas analyses, with no further changes of the respiratory setting thereafter.

A continuous infusion of 3–5 ml · kg^{-1} · h^{-1} of balanced electrolyte solution was administered for adequate hydration.

Arterial access was achieved by introducing an 18-G catheter (Vygon, Ecouen, France) into a femoral artery. A pulmonary artery catheter (model 93A-431-7.5 F; Baxter Healthcare Corporation, Irvine, CA) was advanced into a pulmonary artery under transduced pressure guidance through an 8.5-French sheath (Arrow Deutschland GmbH, Erding, Germany) positioned in a femoral vein. The blood temperature, measured by means of the pulmonary artery catheter, was maintained at 37.8 ± 0.9°C during the experiment using an infrared warming lamp.

Data Acquisition

Hemodynamics. Measurements were taken in prone and supine positions according to the experimental protocol with zero reference level at the midchest. Mean arterial pressure, mean pulmonary arterial pressure, central venous pressure, and pulmonary artery occlusion pressure were transduced (PVP, Kirschseeon/Eglharting, Germany) and recorded (model CS/3; Datex, Achim, Germany). Cardiac output was determined with standard thermodilution techniques (Baxter Deutschland GmbH, Unterschlei*β*heim, Germany) and expressed as the mean of three measurements at random phases of different respiratory cycles. Heart rate was traced by the arterial blood pressure curve.

Gas Exchange. Arterial and mixed venous blood samples were collected anaerobically and immediately analyzed for P_{O_2}, P_{CO_2}, and *p*H using standard blood gas electrodes (ABL 520; Radiometer, Copenhagen, Denmark). Species-specific spectrophotometry was performed to obtain arterial and mixed venous oxygen saturation and total hemoglobin concentration (OSM 3 Hemoximeter; Radiometer). The oxygen contents (ml/dl) of arterial (Ca_{O_2}), mixed venous (Cv_{O_2}), and pulmonary capillary (Cc_{O_2}) samples were calculated using the formula: Content of oxygen = hemoglobin concentration × 1.34 × (% O_2 saturation/100) + P_{O_2} × 0.0031. To calculate Cc_{O_2}, the pulmonary capillary oxygen tension at a $F_{I_{O_2}}$ of 1.0 was assumed to be equivalent to the alveolar P_{O_2}, which was estimated as: barometric pressure − water vapor pressure − Pa_{CO_2}/respiratory quotient (assuming that the respiratory

Table 1. Gas Exchange and Metabolic Data

	Group	$T_{baseline}$	T_{ALI}	T_{30} Prone	T_{60} Supine	T_{90} Supine	T_{120} Prone	T_{150} Supine	T_{180} Prone	T_{210} Supine
Pa_{CO_2}										
[mmHg]	PLV	34 ± 4	52 ± 10	47 ± 9	55 ± 11	55 ± 12	50 ± 8	50 ± 9	48 ± 5	
	GV	42 ± 7	56 ± 9	52 ± 8	58 ± 11	57 ± 11	61 ± 10*	62 ± 6*	63 ± 18*	63 ± 11
Pv_{O_2}										
[mmHg]	PLV	57 ± 7	34 ± 9	48 ± 3†‡	34 ± 10	47 ± 13†	47 ± 7†	45 ± 6†	46 ± 6†	
	GV	56 ± 10	37 ± 10	53 ± 7†‡	38 ± 7	37 ± 7*	51 ± 7†§	39 ± 7*	51 ± 7†‖	39 ± 11
Q_S/Q_T [%]	PLV	20 ± 5	57 ± 12	34 ± 7†‡	54 ± 14	34 ± 12†	27 ± 7†	23 ± 4†	18 ± 4†	
	GV	16 ± 5	64 ± 7	29 ± 9†‡	53 ± 17	53 ± 16†	29 ± 9†§	60 ± 14*	31 ± 14*†‖	64 ± 17
HCO^{3-} [mM]	PLV	26.7 ± 2.2	26.8 ± 1.2	27.3 ± 0.9	27.1 ± 0.9	28.0 ± 0.7†	28.1 ± 1.6†	28.8 ± 1.2†	29.3 ± 1.3†	
	GV	28.3 ± 1.5	25.8 ± 1.3	25.3 ± 1.3	26.3 ± 0.9	26.4 ± 1.1	26.8 ± 0.8†	27.4 ± 1.2†	26.9 ± 1.0†	27.3 ± 1.3
SBE [mM]	PLV	3.6 ± 2.6	1.6 ± 1.7	2.8 ± 1.5	1.8 ± 1.2	2.8 ± 1.2	3.5 ± 1.6†	4.1 ± 1.3†	4.9 ± 1.6†	
	GV	4.1 ± 1.2	1.4 ± 1.9	1.3 ± 0.9	1.26 ± 0.4	1.4 ± 0.8*	0.9 ± 1.3*	0.9 ± 0.7*	0.9 ± 1.5*	1.7 ± 1.9
*p*H	PLV	7.51 ± 0.07	7.34 ± 0.08	7.40 ± 0.08†	7.33 ± 0.07	7.34 ± 0.08	7.38 ± 0.05†	7.39 ± 0.06†	7.41 ± 0.05†	
	GV	7.44 ± 0.05	7.27 ± 0.05	7.29 ± 0.05*	7.27 ± 0.06	7.28 ± 0.05*	7.28 ± 0.06*	7.25 ± 0.06*	7.27 ± 0.10*	7.25 ± 0.04

