Anesthesiology
79:1083–1093, 1993

J. B. Lippincott Company, Philadelphia

Intratracheal Perfluorocarbon Administration as an Aid in the Ventilatory Management of Respiratory Distress Syndrome

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Background: **Respiratory distress syndrome carries a high morbidity and mortality when treated with mechanical ventilation with positive end-expiratory pressure. Perfluorocarbon liquids are employed in liquid ventilation due to low surface tension and high gas solubility. To assess whether intratracheal administration of the perfluorocarbon, perflubron, in combination with conventional mechanical ventilation could be of therapeutic benefit in respiratory distress syndrome, the authors tested the effects of different doses of intratracheal perflubron administration on gas exchange and lung mechanics in adult animals with respiratory failure during a 6-h observation period.**

Methods: **Respiratory failure was induced in 30 rabbits by saline lung lavage (arterial oxygen tension < 100 mmHg at 100% oxygen with the following ventilator settings: tidal volume, 12 ml · kg^{-1}; respiratory frequency, 30 per min; inspiratory/expiratory ratio, 1:2; and positive end-expiratory pressure of 6 cm H_2O). Twenty-four rabbits were treated with different perfluorocarbon doses (3, 6, 9, and 12 ml · kg^{-1}), and the remaining six served as controls while mechanical ventilation was continued with the aforementioned settings. Additionally, in ten healthy rabbits who were used as healthy controls, the lungs were mechanically ventilated either alone or in combination with intratracheal perfluorocarbon administration (3 ml · kg^{-1}) for 6 h.**

Results: **In all treatment groups, arterial oxygen pressure increased significantly ($P < 0.0001$) in a dose-related fashion (193 ± 40, 320 ± 70, 353 ± 125, and 410 ± 45 mmHg at 15 min), and peak airway pressures decreased significantly (range, 18–23%; $P < 0.0001$) from pretreatment values. These findings were in contrast to those for the control group. The improvements were time-dependent in all four tested perfluorocarbon doses. However, the improvements in pulmonary parameters could be extended to 6 h only in groups treated with 9 ml · kg^{-1} and 12 ml · kg^{-1} perflubron. At the end of the 6-h period, the data for these two groups showed significantly higher arterial oxygen pressure (230 ± 84 and 197 ± 130 mmHg, respectively; $P < 0.05$) and lower inflation pressures than the pretreatment data for these groups and the data for the control group at 6 h. There were no clinically significant changes in pulmonary parameters in healthy animals due either to mechanical ventilation alone or mechanical ventilation in combination with intratracheal perfluorocarbon administration for 6 h.**

Conclusions: **The results of this study imply that there is no association between the lung mechanics and gas exchange parameters for mechanical ventilation in combination with intratracheal perfluorocarbon administration. The data suggest that this type of perfluorocarbon administration with conventional mechanical ventilation offers a simple, alternative treatment of respiratory distress syndrome. With this technique, adequate pulmonary gas exchange can be maintained at relatively low airway pressures with high perfluorocarbon doses for several hours. (Key words: Lung: gas exchange, mechanics. Ventilation, mechanical: perfluorocarbon.)**

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Received from the Department of Anesthesiology, University of Istanbul, Istanbul, Turkey, and the Departments of Epidemiology and Biostatistics and Anesthesiology, Erasmus University at Rotterdam, Rotterdam, The Netherlands. Accepted for publication July 22, 1993. Supported in part by the International Foundation for Clinically Oriented Research and the Alliance Pharmaceutical Corporation. Presented in part at the Tenth World Congress of Anesthesiologists, The Hague, The Netherlands, June 12–19, 1992.

This work was performed at the Department of Anesthesiology, Erasmus University Rotterdam, Rotterdam, The Netherlands.

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SINCE the first successful experiment of Clark and Gollan,[1] the efficacy of perfluorocarbon liquids have been studied in liquid breathing techniques. Animal studies have shown perfluorocarbon liquid ventilation to be effective in achieving adequate pulmonary gas exchange in surfactant-deficient lungs by reducing surface tension at the alveolar air-liquid interface.[2–4] Improve-

ments in lung functions have been reported following successful reconversion to gas breathing in diseased lungs.[3-6]

Despite the advances in liquid ventilation techniques, the complexity and the extra technical requirements (*e.g.*, modified liquid ventilator, external oxygenator) for liquid ventilation have discouraged the development of this type of respiratory support in clinical practice. Greenspan *et al.*[7] reported the first human trial of liquid ventilation in premature infants with respiratory distress syndrome (RDS). The observed improvements in gas exchange and lung mechanics after only a short duration of liquid ventilation reaffirmed the results of animal experiments and led us to investigate a simpler way of using perfluorocarbon. Using a combination of conventional mechanical ventilation and intratracheal perfluorocarbon (perflubron, Alliance Pharmaceutical, San Diego, CA) administration at low doses, we recently demonstrated that oxygenation can, in the short-term, be improved in a dose-dependent manner at reduced airway pressures in adult animals with acute respiratory failure.[8] This study was developed to assess the efficacy of this method of perfluorocarbon administration as an aid in the ventilatory management of RDS. This study was designed to investigate the effects of this technique with different perfluorocarbon doses on pulmonary gas exchange and respiratory mechanics in adult animals with induced RDS over a 6-h observation period.

Methods and Materials

This study was approved by the Animal Committee of Erasmus University Rotterdam.

Animal Preparation

Adult New Zealand rabbits (n = 40) weighing 2.8 ± 0.3 kg were anesthetized with intravenous pentobarbital sodium (50 $mg \cdot kg^{-1}$) *via* an auricular vein and then placed in a supine position. An endotracheal tube (ID 3.5 mm) was inserted *via* a tracheostomy, after which mechanical ventilation with a Servo Ventilator 900C (Siemens-Elema, Sweden) was initiated with 100% oxygen, zero end-expiratory pressure, tidal volume (VT) of 12 $ml \cdot kg^{-1}$, respiratory frequency of 30 per min and inspiratory/expiratory ratio of 1:2. An infusion of 5% dextrose/0.45% NaCl solution was administered continuously (7.5 $ml \cdot kg^{-1} \cdot h^{-1}$) *via* the auricular vein as a maintenance fluid. Anesthesia was maintained with continuous infusion of pentobarbital (4 $mg \cdot kg^{-1} \cdot h^{-1}$) and fentanyl (120 $\mu g \cdot kg^{-1} \cdot h^{-1}$); pancuronium bromide was administered to induce muscle paralysis (0.1 $mg \cdot kg^{-1} \cdot h^{-1}$).

