Partial liquid ventilation improves gas exchange and increases EELV in acute lung injury

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Partial liquid ventilation improves gas exchange and increases EELV in acute lung injury. J. Appl. Physiol. 84(5): 1566–1572, 1998.—Gas exchange is improved during partial liquid ventilation with perfluorocarbon in animal models of acute lung injury. The specific mechanisms are unproved. We measured end-expiratory lung volume (EELV) by null-point body plethysmography in anesthetized sheep. Measurements of gas exchange and EELV were made before and after acute lung injury was induced with intravenous oleic acid to decrease EELV and worsen gas exchange. Measurements of gas exchange and EELV were again performed after partial liquid ventilation with 30 ml/kg of perfluorocarbon and compared with gas-ventilated controls. Oxygenation was significantly improved during partial liquid ventilation, and EELV (composite of gas and liquid) was significantly increased, compared with preliquid ventilation values and gas-ventilated controls. We conclude that partial liquid ventilation may directly recruit consolidated alveoli in the lung-injured sheep and that this may be one mechanism whereby gas exchange is improved.

 METHODS

Experimental protocol. Fifteen Suffolk sheep (weighing 22–29 kg) were intravenously anesthetized with ketamine HCl (0.1 mg/kg) and guaifenesin (2.2 ml/kg of a 5% solution in 0.9% NaCl) after fasting for 24–36 h. Anesthesia was maintained with a standardized mixture of guaifenesin (5 g/100 ml) and ketamine (0.15 g/100 ml), as monitored by toe pinch and tachycardic responses. The animals were placed in supine position and maintained as such throughout the entire experimental period. The animals then underwent a neck cutdown to provide them with a tracheostomy using a 9-mm endotracheal tube (Mallinckrodt Medical, St. Louis, MO), carotid artery pressure monitoring, and a pulmonary artery catheter (8-Fr Opticath, Abbott Laboratories, North Chicago, IL). Flow-directed placement was performed as guided by the standard-pressure waveforms. The tracheostomy was tightly sealed and leak tested. After the animal was connected to the ventilator, intravenous pancuronium was administered (0.1 mg/kg) and was redosed before each measurement of EELV. All animals were ventilated in a volume-control mode using a Siemens Servo 900 E (Siemens Elema, Sweden) with an in-line humidifier. The initial ventilator settings were the same for all animals and included an inspired oxygen fraction of 1.0, a tidal volume of 15 ml/kg (measured at the airway), positive end-expiratory pressure (PEEP) of 5–7 cmH2O, inspiratory-to-expiratory ratio of 1:1, and a respiratory rate of 10–16 breaths/min to normalize arterial PCO2 to 35–45 Torr. The animals were then suctioned of their gastric rumen, and a large venting orogastric tube was left in place. All procedures were approved by the University Committee for the Care and Use of Animals.

Experimental design. The sheep were randomly divided into three groups. One group served as gas-ventilated controls (GV) and comprised six sheep, in which a lung injury was induced with intravenous oleic acid (discussed below) and which were supported with conventional gas ventilation volumes. The mechanisms providing the improvement in gas exchange seen with PLV of the lung-injured animal are not completely elucidated. As PFCs are dense liquids capable of gas transport, it has been postulated that they may physically reinflate collapsed and consolidated alveoli, thereby increasing functional residual capacity (FRC) and potentially improving gas exchange. FRC is a crucial oxygen reservoir that is often depleted in the setting of acute respiratory failure. Because FRC is conceptualized as a gas volume, and because PLV involves both gas and liquid volumes, we will use the term "end-expiratory lung volume" (EELV). The concept of this two-phase lung volume has not previously been defined in the literature. Our hypothesis for this study is that PLV with a fluid of high respiratory gas solubility may physically recruit consolidated alveoli and recover lost EELV, contributing to improved respiratory gas exchange in the setting of lung injury.
with the same settings delineated above. The second group similarly comprised six sheep, in which the same acute lung injury was induced and which were then supported with PLV (PLV group) after intratracheal instillation of 30 ml/kg of perflubron. This volume was based on previous studies in the literature (6, 15). The perflubron did not undergo any additional preoxygenation and was administered in neat form as provided by the manufacturer. In all animals, this led to a visible meniscus in the endotracheal tube during ventilator disconnect (end-expiratory pressure of 0 cmH2O). With the exception of a variable respiratory rate, the ventilator settings were the same during PLV as those used in the GV group. Respiratory rate was changed only in response to measured increases in arterial PCO2. Any significant amount of lavaged exudate floating on the perflubron was suctioned, and any perflubron removed by the process was replaced into the airway. The third group of three sheep served as sham controls (SC) and was composed of healthy sheep that underwent measurement of EELV at the same data points but received neither the lung injury nor PLV.