Data are mean ± SD.

PLV = partial liquid ventilation; GV = gaseous ventilation; Pa_{CO_2} = arterial carbon dioxide pressure; Pv_{O_2} = mixed venous oxygen pressure; Q_S/Q_T = venous admixture; HCO^{3-} = bicarbonate concentration; SBE = standard base excess; $T_{baseline}$ = prestudy conditions; T_{ALI} = values after induction of acute lung injury; T_{30} and T_{60} = gaseous ventilation in the GV and the PLV group; T_{90} and T_{120} = PLV with 15 ml/kg C_8F_{18} in the PLV group and gaseous ventilation in the GV group; T_{150} and T_{180} = PLV with 30 ml/kg C_8F_{18} in the PLV group and gaseous ventilation in the GV group; T_{210} = gaseous ventilation in the GV group.

* $P < 0.05$ for comparison of corresponding time points between the GV group and the PLV group, Duncan's multiple comparison test.

† $P < 0.05$ *versus* ALI values, Duncan's multiple comparison test.

‡ $P < 0.05$ *versus* T_{60} in each group separately, Duncan's multiple comparison test.

§ $P < 0.05$ *versus* T_{90} in each group separately, Duncan's multiple comparison test.

‖ $P < 0.05$ *versus* T_{150} in each group separately, Duncan's multiple comparison test.

quotient = 0.8) − perfluorocarbon vapor pressure when PLV was performed (61 mmHg for the perfluorocarbon used in our study).[15,17] The venous admixture (Q_S/Q_T) was derived from the standard shunt equation: $(Cc_{O_2} - Ca_{O_2}) / (Cc_{O_2} - Cv_{O_2})$.

Experimental Procedure

Induction of Lung Injury. The anesthetized animals were positioned supine and lung injury was induced by repeated lung lavage as previously described and evaluated by Lachmann *et al.*[18] After the lungs were filled with 30 ml/kg prewarmed saline (0.15 M; 38°C) through the endotracheal tube, the liquid was drained by tilting the animals head down at an angle of about 45 degrees using the gravitational gradient. A Pa_{O_2} consistently less than 100 mmHg for 1 h at a FI_{O_2} of 1.0 and a positive end-expiratory pressure of 5 cm H_2O after the last lung lavage was chosen as the only endpoint to define acute lung injury. To achieve this value, 10 ± 1 lung lavages were performed in the PLV group, and 11 ± 1 lavages were necessary to induce acute lung injury in the animals submitted to GV.

PLV. Partial liquid ventilation was initiated in the supine animal with the administration of two sequential doses of 15 ml/kg perfluorocarbon (FC 3280; 3M Chemical Products, Neuss, Germany) through the endotracheal tube during inspiration, using a swivel connector (Portex, Kent, UK). Each dose was administered into the airway over 9–10 min resulting in a volume of approximately 2–2.5 ml of perfluorocarbon per inspiration. The total volume of 30 ml/kg perfluorocarbon is approximately equivalent to the normal functional residual capacity of pigs.[1] The perfluorocarbon used in our study (C_8F_{18}, FC 3280; 3M Chemical Products) is a highly purified industrial perfluorocarbon with a density of 1.75 g/cm^3, a vapor pressure of 61 mmHg, and a surface tension of 12 mN/m at 25°C. Up to 40 ml O_2 and 192 ml CO_2 can be dissolved in 100 ml of the liquid (data from 3M Chemical Products).