A femoral artery and a femoral vein were cannulated with polyethylene catheters for arterial and central venous pressure monitoring and blood sampling. Arterial samples were analyzed for blood gases, *p*H, and hemoglobin by conventional methods (ABL-330 and Osm-2 Hemoximeter, Radiometer, Copenhagen, Denmark). Arterial lactate was measured with an Eppendorf-Elan Analyzer (Hamburg, Germany) at baseline, after induction of RDS, and at the end of the 6-h observation period, using the Sigma Diagnostics Lactate Enzymatic Determination procedure (Lactate kit 735-10, Sigma, St. Louis, MO). End-tidal carbon dioxide, carbon dioxide production, and alveolar dead space were measured on-line with a carbon dioxide Analyzer 930 (Siemens, Sweden). Lung mechanics (airway pressures and respiratory compliance) were measured on-line with a Lung Mechanics Calculator 940 (Siemens, Sweden), which has been demonstrated to be a reliable and accurate calculator.¶ Core temperature was maintained at 37 ± 1° C with a heating blanket and monitored with an esophageal thermistor (Elektrolaboratoriet, Copenhagen, Denmark). Intravascular pressures were monitored with Statham P23XL transducers (Spectramed, Oxnard, CA), and all parameters, including electrocardiographic readings, were traced with a Sirecust 1280 monitor (Siemens, Danvers, MA) and recorded with a Siredoc 220 recorder (Siemens, Germany).

Experimental Protocol

In 30 rabbits, acute respiratory failure was induced by lung lavage with 30 $ml \cdot kg^{-1}$ warm saline,[9,10] repeated as often as necessary to achieve an arterial oxygen pressure less than 100 mmHg at the following ventilator settings: volume controlled ventilation; inspired oxygen fraction, 1; VT, 12 $ml \cdot kg^{-1}$; respiratory frequency, 30 per min; inspiratory/expiratory ratio, 1:2; and positive end-expiratory pressure (PEEP), 6 cmH_2O.

The perfluorocarbon administered in this experiment was perflubron (perfluorooctyl bromide; Alliance Pharmaceutical, San Diego, CA), a perfluorocarbon with a specific gravity of 1.918 $g \cdot cm^{-3}$ at 25° C, a surface tension of 18.1 dynes $\cdot cm^{-1}$, a vapor pressure of 10.5

¶ Jonson B, Nordstrom L, Olsson SG, Akerback D. Monitoring of lung mechanics during automatic ventilation: A new device. Eur J Respir Dis 11:729–743, 1975.

mmHg at 37° C, oxygen solubility of 53 ml · 100 ml^{-1}, and carbon dioxide solubility of 210 ml · 100 ml^{-1} at 37° C and 1 atmosphere pressure.

Animals were divided randomly into five groups of six animals, and four groups were treated intratracheally with a different dose of perflubron: group 1, 3 ml · kg^{-1}; group 2, 6 ml · kg^{-1}; group 3, 9 ml · kg^{-1}; and group 4, 12 ml · kg^{-1}. In the fifth group, which was used as a control group (group C), no perflubron was used, and the animals' lungs were ventilated mechanically with gas. In the treated groups, perflubron was administered directly into the endotracheal tube in incremental volumes (at 5 min intervals) not to exceed 15 ml at one instillation. After each administration, the ventilator was immediately reconnected. The ventilator settings were kept constant as noted above, and mechanical ventilation was maintained for 6 h.

During the 6-h observation period, arterial blood gases, *p*H, and hemoglobin were determined initially at 15 min, and at 30 min intervals thereafter. Hemodynamic parameters (arterial pressure, central venous pressure, heart rate), lung mechanics, and carbon dioxide gas exchange parameters were recorded at the same time points. No additional drug treatment was attempted.

To determine any adverse effects of perflubron on the tested variables that might be obscured by the RDS state, a group of six healthy rabbits was given 3 ml · kg^{-1} of perflubron intratracheally following standard animal preparation. Before perflubron administration, PEEP was set to 2 cmH_2O, which was observed to be the minimal required PEEP to prevent the bulk movement of perflubron along the airways in each respiratory cycle.[8] Measurements at this point were considered baseline. The animals' lungs were ventilated for 6 h with volume-controlled ventilation: inspired oxygen fraction, 1; VT = 12 ml · kg^{-1}; respiratory frequency, 30 per min; inspiratory/expiratory ratio, 1:2; and PEEP, 2 cmH_2O.

In another group of four healthy rabbits, no perflubron was administered, but the animals' lungs were ventilated mechanically for 6 h to test the effects of time alone on this preparation. The same ventilator settings used in the first healthy group were used in this group.

Arterial blood gases, *p*H determinations, and respiratory mechanics recordings were made at the same time points as in lung-lavaged animals. All animals were killed with an overdose of pentobarbital at the end of the 6-h observation period.

Statistical Analysis

Results were analyzed with analysis of variance (ANOVA) for repeated measurements, using a maximum likelihood technique (Program 5V of BMDP package, BDMP Statistical Software, Los Angeles, CA), in which the dependent variable was modelled as a linear function of dose, time, time squared, and the interactions between dose and time squared. The statistical significance between all pairs of groups also was tested at separate points in time with the Student–Newman–Keuls test. Statistical analyses within each group were made with the Student's *t*-test. All data are presented as mean ± SD, unless otherwise stated. A P value of less than 0.05 was considered statistically significant.

Results

Lung-lavaged Animals

In all groups of lung-lavaged animals, the measured and calculated variables were comparable before and after lung lavage. The saline lavage model used in this study represents a condition similar to RDS, with similar histologic changes and pathophysiologic features, and therefore is considered as a reliable model.[10–12]

Gas Exchange. All animals in groups 3 and 4 survived for the duration of the experiments. Two animals in group C developed pneumothorax after 3 h (at 200 and 310 min), five animals in group 1 developed pneumothorax after 3.5 h (at 240, 250, 270, 290, and 340 min), and three animals in group 2 developed pneumothorax after 5 h (at 305, 340, and 345 min). Suspicion of pneumothorax was based on observed acute increases in airway pressures and/or decreases in blood pressure in the animals. Suspicions were confirmed by direct inspection of the animals and/or aspiration of free air in the thorax through the diaphragm after an abdominal incision was made. In all the animals who underwent abdominal incision, pneumothorax was diagnosed, no treatment was applied, and measurements were discontinued in those animals. Therefore, data analyses are based on the remaining survivors.

