

# Partial Liquid Ventilation *Versus* Conventional Mechanical Ventilation with High PEEP and Moderate Tidal Volume in Acute Respiratory Failure in Piglets

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## ABSTRACT

This prospective randomized pilot study aimed to test the hypotheses that partial liquid ventilation combined with a high positive end-expiratory pressure (PEEP) and a moderate tidal volume results in improved gas exchange and lung mechanics without negative hemodynamic influences compared with conventional mechanical ventilation in acute lung injury in piglets. Acute lung injury was induced in 12 piglets weighing  $9.0 \pm 2.4$  kg by repeated i.v. injections of oleic acid and repeated lung lavages. Thereafter, the animals were randomly assigned either to partial liquid ventilation ( $n = 6$ ) or conventional mechanical ventilation ( $n = 6$ ) at a fractional concentration of inspired  $O_2$  of 1.0, a PEEP of 1.2 kPa, a tidal volume  $< 10$  mL/kg body weight (bw), a respiratory rate of 24 breaths/min, and an inspiratory/expiratory ratio of 1:2. Perfluorocarbon liquid 30 mL/kg bw was instilled into the endotracheal tube over 10 min followed by 5 mL/kg bw/h. Continuous monitoring included ECG, mean right atrial, pulmonary artery, pulmonary capillary, and arterial pressures, arterial blood gas, and partial pressure of end-tidal  $CO_2$

measurements. When compared with control animals, partial liquid ventilation resulted in significantly better oxygenation with improved cardiac output and oxygen delivery. Dead space ventilation appeared to be lower during partial liquid ventilation compared with conventional mechanical ventilation. No significant differences were observed in airway pressures, pulmonary compliance, and airway resistance between both groups. The results of this pilot study suggest that partial liquid ventilation combined with high PEEP and moderate tidal volume improves oxygenation, dead space ventilation, cardiac output, and oxygen delivery compared with conventional mechanical ventilation in acute lung injury in piglets but has no significant influence on lung mechanics. (*Pediatr Res* 52: 225–232, 2002)

### Abbreviations

**ARDS**, Acute respiratory distress syndrome  
**HR**, Heart rate  
**PEEP**, Positive end-expiratory pressure

ARDS is characterized by acute inflammatory lung injury finally resulting in end-expiratory alveolar collapse, atelectasis, increase in right-to-left shunt, and a decrease in oxygenation (1). The goals of mechanical ventilation should be to maintain lung function and to preserve lung architecture. PEEP is usually applied to prevent end-expiratory collapse of collapsible alveoli, and tidal volume is selected to limit overdistension of lung units (2, 3). However, certain lung regions, mainly in the dependent parts of the lung, are often poorly responsive to PEEP, whereas other regions in the nondependent parts of the lung are very responsive to PEEP (4). Another therapeutic option would be to eliminate the increased forces acting at the

air-liquid interface in ARDS by filling the lungs with a perfluorochemical liquid (5).

In recent years, liquid ventilation with perfluorocarbon has gained increasing interest for improving pulmonary gas exchange in experimental models of acute lung injury (6–8). Perfluorocarbons are hydrocarbon molecules in which carbon-bound hydrogen is replaced by fluorine atoms. They are biologically inert, nonbiotransformable, and immiscible in both aqueous and lipid media. Perfluorocarbon liquids are absorbed minimally by the respiratory epithelium and are eliminated by evaporation through the lungs (9). Oxygenated perfluorocarbon liquids have the ability to lower surface tension in surfactant-deficient lungs, to increase functional residual capacity, and are able to dissolve large amounts of respiratory gases. Fuhrman *et al.* (10) simplified the application of liquid ventilation by combining liquid and gas ventilation. The lungs are filled with perfluorocarbon to their estimated functional residual capacity

Received July 7, 2000; accepted March 20, 2001.  
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DOI: 10.1023/01.PDR.0000020601.28483.A1

(30 mL/kg bw), or liquid is added until at end expiration at 0 PEEP a meniscus is seen in the endotracheal tube and subsequently ventilated by a conventional gas ventilator using the volume-controlled mode with PEEP levels < 0.6 kPa and a tidal volume of 15 mL/kg bw (8, 10). Because of its high density, perfluorocarbon is mainly distributed to dependent lung regions (11). As a noncompressible liquid, it preferentially stabilizes collapsed alveoli in the dependent parts of the lung ("liquid PEEP"). Gas exchange during partial liquid ventilation most likely occurs at the alveolar level both in aerated and liquid filled lung units.

Partial liquid ventilation has been shown to improve lung mechanics, oxygenation, and to decrease further alveolar damage (7, 8, 12–14). However, little is known about the optimal gas ventilatory strategy during partial liquid ventilation. Recently, Cox *et al.* (15) reported a significant risk of barotrauma during partial liquid ventilation when lungs are filled with perfluorocarbon liquid to functional residual capacity levels with a superimposed gas ventilatory strategy of large tidal volumes. Most of the controlled experimental studies on partial liquid ventilation used volume controlled mechanical ventilation with large tidal volumes and low PEEP levels in the partial liquid ventilation as well as in the control groups (6–8, 12, 16). However, there is some evidence that conventional mechanical ventilation with PEEP levels above the lower inflection point combined with low tidal volumes reduces lung injury in experimental studies of acute lung injury (17–19).

