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Hemodynamic effects of partial liquid ventilation with perfluorocarbon in acute lung injury

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Abstract *Objective:* To assess the effect of partial liquid ventilation with perfluorocarbons on hemodynamics and gas exchange in large pigs with induced acute lung injury (ALI).
Design: Randomized, prospective, double-control, experimental study.
Setting: Experimental intensive care unit of a university.
Materials: Eighteen large pigs (50 ± 5 kg body weight) with an average anterior posterior thoracic diameter of 24 cm and induced acute lung injury.
Interventions: All animals were surfactant depleted by lung lavage to a P_aO_2 below 100 mmHg and randomized to receive either perflubron ($n = 6$) or saline ($n = 6$) in five intratracheal doses of 5 ml/kg at 20-min intervals, or no instillation ($n = 6$).
Measurements and results: In all animals heart rate, arterial pressures, pulmonary pressures, cardiac output and blood gases were recorded at 20-min intervals. There was no deleterious effect on any hemodynamic parameter in the perflubron group, whereas systolic and mean pulmonary arterial pressure values showed a persistent decrease after the first 5 ml/kg of perflubron, from 48.7 ± 14.1 to 40.8 ± 11.7 mmHg and from 39.7 ± 13.2 to 35.2 ± 12.0 mmHg, respectively. Perflubron resulted in a significant (ANOVA $P < 0.01$), dose-dependent increase in P_aO_2 values from 86.3 ± 22.4 to a maximum of 342.4 ± 59.4 mmHg at a dose of 25 ml/kg; the other groups showed no significant increase in P_aO_2.
Conclusions: Tracheal instillation of perflubron in induced ALI results in a dose-dependent increase in P_aO_2 and has no deleterious effect on hemodynamic parameters.

Key words Hemodynamics · Gas exchange · Mechanical ventilation · Oxygen · Perfluorocarbon · Respiratory distress syndrome

Introduction

In 1966 Clark and Gollan demonstrated the ability of small mammals to remain alive while breathing oxygenated perfluorocarbons (PFCs) [1]. Since then PFCs have been investigated extensively as an alternative means of respiratory support, and PFCs oxygenated outside the body have been used in the treatment of acute respiratory failure [2, 3]. In 1991 Fuhrman et al. [4] demonstrated the feasibility of applying liquid ventilation in healthy animals without the need for a specialized liquid breathing system. This technique of in vivo bubble oxygenation, combining intratracheal PFC administration with conventional ventilation, brought the use of PFCs for liquid ventilation closer to clinical practice. Our group [5–7] successfully applied this technique using perflubron in rabbits with induced acute lung injury (ALI); the result was improved gas exchange, with no effect on arterial blood pressure. This perflubron (perfluorooctyl bromide; Alliance Pharmaceutical, San Diego, Calif., USA) is a new generation of PFC with a low surface tension of 18.1 dyne/cm, a specific gravity of 1.918 g/cm^3 at 25 °C, a vapor pressure of 3.6 torr at 20 °C and of 10.5 torr at 37 °C, an oxygen solubility of 53 ml/100 ml, a CO_2 solubility of 210 ml/100 ml at 37 °C and an atmospheric pressure of 1.

As a result of PFC filling, pulmonary vascular compression might be present, with a resulting increase in pulmonary arterial pressure and a decrease in cardiac output [8–10]. The above-mentioned studies using PFCs to improve blood gases were performed in small animals. Based on the size of the animals used and therefore on the total weight of the PFCs used, the hydrostatic pressure of the PFCs did not result in pulmonary vascular compression. However, this effect might occur in larger animals, although no studies using partial liquid ventilation and based on this hypothesis have yet been reported. In order to reach high hydrostatic pressures, we investigated the hemodynamic effects of perflubron in large pigs in the supine position with induced ALI, whose thoracic anterior posterior diameter was about 24 cm.

