Pathobiology of the Lung

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Lecture Objective

Biology of the Respiratory System (normal)
- Function
- Structure
  - Respiratory Epithelium
  - Bronchus
  - Bronchioles
  - Alveoli
  - Pulmonary Circulation

Pulmonary Disease States
- Epidemiology, pathophysiology, gross pathology, histopathology, molecular mechanism, genetics
  - Emphysema
  - Asthma
  - Cystic Fibrosis
  - Pneumoconiosis
  - Idiopathic Pulmonary Fibrosis
  - Sarcoid
  - Acute Respiratory Distress Syndrome
  - Pulmonary Embolism
  - Pulmonary Hypertension
  - Excluded
    - Infectious Diseases or Cancer
Respiratory System

• Function:
  – Oxygen is absorbed from the atmosphere and into the blood within the vasculature
  – Carbon dioxide is excreted into the atmosphere

• Two Functional Components:
  – Conducting System
  – Circulatory System
Conducting System

• *Transports inspired and expired gases*

• Single tube that divides with decreasing diameters
• Terminates into blind-ended sacs - the alveoli
• Alveoli bulk tissue of the lung
• Rich capillary network
• Site of gas exchange
The hilar lymph nodes are small and have enough anthracotic pigment (from dusts in the air breathed in, scavenged by pulmonary macrophages, transferred to lymphatics, and collected in lymph nodes) to make them appear greyish-black.
Conducting System

**Tracheal Lining**
Transmission Electron Micrograph (TEM)

- Cilia
- Goblet cell with mucinogen granules (G)
- Ciliated Epithelial Cell (E)

**Bronchial Lining Surface View**
Scanning Electron Micrograph (SEM)

Cilia of the pseudostratified ciliated columnar epithelium. Note how the cilia lean uniformly in the same direction, appearing just as they were when fixed at a specific moment in their wave-like movement.

Goblet cells.
Electron micrograph of the cilia of the pseudostratified epithelium

Microtubules, with 9 peripheral doublets and two central singlets, are critical for the proper function of the airway cilia.

The radial spokes projecting from doublets to a central sheath around the singlets, and the dynein arms projecting between doublets.
Ciliary Dyskinesis

Absent ciliary dynein arms

Decreased ciliary motion predisposes to recurrent infection with inflammation and bronchial destruction known as bronchiectasis.

Kartagener syndrome is an autosomal recessive form of ciliary dyskinesis associated with additional abnormalities, including situs inversus, recurrent pulmonary infections, infertility.
Airway Biology

Zones of the Respiratory System

Conducting Zone
- Hyaline cartilage plates
- Smooth muscle
- Respiratory bronchiole

Respiratory Zone
- Alveoli
- Elastic fibers

A Large Bronchiole
- Vein
- Smooth muscle
- Ciliated columnar epithelium
- Lumen of bronchiole
Circulatory System

- Passive exchange of gases between atmosphere and blood

Alveolar Capillaries

Alveolar-capillary contact surface area is estimated at from 50 to 400 square meters.
Alveoli

- Type I pneumocytes - thin squamous epithelial cells overlying capillary endothelial cell
- Type II pneumocytes - cuboidal cells at septum which differentiate to generate new type I cell and produce surfactant
Dual Blood Supply of the Lung

Alveolar Capillaries

Alveolar-capillary contact surface area is estimated at from 50 to 400 square meters.

Respiratory Zone Circulation

Branch of Pulmonary Artery

Branch of Pulmonary Vein
Emphysema

- Form of COPD
- Prevalence of 280 million worldwide and is the fourth leading cause of death in US
- Asymptomatic to exertional dyspnea and cough
- Recurrent exacerbations
Emphysema

Pathophysiology- Irreversible airways obstruction

Histopathology- Characterized by a loss of lung parenchyma by destruction of alveoli so that there is permanent dilation of airspaces.

Chest reveals numerous large bullae on the surface of the lungs in a patient dying with emphysema
Emphysema

• There are two major types of emphysema: centrilobular (centriacinar) and panlobular (panacinar).

• Centriacinar involves primarily the upper lobes while panacinar involves all lung fields, particularly the bases.

• Centrilobular emphysema occurs with loss of the respiratory bronchioles in the proximal portion of the acinus, with sparing of distal alveoli. *This pattern is typical for smokers.*

• Panacinar emphysema occurs with loss of all portions of the acinus from the respiratory bronchiole to the alveoli. *This pattern is typical for alpha-1-antitrypsin deficiency.*
Emphysema

High magnification of emphysematous lung demonstrating loss of alveolar walls. Remaining airspaces are dilated.

• Smokers have a greater number of neutrophils and macrophages in their alveoli.

