Mechanisms of Lung Injury and Disrupted Development in Neonates

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Disclosure

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Mechanisms of Ventilator Induced Lung Injury

• Barotrauma vs. Volutrauma
• Atelectrauma with Surfactant deficiency/dysfunction
• Increased pulmonary-systemic translocation of cytokines and macromolecules (“Biotrauma”)
• Abnormal O₂ regulation vs. toxicity

Barotrauma vs. Volutrauma

Chest Wall Restriction Eliminates Barotrauma in Young Rabbits

Mechanisms of Lung Injury During Neonatal Resuscitation

• Volutrauma
• Atelectrauma with surfactant deficiency/dysfunction
• Increased pulmonary-systemic translocation of cytokines and macromolecules (“Biotrauma”)
• Abnormal O₂ regulation vs. toxicity
• Barotrauma – not really
• “Barophobia” – absolutely!!!
Antecedents to Volutrauma with Underdeveloped or Injured Lungs

- Inadequate surface area
- Non-uniform inflation
- Surfactant deficiency or inhibition
- V/Q Mismatch
- Overly compliant chest wall

Airspace Surface Area Trails Intrauterine Growth

At 23 weeks GA, SA is only 5% of 40 weeks GA while Birth Wt is 17%

Non-Uniform Inflation in Micropremies

- "normal" tidal volumes = overinflation of too few distal airspaces
- Number of distal airspaces are decreased by both decreased surface area with immaturity and atelectasis due to surfactant deficiency

Relative Distal Airspace Volume at “Normal Tidal Volume” of 5 ml/kg

<table>
<thead>
<tr>
<th>Relative Lung SA/BW</th>
<th>Overall TV</th>
<th>% Atelectasis</th>
<th>Average Relative TV/distal airspace</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 ml/kg</td>
<td>0%</td>
<td>5 ml/kg</td>
</tr>
<tr>
<td>1</td>
<td>5 ml/kg</td>
<td>25%</td>
<td>6.7 ml/kg</td>
</tr>
<tr>
<td>1</td>
<td>5 ml/kg</td>
<td>50%</td>
<td>10 ml/kg</td>
</tr>
<tr>
<td>1</td>
<td>5 ml/kg</td>
<td>75%</td>
<td>20 ml/kg</td>
</tr>
<tr>
<td>5/17</td>
<td>5 ml/kg</td>
<td>25%</td>
<td>23 ml/kg</td>
</tr>
<tr>
<td>5/17</td>
<td>5 ml/kg</td>
<td>50%</td>
<td>34 ml/kg</td>
</tr>
<tr>
<td>5/17</td>
<td>5 ml/kg</td>
<td>75%</td>
<td>68 ml/kg</td>
</tr>
</tbody>
</table>

Non-Uniform Inflation in Micropremies

- "normal" tidal volumes = overinflation of too few distal airspaces
- nonuniform inflation with relative overdistension of the ventilated segments
Dilated Alveolar Ducts, Flattened Alveoli, and Microatelectasis after CMV x 24 hrs in Surfactant-deficient Preterm Lambs


Non-uniform Inflation with RDS

Morgenroth The Surfactant System of the Lungs, 1989

What Does Tidal Volume Mean with Marked Heterogeneity of Ventilation?

Frank et al.: Pathogenesis of VILI. Physiological Basis of Ventilatory Support 2003

Maximum Respiratory Pressures in Trumpet Players

Maximal expiratory pressures at total lung capacity after a maximal inspiration were 235 cm H2O for a full second in experienced trumpet players


Atelectrauma with Surfactant Deficiency/Dysfunction

Pinkerton et al.: Alveolar Epithelial Injury in Ventilator-associated Lung Injury

Atelectrauma with Surfactant Deficiency/Dysfunction


Morgenroth The Surfactant System of the Lungs, 1989

Frank et al.: Pathogenesis of VILI. Physiological Basis of Ventilatory Support 2003


Pinkerton et al.: Alveolar Epithelial Injury in Ventilator-associated Lung Injury
Atelectasis and/or Non-uniform Inflation Prior to Surfactant Instillation Promote Non-uniform Surfactant Distribution

LaPlace's Law  \( P = \frac{2T}{r} \)

- Surfactant: Pressure is greater in the smaller bubble
- + Surfactant: Pressure is equalized in the large and small bubbles

Larger bubble
- \( r = 2 \)
- \( T = 3 \)
- \( P = \frac{2 \times 3}{2} = 3 \)

Smaller bubble
- \( r = 1 \)
- \( T = 3 \)
- \( P = \frac{2 \times 3}{1} = 6 \)

Surface Tension in Lung Mechanics

Law of Laplace: \( P = \frac{2T}{r} \)

