Prospective, Randomized, Controlled Pilot Study of Partial Liquid Ventilation in Adult Acute Respiratory Distress Syndrome

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We evaluated the safety and efficacy of partial liquid ventilation (PLV) with perfluorob in adult patients with acute lung injury and the acute respiratory distress syndrome (ARDS) in a multicenter, prospective, controlled, randomized exploratory clinical trial. Ninety adult patients with PaO2/FIO2 ratios > 60 and < 300 with ARDS for no more than 24 hours were randomized to receive PLV (n = 65) with administration of perfluorob through an endotracheal tube sideport or conventional mechanical ventilation (CMV, n = 25) for a maximum of five days. Although a significant reduction in progression to ARDS was noted among patients with PLV, no significant differences in the number of days free from the ventilator at 28 days (CMV = 6.7 ± 1.8, PLV = 6.3 ± 1.0 days, p = 0.85), the incidence of mortality (CMV = 36%, PLV = 42%, p = 0.63), or any pulmonary-related parameter were observed. During a post hoc subgroup analysis, significantly more rapid discontinuation of mechanical ventilation (p = 0.045) and a trend toward an increase in the number of days free from the ventilator at 28 days (CMV = 3.2 ± 1.9, PLV = 8.0 ± 2.2 days, p = 0.06) were observed during PLV among those patients under 55 years of age with acute lung injury or ARDS. Episodes of hypoxia, respiratory acidosis, and bradycardia occurred more frequently in the PLV group, but these were transient and self-limited. Further evaluation of PLV is warranted to further define beneficial effects in well-defined groups of patients and also to gain additional information regarding safety.

Keywords: fluorocarbon; liquid ventilation; acute respiratory distress syndrome

Liquid ventilation has been investigated as a means to enhance gas exchange and pulmonary function since the concept was described by Clark and Gollan in the 1960s (1). Although initially performed as total liquid ventilation, in which a device is used to liquid ventilate perfluorocarbon-filled lungs, more recent clinical activity has centered on application of partial liquid ventilation (PLV), in which perfluorocarbon-filled lungs are gas ventilated with a conventional gas mechanical ventilator (2–4). Phase I/II trials have been performed to assess the safety and efficacy of PLV in children, preterm newborns, and full-term newborns with respiratory failure (5–9). Similarly, the safety and efficacy of PLV have been evaluated in Phase I/II trials in adult patients with both acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) (10). In 1995, we initiated a pilot study to evaluate the safety and potential efficacy of PLV in adults with ARDS, to address design problems in anticipation of a definitive trial, and to estimate sample size requirements for the definitive trial. We present in this article the results of that pilot study.

METHODS

This was a prospective, nonblinded, randomized study performed at 18 centers between July 1995 and August 1996. Those patients with bilateral infiltrates on chest radiograph (>3 quadrants) for five days or less, who had undergone ventilation for five days or less, an FIO2 (fraction of inspired oxygen) > 0.5, a PaO2/FIO2 (P/F) ratio > 60 and < 200 dependent of positive end-expiratory pressure (EEP) level, and who were between the ages of 15 and 75 years were considered for entry into the study. The Murray Lung Injury Score (LIS) was assessed and, for the first 45 patients, was used as a stratification variable for patients with LIS < 2.5 or > 2.5 (11). It was deleted as a stratification variable for patients number 46–90 because there was no difference in outcome between those with LIS < 2.5 or > 2.5 among the first 45 patients. Exclusion criteria may be seen in Table 1 and, in general, were meant to focus the sample frame for this study to exclude those patients who were pregnant, who had a low chance of survival despite effective treatment of lung failure, who had a tidal volume < 4 ml/kg because of concern about hypoxia during PLV, and/or who had multiple organ system failure. After entry of 45 of the patients into the study, evaluation of the data suggested a trend toward improvement in outcome in those patients with an APACHE II (Acute Physiology and Chronic Health Evaluation II) score < 30. Therefore, the remainder of the study enrollment required that the APACHE II score be < 30. In addition, patients initially could be enrolled only with a P/F ratio of 60 to 300 determined at an FIO2 = 1.0. However, it was felt that this criterion was overly strict and not consistent with the American-European Consensus Conference definition (12). Therefore, after enrollment of the first 45 patients, the P/F criteria were subsequently determined at an FIO2 > 0.5, although categorization into ALI or ARDS was determined by the P/F assessed with FIO2 = 1.0. The P/F was assessed in this way to maintain consistency, and because P/F ratios determined at an FIO2 = 1.0 may provide a more uniform picture of severity of respiratory failure than would otherwise be obtained with P/F ratios determined at variable FIO2 (13). Therefore, we chose to use only those P/F ratios determined at an FIO2 > 1.0 for our analysis. Once inclusion and exclusion criteria had been fulfilled, the patient
and/or family were approached for potential enrollment. After granting of informed consent, a central office at Alliance Pharmaceutical (San Diego, CA) was contacted for group assignment based on the randomization scheme outlined below. This research was approved by the local Institutional Review Boards associated with each institution.

