بسم الله الرحمن الرحيم

DISEASES OF THE RESPIRATORY SYSTEM 2017
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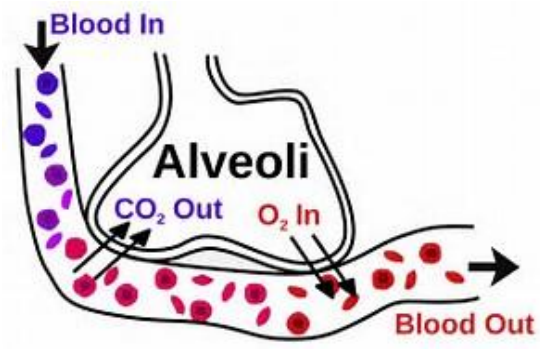
LECTURE 1: RESPIRATORY DISTRESS SYNDROMES

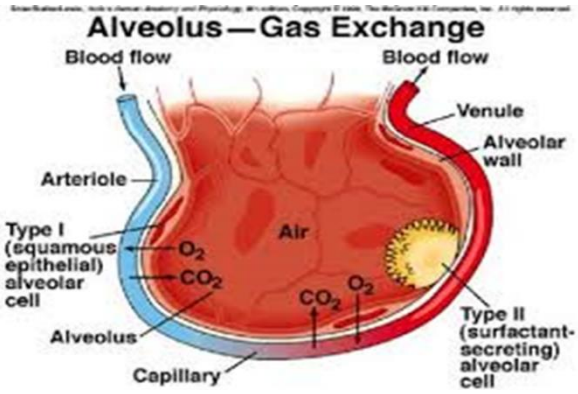
This lecture covers two topics: neonatal respiratory distress syndrome (neonatal RDS) and adult respiratory distress syndrome (ARDS)

Main reference:
Robbins basic pathology, 9th edition page 250-251 for the neonatal RDS and pages 460-462 for ARDS (under the heading: acute lung injury)
If you're reading 10th edition: pages 278-279 for neonatal RDS, and 496-498 for ARDS under the heading: acute respiratory distress syndrome

INTRODUCTION

The function of the lung is to exchange gases between air and blood (ventilation). This gas exchange happens at the level of the alveoli, which are the most terminal airspaces." Alveoli" is pleural for alveolus, a word derived from Latin and it means a little cavity.





This gas exchange occurs via passive **diffusion.** Diffusion is the net movement of molecules from a region of high concentration to a region of low concentration .This is also called movement of a substance down a concentration gradient.

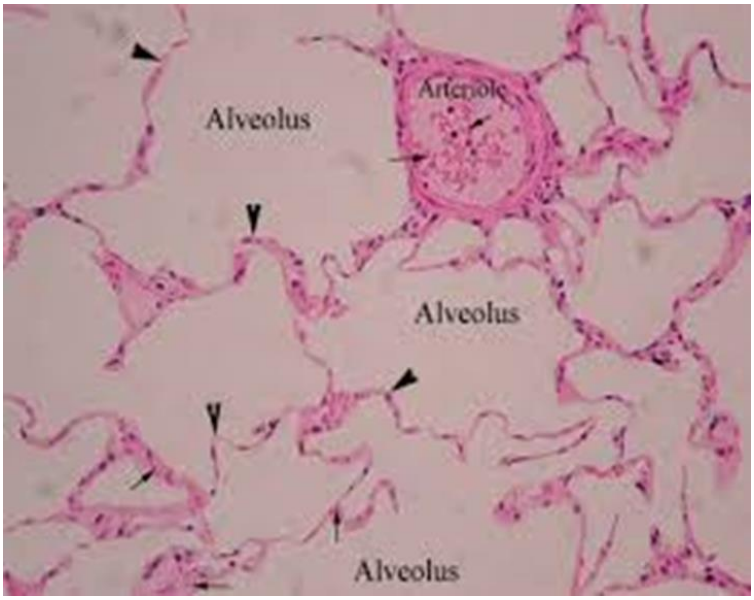
Diffusion depends on: surface area, thickness of the diffusion membrane and concentration gradient. All criteria favoring maximum diffusion are seen in the alveoli. Alveoli are created to achieve maximum gas exchange:

1. Alveoli have a huge surface area. Our lungs contain about 700 million alveoli, producing 70m2 of surface area.

2. Concentration gradient which is kept to a maximum because of the rich blood supply. Each alveolus has capillaries that cover about 70% of its area. This blood takes oxygen away quickly keeping a difference between the oxygen in the alveoli and the capillaries. It also brings CO2 constantly to maintain the CO2 gradient.

3. Alveoli have a thin diffusion membrane, composed of a layer of endothelial cells that line the capillaries and a thin layer of flat epithelial cells that line the alveolus. Between the two there are some collagen and elastic fibers.

