Role of ventilation strategy on perfluorochemical evaporation from the lungs

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Jeng, Mei-Jy, Daniele Trevisanuto, Carla M. Weis, William W. Fox, Aaron B. Cullen, Marla R. Wolfson, and Thomas H. Shaffer. Role of ventilation strategy on perfluorochemical evaporation from the lungs. J Appl Physiol 90: 1365–1372, 2001.—To study the effect of ventilation strategy on perfluorochemical (PFC) elimination profile (evaporative loss profile; EL), 6 ml/kg of perflubron were instilled into anesthetized normal rabbits. The strategy was to maintain minute ventilation (VE, in ml/min) in three groups: VE_L (low-range VE, 208 ± 2), VE_M (midrange VE, 250 ± 9), and VE_H (high-range VE, 293 ± 1) over 4 h. In three other groups, respiratory rate (RR, breaths/min) was controlled at 20, 30, or 50 with a constant VE and adjusted tidal volume. PFC content in the expired gas was measured, and EL was calculated. There was a significant VE- and time-dependent effect on EL. Initially, percent PFC saturation and loss rate decreased in the VE_H > VE_M > VE_L groups, but by 3 h the lower percent PFC saturation resulted in a loss rate such that VE_H < VE_M < VE_L at 4 h. For the groups at constant VE, there was a significant time effect on EL but no RR effect. In conclusion, EL profile is dependent on VE with little effect of VE_H percent PFC saturation resulted in a loss rate such that the PFC elimination profile (EL; percent PFC saturation and PFC loss rate) is dependent on minute ventilation (VE) and the respiratory rate (RR)-tidal volume (VT) combination. Therefore, the present study was designed to test the effects of VE and RR-VT combination on the PFC elimination from the respiratory system. In addition, a secondary endpoint of the study was to evaluate the effect of PFC elimination on pulmonary gas exchange and function.

METHODS

All animals were managed according to the NIH regulations Guide for the Care and Use of Laboratory Animals. In addition, all procedures were approved by the Institutional Animal Care Use Committee of Temple University.

Animal Preparation

Thirty-six New Zealand White juvenile rabbits (weight 2.2 ± 0.1 kg) with normal lungs were anesthetized with an intramuscular injection of a mixture of ketamine (23 mg/kg), acepromazine (0.58 mg/kg), and xylazine (0.8 mg/kg). This particular animal model was chosen on the basis of our previous investigations that have shown that the elimination of PFC from the lungs is associated with the air-PFC liquid interface and influenced by the PFC physical properties, the dosing volume and frequency of dosing, body position, lung volume (possibly in combination with positive end expiratory pressure), and the effect of lung injury in combination with extracorporeal membrane oxygenation (16, 17, 29, 37, 41, 43). However, there is no available information on ventilation strategy and its effects on elimination of PFC during PLV.

With regard to ventilation strategy, we hypothesized that the PFC elimination profile (EL; percent PFC saturation and PFC loss rate) is dependent on minute ventilation (VE) and the respiratory rate (RR)-tidal volume (VT) combination. Therefore, the present study was designed to test the effects of VE and RR-VT combination on the PFC elimination from the respiratory system. In addition, a secondary endpoint of the study was to evaluate the effect of PFC elimination on pulmonary gas exchange and function.

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previous experience with the model, the suitability of the model as it applies to neonatal and pediatric medicine, and the history of this preparation for PLV studies (1, 16, 17, 21, 37–41). The skin and soft tissues were anesthetized with 0.5% lidocaine HCl (4 mg/kg) and instrumented with tracheostomy placement of a 3-mm-ID endotracheal tube (Hi-Lo Jet Tube, Mallinckrodt, Saint Louis, MO). Catheters were placed in a jugular vein and carotid artery. Conventional gas ventilation with a time-cycled, pressure-limited ventilator (BP-200, Bear Medical Systems, Riverside, CA) was established to maintain physiological cardiopulmonary condition. Subsequent anesthesia was maintained with intravenous injection of the above anesthesia drug (one-tenth of initial anesthesia dose) hourly. Muscle relaxation was induced by intravenous administration of pancuronium bromide (0.1 mg/kg) and maintained with continuous infusion (0.15 mg·kg⁻¹·h⁻¹) throughout the experiments. Maintenance fluid was provided by a continuous infusion of 5% dextrose at a rate of 5 mg·kg⁻¹·h⁻¹. Arterial blood pressure was monitored by attaching the arterial catheter to a standard pressure transducer, connected to a neonatal monitor (Athena/Neonatal 9040, S & W Medico Teknik, Albertslund, Denmark). Electrocardiogram electrodes and a rectal temperature probe were inserted for monitoring. The animal's rectal temperature was maintained within 37–38°C.