**Experimental Protocol**

Data were obtained at baseline; at initiation of PLV or conventional mechanical ventilation; at 4, 8, 12, and 24 hours; and daily through the seven-day experimental observation period. These data included demographic, physiologic, and ventilator information. Additional follow-up was performed for both groups on Days 14 and 28. Weight was determined as ideal body weight, using the Metropolitan life height and weight tables (14). The end-inspiratory pressure (EIP) was determined by application of an end-inspiratory pause for a length of time that was at the investigator’s discretion. A pregnancy test was performed at the time of screening for all females who were not surgically sterile or who had not been postmenopausal for at least six months.

Randomization was performed according to a three- or six-block design, was performed within center, and was weighted such that the ratio of partial liquid- to control gas-ventilated patients would be 2:1. The purpose of this weighting was to enhance the experience with PLV among contributing centers during the pilot phase. No masking as to treatment group was attempted. In the first 45 patients enrolled, the experimental period was four days for the conventional mechanical ventilation (CMV) group and a maximum of four days for the PLV group, followed by a 48-hour monitoring period in both. This period was extended for the final 45 patients enrolled to five days for the CMV group and a maximum of five days for the PLV group, with the post-treatment observation period extending through Day 7 for both.

Relaxation of a four-day limit to a five-day protocol was allowed by the Food and Drug Administration. It was hoped that additional benefits would be accorded to the patients with PLV by extending the allowed period of PLV.

### Partial Liquid Ventilation Treatment

Perflubron (LiquiVent; Alliance Pharmaceutical, San Diego, CA) was administered on the basis of ideal body weight in 5-ml/kg increments during the initial fill, with each aliquot administered over five to 15 minutes, with a five-minute waiting period between the first and second, third and fourth, and fifth and sixth doses. A 15- to 30-minute waiting period was included between the second and third and the fourth and fifth doses to allow distribution of the perflubron before progressing with the fill. Dosing was discontinued when one of the following end points was encountered: (1) a meniscus of perflubron was present at the EEP of zero during transient (< 30 seconds) ventilator disconnect; (2) 30 ml/kg had been administered; (3) changes in physiology, including a decrease in cardiac output > 33% of baseline, arterial oxygen saturation (SaO2) < 85%, venous oxygen saturation (SvO2) < 60%, PaO2 < 50 mm Hg, tidal volume < 80% of baseline, a 10-mm Hg decrease in mean arterial pressure, or a heart rate increase by ≥ 25 beats/min. Initial dosing was performed with the patient in the supine position with the FiO2 = 1.0. Endotracheal tubes used for this study were limited to Mallinckrodt (St. Louis, MO), Concord/Portex (Keene, NH), and Kendall-Sheridan (Granville, NY) tubes.