This picture shows the thin alveolar membrane (arrows)



Alveoli are lined by two types of cells

1. Flat pneumocytes (type I pneumocytes) that occupy 95% of the alveolar surface.
2. Type II pneumocytes that **secrete surfactant** and are the main cells involved in **repair** after injury of type I pneumocytes.

Surfactant produced from type II pneumocytes lowers the surface tension inside the alveolar membrane to prevent them from collapsing during exhalation and make it easier for them to expand during inhalation (more details in a minute!)

SO: to breathe normally we need all these physiologic processes to work, if the surface area decreases (like in collapse of the lung segment = Atelectasis) or if there is increased thickness of the diffusion membrane(by fibrosis or other processes) , or if the blood supply decreases (due to heart diseases) or if there is no surfactant to keep alveoli open we will have problems in breathing. If any of these conditions happen we will have difficulty in breathing (respiratory distress) , which manifests as shortness of breath, or dyspnea.

Respiratory distress means difficulty in breathing and is caused by many conditions. However, the term **respiratory distress syndromes (RDS)** refers to certain diseases causing this distress. We have two types of RDS:

1. One occurring in the **adults and is called adult or acute respiratory distress syndrome (ARDS).**
2. The other type occurs in infants and is caused by *decreased surfactant production*, this syndrome is called **neonatal RDS or hyaline membrane disease**.

Please make sure you don't mix these two diseases!

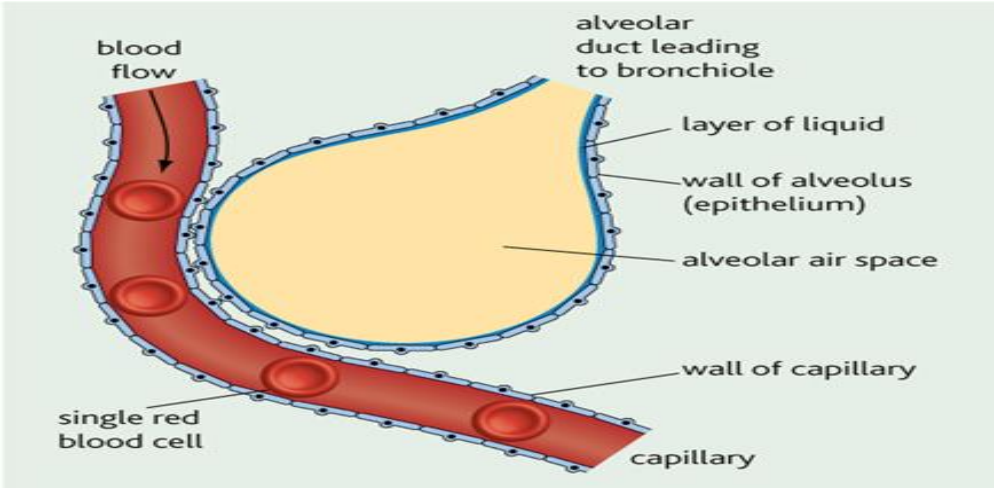
NEONATAL RESPIRATORY DISTRESS SYNDROME

Respiratory distress in the newborn refers to difficulty in breathing at birth and it is caused by many causes that include

1. Neonatal Respiratory distress syndrome (RDS), also known as hyaline membrane disease. This is the most common cause of respiratory distress in the newborn.
2. Excessive sedation of the mother, the sedative drugs reach the fetus and inhibit respiratory centers in the fetus.
3. Fetal head injury during delivery which might affect respiratory centers.
4. Aspiration of blood or amniotic fluid.
5. Intrauterine hypoxia brought about by coiling of the umbilical cord about the neck.

Neonatal respiratory distress syndrome occurs in premature infants and is caused by decreased surfactant production. So: what is surfactant and why it is important??