In this pilot study, we compared the effects of partial liquid ventilation and conventional mechanical ventilation on gas exchange, respiratory mechanics, and hemodynamics in an animal model of acute lung injury using identical gas ventilatory settings with high PEEP and moderate tidal volume in both groups.

We hypothesized that partial liquid ventilation results in improved gas exchange and lung mechanics compared with conventional mechanical ventilation without negative hemodynamic influences.

## MATERIALS AND METHODS

**Animals.** The protocol was approved by the institutional animal research committee, and the care of the animals was in accordance with guidelines for ethical animal research.

In 12 piglets of either sex, weighing  $9.0 \pm 2.4$  kg, premedicated with azaperone (8 mg/kg bw i.m.) and atropine (0.02 mg/kg bw i.m.), anesthesia was induced with ketamine (10 mg/kg bw i.v.) and thereafter maintained by a continuous infusion of fentanyl (0.15  $\mu$ g/kg bw/min), pentobarbital sodium (4 mg/kg bw/h), and pancuronium (0.3 mg/kg bw/h). All animals were placed in supine position. After placing a 5.5 mm (inner diameter) tracheal Hi-Lo cuffed tube (Hi-Lo jet tube, National Catheter Corp., Mallinckrodt, Glen Falls, NY, USA) via tracheostomy, controlled mechanical ventilation was established using the adaptive pressure ventilation option of the Galileo ventilator (Hamilton Medical AG, Rhäzüns, Switzerland) with a 15 mm pediatric breathing system (Intersurgical Inc., Berkshire, UK). Tidal volume was set at 10 to 12 mL/kg bw, respiratory rate at 24 breath/min, inspiratory/expiratory

ratio at 1:2, PEEP at 0.4 kPa, and fraction of inspired oxygen ( $\text{FiO}_2$ ) at 0.3. Initially, a 5 Fr triple-lumen catheter (Hydrocath 5 Fr 15 cm 3 lumen, Ohmeda, Swindon, UK) was inserted into the right subclavian vein to induce anesthesia and to administer maintenance fluid. After induction of anesthesia, a ringer solution was infused, initially, at a rate of 20 mL/kg bw in 30 min followed by a continuous infusion of 5 mL/kg bw/h. A 5.5 Fr thermodilution oxygen-saturation fiber-optic pulmonary artery catheter (Edwards Swan-Ganz TD Catheter, Edwards Critical Care Division, Irvine, CA, USA) was placed into the pulmonary artery by peripheral cutdown of the right external jugular vein. A 4 Fr  $\text{O}_2$ -saturation catheter (Edslab double lumen  $\text{O}_2$  Sat II catheter, Edwards Critical Care Division) was inserted via the right common carotid artery and placed into the thoracic aorta for continuous arterial oximetry measurement. A short 18 gauge catheter (Abbocath, Abbott Ireland LTD, Sligo, Republic of Ireland) was inserted via the left common carotid artery through which a thin optical sensor (Multiparameter Intravascular Sensor MPS7004S <0.5 mm diameter, Biomedical Sensors Ltd, Malvern, PA, USA) was advanced into the aortic arch for continuous blood gas and arterial pressure monitoring using the TrendCare TCM 7000 system (Diametrics Medical Ltd, Buckinghamshire, England). A second 5 Fr triple-lumen catheter (Hydrocath 5 Fr 15 cm 3 lumen, Ohmeda Swindon, UK) was placed via the left external jugular vein into the superior vena cava.

**Hemodynamic monitoring.** ECG, mean right atrial, pulmonary artery, pulmonary capillary, and arterial pressures were recorded continuously on a multichannel recorder (SC 8000, Siemens Medical Systems, Inc., Danvers, MA, USA) using 0.9% saline filled transducers (Monitoring Kit Transpac IV, H674/61, Abbott Critical Care Systems, Sligo, Republic Of Ireland). All pressures were referred to a zero level taken at the middle of the ventral to dorsal thoracic distance. Cardiac output was measured at end expiration by thermodilution technique as the mean of three determinations after injection of 5 mL 0°C 0.9% saline. Systemic and pulmonary vascular resistances were calculated using the following equations: systemic vascular resistance, [(arterial pressure – right atrial pressure) \* 60]/cardiac output; pulmonary vascular resistance, [(pulmonary artery pressure – pulmonary capillary pressure) \* 60]/cardiac output).

**Respiratory monitoring.** Arterial and mixed venous blood samples were taken for measurements of blood gases and Hb concentration using an automatic blood gas system (AVL 995, AVL Corp., Graz, Austria). In addition, the arterial and mixed venous oxygen saturations (CO-Oxylite AVL 912, AVL) were analyzed. End-tidal  $\text{CO}_2$  concentrations were measured with an end-tidal  $\text{CO}_2$  module of the Siemens SC 8000 monitor using the mainstream technique. Barometric pressure was noted daily during the experiment. The alveolar-arterial oxygen tension difference ( $\text{PA} - \text{aO}_2$ ) was calculated using the following formula:  $\text{PA} - \text{aO}_2 = [\text{FiO}_2 * (\text{P}_{\text{atm}} - \text{P}_{\text{H}_2\text{O}}) - (\text{PaCO}_2/0.8) - \text{PaO}_2]$ , where  $\text{FiO}_2$  is fraction of inspired oxygen,  $\text{P}_{\text{atm}}$  is barometric pressure,  $\text{P}_{\text{H}_2\text{O}}$  is partial pressure of  $\text{H}_2\text{O}$ ,  $\text{PaCO}_2$  is partial pressure of arterial  $\text{CO}_2$ , and  $\text{PaO}_2$  is partial pressure of arterial  $\text{O}_2$ . During partial liquid ventilation, the partial pressure of the perfluorocarbon fluid at 37°C was included in the

