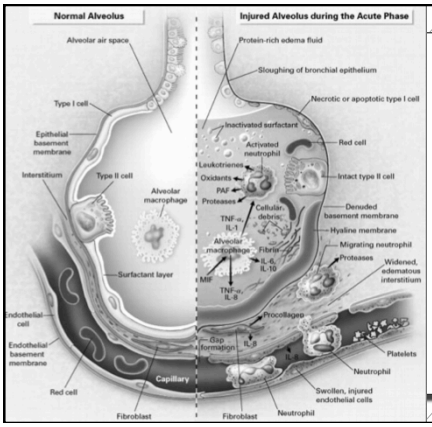
1

Respiratory Distress Syndrome (RDS) in the Newborn

David Lopez, Ed.D., RCP, RRT
RSTH: 421
Neonatal and Pediatric
Respiratory Care

2



Acute Lung Injury in RDS

3

Respiratory Distress in the Newborn

- Incidence
  - Inverse relationship with gestational age
  - 30,000 – 40,000 infants each year
  - Approximately 1% of all pregnancies
  - Most common cause of respiratory distress in premature infants

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Respiratory Distress in the Newborn

- The incidence increases with declining gestational age.
  - Less than 28 weeks 60%
  - 28 - 34 weeks 30%
  - 34 weeks or older < 5%

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Respiratory Distress in the Newborn

- Statistics
  - 1,301 deaths from RDS
  - RDS mortality rate among African Americans was 74.2, versus 26.7 among whites a difference of more than 177 percent.
  - 45-80% of infants born when younger than 28 weeks' gestation
  - approx 1 in 6,800 or 0.01% or 40,000 people in USA

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Respiratory Distress in the Newborn

Cause of RDS

- Surfactant deficiency
- Immature Lung Structure

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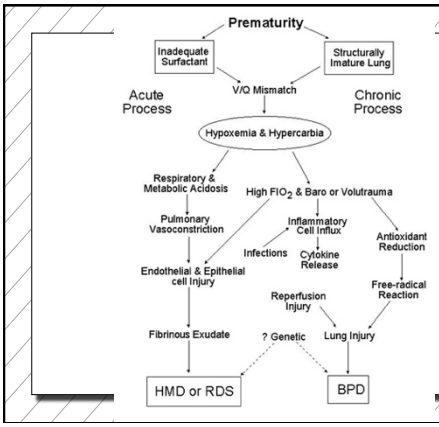

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↑Increased risk of RDS

- Prematurity
- Perinatal asphyxia (hypoxia)
- Maternal diabetes
- Male neonate

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Risks cont.,

- Cesarean delivery (C-section)
- Second-born of twins or multiple births in general
- No, little, or sporatic prenatal care

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Reduced risk of RDS

- SGA (Intrauterine growth retardation)
- Prolonged rupture of membranes(PROM)

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↓ risk of RDS

- Steroids administered pre-natally
  - Significant reduction in incidence of RDS especially when combined with postnatal surfactant administration.
  - Enhances the efficacy of neonatal surfactant

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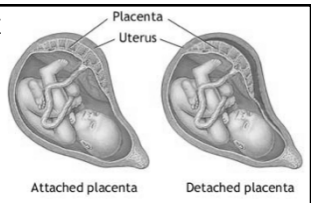
Increased or Decreased risk



- Abruption placentae
- Pre-eclampsia
  - Preeclampsia, Pregnancy Induced Hypertension (PIH) and toxemia are closely related conditions.

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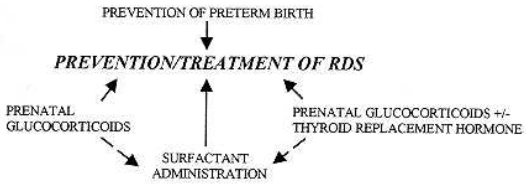
Schematic diagram of potential interventions in RDS



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History

- In contrast, the incidence of RDS decreases with the following:
  - Use of antenatal steroids
  - Pregnancy-induced or chronic maternal hypertension
  - Prolonged rupture of membranes
  - Maternal narcotic addiction

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History

- Secondary surfactant deficiency may occur in infants with the following:
  - Intrapartum asphyxia
  - Pulmonary infections
  - Pulmonary hemorrhage
  - Meconium aspiration pneumonia
  - Oxygen toxicity along with barotrauma or volutrauma to the lungs

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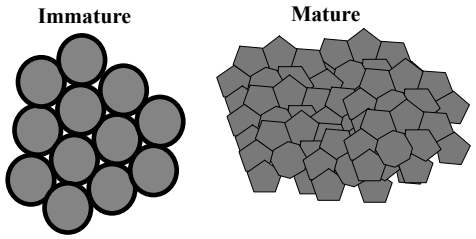
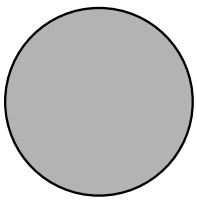
Alveolar Structure



Alveolar Development



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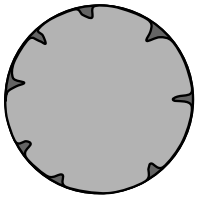
Alveolar Development



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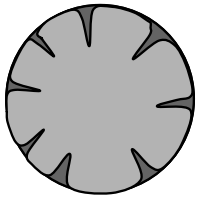
Alveolar Development



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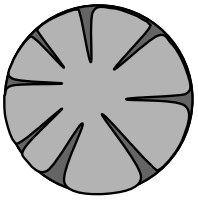
Alveolar Development



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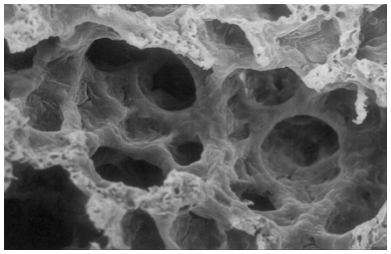
Immature Alveolar Structure