Materials and methods

Animal preparation

The protocol of this study was approved by the university's animal experimental committee. Anesthesia was induced in 18 female Yorkshire pigs (body weight 50 ± 5 kg) with ketamine (10 mg/kg) and midazolam (0.5 mg/kg), and was maintained with continuous infusions of ketamine (80 μg/kg per min) and midazolam (9 μg/kg per min). Muscle relaxation was achieved by a continuous infusion of pancuronium bromide (2.5 μg/kg per min). During the whole experimental period, all animals were in a supine position. They were tracheotomized, intubated with an 8.0-mm endotracheal tube fitted with a Filtraflux heat-moisture exchanger with a built-in bacterial filter (ICHOR AB, Bromma, Sweden) and cannulated with a carotid artery catheter, a 5F pulmonary artery catheter (SP51055H Viggo-Spectramed, Wiltshire, England) and a central venous catheter. During animal preparation, volume-controlled ventilation was provided with a Servo 300 ventilator (Siemens, Solna, Sweden) set at: frequency 20 beats min, inspiratory time 25%, pause time 10%, inspiratory rise time 5%, PEEP 5 cm H_2O and 100% oxygen. Minute ventilation was adjusted to obtain a P_aCO_2 of 40 ± 3 mmHg. These ventilator settings were maintained during the entire study period.

All animals were surfactant depleted according to Lachmann et al. [11] by repeated lung lavage with warm saline (38 °C, 30 ml/kg) to reduce P_aO_2 to below 100 mmHg. To perform the lavage, the animals were disconnected from the ventilator and saline was instilled via an open-bottle-tube connection to a point at which systemic pressure decreased and pulmonary arterial pressure increased significantly. The saline was removed from the lung by gravitational force, i.e. lowering the bottle. After each lavage, the animals were reconnected to the ventilator for at least 10 min before the next lavage was performed. After 1 h of ventilation following the last lung lavage, all animals were randomized to receive either perflubron ($n = 6$) or saline ($n = 6$) in five intratracheal doses of 5 ml/kg at 20-min intervals, or to receive no instillation ($n = 6$) (control group). After the animals were disconnected from the ventilator, perflubron and saline were administered intratracheally as a bolus over a period of 10 s; they were reconnected to the ventilator immediately thereafter.

Measurements

Systolic (SysAP), diastolic (DiaAP) and mean (MAP) arterial pressures, as well as systolic (SysPAP), diastolic (DiaPAP) and mean (MPAP) pulmonary arterial pressures, pulmonary wedge pressure (PWP) and central venous pressure (CVP), were recorded in all animals using Statham P23XL transducers (Spectramed, Oxnard, Calif.). Cardiac output (CO) was measured in triplicate using the thermodilution technique with a Sirecust 1280 monitor (Siemens, Danvers, Mass. USA), which also traced heart rate (HR) and all recorded pressures. This monitor was also used to calculate pulmonary (PVR) and systemic vascular resistance (SVR). Arterial and mixed venous samples were analyzed for blood gases, pH and mixed venous oxygen saturation (SVO_2) by conventional methods (ABL-505 OSM-3 combination, Radiometer, Copenhagen, Denmark, set to measure swine hemoglobin). This combination was used to calculate base excess (BE), intrapulmonary shunt (shunt), arterial oxygen content (C_aO_2), oxygen delivery (DO_2) and anteriovenous oxygen content difference ($C_{a-v}O_2$). All measurements were recorded prior to lung lavage and subsequently at 20-min intervals (at 20 min after each dose in the treated groups in order to reach a steady state). At the end of the study period, all animals were killed with an intracardiac overdose of KCl.

Statistical analysis

All statistical analyses on recorded data were performed using the Instat 2.0 biostatistics package (GraphPad Software, San Diego, Calif., USA). All intra-group comparisons were made with ANOVA repeated measures. If ANOVA resulted in a $P < 0.05$, a Dunnett

post-test was performed. This post-test used the post-lavage data (dose = 0 ml/kg body weight) as control. A P value of 0.05 was regarded as significant. All data are reported as mean values ± standard deviation (SD).

Results

All animals were comparable with regard to body weight and thoracic diameter. Before and after lung lavage, all were also comparable with regard to blood gases and hemodynamic data ($P > 0.05$, ANOVA). An average of 4 ± 1 lavages was needed to obtain a P_aO_2 below 100 mmHg after resumption of ventilation. Although CO before and after lavage was slightly lower in the control group than in the two treated groups, this difference was not statistically significant. All animals survived the study period. Table 1 gives all the data on the hemodynamic parameters measured and calculated during the study; Table 2 gives all the data on the recorded gas exchange parameters.