Figure 1 depicts the response of arterial oxygen pressure to different doses of perflubron over the course of the experiments. After lung lavage (3 to 4 times), mean arterial oxygen tension (PaO_2) values of the groups were between 67 and 78 mmHg with PEEP of 6 cm H_2O before treatment. Compared to the control group, PaO_2 values increased significantly ($P < 0.0001$) in all treatment groups in a dose-related manner with perflu-

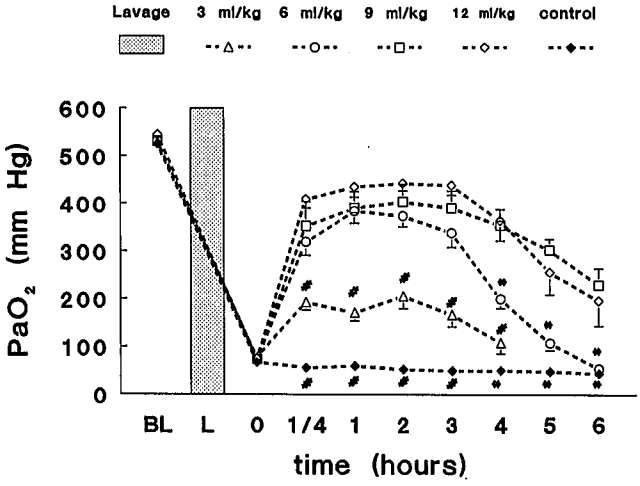

Fig. 1. Arterial oxygen pressure (mean ± SEM) before lavage (BL), after lavage (0 point), and in response to treatment with perflubron at different doses. The bar represents the lavage procedure (L). Aterial oxygen tension increased significantly at each administration dose in conjunction with a decrease in alveolar-arterial oxygen gradient (A-aDO$_2$), reflecting an improvement of lung function, particularly a decrease in intrapulmonary shunt. The data for the 3 ml·kg^{-1} group is not shown after 4 h because there were too few survivors. * = significantly different ($P < 0.0001$) from 9- and 12-ml·kg^{-1} groups; # = significantly different ($P < 0.0001$) from the other groups.

bron treatment. PaO_2 values were significantly lower ($P < 0.0001$) in group 1 than in the other treatment groups until 3.5 h; thereafter, PaO_2 values in groups 1 and 2 were significantly less ($P < 0.0001$) than in groups 3 and 4 at all time points. The mean PaO_2 values at 6 h remained significantly higher ($P < 0.05$) in groups 3 and 4 (230 ± 84 and 197 ± 130 mmHg, respectively) compared to the pretreatment values (after lavage) of these groups and the final readings of the control group. In the control group, PaO_2 gradually decreased to 45 ± 11 mmHg at 6 h.

Mechanical ventilation with tidal volume of 12 ml·kg^{-1} induced hypocapnia in all groups, but lung lavage caused significant increases ($P < 0.001$) in and significant reductions ($P < 0.001$) in *p*H in all groups. After perflubron treatment, only in groups 3 and 4 were arterial PCO_2 values maintained at less than 45 mmHg throughout the study. These values were significantly different ($P < 0.005$) from those found in groups C, 1, and 2 at 6 h (fig. 2). There were significant decreases ($P < 0.05$) in *p*H in all groups toward the end of the observation period (mean *p*H value was slightly lower in group 1 before and after lung lavage compared to other groups; table 1). Despite the well maintained arterial carbon dioxide tensions in groups 3 and 4, these groups experienced metabolic acidosis. Respiratory acidosis accompanied metabolic acidosis in groups C, 1, and 2.

Compared to the control group, perflubron instillation decreased the alveolar dead space to VT ratio significantly ($P < 0.05$) in the treatment groups. In group 4, the decrease in the ratio of alveolar dead space to VT from the pretreatment level was insignificant (table 2). The lower the perflubron dose, the earlier the alveolar dead space to VT ratio started to increase.

Respiratory Mechanics. After perflubron instillation, the peak airway pressure ($Peak_{awp}$) needed to inflate the lungs with a VT of 12 ml·kg^{-1} decreased significantly ($P < 0.0001$), almost to the same extent (range, 17–21%) in all treatment groups at 15 min (fig. 3). On the other hand, airway pressures needed to inflate the lungs increased significantly ($P < 0.001$) over time in the control group. To reflect the actual intrathoracic pressures, the data for end-inspiratory pause airway pressure ($Pause_{awp}$) and mean airway pressure ($Mean_{awp}$) are presented in table 2. The airway pressures ($Peak_{awp}$, $Pause_{awp}$, and $Mean_{awp}$) were significantly lower ($P < 0.0001$) in the treatment groups

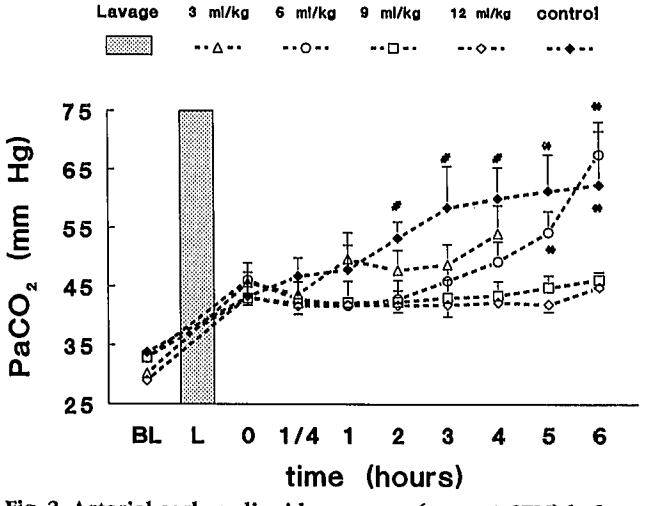

Fig. 2. Arterial carbon dioxide pressure (mean ± SEM) before lavage (BL), after lavage (0 point), and after treatment with perflubron. Arterial carbon dioxide tension levels were more stable than arterial oxygen tension levels for 6 h in the groups treated with high doses (9 ml·kg^{-1} and 12 ml·kg^{-1}). Individual arterial carbon dioxide values in the 3 ml·kg^{-1} group were higher than those in the other groups after 1 h. The data for the 3 ml·kg^{-1} group is not shown after 4 h because there were too few survivors. * = significantly different ($P < 0.005$) from 9- and 12-ml·kg^{-1} groups; # = significantly different ($P < 0.005$) from 6-, 9-, and 12-ml·kg^{-1} groups; L = lavage procedure.

