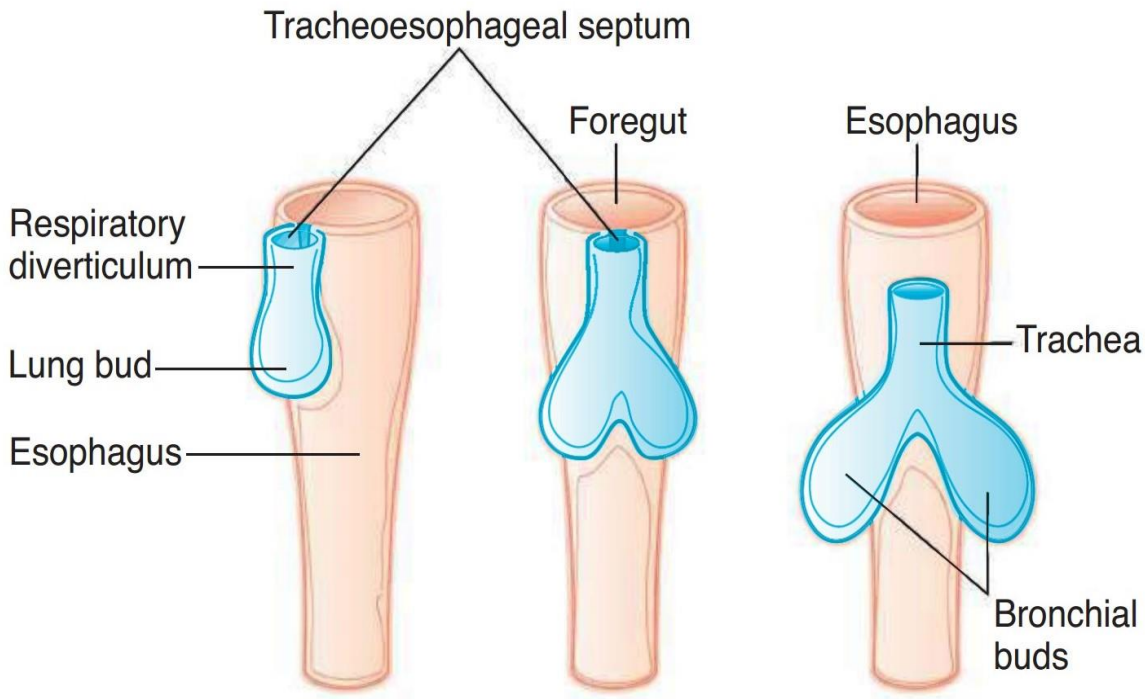
CHAPTER 1

Embryology & Anatomy

Lung development

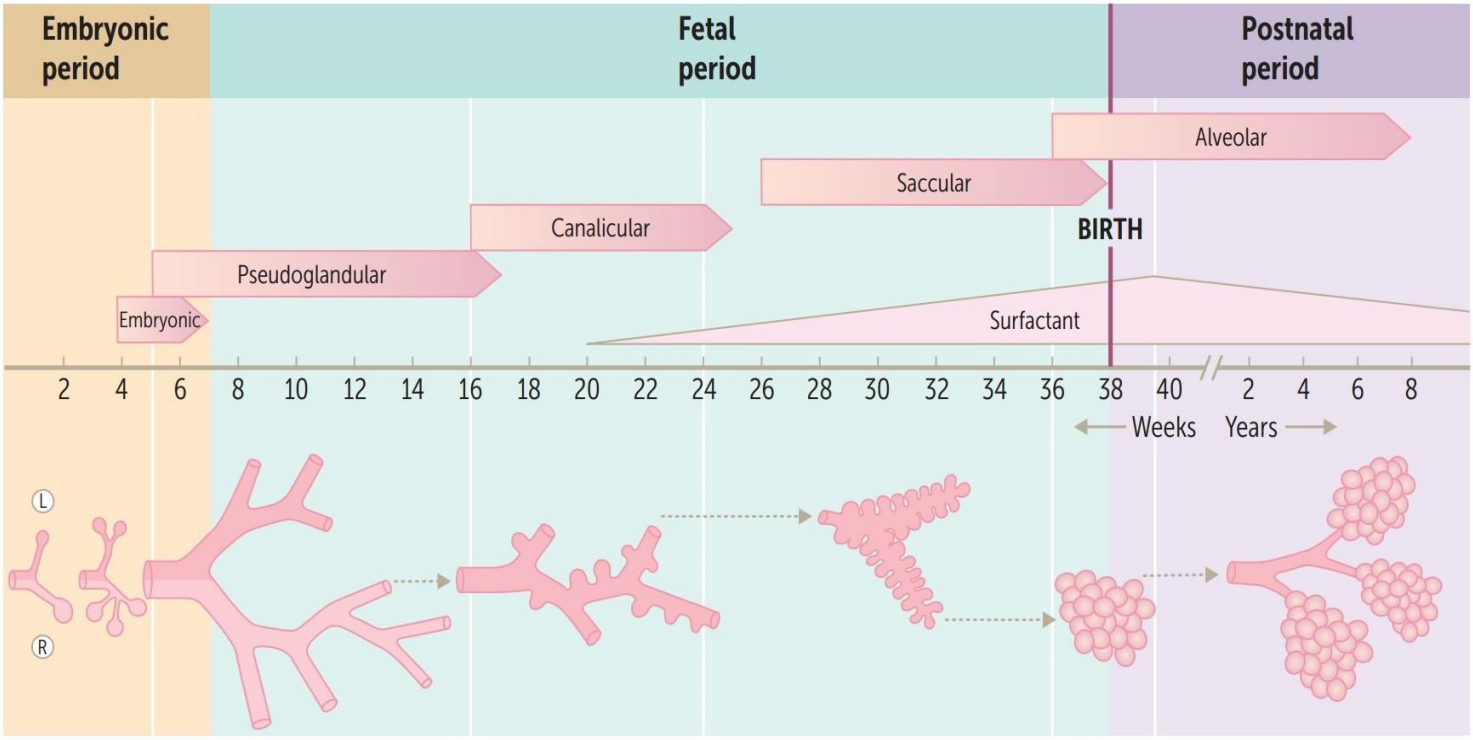
- The respiratory system begins its development in the fourth week from a single respiratory diverticulum of endoderm from the ventral surface of the esophagus (foregut).
- The respiratory diverticulum lengthens to form the lung bud.
- The lung bud then bifurcates into two bronchial (lung) buds.
- The bronchial buds continue to divide through a series of divisions over time to develop into the respiratory tree.
- Since the respiratory system develops from the foregut, initially there is an open communication between the trachea and the foregut.
- This communication is closed by the growth of a mesodermal septum called the tracheoesophageal septum.
- A tracheoesophageal fistula is an abnormal opening that occurs between the trachea and esophagus as a result of an abnormal development of the tracheoesophageal septum.



Lung development

Occurs in five stages. Initial development includes development of lung bud from distal end of respiratory diverticulum during week 4. Every Pulmonologist Can See Alveoli.

STAGE	STRUCTURAL DEVELOPMENT	NOTES
Embryonic (weeks 4–7)	Lung bud → trachea → bronchial buds → mainstem bronchi → secondary (lobar) bronchi → tertiary (segmental) bronchi.	Errors at this stage can lead to tracheoesophageal fistula.
Pseudoglandular (weeks 5–17)	Endodermal tubules → terminal bronchioles. Surrounded by modest capillary network.	Respiration impossible, incompatible with life.
Canalicular (weeks 16–25)	Terminal bronchioles → respiratory bronchioles → alveolar ducts. Surrounded by prominent capillary network.	Airways increase in diameter. Respiration capable at 25 weeks. Pneumocytes develop starting at 20 weeks.
Saccular (week 26–birth)	Alveolar ducts → terminal sacs. Terminal sacs separated by 1° septae.	
Alveolar (week 36–8 years)	Terminal sacs → adult alveoli (due to 2° septation). In utero, "breathing" occurs via aspiration and expulsion of amniotic fluid → ↑ vascular resistance through gestation. At birth, fluid gets replaced with air → ↓ in pulmonary vascular resistance.	At birth: 20–70 million alveoli. By 8 years: 300–400 million alveoli.



Respiratory tree

Conducting zone

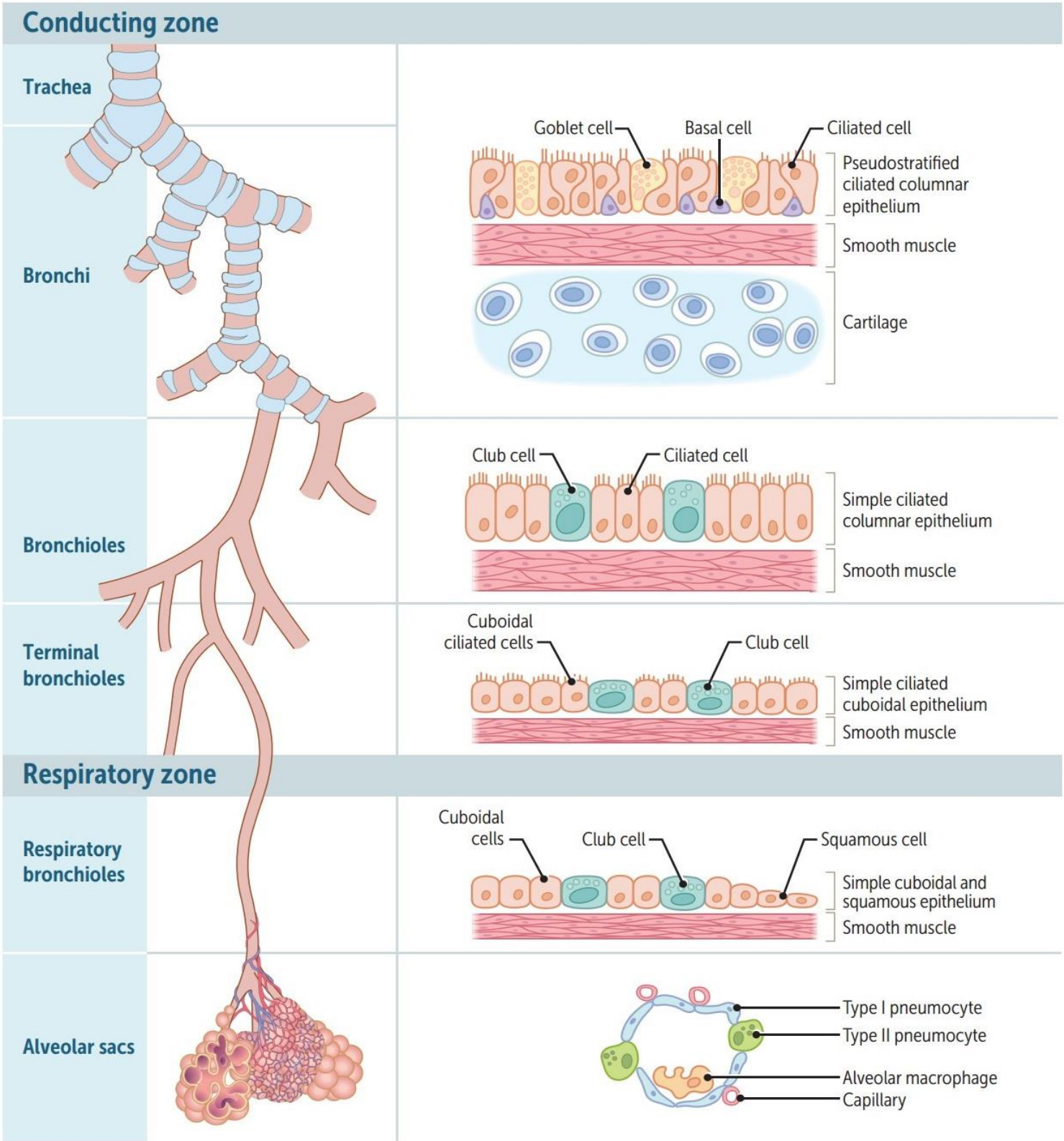
- Large airways consist of nose, pharynx, larynx, trachea, and bronchi.
- Small airways consist of bronchioles that further divide into terminal bronchioles (large numbers in parallel → least airway resistance).
- Warms, humidifies, and filters air but does not participate in gas exchange → "anatomic dead space".
- Cartilage and goblet cells extend to end of bronchi.
- Pseudostratified ciliated columnar cells primarily make up epithelium of bronchus and extend to beginning of terminal bronchioles, then transition to cuboidal cells.
- Airway smooth muscle cells extend to end of terminal bronchioles (sparse beyond this point).

Respiratory zone

- Lung parenchyma; consists of respiratory bronchioles, alveolar ducts, and alveoli.
- Participates in gas exchange.
- Mostly cuboidal cells in respiratory bronchioles, then simple squamous cells up to alveoli.
- Cilia (prevents bronchiolar mucus accumulation and airflow obstruction) terminate in respiratory bronchioles (Cilia is the last to disappear as the epithelium changes along the respiratory tube).
- Alveolar macrophages clear debris and participate in immune response.

❖ N.B:

- From the nose to the terminal bronchioles the respiratory tract is lined by a ciliated mucosal epithelium.
- Goblet cells are responsible for the secretion of mucous onto this epithelial surface.
- When particles suspended in the inspired air are inhaled, they are typically trapped in the epithelial mucous lining the upper airways.
- Particles and mucous are constantly swept upward from the terminal bronchioles toward the pharynx by ciliated cells collectively beating their cilia in the direction of the pharynx.
- This mechanism is termed mucociliary clearance.
- Mucociliary clearance is so effective that only particles 2 micrometers in diameter or smaller are able to reach the alveoli.
- Small particles (less than 2 micro) that manage to reach the alveoli either remain suspended in the air and are exhaled or are trapped in the alveolar surfactant and cleared by alveolar macrophages.


Conducting zone
Trachea
Bronchi
Goblet cell
Basal cell
Ciliated cell
Pseudostratified ciliated columnar epithelium
Smooth muscle
Cartilage
Bronchioles
Club cell
Ciliated cell
Simple ciliated columnar epithelium
Smooth muscle
Terminal bronchioles
Cuboidal ciliated cells
Club cell
Simple ciliated cuboidal epithelium
Smooth muscle
Respiratory zone
Respiratory bronchioles
Cuboidal cells
Club cell
Squamous cell
Simple cuboidal and squamous epithelium
Smooth muscle
Alveolar sacs
Type I pneumocyte
Type II pneumocyte
Alveolar macrophage
Capillary

Lobes and fissures

- The right lung is larger and is divided into three lobes (superior, middle, and inferior) that are separated by the horizontal and oblique fissures.

- The left lung is divided into two lobes separated by the oblique fissure.

- The superior lobe of the left lung contains the lingula, which corresponds to the middle lobe of the right lung.

- The left lung shares space with the heart, and has an indentation in its border called the cardiac notch of the left lung to accommodate this (deviation for about 1 inch to the left from left 4th to 6th costal cartilage).

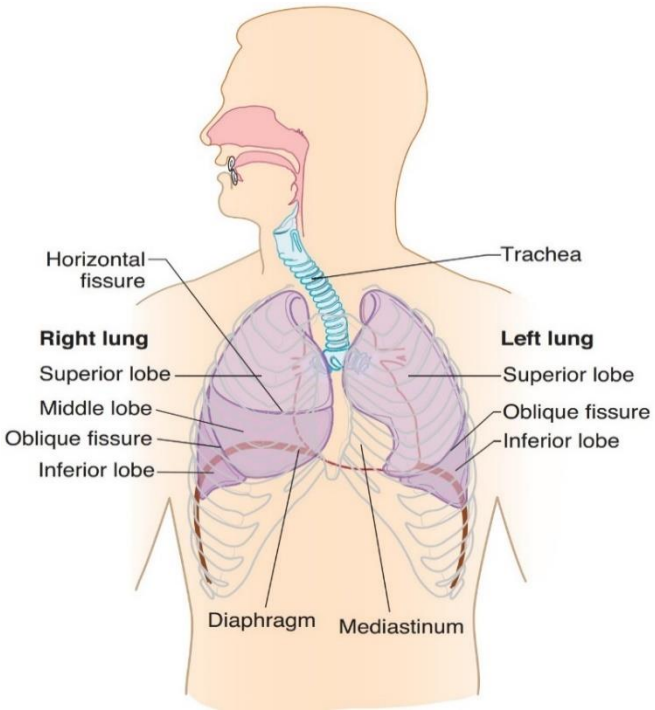
- Fissures:

- Oblique: 5th intercostal space (R & L).
- Horizontal: from right 4th costal cartilage to right 5th intercostal space.

- Lobes:

- Left:
  - Upper: above 5th rib.
  - Lower: below 6th rib.