Study Protocol. Gas-exchange, hemodynamic, and airway pressure data were assessed in supine position in all animals before ($T_{Baseline}$) and after induction of lung injury (T_{ALI}). Two groups of animals were studied. After investigating 10 animals assigned to PLV, the possibility remained that the results were related not to the perfluorocarbon instillation but to independent changes related to time and position. Therefore, we studied a second group of 10 animals submitted to GV to exclude such influences. Measurements of blood gases, hemodynamics, and airway pressure were performed in both groups at the following time points and experimental settings: (1) T_{30}: 30 min after the induction of acute lung injury, prone; (2) T_{60}: 60 min after the induction of acute lung injury, supine; (3) T_{90}: 90 min after the induction of

Table 2. Hemodynamic and Airway Pressure Data

	Group	$T_{baseline}$	T_{ALI}	T_{30} Prone	T_{60} Supine	T_{90} Supine	T_{120} Prone	T_{150} Supine	T_{180} Prone	T_{210} Supine
PIP [kPa]	PLV	1.79 ± 0.22	3.08 ± 0.35	2.76 ± 0.46†‡	3.33 ± 0.26	2.91 ± 0.22	2.85 ± 0.28	3.02 ± 0.25	3.02 ± 0.23	
	GV	1.38 ± 0.09	2.70 ± 0.33	2.37 ± 0.31†‡	2.95 ± 0.36	2.93 ± 0.31	2.49 ± 0.38*§	3.15 ± 0.37	2.48 ± 0.40*‖	3.16 ± 0.57†
HR										
[L · min^{-1}]	PLV	104 ± 13	103 ± 13	100 ± 13	103 ± 18	88 ± 17†	92 ± 22	80 ± 15†	82 ± 14†	
	GV	103 ± 13	111 ± 25	95 ± 22	102 ± 28	103 ± 29	90 ± 18	127 ± 46*	108 ± 35	141 ± 45
MAP										
[mmHg]	PLV	83 ± 11	88 ± 5	100 ± 10†‡	85 ± 11	89 ± 9	93 ± 10	90 ± 9	95 ± 10	
	GV	80 ± 15	94 ± 8	97 ± 5	97 ± 6	99 ± 8	103 ± 13	101 ± 14	99 ± 13	99 ± 19
MPAP										
[mmHg]	PLV	21 ± 4	28 ± 9	26 ± 7	31 ± 5	27 ± 3	25 ± 3	26 ± 2	24 ± 3	
	GV	20 ± 3	32 ± 3	28 ± 3‡	35 ± 6	35 ± 5*	27 ± 5†§	37 ± 6*†	28 ± 4†‖	38 ± 7†
CVP										
[mmHg]	PLV	7.0 ± 1.6	7.1 ± 1.4	7.9 ± 3.1	8.3 ± 2.3	7.4 ± 2.5	7.9 ± 3.2	7.3 ± 3.1	6.7 ± 1.3	
	GV	8.7 ± 2.5	9.0 ± 3.0	8.7 ± 2.6	8.8 ± 3.1	8.5 ± 3.2	7.2 ± 3.8	8.4 ± 3.0	7.7 ± 3.2	8.8 ± 2.6
PAOP										
[mmHg]	PLV	7.9 ± 3.2	5.8 ± 3.0	8.0 ± 2.8	5.8 ± 3.2	8.4 ± 2.8	7.0 ± 2.4	8.3 ± 2.0	7.3 ± 2.9	
	GV	9.7 ± 2.5	9.2 ± 2.9	9.4 ± 1.8	9.2 ± 2.2	9.8 ± 2.8	9.6 ± 2.5	8.5 ± 3.3	9.6 ± 3.9	8.1 ± 3.5†
CO										
[L · min^{-1}]	PLV	5.3 ± 1.1	5.2 ± 1.1	4.9 ± 1.3	4.6 ± 1.3	4.1 ± 1.1†	4.2 ± 1.2†	3.6 ± 1.1†	3.5 ± 1.2†	
	GV	3.8 ± 1.0	5.2 ± 1.7	3.8 ± 0.6†	4.3 ± 0.9	4.3 ± 0.9	3.7 ± 0.8†	4.2 ± 1.6	3.9 ± 1.3†	5.2 ± 2.1

Data are mean ± SD.

PLV = partial liquid ventilation; GV= gaseous ventilation; PIP = peak inspiratory pressure; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; CVP = central venous pressure; PAOP = pulmonary artery occlusion pressure; CO = cardiac output; $T_{baseline}$ = prestudy conditions; T_{ALI} = values after induction of acute lung injury; T_{30} and T_{60} = gaseous ventilation in the GV and the PLV group; T_{90} and T_{120} = PLV with 15 ml/kg C_8F_{18} in the PLV group and gaseous ventilation in the GV group; T_{150} and T_{180} = PLV with 30 ml/kg C_8F_{18} in the PLV group and gaseous ventilation in the GV group; T_{210} = gaseous ventilation in the GV group.