A: \( P = \frac{2 \times 12}{1 \times 1} = 24 \) dyn/cm²

B: \( P = \frac{2 \times 72}{10^{-3}} = 14,400 \) dyn/cm² = 80 cmH₂O

Assume ST is constant at 72 dyn/cm

100X the pressure is required to maintain B then A

Non-uniform Surfactant Distribution Further Augments Non-uniform Ventilation and Atelectasis

Bronchoepithelial Lesions

Frank et al.: Pathogenesis of VILI. Physiological Basis of Ventilatory Support 2003

Hyaline Membrane

Surfactant Inactivation
- primarily caused by edema fluid with high protein content in the airspaces
- procoagulants fibrin and fibrinogen are potent inhibitors
- albumin is a relatively weak inhibitor

Increased Lung Permeability and “Biotrauma”

Lung Protein Permeability Increases with Decreasing GA in Preterm Rabbits

<table>
<thead>
<tr>
<th>Gestation</th>
<th>Lung</th>
<th>AW</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 days</td>
<td>11%</td>
<td>5.2%</td>
</tr>
<tr>
<td>28 days</td>
<td>7.7%</td>
<td>4.0%</td>
</tr>
<tr>
<td>29 days</td>
<td>3.5%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Fullterm (31 days)</td>
<td>1.3%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

30 min recoveries of 131I-labeled albumin given intravenously at birth

Both Endothelial and Epithelial Protein Permeability Increase with Increasing PIP
**Factors Predisposing to BPD at the Time of Rescue Surfactant**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthwt&lt;1000 gms</td>
<td>5.1 (2.4-10.7)</td>
</tr>
<tr>
<td>C-sxn for fetal distress</td>
<td>4.3 (1.7-11.4)</td>
</tr>
<tr>
<td>VEI&lt;0.15</td>
<td>3.0 (1.3-6.7)</td>
</tr>
<tr>
<td>Lowest pCO₂, mm Hg</td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>30-39</td>
<td>3.3 (1.3-8.3)</td>
</tr>
<tr>
<td>≤29</td>
<td>5.6 (2.0-15.6)</td>
</tr>
<tr>
<td>≤29 (PIP&gt;30 cm H₂O)</td>
<td>12.5 (1.2-131)</td>
</tr>
</tbody>
</table>

**Current Strategies to Lessen VILI in Preterm Infants**

- Avoid mechanical ventilation when possible
- Surfactant replacement therapy
- Antenatal maternal corticosteroids
- Use HFOV or CMV with smallest possible TVs and moderate PEEP that prevents collapse
- Permissive hypercapnia
- Sustained Inflation

**Antenatal Corticosteroids Potentiate Dose Responsiveness to Both Endogenous and Instilled Treatment Surfactant**

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![Biodirections](image1.png)

![Factors Predisposing to BPD at the Time of Rescue Surfactant](image2.png)

![Current Strategies to Lessen VILI in Preterm Infants](image3.png)

![Antenatal Corticosteroids Potentiate Dose Responsiveness to Both Endogenous and Instilled Treatment Surfactant](image4.png)
Effects of Maternal ACS and Surfactant on Neonatal Mortality and Morbidity

<table>
<thead>
<tr>
<th></th>
<th>+ ACS</th>
<th>- ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ surf</td>
<td>- surf</td>
</tr>
<tr>
<td>n</td>
<td>57</td>
<td>46</td>
</tr>
<tr>
<td>RDS mortality</td>
<td>0%</td>
<td>7%</td>
</tr>
<tr>
<td>Total mortality</td>
<td>0%</td>
<td>15%</td>
</tr>
<tr>
<td>Air leak</td>
<td>2%</td>
<td>13%</td>
</tr>
<tr>
<td>IVH (3 and 4)</td>
<td>7%</td>
<td>11%</td>
</tr>
<tr>
<td>PDA</td>
<td>28%</td>
<td>22%</td>
</tr>
<tr>
<td>BPD</td>
<td>49%</td>
<td>55%</td>
</tr>
</tbody>
</table>


Pressure vs. Volume Regulation of Mechanical Ventilation

- Pressure regulated ventilation was traditionally used in neonates due to uncuffed endotracheal tubes and flexible ventilator tubing.
- With improvements in pneumotach technology, accurate measurements of expired tidal volumes can be made at the level of the endotracheal tube, making volume regulated mechanical ventilation a possibility.

When is volume regulated ventilation good?

- During increasing compliance following exogenous surfactant
- In full term surfactant sufficient lungs
- Post-operatively to prevent progressive collapse

When could volume regulated ventilation be detrimental?