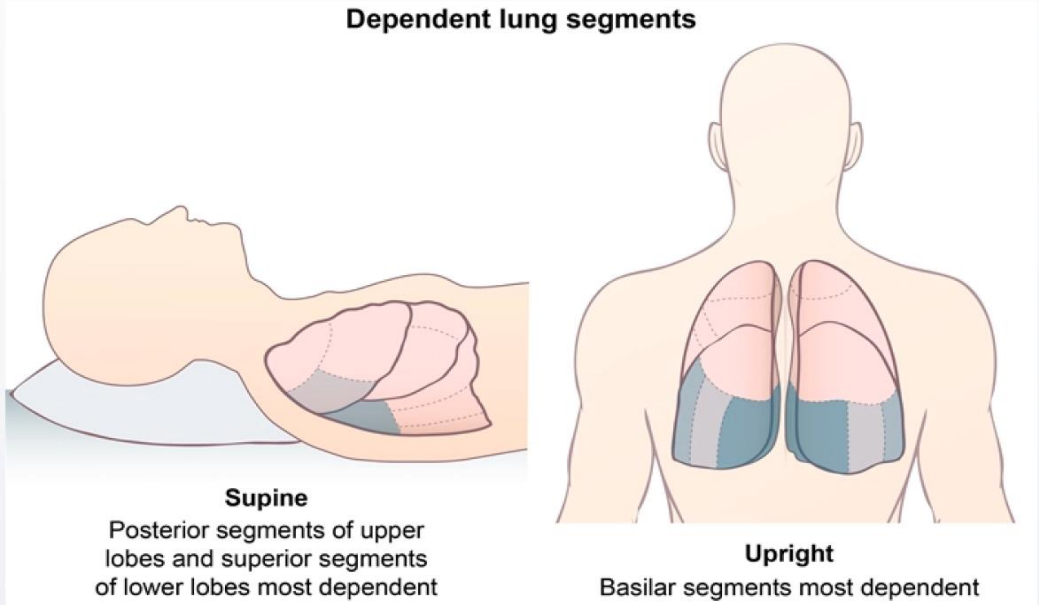
- Right:
  - Upper: above 4th rib.
  - Middle: between 4th & 6th rib.
  - Lower: below 6th rib.



❖ N.B:

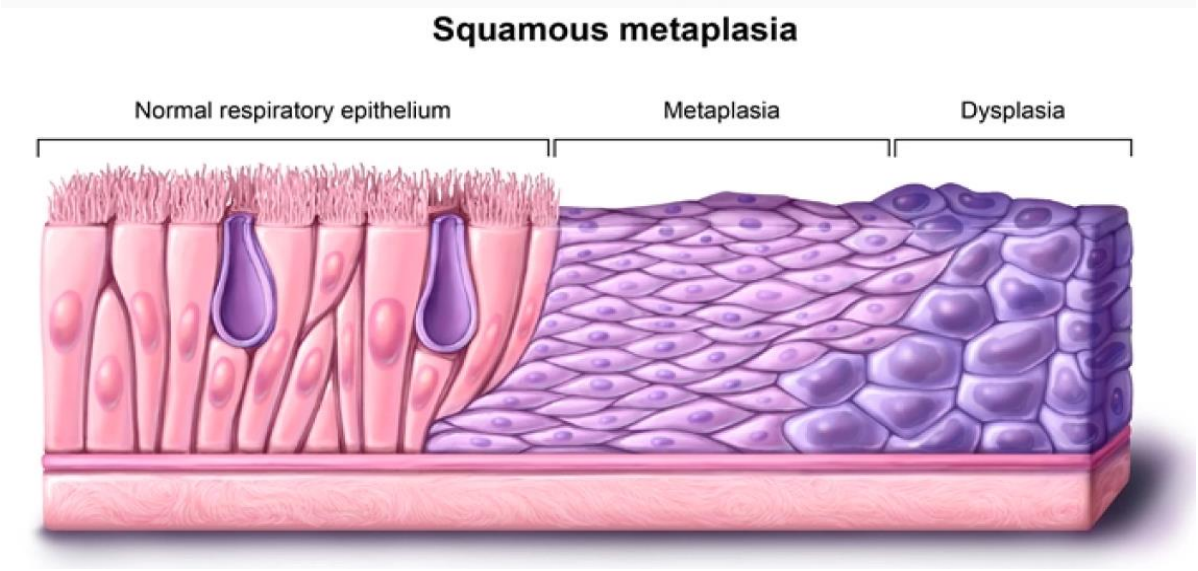
1. The right main bronchus is more prone to aspiration than the left main bronchus because it has a larger diameter, is shorter and is more vertically oriented than the left main bronchus (mnemonic: "Swallow a bite, goes down the right").

- Due to gravity, aspiration pneumonia typically develops in the most dependent portions of the lung.
- Patients who aspirate while lying supine typically have involvement of the posterior segments of the upper lobes and the superior segments of the lower lobes.
- Patients who are upright (or semi-recumbent) tend to aspirate into the basilar segments of the lower lobes. Aspirated material is more likely to travel down the right main bronchus.



2. Squamous metaplasia is a reversible, adaptive response to chronic irritation, such as smoking.

- The normal respiratory columnar epithelium is replaced by squamous epithelium, which is more resistant to irritation but has reduced mucociliary clearance.
- Metaplasia also occurs with Barrett esophagus, in which esophageal squamous epithelium is replaced by columnar epithelium in response to chronic acid exposure.

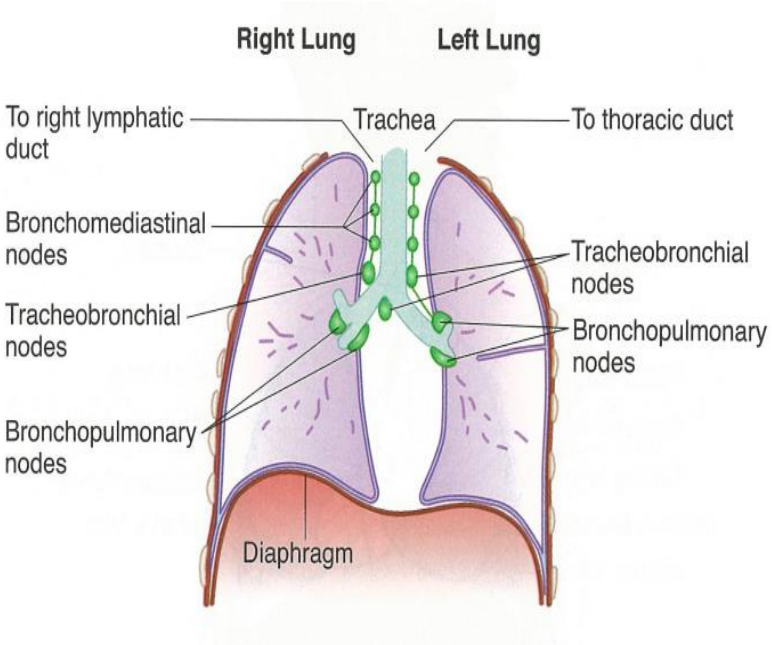


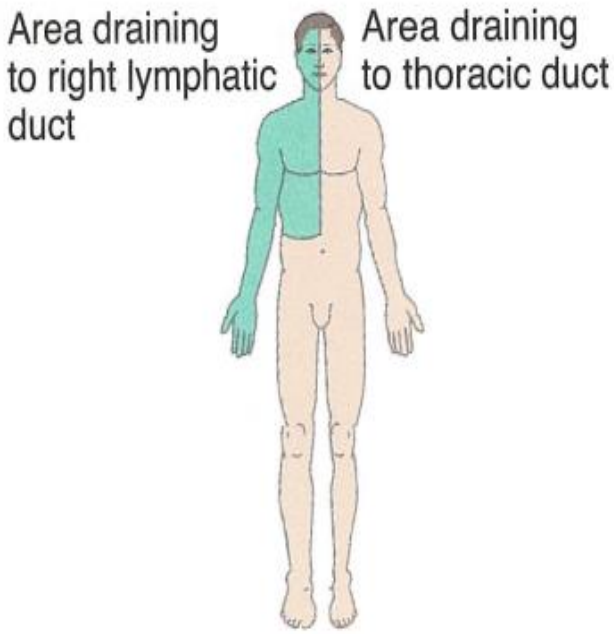
Lymphatic drainage of the lung

- Deep lymphatics follow the bronchioles and bronchi to the hilum, where they drain into the bronchopulmonary nodes (hilar lymph nodes).
- These nodes drain into tracheobronchial nodes at the bifurcation of the trachea.
- Lymphatics ascend on each side of the trachea in the bronchomediastinal nodes that drain into the right and left bronchomediastinal trunk.
- On the right side, the bronchomediastinal trunk drains into the right lymphatic duct.
- On the left side, the trunk drains into the thoracic duct.

❖ N.B:

- The thoracic duct carries all lymphatic drainage from the body below the diaphragm and on the left side of the trunk and head above the diaphragm.
- The right lymphatic duct drains lymph flow from the right head and neck and the right side of the trunk above the diaphragm.





Pneumocytes

- Type I cells:

- 97% of alveolar surfaces.

- Line the alveoli.

- Squamous; thin for optimal gas diffusion.

- Type II cells:

- Cuboidal and clustered.

- Secrete pulmonary surfactant. This surfactant decreases alveolar surface tension by creating a lipid-rich monolayer that separates alveolar gas from the underlying aqueous fluid. The phenomenon prevents atelectasis and end- expiratory collapse and increases pulmonary compliance.

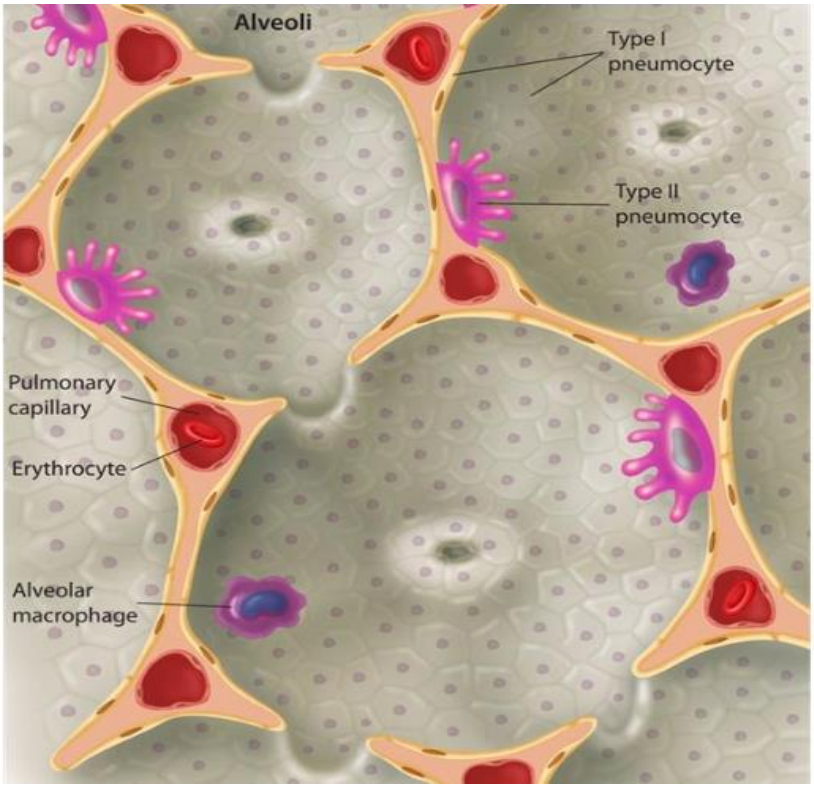
- When there is insufficient surfactant, as in neonatal respiratory distress syndrome, the result is patchy atelectasis (collapse) of alveoli due to increased surface tension.

- Type II cells proliferate during lung damage. It serve as precursors to type I cells and other type II cells.

- Club cells:

- Nonciliated; low-columnar/cuboidal with secretory granules.

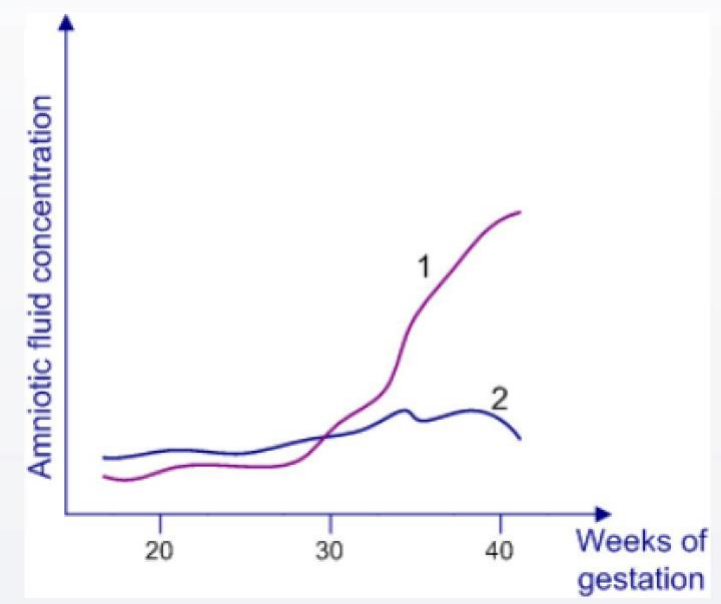
- Secrete component of surfactant; degrade toxins; act as reserve cells.



❖ N.B:

1. Phosphatidylcholine (also known as Lecithin) is a component of pulmonary surfactant and Sphingomyelin is a common membrane phospholipid.

- A commonly used measure of fetal lung maturity is the amniotic fluid lecithin/sphingomyelin (L/S) ratio.
- The amniotic fluid concentration of lecithin approximately equals that of sphingomyelin until the middle of the 3rd trimester, at which point mature type II pneumocytes begin secreting surfactant.
- The lecithin concentration then increases sharply while the sphingomyelin level remains unchanged.
- By 35 weeks gestation, the L/S ratio averages 2: 1 or higher, indicating lung maturity.
- When the lecithin to sphingomyelin (L/S) ratio in amniotic fluid is: 2, the fetal lung is considered mature, meaning that it is producing adequate surfactant to avoid neonatal respiratory distress syndrome after birth.
- The L/S ratio is measured in cases of premature labor and/or premature rupture of the membranes in order to determine the timing of delivery and whether or not to give the mother corticosteroids to induce fetal surfactant production.



2. Maternal and fetal cortisol both help to accelerate fetal lung maturation by stimulating surfactant production and can be assessed through various biochemical tests during amniocentesis.

- Corticosteroids are administered to pregnant mothers who are at risk of having a premature delivery with fetal lung immaturity.

Congenital lung malformations

Pulmonary hypoplasia

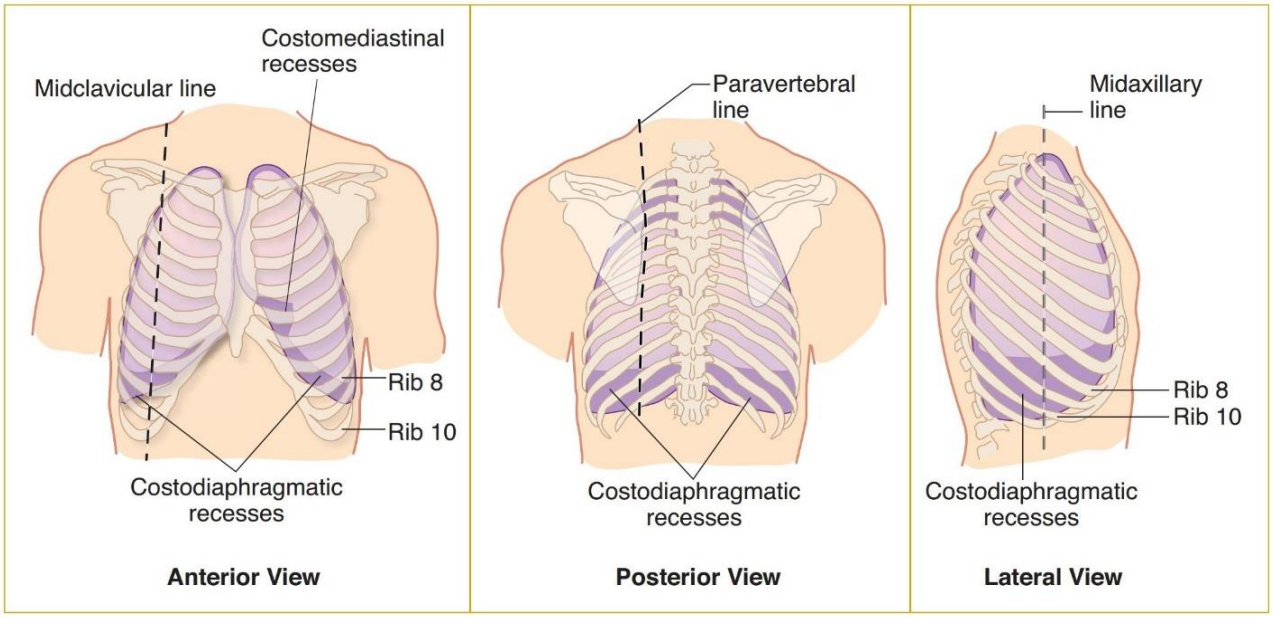
- Poorly developed bronchial tree with abnormal histology usually involving right lung.
- Associated with congenital diaphragmatic hernia, bilateral renal agenesis (Potter sequence syndrome).