Each patient was assessed every four hours for the presence of a meniscus visible within the endotracheal tube during transient ventilator disconnect. If none was present, an additional 1- to 5-ml/kg aliquot of perflubron was administered with end points as during the initial fill used to indicate discontinuation of dosing.

The ventilation guidelines and the target gas exchange values for the CMV and PLV groups are demonstrated in the Appendix. Because of concerns about increased time constants during PLV, the maximum respiratory rate allowed during PLV was less than that during CMV. PLV was discontinued at the discretion of the investigator; there were no guidelines or rules regarding discontinuation of PLV. The mean duration of perflubron administration was 80 ± 3 hours with a range of 17 to 120 hours. Suctioning of airway debris with saline was performed every one to two hours during dosing.

### Conventional Mechanical Ventilation Treatment

After randomization to the CMV group, ventilation guidelines and target gas exchange values were followed and the target gas exchange values met as described in the Appendix. It should be noted, however, that there was no follow-up to ensure that investigators adhered to these guidelines.

### Outcome Measures

The primary end point of the study was the mean number of ventilator-free days (VFD) in each treatment group through Day 28 following initiation of treatment. On Day 28, each survivor received 1 point for every day following discontinuation of mechanical ventilation, in-
cluding the day of extubation, if the patient remained successfully weaned for the remainder of the day. Patients who died during the first 28 days of the study received a VFD score of zero. Patients who were reintubated had days counted toward a VFD only if they remained off the ventilator for the remainder of the 28-day period. For instance, if a patient was extubated for two days and then reintubated for the remainder of the 28 days, the VFD was zero. Only those days for which the patient was extubated and remained extubated for the remainder of the 28-day experimental period counted toward VFD. Weaning and extubation were standardized by the protocol described in the Appendix. Once perflubron dosing was discontinued, patients in the PLV group were continued on CMV and weaned and extubated according to the same protocol.

Secondary outcome measures included 28-day mortality, the calculated \( P_{A\text{CO}_2}/FIO_2 \) ratio, and the alveolar–arterial oxygen difference \( [(\lambda - a)D_{O_2}] \), which was calculated by the equation: \( \lambda \) - a)D_{O_2} = \( P_{A\text{CO}_2} - P_{A\text{CO}_2} \), where \( P_{A\text{CO}_2} = (FIO_2 \times 713) - (P_{A\text{CO}_2}/R) \) for the gas-ventilated lung and \( P_{A\text{CO}_2} = [(FIO_2 \times 713 - Fi_{perflubron})] - (P_{A\text{CO}_2}/R) \) for the perflubron-filled lung, \( R = 0.8 \), and Fi_{perflubron} is the partial pressure of perflubron at 37°C, which equals 11 mm Hg. Semistatic respiratory system compliance was calculated by the equation: \( Vt/(EIP \cdot PEEP) \), where \( Vt \) is the exhaled tidal volume corrected for tubing compliance on the basis of algorithms incorporated into the ventilator software, when such algorithms were available. Additional data gathered over the duration of the treatment period included ventilatory settings, the EIP, arterial and venous blood gas data, and the incidence of new air leak through Day 28 (12, 13, 15). Patients were placed into three categories at the time of enrollment, based on a P/F ratio at \( FIO_2 \) of 1.0: respiratory insufficiency \( (P/F > 300 \text{ mm Hg}) \), ALI \( (P/F = 200-300 \text{ mm Hg}) \), and ARDS \( (P/F < 200 \text{ mm Hg}) \). Patients in the respiratory insufficiency group were enrolled in the trial based on the \( P/F \) measured at \( FIO_2 > 0.5 \), which was in all cases < 300 mm Hg. The progression to ARDS for those subjects without ARDS at baseline was also assessed. Safety data were assessed by noting the nature, incidence, and severity of the adverse events as well as the relationship of the adverse event to the study drug. All adverse events were coded according to the COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) classification scheme (16).