The well-characterized oleic acid model of ARDS was utilized to induce lung injury. A dose (0.07 ml/kg body wt) of pure oleic acid (C18H34O2; Fisher Scientific, Fair Lawn, NJ) was emulsified with 10 ml of blood by vigorous shaking and then injected over 20 min into the right atrium. Within 45 min, an acute lung injury had developed, characterized by hemorrhagic pulmonary edema, increased transpulmonary shunt fraction (Qps/Qt), decreased compliance, and decreased EELV. Null-point body plethysmography measurements were performed in duplicate in all animals at baseline, 1 h after lung injury, and after an additional 30 and 90 min of PLV in the PLV group and after gas ventilation in the GV and SC groups. Physiological data were gathered at each data point. Thermodilution cardiac outputs were measured by using an Oximetrix 3 cardiac output computer calibrated for 5 ml of iced saline injectate (Abbott Laboratories). Five measurements, spaced temporally by 45–60 s, were performed. After elimination of one low and one high outlier value, the remaining three were averaged to derive the cardiac output result. Systemic and pulmonary arterial pressures were transduced (Sorenson Transpac II pressure transducers, Abbott Laboratories) and processed with Hewlett-Packard signal analysis and output (Hewlett-Packard Medical Division, Andover, MA). The pulmonary arterial pressure-monitoring system was calibrated to a low pressure of 0 mmHg and a high pressure of 75 mmHg, with a tolerance of ±2 mmHg. Arterial blood gases were measured with a Rapid Premier (Mallinckrodt Sensor Systems, Ann Arbor, MI). The Qps/Qt was calculated by using the standard formula

\[ \dot{Q}_{ps}/\dot{Q}_{t} = (C_{O_2} - C_{O_2}/(C_{O_2} - C_{V}) \]

where \( C_{O_2} \) is the oxygen content in end-pulmonary capillary blood, and \( C_{O_2} \) and \( C_{V} \) are arterial and mixed venous oxygen contents, respectively.

\[ C_{O_2}(\text{ml/dl}) = [1.0 \times Hb (g/dl) \times 1.39 (\text{ml } O_2 / g)] \]

\[ + [0.003 (\text{ml } O_2 \cdot dl^{-1} \cdot mmHg^{-1}) \times P_{A O_2} (\text{Torr})] \]

where \( Hb \) is hemoglobin and \( P_{A O_2} \) is alveolar pressure of oxygen.

\[ C_{O_2}(\text{ml/dl}) = [S_{A O_2} (\%) \times Hb (g/dl) \times 1.39 (\text{ml } O_2 / g)] \]

\[ + [0.003 (\text{ml } O_2 \cdot dl^{-1} \cdot mmHg^{-1}) \times P_{A O_2} (\text{Torr})] \]

where \( S_{A O_2} \) is arterial oxygen saturation and \( P_{A O_2} \) is arterial PO2.

\[ C_{V}(\text{ml/dl}) = [S_{V O_2} (\%) \times (Hb (g/dl) \times 1.39 (\text{ml } O_2 / g)) \]

\[ + [0.003 (\text{ml } O_2 \cdot dl^{-1} \cdot mmHg^{-1}) \times P_{V O_2} (\text{Torr})] \]

where \( S_{V O_2} \) is mixed venous oxygen saturation, and \( P_{V O_2} \) is mixed venous oxygen pressure.

Conceivably, the presence of perflubron vapor in alveolar gas could alter the \( P_{A O_2} \) calculation and thus, ultimately, the \( C_{O_2} \) and shunt fraction determinations. By our calculations, however, the presence or absence of perflubron vapor (vapor pressure at BTPS = 11 Torr) does not contribute significantly to shunt calculations (<2% error at the observed mean \( P_{A O_2} \) of 170 Torr).