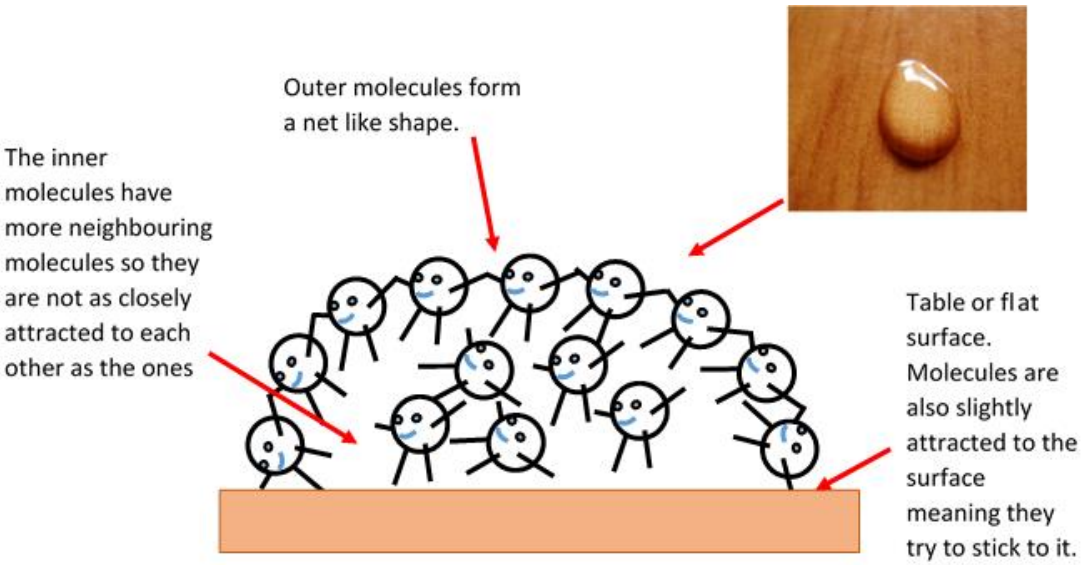
Surfactant is a lipoprotein that lowers surface tension of water in the alveoli. The alveoli contain a thin water layer to keep them moist. See figure below:



During exhalation air goes out of the alveoli, so alveoli become smaller in size. The little amount of water present has hydrogen bonds between the H2O molecules. Each water molecule is pulled equally in every direction by neighboring molecules, resulting in a net force of zero. The molecules at the surface do not have the same molecules on all sides of them and therefore are pulled inwards. This *creates internal pressure and forces liquid surfaces to contract to the minimal area. This phenomenon is called surface tension.*

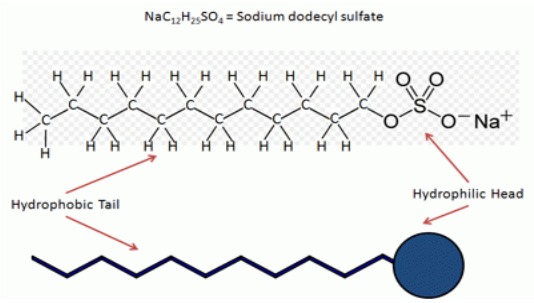
Because alveoli are small and thin walled, the surface tension of the water molecules can collapse the alveoli (completely closes them) if this happens it will be difficult to reopen them during inhalation. This is what happens in infants who lack surfactant.

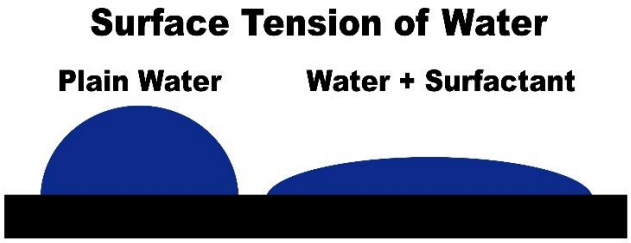
FUN FACT: Surface tension is what allows insects to float on a water surface. It also what makes water condense in droplet like structures.



HOW DOES SURFACTANT LOWER SURFACE TENSION?

Surfactant is a lipoprotein that has a hydrophobic tail and a hydrophobic head. It binds to the water molecules at the surface decreasing their bonds with the underlying water molecules, thus decreasing surface tension.