calculation of  $PA - aO_2 = [FiO_2 * (P_{atm} - P_{H_2O} - P_{perfluorocarbon}) - (PaCO_2/0.8) - PaO_2]$ , where  $P_{perfluorocarbon}$  is partial pressure of perfluorocarbon. Intrapulmonary shunt fraction was calculated using the following formula:  $[Q's/Q't = (Cc'O_2 - CaO_2)/(Cc'O_2 - CvO_2)]$ , where  $Cc'O_2$  is ideal pulmonary capillary oxygen content,  $CaO_2$  is arterial oxygen content, and  $CvO_2$  is mixed venous oxygen content. Dead space-to-tidal volume ratio ( $V_d/V_t$  is physiologic dead space) was calculated according to a modified Bohr alveolar equation:  $V_d/V_t = [(PaCO_2 - PetCO_2)/PaCO_2]$ , where,  $PaCO_2$  is partial pressure of arterial  $CO_2$ , and  $PetCO_2$  is partial pressure of end-tidal  $CO_2$ . For this measurement only, stable capnography curves with a zero baseline and an expiratory plateau phase over a period of 10 ventilatory cycles were taken.

Respiratory mechanics, inspiratory and expiratory gas flow rates, and airway pressures were monitored at the proximal airway using the Hamilton flow sensor (Hamilton Medical AG, Rhäzüns, Switzerland), which was calibrated at the beginning of mechanical ventilation in all animals. Plateau pressure and inspiratory tidal volume were measured after a 5-s inspiratory breath hold followed by waveform freezing and cursor measurement. Total PEEP was measured with an end-expiratory pressure hold of 5 s. These measurements were only done after 10 stable pressure, volume, and flow curves were observed on the monitoring screen of the ventilator. Static pulmonary compliance was calculated from the inspiratory tidal volume and the static inspiratory and expiratory pressures according to the equation  $Cstat: Tidal\ volume/(P_{plateau} - PEEP_{tot})$ . Measurements of tidal volume and pulmonary compliance were indexed to body weight in kilograms. Inspiratory and expiratory resistances were calculated by the Galileo ventilator using the least squares fit method (20).

**Protocol.** After instrumentation, the animals were allowed to rest for 30 min before baseline measurements were performed. Before induction of acute lung injury, the  $FiO_2$  of the ventilator was increased to 1.0 and the PEEP level to 0.6 kPa. Acute respiratory failure was initially induced by repeated injections of oleic acid (0.01 mL/kg bw) into the right atrium followed by repeated lung lavages using warmed 0.9% saline (20 mL/kg bw/lavage). The lung lavage was repeated every 10 min until the  $PaO_2/FiO_2$  ratio fell below 13 kPa. During the induction of acute lung injury, inotropic support with dopamine 10  $\mu$ g/kg bw/min was instituted. After induction of acute lung injury, the animals were allowed to stabilize for at least 30 min. Thereafter, the animals were randomly assigned to either partial liquid ventilation ( $n = 6$ ) or control ( $n = 6$ ) groups using sealed envelopes. Both groups were ventilated with adaptive pressure ventilation using a tidal volume of  $< 10$  mL/kg bw, a PEEP of 1.2 kPa, an inspiratory/expiratory ratio of 1:2, a respiratory rate of 24 breaths/min, and a  $FiO_2$  of 1.0.

Partial liquid ventilation was started using the Rimar 101 perfluorocarbon liquid (Miteni, Milan, Italy). Rimar 101 has a specific gravity of 1.77 g/mL at 25°C, a surface tension of 1.47 dyne/kPa, a vapor pressure of 8.5 kPa at 37°C, an oxygen solubility of 52 mL/100 mL, a  $CO_2$  solubility of 160 mL/100 mL at 37°C, and 1 atm of pressure. The perfluorocarbon liquid was oxygenated at an  $FiO_2$  of 1.0 and warmed to 38°C. Thereafter, in the partial liquid ventilation group, the oxygen-

ated perfluorocarbon liquid was instilled into the lung up to 30 mL/kg bw or a visible meniscus at the endotracheal tube at end expiration without PEEP. Measurements of all cardiopulmonary variables were repeated every 30 min up to 120 min. Evaporative losses of the liquid were compensated by adding 5 mL/kg bw/h of the oxygenated perfluorocarbon liquid without any further control of a visible meniscus at the endotracheal tube at 0 PEEP. To avoid severe acidosis ( $pH < 7.20$ ), tris was infused at a rate of 0.01 mmol/kg bw/min in both groups.

After the end of the experiment, the animals were killed with an overdose of sodium pentobarbital and a rapid injection of potassium chloride.

**Data analysis.** All statistical analyses on recorded data were performed using the Statview 4.5 software for Macintosh. Descriptive statistics were performed on all cardiorespiratory variables and are depicted as median and interquartile range. A comparison of baseline and postinjury data between groups was made by unpaired  $t$  test. As the assumptions on which parametric tests are based were not always fulfilled during the study period, a summary measure was derived for each group including all data from postlung injury up to 2 h of mechanical ventilation (21). The area under the curve (AUC) is the product of the time difference and average of two consecutive measurements  $[AUC_1: (t_2 - t_1) * (y_1 + y_2)/2]$  and is given in U/h. It was calculated using the MS Excel software 98 for Macintosh. The total AUC was calculated as the sum of all half-hourly based areas between acute lung injury and 2 h ( $AUC_{tot}: AUC_1 + AUC_2 + AUC_3 + AUC_4$ ). Thereafter, the summary data were compared using the nonparametric Mann Whitney U-test. A  $p$  value of  $< 0.05$  was considered significant.