Hemodynamics (Table 1)

Control group

After lung lavage, HR in the control group showed a significant increase from 113.2 ± 30.3 to 123.7 ± 33.6 beats/min ($P < 0.05$) and SysAP values increased from 121.0 ± 27.6 to 139.3 ± 14.0 mmHg; there was no significant change in DiaAP, MAP or CO, whereas CVP values decreased from 8.5 ± 3.1 to 6.8 ± 3.5 mmHg ($P < 0.05$). There was no significant change in PWP, PVR, SVR or pulmonary arterial pressures.

Saline group

Following the lavage procedure and subsequent saline instillation, HR increased from 104.2 ± 7.5 to 153.8 ± 28.7 beats/min ($P < 0.01$). There was no significant change in arterial pressures and SysPAP, whereas DiaPAP and MPAP values increased from 30.5 ± 8.4 to 38.7 ± 7.3 mmHg and from 37.7 ± 6.9 to 46.7 ± 5.6 mmHg, respectively. CO values increased from 5.0 ± 0.9 to 7.3 ± 1.3 l/min ($P < 0.01$); CVP values, from 5.7 ± 2.9 to 9.2 ± 3.3 mmHg ($P < 0.01$); and PWP values, from 10.7 ± 4.7 to 13.0 ± 4.6 mmHg ($P < 0.01$). There was no significant change in PVR, whereas SVR values decreased from 1995.8 ± 324 to 1346.3 ± 261 dynes · s/cm^5 ($P < 0.01$).

Perflubron group

Following lung lavage and perflubron treatment, there were no statistically significant changes in HR, arterial pressures, CO, CVP, PVR or SVR. SysPAP and MPAP values decreased from 48.7 ± 14.1 to 40.8 ± 11.7 mmHg ($P < 0.01$) and from 39.7 ± 13.2 to 34.8 ± 11.3 mmHg ($P < 0.01$), respectively. There was an increase in PWP values from 11.2 ± 4.4 to 15.2 ± 3.8 mmHg, resulting in a statistically significant difference ($P < 0.05$) at the 25 ml/kg body weight dose.

Gas exchange parameters (Table 2)

Control group

In the post-lavage period, there were no significant changes in P_aO_2 or shunt; PCO_2 increased from 52.4 ± 10.7 to 62.0 ± 16.9 mmHg ($P < 0.01$), with a subsequent decrease in pH from 7.34 ± 0.05 to 7.28 ± 0.09 ($P < 0.01$); and there was no statistically significant change in BE. SVO_2 values increased over time from 48.8 ± 18.4 to 51.9 ± 13.3% ($P < 0.05$). Analysis of calculated gas exchange parameters C_aO_2, D_aO_2 and $C_{a-v}O_2$ showed no statistically significant changes.

Saline group

Saline instillation resulted in a statistically significant and immediate dose-dependent deterioration of all gas exchange parameters (P_aO_2, PCO_2, pH, BE, SVO_2, shunt, C_aO_2, D_aO_2 and $C_{a-v}O_2$).

Perflubron group

Perflubron treatment resulted in a dose-dependent improvement in the measured gas exchange parameters. P_aO_2 values increased from 86.5 ± 22.4 to 342.1 ± 59.4 mmHg ($P < 0.01$); at doses of 15, 20 and 25 ml/kg, this increase was significantly different from the immediate post-lavage P_aO_2 values. PCO_2 values decreased from 60.4 ± 19.9 to 53.3 ± 15.7 mmHg ($P < 0.01$) and pH increased from 7.28 ± 0.13 to 7.34 ± 0.11 ($P < 0.01$). BE values increased towards pre-lavage (healthy) values (i.e. 3.9 ± 0.9 mmol/l), from −0.5 ± 2.8 to 1.5 ± 2.5 mmol/l ($P < 0.01$). SVO_2 values increased rapidly from 45.6 ± 8.5 to 59.5 ± 16.4% ($P < 0.01$), whereas shunt values decreased from 36.6 ± 17.8 to 14.2 ± 3.1% ($P < 0.01$). C_aO_2 values increased from 11.7 ± 1.5 to

