Inflation Pressure and Lung Vascular Injury in Preterm Lambs*

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Pulmonary microvascular injury and edema develop in >50 percent of lambs that are born prematurely at ~130 days (term = 147 days) gestation.1 Lung overexpansion with high inflation pressure increases pulmonary vascular protein permeability in mature lambs.2 To study the effects of inflation pressure on the pulmonary circulation after premature birth, we measured lung vascular pressures, lymph and pleural liquid protein drainage (Qpr), and extravascular lung water (EVLW) in 25 chronically-catheterized preterm (126 to 129 days) lambs that were mechanically ventilated at a respiratory rate of either 80/min (n = 11) or 30/min (n = 14) for 8 h after operative delivery; 8 of these lambs (4 ventilated at 80/min, 4 at 30/min) received 350 mg of calf lung surfactant (Infasurf) just before birth. Peak inflation pressure (PIP) was adjusted to keep PaCO₂ ~ 40 mm Hg, end-expiratory pressure was 5 to 6 cm H₂O, and FIO₂ was 1.0. Based on our earlier studies, we defined lung vascular injury as a postnatal increase in Qpr (>0.5 g in the 8 h after birth. In addition to the aforementioned variables, we measured circulating neutrophil counts before and after birth. Results are summarized as follows:

<table>
<thead>
<tr>
<th>Lung Vascular Injury of Lambs</th>
<th>PIP, 0-2 h, cm H₂O</th>
<th>PIP, 6-8 h, cm H₂O</th>
<th>PaO₂, 6-8 h, mm Hg</th>
<th>EVLW, g/dry lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 9</td>
<td>42 ± 3</td>
<td>PaO₂, 6-8 h,</td>
<td>36 ± 10</td>
<td>6.6 ± 0.4</td>
</tr>
<tr>
<td>16</td>
<td>30 ± 2*</td>
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</tbody>
</table>

Mean ± SE; 0-2 h and 6-8 h refer to time after birth.

*Significant difference, p < 0.05.

Lung vascular injury developed in six of ten lambs that received no surfactant and were ventilated at 30/min (PIP, 0 to 2 h = 41 ± 2 cm H₂O), three of seven that received no surfactant and were ventilated at 80/min (PIP, 0 to 2 h = 33 ± 4 cm H₂O), and zero of eight that were given surfactant at birth (PIP, 0 to 2 h = 27 ± 2 cm H₂O). The PaO₂ was <50 mm Hg during the last 2 h of study in seven lambs that were ventilated at 30/min, three that were ventilated at 80/min, and none that received surfactant. Severe pulmonary edema (EVLW >6) occurred in seven lambs that were ventilated at 30/min, two that were ventilated at 80/min, and one that received surfactant. Circulating neutrophils decreased in all lambs by 30 to 90 min after birth, but the decrease was more than twice as great (68 ± 5 vs 27 ± 8 percent) in the 9

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lambs with subsequent lung injury compared to the 16 lambs without lung injury.

These results suggest that inflation pressure may influence lung vascular protein permeability and edema in lambs that receive mechanical ventilation after premature birth, and that the degree to which circulating neutrophils decrease soon after birth may help to predict subsequent development of lung vascular injury and edema in preterm lambs.

REFERENCES

Alveolar Type II Cell Na,K-ATPase Is Upregulated During Mechanical Ventilation-induced Pulmonary Edema*

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Pulmonary edema formation occurs by two mechanisms: increased hydrostatic pressures in the pulmonary circulation, as seen in patients with congestive heart failure, and/or increased permeability, as seen in patients with adult respiratory distress syndrome.1-3 Regardless of the etiology, once lung edema is present, its clearance occurs mainly by active epithelial Na⁺ transport.4,5 Previous studies have shown that lung liquid clearance stops completely when active metabolic processes for solute transport are nonspecifically inhibited by hypothermia, and that clearance is partially inhibited by amiloride, ouabain, and atrial natriuretic factor.5,6 Although other mechanisms may have a role, the clearance of pulmonary edema appears to be mostly effected by a combination of alveolar apical Na⁺ channels and the basolaterally located Na⁺,K⁺-ATPases.7-10 Specifically, alveolar Na⁺,K⁺-ATPase has been proposed to play an important role in effecting edema clearance by the active transport of Na⁺.

Recently, it has been shown that mechanical ventilation with high tidal volumes in rats produces a form of barotrauma characterized by increased lung permeability and alveolar edema accumulation.11 Other forms of injury have been shown to upregulate protective mechanisms against lung injury.10,12 Thus, we tested whether alveolar epithelial Na⁺,K⁺-ATPase is upregulated as a protective mechanism against lung edema in this model of acute lung injury.

EXPERIMENTAL DESIGN AND RESULTS

We studied 12 adult, pathogen-free Sprague Dawley male rats (weight ~ 300 g). Two groups of four rats were mechanically ventilated for 25 min with the following: (a) low tidal volumes (3 to 5 ml) to a peak airway pressure of 10 cm H₂O; and (b) high tidal volumes (12 to 15 ml) to a peak airway pressure of 35 cm H₂O and compared to (c) four control nonventilated rats.

Immediately following mechanical ventilation, alveolar type II (ATII) cells were isolated and Na⁺,K⁺-ATPase hydrolytic activity was measured by preincubating microsomal membrane fractions with and without 1 mM ouabain for 45 min. The results were corrected for spontaneous hydrolysis of Na⁺,K⁺-ATPase, and the inorganic phosphate was measured by the method of Fiske and Subbarow. We measured ³H-ouabain binding in these ATII cells in the presence of 10⁻⁶ M ³H-ouabain. We isolated RNA from these ATII cells and measured the α₁ Na⁺,K⁺-ATPase mRNA with a cRNA probe and corrected for the lane loading with 18S. We also measured

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![3 H-ouabain binding](Figure 1. ³H-ouabain binding increased in alveolar type II cells isolated from rats ventilated with high tidal volumes for 25 min.)