Table 1. Hemodynamics, *p*H, and Metabolic Rate Data of Control and Treatment Groups

	Group	Before Lavage	After Lavage	15 min	1 h	2 h	3 h	4 h	5 h*	6 h*
MAP (mmHg)	C	93 ± 15	87 ± 18	88 ± 18	86 ± 11	87 ± 13	82 ± 13	81 ± 16	84 ± 17	86 ± 18
	G1	95 ± 9	95 ± 6	89 ± 10	87 ± 3	91 ± 4	90 ± 8	90 ± 14	—	—
	G2	93 ± 8	89 ± 10	88 ± 10	86 ± 12	82 ± 5	84 ± 9	88 ± 10	84 ± 7	84 ± 3
	G3	93 ± 11	83 ± 12	92 ± 11	90 ± 14	89 ± 5	94 ± 9	95 ± 8	96 ± 9	97 ± 6
	G4	90 ± 17	97 ± 21	89 ± 15	90 ± 11	86 ± 8	88 ± 10	88 ± 10	86 ± 14	85 ± 16
HR (beats · min^{-1})	C	308 ± 17	297 ± 16	304 ± 13	299 ± 16	285 ± 21	274 ± 15†	261 ± 15†	268 ± 16†	263 ± 14†
	G1	315 ± 27	308 ± 40	298 ± 37	280 ± 30	278 ± 31	268 ± 18†	279 ± 13	—	—
	G2	333 ± 36	328 ± 6	318 ± 15	300 ± 19†	270 ± 16†	278 ± 16†	270 ± 21†	258 ± 26†	255 ± 30†
	G3	315 ± 21	318 ± 11	313 ± 18	289 ± 13†	285 ± 19†	285 ± 13†	280 ± 16†	285 ± 23†	288 ± 24†
	G4	323 ± 13	310 ± 10	313 ± 15	298 ± 22	283 ± 31	288 ± 15†	283 ± 15†	288 ± 20†	268 ± 22†
*p*H	C	7.51 ± .04	7.37 ± .04	7.36 ± .04	7.33 ± .02†	7.29 ± .02†	7.24 ± .05†‡	7.21 ± .03†‡	7.19 ± .06†‡	7.19 ± .04†§
	G1	7.49 ± .04	7.33 ± .05	7.33 ± .05	7.30 ± .05‡	7.31 ± .06	7.30 ± .06	7.26 ± .10	—	—
	G2	7.54 ± .06	7.38 ± .03	7.41 ± .03	7.40 ± .03	7.37 ± .03	7.35 ± .04	7.32 ± .03†	7.29 ± .02†	7.23 ± .05†
	G3	7.53 ± .05	7.40 ± .08	7.39 ± .10	7.38 ± .08	7.36 ± .08	7.33 ± .08	7.31 ± .07	7.29 ± .06†	7.29 ± .04†
	G4	7.61 ± .05	7.39 ± .03	7.42 ± .02	7.40 ± .04	7.37 ± .04	7.35 ± .04	7.34 ± .03†	7.32 ± .04†	7.30 ± .03†
$\dot{V}_{CO_2}$ (ml · kg^{-1} · min^{-1})	C	7.7 ± 1.2	6.6 ± 1.6	7.2 ± 1.2	6.9 ± 0.8	7.1 ± 1.1	6.7 ± 0.5	6.6 ± 1.2	6.4 ± 1.2	6.8 ± 0.9
	G1	6.6 ± 1.0	5.7 ± 0.7	6.3 ± 0.9	6.2 ± 1.1	6.3 ± 1.0	6.0 ± 0.8	6.1 ± 0.9	—	—
	G2	7.4 ± 0.7	5.7 ± 0.7	7.3 ± 0.8	6.7 ± 0.6	6.2 ± 0.4	6.0 ± 0.3	5.9 ± 0.5	5.6 ± 0.9	5.6 ± 1.3
	G3	6.7 ± 1.1	5.4 ± 0.9	6.8 ± 1.0	6.6 ± 0.4	6.4 ± 0.4	6.1 ± 0.3	6.0 ± 0.3	6.1 ± 0.4	5.8 ± 0.6
	G4	7.4 ± 0.9	6.5 ± 0.7	7.2 ± 0.6	7.1 ± 0.4	6.8 ± 0.7	6.8 ± 0.4	6.6 ± 0.4	6.5 ± 0.5	6.5 ± 0.5

Data are mean ± SD.

MAP = mean arterial pressure; HR = heart rate; $\dot{V}_{CO_2}$ = carbon dioxide production; C = control; G1 = 3 ml · kg^{-1}; G2 = 6 ml · kg^{-1}; G3 = 9 ml · kg^{-1}; G4 = 12 ml · kg^{-1}.

* Data for group 1 is not depicted because of too few survivors.

† Statistically different ($P < 0.05$) from pretreatment value (after lavage).

‡ Statistically different ($P < 0.05$) from G2, G3, and G4.

§ Statistically different ($P < 0.01$) from G3 and G4.

