Optimal Surfactant Administration - 2016

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Topics I will Cover:

• What is surfactant?
• What are acute effects of surfactant on the preterm lung?
• What is surfactant inactivation?
• What factors can modulate surfactant treatment responses?
• What variables are important for surfactant distribution?
What is Surfactant?

• Composition
• Source
• Basic metabolism
What is Surfactant?
Alveolar Surfactant

SP-B/SP-C

SP-A/SP-B

SP-D
Functions of Surfactant Proteins

Hydrophilic

- **SP-A**: Tubular myelin, host defense
- **SP-D**: Surfactant lipid homeostasis, host defense, antioxidant

Hydrophobic

- **SP-B**: Surface tension reduction, tubular myelin, Type II cell functions
- **SP-C**: Surface tension reduction, film stability
Measurements to Evaluate Surfactant Metabolism

- **Sat PC Radioactivity**
  - **Synthesis**
  - **Net Catabolism**
  - **Net Clearance/Catabolism**
  - **Alveolar Wash**

**HOURS**

- **Precursor Injection**
Labeling of Surfactant Phosphatidylcholine in Airspaces of Infants with RDS

Incorporation of $C^{13}$ from Glucose

Clearance of $C^{13}$-DPPC

Bunt, et al., AJRCCM, 1999
Torresin, et al., AJRCCM 2000
Surfactant Metabolism in Preterm

• Surfactant pools small – 2-10 mg/kg
• Surfactant treatment dose is large – 100-200 mg/kg
• Surfactant components are recycled for re-secretion
• Increase in surfactant pool from synthesis is slow (peak – 3d)
• Loss of alveoli surfactant is slow – half-life of 3d
What are acute effects of surfactant on the preterm lung?
What are acute effects of surfactant on the preterm lung?

- Increase static lung volumes / hysteresis
- Increase dynamic compliance
- Improve oxygenation and gas exchange
- Make alveolar size more uniform
- Decrease work of breathing
Compliance Response of Preterm Rabbits Treated with "Protein Depleted" Surfactant

Robertson, Clin Physiol. 1983
Effect of Adding SP-B to Surfactant in Ventilated Preterm Rabbits

Treatment Responses to 50 mg/kg Natural Surfactant of 120d Preterm Lambs Following Early Respiratory Failure

Surfactant treatment effects on lung architecture of 132 d GA lambs

Unventilated
No treatment to LL Ventilated 10 h
Surfactant treated - RL Ventilated 10 h

Pinkerton et al., 1997
Surfactant is a “Miracle” drug because it

• Transforms lung physiology
• Provides substrate or precursors for endogenous surfactant synthesis
• Has prolonged effects after a single treatment
What is surfactant inactivation?

• Interference with surface film formation.

• Decrease in effective surfactant pool size.
Inhibition of Surfactant Function in RDS

Airway Samples

<table>
<thead>
<tr>
<th></th>
<th>Minimum Surface Tension (mN/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway Sample</td>
<td>[Bars and error bars]</td>
</tr>
<tr>
<td>Isolated Surfactant</td>
<td>[Bars and error bars]</td>
</tr>
<tr>
<td>Supernatant</td>
<td>[Bars and error bars]</td>
</tr>
</tbody>
</table>

Inhibition of Sheep Surfactant

<table>
<thead>
<tr>
<th>Protein from Supernatant (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 0.5 1.0 1.5 2.0 2.5</td>
</tr>
</tbody>
</table>

Ikegami, Jacobs and Jobe, J. Pediatr, 1983
Effect of Surfactant Treatment on Oxygenation and Surface Tension in Preterm Lambs

Ikegami, Jobe & Glatz, J. Appl. Physiol., 1981
Bronchoalveolar Lesions in Airways of Preterm Surfactant Deficient Rabbits are Prevented by Surfactant Treatment

Robertson, 1984
Scanning Electron Micrographs of Airways of Ventilated Preterm Rabbits and Effect of Surfactant Treatment

Robertson, 1984
Oxygenation Responses of Infants with RDS to a Surfactant Treatment

 Been, et al., J. Pediatr., 2010
What factors modulate surfactant treatment responses?
What factors modulate surfactant treatment responses?