## RESULTS

Twelve piglets, six in each group, were studied. Age, body weight, medication, and instrumentation during the experiment were similar for animals in both groups. Baseline cardiorespiratory variables were similar in both groups (Tables 1 and 2). Seven to nine repeated injections of oleic acid (0.01 mL/kg bw) combined with five to eight repeated lung lavages (20 mL/kg bw) in both groups induced a stable model of acute lung injury with no significant differences in cardiorespiratory variables between both groups (Tables 1 and 2).

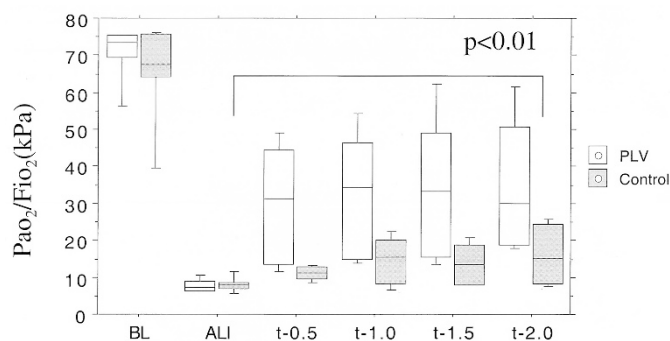
**Gas exchange.** Blood gas, acid base, and respiratory variables are summarized in Table 1. As shown in Figure 1,  $PaO_2/FiO_2$  values were significantly higher during partial liquid ventilation than during conventional mechanical ventilation. Simultaneously, intrapulmonary shunt fraction and alveolar-arterial oxygen tension difference were significantly lower during partial liquid ventilation than during conventional mechanical ventilation, whereas overall  $PaCO_2$  and pH values were not significantly different between both groups.

**Respiratory mechanics.** As shown in Table 1, there were no significant differences in airway pressures, static pulmonary compliance, and inspiratory and expiratory airway resistances between both groups. Dead space ventilation appeared to be lower in the partial liquid ventilation group when compared with the control group.

**Table 1.** Blood gas, acid base, and pulmonary mechanical variables in 12 piglets with acute respiratory failure during partial liquid ventilation ( $n = 6$ ) or conventional mechanical ventilation ( $n = 6$ ) (median  $\pm$  interquartile range)

