Development of the Human Lung

Peter Rothstein, MD
Professor of Clinical Anesthesiology and Clinical Pediatrics
(Retired)

Learning Objectives:

• Understand the growth and functional development of the respiratory system
• Identify the stages of lung development and the major events of each stage
• Understand the physical and biochemical requirements for alveolar development and function
• Identify the developmental causes of neonatal respiratory failure, tracheoesophageal fistula and diaphragmatic hernia

Phases of Lung Development

• Lung Growth
  – Structural development
  – Anatomic development
  – Affected by physical factors
• Lung Maturation
  – Functional development
  – Biochemical development
  – Affected by hormonal factors

The end result of the development of the lung is an organ with a tremendously large surface area that is approximately 50-100 m², capable of exchanging oxygen and carbon dioxide.

<table>
<thead>
<tr>
<th>Maturation of the Lungs</th>
<th>5-10 weeks</th>
<th>10-20 weeks</th>
<th>20 weeks to birth</th>
<th>6 months to childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudoglandular period</td>
<td>Branching has continued to form terminal bronchioles. No respiratory bronchioles or alveoli are present.</td>
<td>Each terminal bronchiole divides into 2 or more respiratory bronchioles, which in turn divide into 3-8 alveolar ducts.</td>
<td>Terminal sacs (primitive alveoli) form, and capillaries establish close contact.</td>
<td>Mature alveoli have well-developed epithelial endothelial (capillary) contacts.</td>
</tr>
<tr>
<td>Cartilaginous period</td>
<td>Terminal sacs form</td>
<td>Terminal sacs form</td>
<td>Terminal sacs form</td>
<td>Terminal sacs form</td>
</tr>
<tr>
<td>Terminal sac period</td>
<td>Terminal sacs form</td>
<td>Terminal sacs form</td>
<td>Terminal sacs form</td>
<td>Terminal sacs form</td>
</tr>
<tr>
<td>Alveolar period</td>
<td>Terminal sacs form</td>
<td>Terminal sacs form</td>
<td>Terminal sacs form</td>
<td>Terminal sacs form</td>
</tr>
</tbody>
</table>
Derivation of lung elements

- Lung buds lined by endodermally derived epithelium—differentiates into respiratory epithelium, which lines airways and specialized epithelium that lines the alveoli
- Ectoderm—contributes to innervation
- Mesoderm—blood vessels, smooth muscle, cartilage and other connective tissue

- The pseudoglandular stage takes place between the 7th and 16th week of embryonic development

- For branching to occur, bronchial mesoderm is required.
- The rate and extent of branching is proportional to the amount of mesenchyme present.
- After 16 weeks, further growth occurs by branching and elongation.
• Cilia appear in the proximal airways by 13 weeks.
• There is a transition from bronchial epithelial cells (ciliated and columnar cells) to alveolar Type II cells.

• Mesenchyme is necessary for epithelial differentiation to occur.
• Differentiation of mesenchyme requires the presence of lung epithelium.

Canalicular Period 16-26 wk

• By 20 weeks the alveolar Type 1 cell is present
• Lamellar bodies start to appear in Type 2 cells

Terminal Sac Period  26 wk →

• Surfactant appears in lamellar bodies of Type 2 cells.
• Stability of the lung at birth correlates with the number of lamellar bodies present.

Primitive Saccule

• By 20 weeks, the alveolar Type 1 cell is present.
• Lamellar bodies start to appear in Type 2 cells.

• Approximately 20 x 10^6 saccules present at birth.
Postnatal stage

“Adult” configuration reached by 5 weeks.

Characteristics of Mature Alveolus

• Connected to alveolar duct
• Lined with Type 1 cells, which are in intimate contact with capillaries
• Each capillary is exposed to 2 alveoli
• Contains surfactant
• Has interconnections with adjacent alveoli through pores of Kohn.
Development of Pulmonary Arterial Muscle

Control of Pulmonary Blood Flow
- Physical Location of Lung Unit
- Gravity
- Oxygen
- Nitric oxide

Hypoxic Pulmonary Vasoconstriction

Physical Influences on Lung Growth
- Lung Liquid

Physical Influences on Lung Growth
- Amniotic fluid
  - Oligohydramnios—Potters syndrome
Physical Influences on Lung Growth

- Congenital diaphragmatic hernia
- Musculoskeletal abnormalities of the chest wall
- Space occupying lesions of the thorax, e.g. pleural effusions
- Oligohydramnios associated with renal or urinary tract abnormalities

Hormonal Influence on the Lung

- Corticotropin stimulates cortisol
- Cortisol stimulates fetal lung fibroblast to produce fibroblast pneumocyte factor, which,
  - Stimulates surfactant production in Type 2 cells
- Thyroid hormone is also necessary for surfactant production
Hormonal Influence on the Lung

- At birth, epinephrine and arginine vasopressin suppress fetal lung fluid production and play a role in its reabsorption

The Problem of Prematurity

- Birth before 36 weeks may be associated with respiratory compromise and failure.
- 80,000 cases/yr of neonatal respiratory failure
- 8,500 deaths
- CNS injury in survivors
- Cost = $4.4 billion/yr

Survanta (beractant)

Fig 1. Mortality for infants 501 to 1500 g, 1991 to 1999, at all 362 network hospitals (solid line) and at 39 hospitals participating in all 9 years (dashed line).
Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK.

Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure.


Neonatal Respiratory Failure

- Incidence
  - 20/1000 boys
  - 15.6/1000 girls
  - 29/1000 blacks

The lung is ignored only at your own peril!

DON’T HOLD YOUR BREATH!