Partial liquid ventilation protects lung during resuscitation from shock

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acutel lung injury; reperfusion injury; hemorrhagic shock; perfluorocarbon

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Partial liquid ventilation (PLV) is a method of respiratory support in which conventional mechanical ventilation is performed in lungs that are partially filled with an oxygen-carrying perfluorochemical. Although the initial clinical experience with this therapy has been in patients with established acute respiratory distress syndrome (ARDS; 6), there is laboratory evidence that, in addition to its mechanical and oxygenating effects, PLV may convey protection to lungs exposed to acute injury. Observations after intravenous (iv) oleic acid exposure in sheep (7) and intravascular complete activation with cobra venom factor in rats (4) have demonstrated not only improved pulmonary compliance and enhanced gas exchange but also preserved histological morphology of the lung.

Hemorrhagic shock is a frequently encountered clinical entity that, when seen in combination with multiple blood transfusions, thoracic blunt trauma, aspiration of gastric contents, or long bone fractures, is second only to sepsis in likelihood of progression to ARDS (8). The mechanisms by which hemorrhagic shock induces acute lung injury remain to be fully elucidated, but they likely involve the rapid generation of inflammatory and chemotactic mediators by ischemic tissue. Pulmonary ultrastructural abnormalities are seen within 20 min of the onset of hemorrhage and include intravascular platelet plugging, leukocyte trapping, and disruption of endothelial and alveolar epithelial cell membranes (5, 10). Neutrophils, sequestered in the pulmonary capillaries either by rheologic mechanisms or through the expression of intercellular adhesion molecules, are likely to play a pivotal role in the development of posttraumatic ARDS (8, 14).

On the basis of these observations, we questioned whether PLV might offer benefits to the lungs in the setting of global ischemia and reperfusion after resuscitation from shock.

To examine the effects of PLV on hemorrhagic shock-induced acute lung injury, we specifically considered 1) whole lung myeloperoxidase (MPO) activity as a measure of neutrophil recruitment into the lung after hemorrhage and resuscitation and 2) leak of \(^{125}\text{I}-\text{labeled albumin}\) into the alveolar space as a marker of pulmonary capillary endothelial and alveolar epithelial injury.

METHODS

Male specific-pathogen-free Sprague-Dawley rats (Harlan Industries, Indianapolis, IN) were used in two sets of experiments. The first set studied the impact of PLV on pulmonary neutrophil content after shock, and the second set considered pulmonary permeability in the same model. These experimental protocols conformed to federal standards of animal use and care and were approved by our institutional animal use committee.

Animal preparation. All animals received ketamine hydrochloride (50 mg/kg sc) and xylazine hydrochloride (10 mg/kg sc) at the beginning of the experiment. A supplemental dose of each was administered 85 min into the protocol. Because of the inherent limitations of heart rate and blood pressure as indicators of depth of anesthesia in models employing hemodynamic instability, neuromuscular blocking agents were not administered. Animals did not receive systemic heparin.

With sedated animals secured in the supine position, a tracheostomy was performed, and both carotid arteries and the left jugular vein were cannulated with polyethylene tubing (PE-50; Clay-Adams, Parsippany, NJ). Arterial blood pressure was continuously monitored (model 78901A; Hewlett-Packard, Andover, MD). Core temperature was measured with a rectal thermometer and was maintained between 35 and 37°C with the use of a heating lamp.

Mechanical ventilation. All animals were ventilated with the use of a rodent ventilator (model 683; Harvard Apparatus, South Natick, MA). Settings included an inspired O\(_2\) fraction of 1.0, tidal volume of 4.5 ml, a rate of 70 breaths/min, and 2 cmH\(_2\)O (0.2 kPa) positive end-expiratory pressure (PEEP). Peak inspiratory pressures (PIP) and PEEP were measured continuously by using an airway pressure monitor (model 400; Sechrist, Anaheim, CA) attached to a side port on the endotracheal tube.