Parameters	Group	Baseline	ALI	AUC <sub>1</sub>		AUC <sub>2</sub>		AUC <sub>3</sub>		AUC <sub>4</sub>		AUC <sub>tot</sub> (U/h)	<i>p</i> value
				t-0.5	t-1.0	t-1.0	t-1.5	t-2.0	t-2.0				
pH	Control	7.36 (7.35–7.37)	7.26 (7.22–7.3)	7.25 (7.12–7.29)	7.20 (7.15–7.29)	7.29 (7.21–7.32)	7.32 (7.27–7.34)	14.5 (14.4–14.6)	NS				
	PLV	7.40 (7.39–7.42)	7.30 (7.26–7.32)	7.30 (7.27–7.32)	7.31 (7.27–7.32)	7.32 (7.29–7.33)	7.33 (7.32–7.34)	14.6 (14.5–14.7)					
PacO <sub>2</sub> (kPa)	Control	5.5 (4.9–5.8)	7.1 (6.6–7.6)	7.7 (7.5–8.5)	8.4 (7.5–9.4)	8.1 (7.3–8.4)	7.9 (7.6–8.1)	15.7 (15.1–17.2)	NS				
	PLV	5.1 (5.1–5.2)	6.4 (6.4–7.3)	7.8 (7.3–8.3)	8.8 (7.8–9.1)	9.1 (8.6–9.4)	8.9 (8.2–9.7)	16.9 (15.7–17.1)					
PA-aO <sub>2</sub> (kPa)	Control	6.8 (4.7–7.3)	80.2 (78–82)	75.8 (75–78)	71.6 (66–80)	73.8 (70–79)	73.1 (64–78)	146 (144–158)	<0.01				
	PLV	4.8 (4.3–6.1)	81 (79–82)	52 (36–70)	49.9 (32–66)	49.9 (28–66)	51.5 (27–63)	108 (72–137)					
Q's/Q't (%)	Control	13.5 (10–17)	57.6 (51–59)	42.2 (42–43)	38 (32–44)	36.2 (32–41)	34.9 (29–36)	82 (78–96)	<0.05				
	PLV	11.5 (8–13.8)	46.6 (43–51)	25.9 (19–40)	29.4 (19–39)	28 (18–39)	26.8 (18–38)	59 (43–78)					
Vt (mL/kg)	Control	9.7 (9.3–10)	9.8 (9.2–14)	9.1 (8.8–10)	8.8 (8.5–9.5)	8.5 (7.9–8.6)	8.9 (8.6–9.8)	18.3 (17.3–19.9)	NS				
	PLV	9.9 (8.9–11)	10.2 (9.6–11)	8.9 (8.1–9.2)	9.1 (8.5–9.8)	9.0 (8.5–9.8)	8.9 (8.7–9.9)	18.4 (17.2–19)					
Paw (kPa)	Control	0.8 (0.7–0.8)	1.45 (1.2–1.6)	1.85 (1.8–2.1)	1.9 (1.8–2.0)	1.8 (1.8–2.0)	1.8 (1.7–2.2)	3.7 (3.5–4.0)	NS				
	PLV	0.8 (0.7–0.8)	1.41 (1.2–1.7)	1.9 (1.7–1.9)	1.9 (1.7–2.0)	1.9 (1.7–2.0)	1.9 (1.8–2.1)	3.5 (3.4–3.9)					
Pplat (kPa)	Control	1.2 (1.1–1.2)	3.2 (3.0–3.3)	3.3 (3.0–3.3)	3.2 (3.0–3.4)	3.3 (3.2–3.4)	3.3 (3.2–3.5)	6.5 (6.3–6.8)	NS				
	PLV	1.34 (1.3–1.4)	3.3 (2.8–3.5)	2.8 (2.5–3.2)	3.0 (2.5–3.4)	2.8 (2.6–3.1)	2.9 (2.7–3.4)	6.0 (5.3–6.6)					
Cstat (mL/kPa/kg)	Control	0.12 (0.1–0.14)	0.038 (0.035–0.05)	0.047 (0.04–0.07)	0.05 (0.04–0.05)	0.043 (0.04–0.05)	0.044 (0.04–0.05)	0.09 (0.08–0.1)	NS				
	PLV	0.11 (0.1–0.12)	0.039 (0.03–0.05)	0.049 (0.05–0.07)	0.05 (0.04–0.06)	0.06 (0.05–0.06)	0.052 (0.04–0.06)	0.1 (0.09–0.12)					
Raw <sub>i</sub> (kPa/L/s)	Control	2.7 (2.3–3.7)	6.1 (5.5–7.9)	4.5 (3.0–7.8)	4.4 (2.7–5.2)	4.0 (3.0–4.1)	3.6 (3.1–4.6)	9.1 (6.3–12.2)	NS				
	PLV	3.5 (3.2–3.5)	5.1 (4.3–5.7)	4.5 (3.7–5.7)	4.3 (3.5–5.6)	4.6 (3.4–6.3)	4.1 (3.2–5.3)	9.2 (7.7–10.7)					
Raw <sub>e</sub> (kPa/L/s)	Control	2.5 (2.3–3.1)	6.3 (4.4–8.7)	5.6 (3.6–7.2)	5.5 (3.7–6.8)	4.7 (4.0–6.8)	4.7 (3.8–6.2)	10.6 (7.5–14.8)	NS				
	PLV	2.9 (2.6–3.1)	6.1 (4.9–9)	5.1 (4.3–6.2)	5.6 (4.0–6.0)	5.3 (3.8–6.8)	5.6 (4.5–6.2)	12.1 (8.0–12.7)					
V <sub>d</sub> /V <sub>t</sub> (%)	Control	6.7 (4.3–19)	43.4 (39–50)	46.3 (43–52)	42.1 (27–52)	41 (31–53)	42.4 (28–53)	83 (68–99)	<0.01				
	PLV	10.7 (10–11)	38.5 (35–38)	28.5 (27–29)	30.7 (29–31)	30 (29–33)	31.1 (29–36)	61 (58–64)					

PA-aO<sub>2</sub>, alveolo-arterial oxygen tension difference; Q's/Q't, intrapulmonary shunt fraction; Vt, tidal volume; Paw, mean airway pressure; Pplat, plateau pressure; Cstat, static pulmonary compliance; Raw, airway resistance; i, inspiratory; e, expiratory; Vd/Vt, physiologic dead space; ALI, acute lung injury; t, time; AUC, area under the curve; PLV, partial liquid ventilation; *p* values denote significant differences of summary measures (AUC<sub>tot</sub>: AUC<sub>1</sub> + AUC<sub>2</sub> + AUC<sub>3</sub> + AUC<sub>4</sub>) between both groups after the induction of acute lung injury using the Mann-Whitney U-test. Conversion: mmHg \* 0.133 = kPa.



**Figure 1.** Box plot graph of  $\text{PaO}_2/\text{FiO}_2$  during partial liquid ventilation and conventional mechanical ventilation in an animal model of acute lung injury. The box plot displays 10th, 25th, 50th, 75th, and 90th percentiles of  $\text{PaO}_2/\text{FiO}_2$ . First summary data were derived for each group, including values postlung injury. Up to 2 hr of mechanical ventilation and then the summary data between both groups were compared using the nonparametric Mann-Whitney U-test. ALI, acute lung injury; BL, baseline; PLV, partial liquid ventilation.

**Hemodynamics.** Hemodynamic data are presented in Table 2. Whereas there were no significant differences in HR, right atrial, pulmonary artery, and systemic arterial pressures between both groups, cardiac output and oxygen delivery were significantly higher during partial liquid ventilation when compared with control animals. The higher cardiac output combined with unchanged pulmonary artery pressure resulted in a significantly lower pulmonary vascular resistance in the partial liquid ventilation group compared with the control group.

All animals survived the 2-h trial.

## DISCUSSION

The main findings of this pilot study suggest that (1) oxygenation was significantly better in the partial liquid ventilation group when compared with the control group and (2) cardiac output and oxygen delivery were significantly higher during partial liquid ventilation compared with conventional mechanical ventilation. An unexpected finding was that dead space appeared to be lower during partial liquid ventilation than during conventional mechanical ventilation.