### Data Analysis

Because this was a pilot study with a goal of determining sample size requirements for future studies, no formal \textit{a priori} power calculations were performed. In addition, because of the limited pilot nature of the trial, no monitoring committee was used. The size of the pilot study was initially 45 patients with a primary end point of oxygenation. However, regulatory requirements changed such that oxygenation was not considered an appropriate outcome measure and was altered to 28 ventilator-free days. In addition, after the initial 45 patients, investigators wished to develop more experience with PLV before embarking on a definitive trial. Therefore, an additional 43 patients were enrolled in the original cohort with an altered end point of 28-day ventilator-free days. Demographic and adverse event data were summarized with descriptive statistics and frequency tabulations. The two-sided Wilcoxon rank sum test was used to compare continuous data (VFD) because data were not normally distributed, whereas categorical data were evaluated by either the Fisher exact test or \( \chi^2 \) analysis. The Bonferroni correction for multiple comparisons was applied where indicated. Physiologic and ventilator data were not amenable to repeated measures analysis because variation in the day of termination of the experimental period or early death resulted in incomplete data. Survival analysis was applied to the rate of discontinuation of mechanical ventilation and comparison between groups were assessed by the log rank test. All data are presented as means ± SEM.

### RESULTS

Table 2 demonstrates the demographics for the patients who were enrolled in this study. No differences between treatment groups were observed with respect to age, weight, height, race, or any of the parameters demonstrated. The majority of the patients developed ARDS secondary to pneumonia or trauma. Patients with PLV were randomized an average of 25 hours later than the CMV group (\( p = 0.12 \)). The randomization scheme resulted in a PLV:CMV ratio of 2.6:1 rather than the 2:1 ratio desired, such that 65 patients were enrolled in the PLV group and 25 in the CMV group. This likely was a reflection of the limited patient enrollment at the majority of sites. Only four sites enrolled more than five patients, and those four sites overall enrolled 52 of the 90 patients (58%). Assessment of mortality as a function of the number of patients enrolled at a site was not possible because of the low number of patients treated at the majority of sites. The initial dose of perflubron administered to the PLV patients was 22.4 ± 0.8 ml/kg over 3.0 ± 0.3 hours, whereas the total dose was 104.4 ± 5.1 ml/kg administered over 79.6 ± 3.3 hours. The perflubron volume administered after the initial dose had a mean value of 1.1 ± 0.1 ml/kg/hour.

Table 3 demonstrates selected mean ventilating and physiologic parameters over the seven-day experimental period in the PLV and CMV groups. No clinically significant between-group differences were observed. The \( P_{A\text{CO}_2} \) in the PLV group was increased when compared with the CMV patients, although not to a statistically significant level. The etiology of this increase is not obvious from the data. Kaplan–Meier curves, demonstrating that the rate of discontinuation of mechanical ventilation and death in the PLV and CMV patients as a function of time was not significantly different between groups, are provided in Figure 1 (\( p = 0.98 \) by log rank test). No significant differences in ventilator-free days at 28 days were noted (VFD: CMV = 6.7 ± 1.8; PLV = 6.3 ± 1.0, \( p = 0.85 \)). Likewise, no significant differences in mortality were noted between groups (mortality: CMV = 36%; PLV = 42%, \( p = 0.63 \)). Progression to ARDS occurred for nine of the 23 (39%) patients with PLV who entered with ALI and nine of the 11 (82%) subjects with CMV who had ALI (\( p = 0.03 \) by Fisher exact test).

