Respiratory distress syndrome in newborn

Eman Badran
Professor of Pediatric

3rd year medical students
December 2018
Outlines

• Definition

• Physiology
  • Respiration
  • Surface tension
  • Lung compliance
  • Lung volume
  • surfactant

• Respiratory distress syndrome in new born
  • Pathophysiology
  • Incidence
  • Presentation
  • management
New perinatal building
Established in April 2014
Case: 1

- M E
- Male new born
- 39 weeks Gestation age
- Born by normal delivery in 25 May 2018

Family History
CLINICAL MANIFESTATION

- Tachypnea
- Nasal flaring
- Intercostal, sternal recession
- Grunting; closure of glottis during expiration
- Cyanosis
Case: 2

- Baby born preterm at 28 week
CLINICAL MANIFESTATION

- Tachypnea
- Nasal flaring
- Intercostal, sternal recession
- Grunting; closure of glottis during expiration
- Cyanosis
Some review

Respiratory physiology
Respiration = Ventilation + the series of exchanges that leads to the uptake of oxygen by the cells, and the release of carbon dioxide to the lungs

Step 1 = ventilation
  - Inspiration & expiration

Step 2 = exchange between alveoli (lungs) and pulmonary capillaries (blood)
  - Referred to as External Respiration

Step 3 = transport of gases in blood

Step 4 = exchange between blood and cells
  - Referred to as Internal Respiration
Ventilation = (inspiration + expiration) responsible muscles

- The diaphragm (only creates about 60-75% of the volume change during inspiration)

- The muscles of inspiration (external intercostals muscles) & muscles of expiration (internal intercostals muscles)
Tidal volume in new born = 4 –6ml / kg
If baby weigh=3kg
TV =12 -18 ml
Surface tension
What is surface tension

It allows this insect to walk on WATER.

**COHESIVE BOND:** WATER ATTRACTION FORCES THROUGH H BOND

**WATER HYDROGEN BOND:** AMONG WATER SURFACE MOLECULES RESIST STRECHING OR BREAKING THE SURFACE.
DEFENETION OF SURFACE TENSION

The attractive force exerted upon the surface molecules of a liquid by the molecules beneath that tends to draw the surface molecules into the bulk of the liquid and makes the liquid assume the shape having the least surface area.
Surface tension could be defined as the property of the surface of a liquid that allows it to resist an external force, due to the cohesive nature of the water molecules.
An air-filled sphere coated with water
An air-filled sphere coated with water has a tendency to collapse (reach a minimum volume) due to the pulling force of water surface tension.
Surface tension

Law of Laplace

\[ P = \frac{2T}{r} \]

Law of Laplace

collapsing pressure: pressure to collapse generated by alveoli (air will go out of alveoli)
Laplace Law

\[ P = \frac{2T}{r} \]

where

- \( P \) = Collapsing pressure on alveolus (dynes/cm²)
- \( T \) = Surface tension (dynes/cm)
- \( r \) = Radius of the alveolus (cm)

- "The pressure inside a balloon is calculated by twice the surface tension, divided by the radius."

- Pressure to collapse generated by alveoli is inversely affected by radius of alveoli
  - \[ \text{Radius} \quad \Rightarrow \quad \text{Pressure to collapse} \]

- The smaller a bubble, the higher the pressure acting on the bubble
- **Smaller alveoli have greater tendency to collapse**
How to decrease ability to collapse

- Increase diameter
- Decrease surface tension
Pulmonary surfactant composition

80% phospholipids
- Dipalmitoylphosphatidylcholine (DPPC) (60%)
- Phosphatidyl glycerol / ethanolamine / inositol (20%)

10% neutral lipids
- Mostly cholesterol

10% Surfactant proteins
- SP-A, SP-D: hydrophilic
- SP-B, SP-C: hydrophobic
Lipids form a monolayer at the air-water interface.

Surface tension decreases as lipid monolayer is compressed.

The **phospholipid** fraction of surfactant is mainly responsible for:
forming surface active films at the respiratory air–liquid interface.

Hydrophilic part: Headgroups oriented towards the aqueous phase.
1. Alveoli are coated with lung surfactant in order to reduce the surface tension of water through:

   a) It scatters among the fluid molecule decreasing the attraction between them.

   b) It also spreads over the fluid preventing air-fluid interface.

