An Optimal Dose of Perfluorocarbon for Respiratory Mechanics in Partial Liquid Ventilation for Dependent Lung-Dominant Acute Lung Injury*

Chae-Man Lim, MD; Younsuck Koh, MD; Byung O. Jung, MD; Sang D. Lee, MD; Woo S. Kim, MD; Dong S. Kim, MD; and Won D. Kim, MD, FCCP

Background: Despite increasing knowledge about partial liquid ventilation (PLV), the optimal dose of perfluorocarbon (PFC) is not yet established. Because there exist normal regions in the lung with ARDS and because PLV in the normal lung results in worsened gas exchange, we postulated that the optimal dose of PFC for PLV may be less than the functional residual capacity (FRC) dose in the lung with limited disease.

Design and setting: Animal study at the Asan Institute for Life Sciences, Seoul, Korea.

Subjects: Twelve rabbits in which dependent lung-dominant lung injury was created by a modified saline solution lavage.

Interventions: PLV performed at six different doses of perfluorodecalin in sequence (3, 6, 9, 12, 15, and 18 mL/kg every 15 min).

Measurements and results: Our modified saline solution lavage induced atelectasis and hemorrhage confined to the dependent lung with severe hypoxia (PaO2/fraction of inspired oxygen = 37 ± 6 mm Hg). Peak airway pressure (Ppeak) and inspiratory pause pressure (Ppause) with PLV were lower at doses of 3 to 15 mL/kg (all p < 0.05), but not different at a dose of 18 mL/kg, when compared with gas ventilation. Ppeak increased at doses of 12, 15, and 18 mL/kg, when each was compared with the preceding PFC dose. At increasing PFC doses, the change in the elastic component of airway pressure (Ppause after minus Ppause before) was negative until the dose of 9 mL/kg, but was positive at doses of 12 mL/kg and above. The change in the resistive component ([Ppeak minus Ppause] after minus [Ppeak minus Ppause] before) was negative until the dose of 6 mL/kg, but was positive at the dose ≥ 9 mL/kg.

Conclusion: Respiratory mechanics during PLV for dependent lung–dominant lung injury were optimal at a PFC dose less than the FRC.

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Key words: ARDS; partial liquid ventilation; perfluorocarbon; respiratory mechanics

Abbreviations: Cdyn = dynamic compliance of the respiratory system; Cst = static compliance of the respiratory system; FiO2 = fraction of inspired oxygen; FRC = functional residual capacity; G = gas ventilation; PEEP = positive end-expiratory pressure; PEEPt = total PEEP; Pelast = elastic component of airway pressure; PFC = perfluorocarbon; PLV = partial liquid ventilation; Pmean = mean airway pressure; Ppause = inspiratory pause pressure; Ppeak = peak airway pressure; Presist = resistive component of airway pressure; Vd/Vt = physiologic dead space; Vt = tidal volume

Partial liquid ventilation (PLV) has been shown to be effective in improving oxygenation and respiratory mechanics in human and animal subjects with severe respiratory failure.1–6 During PLV, perfluorocarbon (PFC) mediates gas exchange and exerts a positive end-expiratory pressure (PEEP)-like effect in an acutely injured lung.7 Currently, for PLV in ARDS, the lungs are filled with PFC liquid until a fluid meniscus is seen in the endotracheal tube, a dose corresponding to the liquid functional residual capacity (FRC).8 The optimal dose of PFC during PLV, however, is not yet known in ARDS.9,10 The lungs of patients with ARDS are heterogeneous in regional pathology, with the dependent lung being more severely collapsed and the nondependent lung less diseased or normal.11,12 In this
situation, the requirement of PEEP differs according to the superimposed pressure along the vertical axis of the thorax. An excessive level of PEEP not only causes hypotension and paradoxical decreases in PaO₂, but it may also impair respiratory mechanics by overdistending airways and alveoli. In the same manner as PEEP, the requirement of PFC (liquid PEEP) may also vary with the severity and extent of lung injury. Theoretically, the optimal volume of PFC should be less than the FRC in ARDS, if part of the lung is functioning normally. Instillation of PFC liquid in the normal lung actually increased the heterogeneity of ventilation. Additionally, moderate levels of PEEP (4 to 6 cm H₂O) are required in conventional PLV to suppress the bulk movement of PFC liquid residing in the central airways.