A disproportionate number of patients in the PLV group (\( n = 18, 25% \)) were more than 55 years of age when compared with the CMV group (2, 8%). Multiple analyses of patient series with ARDS have suggested that age greater than 50 to 65 years is associated with an increase in mortality (17–19). We elected, therefore, to perform a \textit{post hoc} analysis of the data at age 55 years and younger. Overall mortality was 26% in the PLV group and 30% in the CMV group (\( p = 0.67 \)) when all patients 55 years of age or younger were analyzed. The mean number of patients achieving 28 ventilator-free days was 8.3 ± 1.3 in the PLV group and 6.9 ± 2.0 in the CMV group (\( p =

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>PLV (( n = 65 ))</th>
<th>CMV (( n = 25 ))</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>44 ± 2</td>
<td>41 ± 3</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Apache II score</td>
<td>18.8 ± 0.8</td>
<td>19.2 ± 1.6</td>
<td>0.84</td>
</tr>
<tr>
<td>( P_{A\text{CO}_2}/FIO_2 ) &lt; 200</td>
<td>62%</td>
<td>56%</td>
<td>0.63</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td>( p ) Value</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>34%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>23%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Aspiration</td>
<td>17%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>14%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Murray LIS</td>
<td>3.0 ± 0.1</td>
<td>3.0 ± 0.1</td>
<td>0.96</td>
</tr>
<tr>
<td>Period of CMV before randomization, h</td>
<td>77 ± 11</td>
<td>52 ± 12</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CMV = conventional mechanical ventilation; LIS = lung injury score; PLV = partial liquid ventilation.
patients are revealed in Figure 3. A significant increase in the rate of discontinuation of mechanical ventilation was observed in the PLV group when compared with the CMV group (p = 0.045 by log rank test). A reduction in the 28-day mortality from 42% in the CMV group to 25% in the PLV group, among those 55 years of age or younger with ARDS (P/F ratio < 200, p = 0.24), was also noted. In the same group, ventilator-free days were 3.2 ± 1.9 in the CMV group and 8.0 ± 2.2 in the PLV group (p = 0.06, significant p < 0.01 with Bonferroni correction).

Table 4 demonstrates adverse events observed in the CMV and PLV groups by severity. Overall, adverse events were reported for 96% of the patients with CMV and 99% of the patients with PLV. Hypoxia, respiratory acidosis, and bradycardia occurred more frequently in the PLV group when compared with the CMV group, although the difference in incidence of these events was not significant. These were self-limiting, transient events, the duration of which was not measured, and the events appeared to occur at times of dosing, usually requiring minimal intervention. The majority of these adverse events were rated as nonserious by the investigators. Cardiac arrest occurred during the experimental period in 15 of 65 patients (23%) in the PLV group and in four of 25 patients (16%) in the CMV group. None of the incidents of cardiac arrest were attributed to treatment in the CMV group, although it was attributed to treatment in the PLV group. Two of these four cardiac events occurred one and nine days after the last dose of perflubron, whereas the third was associated with a ventilator error. The fourth patient had a serious and unexpected adverse event that was considered possibly related to administration of perflubron. An episode of bradycardia and ventricular fibrillation occurred during the supplemental dosing period on the second day of treatment with PLV. None of these cardiac arrests resulted in deaths in proximity to the event. Pneumothorax was observed in 22 of 65 patients in the PLV group (34%) compared with five of 25 patients in the CMV group (20%, p = 0.30 by Fisher exact test). However, despite criteria that excluded enrollment of such patients, six patients in the PLV group were enrolled with active air leaks. When these subjects were deleted from the analysis, pneumothorax was observed in 20% of the patients with CMV and in 23% of the patients with PLV (p = 0.78 by Fisher exact test).

Hematologic, electrolyte, liver function, and renal function laboratory values demonstrated no difference between PLV and CMV groups (see Table 5). Two of nine CMV patients (22%) and four of 29 patients with PLV (14%) succumbed, primarily due to respiratory failure. No death was attributed to administration of perflubron or performance of PLV.