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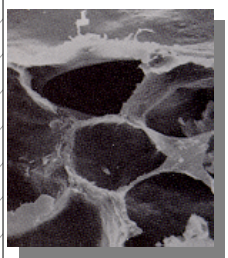
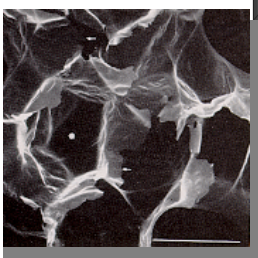
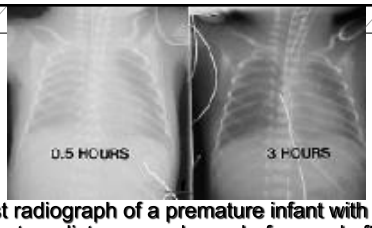
Mature Alveolar Structure





Adult Alveoli



- Chest radiograph of a premature infant with respiratory distress syndrome before and after surfactant treatment. Initially, radiograph exhibits poor lung expansion, air bronchogram, and reticular granular appearance. The chest radiograph repeated when the neonate is aged 3 hours following surfactant therapy demonstrates marked improvement.

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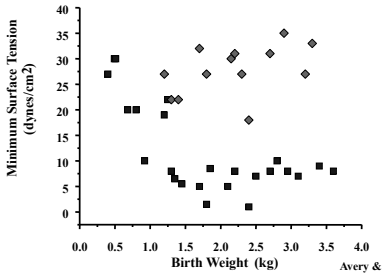
RDS & Defective Surfactant



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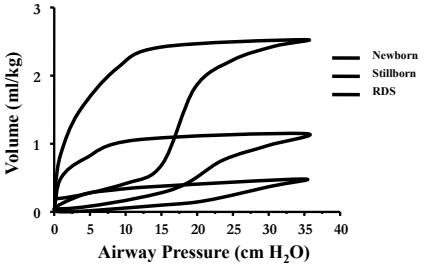
Pressure - Volume Curves



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Respiratory Distress in the Newborn

- Surfactant deficiency
  - Complete absence of surfactant
    - Quantity problem
  - Alteration in production
    - Quality problem
      - Minor phospholipids not present or present in small quantities
      - Proteins may or may not be present

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Surfactant in Infants with RDS

- Qualitative Deficiency
  - Normal stores
  - Decreased release from alveolar type II cell
  - Qualitatively different
    - Increased small aggregate component
  - Inactivation
  - Increased uptake

Surfactant deficiency

- Reutilization Problem
  - Surfactant secreted and recycled by Type II cells.
  - May be regulated by surfactant proteins.

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Infant Respiratory Distress

Type I Cells

- Cover 96% of adult alveolar surface
- Thin, 0.01 - 0.1μm thick
- Diameter 50 - 60 μm
- Few intracellular organelles
- Purpose : Facilitate gas exchange.

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Infant Respiratory Distress

Type II Cells

- Prominent at birth, 90% of alv epith
- Plump, rounded structures
- Situated at corners of air spaces
- Diameter 10 μm
- Bear microvilli
- Contain lamellar bodies : Surfactant
- Differentiate into Type I cells.

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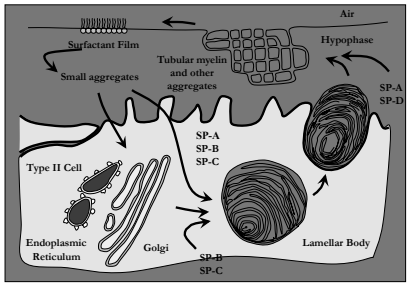
Surfactant Cycle



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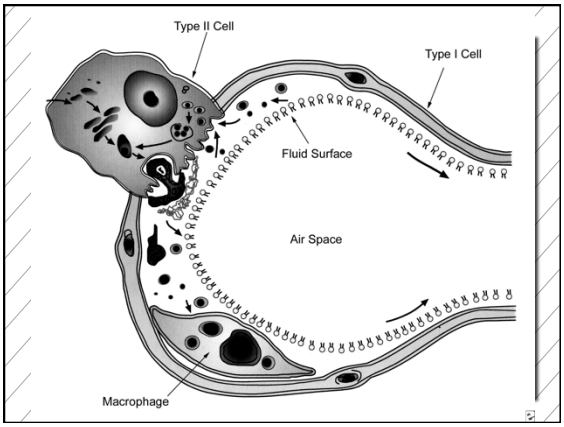

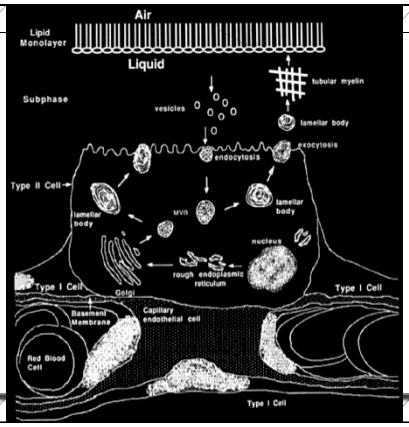

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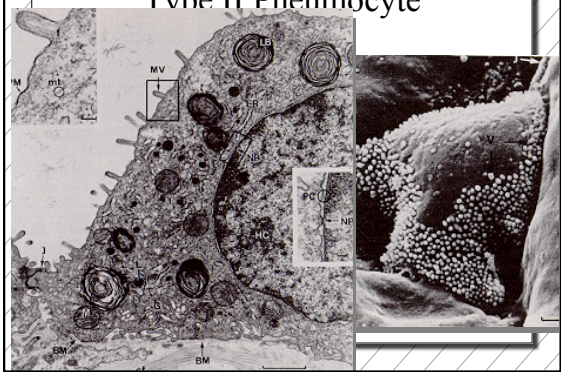
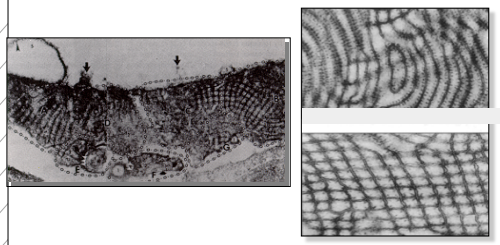
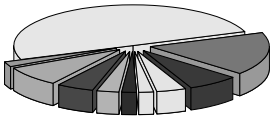
Type II Pneumocyte