The null-point body plethysmography technique of EELV measurement is explained briefly below. In vitro development of the technique by measuring test lungs of known volumes revealed a Pearson’s correlation coefficient 0.98 for body plethysmography (8). This involved a measurement of a rigid container that had a compliant latex diaphragm in the manner of Laver et al. (14).

Body plethysmography measurement of EELV. The sheep were placed in the supine position in a specially constructed full-body plethysmograph constructed of 1/4-in.-thick Plexiglas. When empty, the box had a volume of ~130 liters. An airtight chamber was created when the box lid was sealed over a rubber gasket with multiple threaded thumb screws. A water trough around the outside seat of the lid served to detect any leak of air across the seal. All intravenous and monitoring access communicated through the side of the box via sealed connections. Similarly, the ventilator was coupled to the tracheostomy tube by a sealed connector in the lid of the box. Above this connector was a pinch valve that would tightly occlude the airway during plethysmographic measurements. A strain gauge (CDX III, Cole, Lakewood, CO), calibrated against a manometer from 0 to 100 mmHg, was connected through a sealed adapter in the box’s side and constantly measured box pressure. Through a side port of the airway within the plethysmograph, a differential transducer (PX170–28DV, Omega Engineering, Stamford, CT), protected by a sputum trap, constantly measured the differential between the airway pressure and the ambient box pressure (see Fig. 1 for a schematic of the device). The total volume of the trap was only 10 ml. The trap was necessary only because the differential transducer was a dry-to-dry type, not a wet-to-dry type and, therefore, would have been inaccurate if covered with sputum or perflubron. The signals of both
transducers were processed and displayed in real time by Lab View 2 software (National Instruments, Austin, TX). The virtual instrument displayed both the differential and box pressure side by side in real time, allowing matched post hoc analysis of the tracings.

Measurement of EELV by body plethysmography was based on the original description in dogs by Laver et al. in 1964 (14) and in cats by Colebatch and Engel in 1974 (2). As with all other plethysmographic methods, the null-point variant is based on Boyle’s law and is especially appropriate for paralyzed, mechanically ventilated animals. To perform the measurement, a pinch valve between the ventilator circuit and the plethysmograph was tightly closed during an end-expiratory pause, thus isolating the quantity of gas in the lungs (EELV). Twenty to thirty milliliters of room air were injected as a bolus volume increment (ΔV) into the trachea through the sputum trap access. The value of 20–30 ml was extrapolated per animal size from Colebatch and Engel (2). This caused a rapid (<1 s) deflection and equilibration in the signal from the differential transducer [pressure differential (Pd)] as the airway pressure was slightly increased relative to the constant box pressure (atmospheric pressure). High-flow compressed air then injected into the plethysmograph space around the sheep until the value of Pd was restored to baseline. This process consistently took <4 s, with a total airway occlusion time of 10–12 s. The plethysmograph pressure increase necessary to nullify the Pd was recorded and termed ΔPps. The box was vented back to atmospheric pressure, and mechanical ventilation was resumed. EELV was calculated by the equation derived from Boyle’s law (2): EELV = ΔV × (Ps – P0)/ΔPps (see Appendix for derivation), where Ps is the barometric pressure (measured daily) and P0 is the vapor pressure of water at body temperature. All volumes were expressed in milliliters and pressures in millimeters of Hg. The rapidity of the measurement was necessary to avoid artifact from deterioration of Pd. If ΔV were injected and no compressed air followed, Pd would deteriorate back to baseline within 10–15 s. Although not as noticeably, Pd would deteriorate within 15–20 s, even if ΔV were not injected. As Colebatch and Engel (2) explained, this is not due to simple stress relaxation of the lungs, but, instead, is due to a decrease in contained intrathoracic volume caused by displacement of thoracic blood volume.