* $P < 0.05$ for comparison of corresponding time points between the GV group and the PLV group, Duncan's multiple comparison test.

† $P < 0.05$ *versus* ALI values, Duncan's multiple comparison test.

‡ $P < 0.05$ *versus* T_{60} in each group separately, Duncan's multiple comparison test.

§ $P < 0.05$ *versus* T_{90} in each group separately, Duncan's multiple comparison test.

‖ $P < 0.05$ *versus* T_{150} in each group separately, Duncan's multiple comparison test.

acute lung injury and 30 min after initiation of PLV with 15 ml/kg perfluorocarbon in the PLV group, supine; (4) T_{120}: 120 min after the induction of acute lung injury and 60 min after the initiation of PLV with 15 ml/kg perfluorocarbon in the PLV group, prone; (5) T_{150}: 150 min after the induction of acute lung injury and 30 min after the initiation of PLV with 30 ml/kg perfluorocarbon in the PLV group, supine; (6) T_{180}: 180 min after the induction of acute lung injury and 60 min after the initiation of PLV with 30 ml/kg perfluorocarbon in the PLV group, prone. A 30-min time period was given for equilibration prior to the measurements following each change in position or perfluorocarbon dose.

At the end of the study the anesthetized animals were killed with an intravenous administration of potassium chloride.

Statistical Analysis

All data are expressed as mean ± SD. Statistical analyses were performed using a suitable software package (NCSS 6.0.7.; NCSS, Kaysville, UT). The data were analyzed by analysis of variance (ANOVA) for repeated measurements. The statistical design for the ANOVA procedure was based on three within factors, that is, PLV having two levels (15 ml/kg, 30 ml/kg), positioning having two levels (prone, supine) and group having two levels (GV group, PLV group). For significant ANOVA results Duncan's *post hoc* test was used for comparisons between and within the groups. $P < 0.05$ was considered as significantly different.

Results

Repeated lung lavages (PLV group: 10 ± 1, GV group: 11 ± 1) were performed to induce acute lung injury in all animals as indicated by a decrease of Pa_{O_2} from 510 ± 35 mmHg to 54 ± 11 mmHg and an increase in Q_S/Q_T from 16 ± 7% to 61 ± 10% (table 1). Pa_{CO_2} increased from 38 ± 7 mmHg to 54 ± 9 mmHg after lung lavage. Detailed gas-exchange, hemodynamic, and airway-pressure data at $T_{Baseline}$ and T_{ALI} for each group are presented in tables 1 and 2. There were no significant