• Smoking irritates alveolar macrophages, which in turn release neutrophil chemotactic factors, such as interleukin 8, thus recruiting neutrophils.

• Nicotine is chemotactic for neutrophils, and smoke can activate the alternative complement pathway (an inflammatory cascade).

• Proteases, particularly elastase, are secreted by these neutrophils and macrophages.

• Oxidants and free radicals in smoke also inhibit the alpha-1-antitrypsin circulating in the lung that protects alveoli from proteases.

• Smoke interferes with the ciliary action of the respiratory epithelium and the mucus cannot be cleared. This predisposes the smoker to secondary and repeated infections.
Alpha-1 Antitrypsin Deficiency

- Autosomal Dominant heritable disorder
- Lung and liver disease
- 1% of Emphysema patients
- Early onset disease
- Pananciar Emphysema

- A1AT inactivates neutrophil elastase and may antagonize apoptotic cell death
Asthma

- Form of COPD
- Chronic inflammatory disease
- 10 million children in US
- 7-8% of the US population
- 4000 deaths per year (US)

- Cough, wheezing, shortness of breath, chest tightness

- Pathophysiology- Reversible airflow obstruction and airway hyperreactivity

- Extrinsic asthma: there is typically an association with atopy (allergies) mediated by type 1 hypersensitivity, and asthmatic attacks are precipitated by contact with inhaled allergens. Most often in childhood.

- Intrinsic asthma: asthmatic attacks are precipitated by respiratory infections, exposure to cold, exercise, stress, inhaled irritants, and drugs such as aspirin. Adults most often affected.
Asthma

The hyperinflated lung of a patient dying in status asthmaticus.

These lungs appear essentially normal, but are normal-appearing because they are the hyperinflated lungs of a patient who died with status asthmaticus.
Cast of the bronchial tree is formed of inspissated mucus

Mucus from hypertrophied bronchial submucosal glands, the bronchoconstriction, and dehydration all contribute to the formation of mucus plugs that can block airways in asthmatic patients.
Asthma

Bronchial lumen filled with mucus

Smooth muscle hypertrophy, edema, and inflammation—mainly eosinophils

Bronchial cartilage
Asthma

Mast cells, eosinophils, lymphocytes, and their products are prominent in the airways of patients with asthma.

Inflammatory events and associated alterations in airway smooth muscle function result in asthma symptoms.

These also contribute to structural changes, particularly within the epithelium, subepithelium, fibroblasts, and smooth muscle leading to airway remodeling.

Eosinophils are prominent from their bright red cytoplasmic granules.
Cystic Fibrosis is caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)
Cystic Fibrosis

- Autosomal recessive
- Mutation in CFTR (ATP-binding cassette family member)
- Regulate chloride channel
- Prevelance
Bronchiectasis in CF
CFTR Dysfunction in CF
Molecular Consequences of CFTR Mutations

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Restrictive Lung Diseases:
Idiopathic Pulmonary Fibrosis
Restrictive Lung Disease

Regardless of the etiology for restrictive lung diseases, many eventually lead to extensive fibrosis. The gross appearance, as seen here in a patient with organizing diffuse alveolar damage, is known as "honeycomb" lung because of the appearance of the irregular air spaces between bands of dense fibrous connective tissue.
Pulmonary Fibrosis

A trichrome stain highlights the collagenous connective tissue of pulmonary fibrosis in blue.
Idiopathic Pulmonary Fibrosis

This is an example of pulmonary fibrosis. Some cases of restrictive lung disease have no known etiology--this is, they are known as idiopathic pulmonary fibrosis. The alveolitis that produces fibroblast proliferation and collagen deposition is progressive over time.
Usual Interstitial Pneumonitis

Interstitial fibrosis in a "patchwork pattern", interstitial scarring, honeycomb changes and fibroblast foci
Sarcoid
Sarcoid- Non Caseating Granuloma
Acute Respiratory Distress Syndrome

Acute hypoxic lung disease
1) Acute (<30 days)
2) Bilateral alveolar infiltrates
3) PaO2:FiO2 ratio <200
4) Non-cardiogenic

Incidence 250,000 in US annually
Mortality 40-60%
Acute Respiratory Distress Syndrome
Acute Respiratory Distress Syndrome

Here is an example of diffuse alveolar damage in which the lung is diffusely firm and rubbery. Clinically, this is known as adult respiratory distress syndrome (ARDS).

