Partial Liquid Ventilation in Adult Patients with Acute Respiratory Distress Syndrome

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Rationale: Despite recent clinical trials demonstrating improved outcome in acute respiratory distress syndrome (ARDS), mortality remains high. Partial liquid ventilation (PLV) using perfluorocarbons has been shown to improve oxygenation and decrease lung injury in various animal models.

Objective: To determine if PLV would have an impact on outcome in patients with ARDS.

Methods: Patients with ARDS were randomized to (1) conventional mechanical ventilation (CMV; n = 107), (2) “low-dose” perfluorocarbon (10 ml/kg; n = 99), and (3) “high-dose” perfluorocarbon (20 ml/kg; n = 105). Patients in all three groups were ventilated using volume ventilation, V̇E ≤ 10 ml/kg predicted body weight, rate = 25/min, inspiratory-to-expiratory ratio ≤ 1:1, FIO2 ≤ 0.5, and positive end-expiratory pressure ≥ 13 cm H2O.

Results: The 28-d mortality in the CMV group was 15%, versus 26.3% in the low-dose (p = 0.06) and 19.1% in the high-dose (p = 0.39) PLV groups. There were more ventilator-free days in the CMV group (13.0 ± 9.3) compared with both the low-dose (7.4 ± 8.5; p < 0.001) and high-dose (9.9 ± 9.1; p = 0.043) groups. There were more pneumothoraces, hypoxic episodes, and hypotensive episodes in the PLV patients.

Conclusions: PLV at both high and low doses did not improve outcome in ARDS compared with CMV and cannot be recommended for patients with ARDS.

Keywords: acute respiratory distress syndrome; liquid ventilation; mechanical ventilation; partial liquid ventilation

Despite recent clinical trials demonstrating improved outcome in the acute respiratory distress syndrome (ARDS) (1,2), overall mortality in unselected patients with ARDS remains unacceptably high at 40 to 50% (3–5). As a result, adjuncts and alternatives to standard conventional mechanical ventilation continue to be evaluated in an effort to improve the outcome of these patients (6,7).

One of these alternatives is partial liquid ventilation (PLV), a nontraditional approach to ventilation that has received considerable attention over the past decade (8). With PLV, the lungs are partially filled with perfluorocarbon (PFC), a clear inert liquid, and mechanical ventilation is provided with a standard ventilator (9). The rationale underlying this approach in patients with ARDS is that PFCs improve gas exchange by recruiting dependent lung regions, by clearing retained secretions, and by redistributing blood flow to ventilated regions (10,11); and the use of PLV abrogates lung injury due to the low surface tension properties and anti-inflammatory properties of PFCs (12,13). In animal models of acute lung injury (ALI), PLV has been shown to improve gas exchange and decrease lung injury compared with conventional mechanical ventilation (CMV) (14–16). Preliminary studies have demonstrated that PLV can be performed safely in humans (17–21) and a post hoc analysis of a phase II trial demonstrated more rapid discontinuation of mechanical ventilation and a trend to decreased mortality in patients younger than 55 yr who were treated with PLV (20).

On the basis of the strong animal data (14–16) suggesting the efficacy of PLV in models of lung injury, and on the suggestive human data (20), we performed a randomized clinical trial comparing PLV with CMV in patients with ARDS.

METHODS

Between 1998 and 2000, patients with ARDS were randomized from 56 centers (Appendix 1). Inclusion criteria were as follows: risk factor for ALI/ARDS; prior mechanical ventilation for 120 h or less; acute, bilateral infiltrates on chest radiograph; and a PaO2/FIO2 of 0.5 or greater, and positive end-expiratory pressure (PEEP) of 5 cm H2O or more. Patients were excluded if their age was younger than 16 or older than 65 yr, their Acute Physiology and Chronic Health Evaluation (APACHE) II score was 30 or more, there had been more than 48 h since meeting inclusion criteria, and there was presence of serious nonpulmonary organ dysfunction (Appendix 2). To ensure persistent hypoxemia, only patients with PaO2/FIO2 of 0.5 or greater, less than 300 mm Hg on PEEP of 13 cm H2O or greater and FIO2 of 0.5 or more were included.

Patients were randomly assigned to one of four groups using a block design (22) that ensured a balance of distribution of patients with respect to four strata (ARDS etiology, age, APACHE II score, and alternative therapies). Group assignment was performed using a computerized randomization system. The control group received CMV with no PFC; the low-dose PLV group had their lungs filled with PFC (Perflbron, Alliance Pharmaceutical, San Diego, CA) to the carina in the supine position. This was accomplished by slowly instilling two separate aliquots (5 ml/kg predicted body weight [PBW] per aliquot) of PFC into the lungs. A “suction catheter check” was performed by inserting a suction catheter to the carina while the patient was on zero PEEP. Suction was then applied to the catheter; if PFC was suctioned, then suctioning was continued until no PFC was removed. If no PFC was suctioned, then 5-ml/kg aliquots of PFC were administered, followed by suction catheter checks until some PFC was suctioned. The protocol for high-dose PLV group was similar to that described above, except PFC was delivered at a 0.5 mL/kg PBW per aliquot to PFC into the lungs of the lungs in a 1:1 ratio. A “suction catheter check” was performed by inserting a suction catheter to the carina while the patient was on zero PEEP. Suction was then applied to the catheter; if PFC was suctioned, then suctioning was continued until no PFC was removed. If no PFC was suctioned, then 5-ml/kg aliquots of PFC were administered, followed by suction catheter checks until some PFC was suctioned. The protocol for high-dose PLV group was similar to that described above, except PFC was delivered at a 0.5 mL/kg PBW per aliquot to PFC into the lungs of the lungs in a 1:1 ratio.

