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## Vaporized Perfluorocarbon Improves Oxygenation and Pulmonary Function in an Ovine Model of Acute Respiratory Distress Syndrome

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**Background:** Perfluorocarbon liquids are being used experimentally and in clinical trials for the treatment of acute lung injury. Their resemblance to inhaled anesthetic agents suggests the possibility of application by vaporization. The authors' aim was to develop the technical means for perfluorocarbon vaporization and to investigate its effects on gas exchange and lung function in an ovine model of oleic acid-induced lung injury.

**Methods:** Two vaporizers were calibrated for perfluorohexane and connected sequentially in the inspiratory limb of a conventional anesthetic machine. Twenty sheep were ventilated in a volume controlled mode at an inspired oxygen fraction of 1.0. Lung injury was induced by intravenous injection of 0.1 ml oleic acid per kilogram body weight. Ten sheep were treated with vaporized perfluorohexane for 30 min and fol-

lowed for 2 h; 10 sheep served as controls. Measurements of blood gases and respiratory and hemodynamic parameters were obtained at regular intervals.

**Results:** Vaporization of perfluorohexane significantly increased arterial oxygen tension 30 min after the end of treatment ( $P < 0.01$ ). At 2 h after treatment the oxygen tension was  $376 \pm 182$  mmHg (mean  $\pm$  SD). Peak inspiratory pressures ( $P < 0.01$ ) and compliance ( $P < 0.01$ ) were significantly reduced from the end of the treatment interval onward.

**Conclusion:** Vaporization is a new application technique for perfluorocarbon that significantly improved oxygenation and pulmonary function in oleic acid-induced lung injury. (Key words: Gas exchange; innovative application; lung injury; lung mechanics; perfluorocarbon.)

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THE use of perfluorocarbons (PFCs) represents a new strategy in the treatment of acute respiratory distress syndrome (ARDS). Their low surface tension and their high oxygen and carbon dioxide carrying capacity make them an attractive substance for the treatment of ARDS. PFCs are typically used in one of two techniques in the treatment of ARDS. Total liquid ventilation, in which the lungs are completely filled with PFCs, is achieved by a liquid ventilator with tidal volumes consisting entirely of PFCs. The alternative technique is partial liquid ventilation (PLV), in which the lungs are only partially filled with PFCs and ventilated with gas tidal volumes using a conventional ventilator. In experimental settings both were associated with a significant improvement in gas exchange and lung function.<sup>1-3</sup> Clinical trials with PLV have documented an improvement in oxygenation as well as some unexpected adverse side effects.<sup>4-6</sup> These side effects were partially linked with the mode of PFC application resulting in pneumothoraces, PFC leakage into the pleural cavity, and transient hypoxic events during dosing episodes.<sup>5,6</sup> Therefore, alternative PFC application techniques should be developed that combine the positive effects of PFCs with a safe administration in the treatment of ARDS.

PFCs and volatile anesthetics share some physical sim-

ilarities, suggesting a new and different approach of PFC application by vaporization.<sup>7,8</sup> We hypothesized that vaporized PFC resulting in a fine distribution of PFC inside ventilated lung areas could improve pulmonary function and gas exchange. The aim of this study was to develop the technical methods for this new application technique of PFC vaporization and to investigate its effects on gas exchange and lung function in oleic acid-induced ARDS.

## Materials and Method

The study protocol was approved by the ethics committee of the Carl Gustav Carus University Hospital, Dresden, Germany, and is in accordance with the National Institutes of Health guidelines for animal use.

### Animal Preparation

Adult sheep ( $n = 20$ ) weighing  $28.3 \pm 4.9$  kg were premedicated with Xylazine hydrochloride (0.4 mg) (Bayer, Leverkusen, Germany) intramuscularly. Anesthesia was induced using midazolam, 0.2 mg/kg (Hoffmann-LaRoche, Grenzach, Germany); ketamine, 1 mg/kg (CuraMED, Karlsruhe, Germany); and pancuronium, 0.1 mg/kg (CuraMED) via the antebraclial vein. Anesthesia was maintained with a continuous infusion of ketamine ( $8 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) and midazolam ( $0.7 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ). Pancuronium was administered at regular intervals to ensure complete muscular relaxation. Oral intubation was performed using an 8.0-mm endotracheal tube (Mallinckrodt, Athlone, Ireland). Subsequently, volume-controlled intermittent positive pressure ventilation was initiated using a Cicero EM anesthetic machine (Dräger, Lübeck, Germany) with a partially closed breathing system. The ventilation was set at a tidal volume of 10 ml/kg, a respiratory frequency of 25 per min, a positive end-expiratory pressure (PEEP) of 5 cm H<sub>2</sub>O, an inspired oxygen fraction ( $F_{iO_2}$ ) of 1.0, and an inspiratory:expiratory ratio of 1:1.

The left common carotid artery was cannulated to obtain the systolic, mean, and diastolic arterial blood pressure as well as arterial blood samples. A pulmonary artery catheter (8 French; Abbott, IL) was inserted via a 8.5-Fr introducer into the left jugular vein and advanced into the pulmonary artery to measure systolic, mean, and diastolic pulmonary artery pressures, the pulmonary capillary wedge pressure, and the central venous pressure, and to obtain mixed venous blood samples. Cardiac output was measured by the conventional thermodilution technique.