The smooth, glistening pleural surface of a lung is shown here. This patient had marked pulmonary edema, which increased the fluid in the lymphatics that run between lung lobules. Thus, the lung lobules are outlined in white.
Acute Respiratory Distress Syndrome

At high magnification, the alveoli in this lung are filled with a smooth to slightly floccular pink material characteristic for pulmonary edema. Note also that the capillaries in the alveolar walls are congested with many red blood cells. Congestion and edema of the lungs is common in patients with heart failure and in areas of inflammation of the lung.
This is the microscopic appearance of diffuse alveolar damage (DAD) in the lung. DAD is simply the final common pathway for a variety of severe lung injuries. In early DAD, there are hyaline membranes, as seen here, lining alveoli. Later, type II pneumonocyte proliferation and then interstitial inflammation and fibrosis are seen. High oxygen tensions needed to treat the hypoxia resulting from DAD and its etiologies further potentiates this disease.
Acute Respiratory Distress Syndrome

Normal lung
Acute Respiratory Distress Syndrome
Pulmonary Embolism

Seen in the pulmonary artery to the left lung on cut section is a large pulmonary thromboembolus. Such thromboemboli typically originate in the leg veins or pelvic veins of persons who are immobilized.

Contributing factors include trauma to the extremities, hypercoagulable states (Trousseau's syndrome in patients with carcinomas; protein C or S deficiency; use of oral contraceptives), heart failure, pregnancy, and older age.

Virchow's triad
1. Hypercoagulability
2. Hemodynamic changes (stasis, turbulence)
3. Endothelial injury/dysfunction
Saddle Emboli

Here is a "saddle embolus" that bridges across the pulmonary artery from the heart as it divides into right and left main pulmonary arteries. Such a saddle embolus is a cause for sudden death. This thromboembolus displays the typical gross appearance. The surface is somewhat irregular, and there are areas of pale tan to white admixed with dark red areas. The thrombus often has the outlines of the vein in which it formed.
Large thromboemboli can cause death. Medium sized thrombemboli (blocking a pulmonary artery to a lobule or set of lobules) can produce the lesion seen here—a hemorrhagic pulmonary infarction, because the patient survives. The infarct is wedge-shaped and based on the pleura. These infarcts are hemorrhagic because, though the pulmonary artery carrying most of the blood and oxygen is cut off, the bronchial arteries from the systemic circulation (supplying about 1% of the blood to the lungs) is not cut off.
Here is a larger area of infarction produced by a medium-sized thromboembolus to the lung. This infarction has begun to organize at the margins. It is also possible to have multiple small pulmonary thromboemboli that do not cause sudden death and do not occlude a large enough branch of pulmonary artery to cause infarction. However, if there are lots of small emboli, particularly if they are showered to the lungs over a period of time, then they collectively may block enough small arteries to produce pulmonary hypertension.
Lines of Zahn

This is the microscopic appearance of a pulmonary thromboembolus in a large pulmonary artery. There are interdigitating areas of pale pink and red that form the "lines of Zahn" characteristic for a thrombus. These lines represent layers of red cells, platelets, and fibrin which are layed down in the vessel as the thrombus forms.
Other types of Embolisms

The rounded holes that appear in the vascular spaces here in the lung are fat emboli. Fat embolization syndrome occurs most often following trauma with fracture of long bones that releases fat globules into the circulation which are trapped in pulmonary capillaries. Cumulatively, they have the same effect as a large saddle pulmonary embolus.
Amniotic Embolism

This is a rare finding that may complicate a term pregnancy at delivery. Seen here in a pulmonary artery branch is an amniotic fluid embolus that has layers of fetal squames. Amniotic fluid embolization can have the same outcome as a large saddle pulmonary embolus.
Pulmonary Hypertension

Defined by Physiology:
Mean pulmonary artery pressure exceeds 25 mm Hg (at rest)
Pulmonary Hypertension

WHO Group I - Pulmonary arterial hypertension (PAH)
  - Idiopathic
  - Familial
  - Associated with other diseases collagen vascular disease (e.g. scleroderma), congenital shunts between the systemic and pulmonary circulation, portal hypertension, HIV infection, drugs, toxins, or other diseases or disorders
  - Associated with venous or capillary disease

WHO Group II - Pulmonary hypertension associated with left heart disease
  - Atrial or ventricular disease
  - Valvular disease (e.g. mitral stenosis)

WHO Group III - Pulmonary hypertension associated with lung diseases and/or hypoxemia
  - Chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD)
  - Sleep-disordered breathing, alveolar hypoventilation
  - Chronic exposure to high altitude
  - Developmental lung abnormalities

WHO Group IV - Pulmonary hypertension due to chronic thrombotic and/or embolic disease
  - Pulmonary embolism in the proximal or distal pulmonary arteries
  - Embolization of other matter, such as tumor cells or parasites

WHO Group V - Miscellaneous
Both restrictive and obstructive lung diseases can affect the pulmonary arterial circulation. The loss of normal lung parenchyma leads to pulmonary hypertension that leads to thickening of the small arteries along with reduplication to form a plexiform lesion, as seen here in a peripheral pulmonary artery.