**Experimental Protocol**

**V<sub>E</sub> protocol.** Nineteen animals were randomly assigned to one of three groups to study the effect of V<sub>E</sub> on the PFC elimination profile. Constant V<sub>E</sub> was maintained in each group throughout the experiment: low-range V<sub>E</sub> target (V<sub>E</sub><sub>L</sub> = 205–215), midrange V<sub>E</sub> target (V<sub>E</sub><sub>M</sub> = 245–255), and high-range V<sub>E</sub> target (V<sub>E</sub><sub>H</sub> = 285–395 ml·kg⁻¹·min⁻¹), which were determined by our pilot study to keep the arterial partial pressure of CO<sub>2</sub> (Paco<sub>2</sub>) in a physiological range. The V<sub>E</sub> was maintained constant in each group by monitoring V<sub>R</sub> every 15–30 min using pneumotachography (PEDS-LAB, MAS, Hatfield, PA) and appropriately adjusting ventilator peak inflation pressure. In addition, several healthy rabbits ventilated without PFC were also studied, as described by Tutuncu et al. (40), to confirm cardiopulmonary stability of the animal preparation over time.

**Ventilation strategy protocol.** Seventeen animals were randomly assigned to one of three additional groups to study the effect of varying RR and V<sub>T</sub> on PFC elimination from the respiratory system. RR (breaths/min) was controlled at RR<sub>20</sub> = 20, RR<sub>30</sub> = 30, and RR<sub>50</sub> = 50, and V<sub>T</sub> was corrected by adjusting peak inflation pressure and positive end-expiratory pressure to maintain V<sub>E</sub> (V<sub>E</sub> = 275–290 ml·min⁻¹·kg⁻¹) and mean airway pressure (7–8 cmH<sub>2</sub>O) in a constant range. Mean airway pressure was maintained constant in an attempt to regulate end-expiratory lung volume, which is associated with the air-PFC liquid interface. In all study groups, other ventilation profiles were maintained constant: inspiratory time 0.3 s, positive end-expiratory pressure 5–6 cmH<sub>2</sub>O, inspired O<sub>2</sub> fraction (0.5% lidocaine HCl (4 mg/kg) and instrumented with tracheostomy placement of a 3-mm-ID endotracheal tube (Hi-Lo Jet Tube, Mallinckrodt, Saint Louis, MO). Catheters were placed in a jugular vein and carotid artery. Conventional gas ventilation with a time-cycled, pressure-limited ventilator (BP-200, Bear Medical Systems, Riverside, CA) was established to maintain physiological cardiopulmonary condition. Subsequent anesthesia was maintained with intravenous injection of the above anesthesia drug (one-tenth of initial anesthesia dose) hourly. Muscle relaxation was induced by intravenous administration of pancuronium bromide (0.1 mg/kg) and maintained with continuous infusion (0.15 mg·kg⁻¹·h⁻¹) throughout the experiments. Maintenance fluid was provided by a continuous infusion of 5% dextrose at a rate of 5 mg·kg⁻¹·h⁻¹. Arterial blood pressure was monitored by attaching the arterial catheter to a standard pressure transducer, connected to a neonatal monitor (Athena/Neonatal 9040, S & W Medico Teknik, Albertslund, Denmark). Electrocardiogram electrodes and a rectal temperature probe were inserted for monitoring. The animal's rectal temperature was maintained within 37–38°C.