A crystalloid solution (E153, AWD, Dresden, Germany) was infused at a rate of  $8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  for basic fluid substitution. During oleic acid injection a colloid solution (Haes 6%; Fresenius, Bad Homburg, Germany) was administered at a rate of  $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  to compensate for fluid losses caused by capillary leak. A urinary catheter was inserted to determine the fluid balance. In addition, an orogastric tube was passed to alleviate gastric distension. All animals remained in the prone position throughout the experiment.

### Vaporized Perfluorocarbon

All studies were performed using perfluorohexane ( $\text{CF}_3(\text{CF}_2)_4\text{CF}_3$ ) (ABCR, Karlsruhe, Germany) with a purity of 95%. Perfluorohexane (PFH) was chosen in view of its similarities with existing volatile anesthetics.<sup>7</sup> It is a clear, radiolucent, colorless liquid with a molecular weight of 338, a boiling point of 57°C, a vapor pressure (at 20°C) of 177 mmHg, a density of 1.672 g/ml, a viscosity of 0.66 cP and a surface tension of 11.4 dyne/cm.<sup>8</sup> The infrared absorption of PFH lies between 2.6 and 18.18  $\mu\text{m}$  with a maximum at 8  $\mu\text{m}$ . Its oxygen-carrying capacity is 57 ml O<sub>2</sub> per 100 ml PFH.

In cooperation with Dräger Werke (Lübeck, Germany), standard bypass vaporizers (type, 19 n) were modified by a scaled opening of the dosage control cone and calibrated for PFH using an infrared absorption technique. To increase the inspiratory concentration, two PFH-adapted vaporizers were connected in series in the inspiratory limb of the ventilator circuit. During PFH vaporization, inspiratory and expiratory concentrations of PFH were measured at the proximal end of the endotracheal tube using an infrared absorption technique. Using a continuous sidestream of 200 ml/min, the infrared rapidly identifying analyzer (Dräger), working within an infrared spectrum of 1–50  $\mu\text{m}$ , allowed the continuous on-line monitoring of PFH concentrations (vol%), ensuring a controlled application of PFH. The threshold of detection for PFH was 2.1 vol%. In preliminary *in vitro* experiments a calibration curve for PFH was established in vol% of gas. Actual PFH concentrations were taken from the calibration curve.

### Experimental Protocol

After an initial stabilization period during which the respiratory minute volume was adjusted to produce an arterial carbon dioxide tension ( $\text{Pa}_{\text{CO}_2}$ ) of 36 to 46 mmHg, baseline measurements were taken. Lung injury was induced by emulsifying 15 ml of previously extracted blood with 0.1 ml oleic acid ( $\text{C}_{18}\text{H}_{34}\text{O}_2$ ) per

kilogram body weight and injecting it over 30 min through the proximal port of the pulmonary artery catheter into the right atrium. Severe lung injury was considered established when the ratio  $Pa_{O_2}$  to  $F_{I_{O_2}}$  was < 200 and the pulmonary capillary wedge pressure was < 19 mmHg.<sup>9</sup> Animals were then randomly assigned to one of two groups. Control animals ( $n = 10$ ) were ventilated with the preexisting setting for the study period of 150 min. Animals in the PFH-therapy group (PFH-Tx;  $n = 10$ ) were treated with vaporized PFH at an inspiratory concentration of 18 vol% over 30 min under continuous intermittent positive pressure ventilation and followed for a period of 120 min after end of therapy. During the treatment interval  $9 \pm 1.5$  ml/kg body weight liquid PFH was vaporized. The concentration of PFH was chosen after preliminary pilot studies had shown an improvement of gas exchange in a similar experimental setting. All animals were sacrificed after the end of the experiment.

At the end as well as 30, 60, and 120 min after the end of PFH treatment blood samples were drawn in order to exclude the presence of PFH from the systemic circulation. At the same time bronchial secretions were obtained via bronchoscopic lavage with 5 ml saline to determine how long after vaporization PFC could be detected in the lungs. Blood and bronchial secretions were stored under anaerobic conditions and tested for the presence of PFH at the Institute for Polymer Research e.V., Dresden, Germany, using gas chromatography with the mass detection unit Headspace-GC-MS (Hewlett Packard, Palo Alto, CA). The sensitivity of the system to detect PFH was 0.5 ppm.

#### *Physiologic Data Analysis*

Hemodynamic and respiratory data were collected every 10 s using a Merlin monitoring system (Hewlett Packard, Böblingen, Germany). Complete sets of measurements including hemodynamic and respiratory data as well as cardiac output and blood gases were obtained at baseline, at the time of established lung injury, after the end of PFH treatment, and at 30-min intervals thereafter until the end of the study period. Cardiac output was measured by thermodilution. Five injections of 10 ml cold saline were performed and the cardiac output calculated by averaging the three middle injections using the cardiac-output module of Hewlett Packard. All systemic and pulmonary pressures were assessed using Ohmeda (Erlangen, Germany) pressure transducers and the component monitoring system of Hewlett Packard. Peak, plateau, and mean inspiratory pressures were mea-