- In preterm surfactant-deficient lungs with very non-uniform ventilation
- In very preterm lungs with large protein permeability causing hyaline membranes and surfactant inhibition
- In injured lungs with large protein permeability causing surfactant inhibition

Major Limitations

- What does “tidal volume” mean when there’s deficient surface area and varying degrees of atelectasis?
- Minimizing atelectrauma to one region may promote volutrauma to another region
- The distribution of both ventilation and exogenous surfactant are not uniform and instilled surfactant will preferentially go to the areas of least resistance
- Decreased vascularization and alveolarization lead to a “pseudo alveolar-capillary dysplasia”

The Preterm Baboon Model at UTHSC
140d GA Escobedo “Classic” BPD Model

- First mechanically ventilated preterm animals to survive >96 hrs
- >90% incidence of severe HMD without surfactant at the equivalent of 32 weeks GA in human
- 400-600 gram birthweight
- Minimal chronic lung injury noted when given clinically appropriate O2

“Classic” → “New” BPD


Rationale for Development of 125d GA Baboon Model

- Widespread use of surfactant led to increased survival at <28 wks GA with birthweights <1000 gms and much lower levels of supplemental O2 and assisted ventilation (typically only 25-30% FiO2)
- Neither surfactant nor antenatal corticosteroids had major impact on the incidence of BPD
- “New” BPD histology was characterized by oversimplification and disrupted alveolarization in contrast to the altered inflation pattern of hyperoxic lung injury in “Classic” BPD
- 125d GA was 68% full term equivalent to 26 wks GA in human but even more immature because electively delivered with no prior stress factors

Characteristics of 125d GA Premature Baboons

- 300-450 gms birthweight (F<M)
- Fused eyelids (80-90%)
- Transparent skin/large insensible losses
- Very immature lungs requiring very early surfactant replacement
- Leaky capillaries & edema formation
- Immature kidneys
- High incidence of ductus arteriosus
- Immature glucose regulation

In utero Development

125d GA fetal baboon + 2 wks in utero

In utero Development vs Extra-uterine Adaptation

125d GA fetal baboon + 2 wks in utero + 2 wks vent
Preterm Delivery Depresses NOS Activity

Disrupted Development of Distal Lung Epithelium in Preterm Baboons

Does Disrupted Development in Extremely Immature Lungs Lead to a Milder Form of Alveolar Capillary Dysplasia?

Decreased Angiogenesis and Abnormal PECAM –1 in Human BPD

Disrupted Angiogenesis in Chronically Ventilated Preterm Baboons Delivered at Borderline Viability

Abnormal VEGF in Human BPD
**Decreased VEGF mRNA and Protein in Baboon BPD**

In situ Hybridization

**Abnormal 2nd Crest Formation**

Albertine et al. Am J Respir Care Crit Med 159:945, 1999

**Sequela of "Pseudo" Alveolar Capillary Dysplasia after Disrupted Development and VILI**

Poor alignment of vasculature with airspaces

- Increased physiologic deadspace and V/Q Mismatch
- Increased tidal volumes
- Increased volutrauma

**Evidence from Animal Models**

- Inhibition of pulmonary vascular growth leads to decreased alveolarization
- iNO enhanced pulmonary vascular growth, alveolarization, and lung growth

**iNO Improves Pulmonary Function in Preterm Baboons**

McCurnin et al. AJP Lung 288:L450, 2005

**iNO Stimulates Lung Growth in Preterm Baboons**

McCurnin et al. AJP Lung 288:L450, 2005
**iNO Modifies Elastin Deposition and Increases the Length of Secondary Crests in Preterm Baboons**

McCurnin et al. AJP Lung 288:L450, 2005

**Results of iNO Trials in Human Preterm Neonates**

- Use of iNO in premature neonates remains controversial.
- Lower concentrations for a longer duration initially appeared to have benefits if started before 2 weeks of age but subsequent trials have been disappointing.
- The interaction of ventilator type and treatment requires further studies.
- Potential therapies to enhance the effect of iNO may be required:
  - Antioxidants
  - PDE III and V inhibitors
  - Prostacyclin
  - ET receptor blockers

**MSCs as a Potential Therapy for Lung Injury**

Fung ME and Thebaud B. Stem cell–based therapy for neonatal lung disease: it is in the juice. Pediatr Res 75:2, 2014

**Airway Delivery of Mesenchymal Stem Cells Prevents Arrested Alveolar Growth in Neonatal Lung Injury in Rats**


**MSC Therapy in Chronically Mechanically Ventilated Preterm Baboons**

In collaboration with B.Thebaud and M. Moebius

**Ventilation Index (VI)**

- Static compliance (SC)
- Dynamic compliance (DC)
Questions

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