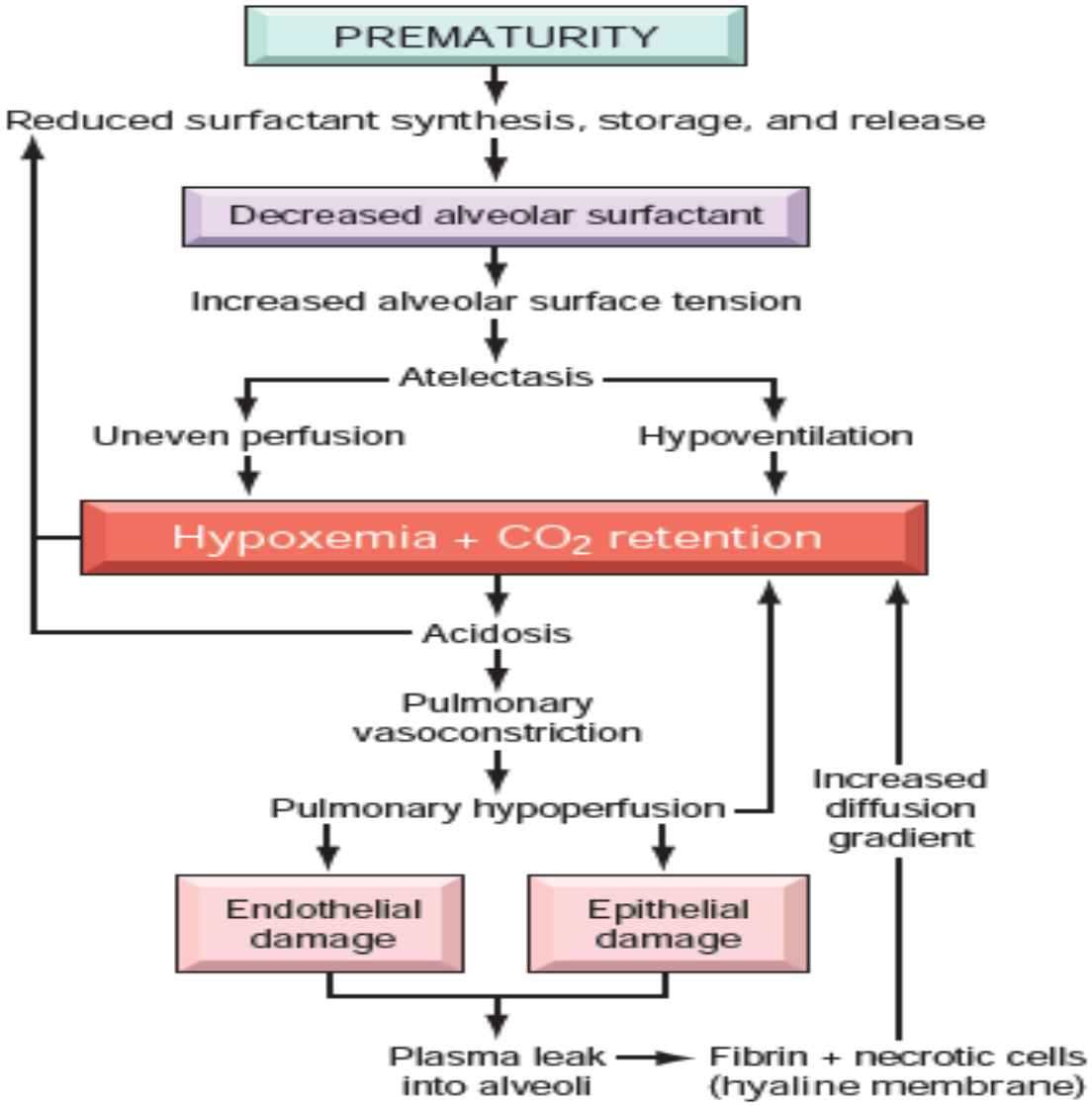
Surfactant production by type II alveolar cells is accelerated after the **thirty-fifth week** of gestation in the fetus. At birth, the first breath of life requires high inspiratory pressures to expand the lungs. With normal levels of surfactant, the lungs retain up to 40% of the residual air volume after the first breath; thus, subsequent breaths require far lower inspiratory pressures. With a deficiency of surfactant, the lungs collapse with each successive breath, and so infants must work as hard with each successive breath as they did with the first.

So if a baby is delivered prematurely, there is a high probability that his lungs are not producing enough surfactant. That's why neonatal RDS occurs mainly in premature infants.

There are strong associations with *male gender*, *maternal diabetes*, and delivery by *cesarean section.*

PATHOGENESIS.

Immaturity of the lungs is the most important factor in developing neonatal RDS. The disease can be encountered in full-term infants but the incidence of RDS is inversely proportional to gestational age. It occurs in 60% of infants born at less than 28 weeks of gestation, 30% of those born between 28 to 34 weeks' gestation, and less than 5% of those born after 34 weeks' gestation. **The fundamental defect in RDS is a deficiency of pulmonary surfactant.** This results in stiff atelectatic (collapsed) .Progressive atelectasis and reduced lung compliance lead to a chain of events resulting in protein-rich, fibrin-rich exudation into the alveolar spaces with the formation of hyaline membranes. *The fibrin-hyaline membranes are barriers to gas exchange*, leading to carbon dioxide retention and hypoxemia. *The hypoxemia itself further impairs surfactant synthesis, and a vicious cycle ensues*.



Surfactant synthesis is modulated by hormones and growth factors, including **cortisol, insulin, prolactin, thyroxine, and TGF-β.** The role of **glucocorticoids (steroids)** is particularly important. Conditions associated with intrauterine stress that increase corticosteroid release lower the risk of developing RDS. If premature delivery is suspected, the mother is given intramuscular steroid injections to reduce the risk of RDS.

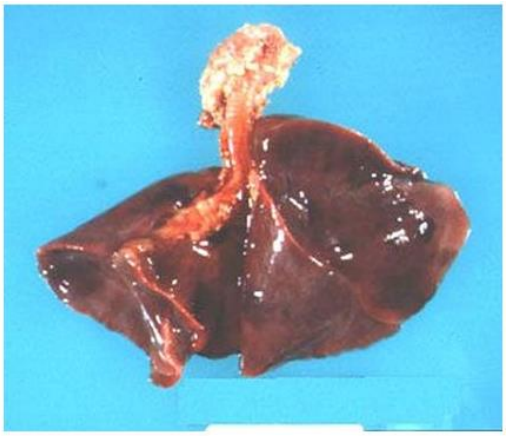
Surfactant synthesis can be suppressed by the compensatory high blood levels of insulin in infants of diabetic mothers, which counteracts the effects of steroids. This may explain, in part, why infants of diabetic mothers have a higher risk of developing RDS.