The rationale for mechanical ventilation in acute lung injury is to apply a PEEP to prevent end-expiratory collapse of collapsible alveoli and to select a tidal volume to limit overdistension of lung units (22). Another therapeutic option would be to eliminate the increased forces acting at the air-liquid interface in the acutely damaged lung by filling the lungs with a perfluorochemical liquid.

**Partial liquid ventilation.** In 1991, Fuhrman *et al.* (10) introduced the technique of perfluorocarbon-associated gas exchange or partial liquid ventilation. This new technique combined liquid ventilation at functional residual capacity and tidal gas volume ventilation using a conventional ventilator. Meanwhile, a number of experimental studies have shown that partial liquid ventilation significantly improves oxygenation, lung mechanics, decreases further alveolar damage, and decreases serum tumor necrosis factor- $\alpha$  concentration in acute lung injury (6–8, 12, 14, 16, 23–25). Most investigators filled the lung with perfluorocarbon liquid at functional residual

capacity level (30 mL/kg bw) and used volume-controlled mechanical ventilation with a tidal volume of 15 mL/kg bw and a PEEP level between 0.2 and 0.6 kPa in both the partial liquid ventilation as well as the control groups.

Recently, Cox *et al.* (15) reported a significant risk of barotrauma during partial liquid ventilation when lungs are filled with perfluorocarbon liquid to functional residual capacity levels with a superimposed gas ventilatory strategy of large tidal volumes. In 1999, we reported that the application of PEEP 1.0 to 1.2 kPa during partial liquid ventilation seems to be optimal to improve oxygenation and lung mechanics without any negative hemodynamic side effects (26). Recently, Kirmse *et al.* (27) set PEEP levels according to the lower inflection point + 0.1 kPa in a lung lavage model of acute lung injury resulting in PEEP values between 1.1 and 1.3 kPa associated with improved oxygenation and lung mechanics. In addition, the same group reported that with PEEP set at the lower inflection point, adequate gas exchange and improved lung mechanics can be obtained in both volume and pressure controlled modes of mechanical ventilation (28). According to these data, we now used adaptive pressure ventilation with a PEEP of 1.2 kPa, a tidal volume of <10 mL/kg bw, and a fixed ventilator rate of 24 breaths/min. A tidal volume of <10 mL/kg bw was selected to reduce the risk of barotrauma, and the ventilator rate was not increased to compensate for moderate hypercapnia. The advantage of adaptive ventilation is that the set target volume is achieved with the lowest pressure possible depending on lung mechanics.

**Oxygenation.** In healthy lungs, partial liquid ventilation increases  $\text{O}_2$  shunt and arterial-alveolar  $\text{CO}_2$  difference due to diffusion limitation, ventilation/perfusion heterogeneity, and intrapulmonary shunt (14, 24, 29). However, oxygenation is significantly improved during partial liquid ventilation in a variety of models of acute lung injury due to recruitment of collapsed lung regions, decrease in surface tension, and redistribution of blood flow to nondependent lung regions (6–8, 12, 29). In our pilot study, this improved oxygenation during partial liquid ventilation is confirmed using a high PEEP and moderate tidal volume gas ventilatory strategy. We speculate that partial liquid ventilation combined with a high PEEP ventilatory strategy might stabilize dependent as well as nondependent lung units, resulting in improved ventilation/perfusion heterogeneity and oxygenation.

**Ventilation.** In this pilot study, both ventilatory strategies with tidal volumes < 10 mL/kg bw resulted in moderate hypercapnia with no significant difference between both groups. In contrast, literature reports improved ventilation during partial liquid ventilation using tidal volumes > 12.5 mL/kg bw (7, 12, 30). This difference in ventilation might be caused by the low gas volume ventilatory strategy and the  $\text{CO}_2$  solubility and diffusibility of the perfluorocarbon fluid used. Whereas there are very few data on dead space ventilation during partial liquid ventilation, Murray *et al.* (31) already reported in 1984 that an arterial-end tidal  $\text{CO}_2$  pressure gradient would be smallest when there is maximal alveolar recruitment by PEEP without alveolar overdistension in acute lung injury. The literature reports both an increase and no change in dead space ventilation during partial liquid ventilation in

**Table 2.** Hemodynamic data in 12 piglets with acute respiratory failure during partial liquid ventilation ( $n = 6$ ) or conventional mechanical ventilation ( $n = 6$ ) (median  $\pm$  interquartile range)