**DISCUSSION**

The significant findings in this study include the following: (1) PLV may be performed with concern for cardiac and respiratory adverse effects that appear to be self-limiting and man-
 ĐoABLE in adult patients with ALI and ARDS; (2) although a significant reduction in progression to ARDS was noted among patients with PLV, no difference in gas exchange, pulmonary function, VFD, or outcome was observed when the control patient group was compared with those undergoing PLV; and (3) a significantly more rapid discontinuation of mechanical ventilation and a trend toward an increase in the 28-day VFD was observed in the PLV patients when compared with the gas-ventilated patients when subgroup analysis was directed at those patients enrolled with ARDS/ALI who were 55 years of age or less.

As mentioned previously, PLV has been evaluated as a means for enhancing gas exchange and pulmonary function among children and newborns with respiratory failure (5–9). The evaluation of the safety and efficacy of PLV in the adult population was initiated in a large, adult-sized, canine oleic acid lung injury ARDS model, which demonstrated improvement in gas exchange during PLV (20, 21). We subsequently demonstrated a decrease in physiologic shunt from a median of 0.72 to 0.46 (p < 0.01) and an increase in static pulmonary compliance from 0.16 to 0.27 ml/cm H2O/kg (p < 0.04) over the first 72 hours of PLV among 10 patients with severe respiratory failure requiring extracorporeal life support (22). Five of these 10 patients survived. No effects on hemodynamics and no consistent adverse events were observed.

In early 1995, a nonrandomized, noncontrolled, Phase I/II multicenter trial involving four institutions evaluating the safety and efficacy of PLV in adult patients was completed (10). A reduction in mean (A–a)DÌ2O from 430 ± 47 to 229 ± 17 (p = 0.013) was observed over the first 48 hours after initiating PLV. No improvement in pulmonary compliance was observed. Adverse effects possibly related to performance of PLV included hypoxia, decrease in cardiac output, hypotension, hyperbilirubinemia, pneumothorax, dyspnea, respiratory acidosis, and rash, whereas “severe” complications, or those that were determined to be life threatening, included only hypoxia (n = 2) and hyperbilirubinemia (n = 1). Seven of the nine patients survived the 28-day outcome measure, whereas two patients subsequently succumbed before discharge.

On the basis of these data we initiated a Phase II, prospective, randomized, controlled, pilot study. The results of that study are reported in this article. Although a decrease in the incidence of progression from respiratory insufficiency and ALI to ARDS was observed in the CMV group when compared with the CMV group, no significant differences in the number of ventilator-free days, the incidence of mortality, or any other parameter of gas exchange, pulmonary function, or ventilation was observed. When we specifically performed a post hoc subgroup analysis of those patients younger than 55 years of age with ALI or ARDS we observed a trend toward a reduction in 28-day ventilator-free days and a nonsignificant reduction in mortality. Intuitively, one would expect that PLV would be most effective in the more severely affected ARDS patients who were young and, therefore, less likely to succumb to nonrespiratory organ system failure. However, stratification for age and the presence of ALI or ARDS was not part of the study design and, therefore, this subgroup analysis can only suggest that a decrease in mortality and VFD may be associated with use of PLV in this younger, more severely affected subgroup.

Previous laboratory studies have suggested that gas exchange during PLV might be increased because of recruitment of atelectatic lung regions as well as redistribution of pulmonary blood flow and reduction in total lung water (23–26). Increase in oxygenation, but not compliance, has been observed during PLV in uncontrolled clinical trials involving adult patients with ARDS (10). In the current study, no between-group differences in the P/F ratio were noted. With this lack of difference between the two groups in any parameter of gas exchange, ventilation, or pulmonary function, it would be important to speculate about other means by which improvement in survival and ventilator-free days might be observed among those patients with ALI or ARDS who were managed by PLV. A number of laboratory studies have suggested that FRC is recruited in the setting of oleic acid lung injury during PLV and that plerufbron tends to distribute predominantly to the dependent lung regions, which are those areas most affected in the clinical setting of ARDS (23, 24). As a result, atelectatic lung regions may be re-inflated, which could provide a protective effect in the setting of lung injury. In addition, other studies have suggested that neutrophil infiltration, intra-alveolar hemorrhage, and total lung water may be decreased during PLV in lung injury models (25, 27–29). Additional studies have suggested that alveolar macrophage function and systemic cytokine levels may be reduced during PLV.