**Calculations**

The E<sub>L</sub> was established by determining the following parameters, based on previous studies (21, 29, 41)

\[
\text{Perfluorobron loss rate} = \frac{\text{Residual perfluorobron in the lungs (ml/kg)}}{\text{Volume loss as % of initial instillation volume (kg)}}
\]

\[
\text{Volume loss as % of initial instillation volume (%) = } \frac{\text{Cumulative loss/kg}}{\text{Initial instillation volume/kg} \times 100}
\]

**Data Analysis**

One-way analysis of variance (ANOVA) was used to compare basic physiological data as a function of time. Two-way ANOVA and post hoc analysis with Student-Newman-Keuls correction for multiple comparisons were performed to compare E<sub>L</sub> and other parameters as a function of time and groups. One-way ANOVA and post hoc analysis with Student-Newman-Keuls correction were performed to compare the values of E<sub>L</sub> and other parameters at each time point. Significance was accepted at the P < 0.05 level.

**RESULTS**

**V<sub>E</sub> Study**

As shown in Table 1 (mean ± SE), body weight did not differ significantly across groups. V<sub>E</sub> was maintained constant in three significantly (P < 0.01) different ranges (V<sub>E</sub><sub>M</sub> = 293 ± 1 > V<sub>E</sub><sub>L</sub> = 250 ± 9 > V<sub>E</sub><sub>H</sub> = 208 ± 2 ml·kg⁻¹·min⁻¹). Figure 1 shows the percent PFC saturations and the loss rate of PFC over time for each group. As shown, the relationship is significantly (P < 0.05) dependent on V<sub>E</sub> and time. After the initial instillation, the expired gas in all groups was saturated with approximately the same amount of PFC (50% saturation). The percent PFC saturation of expired gas declined over time for all groups; however, the expired gas remained relatively saturated with PFC for a longer time at lower levels of V<sub>E</sub>. Initially, the loss rate of the groups with higher V<sub>E</sub> was greater (V<sub>E</sub><sub>H</sub> > V<sub>E</sub><sub>M</sub> > V<sub>E</sub><sub>L</sub>) because of the V<sub>E</sub>, but, by 3 h, the lower percent

\[
\text{Volume loss as % of initial instillation volume (%) = } \frac{\text{Cumulative loss/kg}}{\text{Initial instillation volume/kg} \times 100}
\]
PFC saturation resulted in a loss rate such that $V_{EH} > V_{EM} > V_{EL}$ at 4 h.

The relationship of residual PFC in the lung and the PFC loss as a percentage of initial dose over time for each group is shown in Fig. 2. There were lower amounts of residual PFC in the lungs and a higher loss (percentage of initial PFC dose) in the groups with higher $V_E$ during the first 3 h. Table 2 (means $\pm$ SE) demonstrates how the redosing interval is dependent on the $V_E$ such that replacement doses are needed sooner when the $V_E$ is higher. For example, it takes 20 min longer for the $V_{EL}$ group to lose 20% of the initial dose compared with the $V_{EH}$ group.

Table 2 illustrates the cardiopulmonary profiles of animals in the $V_E$ groups. As a function of time and group, there were significant changes in PaO$_2$ and Cdyn over time ($P < 0.05$). However, there are significant changes in Cdyn% as a function of time only and in PaCO$_2$ as a function of group only ($P < 0.05$).

Ventilation Strategy Study

As shown in Table 1, the body weight and $V_E$ did not differ significantly among groups. By design, different breathing rates were set for each group, and thus $V_T$ was adjusted to maintain a similar $V_E = 283 \pm 4$ SE ml$\cdot$kg$^{-1}$$\cdot$min$^{-1}$. Figure 3 demonstrates that percent PFC saturation and PFC loss rate were each signifi-
Table 3. Cardiopulmonary profiles in Ve study