Table 2. Ventilatory Parameters of Control and Treatment Groups

	Group	Before Lavage	After Lavage	15 min	1 h	2 h	3 h	4 h	5 h*	6 h*
$Pause_{awp}$ (cmH_2O)	C	11.0 ± 2.0	25.2 ± 1.4	26.0 ± 1.4†	26.2 ± 1.6†	27.8 ± †‡	29.6 ± 1.8†‡	31.2 ± 1.3†‡	31.5 ± 1.0†‡	31.5 ± 1.1†‡
	G1	11.5 ± 1.7	23.6 ± 0.7	19.5 ± 1.4‡	20.1 ± 1.3‡	21.6 ± 1.7‡	23.5 ± 2.1	24.8 ± 1.9§	—	—
	G2	10.8 ± 1.7	24.4 ± 0.8	19.3 ± 1.0‡	19.3 ± 1.1‡	20.9 ± 0.8‡	22.8 ± 1.7	24.7 ± 1.6§	25.6 ± 1.5§	26.9 ± 1.1‡§
	G3	12.4 ± 1.1	24.3 ± 0.5	19.7 ± 0.9‡	19.7 ± 1.0‡	20.0 ± 1.5‡	21.0 ± 1.0‡	21.7 ± 0.7‡	22.2 ± 1.2‡	22.8 ± 1.5‡
	G4	12.3 ± 1.2	24.3 ± 1.6	19.8 ± 1.9‡	18.9 ± 1.6‡	19.6 ± 1.0‡	20.7 ± 1.3‡	21.0 ± 1.4‡	21.1 ± 1.4‡	21.3 ± 1.7‡
$Mean_{awp}$ (cmH_2O)	C	3.4 ± 0.5	11.9 ± 0.4	12.1 ± 0.4†	12.2 ± 0.5†	12.6 ± 0.5†‡	12.9 ± 0.4†‡	13.2 ± 0.4†‡	13.3 ± 0.4†‡	13.4 ± 0.4†‡
	G1	3.8 ± 0.7	11.3 ± 0.3	10.2 ± 0.4‡	10.3 ± 0.5‡	10.7 ± 0.5‡	11.0 ± 0.6§	11.3 ± 0.7§	—	—
	G2	3.6 ± 0.5	11.4 ± 0.4	10.0 ± 0.3‡	10.0 ± 0.2‡	10.3 ± 0.3‡	10.9 ± 0.4‡	11.2 ± 0.4§	11.4 ± 0.5§	11.6 ± 0.3§
	G3	4.1 ± 0.3	11.3 ± 0.2	10.0 ± 0.3‡	9.8 ± 0.3‡	9.9 ± 0.4‡	10.2 ± 0.4‡	10.5 ± 0.3‡	10.5 ± 0.4‡	10.6 ± 0.4‡
	G4	4.0 ± 0.2	11.4 ± 0.7	10.0 ± 0.5‡	9.7 ± 0.4‡	9.9 ± 0.4‡	10.2 ± 0.4‡	10.3 ± 0.5‡	10.3 ± 0.4‡	10.3 ± 0.5‡
V_D/V_T	C	0.25 ± 0.02	0.39 ± 0.05	0.39 ± 0.06	0.39 ± 0.05	0.41 ± 0.05	0.41 ± 0.06	0.44 ± 0.03	0.42 ± 0.07	0.38 ± 0.06
	G1	0.28 ± 0.02	0.44 ± 0.04	0.38 ± 0.04‡	0.40 ± 0.04	0.42 ± 0.05	0.43 ± 0.03	0.46 ± 0.05	—	—
	G2	0.27 ± 0.02	0.46 ± 0.04	0.40 ± 0.03‡	0.39 ± 0.04‡	0.43 ± 0.03	0.45 ± 0.03‖	0.49 ± 0.04	0.49 ± 0.04	0.51 ± 0.03‖
	G3	0.28 ± 0.02	0.45 ± 0.04	0.40 ± 0.03‡	0.39 ± 0.04‡	0.40 ± 0.04‡	0.41 ± 0.05	0.43 ± 0.03	0.42 ± 0.02	0.43 ± 0.02‖
	G4	0.27 ± 0.02	0.41 ± 0.07	0.37 ± 0.02	0.36 ± 0.05	0.36 ± 0.04	0.36 ± 0.05	0.36 ± 0.04†	0.35 ± 0.03§	0.36 ± 0.04

Data are mean ± SD.

$Pause_{awp}$ = end-inspiratory airway pressure; $mean_{awp}$ = mean airway pressure; V_D/V_T = dead space to tidal volume ratio; C = control; G1 = 3 $ml \cdot kg^{-1}$; G2 = 6 $ml \cdot kg^{-1}$; G3 = 9 $ml \cdot kg^{-1}$; G4 = 12 $ml \cdot kg^{-1}$.

* Data for group 1 is not depicted because of too few survivors.

† Statistically different ($P < 0.0001$) from other groups.

‡ Statistically different ($P < 0.05$) from pretreatment value (after lavage).

§ Statistically different ($P < 0.0001$) from G3 and G4.

‖ Statistically different ($P < 0.001$) from G4.

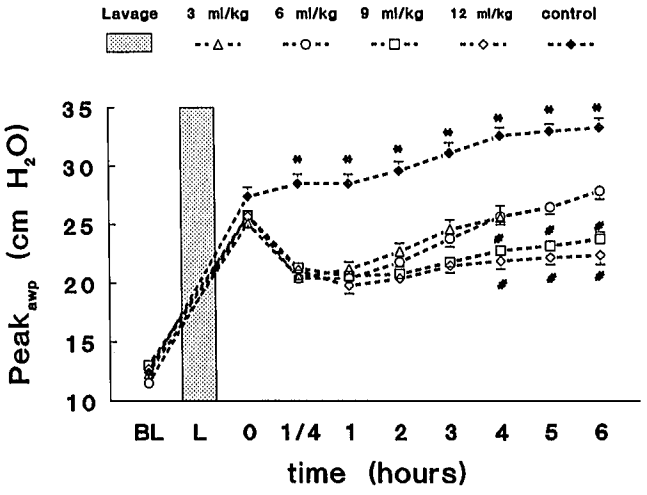

Fig. 3. Changes in peak airway pressure ($Peak_{awp}$; mean ± SEM) in response to perflubron treatment. Positive end-expiratory pressure of 6 cm H_2O is applied during lavage procedure (L), and ventilator settings are kept constant in all groups before and after treatment. Although perflubron administration provided on average a 20% decrease in peak airway pressure in all groups, the linear correlation between peak airway pressure and the function of time is different for each group, favoring the 12 ml · kg^{-1}-treated group to exhibit lower values at all time points. The data for the 3 ml · kg^{-1} group is not shown after 4 h because there were too few survivors. * = significantly different ($P < 0.0001$) from other groups; # = significantly different ($P < 0.0001$) from 3- and 6-ml · kg^{-1} and control groups; BL = before lavage.

than in the control group at 6 h, and in groups 3 and 4 compared to groups 1 and 2 from 3.5 h. Only groups 3 and 4 exhibited airway pressures significantly lower ($P < 0.05$) than the pretreatment values, even at 6 h.