Labor is known to increase surfactant synthesis; hence, cesarean section before the onset of labor may increase the risk of RDS.

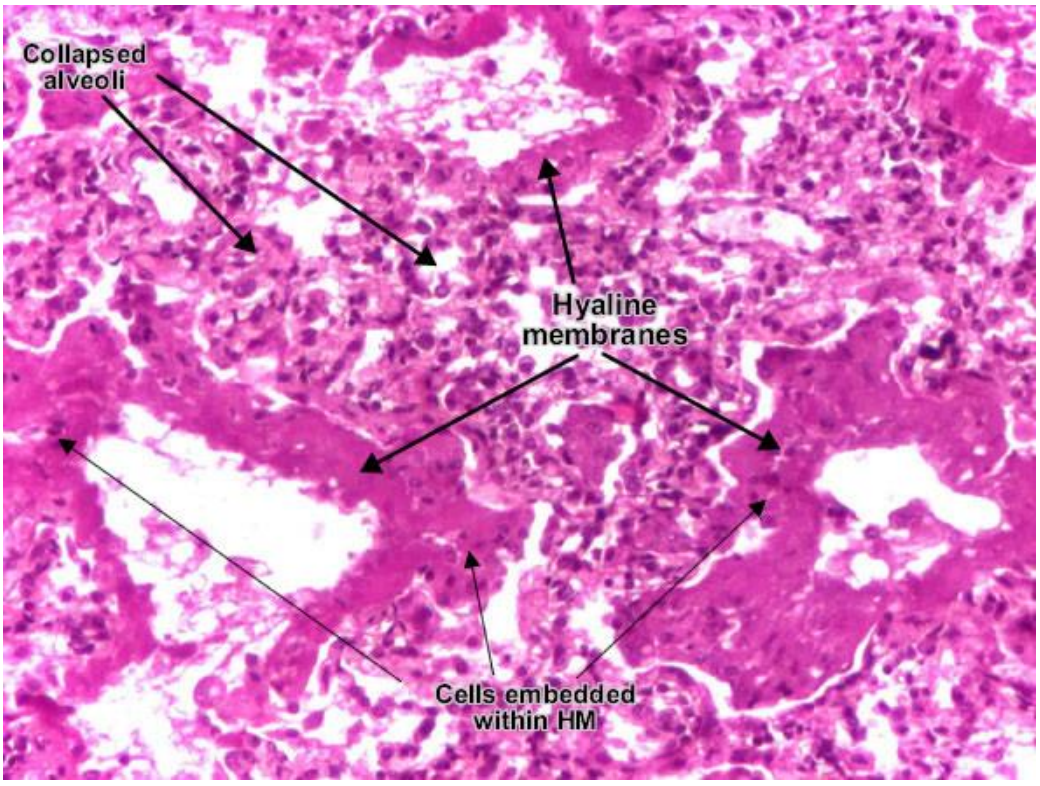
MORPGHOLOGY

The lungs of a neonate with RDS are normal in size, but are solid, airless, and reddish purple, similar to the color of the liver.

Microscopically, **alveoli are poorly developed**, and those that are present **are collapsed**.



When the infant dies early in the course of the disease, necrotic cellular debris can be seen in the terminal bronchioles and alveolar ducts. The necrotic material becomes incorporated within eosinophilic **hyaline membranes** lining the respiratory bronchioles, alveolar ducts, and alveoli. The membranes are largely made up of **fibrin admixed with cell debris derived chiefly from necrotic type II pneumocytes**. There is a remarkable paucity of neutrophilic inflammatory reaction associated with these membranes.