Bronchogenic cysts

- Caused by abnormal budding of the foregut and dilation of terminal or large bronchi.
- Discrete, round, sharply defined and air-filled densities on CXR.
- Drain poorly and cause chronic infections.

Pleura

- In the body cavities, three double-wall serous membranes cover the lungs (pleura), heart (pericardium), and abdominal viscera (peritoneum).
- These membranes provide a mechanism of friction reduction so these viscera can move freely without damage.
- Each of these membranes is formed by an outer layer (parietal) that is continuous with the inner layer (visceral).
- The parietal pleura is the outermost layer that lines the chest wall (costal pleura), diaphragm (diaphragmatic pleura), and mediastinum (mediastinal pleura).
- The apex of the lung is covered by the cervical parietal pleura, which extends superiorly into the root of the neck above the first rib.
- The visceral pleura adheres tightly to all areas of the surface of the lung. It is continuous with the parietal layer at the hilum of the lung.
- The pleural cavity is the potential space between the parietal and visceral layers.



❖ N.B:

- In patients with neck injuries, it is important to remember that the lung apices and cervical pleura extend above the clavicle and first rib through the superior thoracic aperture into the neck.
- Stab wounds immediately above the clavicle and lateral to the manubrium can puncture the pleura and cause pneumothorax, tension pneumothorax, or hemothorax.

- Innervation:

- Pleuritic chest pain can result from any condition that causes inflammation of the pleura.

- The parietal pleura is innervated by somatic sensory (sensory afferent) nerves, which allow the sensation of sharp and localized pain (Parietal is sensitive to pain).

- The phrenic nerve, which is derived from the C3-C5 nerve roots, delivers motor innervation to the diaphragm and additionally carries pain fibers from the diaphragmatic and mediastinal pleura.

- Irritation of the pleura in either of these areas will cause a sharp pain worsened by inspiration that will be "referred" to the C3-C5 distribution, which lies at the base of the neck and over the shoulder.

- Sensory innervation of the remainder of the parietal pleura is accomplished by intercostal nerves.

- The visceral pleura receives innervation from visceral sensory autonomic nerves and is not sensitive to pain.

- Pleural recesses:

- Pleural recesses are narrow, potential spaces of the pleural cavity that the lungs do not completely descend into during quiet respiration.

- The costodiaphragmatic recess is at the base of the lung where the reflections of the diaphragmatic and costal pleurae are in contact with each other.

- In a vertical position, this is where excess pleural fluid collects in a patient.

- Thoracentesis:

- Removal of excess pleural fluid is usually made by inserting a needle into the costodiaphragmatic recess through the eighth or ninth intercostal space at the midaxillary line.

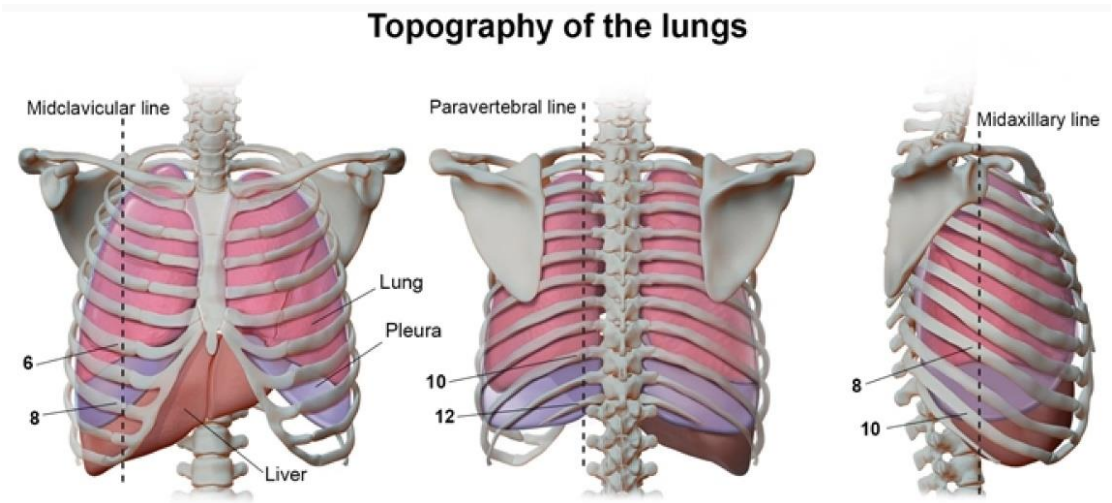
- This avoids penetration of the liver and lung.

- The needle is inserted at the lower aspect of the intercostal space (upper border of the rib) to avoid damage to the intercostal nerves and vessels in the costal groove (subcostal neurovascular bundle).

- To avoid complications while performing a thoracentesis, it is necessary to remember the location of the lungs, pleura, and other organs of the chest and upper abdomen.

- Thoracentesis, therefore, should be performed between 6th and 8th ribs along the midclavicular line, the 8th and 10th ribs along the midaxillary line, and 10th and 12th ribs along the paravertebral line.

- If the needle is inserted higher, there is a risk of lung injury.



Topography of the lungs			
Lower border of pleura	**Midclavicular line**	**Midaxillary line**	**Paravertebral line**
Lungs (& visceral pleura)	6th rib	8th rib	10th rib
Parietal pleura	8th rib	10th rib Right - upper border Left - lower border	12th rib

- <u>So, in a nutshell:</u>

- Thoracocentesis should be performed above the 8th rib in the midclavicular line, the 10th rib along the midaxillary line, and the 12th rib along the paravertebral line.

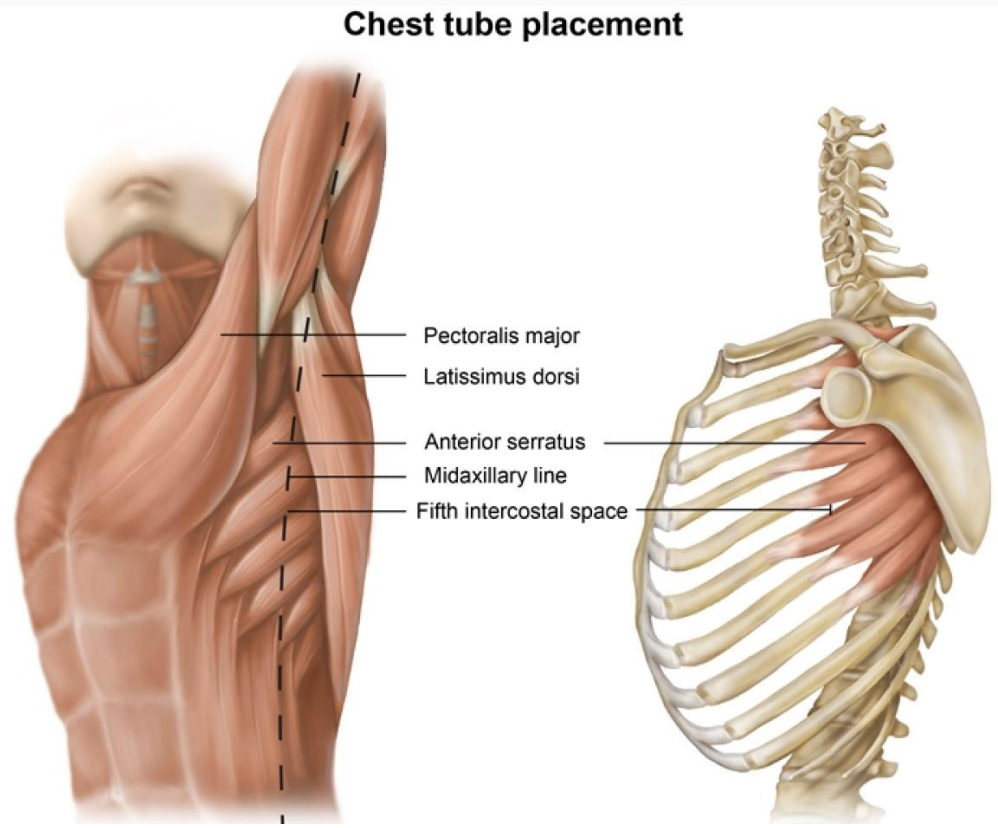
- Insertion of a needle lower than these points increases the risk of penetrating abdominal structures, and insertion of the needle on the inferior margin of the rib risks striking the subcostal neurovascular bundle.

- <u>Chest tube insertion</u>:

- The technique involves placing the chest tube through the skin and subcutaneous fat into the 4th or 5th intercostal space in the anterior axillary or midaxillary line.

- The tube traverses through the serratus anterior muscle, intercostal (external, internal, innermost) muscles, and parietal pleura to reach the pleural cavity.

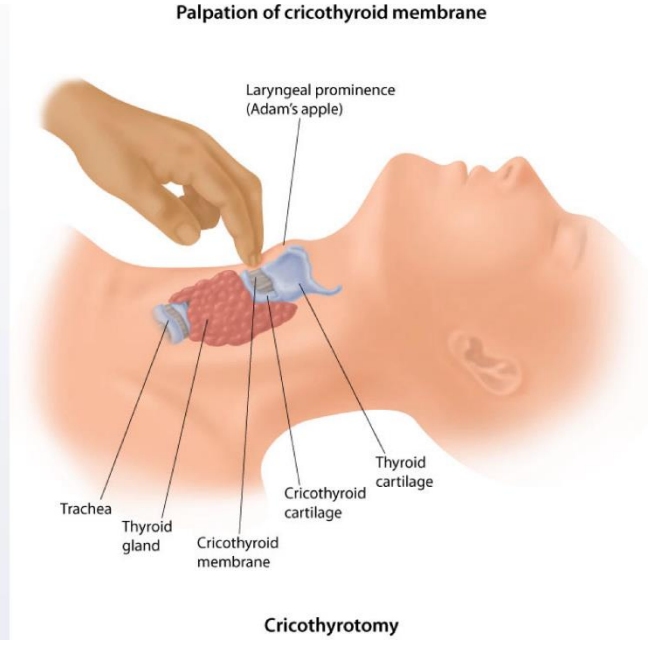
- The serratus anterior originates as multiple branches from the side of the chest along the 1st-8th ribs and inserts along the entire length of the medial scapular border.



❖ N.B:

- Cricothyrotomy is indicated when an emergency airway is required and orotracheal or nasotracheal intubation is either unsuccessful or contraindicated (due to massive hemorrhage, vomiting, facial trauma, or airway obstruction). The procedure establishes an airway through the placement of a tube between the cricoid and thyroid cartilages and requires an incision though the following structures:

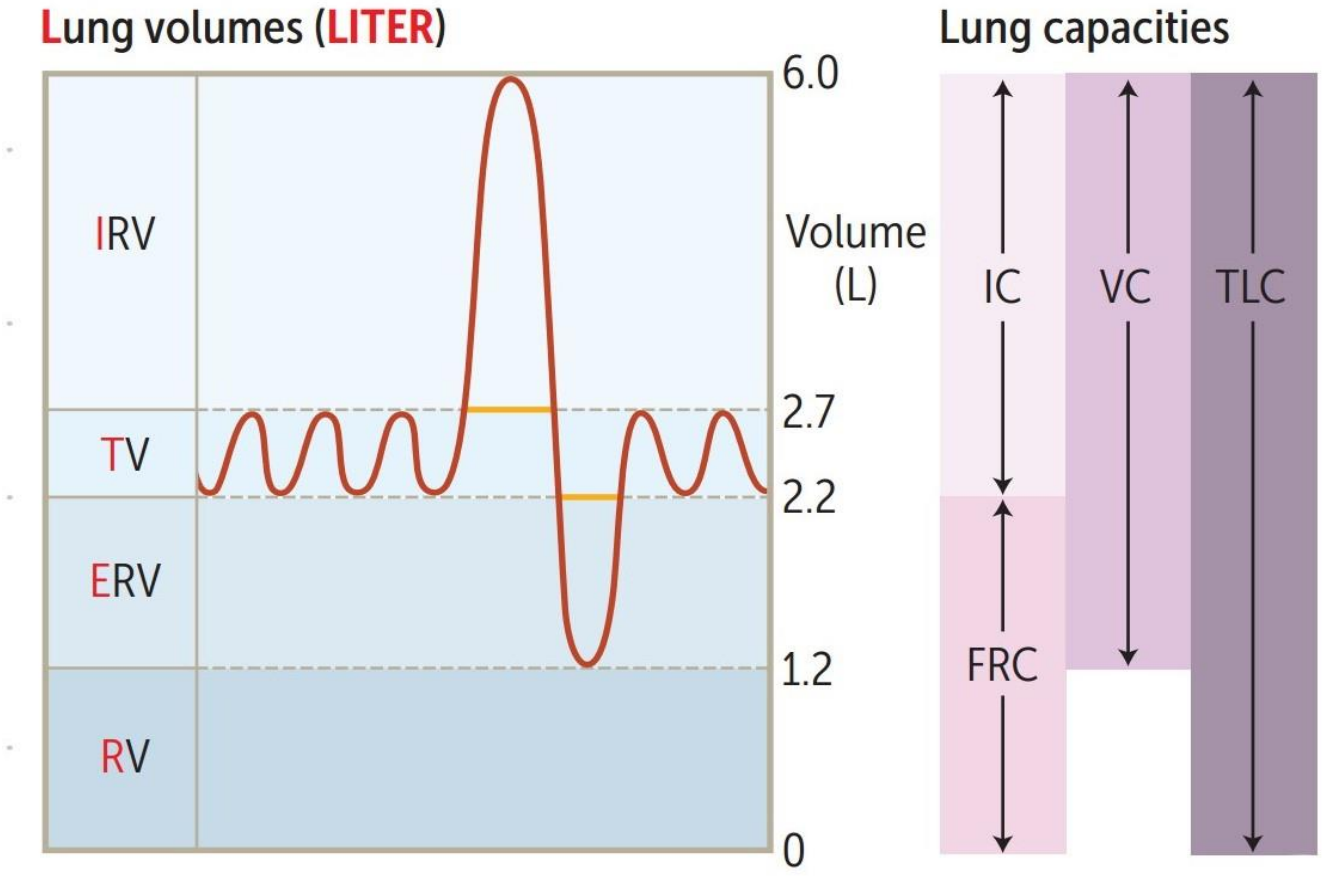
1. Skin.
2. Superficial cervical fascia (including subcutaneous fat and platysma muscle).
3. Investing and pretracheal layers of the deep cervical fascia.
4. Cricothyroid membrane.



CHAPTER 2

Physiology

Lung volumes and capacities



Lung Volumes

- Tidal Volume (V_T): Volume of air inspired/expired at rest (500mL is a good average).
- Residual Volume (RV): Volume of air remaining in the lungs after a maximal expiration.
- Inspiratory Reserve Volume (IRV): Maximum volume of air that can be inspired above resting tidal volume.
- Expiratory Reserve Volume (ERV): Maximum volume of air that can be expired after a resting expiration.

Lung Capacities

- Capacity is a sum of ≥ 2 physiologic volumes.
- Functional Residual Capacity (FRC): The amount of air in the lung system at the end of an expiration at rest. It is also considered the neutral, or equilibrium state, of the respiratory system.

$$FRC = ERV + RV$$

- Inspiratory Capacity (IC): Maximal inspiration from FRC.

$$IC = V_T + IRV$$

- Vital Capacity (VC): Maximum amount of air expired following a maximal inspiration. If done forcefully, Forced Vital capacity.

$$VC = ERV + V_T + IRV$$

- Total Lung Capacity (TLC): The volume of air in the lung system after a maximal inspiration.