sured by an integrated piezoresistive transducer within the Cicero EM anesthetic machine. The plateau pressure was determined 16 ms before the start of expiration. Tidal volumes were measured in the expiratory limb of the ventilator by a flowmeter (hot-wire anemometer). Arterial and mixed venous blood samples were drawn into heparin coated syringes and immediately assessed by an AVL (Graz, Austria) blood-gas analyzer. Baseline transpulmonary shunt fraction ( $Q_{sp}/Q_t$ ) was calculated using the following equation:  $Q_{sp}/Q_t = (Cc_{O_2} - Ca_{O_2}) / (Cc_{O_2} - Cv_{O_2})$ , where  $Q_{sp}$  is the physiologic shunt,  $Q_t$  is the cardiac output,  $Ca_{O_2}$  is the oxygen content of the arterial blood,  $Cv_{O_2}$  is the oxygen content of mixed venous blood, and  $Cc_{O_2}$  is the oxygen content of blood draining from the ideal alveolus ventilated with gas of an  $F_{I_{O_2}} = 1.0$ , as derived from the alveolar gas equation and the oxyhemoglobin dissociation curve; and  $P(A-a)O_2 = PA_{O_2} - Pa_{O_2}$ , where  $PA_{O_2}$  is  $([barometric\ pressure \times F_{I_{O_2}}] - 47) - Pa_{CO_2}$ . Static compliance was calculated using  $C = V_t / (P_{pl} - PEEP) / \text{body weight}$  (in kilograms), where  $V_t$  is the tidal volume and  $P_{pl}$  is the end-inspiratory plateau pressure.

#### *Statistical Analysis*

The data were tested using a covariant analytic model (generalized estimating equation) with an independent factor (control *vs.* therapy group), a correlated factor (six measurement points using compound symmetry), and one covariable (baseline values before therapy).<sup>10</sup> Multiple mean value comparisons were adjusted using the method of Tuckey Kramer. Data are reported as mean values  $\pm$  SD. A *P* value of 0.05 was taken as significant.

## **Results**

Infusion of oleic acid induced acute respiratory failure in all animals. Measurements at baseline and after induction of injury were comparable in both groups (tables 1 and 2). All animals were hemodynamically stable throughout the experiment, with no statistical difference between them (table 2).

#### *Gas Exchange*

With oleic acid administration,  $Pa_{O_2}$  decreased as expected. Following PFH therapy  $Pa_{O_2}$  increased continuously during the entire observation period (fig. 1). A statistical significant increase with respect to injury ( $77 \pm 21$  mmHg) was observed 30 min after the end of

**Table 1. Respiratory Data**

Variable		Baseline	Injury	End of Therapy	Time after End of Therapy			
					30 min	60 min	90 min	120 min
Pa <sub>O<sub>2</sub></sub> (mmHg)	Control	503 ± 105	100 ± 29	68 ± 24	64 ± 29*	68 ± 39*	87 ± 63*	77 ± 35*
	PFH-Tx	542 ± 72	77 ± 21	158 ± 82	290 ± 145*†	343 ± 71*†	326 ± 171*†	376 ± 182*†
Pa <sub>CO<sub>2</sub></sub> (mmHg)	Control	43 ± 3	50 ± 9	57 ± 11	60 ± 13	60 ± 13	60 ± 13	63 ± 15
	PFH-Tx	41 ± 3	48 ± 9	47 ± 7	49 ± 9	47 ± 7	47 ± 10	45 ± 6
PIP (cmH <sub>2</sub> O)	Control	25 ± 2	46 ± 5	46 ± 4*	49 ± 6*	51 ± 7*	52 ± 9*	53 ± 10*
	PFH-Tx	24 ± 3	42 ± 4	32 ± 5*†	36 ± 6*‡	36 ± 5*‡	34 ± 5*‡	35 ± 6*‡
Compliance (ml · cmH <sub>2</sub> O <sup>-1</sup> · kg <sup>-1</sup> )	Control	0.50 ± 0.04	0.24 ± 0.03	0.24 ± 0.02*	0.23 ± 0.03*	0.22 ± 0.03*	0.22 ± 0.04*	0.21 ± 0.04*
	PFH-Tx	0.55 ± 0.16	0.27 ± 0.04	0.38 ± 0.07*†	0.32 ± 0.06*†	0.33 ± 0.06*†	0.34 ± 0.06*†	0.34 ± 0.06*†
Shunt (%)	Control	16 ± 4	43 ± 19	52 ± 13	60 ± 18§	57 ± 17§	56 ± 22§	59 ± 20§
	PFH-Tx	16 ± 6	40 ± 14	39 ± 15	32 ± 13§	24 ± 10§	26 ± 10§	21 ± 8§

Values are means ± SD.

Pa<sub>O<sub>2</sub></sub> = partial pressure of arterial oxygen; Pa<sub>CO<sub>2</sub></sub> = partial pressure of arterial carbon dioxide; PIP = peak inspiratory pressure; PFH-Tx = perfluorohexane treatment.

\*  $P \leq 0.01$  between groups.

†  $P \leq 0.01$  within groups respective to injury.

‡  $P \leq 0.05$  within groups respective to injury.

§  $P \leq 0.05$  between groups.