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All groups received standardized ventilatory support: volume control, Vt of 10 ml/kg PBW or less, rate of 25/min or less, inspiratory-to-expiratory ratio of 1:1, FiO₂ of 0.5 or greater, and PEEP of 13 cm H₂O or more. End-inspiratory plateau pressure was maintained at 35 cm H₂O or lower. PEEP in the treatment groups was maintained at 13 cm H₂O or higher until dosing was stopped. When patients met target gas exchange criteria with PEEP of 8 cm H₂O or less, FiO₂ of 0.5 or less, patients were weaned using spontaneous breathing trials (23, 24).

The primary study outcome was ventilator-free days during the 28 d after randomization. The secondary outcomes were mortality, time to weaning, and time to discontinuation of mechanical ventilation. The secondary outcomes were mortality, time to weaning, and time to discontinuation of mechanical ventilation. The secondary outcomes were mortality, time to weaning, and time to discontinuation of mechanical ventilation.

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; CMV = conventional mechanical ventilation; MODS = multiple organ dysfunction score; PBW = predicted body weight; PEEP = positive end-expiratory pressure; PLV = partial liquid ventilation.

**RESULTS**

A total of 3,817 patients were screened between December 1998 and December 2000, from which 311 patients were enrolled: 107 patients were randomized to CMV, 99 were randomized to low-dose PLV, and 105 were randomized to high-dose PLV. Five patients randomized to PLV (two randomized to low-dose and three randomized to high-dose) never received PLV. These five patients were included in all analyses except for ventilator settings at 24, 72, and 168 h post-randomization. All patients were monitored for the 28-d study period.

Baseline demographic characteristics, disease severity, and ventilator management were similar in the three groups (Table 1). The duration of PLV treatment was 92 ± 39.2 h in the low-dose group (n = 97) and 85 ± 39.5 h in the high-dose group (n = 102). Nine patients (five in the low-dose and four in the high-dose PLV groups) received PLV therapy for more than 5 d. The total volume of Perflubron instilled into the lungs was 82 ± 32.8 ml/kg PBW (5,179 ± 2,150 ml) in the low-dose PLV group.

### TABLE 1. BASELINE CHARACTERISTICS OF THE PATIENTS AND VENTILATOR, GAS EXCHANGE, AND HEMODYNAMIC DATA AT THE TIME OF RANDOMIZATION