Table 1 Data on hemodynamic parameters following induction of anesthesia (healthy) and following lung lavage [0 (lavage)] and following treatment (5–25) in saline-perflubron-treated or control animals ($n = 6$ per group). Intra-group comparisons of ANOVA with Dunnet post-test if ANOVA $P < 0.05$, using the post-lavage data (0–25) with 0 (lavage) as reference value

Dose	Heart rate (beats/min)			Systolic arterial pressure (mmHg)			Diastolic arterial pressure (mmHg)		
(ml/kg BW)	Control	Saline	Perflubron	Control	Saline	Perflubron	Control	Saline	Perflubron
Healthy	113.5 ± 29.8	122.2 ± 23.1	121.8 ± 12.0	124.0 ± 15.7	133.0 ± 18.1	136.2 ± 4.8	100.7 ± 16.2	102.8 ± 12.3	108.2 ± 6.6
0 (lavage)	113.2 ± 30.3	104.2 ± 7.5	106.8 ± 23.1	121.0 ± 27.6	139.8 ± 8.7	132.7 ± 21.8	107.4 ± 25.0	113.3 ± 6.9	105.3 ± 21.8
5	116.0 ± 27.6	115.2 ± 8.6	105.5 ± 22.7	125.2 ± 19.9	140.3 ± 11.8	125.2 ± 15.2	101.4 ± 25.6	113.3 ± 8.2	97.8 ± 16.3
10	120.5 ± 32.7	122.3 ± 12.9	106.0 ± 21.8	128.8 ± 20.8	133.0 ± 14.3	122.2 ± 19.8	107.5 ± 21.8	106.2 ± 8.0	97.2 ± 18.2
15	118.3 ± 33.2	133.8 ± 16.0**	106.7 ± 20.8	133.7 ± 16.3	137.0 ± 18.6	126.4 ± 17.1	108.5 ± 16.2	105.2 ± 12.2	100.6 ± 19.0
20	119.7 ± 34.4	146.5 ± 23.9**	104.7 ± 18.8	134.3 ± 16.0	141.3 ± 21.7	123.0 ± 18.9	110.7 ± 18.7	108.5 ± 14.5	99.7 ± 17.8
25	123.7 ± 33.6*	153.8 ± 28.7**	106.0 ± 17.4	139.3 ± 14.0*	146.3 ± 26.7	121.3 ± 20.1	116.5 ± 17.8	112.0 ± 19.5	97.3 ± 20.3
Dose	Mean arterial pressure (mmHg)			Systolic pulmonary pressure (mmHg)			Diastolic pulmonary pressure (mmHg)		
(ml/kg BW)	Control	Saline	Perflubron	Control	Saline	Perflubron	Control	Saline	Perflubron
Healthy	112.3 ± 16.9	117.4 ± 14.2	122.8 ± 5.5	29.2 ± 6.3	31.6 ± 9.6	30.0 ± 7.2	18.8 ± 3.3	19.0 ± 7.2	19.6 ± 5.0
0 (lavage)	117.2 ± 25.9	127.2 ± 7.6	119.3 ± 21.0	41.3 ± 8.8	48.3 ± 9.3	48.7 ± 14.1	28.0 ± 9.8	30.5 ± 8.4	31.7 ± 12.5
5	110.6 ± 23.2	126.5 ± 11.4	112.5 ± 15.3	44.2 ± 8.8	53.7 ± 12.2	42.7 ± 11.8	28.7 ± 8.0	34.0 ± 6.2	28.3 ± 12.1
10	118.3 ± 22.3	121.0 ± 10.4	110.8 ± 18.7	43.7 ± 7.4	53.0 ± 6.3	42.0 ± 11.2*	29.5 ± 8.0	36.7 ± 4.7**	28.8 ± 11.9
15	120.2 ± 17.4	121.2 ± 13.9	108.2 ± 22.3	43.3 ± 6.6	54.2 ± 6.0	43.3 ± 11.7	28.8 ± 6.8	36.7 ± 3.5**	30.0 ± 11.9