Study groups. Animals were assigned to one of three study groups: control, injury, and PLV. Control animals (n = 20)
were anesthetized, instrumented, and mechanically ventilated, but they were neither hemorrhaged nor resuscitated. Injured animals (n = 20) underwent the hemorrhage and resuscitation protocol described below. PLV animals (n = 20) were treated as injured animals and also received endotracheal perflubron (LiquiVent; supplied by Alliance Pharmaceuticals, San Diego, CA, and Hoechst-Marion-Roussel, Bridgewater, NJ) as part of their resuscitation. Of the animals in each group, 50% were studied for neutrophil content, and the remainder were studied for capillary leak.

Hemorrhage. Rats in the injured and PLV groups were bled from the left carotid artery by using a syringe pump (model 55–4143, Harvard Apparatus) programmed to withdraw 1.5 ml·kg\(^{-1}\)·min\(^{-1}\) of blood into a syringe with citrate-dextrose-phosphate anticoagulant. Blood was removed until a mean arterial blood pressure (MAP) of 25 mmHg was reached. Thereafter, additional blood was removed whenever the arterial pressure exceeded 30 mmHg. Hypotension in this manner was sustained for 45 min. At the conclusion of the hemorrhage phase of the study, total blood loss was recorded.

Resuscitation. Resuscitation consisted of the infusion of shed blood from a 20-min period, followed by 30 ml·kg\(^{-1}\) of normal saline infused over an additional 20 min. All infusions were given through the left internal jugular vein. After resuscitation, each animal was observed for 50 min. Thus the duration of the entire protocol was 135 min.

PLV. At the onset of resuscitation, animals in the PLV group received 5 ml·kg\(^{-1}\) of perflubron via the endotracheal tube during 2 min. At the conclusion of resuscitation, an additional 5 ml·kg\(^{-1}\) was administered to replace evaporative losses.

Measurement of hemodynamics, airway pressure, and blood gas. MAP and PIP were recorded every 5 min. Arterial blood-gas determinations were made at baseline and at 45, 85, and 135 min into the experiment (posthemorrhage, postresuscitation, and postobservation, respectively) with an instrument that performed self-calibrations every 2 h and received a formal multipoint calibration daily. (Gem Premier; Mallinkrodt Sensor Systems, St. Louis, MO). To minimize artifactual blood loss, the volume of blood for blood-gas analysis was kept to 250 µl. Serum bicarbonate concentrations were calculated by using the Henderson-Hasselbach equation. Hematocrit was determined by using the conductivity method. Rather than formal endpoints, hemodynamic and blood-gas data were used to confirm comparability of injury between the injured and PLV-treated animals.

Pulmonary neutrophil content. At the conclusion of the experiment, animals being studied for neutrophil content were killed by rapid exsanguination through the abdominal aorta. The thorax was then opened, and the superior and inferior vena cavae were ligated. After disruption of the left atrial appendage, 10 ml of saline were gently infused into the right ventricle at a pressure never exceeding 20 mmHg, as measured by an in-line manometer, effectively flushing the entire pulmonary intravascular volume. The heart and lungs were removed en bloc, and the left and right lungs were carefully dissected free of mediastinal structures. Particular attention was paid to removal of hilar lymph nodes. The surface of each lung then was washed with an additional 5 ml of saline. After this preparation, all specimens were frozen at −20°C until analysis was performed.

Quantitation of pulmonary neutrophils was done by using an o-dianisidine dihydrochloride assay for whole lung MPO activity (2). Both lungs were homogenized in 100 mM KH\(_2\)PO\(_4\) buffer containing hexadecyltrimethylammonium bromide and EDTA. After centrifugation at 2,300 g for 30 min at 4°C, supernatants were placed in a cuvette with an o-dianisidine dihydrochloride and hydrogen peroxide-containing reagent. With the use of an automated spectrophotometer (DU650; Beckman Instruments, Irvine, CA), sample absorbance at 460 nm was measured every 2 s for 1 min, and a reaction rate was determined by linear regression.