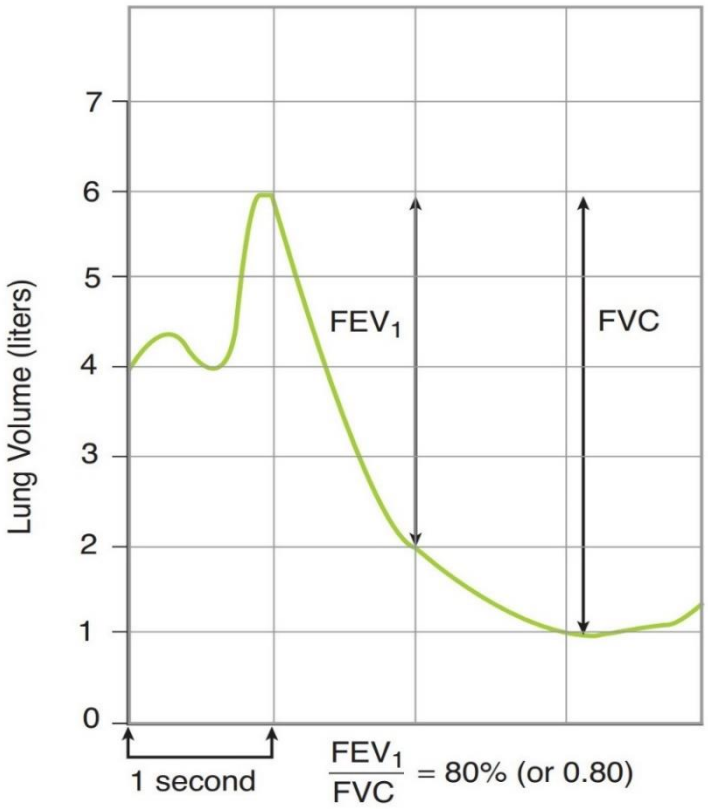
$$TLC = VC + RV$$

Spirometry

- Spirometry measures only changes in lung volume and flow (volume/time).
- It cannot measure RV or any capacity containing RV (TLC, FRC).

Pulmonary Function Testing

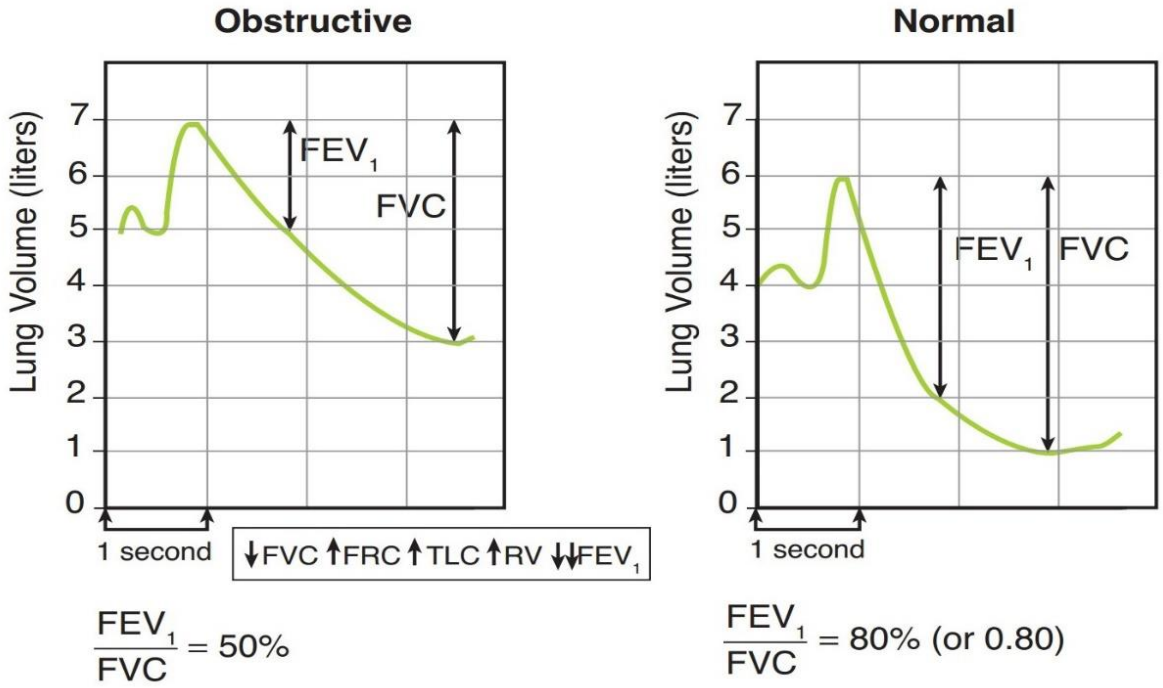
- Three important data values obtained: FVC, FEV_1, (volume expired in the first second), FEV_1/FVC (normally 0.8).



Obstructive versus Restrictive Patterns

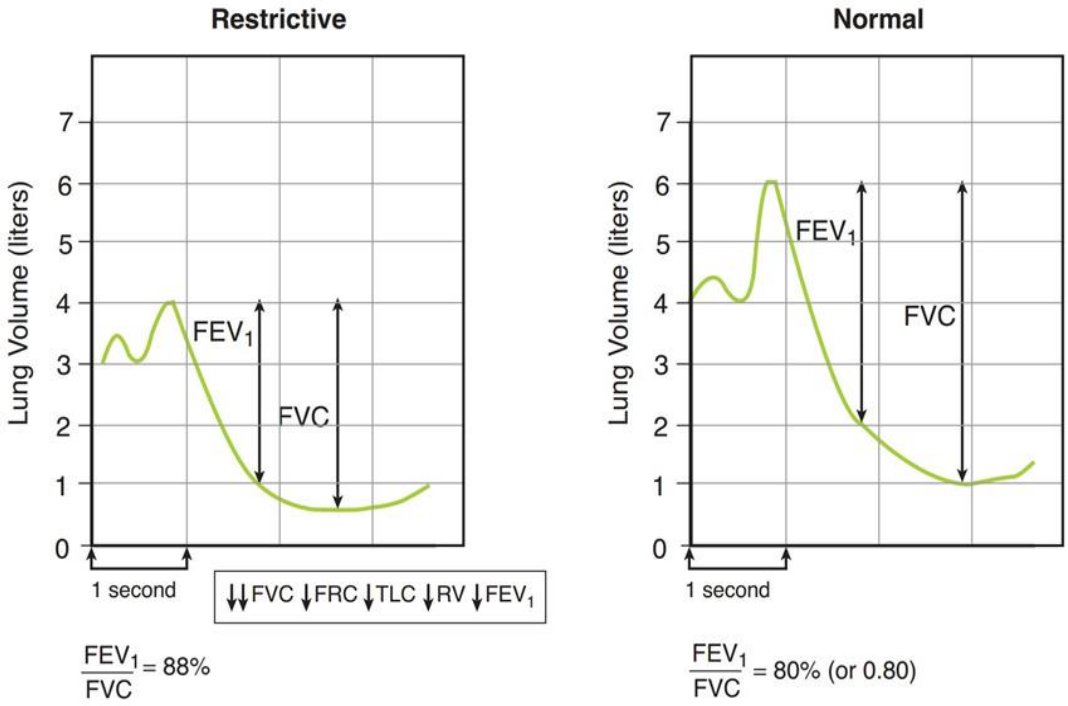
A. Obstructive pulmonary disease:

- Obstructive disease is characterized by an increase in airway resistance that is measured as a decrease in expiratory flow.
- Examples are chronic bronchitis, asthma, and emphysema.
- Total lung capacity (TLC) is normal or larger than normal, but during a maximal forced expiration from TLC, a smaller than normal volume is slowly expired.



B. Restrictive pulmonary disease:

- Restrictive pulmonary disease is characterized by an increase in elastic recoil (a decrease in lung compliance) which is measured as a decrease in all lung volumes.
- Reduced vital capacity with low lung volumes are the indicators of restrictive pulmonary diseases.
- Examples are acute respiratory distress syndrome (ARDS) and interstitial lung diseases such as sarcoidosis and idiopathic pulmonary fibrosis (IPF).
- TLC is smaller than normal, but during a maximal forced expiration from TLC, the smaller volume is expired quickly and more completely than in a normal pattern.
- Therefore, even though FEV1 is also reduced, the FEV1/FVC is often increased.
- However, the critical distinction is low FVC with low FRC and RV.

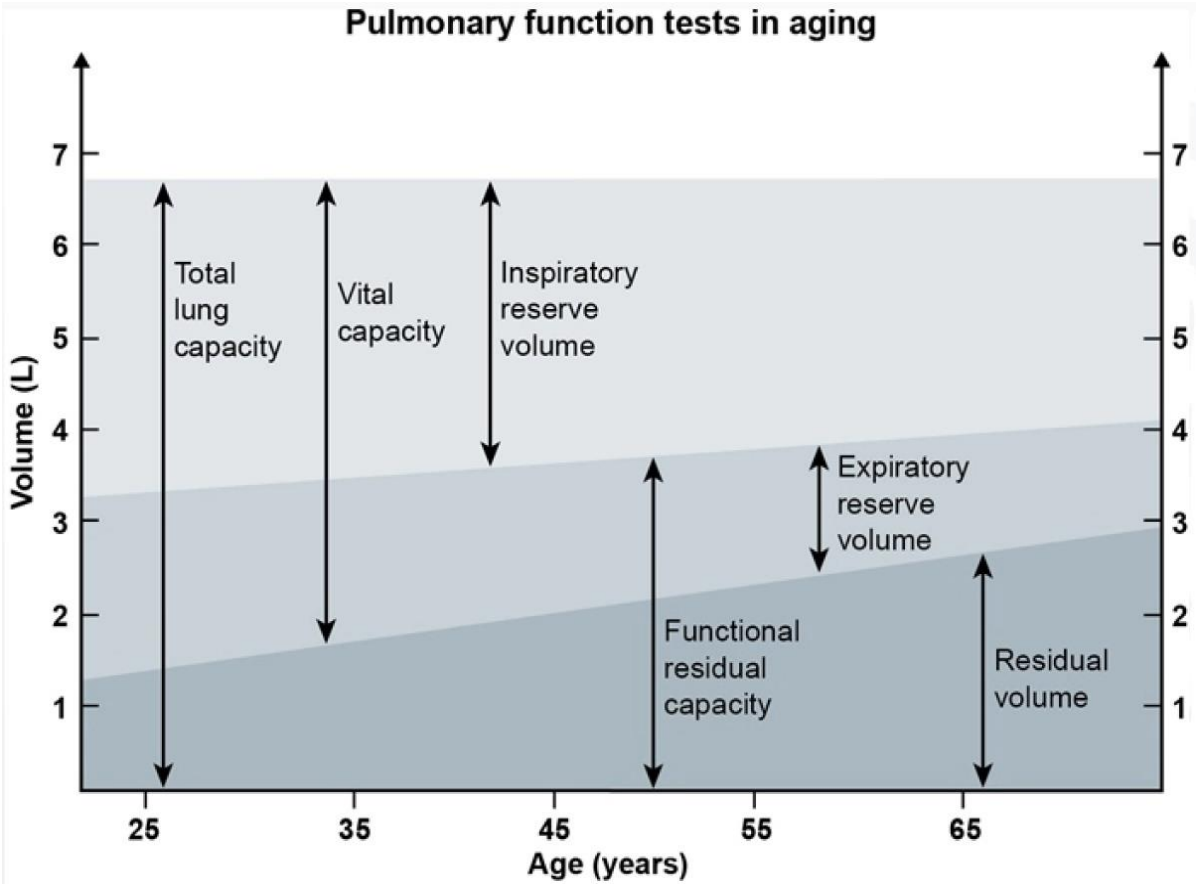


Variable	Obstructive Pattern (Emphysema)	Restrictive Pattern (Fibrosis)
TLC	↑	↓↓
FRC	↑	↓
RV	↑	↓
FEV1	↓↓	↓
FVC	↓	↓↓
FEV1/FVC	↓	↑ or normal

- FVC is always decreased when pulmonary function is significantly compromised.
- A decrease in FEV1/FVC ratio is evidence of an obstructive pattern.
- A normal or increased FEV1/FVC ratio is evidence of a restrictive pattern, but a low TLC is diagnostic of restrictive lung disease.

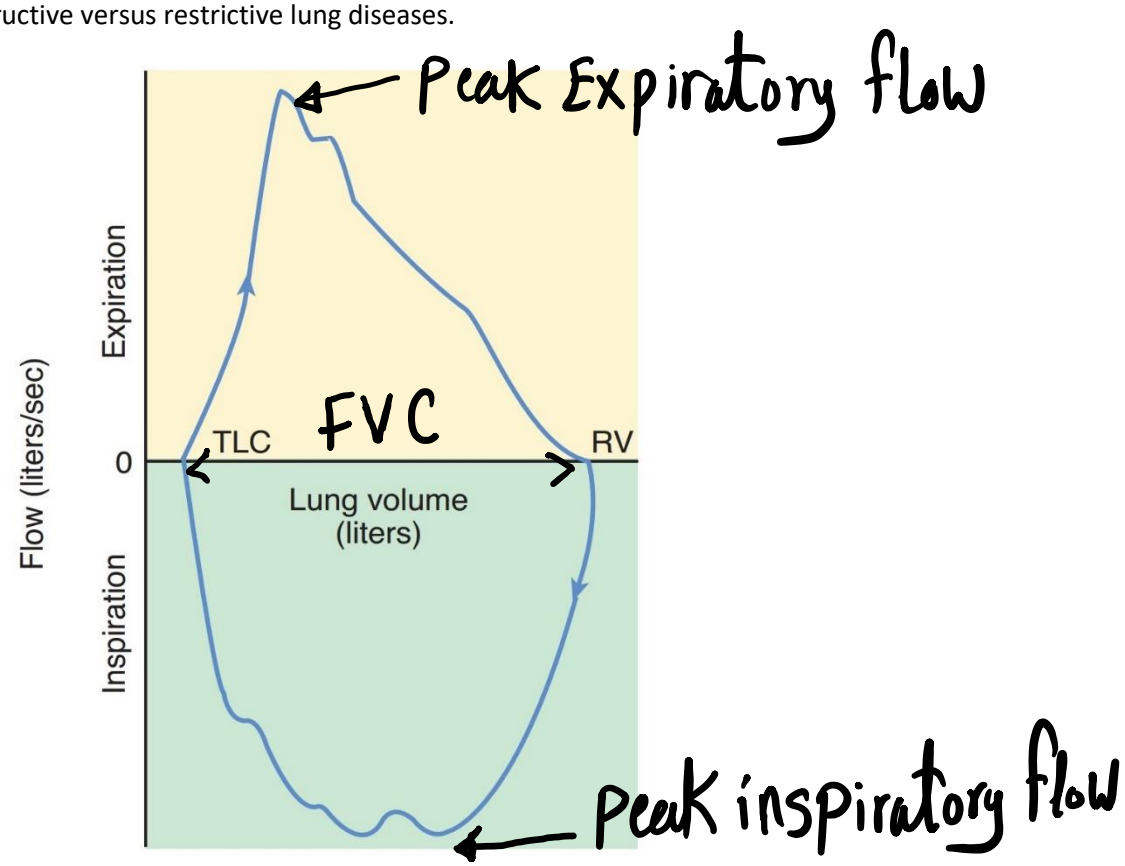
❖ N.B:

- Aging is associated with a number of changes in pulmonary function.
- Patients age >35 experience steady decreases in chest wall compliance as a result of stiffening from rib calcification. In contrast, lung compliance increases with age due to a loss of elastic recoil, particularly in the alveolar ducts.
- Diminished elastic recoil and the collapse of supporting tissues around the airways cause a significant increase in residual volume (RV). However, total lung capacity (TLC) remains unchanged because the decreased chest wall compliance counterbalances increases in lung compliance.
- In addition, as RV becomes a much higher proportion of TLC (due to air trapping), forced vital capacity also decreases.

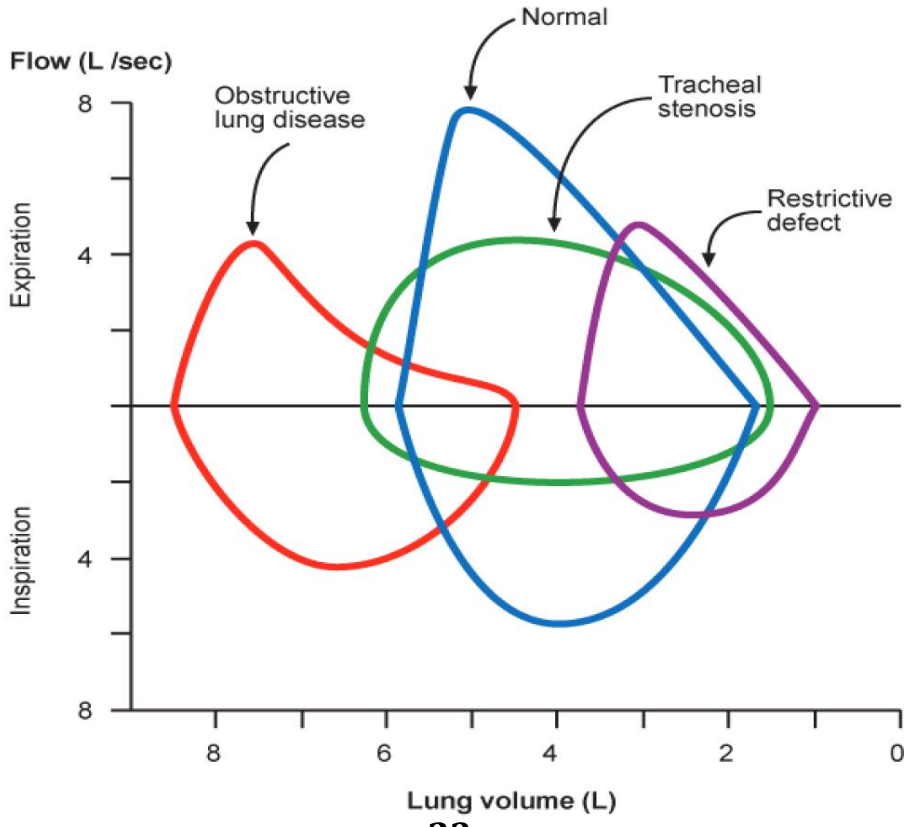

Pulmonary function tests in aging
Volume (L)
7
6
5
4
3
2
1
Total lung capacity
Vital capacity
Inspiratory reserve volume
Expiratory reserve volume
Functional residual capacity
Residual volume
25
35
45
55
65
Age (years)

Volume loops

- The graphic depiction of flow versus lung volume during a maximal expiration from TLC can also separate obstructive versus restrictive lung diseases.