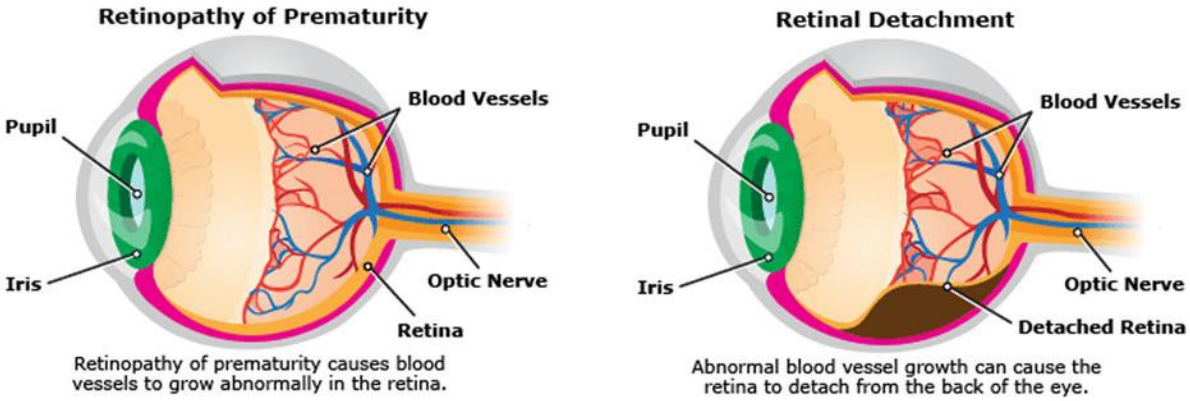


TREATMENT

Prevention of neonatal RDS is very important and can be achieved by giving steroids to mothers as mentioned above and also by giving exogenous surfactant to premature infants.

If the baby is born with the disease they might need resuscitation after birth. Some might need administration of high concentration of oxygen given via a ventilator. If this is needed for a long period two complications might occur

1. Retinopathy of prematurity (ROP) = retrolental fibroplasia. High concentration of oxygen increases vascular endothelial growth factor (VEGF) which causes angiogenesis in the retina which may result in scarring and retinal detachment.



ROP can be mild and may resolve spontaneously, but it may lead to blindness in serious cases.

Please note that this retinopathy occurs due to two causes

A. hypoxia, which occurs due to the RDS, the hypoxia causes endothelial cell apoptosis

B. oxygen toxicity, occurring during treatment, this causes angiogenesis

It is thought that both hypoxia (caused by the disease process) and the oxygen toxicity (due to the treatment) contribute to retinopathy of prematurity.

2. bronchopulmonary dysplasia (BPD): there is decrease in alveolar septation, and abnormal capillary formation. This is thought to be due to several factors including: ventilation, high oxygen concentration and prematurity. Cytokines are also thought to play a role.

These two complications are rare nowadays due to prophylactic steroids and administration of surfactant and also due to improved ventilation that gives patients lower oxygen concentrations,

ADULT RESPIRATORY DISTRESS SYNDROME (ARDS) متلازمة الضائقة التنفسية الحادة

PLEASE NOT: there are differences regarding the definition of ARDS between Robbins 9th and 10th editions. Here we will use the most updated definition.

ARDS is not a single disease entity. It is a complication of several diseases that affect the lungs directly or indirectly. These diseases result in bilateral injury to endothelial lining of capillaries and/or epithelial lining of alveolar walls. This wall damage results in loss of the barrier between the capillary and the alveolus resulting in influx of water to the alveoli which will result in respiratory distress: اني اتنفس تحت الماء

Until recently, the sudden onset of difficulty in breathing along with significant hypoxemia and bilateral pulmonary infiltrates in the absence of cardiac failure was called acute lung injury, and the severe form of acute lung injury was called ARDS.

However this definition is confusing and not specific. So the new definition is: **ARDS is *respiratory failure occurring within 1 week of a known clinical insult with bilateral opacities on chest imaging not fully explained by effusion, atelectasis, cardiac failure or fluid overload. It is graded based on the severity of the changes in arterial blood oxygen level.***

So: to call a condition ARDS you need:

1. Acute onset of dyspnea occurring within one week of a known clinical disease (these will be listed shortly)

2. Decreased arterial oxygen pressure (hypoxemia), which is refractory to oxygen therapy. The problem is not in decreased oxygen but in the water in alveoli so giving oxygen will not help much. However, please note high pressure oxygen can help a bit.

3. Development of **bilatera**l pulmonary infiltrates on the chest radiograph (due to pulmonary edema)

4. Absence of clinical evidence of other causes of such symptoms like primary left-sided heart failure.

NOTE: The pulmonary infiltrates in ARDS are caused by damage to the alveolar capillary membrane, rather than by left-sided heart failure , this is called noncardiogenic pulmonary edema.

CAUSES OF ARDS

Patients who develop ARDS are usually hospitalized due to a severe medical condition that will end in causing damage to the lungs. The effect on the lung direct (pneumonia being the most common cause) or indirect (sepsis is the most common):

Direct lung injury	Indirect lung injury
Common causes: - Pneumonia - Aspiration of gastric contents	Common causes: - Sepsis - Severe trauma with shock and multiple transfusions
Less common causes: - Pulmonary contusion - Fat emboli - Near-drowning - Inhalational injury - Reperfusion pulmonary oedema	Less common causes: - Cardiopulmonary by-pass - Drug overdoes - Acute pancreatitis - Transfusion of blood products

PATHOGENESIS

The alveolar-capillary membrane is formed by two separate barriers: the microvascular endothelium and the alveolar epithelium. In ARDS, the integrity of this barrier is compromised by either endothelial or epithelial injury, or, more commonly, both.