<table>
<thead>
<tr>
<th>Time</th>
<th>Groups</th>
<th>PaO2, mmHg</th>
<th>PaCO2, mmHg</th>
<th>pH</th>
<th>MBP, mmHg</th>
<th>HR, beats/min</th>
<th>Cdyn, ml·cmH2O⁻¹·kg⁻¹</th>
<th>Cdyn%, % of BL</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>VeB1</td>
<td>423 ± 49</td>
<td>39 ± 2</td>
<td>7.46 ± 0.02</td>
<td>59 ± 5</td>
<td>188 ± 14</td>
<td>1.14 ± 0.09</td>
<td>100 ± 0</td>
</tr>
<tr>
<td></td>
<td>VeB2</td>
<td>475 ± 9</td>
<td>39 ± 5</td>
<td>7.42 ± 0.03</td>
<td>53 ± 4</td>
<td>192 ± 11</td>
<td>0.76 ± 0.07</td>
<td>100 ± 0</td>
</tr>
<tr>
<td></td>
<td>VeB3</td>
<td>478 ± 14</td>
<td>25 ± 3</td>
<td>7.49 ± 0.03</td>
<td>47 ± 3</td>
<td>204 ± 17</td>
<td>1.02 ± 0.05</td>
<td>100 ± 0</td>
</tr>
<tr>
<td></td>
<td>VeB4</td>
<td>296 ± 28</td>
<td>39 ± 4</td>
<td>7.37 ± 0.04</td>
<td>71 ± 4</td>
<td>176 ± 5</td>
<td>0.93 ± 0.08</td>
<td>85 ± 12</td>
</tr>
<tr>
<td>1h</td>
<td>VeE1</td>
<td>351 ± 39</td>
<td>39 ± 3</td>
<td>7.40 ± 0.02</td>
<td>56 ± 4</td>
<td>227 ± 14</td>
<td>0.70 ± 0.04</td>
<td>95 ± 9</td>
</tr>
<tr>
<td></td>
<td>VeE2</td>
<td>440 ± 29</td>
<td>26 ± 3</td>
<td>7.48 ± 0.05</td>
<td>55 ± 2</td>
<td>232 ± 21</td>
<td>0.91 ± 0.07</td>
<td>91 ± 9</td>
</tr>
<tr>
<td></td>
<td>VeE3</td>
<td>354 ± 37</td>
<td>37 ± 5</td>
<td>7.39 ± 0.02</td>
<td>73 ± 4</td>
<td>214 ± 10</td>
<td>0.72 ± 0.06</td>
<td>65 ± 9</td>
</tr>
<tr>
<td></td>
<td>VeE4</td>
<td>254 ± 12</td>
<td>37 ± 3</td>
<td>7.40 ± 0.02</td>
<td>66 ± 4</td>
<td>238 ± 15</td>
<td>0.58 ± 0.06</td>
<td>78 ± 10</td>
</tr>
<tr>
<td>2h</td>
<td>VeB1</td>
<td>301 ± 50</td>
<td>41 ± 6</td>
<td>7.37 ± 0.02</td>
<td>69 ± 2</td>
<td>203 ± 7</td>
<td>0.86 ± 0.05</td>
<td>78 ± 9</td>
</tr>
<tr>
<td></td>
<td>VeB2</td>
<td>386 ± 33</td>
<td>37 ± 4</td>
<td>7.38 ± 0.64</td>
<td>56 ± 4</td>
<td>219 ± 9</td>
<td>0.64 ± 0.06</td>
<td>87 ± 11</td>
</tr>
<tr>
<td></td>
<td>VeB3</td>
<td>440 ± 29</td>
<td>26 ± 2</td>
<td>7.48 ± 0.02</td>
<td>59 ± 4</td>
<td>231 ± 19</td>
<td>0.80 ± 0.08</td>
<td>80 ± 10</td>
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<tr>
<td></td>
<td>VeB4</td>
<td>254 ± 37</td>
<td>37 ± 5</td>
<td>7.39 ± 0.02</td>
<td>73 ± 4</td>
<td>214 ± 10</td>
<td>0.72 ± 0.06</td>
<td>65 ± 9</td>
</tr>
<tr>
<td>3h</td>
<td>VeB1</td>
<td>371 ± 33</td>
<td>37 ± 3</td>
<td>7.40 ± 0.02</td>
<td>66 ± 4</td>
<td>238 ± 15</td>
<td>0.58 ± 0.06</td>
<td>78 ± 10</td>
</tr>
<tr>
<td></td>
<td>VeB2</td>
<td>306 ± 49</td>
<td>29 ± 4</td>
<td>7.46 ± 0.05</td>
<td>60 ± 8</td>
<td>220 ± 11</td>
<td>0.62 ± 0.05</td>
<td>62 ± 6</td>
</tr>
<tr>
<td></td>
<td>VeB3</td>
<td>274 ± 41</td>
<td>40 ± 3</td>
<td>7.40 ± 0.02</td>
<td>71 ± 2</td>
<td>202 ± 12</td>
<td>0.69 ± 0.07</td>
<td>63 ± 10</td>
</tr>
<tr>
<td></td>
<td>VeB4</td>
<td>355 ± 41</td>
<td>36 ± 2</td>
<td>7.40 ± 0.01</td>
<td>65 ± 5</td>
<td>236 ± 7</td>
<td>0.52 ± 0.05</td>
<td>74 ± 8</td>
</tr>
<tr>
<td>4h</td>
<td>VeB1</td>
<td>253 ± 59</td>
<td>29 ± 5</td>
<td>7.42 ± 0.13</td>
<td>52 ± 7</td>
<td>234 ± 15</td>
<td>0.61 ± 0.11</td>
<td>62 ± 13</td>
</tr>
<tr>
<td></td>
<td>VeB2</td>
<td>274 ± 41</td>
<td>40 ± 3</td>
<td>7.40 ± 0.02</td>
<td>71 ± 2</td>
<td>202 ± 12</td>
<td>0.69 ± 0.07</td>
<td>63 ± 10</td>
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<td></td>
<td>VeB3</td>
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<td></td>
<td>VeB4</td>
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<td>29 ± 5</td>
<td>7.42 ± 0.13</td>
<td>52 ± 7</td>
<td>234 ± 15</td>
<td>0.61 ± 0.11</td>
<td>62 ± 13</td>
</tr>
</tbody>
</table>