Flow-volume curves for various lung conditions

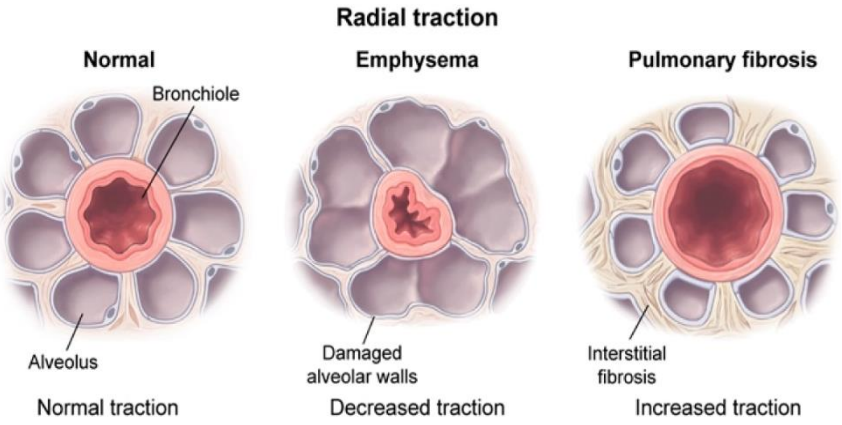


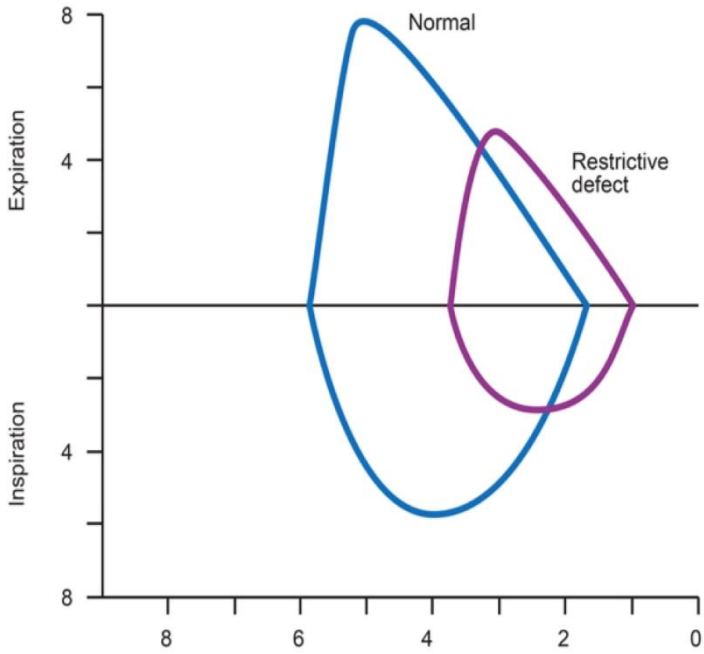
- In the loop shown, expiration starts at total lung capacity and continues to residual volume.
- The width of the loop is the FVC.
- In obstructive disease, the flow-volume loop begins and ends at abnormally high lung volumes, and the expiratory flow is lower than normal. In addition, the downslope of expiration "scallops" or "bows" inward. This scalloping indicates that at any given lung volume, flow is less. Thus, airway resistance is elevated (obstructive).
- In restrictive disease, the flow-volume loop begins and ends at unusually low lung volumes. Peak flow is less, because overall volume is less. However, when expiratory flow is compared at specific lung volumes, the flow in restrictive disease is somewhat greater than normal.

❖ N.B:

1. Most interstitial lung diseases cause progressive pulmonary fibrosis with thickening and stiffening of the pulmonary interstitium.

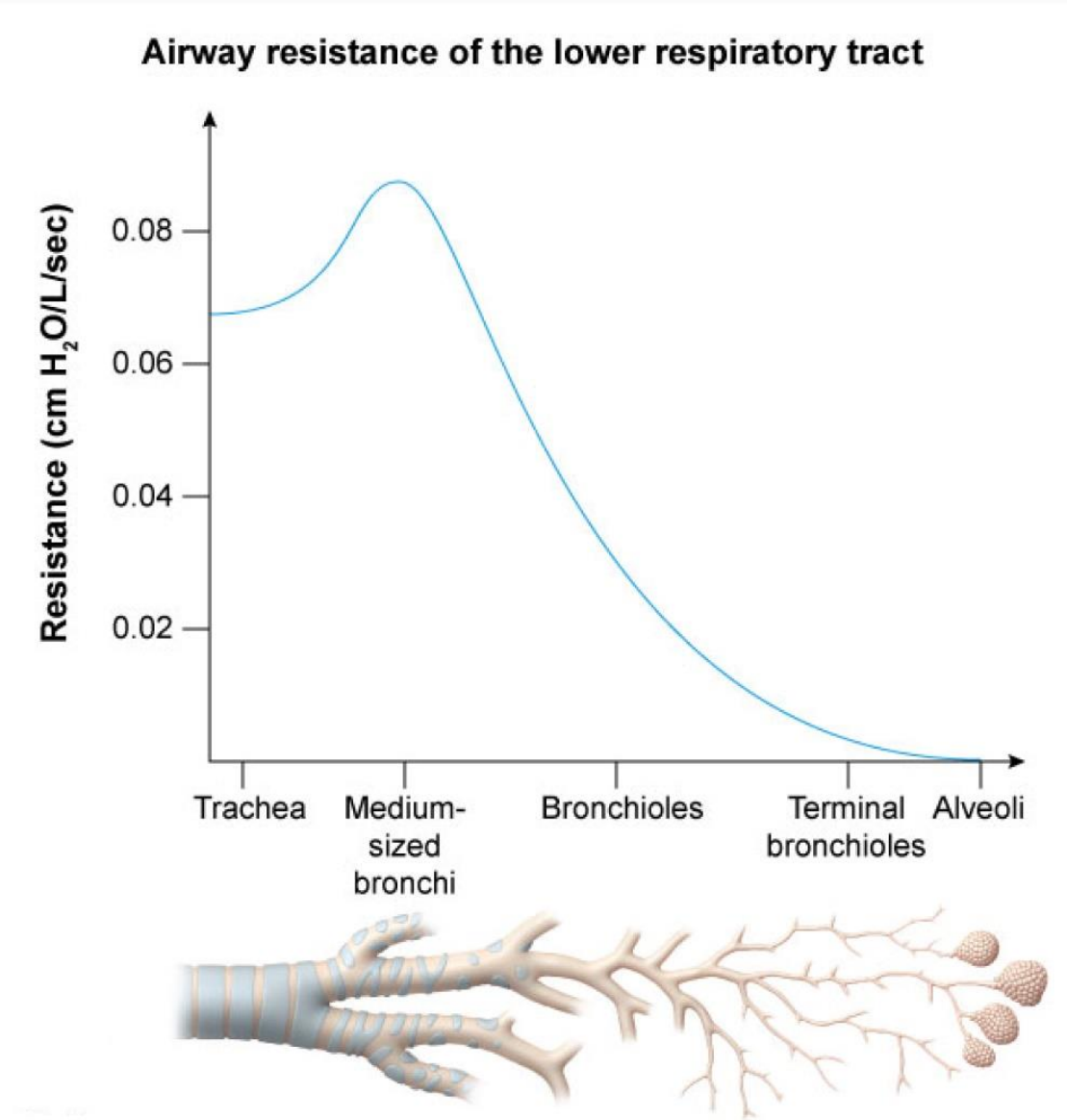
- This causes increased lung elastic recoil, which leads to airway widening due to increased outward pulling (radial traction) by the surrounding fibrotic tissue.
- The resulting decrease in airflow resistance leads to supernormal expiratory flow rates.
- Additional spirometry findings in restrictive lung diseases include reduced total lung capacity, vital capacity, inspiratory capacity, functional reserve capacity, and residual volume.
- Both the forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV) are decreased as well.
- However, the FEV1/FVC ratio is typically increased because the FEV1 decreases less than the FVC (due to airway widening relative to the low lung volumes).





2. The upper respiratory tract (nasal passages, mouth, pharynx, larynx) accounts for about half of the total airway resistance.

- The remainder derives from the lower respiratory tract, which begins at the trachea and consists of about 23 generations of airways.
- Although resistance within the trachea and mainstem bronchi is relatively high, it increases in the medium-sized bronchi because of highly turbulent airflow.
- In contrast, airways <2 mm in diameter (bronchioles) contribute <20% of the total airway frictional resistance.



Ventilation and dead space

- Total ventilation is the volume of air moved in or out of the respiratory system per minute, usually measured as the volume expired per minute.

- This is often referred to as minute ventilation or minute volume.

$$V_E = V_T \times F$$

- V_E = Ventilation volume.

- V_T = Tidal volume.

- F = Respiratory frequency.

- Normal resting individual:
  - V_T = 500 ml.
  - F = 12-20 breaths/min.

Dead space

- Dead space represents any air in the respiratory system that is not exchanging oxygen and carbon dioxide with the pulmonary capillary blood.

- The most important dead space for our purposes is the anatomic dead space.

A. Anatomic Dead Space:

- Anatomic Dead Space (ADS) is the air in the conducting airways all the way down to and including the terminal bronchioles.

- The respiratory bronchioles can be considered a transition region.

- Air within the alveolar ducts and alveoli should be exchanging O_2 and CO_2 and constitutes a respiratory zone.

B. Alveolar (Functional) Dead Space:

- Alveoli ventilated but without capillary blood flow.

- Apex of healthy lung is largest contributor of alveolar dead space (Volume of inspired air that does not take part in gas exchange).

C. Physiological Dead Space:

- The total volume of dead space in the lungs is known as physiologic dead space.

- It consists of both the anatomic dead space of the conducting airways (nose, trachea, bronchi, bronchioles; normally 150 mL) and alveolar dead space due to well-ventilated but poorly perfused alveoli.

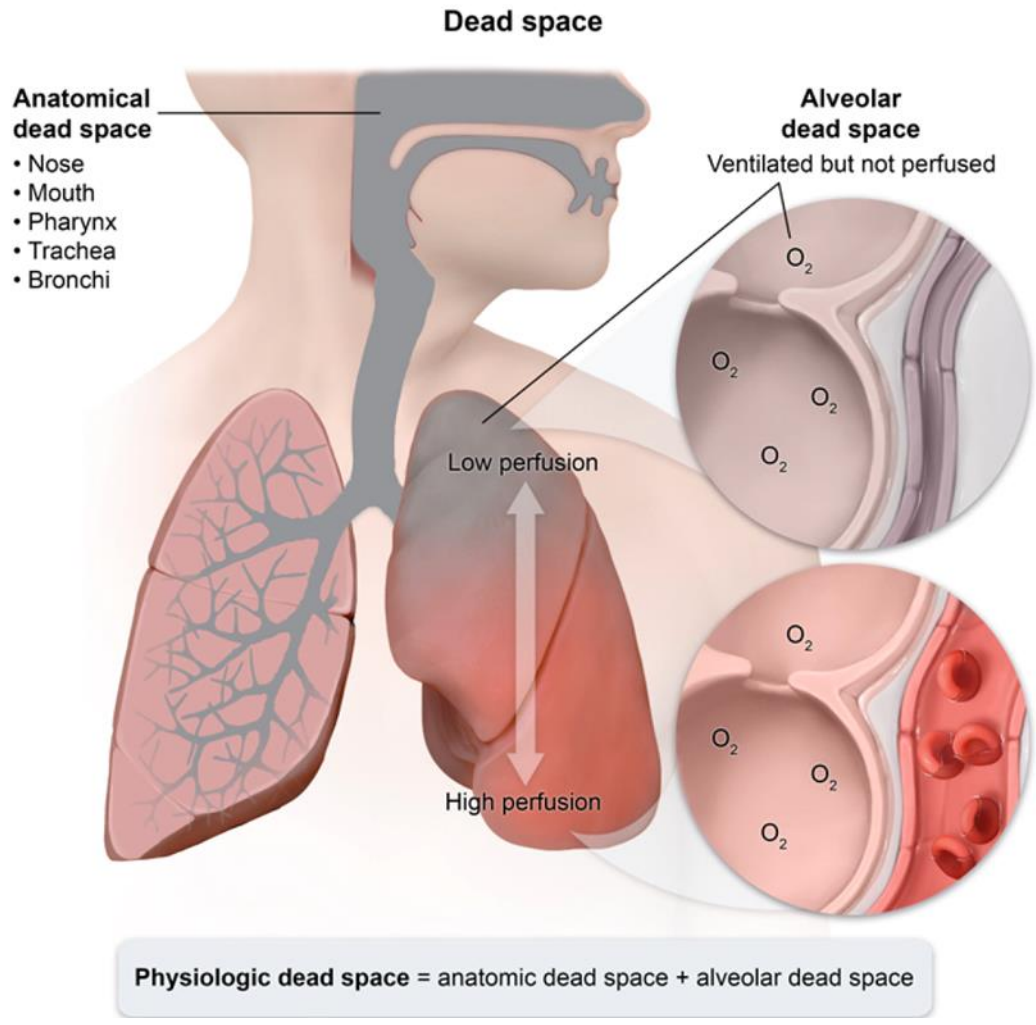
- Because it is difficult to directly measure physiologic dead space, it is often estimated in mechanically ventilated patients by comparing arterial (a) and expiratory (E) pCO_2 levels:

$$V_D = V_T \times \frac{PaCO2 - PEco2}{PaCO2}$$

- V_T = tidal volume.
- P_aco_2 = arterial Pco_2.
- P_Eco_2 = expired air Pco_2.

- Physiologic dead space: approximately equivalent to anatomic dead space in normal lungs.

- Pathologic dead space: when part of the respiratory zone becomes unable to perform gas exchange (Ventilated but not perfused).



Alveolar Ventilation

- Alveolar ventilation is the room air that reaches the respiratory zone (alveoli and respiratory bronchioles) per minute.
- It can be calculated by subtracting dead space volume (which does not participate in gas exchange) from the tidal volume.
- The first 150 ml of the tidal volume fills the dead space and does not contribute to alveolar ventilation.

Alveolar ventilation (L/min) = (tidal volume - dead space volume) X breaths/min

$$V_A = (V_T - V_D) \times f$$

- V_A = alveolar ventilation.
- V_T = tidal volume.
- V_D = dead space = 150 mL/breath.
- f = respiratory frequency.

- Consider the following individuals. With patient A the normal reference and dead space 150 ml:

Ventilation	VT	F	Total ventilation	Alveolar ventilation
Patient A	500 ML	10/min	5,000 mL/min	3,500 mL/min
Patient B	600 ML	10/min	6,000 mL/min	4,500 mL/min
Patient C	500 ML	12/min	6,000 mL/min	4,200 mL/min
Patient D	300 ML	18/min	5,400 mL/min	2,700 mL/min
Patient E	600 ML	15/min	9,000 Ml/min	6,750 mL/min

- Patient B increased depth of breathing at the same rate:
  - Equal increases in total and alveolar ventilation; every additional ml of the tidal volume contributed to alveolar ventilation.

- Patient C increased rate at the same depth:
  - Total ventilation increases more than alveolar ventilation. For each additional tidal volume of 500 ml, only 350 ml contributed to alveolar ventilation.

- Patient D has rapid, shallow breathing:
  - Total ventilation is above normal, but alveolar ventilation is below normal (hypoventilation).
  - In rapid shallow breathing, the patient appears to be moving a lot of air, but it is not generally hyperventilation, rather, it is usually hypoventilation (restrictive diseases).