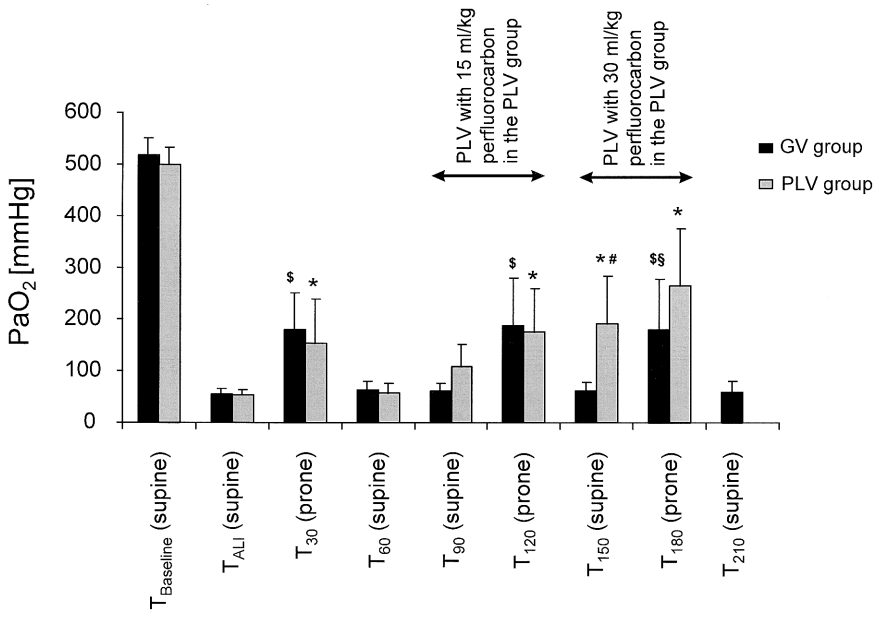

Fig. 1. Changes in arterial oxygen tension (Pa_{O_2}) caused by changes in body position and partial liquid ventilation (PLV) with two different doses of perfluorocarbon. $T_{Baseline}$ denotes prestudy conditions, T_{ALI} denotes values after induction of acute lung injury, T_{30} and T_{60} denote gaseous ventilation (GV) in the GV and the PLV groups, T_{90} and T_{120} denote PLV with 15 ml/kg perfluorocarbon in the PLV group and GV in the other group, T_{150} and T_{180} denote PLV with 30 ml/kg perfluorocarbon in the PLV group and GV in the GV group, T_{210} denotes GV in the GV group. An increase in Pa_{O_2} compared with ALI was observed during GV in prone position in the GV group (T_{30}, T_{120}, T_{180}; $\$P < 0.05$, Duncan's multiple comparison test). In the PLV group, arterial oxygenation improved significantly during GV and PLV with both doses of perfluorocarbon in prone position (T_{30}, T_{120}, T_{180}; $^*P < 0.05$, Duncan's multiple comparison test) and in supine position during PLV with 30 ml/kg of perfluorocarbon (T_{150}; $^*P < 0.05$, Duncan's multiple comparison test). An additive effect of prone position and PLV on Pa_{O_2} was observed at T_{180} in the PLV group compared with PLV with 30 ml/kg of perfluorocarbon in supine position (T_{150}; $\#P < 0.05$, Duncan's multiple comparison test) and to prone position during GV at the corresponding time point in the GV group (T_{180}; $\$P < 0.05$, Duncan's multiple comparison test).

differences between the two groups at these time points for any parameter tested. All animals survived the entire study period.

Effect of Prone Position

Positioning the animals prone during GV (T_{30}) resulted in a significant increase of Pa_{O_2} and Pv_{O_2} and a significant decrease in Q_S/Q_T in both groups compared with subsequent supine positioning (T_{60}) and to T_{ALI} ($P < 0.001$; fig. 1, table 1). Decreases in Pa_{CO_2} resulting from prone position were observed in both groups but did not reach statistical significance; however, *p*H increased significantly in the PLV group during prone position compared with supine at T_{60} (table 1).

Comparison between the GV and the PLV group of gas-exchange and metabolic data at corresponding time points (T_{30} and T_{60}) revealed a significant difference only for *p*H at T_{30} (table 1).

Analyses of the hemodynamic data within each group showed a significant increase of MAP during prone position at T_{30} for the PLV group compared with T_{ALI} and T_{60}. In the GV group CO decreased significantly if the animals were positioned prone at T_{30} compared with T_{ALI} but not compared with subsequent supine position. Mean pulmonary arterial pressure in the same group increased from 28 ± 3 mmHg (T_{30}) to 35 ± 6 mmHg (T_{60}) after turning the animals supine. Comparison of hemodynamic parameters at T_{ALI}, T_{30}, and T_{60} revealed no differences for these time points between the GV and the PLV groups (table 2).

The peak inspiratory pressure increased in both groups after the induction of lung injury. Turning the animals prone resulted in a decrease of peak inspiratory pressure compared with T_{ALI} ($P < 0.05$), which was reversed when the animals were returned to supine position (T_{60}) (table 2).

Effect of PLV

Partial liquid ventilation in supine position resulted in an increase of Pa_{O_2} in the PLV group, which reached statistical significance compared with T_{ALI} only for the higher of the two doses of perfluorocarbon used ($P < 0.001$, fig. 1). However, a simultaneous increase in mixed venous carbon dioxide tension (Pv_{O_2}) and a decrease of Q_S/Q_T were significant at T_{90} and T_{150} compared with T_{ALI} ($P < 0.001$; table 1). Pa_{CO_2} demonstrated no changes following PLV with either dose of perfluorocarbon; *p*H, standard base excess, and HCO_3^- levels increased persistently compared with T_{ALI} after perfluorocarbon was instilled.

Cardiac output decreased significantly after the instillation of perfluorocarbon together with a decrease in heart rate from 103 ± 13 (T_{ALI}) to 88 ± 17 (T_{90}) and 80 ± 15 beats/min (T_{150}) respectively ($P < 0.05$). All

other hemodynamic parameters and the peak inspiratory airway pressure remained unchanged (table 2).

Effect of Combined PLV and Prone Position

Turning the animals from supine to prone position during PLV resulted in a further significant increase of Pa_{O_2} from 109 ± 42 (T_{90}) to 176 ± 83 mmHg (T_{120}) and from 192 ± 92 (T_{150}) to 265 ± 111 mmHg (T_{180}) when time points with similar doses of perfluorocarbon were compared in the PLV group, although changes in Pa_{O_2} during PLV with 15 ml/kg of perfluorocarbon while positioned prone did not exceed the effect that was achieved with prone position alone in the GV group. However, a significant, additive effect of PLV and prone position on arterial oxygenation was observed at T_{180} compared with PLV with the same dose of perfluorocarbon in supine position (T_{150}) and to the corresponding time point in the GV group (T_{180}) as depicted in figure 1.