Data analysis. The mechanical dead space of the apparatus (connectors, valve, and endotracheal tube) was subtracted from all EELV values derived from plethysmography. Anatomic dead space was not measured or calculated. All volumes were corrected to BTPS and normalized for body weight. Thus, all data to follow are expressed as milliliters per kilogram. All EELV values and physiological data were analyzed by using Systat software (Systat, Evanston, IL). Repeated-measures ANOVA with significance defined at P = 0.05 was used for comparisons within the GV and PLV groups, between the postinjury and 30- and 90-min time points. ANOVA was not used in the SC group, as this group was composed of three animals and its purpose was to provide a relative baseline only. Post hoc comparisons were made within the two groups with paired t-tests between the injury and 30-min point and between the injury and 90-min point. Additional post hoc comparisons were made between PLV and GV groups with independent t-tests at the 30- and 90-min points. Bonferroni correction for multiple comparisons was used to define individual significance at P < 0.025 for between-group analyses. All descriptive statistics are expressed as means ± SE.

RESULTS

Various physiological and ventilator data for the GV and PLV groups are shown in Table 1. Improvement in oxygenation was observed during PLV compared with gas ventilation. The baseline PaO2 was 409 ± 52 Torr in the PLV group and 483 ± 31 Torr in the GV controls. After induction of lung injury, the PaO2 was 52 ± 6 and 57 ± 5 Torr in the PLV and GV groups, respectively. After 30 and 90 min of PLV, the PaO2 increased to 171 ± 24 and 114 ± 29 Torr, respectively (P = 0.003 by repeated-measures ANOVA, P = 0.01 (30 min) and P = 0.05 (90 min), compared with the injury time point within group). After 30 and 90 min of gas ventilation, the average PaO2 was 61 ± 6 and 47 ± 3 Torr, respectively (P = 0.04 by repeated-measures ANOVA, P = 0.54 and P = 0.08, compared with the injury time point within group; P = 0.010 and P = 0.059 at 30 and 90 min, respectively, when compared between PLV and GV groups) (see Fig. 2). There was a trend toward a decrease in PaO2 in the SC group throughout the course of the experiment, although no lung injury was induced: the baseline PaO2 was 407 ± 35 Torr. This decreased to 365 ± 75 Torr by the corresponding injury time point and to 268 ± 108 and 222 ± 94 Torr by the 30- and 90-min time points, respectively.

Qps/Qt was 18.7 ± 3.4% at baseline in the PLV group and 14.2 ± 1.8% in the GV group. After oleic acid injury, the Qps/Qt was 56.8 ± 6.6% in the PLV animals and 54.0 ± 2.9% in the GV animals. After 30 and 90 min of liquid ventilation in the PLV group, Qps/Qt decreased to 36.0 ± 3.7 and 43.2 ± 7.6%, respectively (P = 0.002 by repeated-measures ANOVA, P = 0.008 and P = 0.014, compared with injury within group). After 30 and 90 min of gas ventilation, the Qps/Qt was 50.0 ± 5.8 and 54.7 ± 6.3%, respectively, in the GV animals (P = 0.58 by repeated-measures ANOVA; P = 0.073 and P = 0.268 at 30 and 90 min, respectively, when compared between GV and PLV groups) (see Fig. 3). In the SC group, the Qps/Qt was 19.3 ± 0.7% at baseline, 16.3 ± 0.9% at injury, 22.3 ± 5.2% at 30 min, and 29.7 ± 6.2% at 90 min.