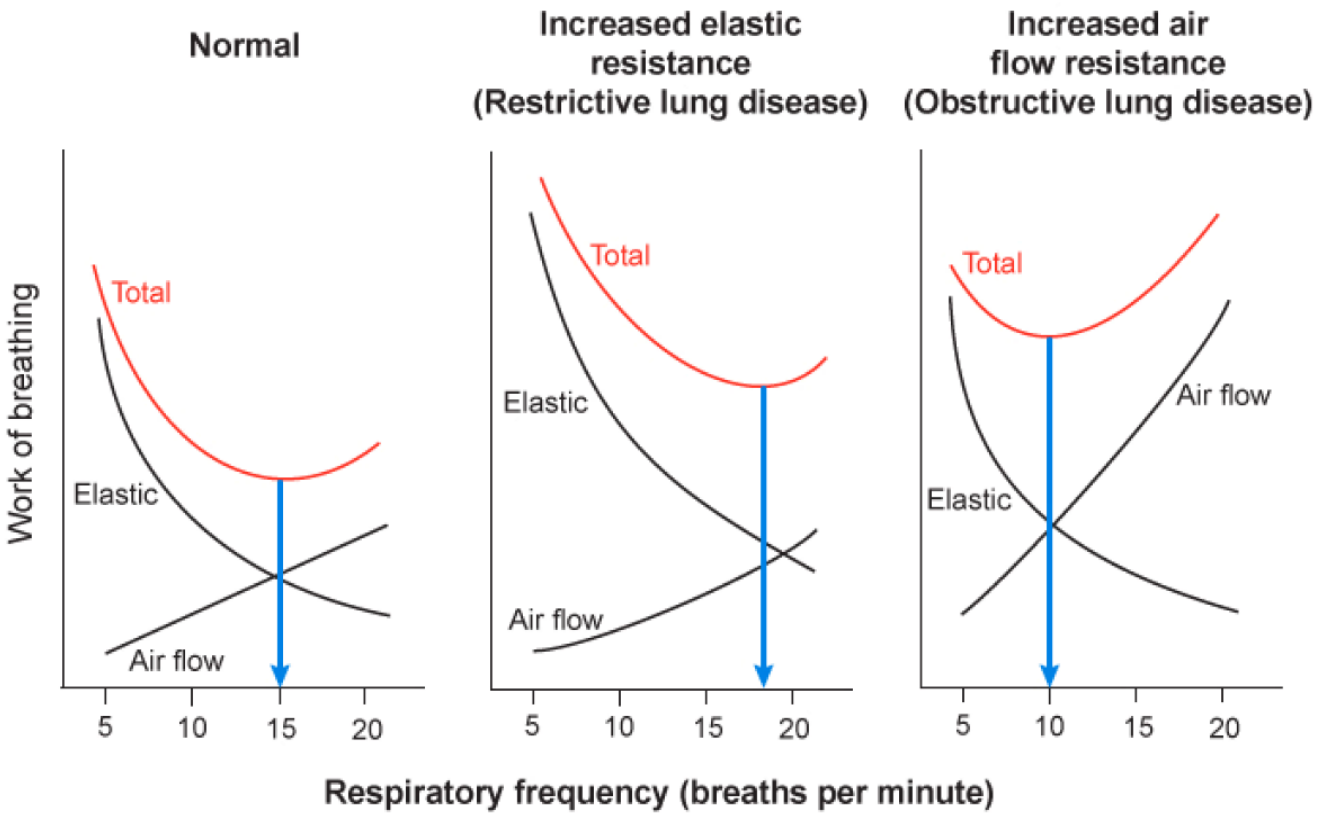
- Patient E has rapid, deep breathing (Kussmaul breathing, diabetic ketoacidosis):

- Alveolar ventilation above normal (hyperventilation).

❖ N.B:

1. Adequate minute ventilation (minute ventilation = tidal volume X respiratory rate) is necessary for maintaining oxygenation and CO_2 excretion.

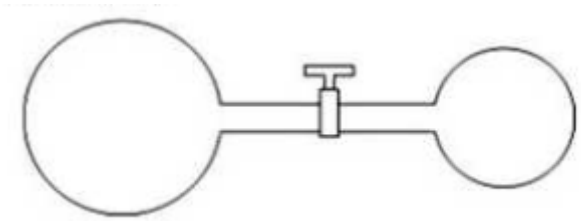
- In order to reduce energy consumption and fatigue, the tidal volume and respiratory rate are optimized by the respiratory control centers to minimize the work of breathing while maintaining adequate minute ventilation.
- The work done against the stiff lung (↑ elastic resistance of the lung) is increased when the tidal volume is increased, while the work done against airflow resistance (asthma, COPD) is increased when the breathing frequency is increased.
- If the two components are summated and the total work is plotted against respiratory frequency, there will be an optimal breathing rate at which the total work of breathing is minimized.
- For the normal adult, this rate is on average 15 breaths per minute.
- For patients with stiff lungs (increased elastic resistance), the work of breathing is minimized when the respiratory rate is high, and the tidal volume is low.
- Therefore, rapid and shallow breaths are favored in diseases that increase elastic resistance (pulmonary fibrosis, pulmonary edema, acute respiratory distress syndrome).
- In contrast, in diseases that cause high airflow resistance (asthma, COPD), patients breathe at a lower rate (slow, deep breaths) in order to minimize the work of breathing.



2. Laplace's law states that the distending pressure (the pressure required to keep a sphere distended) is directly proportional to the surface tension (T) and inversely proportional to the radius (r).

$$P = 2T/r$$

- Assuming a constant surface tension, a sphere with a smaller radius will have a higher distending pressure than a larger sphere.
- When the above clamp is opened, air will flow down its pressure gradient (from the smaller sphere to the larger one).
- Thus, the smaller sphere will completely collapse while the larger sphere increases in size.
- Surfactant counteracts this effect by decreasing the surface tension as a sphere decreases in size.
- As the inside area of the sphere decreases, the surfactant becomes more concentrated and thus is able to decrease surface tension to a greater extent.
- Conversely, as a sphere grows larger, the surfactant molecules become more spread out and do not reduce the surface tension as much.
- Thus, surfactant reduces the variation in distending pressure amongst spheres of varying sizes, preventing the collapse of smaller spheres and the unchecked expansion of larger ones.



Lung mechanics

Forces on the Lung System

A. **Elastic Recoil of the Lung:**

- Created by stretching the elastic and collagen fibers of the lung tissue and the surface tension forces trying to collapse the alveoli.
- Represents the inward force created by the elastic recoil properties of alveoli.
- As the lung expands, recoil increases; as the lung gets smaller, recoil decreases.
- Recoil, as a force, always acts to collapse the lung.

B. **Chest Wall Recoil:**

- Outward force of the chest wall.
- FRC represents the point where this outward recoil of the chest wall is counterbalanced by the inward recoil of the lung.

C. **Intrapleural Pressure (IPP):**

- Represents the pressure inside the thin film of fluid between the visceral pleura, which is attached to the lung, and the parietal pleura, which is attached to the chest wall.
- At FRC, in the neutral or equilibrium state, recoil forces act to collapse the lung, and the rib cage attempts to spring outward. The two opposing forces create a negative pleural pressure (-5 cmH_2O).

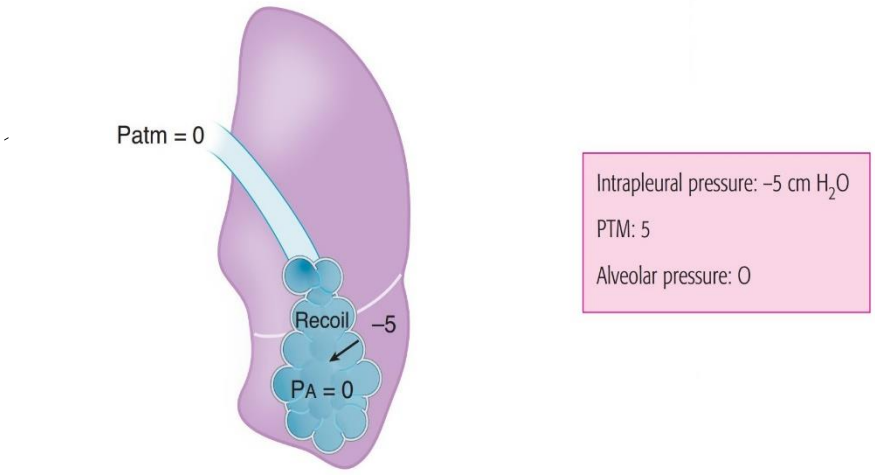
D. **Transmural Pressure Gradient (P_{TM}):**

- Represents the pressure gradient across any wall.
- Calculated as inside pressure minus outside pressure.
- If positive (inside greater than outside), it is a net inflating force.
- If negative (outside greater than inside), it is a net deflating force.
- For the entire lung, transmural pressure is called the transpulmonary pressure (TPP).

The Normal Restful Cycle

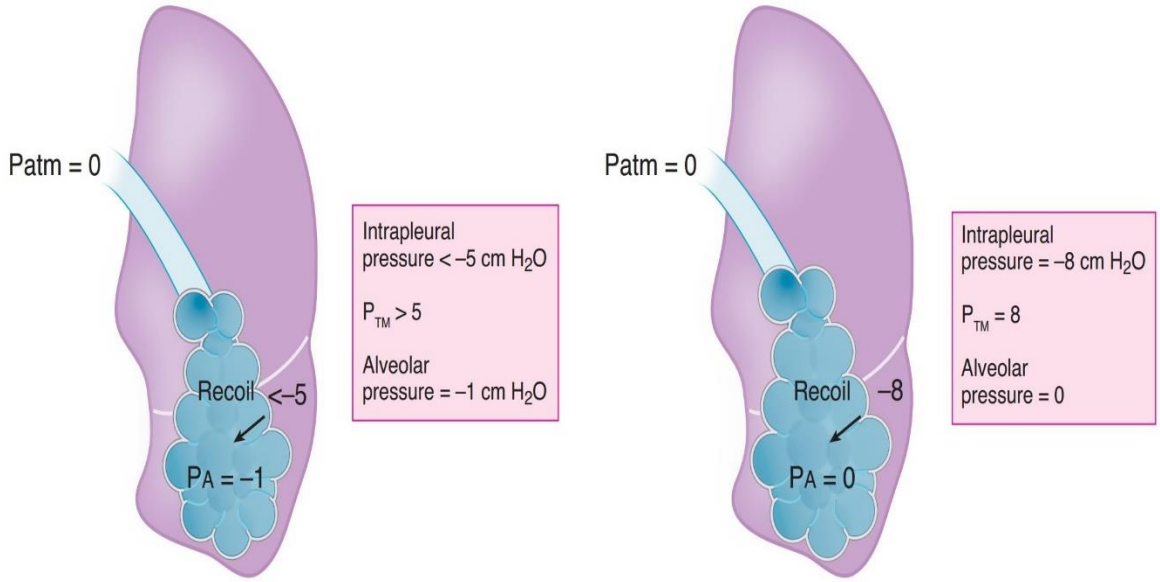
1. Situation at FRC:

- The glottis is open, and all respiratory muscles are relaxed (FRC). This is the neutral or equilibrium point of the respiratory system.
- Intra-pleural pressure is negative at FRC because the inward elastic recoil of the lungs is opposed by the outward-directed recoil of the chest wall.
- Because no air is flowing through the open glottis, alveolar pressure must be zero. By convention, the atmospheric pressure is set to equal zero.



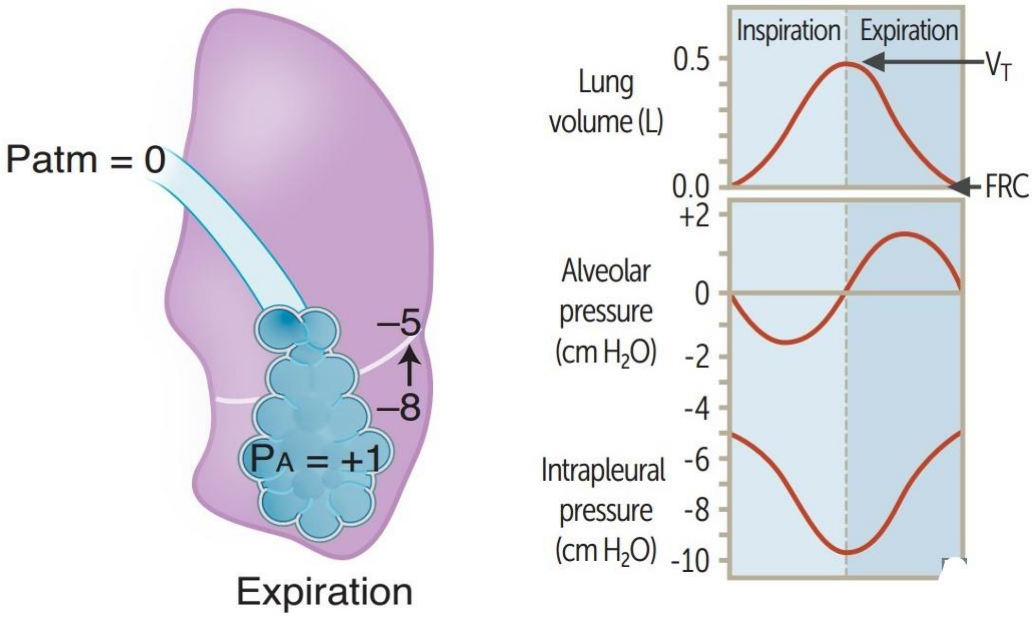
2. Inspiration:

- Inspiration is induced by the contraction of the diaphragm and external intercostal muscles that expand the chest wall.
- The net result is to make intrapleural pressure more negative.
- The more negative IPP causes PTM (TPP) to increase, which in turn causes expansion of the lungs. The greater the contraction, the greater the change in intrapleural pressure and the larger the PTM (TPP) expanding the lung.
- The expansion of the lung increases alveolar volume. The rise in volume causes pressure to decrease, resulting in a negative (subatmospheric) alveolar pressure.
- Because alveolar pressure is now less than atmospheric, air rushes into the lungs.
- The lung expands until alveolar pressure equilibrates with atmospheric pressure. The lungs are at their new, larger volume.
- Under resting conditions, about 500 mL of air flows into the lung system in order to return alveolar pressure back to zero.



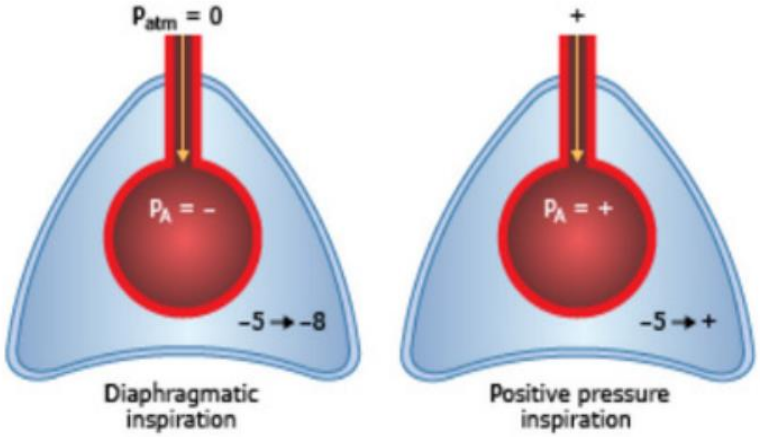
3. Expiration:

- Expiration under resting conditions is produced simply by the relaxation of the muscles of inspiration.
- Relaxation of the muscles of inspiration causes intrapleural pressure to return to –5 cm H_2O.
- This decreases IPP back to its original level of -5 cm H_2O, resulting in a decreased P_{TM}.
- The drop in P_{TM} reduces alveolar volume, which increases alveolar pressure. The elevated alveolar pressure causes air to flow out of the lungs.
- The outflowing air returns alveolar pressure toward zero, and when it reaches zero, airflow stops. The lung system returns to FRC.



Positive Pressure Ventilation

- With diaphragmatic inspiration, pleural pressure becomes more negative, creating a negative alveolar pressure that pulls in the tidal volume.
- With positive pressure ventilation, the tidal volume is pumped into the lungs, as in blowing up a balloon.
- During inspiration, alveolar pressure is becoming more and more positive. It is at its most positive at the end of inspiration.
- On a positive pressure ventilator, tidal volume must be sized appropriately. If tidal volume is inappropriately large, alveolar pressure is excessive at the end of inspiration. This can cause a spontaneous pneumothorax, often at the lung apex.