- Antenatal corticosteroids.
- Injury prior to treatment
- Interactions between surfactant and lung after treatment.
- Distribution of surfactant.
Effects of Surfactant and Corticosteroid Treatments on Lung Volumes of Ventilated Preterm Lambs

Steroid Effect

Surfactant Effect

Ikegami et al., J. Appl. Physiol., 1991
Antenatal Corticosteroids Change Surfactant Dose-response Curves for Both Endogenous and Treatment Dose of Surfactant

Seidner et al., J. Appl. Physiol., 1998
Outcomes of Preterm Infants Treated with Surfactant in Randomized-Controlled Trials Based on Antenatal Corticosteroid Treatments

<table>
<thead>
<tr>
<th></th>
<th>Maternal Corticosteroids + Surfactant</th>
<th>No Surfactant</th>
<th>No Maternal Corticosteroids + Surfactant</th>
<th>No Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient #</td>
<td>57</td>
<td>46</td>
<td>555</td>
<td>566</td>
</tr>
<tr>
<td>Air Leak</td>
<td>1.7%</td>
<td>13%</td>
<td>11.3%</td>
<td>23%</td>
</tr>
<tr>
<td>Grade III/IV IVH</td>
<td>7%</td>
<td>11%</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>28d Mortality</td>
<td>0</td>
<td>15%</td>
<td>18%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Jobe, Mitchell & Gunkel, Am. J. Ob/Gyn., 1993
Maximal Lung Volumes (35 cmH$_2$O) of Preterm Rabbits Ventilated for 45 min

- Treatment at Birth
- Treatment at 30 min

Seidner et al. AJRCCM 152:113, 1995
What variables are important for surfactant distribution?
Physical Variables that Influence Distribution of Surfactant

- Gravity - positioning of lung
- Volume of Instillation
- Speed of Instillation
- Surfactant Properties
  - Adsorption/spreading
- Fluid Volume in Lung
- FLF/Edema fluid
IDEALIZED EFFECT OF SURFACTANT TREATMENT ON ALVEOLAR DIAMETERS

- NO TREATMENT
- UNIFORM TREATMENT
- NONUNIFORM TREATMENT

% OF ALVEOLI

ATELECTATIC  NORMAL  OVERINFLATED

ALVEOLAR DIAMETER
Distribution of Surfactant: Structural limitations

• There are about 20 generations of airways from trachea to saccules in preterm lung

• Therefore, 250,000 binary airway branch points yield 500,000 distal airways leading to saccules

• If distribution of surfactant is not proportionate to number of saccules at end of each branch point, then surfactant distribution will be nonuniform

• The nonuniformity will be amplified at subsequent branch points

∴ Instillation of surfactant should never work because distribution should be very nonuniform
Difference in Surfactant Distribution to Pieces of lungs of Preterm Lambs - Surfactant at Birth or After Ventilation

Surfactant at Birth

Surfactant after Ventilation

Distribution Interval

Modified from Jobe et al., J. Clin. Invest., 1984
Tracheal Instillations of Surfactant Work Because:

- Surfactant spreads quickly - minimizing effects of gravity and nonuniformity of distribution
- Dose-response is wide and dose is high

BUT -

- Surfactant does not spread between lungs or lobes
- Slow/small volume instillations will result in poor distributions
- Aerosols of surfactant go to where lung compliance is best - treat the good lung
Endotracheal Intubation/Mechanical Ventilation – Late 1960’s

Nasal CPAP

Infant Ventilators with PEEP

1940’s
Oxygen

Surfactant

Widespread use of Maternal Corticosteroids

Decrease in Death from RDS