20	122.7 ± 17.2	126.5 ± 17.3	112.2 ± 18.2	44.8 ± 5.6	53.8 ± 6.4	41.5 ± 12.2*	29.5 ± 6.4	39.2 ± 7.1**	30.2 ± 12.3
25	127.8 ± 15.9	131.0 ± 22.5	110.0 ± 20.7	43.2 ± 4.8	55.2 ± 7.5	40.8 ± 11.7*	29.8 ± 7.2	38.7 ± 7.3**	29.7 ± 11.4
Dose	Mean pulmonary pressure (mmHg)			CO (l/min)			Central venous pressure (mmHg)		
(ml/kg BW)	Control	Saline	Perflubron	Control	Saline	Perflubron	Control	Saline	Perflubron
Healthy	23.2 ± 4.1	25.0 ± 8.4	24.6 ± 4.2	4.6 ± 0.9	6.7 ± 1.4	6.6 ± 1.1	6.7 ± 2.9	7.6 ± 2.7	6.8 ± 1.3
0 (lavage)	34.2 ± 9.4	37.7 ± 6.9	39.7 ± 13.2	4.6 ± 1.3	5.0 ± 0.9	5.0 ± 1.7	8.5 ± 3.1	5.7 ± 2.9	7.3 ± 2.3
5	35.5 ± 8.1	42.0 ± 8.0*	35.2 ± 12.0*	4.4 ± 1.3	5.4 ± 1.3	5.1 ± 1.2	8.0 ± 3.9	7.3 ± 2.7	7.7 ± 2.5
10	36.2 ± 7.6	43.7 ± 4.6**	34.8 ± 11.8*	4.6 ± 1.1	5.5 ± 1.1	4.6 ± 1.0	7.3 ± 3.6	7.5 ± 2.7	7.3 ± 2.2
15	36.2 ± 6.4	44.5 ± 4.2**	35.8 ± 11.6	4.9 ± 1.0	6.8 ± 1.5**	5.0 ± 1.6	7.3 ± 4.0	7.7 ± 2.7	7.8 ± 1.3
20	36.7 ± 6.0	46.3 ± 6.3**	35.2 ± 12.1*	4.8 ± 1.0	7.3 ± 1.4**	4.5 ± 1.4	6.7 ± 3.4*	8.8 ± 3.4**	8.2 ± 2.0
25	36.0 ± 5.9	46.7 ± 5.6**	34.8 ± 11.3*	4.9 ± 1.1	7.3 ± 1.3**	4.1 ± 1.1	6.8 ± 3.5*	9.2 ± 3.3**	8.5 ± 2.8
Dose	Pulmonary wedge pressure (mmHg)			PVR (dynes·s/cm^5)			SVR (dynes·s/cm^5)		
(ml/kg BW)	Control	Saline	Perflubron	Control	Saline	Perflubron	Control	Saline	Perflubron
Healthy	7.0 ± 2.9	7.5 ± 4.0	9.2 ± 1.8	310.9 ± 128.9	246.4 ± 134.8	188.0 ± 43.0	1793 ± 421	1370 ± 447	1417 ± 177
0 (lavage)	8.8 ± 4.2	10.7 ± 4.7	11.2 ± 4.4	510.7 ± 334.8	445.0 ± 128.0	502.6 ± 287.5	2182 ± 1105	1996 ± 324	1899 ± 539
5	8.7 ± 4.2	10.8 ± 4.4	10.2 ± 4.2	533.7 ± 266.4	488.1 ± 179.4	426.6 ± 242.5	1988 ± 858	1879 ± 473	1692 ± 556
10	8.2 ± 4.7	11.5 ± 3.6	11.0 ± 4.5	525.0 ± 197.8	481.9 ± 99.8	457.3 ± 289.0	1892 ± 630	1692 ± 303*	1860 ± 485
15	8.3 ± 4.8	12.7 ± 3.7*	11.8 ± 4.9	478.2 ± 184.9	391.4 ± 94.7	451.8 ± 295.7	1965 ± 532	1396 ± 282**	1700 ± 434
20	9.5 ± 4.8	13.0 ± 4.0**	13.2 ± 8.0	492.2 ± 213.6	389.8 ± 161.4	435.1 ± 199.9	2020 ± 544	1311 ± 259**	1939 ± 437
25	10.2 ± 3.8	13.0 ± 4.6**	15.2 ± 3.8*	457.3 ± 189.4	389.2 ± 146.9	441.0 ± 292.4	2024 ± 511	1346 ± 261**	2029 ± 472