Pulmonary capillary permeability. In a separate set of experiments, \(^{125}\)I-labeled bovine serum albumin (\(^{125}\)I-BSA) was used to measure pulmonary capillary leak. Labeling quality was measured at least weekly by using instantaneous thin layer chromatography (Biodex Medical, Shirley, NY). Aliquots with >10% free iodine were purified in a gel column before use. Label was diluted in normal saline (700,000–900,000 counts·min\(^{-1}\)·ml\(^{-1}\)) and given iv 30 min before the end of the experiment. At the conclusion of the experiment, a reference arterial blood sample was collected, and animals were killed as in the MPO studies. In situ whole lung bronchoalveolar lavage (BAL) was carried out with an 18-gauge iv catheter inserted into the trachea ~2 cm above the carina. Ten milliliters of warm saline were instilled gently into the lungs. This fluid was withdrawn and reinfused twice more; on the final withdrawal, animals were tilted head down to maximize lavage yield. After lavage, the volume of fluid remaining was measured in a graduated cylinder. In specimens from animals receiving PLV, lavage specimens were centrifuged at 2,300 g for 5 min at 20°C, and the aqueous and perfluorocarbon portions were separated for volume and radioactivity determination. All samples were analyzed for 1 min with a gamma counter (Gamma 5500; Beckman). From the blood and BAL fluid activity, an alveolar permeability index was calculated as follows

\[
\text{Permeability} = \frac{(\text{BAL counts} - \text{background}) + (\text{perflubron counts} - \text{background})}{\text{counts in 1 ml blood} - \text{background}}
\]

where the perflubron term was included in the PLV animals.

Statistical methods. Results were expressed as means ± SD, except for the MPO and \(^{125}\)I-BSA permeability results, which were expressed as means and 25th and 75th percentile (interquartile range). The MPO and \(^{125}\)I-BSA studies were considered the principal outcomes. These results were examined with analysis of variance followed by Tukey post hoc comparisons of the injured and PLV-treated animals. Blood was drawn for blood-gas measurements and reported for four time points but was formally analyzed only twice: as a comparison among all three groups at baseline, and as a comparison of injury severity between injured and PLV animals immediately before resuscitation from hemorrhage. Because of the extensive repeated-measures structure of the peak airway pressure and blood pressure data, statistical analysis of these data was restricted to a t-test comparing MAP between the injured and PLV animals at their nadir blood pressure (i.e., immediately before the onset of resuscitation). Sample size was determined from similar previous work with this model in our laboratory. All statistical procedures were performed by using the univariate and general linear model techniques provided in SAS 6.11 (SAS Institute, Cary, North Carolina).

RESULTS

Sixty animals were studied, with ten control, ten injured, and ten PLV animals in the neutrophil content and in the alveolar permeability protocols of the project. As shown in Table 1, the only statistically significant differences among experimental groups at baseline were arterial pH and the serum bicarbonate concentra-
tion calculated from this result. The magnitude of these differences was not seen as physiologically relevant.

Hemodynamic, airway pressure, and metabolic changes. In the injured and PLV animals, hypotension was quickly and consistently achieved within 20 min of the onset of hemorrhage (Fig. 1). Although the nadir (preresuscitation) arterial pressures in the injured group were slightly lower than in the PLV group (25.3 ± 4.8 vs. 30.0 ± 8.9 mmHg; P < 0.05), the magnitude of the difference was not seen as physiologically important, and similar trends were not seen in the metabolic measures of injury severity detailed below. The initiation of PLV was well tolerated hemodyamically. The blood pressure response to reinfusion of shed blood was similar in the injured and PLV animals.

A change in PIP was not a significant feature of our model. During periods of severe hypotension, animals would occasionally attempt to initiate spontaneous breaths against the ventilator, which is reflected in the increased airway pressure variance seen in the 20-min through 45-min time points. During resuscitation, the peak airway pressures in the liquid-ventilated group in general were higher than in the gas-ventilated injured animals, a likely result of the larger end-expiratory lung volume achieved in the partially fluid-filled lungs.