Respiratory system compliance (CRS; ml · cm H_2O^{-1} · kg^{-1}) increased significantly ($P < 0.0001$) in all treatment groups after treatment with perflubron, but in the control group, this value decreased (fig. 4). For the first 2 h, there were no statistically significant differences in CRS in groups 3 and 4 compared to CRS before lung lavage. Mean values of CRS in groups 3 and 4 remained significantly higher ($P < 0.0001$) than those in groups 1 and 2 after 3 h. At the end of the observation period, CRS was still significantly higher ($P < 0.05$) in group 4 only (2.29 ± 0.20 ml · cm H_2O^{-1} · kg^{-1}) compared with this group's pretreatment value (1.90 ± 0.16 ml · cm H_2O^{-1} · kg^{-1}).

Hemodynamics. Mean arterial pressure and central venous pressure (5 ± 1 mmHg at pretreatment) remained stable in all groups throughout the observation period. There were significant changes ($P < 0.05$) in heart rate in all groups towards the end of the study (table 1).

Although carbon dioxide production decreased slightly in all groups, at the end of the study (table 2), arterial lactate levels had increased significantly ($P < 0.0001$) in the control group (from 2.6 ± 0.7 to 8.2 ± 1.5 mM · l^{-1}), group 1 (from 2.8 ± 0.7 to 9.4 ± 2.5 mM · l^{-1}), and group 4 (from 3.0 ± 0.9 to 8.0 ± 1.5 mM · l^{-1}). These levels had increased insignificantly in groups 2 and 3 (from 3.0 ± 1.1 to 5.0 ± 2.5 mM · l^{-1} and from 2.9 ± 0.9 to 4.2 ± 1.5 mM · l^{-1}, respectively) at 6 h from pretreatment levels.

Healthy Animals

All animals survived for the duration of the experiment, and the baseline data were comparable in both groups. Animals tolerated intratracheal perflubron administration well. There were no harmful effects because of mechanical ventilation alone for 6 h, nor because of mechanical ventilation in combination with intratracheal perflubron (3 ml · kg^{-1}) administration on measured parameters in healthy animals during the 6 h study period.

There was no change in arterial oxygenation following perflubron administration for 2 h compared to baseline level: mean PaO_2 remained higher than 500 mmHg; pulmonary gas exchange parameters were

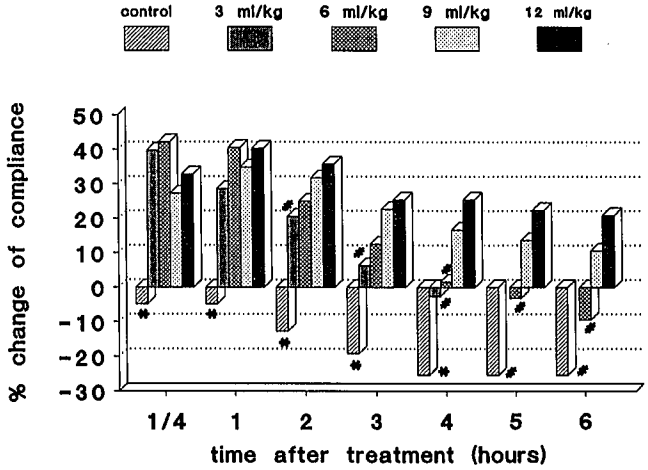

Fig. 4. Percentage changes from the pretreatment level in lung compliance over time in the treatment groups. Following repeated lung lavage, there was marked decrease in lung compliance in all groups in the range of 33–42% (not shown in the figure). * significantly different ($P < 0.0001$) from other groups; # = significantly different ($P < 0.0001$) from 9- and 12-ml · kg^{-1} groups.

comparable, and there were no clinically significant changes in both groups during the 6 h observation period (table 3).

The only significant difference between the two groups was in respiratory mechanics parameters (table 3). When compared to baseline level, airway pressures ($Peak_{awp}$, $Pause_{awp}$, and $Mean_{awp}$) were significantly higher ($P < 0.05$) in the perflubron-treated group for 4 h, but decreased to baseline levels thereafter. However, $Peak_{awp}$ and $Pause_{awp}$ did not differ significantly between the two groups throughout the study.

Discussion

This study demonstrated at least three points of practical interest regarding mechanical ventilation in combination with intratracheal perfluorocarbon administration. First, it suggested that pulmonary gas exchange can be improved by increasing the administered perflubron dose in animals with acute respiratory failure secondary to surfactant depletion. Second, airway pressures can be decreased and respiratory system compliance can be improved to almost the same extent at all perflubron doses. Finally, and most importantly, it suggests that these beneficial effects can be maintained for several hours, again in a dose-dependent fashion. In other words, this study demonstrates a time-dependent characteristic of the four tested perflubron doses in their ability to maintain the improvements in lung functions in acute respiratory failure induced-animals. A dose-dependent relationship for pulmonary gas exchange, but not for respiratory mechanics, indicates different mechanisms of action of intratracheal perflubron administration in diseased lungs.

Alveolar collapse, resulting from increased alveolar surface tension, is one of the main pathophysiologic features of RDS that lead to intrapulmonary shunt. It normally can be prevented by high end-expiratory pressures. Perfluorocarbon liquids have low surface tensions, which make them potentially useful in liquid ventilation in RDS. We speculate that, following intratracheal administration of even a low dose of perflubron, alveoli and airways in the whole lung are covered with a perflubron film; therefore, the increased surface tension at the air-liquid interface is reduced to that of the perflubron liquid. This mechanism allows for relatively low pressure lung inflation. Our experimental results support this hypothesis, in that the airway pressures were reduced independently of the dose administered.

In view of the dose-related improvement of oxygenation, we suggest that, despite the reduction of alveolar surface tension by perflubron in diseased lungs, this low but constant surface tension still does not prevent alveoli from end-expiratory collapse at a PEEP of 6 cm H_2O. The improvement of gas exchange at increasing doses, and therefore the recruitment of previously collapsed units (presumably the nonfilled alveoli in the upper lung regions), can be attributed only to the amount of the administered perfluorocarbon liquid (*i.e.,* the administration of high volumes of perfluorocarbon results in the filling of more affected alveoli). This "splinting" of alveoli prevents end-expiratory collapse so that gas exchange can be facilitated during the whole respiratory cycle. Perflubron's ability to dissolve large amounts of oxygen and carbon dioxide results in continuous alveolar gas exchange and decreased intrapulmonary shunt.