* $P < 0.05$ ** $P < 0.01$

Table 2 Data on exchange parameters following induction of anesthesia (healthy) and following lung lavage [0 (lavage)] and following treatment (5–25) in saline-perflubron-treated or control animals ($n = 6$ per group). Intra-group comparisons of ANOVA with Dunnet post-test if ANOVA $P < 0.05$, using the post-lavage data (0–25) with 0 (lavage) as reference value

Dose	PO_2 (mmHg)			PCO_2 (mmHg)			pH		
(ml/kg BW)	Control	Saline	Perflubron	Control	Saline	Perflubron	Control	Saline	Perflubron
Healthy	537.0 ± 29.3	530.3 ± 30.8	536.1 ± 14.2	32.4 ± 3.9	33.0 ± 2.1	35.5 ± 1.6	7.55 ± 0.04	7.50 ± 0.04	7.49 ± 0.02
0 (lavage)	85.8 ± 19.2	86.1 ± 28.1	86.5 ± 22.4	52.4 ± 10.7	46.9 ± 17.7	60.4 ± 19.9	7.34 ± 0.05	7.37 ± 0.12	7.28 ± 0.13
5	101.5 ± 37.2	54.6 ± 18.8**	85.1 ± 18.4	55.0 ± 10.3	52.8 ± 17.7	60.3 ± 21.5	7.30 ± 0.07	7.30 ± 0.11*	7.28 ± 0.13
10	89.7 ± 26.5	45.5 ± 13.8**	138.5 ± 60.5	56.7 ± 11.9	57.5 ± 15.0**	58.6 ± 21.2	7.28 ± 0.09*	7.24 ± 0.13**	7.30 ± 0.13
15	100.1 ± 41.9	43.0 ± 12.4**	184.3 ± 83.4**	58.6 ± 15.2	62.1 ± 15.6**	58.1 ± 21.4	7.28 ± 0.09**	7.23 ± 0.09**	7.32 ± 0.13*
20	97.8 ± 47.5	37.0 ± 7.8**	276.2 ± 82.0**	61.0 ± 16.1**	68.0 ± 16.3**	55.5 ± 19.0	7.29 ± 0.09*	7.19 ± 0.09**	7.33 ± 0.13**
25	89.2 ± 38.3	35.4 ± 7.5**	342.1 ± 59.4**	62.0 ± 16.9**	77.2 ± 21.2**	53.3 ± 15.7**	7.28 ± 0.09*	7.13 ± 0.10**	7.34 ± 0.11**
Dose	Base excess (mmol/l)			SVO_2 (%)			Shunt (%)		
(ml/kg BW)	Control	Saline	Perflubron	Control	Saline	Perflubron	Control	Saline	Perflubron
Healthy	5.5 ± 1.0	2.5 ± 3.2	3.9 ± 0.9	70.4 ± 5.3	72.2 ± 6.3	76.4 ± 8.1	6.5 ± 1.8	7.8 ± 2.0	10.0 ± 3.6