PFH treatment period ( $290 \pm 145$  mmHg) and during the remaining observation period ( $P < 0.01$ ). The highest Pa<sub>O<sub>2</sub></sub> ( $376 \pm 182$  mmHg) was reached 2 h after the end of therapy. A significant difference in Pa<sub>O<sub>2</sub></sub> between both groups was seen at all times 30 min after the end of therapy. There were no statistically relevant differences in Pa<sub>CO<sub>2</sub></sub> within or between both groups during the entire study period, although Pa<sub>CO<sub>2</sub></sub> declined slightly during PFH treatment.

Statistically significant differences in shunt between both groups were observed 30 min after the end of the treatment period ( $32 \pm 13\%$  PFH-Tx vs.  $60 \pm 18\%$  con-

rol;  $P < 0.05$ ) and for the remaining observation period (fig. 2).

#### Pulmonary Function

After oleic acid injection, peak inspiratory pressures (PIPs) increased to  $42 \pm 4$  cm H<sub>2</sub>O (PFH-Tx) and to  $46 \pm 5$  cm H<sub>2</sub>O (control) (table 1). At the end of the PFH treatment interval a significant reduction of PIP to  $32 \pm 5$  cm H<sub>2</sub>O ( $P < 0.01$ ) was observed, which remained statistically significant with respect to injury for the entire observation period. Statistically significant differences between the groups were observed during the

**Table 2. Hemodynamic Data**

Variable		Baseline	Injury	End of Therapy	Time after End of Therapy			
					30 min	60 min	90 min	120 min
HF (bpm)	Control	91 ± 21	115 ± 21	124 ± 24	121 ± 30	112 ± 15	105 ± 20	106 ± 22
	PFH-Tx	92 ± 18	100 ± 28	108 ± 27	110 ± 23	108 ± 22	103 ± 21	97 ± 17
MAP (mmHg)	Control	99 ± 17	84 ± 18	90 ± 11	84 ± 16	84 ± 20	96 ± 14	94 ± 8
	PFH-Tx	105 ± 11	101 ± 17	101 ± 15	97 ± 19	103 ± 13	106 ± 9	104 ± 9
MPAP (mmHg)	Control	22 ± 5	36 ± 5	36 ± 6	35 ± 6	36 ± 7	40 ± 8	41 ± 8
	PFH-Tx	21 ± 4	35 ± 4	34 ± 9	31 ± 9	28 ± 8	29 ± 8	28 ± 8
CVP (mmHg)	Control	11 ± 3	11 ± 7	10 ± 4	11 ± 4	11 ± 4	12 ± 4	14 ± 6
	PFH-Tx	10 ± 4	12 ± 6	11 ± 6	13 ± 3	11 ± 5	13 ± 4	12 ± 6
CO (l/min)	Control	3.3 ± 0.8	2.9 ± 0.6	3.8 ± 1.1	3.2 ± 0.9	3.2 ± 0.8	3.5 ± 0.6	3.6 ± 0.8
	PFH-Tx	2.5 ± 0.8	2.0 ± 0.6	2.8 ± 0.6	2.6 ± 0.5	2.5 ± 0.5	2.3 ± 0.5	2.5 ± 0.5

Values are mean ± SD.

HF = heart frequency; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; CVP = central venous pressure; CO = cardiac output; PFH-Tx = perfluorohexane treatment.