TABLE 4. ADVERSE EVENTS OBSERVED IN THE PARTIAL LIQUID VENTILATION AND CONVENTIONAL MECHANICAL VENTILATION GROUPS

<table>
<thead>
<tr>
<th>Event</th>
<th>CMV (%)</th>
<th>PLV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td>44</td>
<td>57</td>
</tr>
<tr>
<td>Hypotension</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>New pneumothorax</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Renal failure</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** AST = aspartate aminotransferase; Hb = hemoglobin; WBC = white blood cell count.
when compared with gas ventilation (30, 31). The exact mechanisms behind such findings are unclear, although an anti-inflammatory effect of perflubron has been postulated. All in all, there is evidence to suggest that other non–gas exchange-related protective lung effects could play a role in enhancing outcome among patients with respiratory failure.

Among adverse events that were increased in incidence, although not significantly, in the PLV group when compared with the control group were hypoxia, bradycardia, and respiratory acidosis. The majority of these adverse events appeared to occur during periods of dosing. As dosing progresses, tidal volume may be compromised, especially as FRC is approached or exceeded during the pressure-controlled ventilation mode used to ventilate the majority of the patients in this study (10). Our anecdotal clinical experience has suggested that as long as tidal volume is maintained, compromise of oxygenation and carbon dioxide elimination is not usually observed. However, if tidal volume is allowed to decrease by more than 10% to 20%, hypoxia and respiratory acidosis, along with associated mild bradycardia, may ensue. As was noted by the investigators in this study, such adverse events are usually transient and rarely serious in nature, although one episode of cardiac arrest was temporally related to administration of perfluorocarbon. The other three episodes of cardiac arrest in the PLV group, which were considered possibly related to performance of PLV, were either not temporally related to the PLV period or, in one case, was explained by ventilator technical error. As with other preclinical and clinical studies, no increased difficulties associated with the presence of residual perfluorocarbon in the lungs were noted (10, 22, 32, 33). Overall, adverse events were increased in the PLV group when compared with the CMV group in seven of eight categories examined. There is a tendency among nonblinded observers to document more adverse events in an experimental group when compared with a control group. Further and larger studies will be required to evaluate the safety of this technique.

Preliminary results from the National Institutes of Health (NIH, Bethesda, MD) ARDS Network suggest decreased mortality and organ failure–free days with application of a 6-ml/kg instead of a 12-ml/kg ventilator volume strategy (34). In the current study, $V_t$ ranged from 4.1 to 16.1 ml/kg (mean = 8.4 – 9.8 ml/kg across all time points) in patients with CMV and from 3.1 to 17.9 ml/kg of predicted body weight (mean = 9.1 – 10.9 ml/kg across all time points) in patients with PLV. No attempt to control tidal volume or EIP was made in this study except for providing the guideline that EIP should be maintained at less than 45 cm H2O. No between-group differences in EIP or $V_t$ were noted. However, a lower volume ventilator approach may have had an effect on the outcome measure data in this study. Future studies will likely incorporate such low-volume ventilator strategies into the trial design.

There are many questions left unanswered with regard to the technique of PLV, including those of optimal dosing, positioning, and ventilator management. A randomized, multicenter study, just being completed, explores dosing strategies during PLV and compares the safety and efficacy of PLV and CMV in patients younger than 65 years of age with ARDS. Other studies will, in addition, evaluate leukocyte function and cytokine expression in serum and bronchoalveolar lavage specimens to identify the presence of a protective pulmonary effect during PLV in the clinical setting.