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CMV Group (n = 107)</th>
<th>Low-Dose PLV Group (n = 99)</th>
<th>High-Dose PLV Group (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>46 ± 12</td>
<td>45 ± 14</td>
<td>45 ± 13</td>
</tr>
<tr>
<td>Age &lt; 55 yr, %</td>
<td>73.8</td>
<td>71.7</td>
<td>73.3</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>59.8</td>
<td>60.6</td>
<td>57.1</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>18 ± 5</td>
<td>17 ± 5</td>
<td>18 ± 5</td>
</tr>
<tr>
<td>APACHE II score &lt; 20, %</td>
<td>62.6</td>
<td>69.7</td>
<td>64.8</td>
</tr>
<tr>
<td>MODS</td>
<td>5.0 ± 2.7</td>
<td>5.7 ± 2.3</td>
<td>5.9 ± 2.2</td>
</tr>
<tr>
<td>Lung injury etiology, %</td>
<td>58.9</td>
<td>56.6</td>
<td>55.2</td>
</tr>
<tr>
<td>Primary</td>
<td>30.8</td>
<td>30.3</td>
<td>37.1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>14.0</td>
<td>12.1</td>
<td>9.5</td>
</tr>
<tr>
<td>Aspiration</td>
<td>11.2</td>
<td>13.1</td>
<td>5.7</td>
</tr>
<tr>
<td>Lung contusion</td>
<td>1.9</td>
<td>1.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Near drowning</td>
<td>0.9</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Other</td>
<td>41.1</td>
<td>43.4</td>
<td>44.8</td>
</tr>
<tr>
<td>Secondary</td>
<td>25.2</td>
<td>26.3</td>
<td>30.5</td>
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<tr>
<td>Trauma (nonthoracic)</td>
<td>2.8</td>
<td>5.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td>3.7</td>
<td>2.0</td>
<td>3.8</td>
</tr>
<tr>
<td>Multiple transfusions</td>
<td>2.8</td>
<td>1.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Other</td>
<td>6.5</td>
<td>9.1</td>
<td>7.6</td>
</tr>
<tr>
<td>Weight actual, kg</td>
<td>82.6 ± 22</td>
<td>78.6 ± 21</td>
<td>76.9 ± 19</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170.5 ± 10</td>
<td>169.3 ± 11</td>
<td>170.3 ± 10</td>
</tr>
<tr>
<td>Weight predicted, kg</td>
<td>65.0 ± 11</td>
<td>63.9 ± 11</td>
<td>64.8 ± 11</td>
</tr>
<tr>
<td>Assist ventilation before enrollment, h</td>
<td>46.8 ± 28</td>
<td>41.2 ± 26</td>
<td>44.6 ± 30</td>
</tr>
<tr>
<td>Hours from ARDS onset</td>
<td>21.9 ± 14</td>
<td>20.4 ± 16</td>
<td>20.4 ± 16</td>
</tr>
<tr>
<td>Vt, ml/kg PBW</td>
<td>9.3 ± 2.0</td>
<td>9.0 ± 1.8</td>
<td>9.0 ± 1.9</td>
</tr>
<tr>
<td>Rate, breaths/min</td>
<td>16.9 ± 4.7</td>
<td>18.0 ± 4.8</td>
<td>18.6 ± 5.4</td>
</tr>
<tr>
<td>Plateau pressure, cm H₂O</td>
<td>30.0 ± 7.1</td>
<td>31.4 ± 6.1</td>
<td>32.6 ± 7.2</td>
</tr>
<tr>
<td>Compliance, ml/cm H₂O</td>
<td>43.1 ± 14.5</td>
<td>40.2 ± 14.6</td>
<td>36.7 ± 14.9</td>
</tr>
<tr>
<td>FiO₂</td>
<td>0.7 ± 0.19</td>
<td>0.7 ± 0.18</td>
<td>0.7 ± 0.20</td>
</tr>
<tr>
<td>Total PEEP, cm H₂O</td>
<td>13.9 ± 1.5</td>
<td>14.3 ± 2.0</td>
<td>14.2 ± 2.2</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>11.1 ± 5.2</td>
<td>10.6 ± 2.3</td>
<td>11.4 ± 2.9</td>
</tr>
<tr>
<td>PaO₂/FiO₂, mm Hg</td>
<td>147 ± 54</td>
<td>137 ± 58</td>
<td>143 ± 52</td>
</tr>
<tr>
<td>Peak pressure, cm H₂O</td>
<td>35.5 ± 6.1</td>
<td>36.5 ± 6.0</td>
<td>37.0 ± 6.2</td>
</tr>
<tr>
<td>Mean airway pressure, cm H₂O</td>
<td>20.6 ± 3.7</td>
<td>21.3 ± 4.8</td>
<td>22.7 ± 10.9</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>44 ± 13</td>
<td>43 ± 10</td>
<td>46 ± 12</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 ± 0.09</td>
<td>7.37 ± 0.10</td>
<td>7.36 ± 0.09</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>107 ± 21</td>
<td>107 ± 18</td>
<td>108 ± 20</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>118 ± 17</td>
<td>118 ± 19</td>
<td>119 ± 20</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>62 ± 12</td>
<td>60 ± 11</td>
<td>62 ± 13</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>37.9 ± 0.9</td>
<td>37.8 ± 0.9</td>
<td>37.7 ± 0.8</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; CMV = conventional mechanical ventilation; MODS = multiple organ dysfunction score; PBW = predicted body weight; PEEP = positive end-expiratory pressure; PLV = partial liquid ventilation.*
and 107 ± 45.8 ml/kg PBW (6.910 ± 3.278 ml) in the high-dose group.

During the study period, prone ventilation was used in five patients randomized to CMV, two patients randomized to low-dose PLV, and four patients randomized to high-dose PLV. In addition, six patients in the CMV group received inhaled nitric oxide; seven in the low-dose PLV group and 10 in the high-dose PLV group also received inhaled nitric oxide. Two patients received high-frequency oscillatory ventilation in the low-dose PLV group, and three patients in the high-dose PLV group received unidentified adjunctive therapy.

Efficacy

Ventilatory and gas exchange variables at 24, 72, and 168 h after randomization are provided in Table 2. The results for the primary outcome variables (ventilator-free days) and secondary outcome variables (28-d mortality, time to resolution of ALI/ARDS, alive and off the ventilator at Day 28, and time to unassisted ventilation) were similar in all treatment groups for both the intention to treat (all randomized regardless of treatment) and per-protocol populations (all patients actually receiving randomized treatment).

Ventilator-free days and mortality data by stratification group are presented in Table 4. Stratification had little effect on ventilator-free days. However, both age and APACHE II score affected mortality primarily in the high-dose and CMV groups. Mortality was 7.6% for those younger than 55 yr (n = 79) and 6.0% for those with an APACHE II score of less than 20 (n = 67) in the CMV group. Mortality was 35.7% for all groups 55 yr and older.