## VAPORIZED PERFLUOROCARBON IMPROVES LUNG FUNCTION

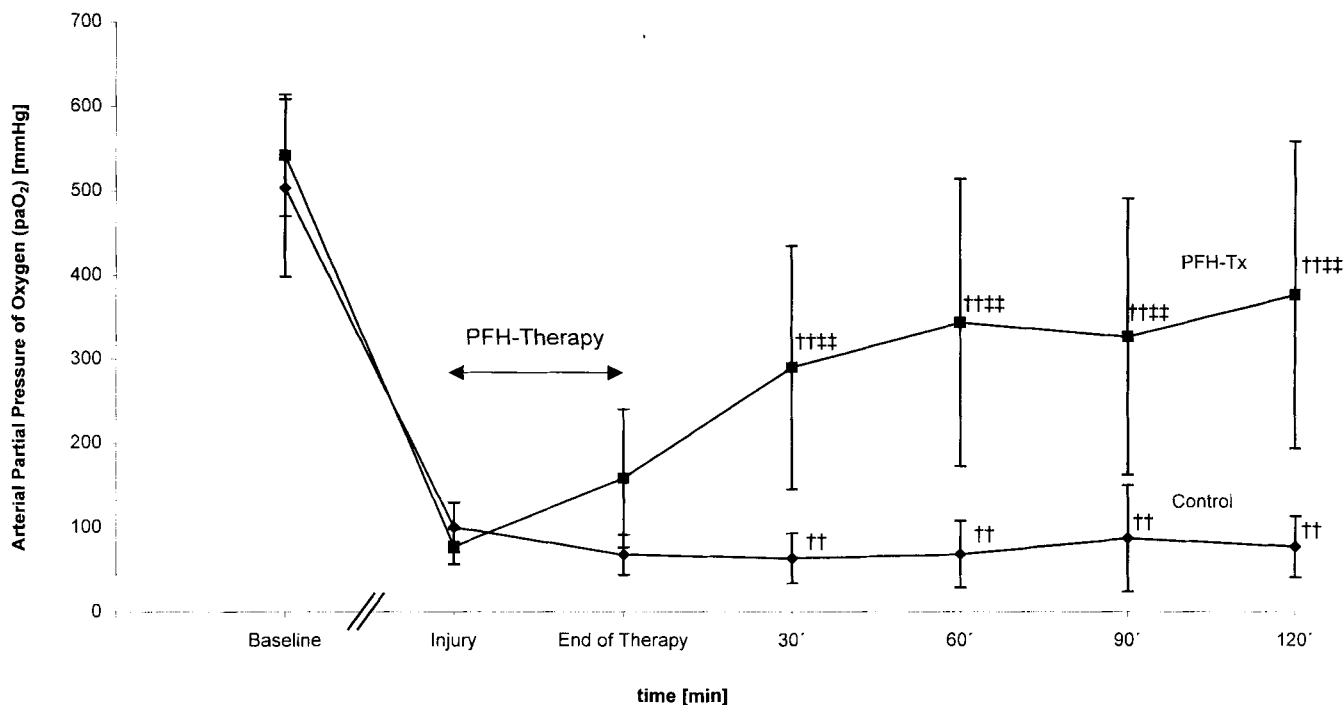


Fig. 1.  $\text{PaO}_2$  at baseline, after lung injury, after end of therapy, and at 30, 60, 90, and 120 min after therapy in the perfluorohexane-treatment group (PFH-Tx) and in the control group. After perfluorohexane vaporization  $\text{PaO}_2$  increased significantly 30 min after the end of therapy with respect to injury and in comparison with the control group. Values are means  $\pm$  SD.  $\dagger P \leq 0.05$  between groups,  $\dagger\dagger P \leq 0.01$  between groups,  $\ddagger P \leq 0.05$  within groups respective to injury,  $\dagger\dagger\dagger P \leq 0.01$  within groups respective to injury.

entire observation period (fig. 3). After the oleic acid application the static compliance decreased to  $0.27 \pm 0.04 \text{ ml} \cdot \text{cm H}_2\text{O}^{-1} \cdot \text{kg}^{-1}$  in the PFH-Tx group and to  $0.24 \pm 0.03 \text{ ml} \cdot \text{cm H}_2\text{O}^{-1} \cdot \text{kg}^{-1}$  in the control group. Following PFH vaporization, compliance improved significantly to  $0.38 \pm 0.07 \text{ ml} \cdot \text{cm H}_2\text{O}^{-1} \cdot \text{kg}^{-1}$  ( $P < 0.01$ ), remaining significant for the follow-up period. Significant differences between the groups were seen from the end of PFH treatment period onward (fig. 4).

#### Perfluorohexane

All animals tolerated vaporized PFH well without any signs of adverse effects. Inspiratory concentrations of 18 vol% PFH were reached within 1 min of opening the vaporizers and were sustained throughout the treatment period in all animals. Differences in inspiratory and expiratory PFH concentrations were observed up to 10 min after the start of PFH therapy, after which a saturation of 18 vol% PFH was reached. Expiratory PFH concentrations could be detected by the infrared rapidly identifying analyzer as long as 5 min after the end of PFH treatment. A calculation based on inspiratory and expiratory PFH concentrations showed that approximately

20% of the vaporized PFH was retained in the lung during treatment.

Traces of PFH were repeatedly found in the bronchial lavages 1 h after the end of PFH treatment. PFH, however, was not detected in blood samples drawn at the respective measurement intervals tested by gas chromatography with a detection limit of 0.5 ppm.

#### Discussion

This study presents a new PFC application technique, vaporization, and its effect on oxygenation and pulmonary function in an ovine model of oleic acid-induced ARDS.

The oleic acid lung-injury model was chosen because it has been repeatedly used to study new therapeutic strategies in treatment of severe lung injury including total liquid ventilation and PLV. Furthermore the oleic acid model is known for its reliability in causing severe lung injury. Infusion of oleic acid into the pulmonary circulation results in direct and acute damage to the pulmonary capillary endothelium with consecutive extravasation of proteinaceous fluid and erythrocytes into the lung inter-