0 (lavage)	− 0.4 ± 1.2	0.5 ± 1.9	− 0.5 ± 2.8	48.8 ± 18.4	53.1 ± 12.9	45.6 ± 8.5	32.2 ± 6.6	35.0 ± 10.5	36.6 ± 17.8
5	0.3 ± 0.6	− 1.5 ± 3.9	− 0.4 ± 2.5	46.7 ± 14.8	39.2 ± 15.2**	51.0 ± 13.8	29.9 ± 7.0	55.2 ± 14.0**	36.8 ± 5.0
10	− 0.9 ± 2.4	− 3.4 ± 6.0**	0.2 ± 2.7*	49.6 ± 15.7*	29.9 ± 15.2**	56.6 ± 16.8**	36.9 ± 7.9	65.5 ± 7.5**	28.6 ± 5.5
15	− 0.9 ± 2.7	− 2.9 ± 3.0*	1.0 ± 2.8**	50.4 ± 14.2	23.7 ± 14.0**	53.5 ± 13.0	35.1 ± 9.7	68.3 ± 12.9**	24.8 ± 5.2
20	0.4 ± 1.2	− 4.1 ± 3.4**	1.3 ± 2.8**	51.3 ± 15.8*	16.5 ± 11.5**	58.6 ± 16.5**	35.8 ± 9.7	76.9 ± 7.3**	17.4 ± 2.3**
25	0.3 ± 2.0	− 5.9 ± 4.2**	1.5 ± 2.5**	51.9 ± 13.3*	10.7 ± 7.0**	59.5 ± 16.4**	29.4 ± 11.2	79.6 ± 6.5**	14.2 ± 3.1**
Dose	Arterial oxygen content C_aO_2 (ml/dl)			Oxygen deliverey D_aO_2 (ml/min · m^2)			O_2 content differnce $C_{a-v}O_2$ (ml/dl)		
(ml/kg BW)	Control	Saline	Perflubron	Control	Saline	Perflubron	Control	Saline	Perflubron
Healthy	11.4 ± 5.0	14.5 ± 0.8	13.2 ± 1.5	426.1 ± 182.6	858.7 ± 169.9	720.1 ± 57.1	5.1 ± 0.7	5.1 ± 0.7	4.2 ± 1.0
0 (lavage)	11.4 ± 2.6	12.5 ± 1.1	11.7 ± 1.7	413.6 ± 149.4	520.3 ± 123.9	473.3 ± 101.6	5.3 ± 2.5	5.2 ± 1.1	5.7 ± 2.0
5	12.7 ± 1.3	9.6 ± 2.2**	12.0 ± 1.5	460.4 ± 142.2	433.7 ± 164.6	498.2 ± 103.3	6.3 ± 1.6	4.3 ± 0.9	5.2 ± 1.5
10	12.4 ± 1.5	8.2 ± 2.0**	12.7 ± 1.9	464.6 ± 130.5	366.0 ± 116.3**	488.6 ± 125.9	5.2 ± 0.8	3.9 ± 0.6	5.2 ± 1.7
15	12.7 ± 1.7	6.9 ± 3.2**	13.3 ± 1.8	516.4 ± 122.5	380.6 ± 183.2**	554.5 ± 207.9	5.6 ± 0.8	3.4 ± 1.7*	6.1 ± 1.3
20	12.5 ± 1.5	5.7 ± 1.9**	13.8 ± 1.8**	487.7 ± 112.5	334.5 ± 105.8**	515.5 ± 179.1	5.3 + 0.9	3.2 ± 0.8**	6.0 ± 2.0
25	12.5 ± 1.3	4.8 ± 1.6**	13.9 ± 2.0**	495.8 ± 106.0	290.7 ± 120.2**	475.8 ± 139.9	5.1 ± 0.8	3.1 ± 0.6**	6.1 ± 2.3