Safety

Adverse events, as reported by the investigators are listed in Table 5. There were no statistically significant differences in the incidence of bradycardias, arrhythmias, or cardiac arrests reported during the first 28 d. However, there were more reported pneumothoraces, hypoxic episodes, and hypotensive episodes in PLV patients compared with CMV patients during the first 28 d. Most of the hypoxic and hypotensive adverse events in the PLV groups occurred over the first 5 d of drug delivery and were associated with the initial and subsequent filling of the lung with PFC.

DISCUSSION

The most important findings of this study are as follows: (1) PLV at both low and high doses did not improve outcome compared with CMV. (2) A greater number of serious adverse reactions were observed with PLV than with conventional ventilation, and (3) the conventional ventilation strategy used in this study resulted in an improvement in ventilator-free days and a nonsignificant trend to decreased mortality.

The results of this trial are disappointing. The hypothesis of the current study was based on animal data and a post hoc analysis of a phase II trial comparing PLV with a non-PLV control group (20). In the previous study, the PLV group had a significantly greater number of ventilator-free days and a trend toward a lower mortality rate compared with control in patients younger than 55 yr (20). The plateau pressures in the phase II trial for all groups were 35 to 39 cm H2O, and in the current study they were 26 to 30 cm H2O in the CMV group. This

| Table 2. Gas Exchange and Ventilator Data at 24, 72, and 168 h After Randomization |
|-----------------|----------------|----------------|
|                | CMV (n = 105) | Low-Dose PLV (n = 96) | High-Dose PLV (n = 101) |
| Vt, ml/kg of PBW | 9.0 ± 2.0 | 8.3 ± 1.6* | 8.6 ± 1.8 |
| Plateau pressure, cm H2O | 38.5 ± 5.0 | 32.9 ± 6.7* | 32.0 ± 6.8* |
| Compliance, ml/cm H2O | 35.7 ± 17.7 | 33.7 ± 14.1* | 35.5 ± 15.5* |
| Peak inspiratory pressure, cm H2O | 33.6 ± 7.6 | 37.3 ± 7.5* | 37.7 ± 7.0* |
| Mean airway pressure, cm H2O | 18.6 ± 6.0 | 22.3 ± 4.8* | 22.1 ± 4.9* |
| Respiratory rate, breaths/min | 17.2 ± 4.7 | 19.3 ± 4.4* | 19.5 ± 4.7* |
| Minute ventilation, L/min | 10.8 ± 2.8 | 10.9 ± 1.2 | 11.0 ± 2.6 |
| FIO2 | 0.60 ± 0.17 | 0.7 ± 0.20* | 0.7 ± 0.17* |
| Total PEEP, cm H2O | 12.5 ± 3.6 | 15.2 ± 3.1* | 15.3 ± 3.3* |
| PAO2/FIO2 | 180 ± 63 | 138 ± 61* | 132 ± 62* |
| PAO2/mm Hg | 43 ± 11 | 48 ± 12* | 52 ± 13* |
| Arterial pH | 7.38 ± 0.09 | 7.35 ± 0.09* | 7.34 ± 0.10* |

Definition of abbreviations: CMV = conventional mechanical ventilation; PBW = predicted body weight; PEEP = positive end-expiratory pressure; PLV = partial liquid ventilation.

*p < 0.05 versus CMV for the specific time period.
### TABLE 3. MAIN OUTCOME VARIABLES

<table>
<thead>
<tr>
<th>Variable</th>
<th>CMV Group</th>
<th>Low-Dose PLV Group</th>
<th>High-Dose PLV Group</th>
<th>p Value vs. Low-Dose*</th>
<th>p Value vs. High-Dose†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator-free days (to Day 28), mean ± SD</td>
<td>13.0 ± 9.3</td>
<td>7.4 ± 8.5</td>
<td>&lt; 0.001</td>
<td>9.9 ± 9.1</td>
<td>0.043</td>
</tr>
<tr>
<td>Mortality to Day 28, %</td>
<td>15.0</td>
<td>26.3</td>
<td>0.064</td>
<td>19.1</td>
<td>0.39</td>
</tr>
<tr>
<td>Alive and off ventilator at Day 28, %</td>
<td>76.0</td>
<td>53.0</td>
<td>&lt; 0.001</td>
<td>61.0</td>
<td>0.027</td>
</tr>
<tr>
<td>Time to resolution of ARDS, d (median, 25%, 75%)</td>
<td>10 (4.9, 19.2)</td>
<td>14.6 (8.8, N/A)</td>
<td>&lt; 0.001</td>
<td>10.6 (6.5 ± 25.6)</td>
<td>0.12</td>
</tr>
<tr>
<td>Time to unassisted ventilation, d (median, 25%, 75%)</td>
<td>12.5 (6.0, 17.8)</td>
<td>18.9 (10.8, N/A)</td>
<td>&lt; 0.001</td>
<td>13.9 (8.7, N/A)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** ARDS = acute respiratory distress syndrome; CMV = conventional mechanical ventilation; N/A = not applicable; PLV = partial liquid ventilation.