Comparison of supine and prone position during PLV with equal doses of perfluorocarbon in the PLV group revealed no changes for Pv_{O_2}, Pa_{CO_2}, Q_S/Q_T, or any hemodynamic or metabolic parameter.

In the GV group, arterial and venous oxygenation and the venous admixture increased reproducibly if the animals were positioned prone compared with supine position and T_{ALI}, whereas turning them supine again reversed this improvement to lung-injury values. Pa_{CO_2} increased slowly but continuously over the study period, with a concomitant decrease in standard base excess and *p*H that was significantly different from the PLV group for all time points from T_{90} through T_{180}. No changes in hemodynamics caused by changes in positioning were observed in the GV group, except a significant increase in mean pulmonary arterial pressure when the animals were supine. Similarly, a decrease in peak inspiratory pressure was observed when the animals were turned prone (table 2).

Effect of Time. Comparison of gas-exchange, airway-pressure, and hemodynamic data at T_{210} and at T_{ALI} in the GV group revealed statistical differences only for peak inspiratory pressure, mean pulmonary arterial pressure, and pulmonary artery occlusion pressure. All other hemodynamic and gas-exchange parameters remained stable over the entire study period and were not influenced by intermittent changes in positioning or time.

Discussion

The objective of our study was to evaluate combined effects of prone position and PLV on pulmonary gas exchange in a saline lung lavage model of acute lung injury in medium-sized pigs. We demonstrated that a combination of prone position and PLV can improve arterial oxygenation depending on the dose of perfluorocarbon. There was a tendency for the prone position to decrease Q_S/Q_T in the PLV group, although it did not reach statistical significance. The maximum effect of the combined application of these techniques on Pa_{O_2} exceeded the effects that were obtained with prone position or PLV in supine position alone.

Two mechanisms are proposed to explain the increase of Pa_{O_2} during PLV. First, the intratracheal instillation of perfluorocarbon can cause a recruitment of atelectatic lung segments, thereby improving the impaired ventilation/perfusion ratio. Atelectasis, especially of the dependent lung segments is a typical feature generated by the well-established and extensively used lung lavage model employed in this study.[18] Second, perfluorocarbon may compress pulmonary capillaries in the dependent lung regions because of the high density of the liquid.[3,19] The redistribution of pulmonary blood flow from dependent poorly or nonventilated lung segments to well-ventilated, nondependent lung regions may result in a reduction of pulmonary shunt and an improvement of arterial oxygenation.[4]

In our investigation, PLV in supine position caused a significant increase in Pa_{O_2} only after the larger of the two doses of perfluorocarbon (equivalent to the functional residual capacity of the pigs) was given. A dose-dependent increase of arterial oxygenation during PLV has been described by other authors using the same model of acute lung injury in different species.[5,20] However, although improvements in small-animal models and human newborns have been achieved already with small doses of perfluorocarbons,[20,21] medium-sized animals and adult patients seem to require larger doses for significant improvements in Pa_{O_2}, as observed in our study.[22] It is suggested that the larger anteroposterior thoracic diameter results in a more inhomogenous distribution of perfluorocarbon and gas in the lung, with a pooling of the liquid in the dependent lung regions.[22–24] Because of the increase of the preexisting gravitational pleura pressure gradient in supine position during PLV[25], ventilation of the dependent, liquid-filled lung areas and concomitantly the oxygenation of the perfluorocarbon may be poor.[26] Therefore, the dorsal lung segments will remain hypoxic until the perfluorocarbon dose is increased and there is a reflux of the liquid into central airways, where it can be better reoxygenated and

subsequently redistributed to the peripheral airways by the inspiratory gas flow.

Several investigators report that the prone position increases Pa_{O_2} in patients with ARDS.[10,11,27] A number of animal studies have shown that this improvement is associated with more homogenous ventilation, resulting from an increase of the vertical pleura pressure gradient when the animals were turned from supine to prone position.[15,26,28,29] An additional increase of the pleura pressure gradient during PLV in supine position has been shown,[25] and it can be assumed that a decrease of this gradient in prone position as observed during GV also occurs if PLV is performed. A more uniform dispersal of the gaseous tidal volume and a reduction of the airway pressures necessary to apply sufficient tidal volumes and to move the liquid column in the dependent lung segments could cause a more efficient recruitment and ventilation of alveoli in all lung regions and a facilitated reoyxgenation of the perfluorocarbon as indicated by the increase of Pa_{O_2} and the marked but not significant decrease in Pa_{CO_2} during PLV in prone position in our investigation.