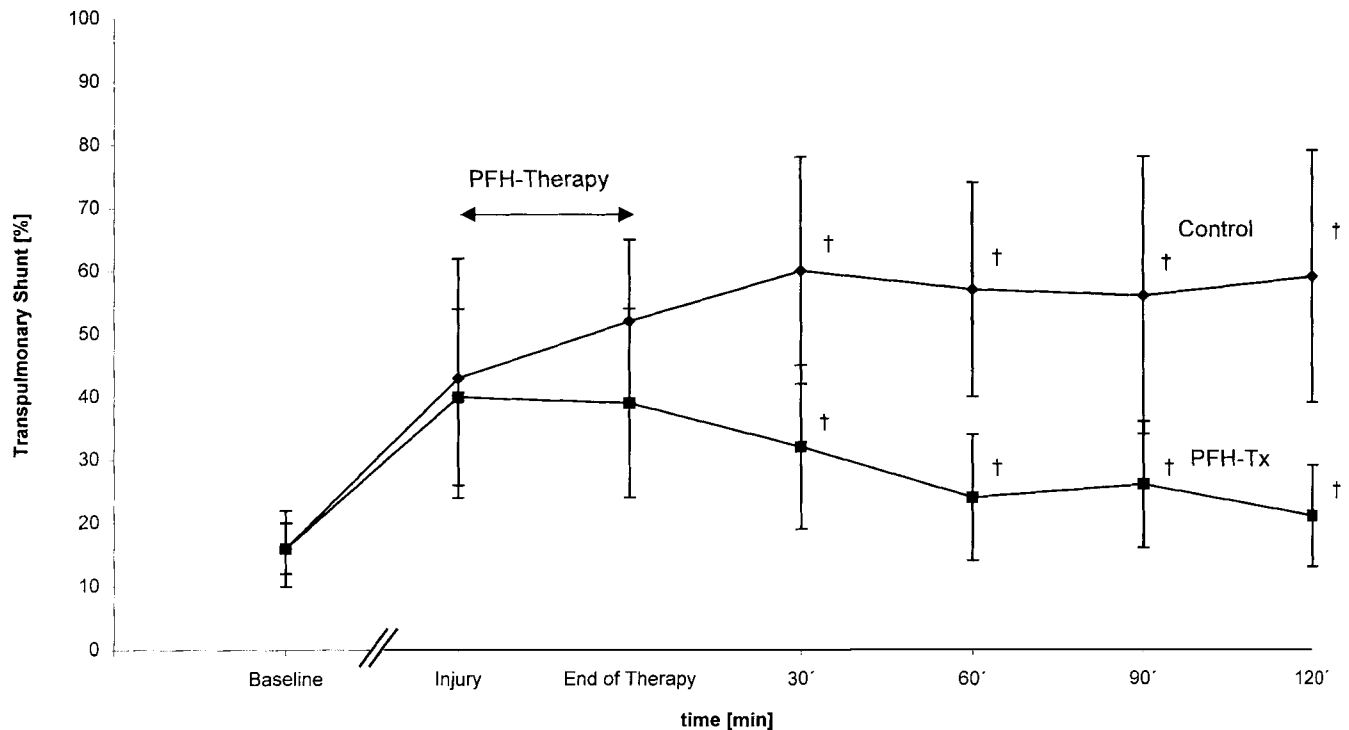


Fig. 2. Transpulmonary shunt at baseline, after lung injury, after end of therapy, and at 30, 60, 90, and 120 min after therapy in the perfluorohexane-treatment group (PFH-Tx) and in the control group. Values are means  $\pm$  SD. † $P \leq 0.05$  between groups, †† $P \leq 0.01$  between groups.

stitium and alveoli. This leads to a decrease in lung compliance, to a reduction of the functional residual capacity, and to an increase in transpulmonary shunt.<sup>11-13</sup> Animals in this study showed these well-described signs at the time of established lung injury, which was achieved approximately 1 h after initiation of injury.

PFH was chosen because of its physical similarities to existing volatile anesthetic agents, making it applicable for the technique of vaporization. Vaporization is a technique used in daily anesthetic routine, in which vapor of the inhalation agent is carried by the inspiratory gas flow into ventilated lung areas. Vaporization of PFH was performed analogous to the vaporization of inhaled anesthetics and proved to be a safe application technique. Application and distribution of vaporized PFH is in contrast to the liquid application and the mainly gravitational distribution of PFC during PLV.<sup>14</sup> Whether these differences can prevent some of the side effects encountered during PLV but not seen in this study needs to be addressed in further studies.

The method of PFC application, avoiding the disconnection from the ventilator and therefore preventing the

loss of PEEP and auto-PEEP, is of advantage in severe lung injury. A further advantage lies within the availability of dosing and monitoring equipment to control the application of vaporized PFH. Maximal inspiratory PFH concentrations reached during the treatment interval were consistently 18 vol% in all experiments. Measurements of PFH were conducted using an infrared absorption technique integrated in many anesthetic ventilators for routine inspiratory and expiratory gas analysis. The ability to measure inspiratory and expiratory PFH concentrations holds the promise to establish an individual dose-response curve and a titrated PFH dose for the treatment of acute lung injury in the future.

Vaporized PFH leads to a lasting improvement of oxygenation and pulmonary function. An improvement of oxygenation occurring during the treatment interval was already observed at the end of PFH application. The improvement of oxygenation was sustained past the treatment phase, reaching statistical significance 30 min after the end of therapy. Peak  $Pa_{O_2}$  levels were reached 2 h after the end of the treatment period. This continuous process of improving oxygenation past the treatment interval has not been described for PLV or total