The EELV measured by body plethysmography was 33.3 ± 1.4 ml/kg for the PLV group and 34.3 ± 2.0 ml/kg in the GV group at baseline (see Fig. 4). One hour after oleic acid administration, the EELV was 23.5 ± 2.3 and 24.7 ± 1.3 ml/kg for the PLV and GV groups, respectively (both groups, P = 0.01 compared with baseline by paired t-test). There was no significant change in EELV in the GV group during ongoing gas ventilation (compared with the postinjury time point), with mean volumes of 24.8 ± 1.7 ml/kg at 30 min and 22.3 ± 2.1 ml/kg at 90 min (P = 0.170 by repeated-measures ANOVA). The gas volume EELV values in the PLV group were 13.7 ± 1.7 ml/kg at 30 min and 11.8 ± 1.4 ml/kg at 90 min (P = 0.001 by repeated-measures ANOVA, P = 0.004 and P = 0.002 at 30 and 90 min compared with injury within group; P = 0.001 and P = 0.397 at 30 and 90 min, respectively, when compared between groups). Although the gas volume EELV in the animals undergoing PLV was lower than in those undergoing GV, plethysmography does not measure liquid-volume EELV. Therefore, the 30 ml/kg occupied by perflubron were added to derive the final EELV, which was a composite of gas and liquid volumes.
Table 1. Tabulated physiological data for all 3 groups at baseline, after lung injury, and after 30 and 90 min of gas or partial liquid ventilation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Injury</th>
<th>Ventilation</th>
<th>P (ANOVA)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 min</td>
<td>90 min</td>
</tr>
<tr>
<td>Mean systemic arterial pressure, mmHg</td>
<td>94 ± 6</td>
<td>81 ± 7</td>
<td>74 ± 6*</td>
<td>70 ± 7</td>
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<tr>
<td>PLV</td>
<td>107 ± 9</td>
<td>80 ± 4</td>
<td>97 ± 5*</td>
<td>92 ± 6</td>
</tr>
<tr>
<td>GV</td>
<td>91 ± 15</td>
<td>106 ± 3</td>
<td>107 ± 3</td>
<td>83 ± 12</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure, mmHg</td>
<td>18 ± 1</td>
<td>23 ± 1</td>
<td>26 ± 2</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>PLV</td>
<td>14 ± 1</td>
<td>21 ± 1</td>
<td>26 ± 1†</td>
<td>29 ± 1†</td>
</tr>
<tr>
<td>GV</td>
<td>16 ± 2</td>
<td>20 ± 4</td>
<td>20 ± 4</td>
<td>19 ± 2</td>
</tr>
<tr>
<td>Cardiac output, l·min⁻¹·kg⁻¹</td>
<td></td>
<td></td>
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<tr>
<td>PLV</td>
<td>0.22 ± 0.03</td>
<td>0.17 ± 0.02</td>
<td>0.21 ± 0.01</td>
<td>0.26 ± 0.04</td>
</tr>
<tr>
<td>GV</td>
<td>0.19 ± 0.01</td>
<td>0.21 ± 0.02</td>
<td>0.20 ± 0.02</td>
<td>0.19 ± 0.03</td>
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<tr>
<td>SC</td>
<td>0.19 ± 0.05</td>
<td>0.13 ± 0.01</td>
<td>0.18 ± 0.04</td>
<td>0.24 ± 0.04</td>
</tr>
<tr>
<td>Peak inspiratory pressure, cmH₂O</td>
<td>26.7 ± 0.9</td>
<td>43.5 ± 1.1</td>
<td>41.5 ± 2.1</td>
<td>44.7 ± 3.1</td>
</tr>
<tr>
<td>PLV</td>
<td>23.8 ± 1.8</td>
<td>37.7 ± 3.5</td>
<td>41.0 ± 2.9</td>
<td>43.2 ± 3.7†</td>
</tr>
<tr>
<td>GV</td>
<td>25.3 ± 0.9</td>
<td>24.7 ± 2.4</td>
<td>27.0 ± 0.6</td>
<td>25.3 ± 1.2</td>
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<tr>
<td>Mean arterial saturation, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLV</td>
<td>100.0 ± 0</td>
<td>71.7 ± 8.2</td>
<td>97.8 ± 2.2†</td>
<td>89.5 ± 7.6</td>
</tr>
<tr>
<td>GV</td>
<td>99.8 ± 0.2</td>
<td>79.3 ± 7.0</td>
<td>82.7 ± 6.6</td>
<td>72.5 ± 8.9</td>
</tr>
<tr>
<td>SC</td>
<td>100.0 ± 0</td>
<td>100.0 ± 0</td>
<td>100.0 ± 0</td>
<td>98.3 ± 1.2</td>
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<tr>
<td>Arterial PCO₂, Torr</td>
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<tr>
<td>PLV</td>
<td>39.2 ± 1.4</td>
<td>41.5 ± 0.7</td>
<td>37.3 ± 1.7</td>
<td>40.0 ± 2.3</td>
</tr>
<tr>
<td>GV</td>
<td>38.5 ± 0.8</td>
<td>41.0 ± 2.0</td>
<td>42.3 ± 1.3</td>
<td>43.7 ± 2.2</td>
</tr>
<tr>
<td>SC</td>
<td>36.7 ± 0.3</td>
<td>35.7 ± 0.7</td>
<td>37.0 ± 0.6</td>
<td>41.0 ± 3.0</td>
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<tr>
<td>Mixed venous oxygen saturation, %</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLV</td>
<td>83 ± 2</td>
<td>44 ± 9</td>
<td>79 ± 4†</td>
<td>67 ± 6†</td>
</tr>
<tr>
<td>GV</td>
<td>81 ± 5</td>
<td>54 ± 10</td>
<td>54 ± 8*</td>
<td>43 ± 9</td>
</tr>
<tr>
<td>SC</td>
<td>82 ± 4</td>
<td>73 ± 7</td>
<td>74 ± 6</td>
<td>74 ± 6</td>
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</table>