Tubular Myelin



Human Surfactant Composition



- DPPC – dipalmitoylphosphatidylcholine 50%
- Unsaturated phosphatidylcholine 17%
- Phosphatidylglycerol 17%
- Phosphatidylethanolamine 4%
- Syphngomyelin 2%
- Phosphatidylinositol 2%
- Other phospholipids 3%
- Other lipids 5%
- Serum proteins 8%
- Apoproteins or surfactant specific proteins 2%

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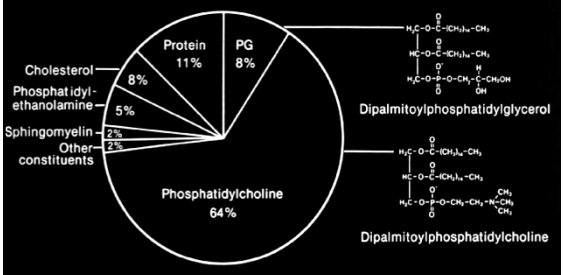
Composition of Surfactant



Structure of Major Phospholipids

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Surfactant Proteins

Present	Characteristics	Main Effects
SP-B & SP-C	Low molecular weight Hydrophobic	Adsorption and spreading of phospholipids

Absent	Characteristics	Main Effects
SP-A & SP-D	High molecular weight Hydrophilic	Host defense

Van Golde L, *Biol Neonate*. 1995;67(suppl 1):2-17
Jobe A, *N Engl J Med*. 1993;328:861-868

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Approved Surfactants

Surfactant Source	Proprietary Name	Composition
Synthetic	**Exosurf®** Burroughs-Wellcome	Colfosceril palmitate Cetyl alcohol Tyloxapol
Natural Surfactants Species Heterologous	**Surfanta®** Ross Laboratories	Bovine lung homogenate Synthetic PC & PG
	Infasurf® Forrest Pharmaceuticals	Bovine lung lavage
	Curosurf® Chiesi Farmaceutici Dey Laboratories	Porcine lung homogenate Synthetic PC & PG

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Clinical Administration

	Exosurf®	Survanta®	Infasurf®	Curosurf®
Composition	Synthetic	Enhanced Bovine	Enhanced Bovine	Enhanced Porcine
Dose	67.5 mg of PL / kg	100 mg of PL / kg	100 mg of PL / kg	100 mg of PL / kg
Liquid Volume	5 mL/kg	4 mL/kg	3 ml/kg	1.25 mL/kg
Method of Administration	½ dose slowly Supine then rotated	¼ dose quickly in each of 4 positions	½ dose slowly Supine then rotated	Whole or ½ dose Supine
Dosing Interval	≥ q 12 h	≥ q 6 h	≥ q 12 h	≥ q 12 h

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Properties of Surfactant

Biophysical Properties	Effects on Lung Physiology	Clinical Findings with poor function
↓ Surface Tension	Alveolar expansion ↑ Compliance ↓ Work of Breathing	↓ Compliance ↑ Work of Breathing Retractions
Variable Surface Tension	↓↓ Surface Tension at lowest lung volume	↓ Lung volume V/Q → 0 (shunt) Grunting
↓ negative pressure under curved fluid surface	Prevent pulmonary edema	Heavy wet lungs

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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

Surfactant proteins

- SP-A: hydrophilic
  - formation of tubular lattice
  - regulatory function
  - defense function
- SP-B: hydrophobic
  - re-formation of layer after compression
- SP-C: hydrophobic
  - spreading function
- SP-D: hydrophilic
  - regulatory function
  - defense function

Comparison of Surfactant Preparations

Agent	Composition	Phospholipids	SP-B mg/ml
Beractant *Survanta®*	Minced bovine lung extract DPPC, tripalmitin, palmitic acid	84%	< 1.0 (SP-B + SP-C)
Calfactant *Infasurf®*	Bovine lung lavage	95%	0.26
Poractant alfa *Curosurf®*	Minced porcine lung extract	99%	0.3
Colfosceril palmitate* *Exosurf Neonatal®*	DPPC, hexadecanol, tyloxapol	85%	0.0

*Colfosceril palmitate is protein free and mixed in weight proportions 13.5 : 1.5 : 1

Notter RH, New York: Marcel Dekker, Inc; 2000;320. *Lung Biology in Health and Disease*, v 149
Halliday HL et al, *Arch Dis Childl. 1993;69:276-280*

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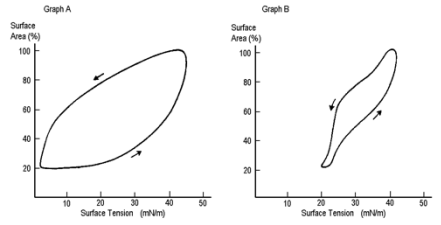
Relationship between surface area and surface tension



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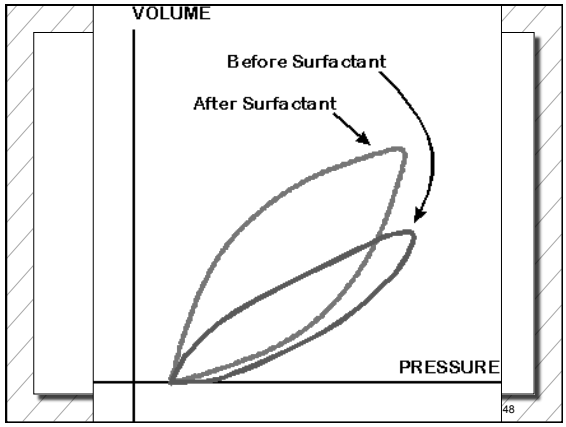

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Treatment of RDS

- 60% have a good or sustained response;
- 30% respond but relapse;
- 10% have a poor or unsatisfactory response. Babies who are slow in responding can relapse and may need a second or even third dose of surfactant.