Additional markers of injury severity are shown Fig. 2. The severity of hemorrhagic insult, reflected in the 45-min time point measurements, was similar between the injured and PLV animals, as shown by preresuscitation hematocrit (injury = 30.2 ± 4.9%, PLV = 28.0 ± 2.2%, P = 0.09), serum bicarbonate concentration (injury = 10.6 ± 3.8 meq/dl, PLV = 11.5 ± 2.8 meq/dl, P = 0.40), and total hemorrhage volume (injury = 27.2 ± 2.9 ml/kg, PLV = 28.4 ± 5.0 ml/kg, P = 0.38). The only dissimilarity between the injured and PLV group was an expected decrease in arterial O2 tension (PaO2) seen in the PLV animals after resuscitation with perfluorobron (final PaO2: injury = 485 ± 155 Torr, PLV = 282 ± 123 Torr, P < 0.01).

In summary, the hemodynamic, airway pressure, and metabolic data demonstrate a comparable degree of systemic injury between the gas-ventilated and PLV animals.

Pulmonary neutrophil content. Whole lung MPO results are shown in Table 2. Resuscitation from hemorrhagic shock produced a large increase in MPO enzymatic activity seen in lung homogenates. Animals treated with perfluorobron as part of their resuscitation were protected from this phenomenon. To confirm that perfluorobron did not interfere with the MPO assay, perfluorobron was added to MPO-containing solutions.

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Table 1. Baseline characteristics of study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Injury</th>
<th>PLV</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, g</td>
<td>440 ± 45</td>
<td>440 ± 46</td>
<td>435 ± 43</td>
<td>0.91</td>
</tr>
<tr>
<td>pH</td>
<td>7.47 ± 0.04</td>
<td>7.45 ± 0.05</td>
<td>7.42 ± 0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>P O2, Torr</td>
<td>513 ± 140</td>
<td>522 ± 136</td>
<td>504 ± 126</td>
<td>0.92</td>
</tr>
<tr>
<td>HCO3, meq/dl</td>
<td>25.6 ± 3.1</td>
<td>24.1 ± 2.5</td>
<td>23.4 ± 2.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>41 ± 3</td>
<td>41 ± 4</td>
<td>41 ± 3</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 20 rats in each group (control, injury, and partial liquid ventilation (PLV)). P value is based on F-test for overall analysis of variance.

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Fig. 1. Peak inspiratory pressure (PIP) and mean arterial pressure responses in 3 groups: controls (●), injury (●), and partial liquid ventilation (●); n = 20 rats in each group. Values are means ± SD except for controls (means only).

Fig. 2. Hematocrit, arterial oxygen tension (PaO2), and calculated serum bicarbonate concentration (HCO3) in 3 groups: controls (●), injury (●), and partial liquid ventilation (●); n = 20 rats in each group. Values are means ± SD except for controls (means only).
After they were mixed, the samples were centrifuged to separate the perfluorocarbon and aqueous phases, and the MPO activity of the aqueous supernatant was found to be unchanged.

### Pulmonary permeability

Permeability index results are also shown in Table 2. Because of the nonnormal distribution of the permeability scores, statistical analysis of these values was performed on their base-10 logarithm transformations. Permeability after hemorrhagic shock increased roughly threefold. Although there was a trend toward lowered permeability in the PLV animals, the difference was not statistically significant (permeability indexes: injury = 0.094, PLV = 0.045; 95% confidence interval [CI] for injury – PLV: −0.024, 0.121)]. We found that, in both injury and PLV animals, the volume of recoverable BAL fluid was decreased compared with sham gas-ventilated animals (P < 0.01). Similarly, there was a trend toward decreased recovered BAL volumes in the PLV animals compared with the injury animals (injury = 6.2 ± 0.9 ml, PLV = 5.4 ± 1.1 ml; 95% CI for injury – PLV: −0.26, 1.86). The impact of observed differences in recovered BAL volume on our permeability results was explored by correcting the permeability index for the volume of BAL returned. Assuming that the BAL fluid was in equilibrium with the alveolar lining fluid after three cycles of instillation and withdrawal, we divided the permeability index by the fraction of BAL fluid recovered and reported it as the corrected index. This correction did not alter our conclusions regarding capillary leak (Table 2).