## VAPORIZED PERFLUOROCARBON IMPROVES LUNG FUNCTION

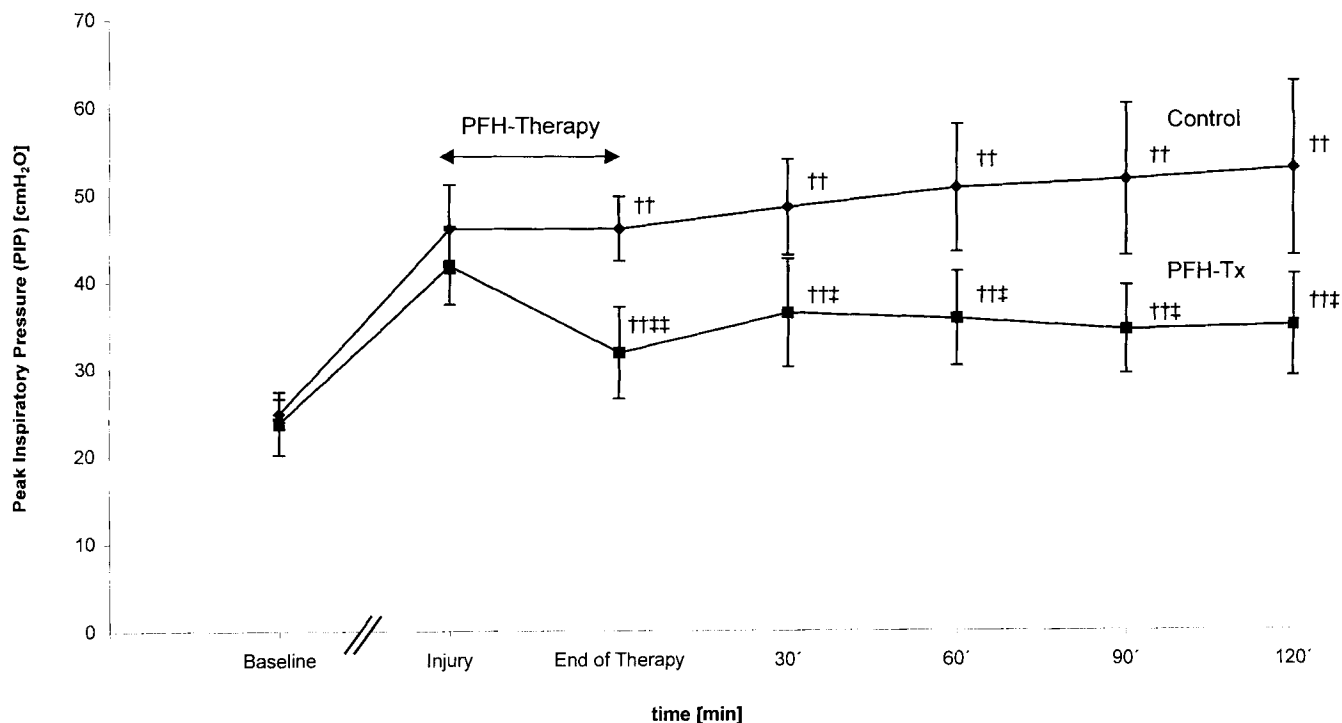


Fig. 3. Peak inspiratory pressure at baseline, after lung injury, after end of therapy, and at 30, 60, 90, and 120 min after therapy in the perfluorohexane-treatment group (PFH-Tx) and in the control group. Statistically significant differences between both groups were seen from the end of the treatment period onward throughout the observation period. Values are means  $\pm$  SD. † $P \leq 0.05$  between groups, †† $P \leq 0.01$  between groups, ‡ $P \leq 0.05$  within groups respective to injury, ‡‡ $P \leq 0.01$  within groups with respect to injury.

liquid ventilation in models of ARDS until now. Maximal effects that were shown to be dose-dependant were observed during treatment.<sup>15-17</sup> However, Shaffer *et al.*<sup>18</sup> were able to show a persistence of improved oxygenation and lung compliance after drainage of PFC from the lungs in a model of infant respiratory distress syndrome. These results were explained with small residual amounts of PFC lining the alveoli. Yet Curtis *et al.*<sup>19</sup> were not able to reproduce the effect on oxygenation in oleic acid-induced acute canine lung injury. They observed a marked decrease of PaO<sub>2</sub> when PFC was allowed to drain from the lungs after PLV.

Apart from the beneficial effects on gas exchange, vaporized PFH was also associated with a significant improvement of pulmonary mechanics. At the end of the PFH vaporization interval, PIP and lung compliance were significantly improved both with respect to injury within the PFH-Tx group and in comparison with the control group. These improvements of PIP and lung compliance continued to be significant past the treatment period for the entire follow-up period. They were, however, most pronounced immediately after the end of treatment.

Positive effects of PFC on PIP and lung compliance during PLV and total liquid ventilation are well described.<sup>20-22</sup> The effect of PFC on PIP is thought to be a dose-independent process as very small dosages of PFC (3 ml/kg) lead to a significant improvement of PIP, which could not be further enhanced by increasing dosages.<sup>23</sup> No change or increase in PIP and decrease in compliance was seen in other experimental studies during PLV.<sup>1,24,25</sup> It occurred mainly when larger dosages were used and is thought to be caused by the interaction of applied tidal volumes and the increasing weight of the PFC-filled lungs. The vaporizing technique avoids this problem with dosages of liquid PFC.

The mechanism of action of vaporized PFH is still poorly understood and requires further research. In our opinion vaporized PFH acts beside its oxygen-carrying capacity by covering bronchial and alveolar epithelium with a thin layer of PFC. This film of PFH with a low surface tension forming at the air-liquid interface has a surfactant-like effect, resulting in a redistribution and lowering of surface tension within alveoli and a recruitment of alveolar gas-exchange area over a period of time.