PLV, partial liquid ventilation group; GV, gas-ventilated group; SC, sham control group. Note that all groups are gas ventilated at baseline and at injury data points. Repeated-measures ANOVA (significant P < 0.05) performed between injury, at 30-, and 90-min data points (*P < 0.025 by independent t-test at 30- or 90-min data points between groups; †P < 0.025 by paired t-test comparing 30- and 90-min data with injury data within groups).

Table 1 shows the tabulated physiological data for all 3 groups at baseline, after lung injury, and after 30 and 90 min of gas or partial liquid ventilation. The data include variables such as arterial oxygen tension (PaO₂), mixed venous oxygen saturation, and cardiac output, measured at various time points.

Potentially capable of gas exchange. After 30 and 90 min of PLV, the composite EELV was 43.7 ± 1.7 and 41.8 ± 1.4 ml/kg, respectively (P ≤ 0.001 by repeated-measures ANOVA, P ≤ 0.001 and P ≤ 0.001 when compared within group with the postinjury time point; P ≤ 0.001 and P ≤ 0.001 at 30 and 90 min, respectively, when compared between groups). These results are displayed in Fig. 4. In the SC group, the EELV values measured by body plethysmography at baseline, after injury, and at the 30- and 90-min points were 36.7 ± 1.3, 36.7 ± 2.4, 37.0 ± 1.5, and 36.7 ± 2.9 ml/kg, respectively.

Because the composite EELV values are greater than the baseline EELV values, the possibility is raised that PLV during volume-controlled ventilation may also increase total lung capacity. To address this question, we measured the volume used to inflate the lungs from EELV to a 30-cmH₂O pressure level, which has been measured in Fig. 4. In the SC group, the EELV values measured by body plethysmography at baseline, after injury, and at the 30- and 90-min points were 36.7 ± 1.3, 36.7 ± 2.4, 37.0 ± 1.5, and 36.7 ± 2.9 ml/kg, respectively.

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equated with the “inspiratory capacity” (IC) in the paralyzed ventilated subject. At baseline, these volumes were 21.8 ± 2.3 ml/kg for PLV and 23.3 ± 1.6 ml/kg for GV. With induction of lung injury, these volumes were 13.2 ± 1.5 and 16.0 ± 1.3 ml/kg for PLV and GV, respectively. With GV, these values remained relatively constant with means of 15.9 ± 1.0 ml/kg at 30 min and 16.0 ± 0.8 ml/kg at 90 min (P = 0.974 by repeated-measures ANOVA). After the lungs were filled with 30 ml/kg PFC in the PLV group, a trend was observed toward a decrease in these values of 9.3 ± 2.5 ml/kg at 30 min and 9.3 ± 2.6 ml/kg at 90 min (P = 0.009 by repeated-measures ANOVA, P = 0.035 and P = 0.042 compared with injury at 30 and 90 min, respectively; P = 0.085 and P = 0.087 at 30 and 90 min, respectively, when compared post hoc between groups). The values were relatively constant in the SC group with means of 18.8 ± 2.0, 19.0 ± 0.1, 19.6 ± 1.8, and 19.9 ± 0.3 ml/kg at the same four data points.