Values are means ± SE. PaO2, arterial partial pressure of O2; PaCO2, arterial partial pressure of CO2; MBP, mean arterial blood pressure; HR, heart rate; Cdyn, dynamic compliance; BL, baseline. As a function of time (t P < 0.05) and group (t P < 0.05), there are significant changes in PaO2 and Cdyn. There are significant changes in Cdyn% as a function of time (t P < 0.05) only and in PaCO2 as a function of group (t P < 0.05) only.

Fig. 3. PFC saturation in expired gas samples (top) and PFC evaporative loss rate (bottom) for each group with different ventilation strategy as a function of time after administration. All 3 groups changed significantly (P < 0.05) over time after instillation. However, there was no significant difference among groups. All data are presented as means ± SE. RR, respiratory rate; RR50, RR50, and RR50, 20, 30, and 50 breaths/min groups, respectively.

Fig. 4. PFC loss as a % of initial dose (top) and residual PFC in the lungs (bottom) for each group with different ventilation strategy as a function of time after instillation. All 3 groups changed significantly (P < 0.05) over time after instillation. However, there was no significant difference among groups. All data are presented as means ± SE.
Deterioration in both oxygenation and lung compliance.

Diminished as a result of evaporative loss, there is a correlation between oxygenation, lung mechanics, and residual PFC. These data indicate a physiological correlation between the amount of residual PFC and Cdyn% (r = 0.87). These data show a significant (P < 0.001) positive correlation between the amount of residual PFC and Cdyn% (r = 0.87). These data indicate a physiological correlation between oxygenation, lung mechanics, and residual perflubron in the lungs; thus, as residual perflubron is diminished as a result of evaporative loss, there is a deterioration in both oxygenation and lung compliance.