   Thus preventing collapse (atelectasis) upon exhalation and decreasing the force necessary to expand the alveoli upon inhalation.

The higher the concentration of phospholipid molecules at the interface (air – water), the fewer the number of water molecules exposed to air and the lower the surface tension.
Surface tension

\[ P \text{ (collapsing Pressure)} = \frac{2 \times T}{r} \]

Lipids form a monolayer at the air-water interface.
The higher the concentration of phospholipid molecules at the interface, the fewer the number of water molecules exposed to air and the lower the surface tension.

Surfactant reduces the Alveolar Surface Tension

\[ P = \frac{2T}{r} \]  

- If we regard the alveoli as spherical bubbles, then: 
- \( P = \text{inward directed collapsing pressure} \) 
- \( T = \text{Surface Tension} \) 
- \( r = \text{radius of the bubble} \)

**Type II Alveoli**

- It lowers alveolar surface tension by interspersing between the water molecules lining the alveoli.
- Surfactant lowers the surface tension of smaller alveoli more than that of large alveoli.
- This prevents smaller alveoli from collapsing and emptying their air contents into the larger alveoli.
Lung Function in respiratory distress syndrome (RDS)

• Reduction in FRC from 30 ml/kg, to as low as 4-5 ml/kg
Source of surfactant

- produced by alveolar type II cells
Endogenous Surfactant composition and functions

- **Proteins (~10%)**

- **SP-As**
  - Host defense
  - Surfactant homeostasis

- **P-D:** Phagocytic function
  - **SP-B**
    - is the most important protein in surfactant
    - required for the biogenesis of pulmonary surfactant and its packing into lamellar bodies
    - For , Spreading, ↓surface tension
  - **SP-C**
    - Adsorption
Surfactant pulmonary mutations disorders

Mutations in one of the genes encoding **SP-A** (*SFTPA2*) have been reported as a cause of pulmonary fibrosis and lung cancer in adults.

- **Mutation in SP-B** gene and neonatal RDS.
- Mutations in the gene encoding **ABCA3**
Surfactant proteins

Surfactant proteins are divided into 2 groups:

- Large and water-soluble SP-A and SP-D proteins
- small, hydrophobic SP-B and SP-C proteins.
Surfactant synthesis

- Synthesized in the smooth endoplasmic reticulum moved to Golgi apparatus

**1-Lipid**

phosphatidylcholine (PC), a large fraction of which contains two palmitic acid side chains that are fully saturated = dipalmitoyl + phosphatidy + choline (DPPC)
Component

Lipid

- The main constituent is dipalmitoylphosphatidylcholine (DPPC).
- Phosphatidylcholine (PC), a large fraction of which contains two palmitic acid side chains that are fully saturated = 2 dipalmitoyl + phosphatidyl + choline (DPPC has a hydrophilic ‘head’ and a lipophilic ‘
- Choline as a head group
Surfactant Synthesis: transport of phospholipids into lamellar bodies: ABCA3 Transporter

ABCA3:

• A member of the ATP-binding cassette family of membrane transporters,

• is located on the limiting membrane of lamellar bodies

• transport of phospholipids into lamellar bodies during the biosynthesis of surfactant.
- **Surfactant** is synthesized by **type II alveolar cells** from fatty acids that either reach the lung from blood or formed (de novo) inside it. It is stored in organelles know as "**lamellar bodies**".
Surfactant synthesis

Exocytosis of lamellar body and formation of tubular myelin

SP-A also interacts with surfactant phospholipids, calcium, and SP-B in order to form tubular myelin
Surfactant Monolayer M
Surfactant-associated proteins SP-B and SP-C are essential for the transition to a monolayer at the air-liquid interface
Surface Tension

- tubular myelin (TM)
Surfactant Monolayer

Surfactant Monolayer

Surfactant-associated proteins SP-B and SP-C are essential for the transition to a monolayer at the air-liquid interface.
Recycling of surfactant

Surfactant is recycled (alveolar type II epithelial cell (AEC2)), catabolized by alveolar macrophages.
Case: 1

- M E
- Male new born
- 39 weeks Gestation age
- Born by normal delivery in 25 May 2018
Mutations in ATP-binding cassette subfamily A3 (ABCA3) are the most common causes of genetic surfactant deficiency. ABCA3-associated surfactant deficiency is inherited in an autosomal recessive manner and has been associated with lethal neonatal respiratory failure and childhood interstitial lung disease.