The decrease in cardiac output during PLV has already been observed by other investigators and is likely to be the result of a compression of the pulmonary vascular bed with a subsequent decrease of right ventricular preload and an increase of right ventricular afterload.[22] However, the changes in cardiac output during PLV did not result in a decrease of Pv_{O_2} or mixed venous oxygen saturation in our study, indicating that oxygen delivery and cardiac function were still sufficient to avoid an increase in the arterial/venous P_{O_2} difference.

Time may be a crucial factor if changes in gas exchange are evaluated over a prolonged study period. However, in our investigation we did not see any difference in gas-exchange parameters when values of the GV group at the end of the study were compared with those after the induction of lung injury, indicating a high stability of the lung injury model applied.

Despite the efficacy of the perfluorocarbon used in our study, the type of perfluorocarbon may influence the response to PLV, although chemical and physical properties of the different perfluorocarbons presently tested for PLV are very similar. Previous investigations of our group revealed no differences in the efficacy of C_8F_{18}, the perfluorocarbon used in our study, compared with the perfluorocarbon recently under investigation in human trials (Perflubron, Liquivent; Alliance, San Diego, CA).[8,21] Regarding the physical properties, C_8F_{18} reveals a higher vapor pressure than Perflubron. This can result in a faster evaporation of perfluorocarbon from the lungs, which is more likely to account for a slight, continuous decrease of Pa_{O_2} and an increase of Q_S/Q_T during long study periods. Other investigators compensated this effect by a continuous substitution for losses resulting from evaporation.[7,21] However, because of the short time period between two measurements with the same dose of perfluorocarbon (30 min) we did not administer subsequent doses of perfluorocarbon in the present investigation.

Our data suggest that the combined application of PLV and prone position can be an efficient technique to further improve the beneficial effect on pulmonary gas exchange that has been observed during PLV in supine position. Changing the position of the pigs during the experiment did not cause any incident compromising the animals. The mechanisms by which PLV in supine position improves pulmonary gas exchange and lung mechanics are still not completely clarified. There are controversial data concerning the hypothesized redistribution of pulmonary blood flow in animal models[3] and the effect on arterial oxygenation in clinical trials on patients with ARDS.[8] Therefore, it is difficult to predict the mechanisms that may account for the observed improvement during PLV in prone position in our study, and explanations have to remain hypothetical. To clarify these questions, further studies investigating the mechanism of PLV when combined with other therapeutic strategies or alone are required.

The authors thank Gabriele Wettmann, Helmut Wiese, and Rolf Dembinski for their excellent technical assistance.

References

1. Fuhrman BP, Paczan PR, DeFrancisis M: Perfluorocarbon-associated gas exchange. Crit Care Med 1991; 19:712–22

2. Gauger PG, Overbeck MC, Chamber SD, Wise C, Cailipan CI, Hirschl RB: Perfluorocarbon partial liquid ventilation improves gas exchange while augmenting decreased functional residual capacity in an animal model of acute lung injury. Surg Forum 1995; 46:669–71

3. Gauger PG, Overbeck MC, Koeppe RA, Shulkin BL, Hrycko JN, Weber ED, Hirschl RB: Distribution of pulmonary blood flow and total lung water during partial liquid ventilation in acute lung injury. Surgery 1997; 122:313–23

4. Quintel M, Hirschl RB, Roth H, Loose R, van Ackern K: Computer tomographic assessment of perfluorocarbon and gas distribution during partial liquid ventilation for acute respiratory failure. Am J Respir Crit Care Med. 1998; 158:249–55

5. Houmes RJ, Verbrugge SJ, Hendrik ER, Lachmann B: Hemodynamic effects of partial liquid ventilation with perfluorocarbon in acute lung injury. Intensive Care Med 1995; 21:966–72

6. Hirschl RB, Tooley R, Parent AC, Johnson K, Bartlett RH: Improve-

ment of gas exchange, pulmonary function, and lung injury with partial liquid ventilation: A study model in a setting of severe respiratory failure. Chest 1995; 108:500–8

7. Leach C, Greenspan JS, Rubenstein SD, Shaffer TH, Wolfson MR, Jackson JC, DeLemos R, Fuhrman BP: Partial liquid ventilation with Perflubron in premature infants with severe respiratory distress syndrome. N Engl J Med 1995; 335:761–7