After filling the lungs with high doses of perfluorocarbon (>12 ml $\cdot$ kg^{-1}) and maintaining a gas tidal volume above this volume, one would expect high airway pressures to expand the lungs. To clarify this hypothesis, we performed an additional experiment for dynamic pressure-volume measurements in the lung-lavaged animals. Table 4 indicates that, in RDS-induced animals at a PEEP level of 6 cm H_2O, gas tidal volume was maintained at considerably lower airway pressures, even after filling the lungs with a perflubron volume of 20 ml $\cdot$ kg^{-1}, than only gas ventilation state (0 point). At increasing doses of perflubron (up to 40 ml $\cdot$ kg^{-1}), gas ventilation resulted in high peak airway pressures. Even though this result may reflect the compression of gas tidal volume in a lung largely full of perfluorocarbon liquid, the data suggest that the alveoli were nearly at full expansion, at which point the tissue elasticity became the predominant component of alveolar retractive forces, thereby leading to significant airway pressure changes. This mechanical behavior of the lavaged lungs with increasing perflubron volumes resembled the pressure-volume characteristics of saline-filled lung.[13]

Perfluorocarbon liquids are metabolically inert and are eliminated *via* the expired air. Although systemic absorption and distribution of perfluorocarbon to the blood and other tissues in small amounts have been demonstrated after liquid ventilation, measurements of perfluorocarbon in expired gases have documented the rapid elimination of perfluorocarbon through the

Table 3. Blood Gases, *p*H, and Respiratory Mechanics Data of Healthy Control Groups

		0	1 h	2 h	3 h	4 h	5 h	6 h
Pa_{O_2} (mmHg)	C1	537 ± 17	503 ± 27	500 ± 38	525 ± 18	520 ± 24	548 ± 25	527 ± 25
	C2	531 ± 22	512 ± 18	505 ± 18	527 ± 6	507 ± 25	524 ± 18	511 ± 18
Pa_{CO_2} (mmHg)	C1	34 ± 3	41 ± 3*	42 ± 3*	43 ± 3*	42 ± 2*	40 ± 3*	40 ± 3*
	C2	36 ± 5	39 ± 4	40 ± 3	43 ± 4	38 ± 3	41 ± 3	40 ± 5
*p*H	C1	7.48 ± 0.02	7.39 ± 0.05*	7.37 ± 0.03*	7.35 ± 0.02*	7.35 ± 0.01*	7.37 ± 0.02*	7.35 ± 0.01*
	C2	7.45 ± 0.05	7.41 ± 0.05	7.38 ± 0.03*	7.37 ± 0.02*	7.36 ± 0.02*	7.36 ± 0.01*	7.36 ± 0.03*
$Peak_{awp}$ (cmH_2O)	C1	15.6 ± 1.3	17.7 ± 0.9*	18.8 ± 1.2*	18.1 ± 1.2*	17.3 ± 1.0*	16.3 ± 2.0	16.4 ± 1.1
	C2	16.6 ± 1.1	16.8 ± 0.7	16.3 ± 1.0	16.0 ± 0.6	15.6 ± 0.6	15.6 ± 0.8	15.6 ± 0.8
$Pause_{awp}$ (cmH_2O)	C1	13.5 ± 0.5	15.0 ± 1.0*	16.5 ± 1.6*	16.4 ± 1.7*	15.6 ± 1.6*	14.6 ± 2.8	14.8 ± 1.7
	C2	14.8 ± 1.5	15.6 ± 0.9	15.4 ± 1.0	15.0 ± 0.6	14.3 ± 0.4	14.5 ± 0.9	14.4 ± 0.8
$Mean_{awp}$ (cmH_2O)	C1	5.6 ± 0.2	6.4 ± 0.1*	6.4 ± 0.1*	6.3 ± 0.2*	6.0 ± 0.2*	5.6 ± 0.5	5.6 ± 0.4
	C2	5.8 ± 0.4	5.8 ± 0.4†	5.6 ± 0.5†	5.5 ± 0.3†	5.5 ± 0.3	5.4 ± 0.4	5.4 ± 0.4

Data are mean ± SD.

Pa_{O_2} = arterial oxygen tension; Pa_{CO_2} = arterial carbon dioxide tension; $peak_{awp}$ = peak airway pressure; $pause_{awp}$ = end-inspiratory airway pressure; $mean_{awp}$ = mean airway pressure; C1 = perfluorocarbon-treated; C2 = only ventilated.

* Statistically different ($P < 0.05$) from baseline value (0 point).

† Statistically different ($P < 0.005$) from perfluorocarbon-treated group (C1).

lungs.[14]# The relationship between the dose of perfluorocarbon administered and the time at which impairment of lung function was seen strongly supports the suggestion that evaporation of perfluorocarbon over time would cause the affected alveoli to collapse and, therefore, limit efficacy of pulmonary gas exchange. This will occur sooner with small doses of perfluorocarbon, as observed in this study.

Another possibility could be damage of the alveolar structure by the perfluorocarbon liquid itself. In liquid ventilation studies in healthy animals, a reversible change in pulmonary function has been observed and speculated to be caused by the residual perfluorocarbon in the lungs rather than the pathophysiologic changes.[15–17] Histologic studies in preterm animals have revealed that after ventilation with perfluorocarbon liquids, the alveolar structure remained intact and no damage to the lung architecture was demonstrated compared to conventional gas ventilation.[2,18**] After filling the lungs with perfluorocarbon at a volume of functional residual capacity, Fuhrman *et al.* recently demonstrated that adequate pulmonary gas exchange can be provided with conventional mechanical ventilation in healthy animals.[19] Our results from healthy animals are in agreement with Fuhrman's report that healthy animals can tolerate intratracheal perfluorocarbon administration during mechanical ventilation without showing any clinically evident harmful effects on lung functions.