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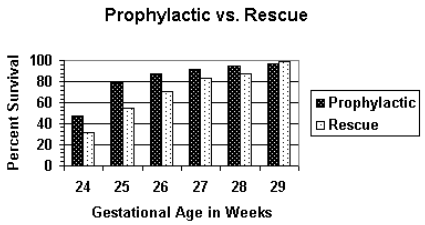
Comparison of mortality rate after prophylaxis and rescue surfactant therapy



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Clinical Criteria for the Use of Exogenous Surfactant

PROPHYLACTIC THERAPY	RESCUE THERAPY
Gestational age < 30 weeks	Clinical features of RDS, including:
Very low birth weight (<1,250 g) Immature lecithin-sphingomyelin ratio Absence of phosphatidylglycerol in amniotic fluid	Refractory hypoxemia Decreased lung compliance and lung volumes that require mechanical ventilatory support Diffuse alveolar infiltrates on chest radiograph

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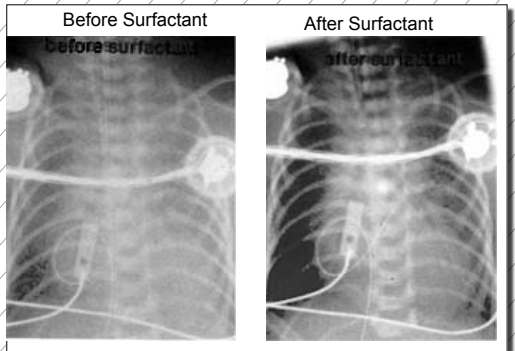

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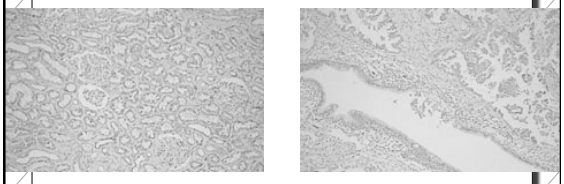
Surfactant



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Strategies of Use

	Prophylactic	Rescue
Definition	Administered immediately post-birth	Administered post-diagnosis
Types		Early — All RDS Late — Moderate - severe RDS
Advantages	↓ Severe RDS ↓ Adverse outcome	↓ Air leak syndrome ↓ Adverse outcomes
Disadvantages	Therapy in non-RDS infants ↑ Risk of errors ↑ Cost	↑ Adverse outcomes in smaller infants

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Side Effects of Surfactant Administration

- Oxygen desaturation
- Bradycardia
- Surfactant reflux

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Safety Concerns for Surfactant Usage

- Intraventricular Hemorrhage
  - Not decreased
  - Increased in isolated Survanta studies
- Pulmonary Hemorrhage
  - Increased
    - Exosurf
    - Perhaps Survanta
- Post-treatment Infection
  - Increased with Survanta only

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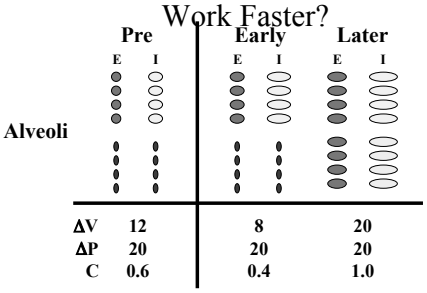
Why Doesn't Surfactant Therapy Work Faster?



	Pre	Early	Later
ΔV	12	8	20
ΔP	20	20	20
C	0.6	0.4	1.0

From Cotton

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Why Doesn't Surfactant Therapy Work Better?

- Surfactant preparation
- Surfactant protein
  - Protein characteristics
  - Protein functions
  - Effect of surfactant protein on compliance
  - Effect of surfactant protein on lung stability
  - Effect of plasma protein on surfactant inhibition
- Not Treating Immaturity

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Surfactant Protein Function

Protein	Function
SP – A	Tubular myelin, Opsonin, Uptake & secretion of surfactant lipids, Reduces inactivation
SP – B	Tubular myelin, Lipid adsorption, Minimal surface tension, Reduces inactivation
SP – C	Affects lipid order, Synergy with SP – B for surface activity, Reduction of inactivation
SP – D	Opsonin

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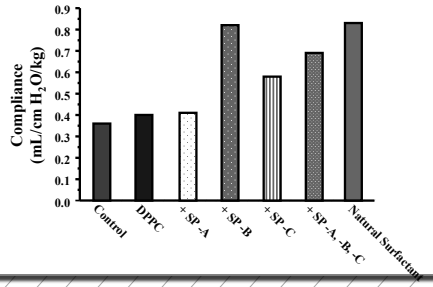
Effect of Surfactant Protein on Lung Compliance



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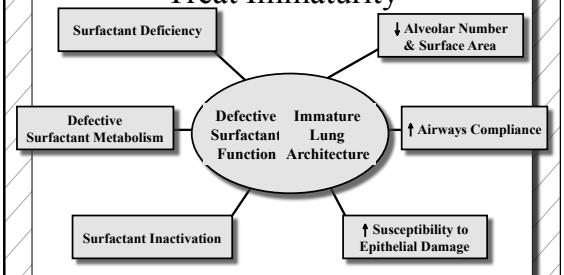
Surfactant Doesn't Treat Immaturity



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Pathologic causes for surfactant inhibition

- Hypoxia
- Hyperoxia
- Acidosis
- Hypothermia

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Infant Respiratory Distress
Pulmonary Fluid

Ultrafiltrate of plasma

Almost no protein
pH : 6.4 (Amniotic fluid pH:7.07)
CO2 : 4.4 mmol/L (Amn fluid :18.4)
Bicarbonate : < 3 mmol/L
Chloride 150 mEq/L (plasma 100)

It is NOT Amniotic Fluid.