We therefore postulated that the PFC dose response in respiratory mechanics during PLV may not be linear in the lung with limited extent of injury, or lower doses may be more appropriate in this situation.

**Materials and Methods**

**Animal Preparation**

Twelve New Zealand White rabbits (2.7 ± 0.7 kg) were used for this study. The rabbits were cared for and handled according to the guidelines of the US National Institutes of Health. Ten rabbits were used for the PLV trial, and the other 2 were used for gross pathologic examination or CT scanning of the lungs after the modified saline solution lavage described below. The following experimental protocol was approved by our institutional Animal Care Committee.

The animal was placed in the supine position under a radiant warmer to keep rectal temperature between 38°C and 39°C. After ketamine 25 mg/kg was injected in the thigh muscle, a peripheral ear vein was cannulated with a 24-gauge angiocatheter for IV anesthesia. Under local anesthesia with 2% lidocaine, a tracheostomy was performed and a 3.5-mm°C-diameter cuffless endotracheal tube was inserted into the trachea and firmly tied to prevent gas or liquid leak. The carotid artery was cannulated with a 22-gauge angiocatheter and connected to a pressure monitor (Servo II; Medical Data Electronics; Arleta, CA) to monitor arterial pressure and pulse rate and to obtain arterial blood for blood gas analysis. Anesthesia was induced with 20 mg/kg thiopental sodium (divided into two IV doses) and maintained by 3 mg/kg/min continuous infusion. Muscle paralysis was maintained during the study with intermittent IV administration of pancuronium (0.1 mg/kg). Mechanical ventilation (Servo 900C; Siemens-Elema; Solna, Sweden) was performed at tidal volume (VT) of 18 mL/kg; frequency, 34/min; fraction of inspired oxygen (F₁O₂), 1.0; PEEP, 2 cm H₂O; and inspiratory to expiratory ratio, 1.1. The settings remained constant throughout the experiment. Blood gases were analyzed using standard electrodes (Blood gas system 288; Ciba-Corning; Medfield, MA). Expired gas from the rabbit was collected in a 1.0-L mixing chamber positioned distal to the expiratory valve of the ventilator. Mixed expired CO₂ was measured using a sidestream infrared capnometer (Normocap; Datex; Helsinki, Finland). The rabbits were given 5% dextrose in 0.45% saline solution at 7.5 mL/kg/h by an infusion pump throughout the study.

**Modified Saline Solution Lavage**

To better test our hypothesis, we modified the method of saline solution lavage used by Lachmann et al by varying the amount of saline solution and the animal’s position during the lavage. Through the endotracheal tube, 20 mL/kg of warmed saline solution (70% of the quantity used in the method of Lachmann et al) was administered into the lung over a 20-s period. The rabbits were not turned to different positions during the repeated lavages, but were kept in the supine position in an attempt to spare the upper lung from injury. Half of the saline solution was poured into the right and left lungs in each lateral decubitus position. The saline solution remained in the rabbit’s lung, and the mechanical tidal breaths were continued for 1 min or until severe bradycardia (<40/min) ensued. Saline solution was drained out of the lung by gravity using a 1-m-long siphon. The peak airway pressure (Ppeak) was kept below 35 cm H₂O during the lavage by temporarily adjusting VT when necessary. Lavage was repeated two or three times, and 60 min was allowed after the last lavage for the injury to be stabilized. Acute lung injury was defined as a PaO₂/F₁O₂ ratio of <100 mm Hg at the end of the 60-min injury period.

To confirm the appropriateness of the modified lung injury model, a thoracotomy was performed in one rabbit to examine the gross appearance of the lungs, and a CT scan was obtained in another rabbit at the lower thorax to delineate the distribution of the pathologic changes.

**PLV**

PLV was started with 3 mL/kg of perfluorodecalin liquid (perfluoro-decahydronaphthalin, C₁₅H₁₉F₁₅; Fluka Chemie AG; Buchs, Switzerland), warmed to 38°C before instillation. Each half of the PFC dose was administered with the rabbit in the left or right lateral decubitus position, respectively, so that PFC would be distributed evenly to both lungs. After physiologic measurements were taken after 15 min of 3 mL/kg of PFC, the dose was sequentially increased to 6, 9, 12, 15, and 18 mL/kg at 15-min intervals. Evaporative loss of PFC (estimated to be 0.5 mL/kg/15 min) was taken into consideration when increasing the dose. The PFC meniscus was observed in the endotracheal tube during expiratory phase at a dose of 18 mL/kg in nine rabbits and at a dose of 15 mL/kg in one rabbit.