We can not exclude the possibility that the proteinaceous exudate elicited by the saline lavage could mix with the perfluorocarbon and, in the groups receiving low-dose perfluorocarbon, reduce its surface tension effect by dilution; however, combined with the aforementioned reports, the present experimental data from healthy controls, which revealed no harmful effects

Table 4. Dynamic Volume–Pressure Measurements

PFC Volume ($ml \cdot kg^{-1}$)	Pressure (cmH_2O)
0 (after lavage)	25.0 ± 1.5
5	18.9 ± 0.4
10	18.9 ± 1.4
15	19.4 ± 1.8
20	21.6 ± 3.1
25	24.1 ± 3.9
30	28.2 ± 5.4
35	32.2 ± 6.0
40	37.2 ± 7.9

Data are mean ± SD from three lung-lavaged and volume-controlled ventilated rabbits (with the same experimental protocol).

The pressure represents the end-inspiratory airway pressure recorded at zero flow after five breaths of gas tidal ventilation (12 $ml \cdot kg^{-1}$, 100% oxygen) after administration of each perflubron dose in 5-$ml \cdot kg^{-1}$ increments.

Wolfson MR, Clark LC, Hoffmann RE, Davis SL, Greenspan JS, Rubenstein SD, Shaffer TH: Liquid ventilation of neonates: Uptake, distribution and elimination of the liquid (abstract). Pediatr Res 27: 37A, 1990.

** Forman D, Bhutani VK, Hilfer SR, Shaffer TH. A fine structure study of the liquid-ventilated newborn rabbit. Fed Proc 43:647, 1984.

caused by perflubron itself or the time factor involved, suggest that elimination of perfluorocarbon by evaporation through the lungs remains the major determinant of the efficacy of this ventilatory support technique. An important observation was that significant impairment of gas exchange occurred earlier than did the increase in airway pressures. This observation also indirectly supports our hypothesis that perfluorocarbon acts by different mechanisms for oxygenation and lung mechanics properties in the diseased lung. In the groups treated with 3 $ml \cdot kg^{-1}$ and 6 $ml \cdot kg^{-1}$ of perfluorocarbon, animals developed pneumothorax at the time points where the peak airway pressures were greater than the pretreatment levels. However, end-inspiratory airway pressures never exceeded the pretreatment inflation pressures in the groups treated with 9 $ml \cdot kg^{-1}$ and 12 $ml \cdot kg^{-1}$ of perfluorocarbon (6% and 12% less than the pretreatment levels at 6 h, respectively), and no pneumothorax occurred in these groups. Therefore, we may conclude that cyclic reopening and collapse of the alveoli and airways with high pressure amplitudes could lead to high shear forces along the epithelial surfaces and, thus, result in barotrauma.[20] In addition to well sustained lung mechanics (reduced airway pressures, increased respiratory system compliance), maintenance of adequate pulmonary gas exchange for several hours suggests that this technique offers an effective means of ventilatory support with high perfluorocarbon doses and minimizes the risk of barotrauma. Considering the experimental results, it can be suggested that the progress of functional lung impairment due to evaporation of perfluorocarbon can be prevented by replacement of perfluorocarbon liquid at the time that decrease in efficacy is observed.

It is noteworthy that the vapor pressure of a particular perfluorocarbon could be important for both producing efficient evaporation from the lungs at the termination of this supportive technique and avoiding frequent replacement during long-term applications used to decrease the cost. Moreover, the vapor pressure of perfluorocarbon appears to be an important determinant for the theoretical alveolar oxygen level. The perfluorocarbon tested in this experiment, perflubron, has a low vapor pressure of 10.5 mmHg at 37° C and 3.6 mmHg at 20° C. Therefore, the presence of saturated perflubron vapor would only decrease the maximal alveolar oxygen pressure by 10.5 mmHg, much less than would be expected when other more volatile perfluorocarbons were employed. The low vapor pressure makes perflubron the preferred perfluorocarbon for this type of application, with respect to evaporative losses and maintenance of alveolar oxygen tensions.

Before clinical application is undertaken, perfluorocarbon liquids must be shown to be safe regarding side effects, tissue retention, and toxicity. A considerable number of animal toxicology studies have been performed on perflubron, which has been used also in humans as an oral magnetic resonance contrast agent for the gastrointestinal tract.[21,22] Moreover, perflubron is presently in clinical trials in the United States as an intravenous contrast agent for blood pool imaging with computed tomography, and the limited data have shown no significant side effects.[23]

The development of lactic acidosis is thought to reflect an imbalance between the metabolic requirements and oxygen supply to the tissues. Despite the small, insignificant changes in metabolic rate of the animals as evaluated by carbon dioxide production, lactic acidosis (unrelated to the perflubron dose) developed in the treatment groups. Considering the limited available data, the occurrence of lactic acidosis is likely to be a reflection of cardiovascular dysfunction, because uncomplicated hypoxemia generally does not cause lactic acidosis,[24] and intravascular fluid volume plays an important role in maintaining adequate oxygen supply during positive-pressure ventilation.[25] Further studies are required to evaluate the possible mechanisms of cardiocirculatory adjustments and increased lactate levels during this type of perfluorocarbon application.

In conclusion, intratracheal perflubron administration combined with conventional mechanical ventilation offers an easier and more clinically acceptable approach to perfluorocarbon use compared to total liquid ventilation. It also provides a degree of respiratory support that is unlikely to be achieved with conventional ventilation alone at the same ventilatory settings. Intratracheal perflubron instillation combined with mechanical gas ventilation provides adequate oxygenation, improves ventilation, and allows for low inflation pressures without compromising hemodynamics in acute respiratory failure. These results indicate that even very low doses of perflubron permit significant improvement in lung function, and higher doses (reaching to functional residual capacity volume) are required for adequate ventilatory support for periods up to 6 h in severe RDS in animals. Exogenous surfactant treatment has been shown to be a promising adjunct in various experimental models and in a limited number of clinical cases of RDS.[26] The present study

suggests that intratracheal perfluorocarbon treatment also may play a role in achieving the goals of ventilatory support in humans with RDS (*i.e.*, pulmonary support avoiding high inflation pressures) and, thus, further lung damage, until sufficient recovery from the primary disease is achieved.

The authors thank Mrs. Laraine Visser-Isles for her English language editing, Mr. Ari Kok for his technical assistance, and Siemens-Elema, Sweden for providing the equipment.

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