Parameters	Group	Baseline	ALI	AUC <sub>1</sub>		AUC <sub>2</sub>		AUC <sub>3</sub>		AUC <sub>4</sub>		AUC <sub>tot</sub> (U/h)	p value
				t-0.5	t-1.0	t-1.0	t-1.5	t-1.5	t-2.0				
HR (beats/min)	Control	92 (86–94)	141 (84–165)	110 (86–165)	117 (83–163)	129 (78–162)	120 (94–131)	244 (174–325)	NS				
	PLV	92 (91–97)	127 (101–138)	145 (126–163)	152 (129–169)	134 (116–165)	143 (127–157)	278 (256–308)					
mean Pa (kPa)	Control	11.4 (9.6–12)	9.1 (8.5–10)	8.6 (6.4–8.8)	8.9 (8.4–9.3)	8.7 (8.5–9.3)	8.9 (8.0–9.4)	17.6 (16.1–17.9)	NS				
	PLV	12.3 (11.4–13)	9.4 (9.2–9.8)	9.3 (8.5–9.8)	9.6 (8.9–9.9)	9.6 (8.5–10)	9.1 (8.7–9.4)	18.8 (18.1–20.1)					
mean Pra (kPa)	Control	0.79 (0.7–0.9)	0.86 (0.7–0.9)	1.0 (0.9–1.2)	1.0 (0.9–1.3)	1.26 (1.0–1.4)	1.26 (0.9–1.4)	2.3 (1.9–2.5)	NS				
	PLV	0.61 (0.5–0.7)	0.55 (0.4–0.8)	0.87 (0.7–1.0)	0.86 (0.7–1.0)	0.87 (0.7–1.1)	1.0 (0.7–1.2)	1.8 (1.3–2.0)					
mean Ppa (kPa)	Control	2.3 (2.1–3.1)	4.5 (4.1–5.6)	3.8 (3.6–4.2)	4.3 (4.1–4.8)	4.4 (4.2–4.6)	4.3 (4.1–5.1)	8.5 (8.1–9.1)	NS				
	PLV	2.5 (2.5–2.9)	4.8 (4.1–4.8)	4.4 (3.7–4.9)	4.6 (4.1–4.9)	4.3 (4.1–4.5)	4.2 (4.1–4.4)	8.8 (8.3–9.5)					
PVR (kPa/L/s)	Control	51 (36–69)	161 (136–177)	135 (106–203)	150 (103–173)	183 (151–213)	155 (135–206)	315 (272–386)	<0.05				
	PLV	57 (46–62)	139 (125–205)	103 (88–127)	113 (90–175)	114 (70–186)	141 (91–158)	240 (215–281)					
SVR (kPa/L/s)	Control	469 (341–603)	476 (381–502)	426 (328–504)	509 (454–588)	546 (509–593)	513 (496–574)	1001 (902–1129)	NS				
	PLV	498 (456–649)	489 (432–501)	363 (351–454)	445 (300–499)	462 (358–550)	454 (380–541)	820 (767–941)					
Q' (ml/min/kg)	Control	148 (116–164)	123 (91–142)	106 (90–122)	98 (84–153)	97 (67–118)	96 (81–111)	210 (179–236)	<0.01				
	PLV	178 (161–192)	127 (121–170)	155 (141–239)	140 (133–178)	153 (112–165)	134 (99–181)	309 (303–327)					
DO <sub>2</sub> (ml/min)	Control	19.2 (15–19.5)	11.1 (10–12.5)	11.3 (9.3–14.1)	10.6 (9.8–15.1)	10.5 (7.7–13.6)	10.6 (9.4–13.1)	22.2 (13.5–26.7)	<0.01				
	PLV	23.6 (21–25.1)	12.9 (12.4–18.8)	18.4 (15.1–24)	16.9 (15.1–22)	17.9 (12–21)	16.7 (13.1–21.4)	36.5 (33.9–40.1)					
VO <sub>2</sub> (ml/min)	Control	4.6 (4.6–5.9)	3.5 (3.4–3.8)	3.5 (3.1–4.7)	4.1 (3.2–4.8)	3.5 (3.1–5.1)	4.1 (2.9–5.1)	7.3 (6.7–10)	NS				
	PLV	5.8 (4.8–7.3)	5.3 (5.2–5.6)	5.0 (3.8–6.4)	4.4 (4.1–6.1)	4.3 (3.6–4.6)	4.2 (3.4–5.1)	9.2 (8.6–10.5)					

HR, heart rate; Pa, arterial pressure; Pra, right atrial pressure; Ppa, pulmonary artery pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; Q', cardiac output; DO<sub>2</sub>, oxygen delivery; VO<sub>2</sub>, oxygen consumption; ALI, acute lung injury; t, time; AUC, area under the curve; PLV, partial liquid ventilation; p values denote significant differences of summary measures (AUC<sub>tot</sub>; AUC<sub>1</sub> + AUC<sub>2</sub> + AUC<sub>3</sub> + AUC<sub>4</sub>) between both groups after the induction of acute lung injury using the Mann-Whitney U-test. Conversion: mmHg \* 0.133 = kPa.

healthy as well as in acutely injured lungs (29, 32–34). Mates *et al.* (32) speculated that a diffusion barrier imposed by a layer of perfluorocarbon might be responsible for this increased dead space ventilation in healthy piglets. In contrast to these findings, in our pilot study, dead space ventilation appeared to decrease rapidly during partial liquid ventilation, whereas in the control group with similar gas ventilatory parameters, dead space appeared to be significantly higher with some decrease over time. We speculate that the use of higher PEEP levels during partial liquid ventilation would improve perfluorocarbon distribution within the lung, would redistribute pulmonary blood flow to nondependent parts of the lung, and would improve ventilation/perfusion heterogeneity, resulting in lower physiologic dead space. However, there are some limitations to calculate dead space during partial liquid ventilation using the Bohr equation 1. The basic assumption of the Bohr equation to calculate physiologic dead space is that pulmonary capillary blood fully equilibrates with alveolar gas (35). However, this complete arterial-alveolar equilibration is probably not given during partial liquid ventilation because of diffusion limitation and heterogeneity of perfluorocarbon distribution (36). Therefore, Mates *et al.* (37) proposed to use the multiple inert gas elimination technique to measure physiologic dead space during partial liquid ventilation and observed no significant difference between partial liquid ventilation and gas ventilation in healthy piglets. For the classical Bohr equation, the mean partial pressure of CO<sub>2</sub> in the expired gas and not the end-tidal CO<sub>2</sub> is used. High levels of PEEP may significantly increase the slope of the alveolar plateau, resulting in falsely low dead space values (38). In our pilot study, expiratory CO<sub>2</sub> curves were very stable without any positive or negative slope of the alveolar plateau both during partial liquid ventilation and conventional mechanical ventilation. On the basis of our stable expiratory CO<sub>2</sub> curves, we might exclude dead space calculation errors either induced by high PEEP levels or by the heterogeneity of perfluorocarbon distribution in the lung. Our contradictory results on ventilation and physiologic dead space during partial liquid ventilation might be explained on the one hand by diffusion limitation combined with improved ventilation/perfusion heterogeneity and on the other hand by the limitations of the modified Bohr equation during partial liquid ventilation.