Mean airway pressure (MAP) was also recorded. At baseline, the MAP was 11.4 ± 0.3 cmH$_2$O in the PLV group and 10.8 ± 0.8 cmH$_2$O in the GV group. After induction of lung injury, the MAP increased to 15.9 ± 0.4 cmH$_2$O for the PLV animals still undergoing gas ventilation at that point and to 13.4 ± 0.9 cmH$_2$O for the GV group. With the continuation of GV, the MAP was 15.0 ± 1.2 cmH$_2$O at 30 min and 16.5 ± 1.7 cmH$_2$O at 90 min (P = 0.004 by repeated-measures ANOVA, P = 0.009 and P = 0.022 when compared within groups with injury at 30 and 90 min). With the same ventilatory pattern during PLV, the MAP was 18.0 ± 0.9 cmH$_2$O at 30 min and 18.1 ± 1.0 cmH$_2$O at 90 min (P = 0.024 by repeated-measures ANOVA, P = 0.058 and P = 0.055 when compared within groups with injury at 30 and 90 min, respectively; P = 0.073 and P = 0.414, when compared post hoc to GV at 30 and 90 min, respectively).

Effective compliance (Ceff) was calculated as $V_{\text{inspired}}/ (P_{\text{plateau}} - \text{PEEP})$, where $V_{\text{inspired}}$ is inspired tidal volume and $P_{\text{plateau}}$ is plateaued pressure. Ceff is normalized for body weight and expressed as milliliters per centimeters H$_2$O per kilogram. At baseline, the Ceff was $0.79 ± 0.04$ ml·cmH$_2$O$^{-1}$·kg$^{-1}$ for the PLV animals and $0.93 ± 0.11$ ml·cmH$_2$O$^{-1}$·kg$^{-1}$ for the GV animals. After oleic acid lung injury, the values were $0.41 ± 0.01$ and $0.52 ± 0.06$ ml·cmH$_2$O$^{-1}$·kg$^{-1}$ for PLV and GV, respectively. After 30 and 90 min of PLV, the Ceff was $0.45 ± 0.03$ and $0.41 ± 0.04$ ml·cmH$_2$O$^{-1}$·kg$^{-1}$ (P = 0.205 by repeated-measures ANOVA). After 30 and 90 min of gas ventilation, the Ceff was $0.46 ± 0.05$ and $0.44 ± 0.05$ ml·cmH$_2$O$^{-1}$·kg$^{-1}$, respectively, in the GV animals (P = 0.001 by repeated-measures ANOVA; P = 0.024 and P = 0.006 at 30 and 90 min compared with injury within group; P = 0.794 and P = 0.634 at 30 and 90 min when compared between GV and PLV groups).

In the SC group, Ceff was $0.83 ± 0.07$ ml·cmH$_2$O$^{-1}$·kg$^{-1}$ at baseline, $0.72 ± 0.05$ ml·cmH$_2$O$^{-1}$·kg$^{-1}$ after injury, $0.71 ± 0.03$ ml·cmH$_2$O$^{-1}$·kg$^{-1}$ at the 30-min data point, and $0.73 ± 0.01$ ml·cmH$_2$O$^{-1}$·kg$^{-1}$ at the 90-min data point.

**DISCUSSION**

In this model of acute respiratory failure, we were able to demonstrate an improvement in pulmonary gas exchange during PLV. Associated with this improvement was an increase in the composite liquid and gas-phase EELV, which was demonstrated by null-point body plethysmography.

As stated earlier, the improvement in gas exchange during PLV in lung-injury models has been demonstrated clearly, and similar improvement has been suggested in the early human experience. However, the exact mechanisms of action are not clear. It is likely that many complementary mechanisms are involved. Pulmonary blood flow, which is normally distributed in greatest proportion to the dependent (and often the most diseased) zones of the lungs, may be redistributed to the nondependent (and better ventilated) zones of the lungs due to the physical density of PFC in the most dependent zones. This has been suggested by experimental data from isolated perfused animal lungs that were completely filled with PFC but it needs to be investigated in the intact lung-injured animal undergoing PLV, in which the lungs are partially filled with liquid and partially filled with gas (15). Also, exudate in the peripheral airways is lavaged during liquid ventilation and collected in the central airways, where it can effectively be removed by suctioning. Currently, many investigators are exploring the possibility that PFCs may ameliorate transalveolar exudation and may even have direct anti-inflammatory effects within the alveolar environment (3, 19).

Cross-sectional imaging of the lungs in animals and patients with ARDS has revealed the regional preponderance of atelectasis and consolidation in the dependent zones of the lungs (7). The low surface tension and high density of PFCs appear to recruit consolidated alveoli in the dependent lung zones (10, 20). Through this mechanism, one would expect to increase the EELV of the diseased lung undergoing PLV. Indeed, the
composite EELV was increased in this study during PLV compared with GV, even though the gas EELV was reduced. We suggest that it is this composite volume that is potentially available for gas exchange and that the increase in the composite EELV is a possible means by which gas exchange is improved during PLV.