8. Hirschl RB, Pranikoff T, Wise C, Overbeck MC, Gauger PG, Schreiner RJ, Dechert R, Bartlett RH: Initial experience with partial liquid ventilation in adult patients with the acute respiratory distress syndrome. JAMA 1996; 275:383–9

9. Piehl MA, Brown RS: Use of extreme position changes in respiratory failure. Crit Care Med 1976; 4:13–4

10. Blanch L, Mancebo J, Perez M, Martinez M, Mas A, Betbese AJ, Joseph D, Ballus J, Lucangelo U, Bak E: Short-term effects of prone position in critically ill patients with acute respiratory distress syndrome. Intensive Care Med 1997; 23:1033–9

11. Pappert D, Rossaint R, Slama K, Gruning T, Falke KJ: Influence of positioning on ventilation-perfusion relationships in severe adult respiratory distress syndrome. Chest 1994; 106:1511–6

12. Fridrich P, Krafft P, Hochleuthner H, Mauritz W: The effects of long-term prone positioning in patients with trauma-induced adult respiratory distress syndrome. Anesth Analg 1996; 83:1206–11

13. Mutoh T, Guest RJ, Lamm WJE, Albert RK: Prone position alters the effect of volume overload on regional pleural pressures and improves hypoxemia in pigs in vivo. Am Rev Respir Dis 1992; 146:300–6

14. Glenny RW, Lamm WJ, Albert RK, Robertson HT: Gravity is a minor determinant of pulmonary blood flow distribution. J Appl Physiol 1991; 71:620–9

15. Lamm WJ, Graham MM, Albert RK: Mechanism by which the prone position improves oxygenation in acute lung injury. Am J Respir Crit Care Med 1994; 150:184–93

16. West JB: Respiratory Physiology: The Essentials, 5th ed. Baltimore, Williams & Wilkins, 1995, pp 98–101

17. Mates EA, Hildebrandt J, Jackson JC, Tarczy HP, Hlastala MP: Shunt and ventilation-perfusion distribution during partial liquid ventilation in healthy piglets. J Appl Physiol 1997; 82:933–42

18. Lachmann B, Jonson B, Lindroth M, Robertson B: Modes of artificial ventilation in severe respiratory distress syndrome: Lung function and morphology in rabbits after wash-out of alveolar surfactant. Crit Care Med 1982; 10:724–32

19. Lowe CA, Shaffer TH: Pulmonary vascular resistance in the fluorocarbon-filled lung. J Appl Physiol 1986; 60:154–9

20. Tütüncü AS, Faithfull NS, Lachmann B: Intratracheal perfluorocarbon administration combined with mechanical ventilation in experimental respiratory distress syndrome: Dose-dependent improvement of gas exchange. Crit Care Med 1993; 21:962–9

21. Kaisers U, Max M, Schnabel R, Böhm S, Hendrik ER, Rossaint R, Lachmann B: Partial liquid ventilation with FC 3280 in experimental lung injury: Dose-dependent improvement of gas exchange and lung mechanics. Appl Cardiopulm Pathophysiol 1996; 6:163–70

22. Overbeck MC, Pranikoff T, Hirschl RB: Partial liquid ventilation provides effective gas exchange in a large animal model. J Crit Care 1996; 11:37–42

23. Hirschl RB, Tooley R, Parent AC: Evaluation of gas exchange, pulmonary compliance, and lung injury during total and partial liquid ventilation in the acute respiratory distress syndrome. Crit Care Med 1996; 24:1001–8

24. Meaney JF, Kazerooni EA, Garver KA, Hirschl RB: Acute respiratory distress syndrome: CT findings during partial liquid ventilation. Radiology 1997; 202:570–3

25. Barbas CSV, AmatoM.B.P, Goldner M, Adams A, Shapiro R, Nahum A, Marini JJ: Effect of PEEP on regional pleural pressures (PPL) during partial liquid ventilation (PLV) in dogs with oleic acid induced lung injury (OAI). Am J Respir Crit Care Med 1997; 155:A86

26. Yang QH, Kaplowitz MR, Lai FS: Regional variations in lung expansion in rabbits: prone vs. supine positions. J Appl Physiol 1989; 67:1371–6

27. Gattinoni L, Pelosi P, Vitale G, Pesenti A, D'Andrea L, Mascheroni D: Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. ANESTHESIOLOGY 1991; 75:15–23

28. Wiener KJP, Gropper MA, Lai FS: Pleural liquid pressure in dogs measured using a rib capsule. J Appl Physiol 1985; 59:597–602

29. Olson LE, Lai FS: Pleural liquid pressure measurement with rib capsules in ponies. J Appl Physiol 1988; 64:102–7