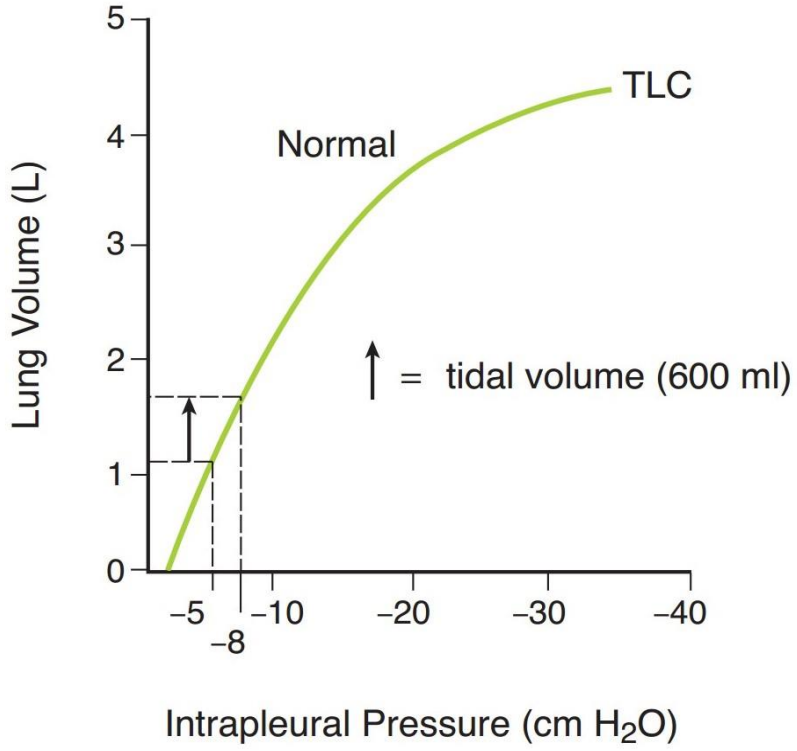
b

Lung Compliance

- Lung compliance is defined in the following equation. However, calculations are based on inspiration rather than expiration.

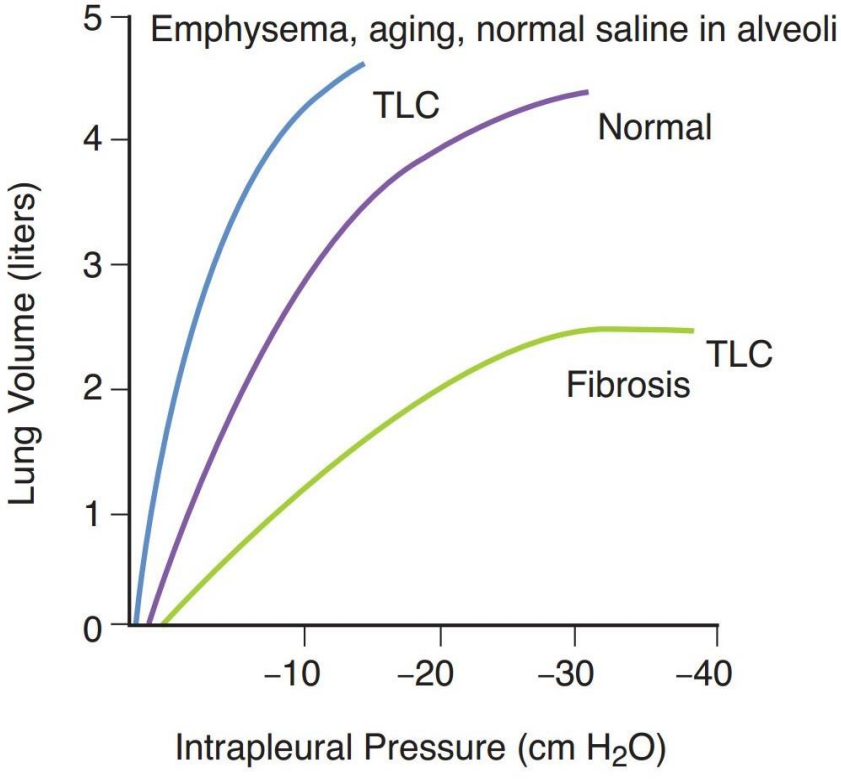
$$\text{Compliance} = \frac{\Delta V}{\Delta P}$$

- Increased compliance means more air will flow for a given change in pressure.
- Reduced compliance means less air will flow for a given change in pressure.



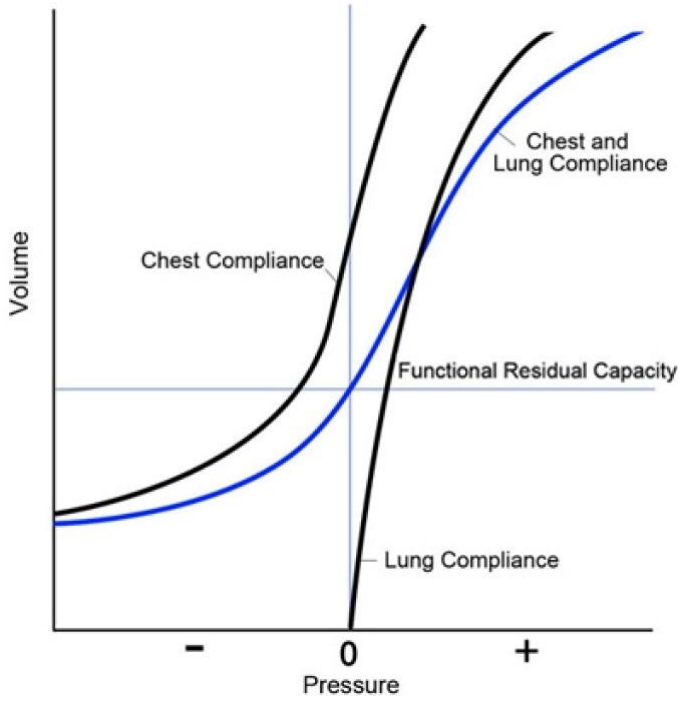
- Emphysema, often caused by smoking, results in destruction of the alveolar septa and capillaries. This reduces the elastic recoil and increase compliance.

- Fibrosis has increased collagen fiber deposition, which increases the tissue component of elastic recoil and decease compliance.



Inflation Curves

- The following figure shows inflation curves for the lung, chest wall, and the entire respiratory system.
- The pressure-volume curve below demonstrates the compliance of the lung and the chest wall and the net combined compliance of these structures.
- Due to the elasticity of the lungs, the alveolar transmural pressure is always positive, resulting in a perpetual collapsing force on the lungs; this is why the curve marked "lung" always has a positive value.
- Inversely, the chest wall tends to transmit an expanding force to the lungs, resulting in a negative transmural pressure, except during maximal inspiration.
- These two forces, the positive alveolar transmural pressure, and the negative chest wall transmural pressure oppose one another equally at the functional residual capacity (FRC), resulting in an airway pressure of zero.
- Thus, at the FRC, the airway pressure is zero and there is no tendency for air to flow either into or out of the lungs at this point.
- At the FRC, the tendencies of the chest wall to expand and the lung to collapse oppose one another, creating a negative intrapleural pressure of approximately -5 cm H_2O.



Pulmonary circulation

- Under normal conditions in a healthy adult living at sea level, the pulmonary circulation is a low-pressure, high-compliance system.

- In order to provide continuous blood flow to the body, the blood flow per minute (ml/min) in the pulmonary circulation must be identical to the blood flow in the systemic circulation. This is true for conditions of both exercise and rest.

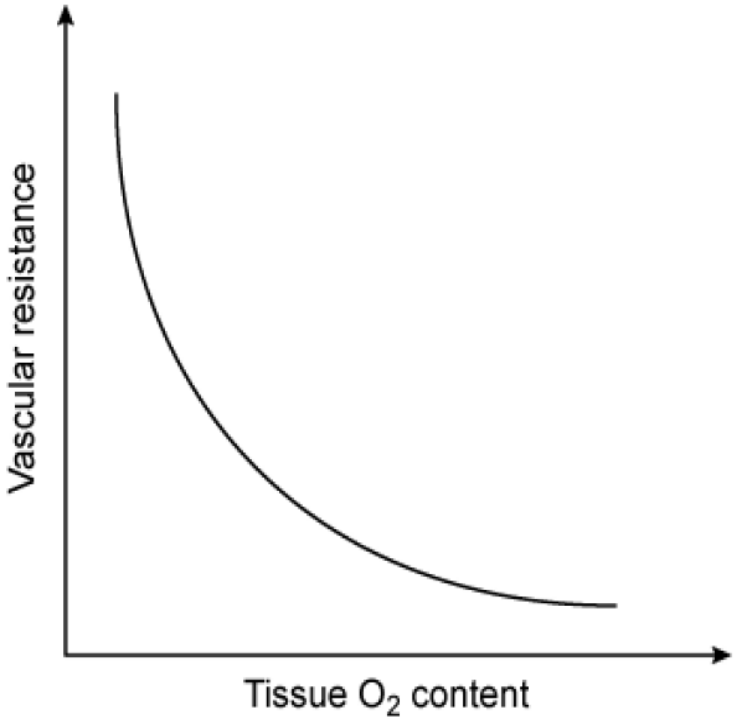
- Because the circulatory system is a continuous circuit, the volume output of the left ventricle must equal the output of the right ventricle at all times.

- The low afterload pressures of the pulmonary circulation allow the thin right ventricle to keep pace with the more substantial left ventricle.

❖ N.B:

1. The graph below depicts a vascular bed where the arterial/arteriolar resistance increases as the blood oxygen content decreases.

- This sort of hypoxic vasoconstriction occurs in the pulmonary circulation so that blood flow is diverted away from underventilated regions of the lung and towards more well-ventilated areas.
- In other tissues, hypoxemia directly dilates arteries and arterioles to increase oxygen delivery to hypoxic tissues.



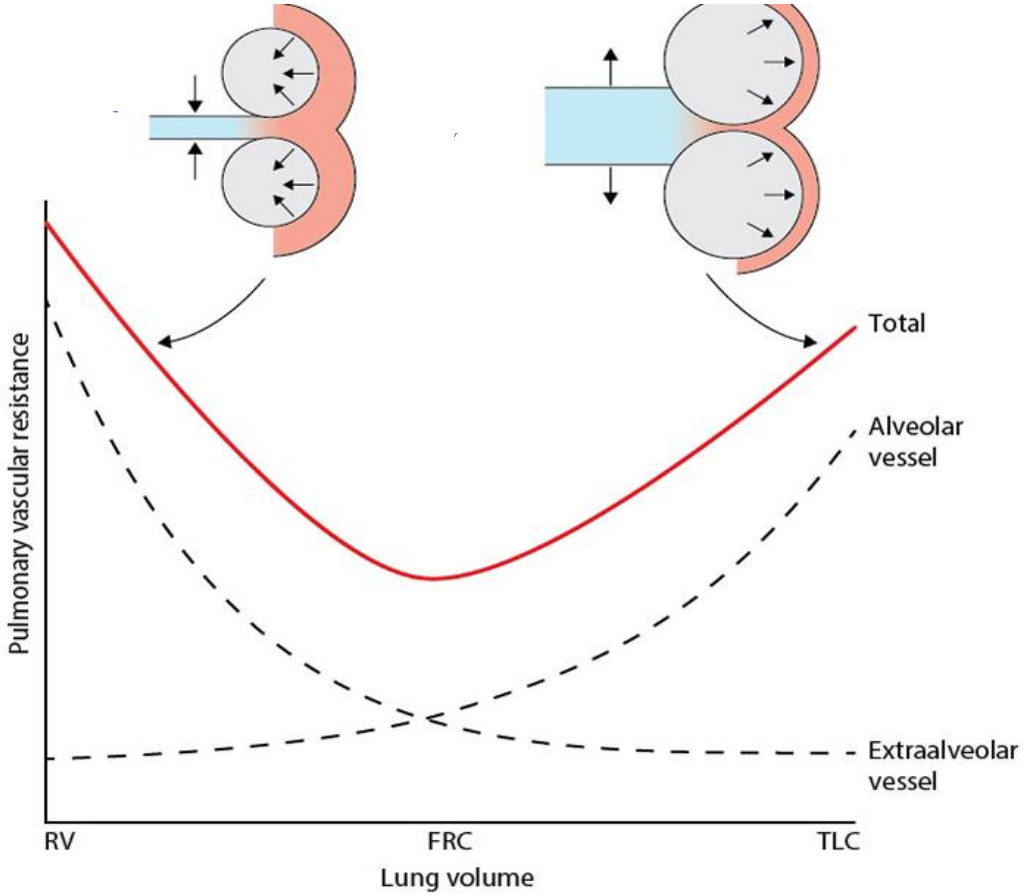
2. The highly compliant nature of the pulmonary circulation means that the degree of lung distension has a large effect on pulmonary vascular resistance (PVR).

- This results primarily from the following effects of lung volume on the alveolar and extra-alveolar vessels:

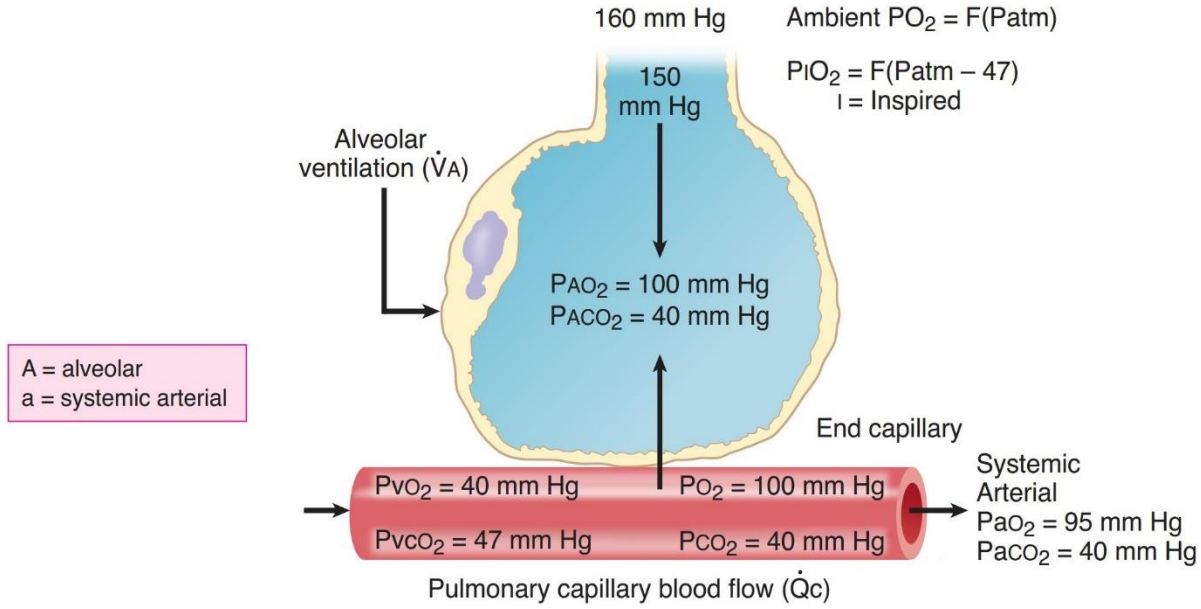
A. Increased lung volumes cause alveolar expansion and lengthwise stretching of the interstitial alveolar blood vessels → This increases their length and reduces their diameter, thus increasing alveolar vessel resistance.

B. Decreased lung volumes during expiration cause the extra-alveolar arteries and veins to become narrowed due to decreased radial traction from adjacent tissues and compression by the positive intrathoracic pressure. This leads to an increase in extra-alveolar vessel resistance.

- Pulmonary vascular resistance (PVR) is calculated as a sum of the alveolar and extra-alveolar resistances as these vessels lie in series with each other.
- Because alveolar and extra-alveolar resistances are increased at high and low lung volumes, respectively, the total PVR takes the shape of a U curve.
- Pulmonary vascular resistance (PVR) is lowest at the functional residual capacity.



Gas exchange in the lung



- This graph illustrates the PO_2 of blood as it moves from the venous system through the lungs and into the systemic circulation.
- As blood enters the right heart from the venous system, it has a low PO_2 because much of its oxygen has been removed for use in the tissues.
- Blood is subsequently pumped from the right ventricle into the pulmonary arteries for oxygenation in the lungs.
- Normally, as blood moves through the pulmonary capillaries, it becomes progressively more oxygenated until it equilibrates with the alveolar PO_2, which is generally about 100 mm Hg when breathing room air.
- After becoming fully oxygenated in the pulmonary capillaries, blood returns to the left heart via the pulmonary veins.
- Blood in the left atrium, however, has a lower PO_2 (95 mmHg) than blood in the pulmonary capillaries.
- This decrease is due to the admixture of deoxygenated bronchial blood with the oxygenated blood in the pulmonary veins.
- The left and right bronchial arteries arise from the descending thoracic aorta.
- These vessels carry oxygenated blood to the bronchi and bronchioles, and together with the pulmonary artery, form the dual blood supply to the lungs.