* $P < 0.05$ ** $P < 0.01$

13.9 ± 2.0 ml/dl ($P < 0.01$), whereas there were no significant changes in D_aO_2 or $C_{a-v}O_2$.

Discussion

Since the introduction of partial liquid ventilation, only reports describing the influence of PFCs on gas exchange in small animals have appeared in the literature [5–7, 12, 13]. The results of the present study show that the use of perflubron for partial liquid ventilation in induced ALI is an easy and effective therapy for improving gas exchange in large animals, as well. Additionally, this study shows that the use of perflubron did not result in any deleterious effect on the hemodynamic parameters measured.

In the present study, in order to achieve high hydrostatic pressures, we used pigs with an average thoracic anterior-posterior diameter of 24 cm; in a totally PFC-filled lung, this would result in an average hydrostatic pressure of 46 cmH_2O at the basal lung regions, as the specific gravity of perflubron is 1.918 g/cm^3 at 25 °C.

Perflubron instillation in these animals shows that the use of partial liquid ventilation does not result in statistically significant changes in arterial pressures, CO, PVR or SVR. Systolic and mean pulmonary arterial pressures showed a decrease after administration of only 5 ml/kg body weight perflubron and remained low throughout the study period. PWP showed a dose-dependent increase in both the perflubron- and saline-treated groups. This may be attributed to the weight of the fluid-filled lung on the heart, resulting in a reduction of the diastolic filling phase. On the other hand, a fluid-filled lung might interfere with zone 3 conditions and therefore result in erroneous PWP readings.

In the perflubron group, there was no significant dose-dependent effect on PVR. This may be attributed in part to a decrease in MPAP and to the small decrease in CO, combined with the observed increase in PWP. However, an actual change in PVR cannot be excluded, and we speculate that this could result from the following interactions: with increasing doses of perflubron, oxygenation improves, resulting in a dose-dependent decrease in hypoxic vasoconstriction; this, in turn, results in a decrease in PVR. However, this decrease in PVR might be counteracted by a hydrostatic vascular compression due to the instillation of perflubron (because of its high specific gravity), leading to an increase in PVR. The amount of increase in PVR due to hydrostatic vascular compression might be smaller than expected, as in vivo bubble oxygenation in partial liquid ventilation, together with the fact that the lung is only partially fluid filled, prevents the formation of uninterrupted vertical fluid columns. Therefore, the actual hydrostatic pressure will be lower than expected, as a surface pressure is dependent on the height of the fluid column above it. This situation is different from that during total liquid ventilation, where the lung is totally filled with fluid. A few studies reported hemodynamic compromise during total liquid ventilation. The authors of these studies attributed this result to the filling of the lung with high-density PFCs [2, 3]. The observed hemodynamic compromise in these total liquid ventilation studies is speculated to result from pulmonary vascular compression, which is caused by an increase in the alveolar hydrostatic pressure gradient [9], and/or through an impairment of CO via a decrease in right ventricular preload combined with an increase in right ventricular afterload [10]. One report showed that this hemodynamic compromise could be corrected by adequate intravascular fluid administration [10].

The induced-ALI model used in the present study results in a decrease in arterial oxygenation as a result of a surfactant-deficiency-induced end-expiratory collapse, and is comparable to the changes found in respiratory distress syndrome (RDS) [14–16]. The results of this study confirm the positive effect of perflubron on gas exchange, as arterial oxygenation showed a significant dose-dependent increase and carbon dioxide elimination was significantly improved by perflubron treatment. This positive effect of partial liquid ventilation might be mediated through the prevention of end-expiratory collapse by the physical presence of PFC in the alveolus. Due to the high transport capabilities for O_2 and CO_2, PFCs can maintain gas exchange through in vivo bubble oxygenation [4]. This high transport capability results in a high dissolved volume of O_2 that continues to oxygenate the blood during the expiratory period, which in a normal pattern of breathing is two-thirds of the respiratory cycle.

The fact that the study was performed in large animals and used a post-lavage waiting period of 1 h makes this model comparable to other models of ALI and shows that the improvement in gas exchange can also occur in flooded alveoli [17]. In the perflubron-treated group, SVO_2 showed a dose-dependent improvement, whereas CO, DO_2 and $C_{a-v}O_2$ showed no statistically significant improvement. This could indicate a better balance of oxygen demand and availability, which is also indicated by the improvement in BE (see below). However, firm conclusions can not be drawn from these data. The same effect was observed in the control group, in which SVO_2 improved over time.

In contrast to the saline and control groups, the arterial pH in the perflubron-treated group showed

a statistically significant, dose-dependent increase towards physiological values, as did the arterial BE, indicating that the metabolic acidosis observed by others [6] did not occur in the present study. The fact that pH and BE improved in the perflubron group could be speculated to result from the adequate hemodynamic status (i.e. stable CO and DO_2), preventing the development of lactic acidosis.

Based on the promising results of the present study, further investigations should be directed towards clinical outcome as well as towards the financial benefits of this easy-to-administer and highly effective type of ventilatory support.

In conclusion, this study demonstrates that (1) the use of perflubron for partial liquid ventilation does not lead to hemodynamic depression; (2) perflubron partial liquid ventilation is an efficacious method for optimizing gas exchange in induced ALI; and (3) the use of perflubron does not result in metabolic acidoses, but improves pH towards physiological values.

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