In conclusion, PLV may be performed reasonably safely in adult patients with respiratory failure with few adverse affects, which appear to be transient, self-limited and, with appropriate vigilance, manageable. Although there was a significant reduction in the trend toward development of ARDS in the PLV group, overall no significant difference in ventilator-free days, mortality, or any other parameter of oxygenation or ventilation was observed. However, a post hoc analysis suggests that PLV may be beneficial in patients younger than 55 years of age with ALI or ARDS. Further studies are needed to confirm these findings and to demonstrate the safety and efficacy of PLV.

References

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APPENDIX: VENTILATOR MANAGEMENT GUIDELINES ESTABLISHED FOR PARTIAL LIQUID VENTILATION AND CONVENTIONAL MECHANICAL VENTILATION GROUPS

Ventilation guidelines established for CMV and PLV:
- SaO2 > 90%
- PaCO2 < 50 mm Hg
- EIP < 45 cm H2O
- RR < 25 (CMV)
- RR < 20 (PLV)

Ventilator weaning/extubation by the following protocol:

1. An attempt to wean and extubate a patient will be performed once the following criteria are identified:
   a. FiO2 < 0.4.
   b. Not receiving neuromuscular blocking agents.
   c. Patient exhibiting inspiratory efforts. Ventilator rate will be decreased to 50% of baseline level for up to five minutes to detect inspiratory efforts if no efforts are evident at baseline ventilator rate.
   d. Systolic arterial pressure > 90 mm Hg without vasopressor support.

If criteria a through d are met, weaning potential will be assessed during a CPAP trial of five minutes at CPAP 5 cm H2O and FiO2 = 0.5. If respiratory rate remains < 35 breaths/min during the five-minute CPAP trial, the patient will have met the commencement of weaning criteria and will enter the pressure support wean procedure (Section 2). If failure to maintain the respiratory rate < 35 breaths/min during the CPAP trial is attributed primarily to anxiety, then appropriate treatment for anxiety will be given and a second five-minute CPAP trial initiated.

2. Initial pressure support (PS) setting (for subjects whose respiratory rates remain < 35/min during the five-minute CPAP trial):
   a. If respiratory rate < 25 breaths/min during the five-minute CPAP trial, then initiate PS = 5 cm H2O. If respiratory rate = 26-35 breaths/min during the five-minute CPAP trial, then set initial PS = 20 cm H2O and make adjustments in PS within five minutes if necessary to achieve respiratory rate between 26 and 35 breaths/min.
   b. PEEP = 5 cm H2O.
   c. FiO2 = 0.5.

3. Assessment for tolerance: Patients will be assessed for tolerance according to the following criteria:
   a. Total respiratory rate < 35 breath/min.
   b. SpO2 > 88%.
   c. Evidence of respiratory distress (two or more of the following):
      i. Heart rate greater than 120% of the 6:00 AM rate.
      ii. Marked use of accessory muscles.
      iii. Abdominal paradox.
      iv. Diaphoresis.
      v. Marked subjective dyspnea.

4. Subsequent ventilator settings:
   a. Reduce PS level by 5 cm H2O every hour until PS = 5 cm H2O.
   b. If PS level = 5 cm H2O is not tolerated or if PS level cannot be weaned to 5 cm H2O, return to ventilator.
   c. If PS = 5 cm H2O is tolerated for two or more hours, assess for ability to sustain unassisted breathing.

5. Assess for ability to sustain unassisted breathing: Initiate a trial of spontaneous breathing on CPAP < 5 cm H2O, T-piece, or tracheostomy mask with FiO2 < 0.5. Monitor for the following:
   a. SpO2 < 90% and/or PaO2 < 60 mm Hg.
   b. Spontaneous tidal volume < 4 ml/kg ideal body weight.
   c. Respiratory rate < 35 breaths/min.
   d. pH < 7.30 if measured.

If criteria a through d are met for > 120 minutes continue with unassisted breathing. If any of criteria a through d are not met during the 120-minute trial, then resume mechanical ventilation.

6. Definition of unassisted breathing:
   a. Extubated with face mask, nasal prong oxygen, or room air, or
   b. Tracheostomy mask breathing.