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Infant Respiratory Distress
Pulmonary Fluid

Volume Produced : 2 - 5 mls / kg / hr.

Volume in potential air sacs :
4 - 6 mls / kg in mid gestation
20 mls / kg near term
70 - 100 mls at term.

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Diagnosis

- Lecithin-Sphingomyelin ratio
- Foam stability tests
- Phosphotidylglycerol
- TDx-FLM, a measures the segregation between surfactant and albumin.

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Diagnosis

- Foam stability tests
  95% ethanol, 15 sec
  1:1
  1:2
  1:3
  1:4

Bubbles on surface, complete ring

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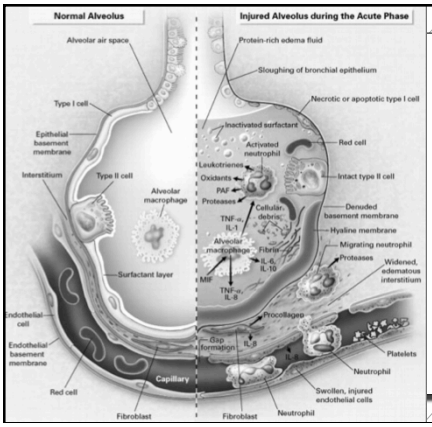

Acute Lung Injury in RDS

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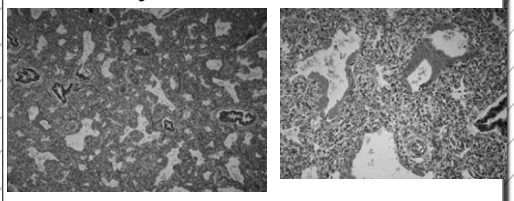
Photomicrograph demonstrates the collapsed alveoli filled with hyaline membranes.



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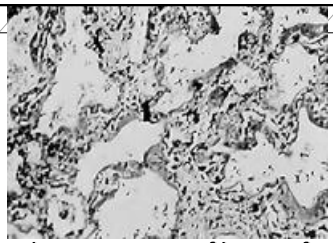

- Microscopic appearance of lungs of an infant with respiratory distress syndrome. Hematoxylin and eosin stain exhibits the presence of hyaline membranes (pink areas).

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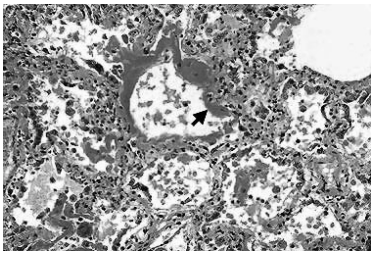
Respiratory Distress Syndrome



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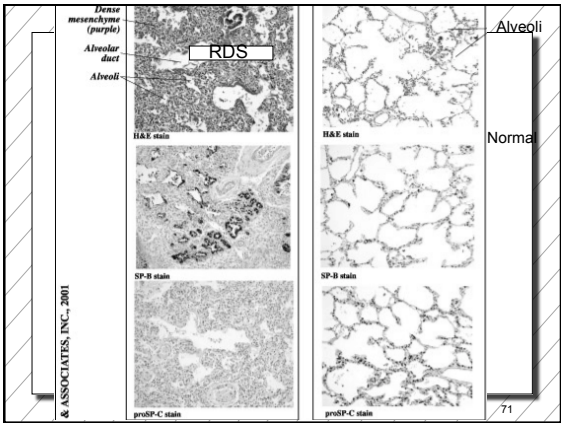

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Respiratory Distress in the Newborn

- Patent Ductus Arteriosus
  - Left to right shunt
  - Pulmonary edema
    - Pulmonary edema proteins inactivate surfactant!

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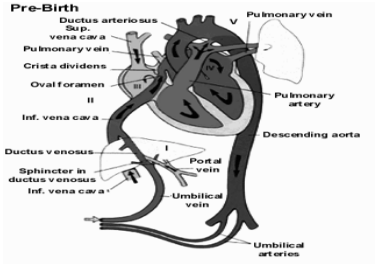

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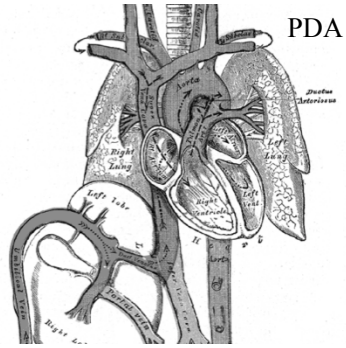


74

Pathophysiology of RDS

- Surfactant deficiency
- Decreased functional residual capacity
  - Increased chest wall compliance
- Decreased alveolar surface area
- Increased airways compliance

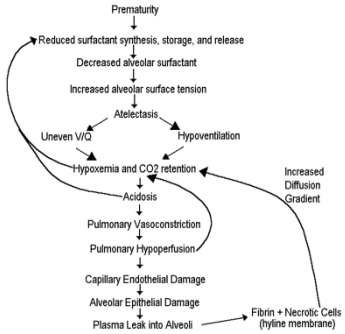
75

Respiratory Distress in the Newborn

- Immature Lung Structure
  - Increased capillary permeability
  - Decreased surface area

76

A schematic diagram outlining the pathogenesis of RDS



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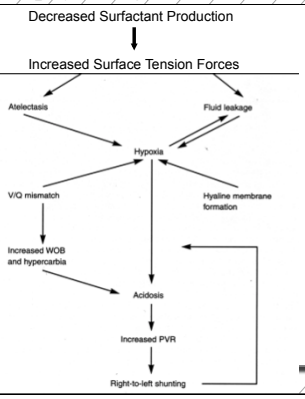
Pathophysiology of RDS



78

Physical

- Physical findings are consistent with the infant's maturity assessed by Dubowitz examination or its modification by Ballard.
- Progressive signs of respiratory distress are noted soon after birth and include the following:
  - Tachypnea
  - Expiratory grunting (from partial closure of glottis)
  - Subcostal and intercostal retractions
  - Cyanosis
  - Nasal flaring
- Extremely immature infants may develop apnea and/or hypothermia.