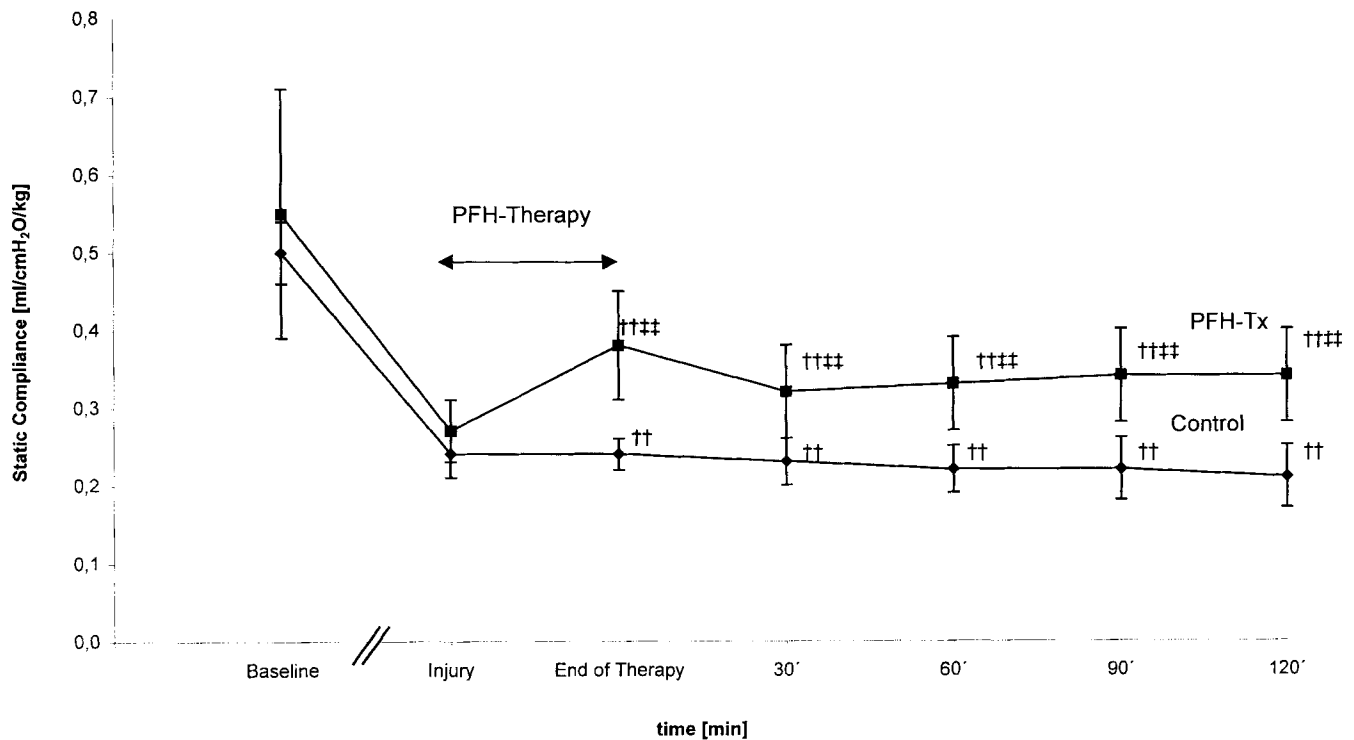


Fig. 4. Static lung compliance at baseline, after lung injury, after end of therapy, and at 30, 60, 90, and 120 min after therapy in the perfluorohexane-treatment group (PFH-Tx) and in the control group. Values are mean  $\pm$  SD. † $P \leq 0.05$  between groups, †† $P \leq 0.01$  between groups, ‡ $P \leq 0.05$  within groups respective to injury, ‡‡ $P \leq 0.01$  within groups respective to injury.

Thus the reduction of high surface tension at the air-liquid interface in the surfactant-deficient lung facilitates alveolar expansion, thus improving oxygenation and lung compliance and reducing airway pressure. Whether these effects are the result of an interaction between existing surfactant and vaporized PFH or of PFH alone needs to be addressed in the future. Furthermore we assume that the vaporous distribution of PFH within ventilated alveoli increases the effectiveness of the treatment. In contrast to PLV, in which PFC remains mostly restricted to dependent lung areas, vaporized PFH reaches dependent and nondependent lung areas, thus increasing the treated lung area.<sup>14</sup> Therefore smaller amounts of vaporized PFC may actually be needed to achieve an improvement of gas exchange and pulmonary function. This assumption is supported by dose-independent improvement of PIP and lung compliance during PLV and by first results of bronchial-alveolar lavage with a small dose of PFC (10 ml/kg), showing an improvement of oxygenation.<sup>23,26</sup>

In conclusion, vaporization of PFH is a new technique of PFC application leading to a marked and sustained improvement in oxygenation and pulmonary function in

an ovine model of oleic acid-induced ARDS. If these results are confirmed, this application technique may enable the development of a controlled and individually titrated dosage of PFH in the treatment of ARDS.

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