The acute consequences of damage to the alveolar / capillary membrane include:

1. Increased vascular permeability and alveolar edema

2. Loss of diffusion capacity due to the alveolar edema.

3. Widespread surfactant abnormalities caused by damage to type II pneumocytes. Note: in ARDS surfactant is affected in an indirect way, so there are some similarities between neonatal and adult RDS although their initial pathogenesis is different.

So: what exactly causes this membrane damage?

The disease process in the patient (pneumonia, sepsis..) causes injury of pneumocytes and pulmonary endothelium. The injured endothelium and epithelium is recognized by alveolar macrophages (remember inflammasomes and that they recognize products of cell injury) . The stimulated macrophages produce chemokines (like IL8) and TNF. IL8 attract neutrophils to the area and they produce more chemical mediators producing more damage.

The first mediator released is interleukin 8 (IL-8), a potent neutrophil chemotactic and activating agent, it is produced by pulmonary macrophages and is recognized as early as the first 30 minutes of lung injury. So neutrophils are attracted to the area and they release a variety of oxidants, proteases, leukotrienes that cause damage to the alveolar and capillary walls; this combined assault on the endothelium and epithelium increases vascular leakiness and loss of surfactant that render the alveolar unit unable to expand.

There is also increased release of IL-1 and tumor necrosis factor (TNF), leading to endothelial activation and inflammatory damage.

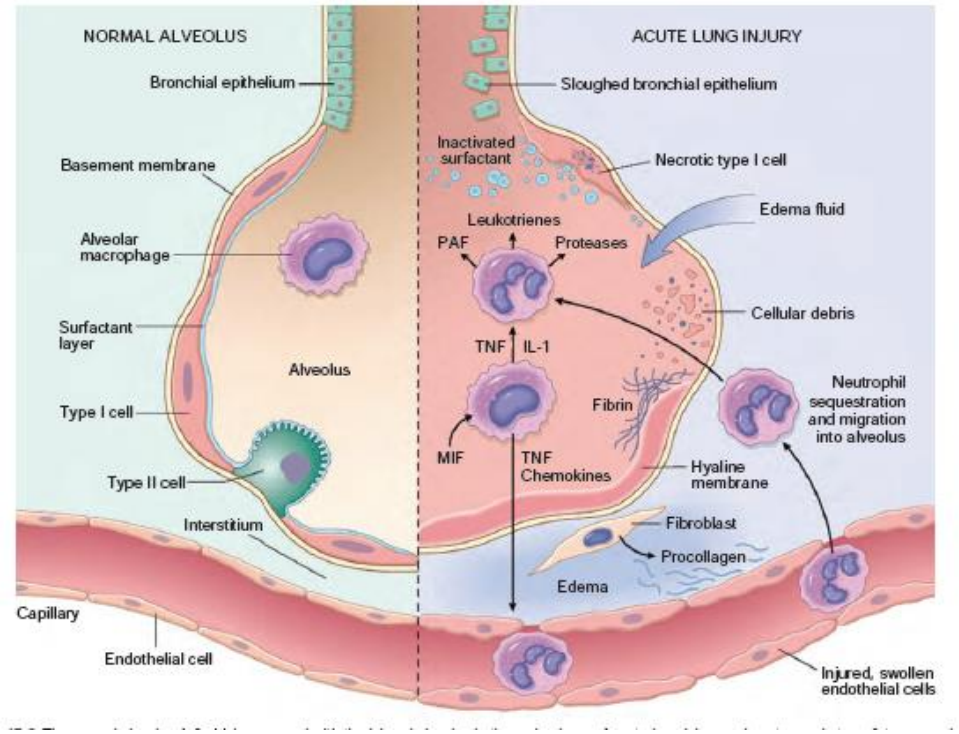
However, The destructive forces by neutrophils can be counteracted by

1. antiproteases

2. antioxidants

3. anti-inflammatory cytokines (e.g., IL-10)

In the end, it is the balance between the destructive and protective factors that determines the degree of tissue injury and clinical severity of ARDS



MORPHOLOGY

In the acute stage, the lungs are heavy, firm and. red

The microscopic features of ARDS are called diffuse alveolar damage (DAD)

They exhibit congestion, interstitial and intra-alveolar edema, inflammation, fibrin deposition, and diffuse alveolar damage.

The alveolar walls become lined with waxy hyaline membranes that are morphologically similar to those seen in hyaline membrane disease of neonates.