Tracer was found in the perfluorobron portion of the lavage specimen. This was felt to be due to contamination of the perfluorobron phase by label-containing airway secretions after centrifugation. We did not find that, even after vigorous centrifugation, the interface between the aqueous and perfluorocarbon phases of BAL fluid contained a thin layer of presumably emulsified perfluorobron. We are not aware of data demonstrating any significant protein solubility in perfluorobron.

### Discussion

We found that, in animals subjected to profound hemorrhagic shock and resuscitation, PLV with perfluorobron resulted in large reductions in whole lung MPO activity and a trend toward improvement in the bronchoalveolar content of extravasated 125I-albumin. These findings support previous evidence of an antiinflammatory effect of PLV. Additionally, we found that severely hypotensive and hypovolemic animals tolerated the administration of 5 ml/kg of intrapulmonary perfluorobron without suffering the hemodynamic compromise seen after larger doses of liquid. Mild impairment of gas exchange (as reflected by lower PaO2) was seen in animals treated with perfluorobron. Although PLV appears to improve gas exchange in animals with extensive parenchymal lung injury, in models such as ours with near-normal oxygenation, PLV has been associated with mild impairment in oxygenation (11).

There is an increasing body of evidence supporting a suppressive effect of PLV on neutrophils, extending across both species and method of injury (3, 4, 7). The mechanism by which PLV inhibits neutrophil accumulation in the lung after injury remains unknown. It has been suggested that liquid ventilation may act as “liquid PEEP,” improving gas exchange and compliance by splinting open collapsed alveoli. Colton and associates (4) found that PLV with zero end-expiratory pressure provided protective effects similar to those of PEEP alone.

Alternatively, perfluorobron may in some way directly interfere with neutrophil-endothelial interactions within the lung, preventing neutrophil accumulation during acute injury. Similar degrees of protection have been found at doses of perfluorobron of 35 ml/kg [Hirschl et al. (7)], 10 ml/kg [Colton et al. (4)], 5 ml/kg (the present study), and 1 ml/kg [Bradley et al. (3)]. Bradley and associates (3) have shown a trend toward decreased pulmonary MPO activity after iv cobra venom administration in rats exposed only to perfluorobron vapor. Babitt et al. (1) have shown that perfluorocarbon emulsions decrease neutrophil-mediated endothelial injury. In vitro experiments with the human pulmonary epithelial line A549 have demonstrated a clear interference in neutrophil adhesion in the presence of perfluorobron, suggesting that perfluorocarbons may establish a physical barrier preventing neutrophil invasion (12).

In the present study, unlike prior studies examining PLV therapy, we were unable to show a decrease in lung permeability during PLV. Colton and associates (4) demonstrated a significant decrease in pulmonary capillary permeability after systemic complement activation and lung injury induced by cobra venom factor. Their methodology consisted of single-tracer (125I-BSA) whole lung activity standardized to a whole blood reference. To specifically detect alveolar disruption, we examined only intra-alveolar and airway activity and found only a trend toward improvement. We do not yet know how perfluorobron affects the sampling of intra-alveolar contents with BAL. Perfluorobron has a density of 1.92 g/cm³ and is immiscible in nearly all aqueous