### Table 4. Cardiopulmonary profiles in ventilation strategy study

<table>
<thead>
<tr>
<th>Time</th>
<th>Groups</th>
<th>PaO₂ mmHg</th>
<th>PaCO₂ mmHg</th>
<th>pH</th>
<th>MPB, mmHg</th>
<th>HR, beats/min</th>
<th>Cdyn, ml·cmH₂O⁻¹·kg⁻¹</th>
<th>Cdyn%, % of BL</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>RR₂₀</td>
<td>497 ± 10</td>
<td>26 ± 3</td>
<td>7.50 ± 0.03</td>
<td>63 ± 9</td>
<td>220 ± 10</td>
<td>1.09 ± 0.11</td>
<td>100 ± 0</td>
</tr>
<tr>
<td></td>
<td>RR₄₀</td>
<td>468 ± 9</td>
<td>28 ± 2</td>
<td>7.46 ± 0.01</td>
<td>52 ± 4</td>
<td>197 ± 11</td>
<td>0.87 ± 0.06</td>
<td>100 ± 0</td>
</tr>
<tr>
<td></td>
<td>RR₆₀</td>
<td>464 ± 14</td>
<td>34 ± 3</td>
<td>7.40 ± 0.03</td>
<td>53 ± 8</td>
<td>220 ± 13</td>
<td>0.98 ± 0.08</td>
<td>100 ± 0</td>
</tr>
<tr>
<td>1h</td>
<td>RR₂₀</td>
<td>442 ± 14</td>
<td>26 ± 3</td>
<td>7.49 ± 0.03</td>
<td>65 ± 6</td>
<td>244 ± 11</td>
<td>1.16 ± 0.09</td>
<td>107 ± 7</td>
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<tr>
<td></td>
<td>RR₄₀</td>
<td>405 ± 28</td>
<td>32 ± 2</td>
<td>7.44 ± 0.03</td>
<td>52 ± 4</td>
<td>225 ± 11</td>
<td>0.85 ± 0.07</td>
<td>99 ± 7</td>
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<td></td>
<td>RR₆₀</td>
<td>350 ± 42</td>
<td>37 ± 4</td>
<td>7.36 ± 0.04</td>
<td>67 ± 6</td>
<td>242 ± 19</td>
<td>0.73 ± 0.05</td>
<td>93 ± 2</td>
</tr>
<tr>
<td>2h</td>
<td>RR₂₀</td>
<td>387 ± 54</td>
<td>30 ± 4</td>
<td>7.46 ± 0.05</td>
<td>64 ± 5</td>
<td>254 ± 10</td>
<td>0.99 ± 0.04</td>
<td>94 ± 8</td>
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<tr>
<td></td>
<td>RR₄₀</td>
<td>383 ± 32</td>
<td>31 ± 2</td>
<td>7.44 ± 0.02</td>
<td>53 ± 6</td>
<td>224 ± 10</td>
<td>0.66 ± 0.04</td>
<td>76 ± 4</td>
</tr>
<tr>
<td></td>
<td>RR₆₀</td>
<td>382 ± 27</td>
<td>35 ± 3</td>
<td>7.38 ± 0.03</td>
<td>56 ± 5</td>
<td>248 ± 24</td>
<td>0.70 ± 0.07</td>
<td>89 ± 5</td>
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<tr>
<td>3h</td>
<td>RR₂₀</td>
<td>333 ± 68</td>
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<td>7.47 ± 0.05</td>
<td>61 ± 8</td>
<td>244 ± 13</td>
<td>0.84 ± 0.10</td>
<td>77 ± 5</td>
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<td>380 ± 40</td>
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<td>225 ± 9</td>
<td>0.60 ± 0.06</td>
<td>68 ± 4</td>
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<td>RR₆₀</td>
<td>317 ± 40</td>
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<td>7.34 ± 0.03</td>
<td>66 ± 8</td>
<td>230 ± 17</td>
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<td>72 ± 6</td>
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<tr>
<td>4h</td>
<td>RR₂₀</td>
<td>273 ± 77</td>
<td>32 ± 3</td>
<td>7.40 ± 0.05</td>
<td>68 ± 7</td>
<td>227 ± 27</td>
<td>0.68 ± 0.05</td>
<td>67 ± 12</td>
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<td>RR₄₀</td>
<td>344 ± 65</td>
<td>31 ± 2</td>
<td>7.42 ± 0.02</td>
<td>54 ± 5</td>
<td>216 ± 10</td>
<td>0.56 ± 0.06</td>
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<tr>
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<td>RR₆₀</td>
<td>315 ± 49</td>
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<td>62 ± 9</td>
<td>241 ± 9</td>
<td>0.50 ± 0.03</td>
<td>64 ± 5</td>
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</tbody>
</table>