* Low-dose PLV compared with CMV.
† High-dose PLV compared with CMV.

The difference may have contributed to the CMV mortality benefit in our trial versus the phase II trial. Outcome data for the PLV groups in this study were similar to those from the post hoc analysis of the phase II trial; however, in the present study, the control group had a much improved outcome. This study joins a large group of negative studies that were based on promising post hoc analyses (7, 25, 26). The reason for the large number of negative post hoc trials is likely related to the statistical issue of multiple testing in which “false positives” occur by chance alone. However, it should also be understood that it is still unclear how to optimally dose PFCs and adjust ventilator settings in patients receiving PLV. Therefore, the overall role, if any, of PFCs in ventilator management of ARDS remains to be determined despite this negative study.

**Why the Negative Results?**

Given the putative benefits of PLV, which include decreased surface tension (9), antiinflammatory properties (12), “liquid PEPP,” and redistribution of blood flow to better ventilated areas (10, 11), and given the promising animal data (14–16), why was this trial negative? There are a number of possibilities, including the heavy sedation and paralysis required in many patients on PLV, the requirement for at least 48 h of PLV before discontinuation, the fact that PLV requires about 24 h for the PFC to evaporate, and possible repeated derecruitment of unstable lung units since patients in the PLV arm had to be disconnected from the mechanical ventilator every 3 h for either redosing or evaluation of the PFC level. However, the negative results may have been a result of the ventilatory strategy used in all groups. As we now know, a low Vt (~ 6 ml/kg) is ideal in ARDS (1, 2). This study used Vts of about 9 ml/kg PBW, lower than those used in the animal studies cited above. These lower Vts may have prevented the beneficial effects of PLV from being observed. In addition, plateau pressures were higher in the PLV groups by about 3 cm H2O throughout the study. It may be that the benefits of adjunctive therapies demonstrated in animals ventilated with large Vts are simply overshadowed by the benefits of low ventilating pressures and Vts currently used in patients with ARDS. This combined with the unexpectedly low mortality in the control group were the primary reasons why we believe the trial results were negative.

An additional reason for this negative trial may have been the population of patients studied; it may be that a different population of patients would have benefited from PLV. Finally, it may be that the high peak alveolar pressure in the most gravity-dependent lung in the PLV group when applied over time enhanced injury in this group. Although plateau pressures were about 30 to 32 cm H2O in the PLV groups, plateau pressure does not reflect the impact of the PFCs on the dependent lung. The combined effect of pressure exerted by the PFC and the airway gas pressure may have enhanced injury over time in the PLV groups. Finally, the overall volume of fluid plus gas in the PLV groups may have markedly over distended lung, increasing susceptibility to injury.

The ARDSNet data (2) became available during the conduct of this trial. This brings up the question of whether this study should have changed to a lower Vt strategy in the control group. This is a complex issue. The current study was almost completed.

**Figure 1.** All-cause mortality for all patients enrolled into the three studied groups over the first 28 d of the study. Treatment groups: solid line, low-dose; dotted line, high-dose; dashed line, conventional mechanical ventilation.
when the ARDSNet results were published. The Vt’s used in
our study were about midway between those of the control
arm and the conventional arm of the ARDSNet trial, and the
mortality rates that were seen by the Data Safety Monitoring
Board (albeit in a blinded fashion) were comparable to the
6-ml/kg group in the ARDSNet trial. When entry criteria differ
and outcomes of the study being conducted are good, decisions
are frequently made to continue the trial as designed. A good
example of this is the recent prone-positioning trial by Guerin
and coworkers (27), which used a Vt of about 10 ml/kg PBW.

TABLE 4. PRIMARY OUTCOME BASED ON STRATIFICATION

<table>
<thead>
<tr>
<th>Etiology</th>
<th>CMV</th>
<th>Low-Dose PLV</th>
<th>High-Dose PLV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct</td>
<td>n = 63</td>
<td>n = 56</td>
<td>n = 58</td>
</tr>
<tr>
<td>VFD</td>
<td>12.3</td>
<td>5.6</td>
<td>8.3</td>
</tr>
<tr>
<td>Mortality</td>
<td>14.3%</td>
<td>30.4%</td>
<td>20.7%</td>
</tr>
<tr>
<td>Indirect</td>
<td>n = 44</td>
<td>n = 43</td>
<td>n = 47</td>
</tr>
<tr>
<td>VFD</td>
<td>10.9</td>
<td>8.2</td>
<td>8.8</td>
</tr>
<tr>
<td>Mortality</td>
<td>15.9%</td>
<td>20.9%</td>
<td>17.0%</td>
</tr>
</tbody>
</table>