The potential limitations of the work include the fact that plethysmography measures only gas volume EELV and, by necessity, the PFC volume is added to calculate the final composite EELV, which is then, by definition, an indirectly obtained value. To our knowledge, there is no accepted method of measuring the liquid phase EELV directly, aside from recording the volume administered into the trachea. It is not clear whether most or all of the PFC takes place in gas exchange. Certainly, at end expiration, some of the PFC refluxes into the major airways and is not taking part in gas exchange at that instant.

It is noted that the magnitude of improvement in oxygenation noted at 30 min of PLV is diminished somewhat at 90 min into the study. This is likely an aspect of the injury model that is known to progress histologically and clinically to a peak around 6 h from the time point of oleic acid infusion (5, 12). This is suggested by the parallel trends toward increasing shunt fraction seen in the PLV and GV groups in Fig. 3. A steady trend toward decreasing oxygenation was also seen in the SC group, possibly because of ongoing atelectasis. The decrement in gas exchange seen in the PLV group may also be due, in part, to ongoing evaporative loss of PFC, which at this point has been difficult to quantify directly. It is interesting, however, that the meniscus was still visible at 0 cmH₂O end-expiratory pressure (during ventilator disconnect) in all animals after 30 min of PLV.

As the sheep underwent volume-controlled, not pressure-controlled, ventilation, and since pulmonary compliance did not improve significantly during PLV, it is conceivable that significant increases in MAP could have contributed to increases in oxygenation. However, the differences between MAP in the two groups were not significant (see RESULTS).

As indicated previously, we measured the amount of gas volume required to inflate the lungs from EELV to 30 cmH₂O pressure and equated this with IC. As compliance decreased with induction of oleic acid injury, both the EELV and IC decreased (see Fig. 5, A and B). After the lungs were filled with perflubron, the IC decreased further (P = 0.009 by repeated-measures ANOVA, P = 0.035 and P = 0.042 compared with injury at 30 and 90 min, respectively). A similar phenomenon has been observed both in the laboratory and in the clinical setting: pulmonary compliance and tidal volume may be compromised as the volume of PFC administered approaches a volume equivalent to EELV, especially if filling proceeds at a rate exceeding that of alveolar recruitment. As EELV is exceeded, pulmonary compliance may become compromised even further, with an associated decrement in gas exchange and IC. The optimum level of filling during PLV is, as yet, not fully defined.

![Graph of the sum of measured EELV and the inspiratory capacity (IC; amount of volume inspired to reach an airway pressure of 30 cmH₂O) at baseline, after injury, and after 30 and 90 min of partial liquid or gas ventilation. Note that during PLV, total lung capacity (sum of EELV and IC) may increase. IC, gray area; EELV, solid black area.](image)

**Conclusion.** In this model of acute respiratory failure in sheep, the use of PLV with perfluorocarbon resulted in a significant increase in PAo₂ and a decrease in physiological shunt fraction, compared with the post-lung injury timepoint. Associated with these changes was an increase in the composite air and liquid EELV measured by null-point body plethysmography, relative to the volume of perfluorocarbon administered. This may be one of the mechanisms whereby improved gas exchange is effected in the lung-injured subject during PLV.

**APPENDIX**

**Derivation of Null-Point Body Plethysmography Equation**

Begin with Boyle’s law \( P_1V_1 = P_2V_2 \). Then

\[
(P_B - P_{H_2O}) \times (EELV + \Delta V) = (P_B - P_{H_2O} + \Delta P_{pg}) \times EELV
\]

where \( P_{H_2O} = 47 \text{ mmHg} \), \( \Delta V \) is the volume increment injected into the airway at end expiration, and \( \Delta P_{pg} \) is the pressure increment above atmospheric required to reduce the volume EELV + \( \Delta V \) back to EELV. Solving for EELV, the equation becomes

\[
EELV(\text{ml}) = \frac{\Delta V(\text{ml}) \times P_B - P_{H_2O}}{\Delta P_{pg}}
\]

All volumes are corrected to BTPS.

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