Values are means ± SE. As a function of time (*P < 0.05) and group (**P < 0.05), there is a significant change in Cdyn. There are significant changes in Cdyn% and PaO₂ as a function of time (*P < 0.05) only and in PaCO₂ as a function of group (**P < 0.05) only.

**DISCUSSION**

The data presented herein demonstrate that when V̇E is increased during PLV, the evaporative loss of PFC is increased. This information has significant implications with respect to subsequent redosing during the clinical application of PLV. Higher evaporative loss from the lungs in subjects treated with higher V̇E indicates it is necessary to replace PFC sooner than those with lower V̇E. As noted herein, to maintain 80% of the initial dose in the lungs, the V̇E₃₀ group would require dosing 20 min more frequently than the V̇E₄₀ group. In addition, as noted in Fig. 5, there are graded physiological consequences in oxygenation and pulmonary compliance associated with evaporative loss and no replacement dosing. Furthermore, during PLV with the same V̇E, it was shown that all components of E_L are dependent on time after instillation and not ventilation strategy (high RR vs. low RR). Thus ventilation strategy has little impact on PFC redosing schedule during PLV.

The physiochemical properties of PFC liquid have been studied by previous investigators (7, 18, 22, 27, 44). The vapor pressure of breathable PFC liquids ranges from 0.2–400 mmHg at a temperature of 37°C, so the rate of evaporative loss from the respiratory system is vapor pressure dependent (29). Also, PFC volatilization from the lungs is the major route of elimination from the body, because PFC is not metabolized in the body (31, 43). In addition to vapor pressure, several other factors influence the elimination of PFC from the lungs, including the physicochemical properties of PFC and physiological factors of animals or humans (43).

As previously reported, it appears that maintaining the amount of PFC liquid in damaged lungs prevents time-dependent changes in gas exchange and pulmonary function during PLV (1, 6, 8, 9, 11–14, 23–25, 38, 39, 42, 44). Therefore, it is valuable to have a continuous assessment of the amount of PFC in the lung to maintain the physiological effectiveness of PLV. Sev-
Several radiological studies have also confirmed the evaporation and redistribution processes in animals and humans after administration of various amounts of PFC into the lungs (8, 10, 17, 34, 36, 45). On the basis of these findings, investigators focused on the design of methods for monitoring the elimination of PFC from the lungs (15, 21, 29). Using the thermal detector method, Miller et al. (17) reported that the elimination rate after multiple doses of PFC would be significantly higher than that after a single dose. Likewise, Weis et al. (41) reported that the elimination of PFC was dependent on the initial dose and the time after instillation. Preliminary data indicate that repositioning during PLV modulates PFC elimination from the lungs and that position (supine vs. prone) during PLV results in a different loss rate (5, 17, 29). To prevent PFC elimination during PLV, several ventilator circuit designs for PFC dose maintenance are currently under investigation (19, 28).

In the present study, the primary focus was on $V_e$ and ventilation strategy and subsequent effects on perflubron elimination during 4 h of PLV. In addition, the physiological consequences associated with perflubron evaporation were correlated with $V_e$ and ventilation strategy. Numerous animal and clinical studies have reported the need to redose perflubron during short-term and long-term PLV; however, none of these studies was able to correlate the need for redosing with the actual evaporative loss of perflubron (9, 11–13, 23, 26, 42). The results presented herein show that, with regard to ventilator management, $V_e$ is a major factor that influences the elimination of perflubron from the lungs. Thus, whenever $V_e$ is adjusted during PLV as a result of ventilator management and clinical care, it is necessary to consider the influence of $V_e$ changes on perflubron elimination and to adjust the redosing schedule appropriately. As noted by Weis et al. (41), the need for redosing is potentiated by initial dose requirements; that is, lower initial doses (6 ml/kg) require more frequent dosing than larger initial doses (18 ml/kg). It is also noteworthy that in the present study it was found that, as long as $V_e$ was maintained constant, alterations in RR from 20 to 50 breaths/min had little effect on PFC loss profile.