### Table 2. Lung injury measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Injury</th>
<th>PLV</th>
<th>p Value</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil accumulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloperoxidase activity (µ)</td>
<td>0.347</td>
<td>0.087</td>
<td>0.256</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>IQR</td>
<td>0.222, 0.498</td>
<td>0.418, 1.003</td>
<td>0.166, 0.374</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capillary permeability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permeability index (µ)</td>
<td>0.031</td>
<td>0.094</td>
<td>0.045</td>
<td>0.09†</td>
<td></td>
</tr>
<tr>
<td>IQR</td>
<td>0.017, 0.033</td>
<td>0.034, 0.118</td>
<td>0.013, 0.049</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAL fluid recovered, ml</td>
<td>7.3±0.9</td>
<td>6.2±0.9</td>
<td>5.4±1.1</td>
<td>&lt;0.01†</td>
<td></td>
</tr>
<tr>
<td>Corrected index (µ)</td>
<td>0.042</td>
<td>0.160</td>
<td>0.095</td>
<td>0.15†</td>
<td></td>
</tr>
<tr>
<td>IQR</td>
<td>0.022, 0.061</td>
<td>0.049, 0.190</td>
<td>0.026, 0.101</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In each group, n = 10. Values of bronchoalveolar lavage (BAL) fluid are means ± SD. IQR, interquartile range. P values by F-test for overall analysis of variance. †P < 0.01 for injury vs. PLV groups; ‡P is not significant for injury vs. PLV groups.
environments (14). When this liquid is instilled into the lungs of patients with ARDS, a visibly large volume of secretions is displaced into the larger airways (6). By increasing the protein yield of BAL in the present study, a similar effect may have caused an overestimation of alveolar leak in the PLV group and an underestimation of any beneficial effect. Alternatively, intra-alveolar perflurbron might serve to block the capture of alveolar lining fluid by aqueous lavage. In this instance, the trend toward improved permeability obtained in the present study may be overly optimistic.

We were encouraged by the hemodynamic and airway pressure responses of animals given PLV. Despite having critically low blood pressures and acid-base disturbances, animals tolerated the filling dose given at the onset of resuscitation. Although inferences regarding the hemodynamic response of larger animals or humans should be made very cautiously, the blood pressure data in our animals suggest that low-dose perfluorocarbon instillation into the airway of hypoplastic individuals might well be possible. Hemodynamic studies in larger animals are needed to further confirm these preliminary findings.

An important limitation of the current work is its very acute nature. To produce an appropriately severe lung injury through global ischemia and reperfusion, long-term survival of the animals was all but precluded. Understanding the full consequences of PLV on lung injury after shock will require observation for several days. The immediate interaction of neutrophils with the pulmonary vascular bed is only one phase of the cellular immune response to acute injury. Furthermore, the absolute necessity of neutrophils in the development of pulmonary lesions after hemorrhage and resuscitation has been questioned (13), so that the effects seen in our study might have limited impact on the ultimate outcome of the injury produced.

In conclusion, in a rat model of hemorrhagic shock and resuscitation, we found that low-dose PLV was well tolerated and caused a significant decrease in lung MPO activity when delivered as a component of resuscitation. A trend toward a decrease in the bronchoalveolar cell content of $^{125}$I-labeled albumin in animals treated with perflurbron was also observed. Further investigation into the mechanism of lung protection and the hemodynamic responses of injured animals to this therapy is indicated.

The authors thank the staff of the University of Michigan Extracorporal Life Support and Liquid Ventilation Laboratory and Dr. Robert Bartlett for their constant support and thoughtful consideration of our data. We also thank Drs. Susan Stern and Steve Dronen of the University of Michigan and Dr. Ping Wang of Brown University for their assistance in model development. We also thank Alliance Pharmaceutical, San Diego, CA, and Hoechst-Marion-Roussel, Bridgwater, NJ, for providing the perflurbron used in this study.

This project was supported in part by a research fellowship grant from the Emergency Medicine Foundation and by National Heart, Lung, and Blood Institute Research Grant R29-HL-54224. R. B. Hirschl is a consultant for Alliance Pharmaceutical Corp., San Diego, CA.

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Received 10 February 1997; accepted in final form 18 July 1997.

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