79

Clinical Findings

- General signs of respiratory distress in the newborn

  - Tachypnea
  - Retractions
    - Intercostal, substernal or suprasternal
  - Grunting
  - Nasal flaring

80

Clinical Findings

- Straining of chest and neck muscles with the effort of breathing
- Abnormally rapid heartbeat
- Absence of or long pause in breathing (apnea)

81

Clinical Findings

- Tachycardia
- Central cyanosis
- Breath sounds: Decreased or dry crackles
- Poor capillary refill
- Urinary output decreases

82

Other Problems:

Pneumonia is often secondary to group B beta hemolytic streptococci (GBBS) and often coexists with RDS.

Metabolic problems (eg, hypothermia, hypoglycemia) may occur.

Hematologic problems (eg, anemia, polycythemia) may occur.

Transient tachypnea of the newborn usually occurs in term or near-term infants, usually after cesarean delivery.

Aspiration syndromes may result from aspiration of amniotic fluid, blood, or meconium. Aspiration syndrome is also observed in more mature infants and is differentiated by obtaining a history and by viewing the chest radiograph findings.

Pulmonary air leaks (eg, pneumothorax, interstitial emphysema, pneumomediastinum, pneumopericardium) may occur. In premature infants, these complications may occur from excessive positive pressure ventilation, or they may be spontaneous.

Congenital anomalies of the lungs (eg, diaphragmatic hernia, chylothorax, congenital cystic adenomatoid malformation of the lung, lobar emphysema, bronchogenic cyst, pulmonary sequestration) and heart (eg, cardiac anomalies) are rare in premature infants. These entities can be diagnosed based on chest radiograph or ultrasound examination findings and, on rare occasion, may coexist with RDS.

83

Laboratory Findings

- Blood gases are usually obtained as clinically indicated from either an indwelling arterial (umbilical) catheter or an arterial puncture. Blood gases exhibit respiratory and metabolic acidosis along with hypoxia.
  - Respiratory acidosis occurs because of alveolar atelectasis and/or overdistension of terminal airways.
  - Metabolic acidosis is primarily lactic acidosis, which results from poor tissue perfusion and anaerobic metabolism.
  - Hypoxia occurs from right-to-left shunting of blood through the pulmonary vessels, PDA, and/or foramen ovale. Pulse oximetry is used as a noninvasive tool to monitor oxygen saturation, which should be maintained at 90-95%.

84

X-Ray findings

- "Reticulogranular"
  - Ground glass appearance
- Air bronchograms
- Underaerated, elevated diaphragms
- May be complicated by a PDA and enlarged heart

85

Radiograph-Imaging

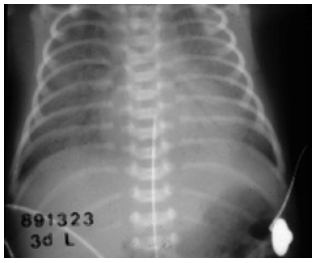
- Chest radiographs of an infant with RDS exhibit bilateral diffuse reticular granular or ground glass appearance, air bronchograms, and poor lung expansion .
  - The prominent air bronchograms represent aerated bronchioles superimposed on a background of collapsed alveoli.
  - The cardiac silhouette may be normal or enlarged. Cardiomegaly may be the result of prenatal asphyxia, maternal diabetes, PDA, an associated congenital heart anomaly, or simply poor lung expansion.
  - These findings may be altered with either early surfactant therapy or indomethacin treatment with mechanical ventilation.
  - The radiologic findings of RDS cannot be differentiated reliably from those of pneumonia, which is caused most commonly by GBBS.
- Echocardiographic evaluation is performed in selected infants to assist the clinician in diagnosing PDA and determine the direction and degree of shunting. It is also useful in making the diagnosis of pulmonary hypertension and excluding structural heart disease.

86

X-Ray Findings

87

X-Ray findings cont.



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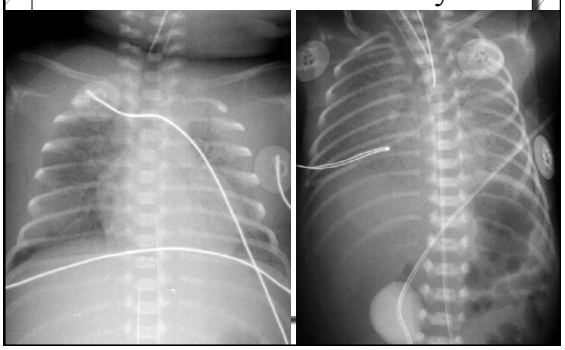
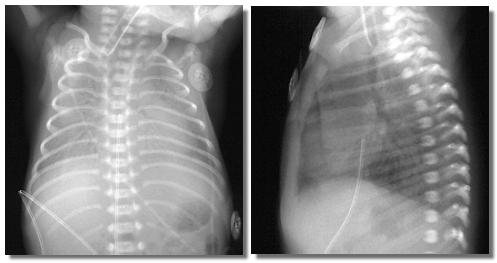
Respiratory Distress Syndrome