The issue of an “optimum initial PFC dose” is still under investigation, although doses from 25 to 100% of FRC have been studied with varied success (6, 14, 26, 32, 42). In the present experiment, we initially administered 6 ml/kg perflubron into the lungs, ~1/3 the normal FRC volume of a juvenile rabbit (17, 41). We based this initial dose on previous studies (17, 41) as well as on the low dose protocol for the current phase III, adult clinical trial for PLV (personal communication, Dr. Mark Wedel, Alliance Pharmaceutical). In addition, it has been reported that this volume of perflubron is sufficient to coat the lung because of a conformational change from a droplet to a film during inflation (35).

Partial liquid ventilation with PFC liquid has been reported to be effective in treating experimental respiratory failure (12, 44). Success has been associated with the high solubility of respiratory gases in the PFC liquid that support gas exchange. Furthermore, several investigators also noticed that lung compliance could improve due to the recruitment of alveoli and reducing the surface tension in damaged lungs (23, 35, 38, 39, 41, 42). In contrast to the injured lung, numerous studies have shown that residual PFC liquid in a healthy lung does not improve pulmonary mechanics or gas exchange. In addition, it has been shown that the gas exchange response to residual PFC liquid in the lungs is inversely related to lung condition (30).

Furthermore, it has been shown that during prolonged PLV (without replacement dosing), there is a deterioration of lung mechanics, gas exchange, and histology, which suggested that atelectasis does occur during return to conventional mechanical ventilation. These findings have also been shown in the short-term studies presented herein. It is noteworthy that time-dependent deterioration in oxygenation and compliance were not observed in our pilot studies of rabbits with healthy lungs without PLV. In addition, to the degree that these studies were in agreement with that of Tutuncu et al. (40), time-dependent deterioration in cardiopulmonary function can be excluded, with reason, as a possible covariant in the relationship between oxygenation and compliance with residual PFC volume.

The mechanism for alterations in gas exchange and lung mechanics can be explained as illustrated in Fig. 6. As shown, when the lungs are initially instilled with PFC (depending on the initial dose), most of the alveoli are recruited. Thus the lung is divided into three compartments: 1) gas filled with a PFC film lining (nondependent); 2) partially gas filled with a PFC film lining...
and partially PFC liquid filled (midlung region); and 3) PFC liquid filled (dependent). As PFC liquid evaporates and the animals are still paralyzed, the alveoli with PFC are more likely to remain expanded. Nondependent and midlung regions demonstrate the highest degree of clearing, whereas the dependent regions remain relatively liquid filled (17). Thus derecruitment of alveoli secondary to PFC evaporation is probably associated with the observed deterioration in oxygenation and compliance (Fig. 5). Although the present study is not supported with histopathological evidence, previously we have shown that nonuniform PFC distribution and histopathological correlates during PLV of the respiratory distress syndrome lung (44). Therefore, to prevent unnecessary compromise in oxygenation and lung mechanics, as shown herein, accurate replacement of evaporated PFC is crucial to maintain optimum treatment with PLV, especially when the V°E is changed.

In conclusion, for the presented juvenile animal model, it was found that the evaporative loss profile is dependent on V°E with little effect of the RR-V°e combination. Thus assessment of PFC evaporative loss and V°E should be considered for the replacement dosing schemes during PLV. Finally, the present study was conducted in healthy juvenile animals. These data suggest that further studies of injured, larger, and human lungs in a clinical setting are warranted to evaluate the effect of ventilation strategy on PFC elimination.

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