Age

<table>
<thead>
<tr>
<th>&lt; 55 yr</th>
<th>CMV</th>
<th>Low-Dose PLV</th>
<th>High-Dose PLV</th>
</tr>
</thead>
<tbody>
<tr>
<td>VFD</td>
<td>12.8</td>
<td>7.8</td>
<td>10.9</td>
</tr>
<tr>
<td>Mortality</td>
<td>7.6%</td>
<td>22.6%</td>
<td>13.0%</td>
</tr>
<tr>
<td>≥ 55 yr</td>
<td>n = 28</td>
<td>n = 28</td>
<td>n = 28</td>
</tr>
<tr>
<td>VFD</td>
<td>10.5</td>
<td>6.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Mortality</td>
<td>35.7%</td>
<td>35.7%</td>
<td>35.7%</td>
</tr>
</tbody>
</table>

APACHE II

<table>
<thead>
<tr>
<th>&lt; 20</th>
<th>CMV</th>
<th>Low-Dose PLV</th>
<th>High-Dose PLV</th>
</tr>
</thead>
<tbody>
<tr>
<td>VFD</td>
<td>14.5</td>
<td>7.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Mortality</td>
<td>6.0%</td>
<td>24.7%</td>
<td>16.3%</td>
</tr>
<tr>
<td>≥ 20</td>
<td>n = 40</td>
<td>n = 30</td>
<td>n = 37</td>
</tr>
<tr>
<td>VFD</td>
<td>8.7</td>
<td>6.3</td>
<td>7.6</td>
</tr>
<tr>
<td>Mortality</td>
<td>30.0%</td>
<td>30.0%</td>
<td>24.6%</td>
</tr>
</tbody>
</table>

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CMV = conventional mechanical ventilation; PLV = partial liquid ventilation; VFD = ventilator-free days.

Mortality indicates 28-d mortality.

TABLE 5. INVESTIGATOR-REPORTED ADVERSE EVENTS, DAYS 1–28

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>CMV Group (n = 107)</th>
<th>Low-Dose PLV Group (n = 99)</th>
<th>High-Dose PLV Group (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax*</td>
<td>During treatment</td>
<td>3 (3.1%)</td>
<td>8 (7.8%)</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>6 (6.2%)</td>
<td>22 (21.6%)</td>
<td>17 (15.9%)</td>
</tr>
<tr>
<td>Hypoxia*</td>
<td>During treatment</td>
<td>13 (13.4%)</td>
<td>21 (20.6%)</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>8 (8.2%)</td>
<td>10 (9.8%)</td>
<td>17 (15.9%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>During treatment</td>
<td>1 (1.0%)</td>
<td>7 (6.9%)</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>8 (8.2%)</td>
<td>4 (3.9%)</td>
<td>12 (11.2%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>During treatment</td>
<td>14 (14.4%)</td>
<td>16 (15.7%)</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>20 (20.6%)</td>
<td>14 (13.9%)</td>
<td>20 (18.9%)</td>
</tr>
<tr>
<td>Hypotension*</td>
<td>During treatment</td>
<td>5 (5.2%)</td>
<td>16 (15.7%)</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>14 (14.4%)</td>
<td>9 (8.8%)</td>
<td>13 (12.1%)</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>During treatment</td>
<td>0 (0%)</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>3 (3.1%)</td>
<td>1 (1.0%)</td>
<td>2 (1.9%)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CMV = conventional mechanical ventilation; PLV = partial liquid ventilation.

During treatment indicates the first 5 d for the CMV groups and for as long as PLV was administered in the PLV groups; post-treatment indicates the period after treatment up to the 28th day.

* p < 0.05 versus CMV group.

**Adverse Events**

The increased numbers of hypoxic and hypotensive episodes in the PLV groups were primarily related to the interruption of ventilatory support that was required for initial dosing and subsequent dosing of PFC. In addition, the greater distending pressure in the dependent lung regions may have contributed to the higher pneumothorax rate in the PLV groups (9.3 vs. 29.4 and 28%) (10, 11). Although all of the short-term preclinical data indicated less lung injury with PLV (30, 31), it is easy to speculate how the long-term application of PLV might have induced this level of barotrauma.