**Physiologic Measurements**

When the rabbit was stable after the surgical procedures and instrumentation, mean arterial pressure, pulse rate, blood gases, airway pressures (Ppeak, inspiratory pause pressure [Ppause], mean airway pressure [Pmean], and total PEEP [PEEPt]) were measured. Ppeak was measured by inspiratory hold of 5 s. PEEP was measured by end-expiratory hold of 5 s. Dynamic and static compliance of the respiratory system (Cdyn and Cst, respectively) were calculated as VT/(Ppeak – PEEPt) and VT/(Ppeak – PEEPt), respectively. To delineate the respective change in the elastic and resistive components of the airway pressure (Pelast and Presist, respectively) at increasing PFC dose, ∆Pelast ([Ppause] after a next dose minus Ppause before) and ∆Presist ([Ppeak – Ppause] after a next dose minus [Ppeak – Ppause] before) were calculated. Physiologic dead space (VD/VT) was calculated according to Enghoff’s modification of the Bohr equation. The same hemodynamic and respiratory data were obtained 60 min after the last saline solution lavage under general anesthesia (GV) and at 15 min of PLV with each PFC dose.
Statistics

All data are expressed as mean ± SD unless otherwise stated. Comparison between GV and PLV was performed by paired *t* test. Statistical significance of the difference in values at different doses of PFC was evaluated by Friedman repeated-measures analysis of variance on ranks. Multiple pairwise comparisons were made with the Student-Newman-Keuls method. A *p* value of < 0.05 was considered statistically significant.

**Results**

**Physiologic Changes, Gross Examination, and CT Scan of the Rabbit's Lung After the Modified Saline Solution Lavage**

Modified saline solution lavage resulted in increases in Ppeak (13.3 ± 1.5 cm H₂O vs 21.1 ± 1.9 cm H₂O), Ppause (12.2 ± 1.6 cm H₂O vs 18.7 ± 2.0 cm H₂O), and Pmean (5.3 ± 0.6 cm H₂O vs 8.2 ± 1.0 cm H₂O) compared with baseline (all *p* < 0.001), and decreases in Cdyn (4.5 ± 0.5 mL/cm H₂O vs 2.7 ± 0.2 mL/cm H₂O; *p* < 0.001) and Cst (5.0 ± 0.6 mL/cm H₂O vs 3.1 ± 0.3 mL/cm H₂O; *p* < 0.001). Arterial pH and PaO₂/FiO₂ decreased, whereas PacO₂ and Vd/Vt increased (all *p* < 0.005; Table 1). Mean arterial pressure (72 ± 13 mm Hg vs 75 ± 16 mm Hg; *p* = 0.652) and pulse rate (229 ± 17 beats/min vs 224 ± 31 beats/min; *p* = 0.736) were not changed.

After 60 min of the limited lung injury, the lungs were found to be hemorrhagic at the dependent lung regions but were normal at the ventral lung regions, except for the anterior margins of the lower lobes (Fig 1). CT scan taken at the lower thorax showed bilateral atelectasis and edema confined to the dorsal lung regions with the ventral lung regions spared (Fig 2).

**Effect of Incremental Dose of PFC in Limited Lung Injury**

**Respiratory Mechanics:** Compared with GV, Ppeak was lower with PFC doses of 3 to 15 mL/kg, but not different at a dose of 18 mL/kg (Fig 3). Ppause was lower at doses of 3 to 15 mL/kg, but not different at a dose of 18 mL/kg. Pmean was lower at doses of 3 to 9 mL/kg, but not different at doses of 12 to 18 mL/kg. PEEPt was not changed across all the PFC doses. Ppeak increased at doses of 12, 15, and 18 mL/kg, and Pmean increased at doses of 12 and