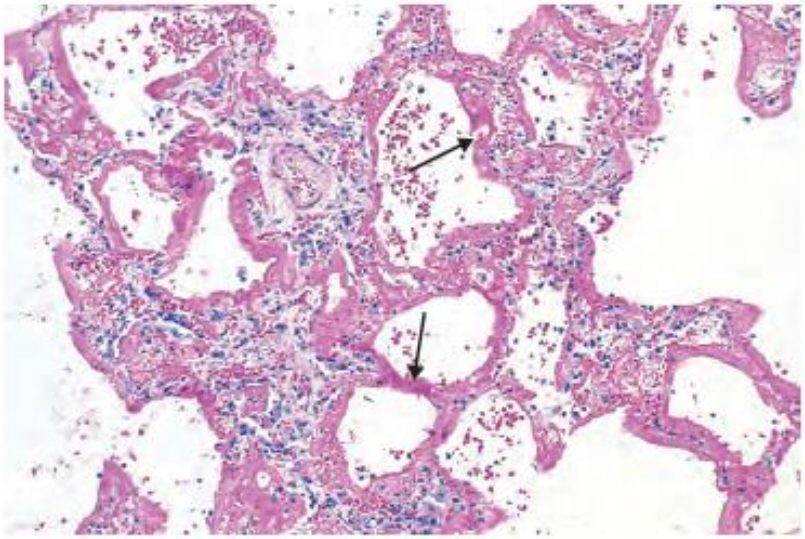


Figure 15-4 Diffuse alveolar damage (acute respiratory distress syndrome). Some of the alveoli are collapsed, while others are distended. Many are lined by hyaline membranes *(arrows)*.

Alveolar hyaline membranes consist of fibrin-rich edema fluid mixed with the cytoplasmic and lipid remnants of necrotic epithelial cells.

In the organizing stage, type II pneumocytes proliferate, and granulation tissue forms in the alveolar walls and spaces.

In most cases the granulation tissue resolves, leaving minimal functional impairment. Sometimes, however, fibrotic thickening (scarring) of the alveolar septa ensues.

CLINICAL FEATURES

Patients who develop ARDS are usually hospitalized for one of the predisposing conditions listed earlier. Patients have severe dyspnea and tachypnea, followed by increasing cyanosis and hypoxemia, respiratory failure, and the appearance of diffuse bilateral infiltrates on radiographic examination. Hypoxemia may be refractory to oxygen therapy.

Prognosis has improved due to improvements in therapy for sepsis, mechanical ventilation, and supportive care, so the mortality rate in the United States has decreased from 60% to about 40%.

Predictors of poor prognosis include

- Advanced age

- Underlying bacteremia (sepsis)

- The development of multisystem (especially cardiac, renal, or hepatic) failure.

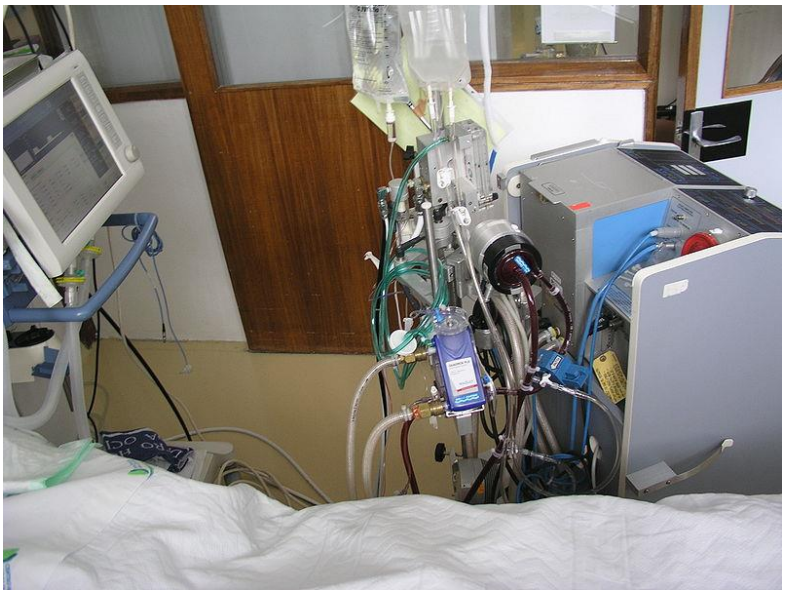
Outcome

40-60% die! Most survivors recover pulmonary function but many have persistent impairment in physical and cognitive functions. In a minority of patients, the exudate and diffuse tissue destruction result in scarring, interstitial fibrosis, and chronic pulmonary disease

Treatment

There is no curative treatment. We rely on Supportive treatment: patients are admitted to the ICU and are intubated to give them mechanical ventilation (oxygen given at a relatively high pressure). Also: Treat the underlying cause.

A relatively new treatment is ECMO (Extracorporeal membrane oxygenation, see pic below). This is expensive and not widely available. In the UK for example only few specialized centers have it. Here the patients' blood is oxygenated via a machine (artificial lung) bypassing the lungs so they have a chance to rest and recover. This is similar to dialysis where you filtrate the blood with artificial membrane rather than in the kidneys.



THANK YOU