**Conventional Ventilation**

Although direct comparison of mortality among different studies is fraught with uncertainty due to a number of factors, it is interesting to compare the mortality in our control group with those of other studies. The mortality rate of 15% in our control group is the lowest mortality reported in any reported randomized controlled trial of mechanical ventilation in ARDS (1, 2, 7, 25, 26, 32–35). This low mortality rate may be due to a number of factors. First, patients enrolled in our trial had fewer organ failures than many other ARDS trials and were ventilated for less than 48 h after the diagnosis of ARDS was made. In addition, the inclusion criteria only included patients younger than 65 yr; increased age is a well-known determinant of increased mortality in patients with ARDS (36, 37). However, our patients may have had more severe lung injury at the time of enrollment based on oxygenation criteria, since we assessed oxygenation using a relatively high PEEP of 13 cm H2O or greater, and only patients with an FiO2 of 0.5 or more and a PaO2/FiO2 less than 300 mm Hg were randomized. When the ventilation strategy used in our study is compared with that of the ARDSNet trial (2), striking differences exist. Vt in our CMV arm was about 9.0 ml/kg PBW, somewhat lower than those used in Stewart and coworkers’ (32) and Brochard and colleagues’ (33) studies, but greater than the 6.0 ml/kg PBW in the ARDSNet treatment arm. However, we used a PEEP level that was about 14 cm H2O at randomization, a value greater than that used in the three previously mentioned trials. A number of animal studies have demonstrated that higher levels of PEEP produce marked protection from ventilator-induced lung injury. Plateau pressures in both the present study and in the ARDSNet study (2) were about 28 cm H2O. Given that we used a higher Vt and a higher PEEP level, this would suggest that there was marked recruitment of the lung by the application of PEEP of 13 cm H2O or greater from the first or second day of ARDS in our study. This leads one to speculate on the relative importance of volume, PEEP, and plateau pressure on outcome in ARDS.
Limitations

The major limitation of this study was the methodology used to check whether further dosing of PFC was required. The repetitive disconnection of the mechanical ventilator may have disadvantaged patients in the PLV groups. Only two dosing levels were used; it is possible that a much lower dose of PFC may have been more advantageous. The approach to ventilation used during PLV may not have been ideal. The use of a smaller well-defined VT in all groups may have affected outcome. It is possible that use of high-frequency ventilation during PLV would have been more advantageous than CMV. It can be argued that this trial, similar to many other trials of innovative medical approaches, was conducted too soon. However, the results of animal studies (14–16) were positive, a Phase II trial (20) identified a group of patients that might benefit from PLV, and much of the human lung protective mechanical ventilation data we know today were not available in 1998. In addition, ventilator adjustments were not guided by specific algorithms. Ranges (i.e., VT = 10 ml/kg PBW) were defined but the clinician was free to adjust settings within the defined range as they considered clinically appropriate.

In addition, the delay between study completion and study publication must be addressed. Multiple factors clearly affect the speed of publication. Positive results are embraced by everyone and enthusiasm for publication is high. However, negative trials are not as enthusiastically embraced. The investigators' interest in pursuing the effort required to publish is diminished, and journals overall are less interested in publishing negative trials than positive trials. Despite this, it is critical that data from negative trials be available for the entire medical community to evaluate to help guide future studies. Finally, as with all studies, our results can only be generalized to others meeting our inclusion criteria including a PaO2/FiO2 of 300 mm Hg or less or a PEEP of 13 cm H2O or greater and FiO2 of 0.5 or greater.

In conclusion, the use of PLV as applied in this study results in a greater number of serious adverse outcomes than CMV and does not improve outcome compared with CMV. PLV is not indicated in patients with severe ARDS.

Conflict of Interest Statement: R.M.K. received a $65,000 grant from Alliance Pharmaceuticals in 1999 to support studies on the approach to mechanical ventilation during partial liquid ventilation. H.P.W. served as a consultant for Alliance Pharmaceuticals prior to and during the conduct of this clinical trial, for which he received at most $10,000/yr during 1994–2000. P.T.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.K.W. was a full-time employee of Alliance Pharmaceuticals at the time of the study. A.S.T. was an employee of Alliance Pharmaceuticals, which sponsored the clinical trial. A.S.T. has been a paid consultant to Maquet in the time of the study. H.P.W. served as a consultant for Alliance Pharmaceuticals in 1999 to support studies on the approach to mechanical ventilation used in the present study, but received no financial compensation for this.

References


**APPENDIX 1**

**PLV Study Investigators**

**Principal Investigator**

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Habashi, Nader, M.D.

Sandifer, Dean, M.D.

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Schuster, Daniel, M.D.

Mallampalli, Antara, M.D.

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Wiedemann, Herbert, M.D.

Woda, Russell, M.D.

James Allen, M.D.

Zwischenberger, Jay, M.D.

Johnson, Steven, M.D.

Tsuei, Betty, M.D.

Moncure, Michael, M.D.

Rouben, Lawrence, M.D.

Senkowski, Michael, M.D.

Heard, Stephen, M.D.

Shapiro, Michael, M.D.

Strange, Charlie, M.D.

Raoff, Suhaill, M.D.

Garland, Alan, M.D.

Cardinal, Pierre, M.D.

Fenwick, John, M.D.

Goldberg, Peter, M.D.

Hamielee, Cindy, M.D.

Laporta, Denny, M.D.

Mazer, David, M.D.

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Smith, Terry, M.D.