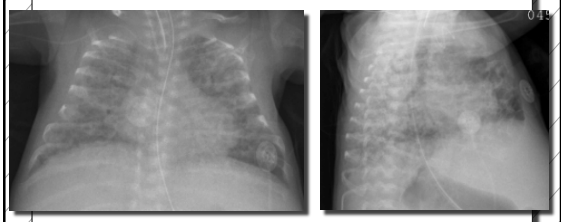


Respiratory Distress Syndrome



90

Bronchopulmonary Dysplasia



91

Blood gas and Pulmonary Function Findings

- Hypoxemia, most common abnormality
- ↑ PaC02
- ↓ Ph, in severe disease
- Possibly metabolic acidosis
  - Especially with PDA

92

Blood gas and Pulmonary Function Findings

- Decreased compliance
- Decreased FRC
- Increased work of breathing
- Decreased Tidal volume
- Increased Respiratory Rate

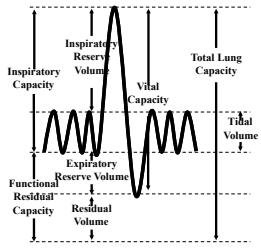
93

Pulmonary Mechanics

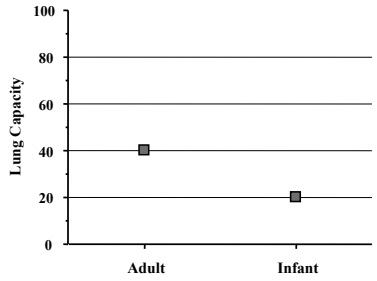
- Constant PMT monitoring may be helpful in preventing volutrauma from alveolar and airway overdistension. Monitoring may also facilitate weaning the infant from the ventilator after surfactant therapy or determining if the infant can be extubated.
- Infants with RDS have significant decrease in lung compliance with a range of 0.0005-0.0001 L/cm H2O. Therefore, for the same pressure gradient (compared to healthy lungs), the delivered tidal volume is reduced in infants with RDS. The resistance (airway and tissues) may be normal or increased. The time constant and the corresponding pressure and volume equilibration are shorter. The anatomic dead space and the functional residual capacity are increased.

94

Functional Residual Capacity



Comparative FRC's



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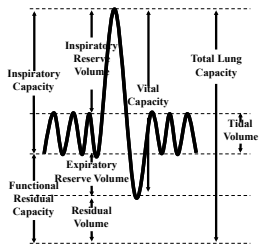
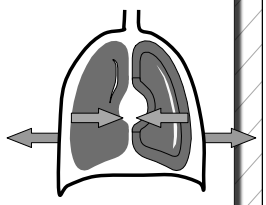
Functional Residual Capacity





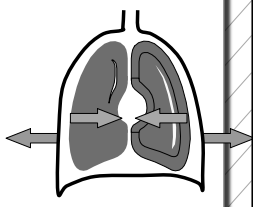
Forces Regulating FRC

Collapse of the Lung

- Elastic Recoil
- Alveolar Surface Tension

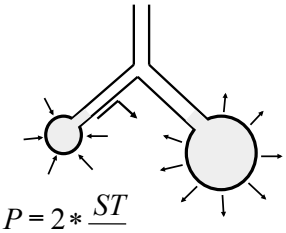
Expansion of the Chest Wall

- Muscles
- Bones



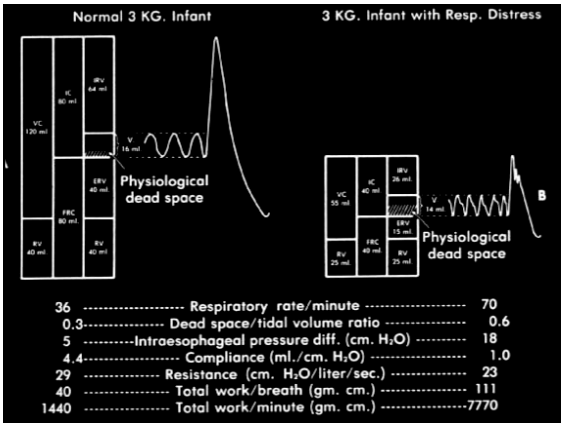
98

La Place's Law

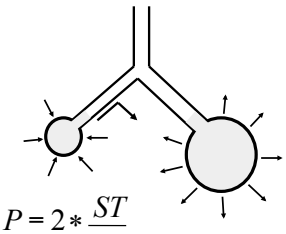


$$P = 2 * \frac{ST}{r}$$

99



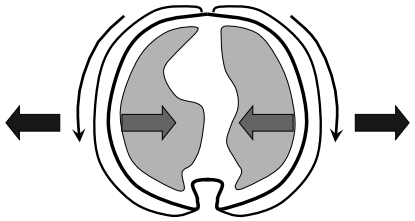
La Place's Law



$$P = 2 * \frac{ST}{r}$$

101

Chest Wall Expansion



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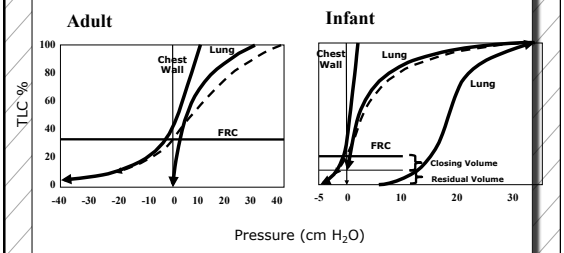
Chest Wall Compliance



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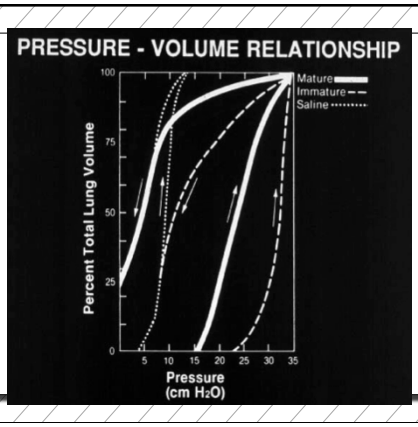