**Table 1—Gas Exchange in GV and at Different Doses of PFC in PLV for a Dependent Lung-Dominant Lung Injury**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal GV</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.42 ± 0.06</td>
<td>7.12 ± 0.16</td>
<td>7.13 ± 0.13</td>
<td>7.17 ± 0.13</td>
<td>7.19 ± 0.12</td>
<td>7.20 ± 0.13</td>
<td>7.20 ± 0.13</td>
</tr>
<tr>
<td>PaO₂/FiO₂, mm Hg</td>
<td>544 ± 32</td>
<td>37 ± 6</td>
<td>67 ± 24</td>
<td>89 ± 55</td>
<td>138 ± 88</td>
<td>121 ± 65</td>
<td>137 ± 90</td>
</tr>
<tr>
<td>PacO₂, mm Hg</td>
<td>38 ± 10</td>
<td>77 ± 21</td>
<td>69 ± 13</td>
<td>70 ± 15</td>
<td>64 ± 16</td>
<td>68 ± 18</td>
<td>74 ± 20</td>
</tr>
<tr>
<td>BE, mEq/L</td>
<td>-1.7 ± 2.2</td>
<td>-5.7 ± 5.3</td>
<td>-6.4 ± 4.6</td>
<td>-3.7 ± 5.0</td>
<td>-4.1 ± 6.5</td>
<td>-2.7 ± 7.1</td>
<td>-1.4 ± 4.5</td>
</tr>
<tr>
<td>Vd/Vt</td>
<td>0.70 ± 0.07</td>
<td>0.92 ± 0.04</td>
<td>0.87 ± 0.02</td>
<td>0.85 ± 0.03</td>
<td>0.87 ± 0.03</td>
<td>0.87 ± 0.03</td>
<td>0.89 ± 0.04</td>
</tr>
</tbody>
</table>

*Data expressed as mean ± SD. BE = base excess.
†*p* < 0.05 compared with GV by paired *t* test.
‡*p* < 0.05 compared with the preceding dose in PLV by *post hoc* multiple comparison.
At increasing PFC doses, $\Delta\text{Presist}$ was negative until the dose of 6 mL/kg, but was positive at doses of $\geq 9$ mL/kg. $\Delta\text{Pelast}$ was negative until the dose of 9 mL/kg, but was positive at doses of $\geq 12$ mL/kg (Fig 4).

**Gas Exchange:** Compared with GV, $\text{PaO}_2/\text{FiO}_2$ with PLV was higher at all the doses tested (Table 1). $\text{Paco}_2$ was lower only at a dose of 3 mL/kg, and $\text{Vd}/\text{Vt}$ was lower at doses of 3, 9, 12, and 15 mL/kg, but not at doses of 6 and 18 mL/kg.

**Hemodynamics:** For mean arterial pressure and pulse rate, there were no differences between PLV and GV, or between different doses of PFC.

**Discussion**

In our model of dependent lung-dominant acute lung injury, the overall respiratory mechanics were optimal at the low doses of PFC (around 9 mL/kg). Cdyn in the rabbit deteriorated at the high doses of PFC ($\geq 12$ mL/kg). After early improvement, Cst plateaued at and beyond the dose of 9 mL/kg. Increases in airway pressure at the high-dose range were attributable to the increase of both elastic and resistive components.

There is growing interest regarding the dosing of PFC.\textsuperscript{10,19} Originally, PFC was filled up to the liquid FRC for PLV.\textsuperscript{8} In addition to the economical concerns relating to the high dose of PFC, use of a large amount of PFC in the lung may increase pulmonary vascular resistance\textsuperscript{20} and increase diffusion limitation and heterogeneity of ventilation.\textsuperscript{15} Moreover, use of PFC in the normal lung results in histologic injury.\textsuperscript{21} Kaisers et al\textsuperscript{10} showed that PLV using FC 3280 was effective at doses of 7.5 mL/kg and 15 mL/kg (both

![Figure 3](https://example.com/f3.png) Change in $\text{Ppeak}$ (closed circles), $\text{Ppause}$ (open circles), and $\text{Pmean}$ (closed squares) in PLV at incremental PFC doses in dependent lung-dominant acute lung injury. *$p < 0.05$ compared with GV. #$p < 0.05$ compared with the preceding PFC dose in PLV.