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Princeton Pulmonary Group PC, Birmingham, AL

University of Tennessee, Memphis, TN

University of Cincinnati Medical Center, Cincinnati, OH

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Lehigh Valley Hospital, Allentown, PA

Maine Medical Center, Portland, ME

University of Missouri–Columbia School of Medicine, Columbia, MO

R.A. Cowley Shock Trauma Center, Baltimore, MD

Lakeland Regional Medical Center Watson Clinic, Lakeland, FL

Veterans Affairs Medical Center, University of Miami, Miami, FL

Washington University School of Medicine, St. Louis, MO

University of Louisville Health Sciences Center, Louisville, KY

Massachusetts General Hospital, Boston, MA

Cleveland Clinic Foundation, Cleveland, OH

Ohio State University Medical Center, Columbus, OH

Ohio State University Medical Center, Columbus, OH

University of Texas Medical Center, Galveston, TX

University of Arizona Health Sciences Center, Tucson, AZ

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University of Kansas Medical Center, Kansas City, KS

Jewish Hospital, Heart and Lung Institute, Louisville, KY

Memorial Medical Center, Savannah, GA

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University of Pennsylvania, Philadelphia, PA

Medical University of South Carolina, Charleston, SC

Nassau County Medical Center, East Meadow, NY

Robert Wood Johnson Medical School, New Brunswick, NJ

Ottawa General Hospital, Ottawa, ON, Canada

Vancouver Hospital and Health Sciences Center, Vancouver, BC, Canada

Royal Victoria Hospital, Montreal, PQ, Canada

Hamilton Health Sciences, Hamilton, ON, Canada

Jewish General Hospital, Montreal, PQ, Canada

St. Michael’s Hospital, Toronto, ON, Canada

Foothills Hospital, Calgary, Alberta

Sunnybrook Health Sciences Center, Toronto, ON
Summary of Exclusion Criteria

- Age < 16 and > 65 yr
- Inability to obtain informed consent
- APACHE II score ≥ 30
- Time window for inclusion exceeded (> 48 h)
- Significant nonpulmonary organ dysfunction as defined by the following:
  1. Chronic renal failure requiring dialysis
  2. Acute liver disease with significant hepatocellular or cholestatic liver injury (acute hepatitis or acute cholestasis)
  3. Severe chronic liver disease (bilirubin > 3 mg/dl and serum albumin < 3 g/dl)
  4. Hematologic dysfunction, defined by either a total polymorphonuclear leukocyte (PMN) count < 0 or 5 × 10^9/m
- Systolic blood pressure < 90 mm Hg, unresponsive to treatment with fluids and vasopressors
- Congestive heart failure, defined by either a pulmonary arterial occlusion pressure of > 18 mm Hg or by clinical examination
- Clinical history of decompensated left ventricular dysfunction as indicated by New York Heart Association class III or IV or left ventricular ejection fraction < 30%
- Documented myocardial infarction within the last 3 mo; or life threatening arrhythmia during the present hospital admission
- Glasgow Coma Score < 10 determined before the administration of confounding medications, such as narcotics, sedatives, or neuromuscular blockers
- Active air leak from the lung into the pleural space in the 24 h before randomization (chest tube to pleuravac with water seal without leak and not requiring suction for a minimum of 24 h was allowed)
- Evidence for increased intracranial pressure or history of an intracerebral hemorrhage within the past 3 mo
- Status asthmaticus or severe asthma currently under treatment with pharmacologic doses of intravenous corticosteroids
- Chronic lung disease requiring chronic oxygen therapy or presenting with a baseline FEV1 < 700 ml
- Spinal cord injury above T-1
- Myasthenia gravis or Guillain-Barré syndrome or other neurologic disorder that impairs the patient’s ability to breathe spontaneously
- Organ transplantation (i.e., bone marrow, heart, lung, liver, kidney, pancreas)
- Seizures refractory to anticonvulsant therapy
- Acute parenchymal lung injury secondary to suspected overdose of narcotics
- Burn injury (2° or 3°) with greater than 30% of total body surface area or with a restrictive chest injury
- Life expectancy of less than 3 mo for other than ALI/ARDS-associated complications
- Positive blood test for HIV with CD-4 count < 200
- Received chemotherapy within 30 d before enrollment
- Morbid obesity (> twice ideal body weight).
- Tracheostomy
- Vascular lung disease with alveolar hemorrhage or pulmonary hypertension (e.g., lupus, scleroderma, Wegener’s)
- Hypersensitivity to PFCs
- Positive serum β-human chorionic gonadotrophin indicating pregnancy (test was required for females who were not surgically sterile or who were not postmenopausal for at least 6 mo)
- Received any other experimental therapy within 30 d before screening (except nitric oxide, provided nitric oxide had been discontinued at least 4 h before initiation of standardized mechanical ventilation)

APPENDIX 3

Members of the Data Safety Monitoring Board
Kenneth Steinberg, M.D., University of Washington School of Medicine, Seattle, WA
Avi Nahum, M.D., Regents Hospital, St. Paul, MN
Jesus Villar, M.D., Hospital del la Candelaria, Canary Islands
David Schoenfeld, Ph.D., Boston Biostatics, Inc., Boston, MA