**Respiratory mechanics.** There are several reports on improved static compliance of the respiratory system in different models of acute lung injury during partial liquid ventilation (8, 12, 27, 30, 39, 40). However, compliance measurements might be problematic during partial liquid ventilation because the gas-volume based compliance measurements are restricted to the gas filled parts of the lung and may not reflect the whole lung compliance. Recently, Hirschl *et al.* (12) demonstrated that compliance measurements are significantly different in the same animal when gas *versus* liquid is used to assess compliance. In 1998, Kirmse *et al.* (27) noticed a significantly higher static compliance of the respiratory system at high PEEP levels compared with low PEEP levels in sheep with a lung lavage induced model of acute lung injury. These findings were confirmed by our study in piglets with acute lung injury induced by oleic acid infusion and repeated lung lavages when

PEEP levels were increased from 0 to 1.5 kPa during partial liquid ventilation (26). In this pilot study, our hypothesis that pulmonary mechanics would be significantly improved during partial liquid ventilation compared with conventional mechanical ventilation was not confirmed. In contrast to the previous study, we now used much lower tidal volumes, which might have influenced pulmonary compliance in this model of acute lung injury (26). In addition, differences in compliance data during partial liquid ventilation might be explained by different measuring techniques (quasi-static *versus* static technique with or without PEEP) and by the differences in lung injury models in different animals. In this pilot study, we used inspiratory and expiratory hold techniques of 5 s and the inspiratory tidal volume for compliance measurement on the one hand to obtain reliable static pressure conditions and on the other hand to avoid influences of the high vapor pressure of the perfluorocarbon liquid on expiratory flow and volume measurements.

The literature reports on both increases and decreases in airway resistance during partial liquid ventilation depending on the lung injury model and the gas ventilatory strategy superimposed to partial liquid ventilation (6, 7, 40). In this pilot study, no differences in inspiratory and expiratory airway resistances were noticed between partial liquid ventilation and conventional mechanical ventilation using similar gas ventilatory parameters.

**Hemodynamics.** During total liquid ventilation, hemodynamic compromise was reported, which was not observed later during partial liquid ventilation even in large animals (41–43). Hemodynamic compromise was speculated to result from pulmonary vascular compression due to the high hydrostatic pressure induced by the high specific gravity of the perfluorocarbon fluid. In 1995, Houmes *et al.* (44) reported that partial liquid ventilation significantly improves gas exchange and does not lead to hemodynamic depression in large pigs with lung lavage induced acute lung injury. In addition, these authors observed an improvement in pH during partial liquid ventilation and speculated that a stable cardiac output and oxygen delivery would be responsible for this improvement. In our pilot study, cardiac output and oxygen delivery were significantly improved during partial liquid ventilation compared with conventional mechanical ventilation. One reason might be that cardiac output was slightly higher at baseline and after inducing acute lung injury in the partial liquid ventilation group than in the control group. In addition, we speculate that improved oxygenation and higher PaCO<sub>2</sub> values over time might have influenced cardiac output in the partial liquid ventilation treated animals.

**Limitations of the study.** Because of the small sample size in each group ( $n = 6$ ), a large beta error may have existed, that is, some of the comparisons that did not reach significance might have done so with a larger number in each group. Another limitation of this pilot study is the short duration of the experiment. Clinically, it would be very important to evaluate cardiorespiratory data for a longer period of time combined with radiologic and histologic evaluation of the lungs. Although we used a “lung protective” gas ventilatory strategy in both groups, lung protection was not the focus of this pilot

study, and further research is needed before protective effects of PEEP during partial liquid ventilation can be established.

## CONCLUSION

The results of this pilot study suggest that partial liquid ventilation combined with a superimposed gas ventilatory strategy including high PEEP and moderate tidal volume significantly improves oxygenation, cardiac output, and oxygen delivery compared with conventional mechanical ventilation in acute lung injury in piglets but has no significant influence on lung mechanics. In addition, dead space ventilation appeared to be lower during partial liquid ventilation compared with conventional mechanical ventilation. However, further studies are required to assess the optimal gas ventilatory strategy during partial liquid ventilation to obtain adequate gas exchange, stable hemodynamics, and lung protection.

**Acknowledgments.** The authors want to thank Mrs. Gabriele Gruber, Mrs. Elisabeth Perstaller, Mrs. Ursula Schreiner, Mrs. Franziska Sommer, and Mrs. Simone Sprinz for their great support throughout the experiment and Mr. Peter Rehak, PhD, for statistical assistance.

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