**POSITIVE RESULT**

Likely pathogenic variant identified

**INTERPRETATION**

A homozygous likely pathogenic variant was identified in the ABCA3 gene. The result is consistent with the genetic diagnosis of autosomal recessive surfactant metabolism dysfunction type 3.

**RECOMMENDATIONS**

- Genetic counselling is recommended.
- We recommend parental carrier testing to confirm homozygosity of the ABCA3 variant in place of compound heterozygosity for a large deletion.
Pathology report

Dysfunction of lamellar Body

ANATOMIC PATHOLOGY CONSULTATION REPORT

Order Number: OC-18-14314  Refer to:
First Name: AL-ABBADI, MOUSA
Last Name: JORDAN UNIVERSITY HOSPITAL
MRN: REFCXX0007100  QUEEN RANIA ST
Gender: Male  Age: 80  DOB: 5/24/2018
Date Received: 06/13/2018  Date Completed: 07/23/2018

DIAGNOSIS:
A. Lung, postmortem right lung biopsy (A1-18, 5/2/2018): Desquamative interstitial pneumonia with focal intraalveolar eosinophilic debris and significant alveolar remodelling. See comment.

Dear Dr. Al-Abdai,

The lung parenchyma significant alveolar epithelial hyperplasia, interstitial widening with scattered lymphocytes. The alveolar spaces contain numerous macrophages and some show amorphous eosinophilic debris highlighted by PAS. There is also significant interstitial fibroblast proliferation and collagen deposition as revealed by Trichrome stain. Focal necrotizing bronchitis and bronchiolitis with intraluminal bacteria is noted. Some alveoli show multinucleated giant cells resembling viral especially RSV related effect. No alveolar deficiency, features of alveolar capillary dysplasia/misalignment of pulmonary veins, congenital infectious etiology or significant hypertensive vascular histologic changes noted.

Electron microscopy shows significant autolytic changes likely related to postmortem effect and delay in processing due to transport. There is a mixture of normal appearing lamellar bodies and some are small and somewhat irregular. Few cells contain lamellar bodies with densely packed membranes and denser cores resembling the fried eggs appearance.

The constellation of the morphologic and ultrastructural features in this case are consistent with desquamative interstitial pneumonia pattern and significant alveolar remodelling most consistent with congenital surfactant dysfunction disorders especially ABCA3 mutation. Definitive diagnosis of these disorders rests on mutation analysis.

Thank you for allowing us to participate in this patient’s care. Please do not hesitate to contact me if I can be of further assistance.
• Functions of surfactant:
Function of Surfactant

- function to protect the lungs from injuries and infections caused by inhaled particles and microorganisms

SP_A
SP-D
Functions of surfactant:

1. This decreased surface tension:
   - Prevent atelectasis at the end of expiration
   - Facilitate recruitment of collapsed airways during inhalation

Roles of Lung surfactant

- Surfactant decreases surface tension
- Pulmonary compliance ↑
- Alveolar collapse ↓
- Fetal lung maturity
  - L/S ratio
  - Phosphatidylglycerol
  - Foam stability or shake test

L/S < 1.5 immature
L/S 1.5-1.9 intermediate
L/S ≥ 2 lung maturity
Functions of surfactant:

• This decreased surface tension:
  • Increase the lung compliance
    ▪ Helps lung expansion during inspiration
Ventilation in the presence of surfactant

- Disrupts the surface tension & cohesion of water molecules
- Impact?
  - prevents alveoli from sticking together during expiration
Functions of surfactant:

\[
\text{Lung compliance} = \frac{\Delta \text{Lung volume}}{\Delta (P_{\text{alv}} - P_{\text{ipl}})}
\]

- Normal compliance
- Decreased compliance
Functions of surfactant:

This decreased surface tension:

- Protects against pulmonary edema as it decreases the filtration forces for the fluid from pulmonary capillaries into alveoli.
Phases of Lung Development

**Embryonic Period**
- Week 4: Formation of major airways
- Week 6: Formation of bronchial tree and portions of respiratory parenchyma
- Week 8: Birth of the acinus

**Fetal Period**
- Week 16: Last generations of the lung periphery formed
- Week 20: Epithelial differentiation
- Week 22: Air-blood barrier formed
- Week 24: Expansion of air spaces
- Week 26: Surfactant detectable in amniotic fluid
- Week 36: Alveolar
- Week 38: Birth

**Organogenesis**
- Formation of major airways
- Formation of bronchial tree and portions of respiratory parenchyma
- Birth of the acinus

**Differentiation**
- Last generations of the lung periphery formed
- Epithelial differentiation
- Air-blood barrier formed
- Expansion of air spaces
- Surfactant detectable in amniotic fluid
- Secondary septation
Surfactant production

• The production of ABCA3 and surfactant proteins A, B, C, and D is:
  • Developmentally regulated:
    • Increases during gestation.