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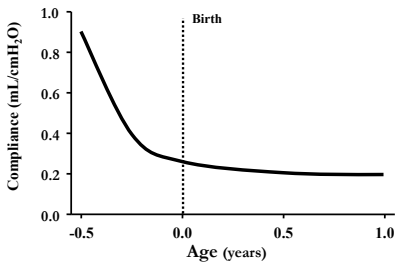
Airways Compliance



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Treatment of RDS

- General supportive care
  - Stabilization of temperature
  - Conservation of heat
- Monitoring and Treatment Goals
  - Blood gases
  - Blood pressure
    - May need inotropic support

106

Treatment of RDS

- Monitoring (cont.)
  - Electolytes
  - Glucose
- Maintain oxygen carrying capacity
- Fluid management
  - Avoid overhydration
- Correct metabolic acidosis

107

Treatment of RDS

- Respiratory Care Goals
  - Recruit and maintain FRC
  - Improve V/Q- improves Pa02 and PaC02
  - Pa02 between 55 and 75 mmHg
- ROP
- Maintain NTE
- CPAP Therapy

108

Nitric Oxide Metabolism

NO reacts with oxygen and water to form nitrates and nitrites. NO toxicity is linked to its ability to combine with superoxide anions (O^{2-}) to form peroxynitrite ($ONOO^-$), an oxidizing free radical that can cause DNA fragmentation and lipid oxidation. In the mitochondria, $ONOO^-$ acts on the respiratory chain (I-IV) complex and manganese superoxide dismutase (MnSOD), to generate superoxide anions and hydrogen peroxide (H_2O_2), respectively.

109

High Frequency Ventilation

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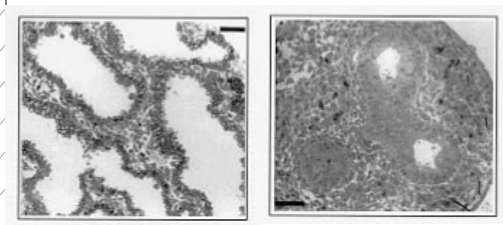
Mechanical Ventilation



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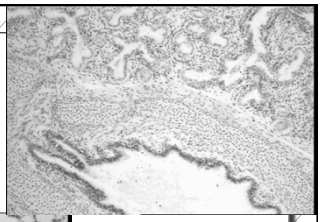
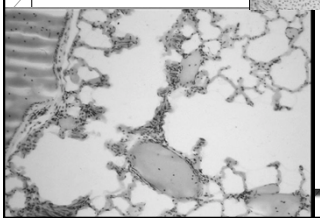
Mechanical Ventilation





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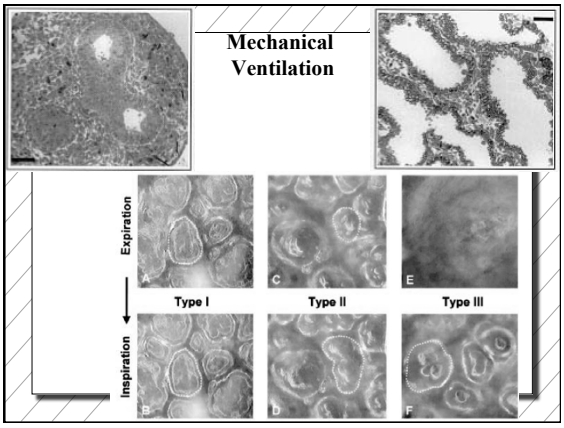


Nitric Oxide Metabolism

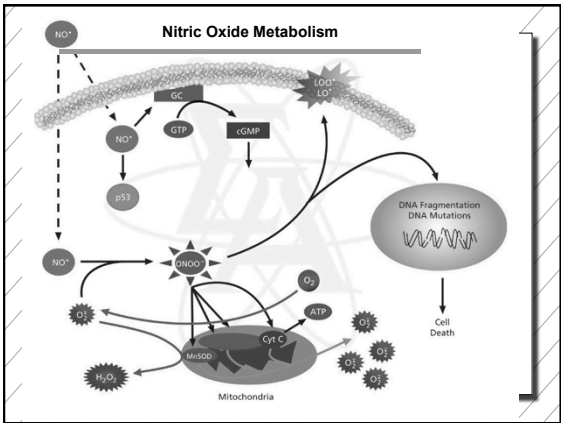
NO reacts with iron in the active site of the enzyme guanylyl cyclase (GC), stimulating it to produce the intracellular mediator cyclic GMP (cGMP), that in turn enhances the release of neurotransmitters resulting in **smooth muscle relaxation and vasodilation**. NO may also be involved in the regulation of protein activity.

114

Nitric Oxide Metabolism

Nitric oxide (NO) is a major signaling molecule in neurons and in the immune system, either acting within the cell in which it is produced or by penetrating cell membranes to affect adjacent cells. Nitric oxide is generated from arginine by the action of nitric oxide synthase (NOS). NO has a half-life of only a few seconds *in vivo* . However, since it is soluble in both aqueous and lipid media, it readily diffuses through the cytoplasm and plasma membranes. In the vasculature.

115



The Future

- New surfactant preparations
  - KL-4
- Improved / safer instillation
- Better understanding for promoting a response
  - Ventilator, Fluids, PDA
- Combination therapy
  - Lung maturation
  - Maintain “active” surfactant forms

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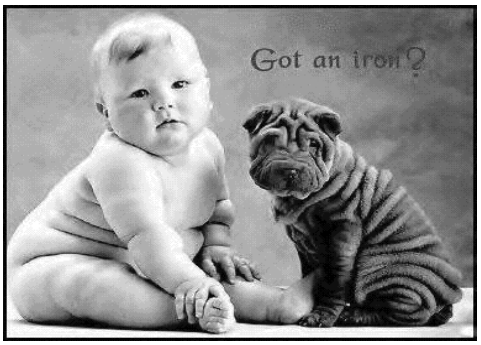

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