![Figure 4](https://example.com/f4.png) Respective changes in Pelast and Presist in PLV during incremental PFC doses in dependent lung-dominant acute lung injury.
far below the estimated FRC) in improving gas exchange and survival time in a pig ARDS model. They did not, however, systematically evaluate the dose–airway pressure response relationship. In the present study, we hypothesized that if excess PFC were to occupy normal alveoli and airways beyond the diseased portion, the benefits of PFC on respiratory mechanics would be offset or even lost. This can be anticipated because (1) the fixed amount of gas (Vt) coming from the ventilator should now face the heightened inertia of a greater amount of PFC, and (2) the natural surfactant system of the preserved lung region is replaced by less efficient PFC liquid. In a previous study by Tüütüncü et al., Ppeak was markedly improved at a low dose (6 mL/kg) and did not change further at high doses. The results of our study in a different lung injury model complement their findings, and also suggest that the optimal dose of PFC during PLV may vary according to the extent and predominant loci of lung injury. PFC in excess of the optimal amount actually made the acutely injured lung function poorly in terms of both the resistive and elastic pressures needed to accommodate tidal gas volume. Time-dependent deterioration of lung injury did not seem to be a likely explanation for the worsened respiratory dynamics of our rabbits. Acute lung injury induced by saline solution lavage, in contrast to that induced by oleic acid, is known to be stable for a 2- to 4-h period after ventilation, in contrast to that induced by oleic acid, is known to be stable for a 2- to 4-h period after stabilization. Moreover, the tendency of PaO2/FIO2 to increase at the high doses of PFC in our study reduces the probability that lung injury was progressing during the 1.5-h period of our liquid ventilation.

Some unique features of liquid PEEP (PFC) can be summarized from the previous studies on PLV,1,10,19 including our own. First, PFC can be more selective than PEEP in addressing the alveolar collapse of the dependent lung region. Unlike PEEP, which has no gravity-dependent distribution, PFC tends to distribute according to gravity. By virtue of this property, all the lowest doses of PFC ever tested resulted in concomitant improvement of oxygenation and static respiratory compliance. Second, while greater improvement in static respiratory compliance during CV is obtained with a relatively high level of PEEP (above the inflection point), the change in the static respiratory compliance with PLV was the reverse, ie, progressively decreasing benefit with increasing dose. Thirdly, the change in mean airway pressure with PFC also contrasts with PEEP. While PEEP elevates mean airway pressure, PFC did not raise mean airway pressure above the baseline value, even at the highest dose. Hemodynamically, mean arterial pressure and pulse rate were not changed across the whole range of PFC doses, which would certainly be different in the case of increasing levels of PEEP.

There are some limitations in our study. First of all, the dynamics (Ppeak, Presist) of a lung filled with gas and liquid at the same time carry inherent mechanical complexities. High-density fluid, when faced with tidal gas flow, will elicit phase-related fluctuations in pressure related to the composite frictional force of fluid and gas. With the onset of gas flow, the liquid column in the central airways will recede peripherally and break into multiple parallel columns in the intermediate airways, and consequently, the start of expiration. In this situation, it is difficult to determine the degree to which gas-airway friction and the inertial force of PFC liquid are each responsible for the change in the resistive pressure during PLV. This phenomenon should be most prominent with an intermediate dose of PFC, which corresponds to the dose of our interest. Chemical differences between different PFC liquids should be also taken into consideration in interpreting our results. Perfluorodecalin (C10F18) used in our study differs from perfluorobron (perfluorooctylbromide, C8F17Br1), which has been used in many previous PLV studies, in several aspects: lower surface tension (15 vs 18 dyne/cm at 25°C), higher vapor pressure (14 vs 11 mm Hg at 37°C), and lower CO2 solubility (140 vs 210 mL/100 mL at 37°C). Unfortunately, information is not available on how gas exchange and respiratory mechanics are affected by different formulas of PFC. Although there is little evidence, the greater amount of perfluorodecalin vapor vs perfluorobron vapor at the same dose might have benefited more alveoli. In examining our modified model of acute lung injury, the gross pathologic findings and CT scan in two rabbits showed that the model was satisfactory for mimicking the preferential distribution of lung injury in the dependent lung. The rabbits’ physiologic status was also appropriate for the definition of experimental acute lung injury in terms of respiratory mechanics and gas exchange. We did not, however, perform a microscopic examination of the rabbits’ lungs; future evaluations should include this step. It would be also interesting to investigate whether the histologic outcome of PLV with a low PFC dose is better than the outcome with the FRC dose in this type of limited lung injury or in human ARDS.

In conclusion, the optimal dose of PFC for respiratory mechanics during PLV was found to be less than the liquid FRC dose in an acute lung injury model in which the dependent region was preferentially affected. Our study showed that excess PFC beyond a certain dose was not desirable in terms of both resistive and elastic impedance of the lung. Our results imply that the dose of PFC for clinical ARDS
can be further reduced, and the use of liquid PEEP (PFC) should be tailored in individual cases according to the extent and predominant loci of disease.

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