  24 weeks of gestation (production will start)

  34 weeks of gestation (Mature)

Synthesis is enhanced by cortisol
Respiratory distress: mean labored breathing
Respiratory distress syndrome: RDS
Infant respiratory distress syndrome

- Infant respiratory distress syndrome (IRDS), also called neonatal respiratory distress syndrome or respiratory distress syndrome of newborn, previously called hyaline membrane disease.
- It is a syndrome in premature infants caused by developmental insufficiency of surfactant production and structural immaturity in the lungs. It can also result from a genetic problem with the production of surfactant associated proteins.
- RDS affects about 1% of newborn infants and is the leading cause of death in preterm infants.
- The incidence decreases with advancing gestational age, from about 50% in babies born at 26–28 weeks, to about 25% at 30–31 weeks.
Identification of a Novel Genetic Variant Causing abca3 Surfactant Deficiency in a Newborn

Joan Choi, Min Hwang, Jacob Hogue, Levi Funches, Jason Caboot, Katie H....

Background: Surfactant is produced by alveolar type 2 cells and secreted into the alveoli to prevent atelectasis. Respiratory Distress Syndrome (RDS) is caused by surfactant deficiency due to immature lungs in premature infants. Congenital surfactant deficiency is a rare condition caused by mutations in specific surfactant proteins, which can present like RDS in term infants. Mutations in ATP-binding cassette subfamily A3 (ABCA3) are the most common causes of genetic surfactant deficiency. ABCA3-associated surfactant deficiency is inherited in an autosomal recessive manner and has been associated with lethal neonatal respiratory failure and childhood interstitial lung disease (ILD)....

Novel Mutation in the ATP-Binding Cassette Transporter A3 (ABCA3) Encoding Gene Causes Respiratory Distress Syndrome in a Term Newborn in Southwest Iran

Jafar Dehestani, Mohammad Shafiee, Gholamrezah Shariati, Ali Dehestani, Maryam Mehebri, and Hamid Galehdar

Introduction: ABCA3 gene is known to transport phospholipids and cholesterol from the plasma membrane of the alveolar type II cells to the extracellular environment, where they are incorporated into surfactant. The ABCA3 gene is located on chromosome 12q13 and consists of 12 exons. The protein product of the ABCA3 gene is a transmembrane protein that is highly expressed in the type II alveolar cells.

1. Introduction

ABCA3 gene is involved in the transport of phospholipids and cholesterol from the plasma membrane of type II cells to the extracellular environment. This process is critical for the formation and maintenance of surfactant, which is essential for proper lung function. Mutations in the ABCA3 gene have been associated with respiratory distress syndrome (RDS) in newborns. The most common mutations are located in the encoding region of the gene, which affects the production and secretion of surfactant.

Key words: gene polymorphism; haplotype; respiratory distress syndrome; pulmonary surfactant; ABCA3.
Diminished surfactant:

- Progressive Atelectasis
- Loss of functional residual capacity
  - Small lungs and small tidal volume
- Alterations in ventilation perfusion ratios
- Uneven distribution of ventilation
Lung compliance in RDS

• Lung Compliance is also reduced: from 1-2 to 0.2 - 0.5 ml/cmH$_2$O/kg
RDS: clinical picture

• At admission of the baby he has
  • Cyanosis
    • $\downarrow$ Pulse Oximeter 75% (normal > 95%)

Blood gas:
  • $\downarrow$ PaO2 = 45% mmHg (normal 80-108)
  • $\downarrow$ Ph= 7.2 (normal 7.35-7.45)
  • $\uparrow$ CO2 = 65 mmHg (normal 35-45)
Lung hypo perfusion
V/Q mismach
Hyline membrane- combination of sloughed epithelium, protein & edema.
Hyaline membrane - combination of sloughed epithelium, protein & edema.
Photograph of an autopsy specimen demonstrates small atelectatic lungs with focal hemorrhage (arrow) visible on the pleural surface.
Incidence

Respiratory Distress Syndrome (RDS)

- Also known as **Hyaline Membrane Disease (HMD)**
- Commonest cause of preterm neonatal mortality
- RDS occurs primarily in premature infants; its incidence is inversely related to gestational age and birth weight

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 28 wks</td>
<td>60-80%</td>
</tr>
<tr>
<td>32-36 wks</td>
<td>15-30%</td>
</tr>
<tr>
<td>37-39 wk</td>
<td>5%</td>
</tr>
<tr>
<td>Term</td>
<td>Rare</td>
</tr>
</tbody>
</table>

*Nelson Textbook of Pediatrics, 18th Ed.*
Case: 2

- Baby born preterm at 28 week
## Risk Factors

<table>
<thead>
<tr>
<th>Increased Risk</th>
<th>Decreased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Maternal diabetes</td>
<td>• Chronic or pregnancy-associated hypertension</td>
</tr>
<tr>
<td>• multiple births</td>
<td>• maternal heroin use</td>
</tr>
<tr>
<td>• cesarean section delivery</td>
<td>• prolonged rupture of membranes</td>
</tr>
<tr>
<td>• perinatal asphyxia</td>
<td>• antenatal corticosteroid prophylaxis</td>
</tr>
<tr>
<td>• cold stress</td>
<td></td>
</tr>
<tr>
<td>• history of previously affected infants</td>
<td></td>
</tr>
</tbody>
</table>
Prevention

• Prevent preterm
• Identify patients at risk
• Antenatal steroid
Antenatal Corticosteroid Effects

1- speed up lung development
2- Enhance surfactant synthesis
Treatment

• Support respiration
  • Invasive and none invasive methods
• Oxygen (judgment USE)
CPAP (none invasive)
Pulmonary surfactant Use

Aerosol delivery of synthetic lung surfactant

Franz J. Walter, José M. Hernández-Joñel and Alan J. Waring

ABSTRACT

Background. Nasal continuous positive airway pressure (nCPAP) is a widely accepted technique of non-invasive respiratory support in preterm infants with respiratory distress syndrome due to lack of lung surfactant. If this approach fails, the next step is often intubation, mechanical ventilation (MV) and intratracheal instillation of clinical lung surfactant.

Objective. To investigate whether aerosol delivery of advanced synthetic lung surfactant, consisting of peptide mimics of surfactant protein B and C (SP-B and SP-C) and synthetic lipids, during nCPAP improves lung function in surfactant-deficient rabbits.

Methods. Experimental surfactant preparations were produced by formulating 8% Super Mini-B peptide (SB surfactant), a highly active SP-B mimic, and a combination of 1.5% SB and 1.0% of the SP-C mimic SP-Ca ion-lock 1 (BC surfactant), with a synthetic lipid emulsion. After testing aerosol generation using a vibrating membrane nebulizer and aerosol conditioning, the size, surfactant composition and surface activity, we investigated the effects of aerosol delivery of synthetic SB and BC surfactant preparations on oxygenation and lung compliance in saline-lesioned, surfactant-deficient rabbits, supported with either nCPAP or MV.

Results. Particle size distribution of the surfactant aerosols was within the 1-3 μm distribution range and surfactant activity was not affected by aerosolization. A dose equivalent to clinical surfactant therapy in preterm infants (100 μg/kg) aerosol delivery of both surfactant preparations led to a quick and clinically relevant improvement in oxygenation and lung compliance in the rabbits. Lung function recovered to a greater extent in rabbits supported with MV than with nCPAP. BC surfactant outperformed SB surfactant in improving lung function and was associated with higher phospholipid values in bronchoalveolar lavage fluid; these findings were irrespective of the type of ventilatory support (nCPAP or MV) used.

Conclusions. Aerosol delivery of synthetic lung surfactant with a combination of highly active second generation SP-B and SP-C mimics was effective as a therapeutic approach towards alleviating surfactant deficiency in spontaneously breathing rabbits supported with nCPAP. To obtain similar results with nCPAP as with intratracheal instillation, higher dosage of synthetic surfactant and reduction of its retention by the delivery circuit will be needed to increase the lung dose.
Thank YOU