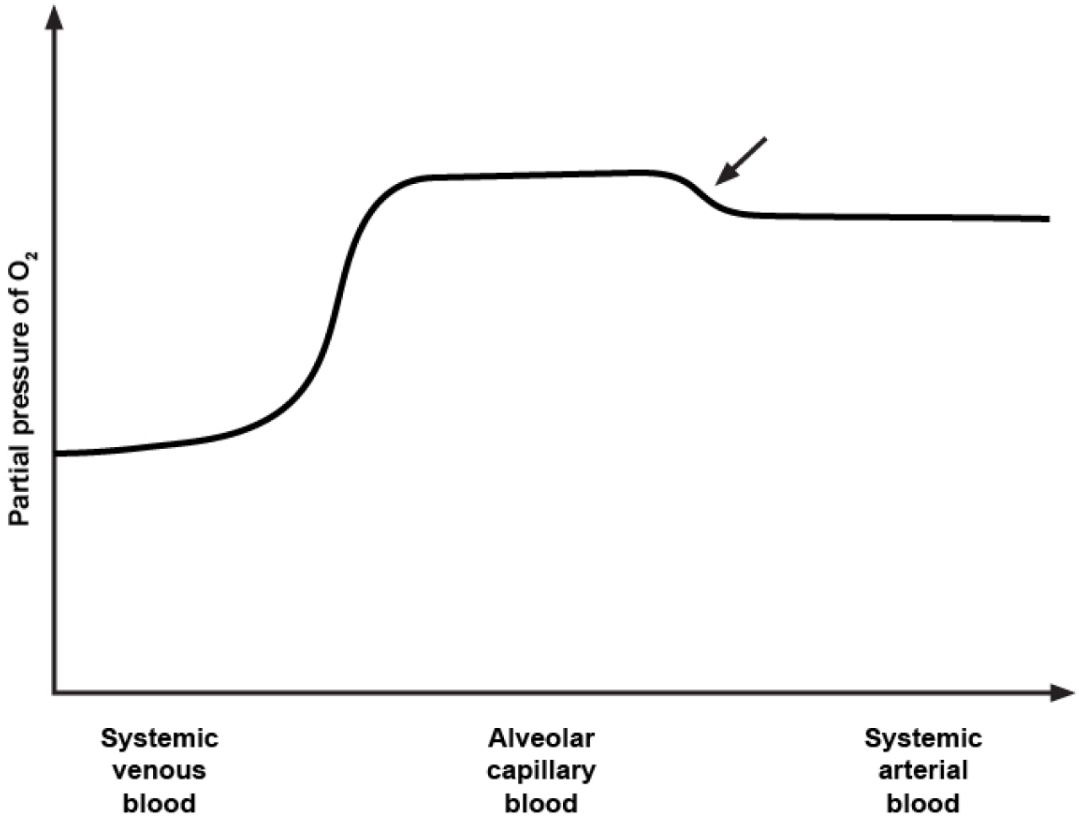
- The majority of blood supplied by the bronchial arteries is returned to the left heart in deoxygenated form via the pulmonary veins (Pulmonary shunt).

- Overall, for PO_2, and PCO_2:

End-tidal air = alveolar = pulmonary end-capillary = systemic arterial

❖ N.B:

- Blood in the left atrium and ventricle has a slightly lower PO_2 than blood in the pulmonary capillaries.
- This is due to the mixing of deoxygenated blood with oxygenated blood from the pulmonary veins and is represented by the downward deflection identified by the arrow.
- This deoxygenated blood comes from the bronchial arteries carry blood to the bronchi and bronchioles and, together with the pulmonary artery, form the dual blood supply to the lungs. The bronchial veins return only a portion of this blood to the right heart via the azygos and hemi-azygos veins; most of the blood supplied by the bronchial arteries returns to the left heart via the pulmonary veins.



Diffusion Capacity of the lung DLco

- The factors that affect the diffusion rate of oxygen and carbon dioxide across lung membranes are the same for any other substance across any membrane system.

- Diffusion is passive and depends on a gradient that is, at a maximum, at the beginning of the capillary. Thus, net diffusion is at a maximum at the capillary entrance and decreases downstream as the gradient diminishes.

$$\dot{V}gas = \frac{A}{T} \times D \times (P_1 - P_2)$$

- This equation states that there are structural factors of the membrane and gas factors that affect the rate of diffusion.

- The factors that affect the rate of diffusion are:

A. Structural factors:

1. The total surface area available for diffusion (A)

- ↓ Emphysema, removing lung lobe.

- ↑ Exercise.

2. Total thickness of the membrane system (T)

- ↑ Fibrosis, interstitial and alveolar edema, other restrictive diseases.

- ↓ Slightly during exercise.

B. Gas Factors:

- The more soluble the gas, the faster it diffuses across the membranes.

- CO_2 is 20 times more soluble than O_2. As such, CO_2, always diffuses faster than O_2.

Perfusion-Limited vs. Diffusion-Limited

- There are 2 terms that describe the dynamics of the transfer of individual substances between the interstitium and the capillary:

A. Perfusion limited:

- If the gas equilibrates between the capillary and interstitium, it is said to be in a perfusion-limited situation.

- To increase diffusion further in perfusion-limited gases, you need to increase their perfusion by increasing blood flow.

- So, these gases are perfusion limited, meaning they are limited by blood flow, which would essentially increase their diffusion.

- Ex: O_2 (normal health), CO_2, N_2O.

B. Diffusion limited:

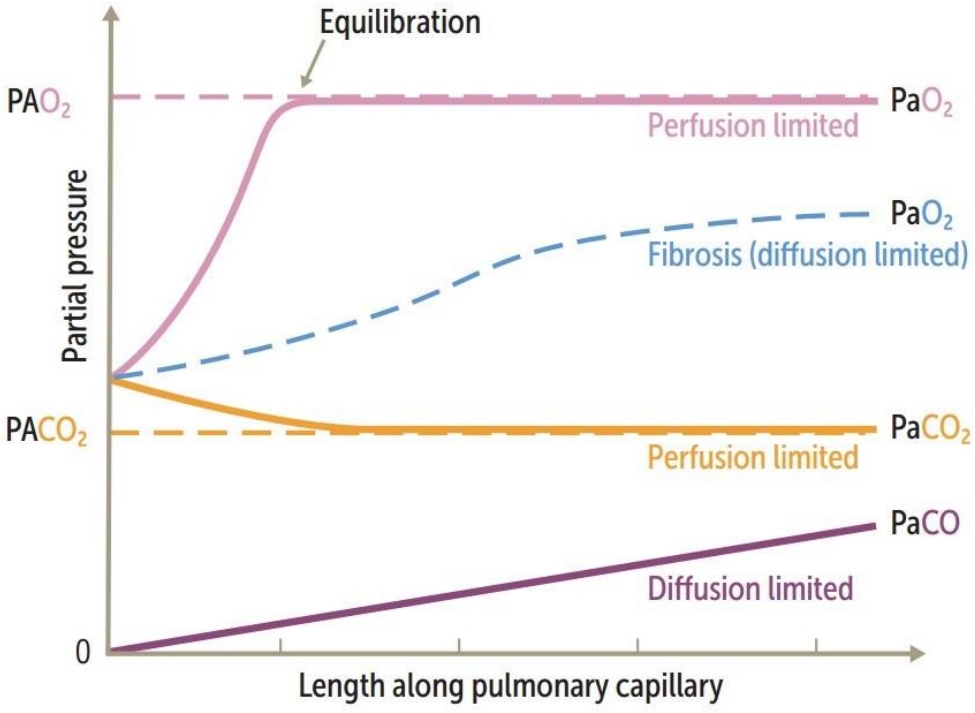
- If the gas does not equilibrate between the capillary and interstitium, it is said to be in a diffusion-limited situation.

- Carbon monoxide is a unique gas in that it typically doesn't equilibrate between the alveolar air and the capillary blood. Thus, it is a diffusion-limited gas.

- When carbon monoxide diffuses across the alveolar membranes, it attaches to hemoglobin. Almost none dissolves in the plasma, so its partial pressure in the blood can be considered zero.

- Because the partial pressures do not equilibrate across the membrane system, it is always in a diffusion-limited situation.

- Ex: O_2 (emphysema, fibrosis → diffusion across the alveolar membrane is relatively slow enough to become the major limitation to gas exchange), CO.



Pa = partial pressure of gas in pulmonary capillary blood
PA = partial pressure of gas in alveolar air

Factors Determining Alveolar PCO_2

- The following relationship states that only two variables affect alveolar PCO_2.
- If the metabolic rate is constant, the only factor affecting alveolar CO_2 is alveolar ventilation.
- There is an inverse relationship between alveolar PCO_2 and alveolar ventilation.
- During exercise, as the metabolic rate increases, ventilation must have an equivalent increase to maintain PCO_2 in the normal range.
- Arterial $PaCO_2$ is a direct indicator of alveolar ventilation status:
  - Hypocapnia implies ongoing alveolar hyperventilation.
  - Upper airway obstruction, reduced ventilatory drive, respiratory muscle fatigue, and decreased chest wall compliance are possible causes of alveolar hypoventilation and hypercapnia.

$$PACO_2 \propto \frac{\text{metabolic } CO_2 \text{ production}}{\text{alveolar ventilation}}$$

Factors Determining Alveolar PO_2

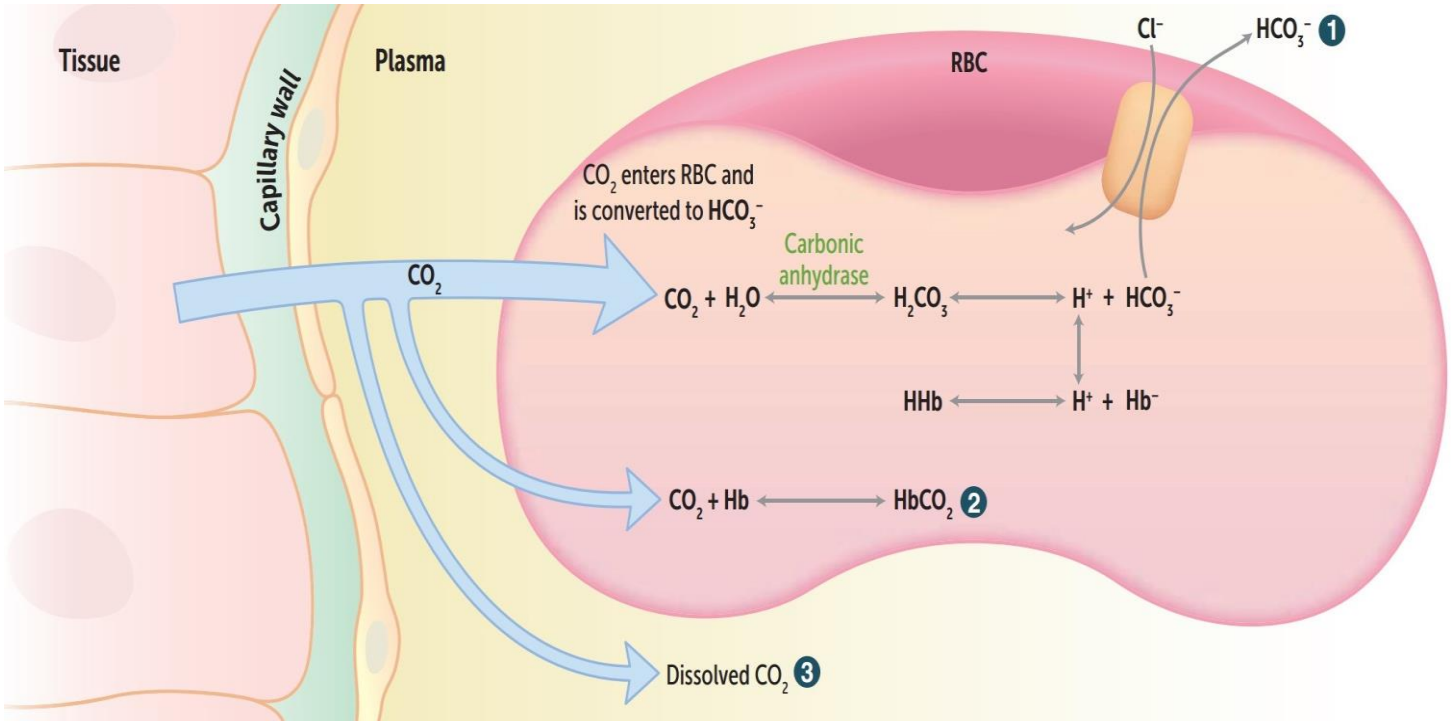
- The following is the alveolar gas equation, which describes the three important factors that affect P_AO_2:

$$PAO_2 = (Patm - 47)FiO_2 - \frac{PACO_2}{RQ}$$

$$RQ = \text{respiratory exchange ratio} = \frac{CO_2 \text{ produced mL/min}}{O_2 \text{ consumed mL/min}}; \text{ normally } 0.8$$

1. P_{atm} = atmospheric pressure:
   - At high altitude, we still breathe 21% oxygen, but at a low PO_2.
   - Therefore, because we are continuously breathing low-pressure oxygen, alveolar PO_2 is permanently low.
   - High altitude causes hypoxemia.
2. F_IO_2: the fractional concentration of oxygen in the inspired air normally 0.21:
   - If a patient is given supplemental oxygen alveolar PO_2 always rises.
   - The oxygen is replacing the nitrogen in the inspired air.
3. P_ACO_2 = alveolar pressure of carbon dioxide, normally 40 mm Hg.

Carbon Dioxide Transport



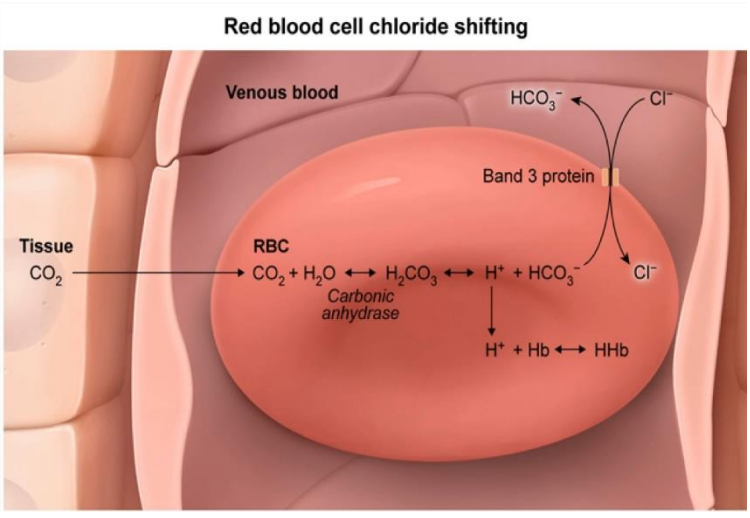
Bicarbonate

- Only a small percentage of total blood CO_2 is carried by hemoglobin. The majority (70%) of total blood CO_2 is carried in the plasma as bicarbonate ion (HCO_3) via the following process:

- The CO_2 produced by tissue metabolism enters RBCs and is hydrated by the enzyme carbonic anhydrase to form carbonic acid (H_2CO_3).

- H_2CO_3 then undergoes spontaneous conversion to HCO_3 and H.

- The excess HCO_3 is then transferred out of RBCs into the plasma via band 3 protein in exchange for chloride ions (Ch) to maintain electrical neutrality. This exchange is known as "chloride shift" and is the principal cause of high RBC chloride content in venous blood.



Carbamino Compounds

- Carbon dioxide reacts with terminal amine groups of proteins to form carbamino compounds. The protein involved appears to be almost exclusively hemoglobin.
- About 25% of the total CO_2 is carried as carbamino compounds.
- The attachment sites that bind CO_2 are different from the sites that bind O_2.

Dissolved Carbon Dioxide

- Carbon dioxide is 20 times more soluble in blood than oxygen is.
- Even though the blood has a PCO_2 of only between 40 and 47 mm Hg, about 5% of the total CO_2 is carried in the dissolved form.

Oxygen Transport

- The concentration of blood oxygen is usually referred to as blood oxygen content.
- In the systemic arterial blood, it varies with hematocrit, but a value of 20 volumes percent (vol %), (20 mL oxygen/100 mL blood) is a normal value.
- <u>The 20 vol% comes in two separate forms:</u>

- 19.7 Hb.
- 0.3 dissolved in the plasma.

- Normally 1 g Hb can bind 1.34 mL O_2; normal Hb amount in blood is 15 g/dL.
- Blood O_2 content = Hb x 1.34 x S_aO_2/100.
- 15 g/100 ml x 1.34 x 100/100 = 19.7 vol% plus dissolved O_2 = 20 vol%.

Plasma Oxygen

- Represents an insignificant form delivered to the tissues (0.3).
- It is the dissolved and only the dissolved that creates the PO_2.
- There is a direct linear relationship between dissolved O_2 and PO_2.
- PO_2 can be considered a force that maintains that attachment of O_2 on Hb.
- High-affinity Hb site needs only a low PO_2 to maintain O_2 attachment.

- Lower-affinity Hb site needs a higher PO_2 to maintain O_2 attachment.

Oxyhemoglobin

- Hemoglobin (Hb) is composed of 4 polypeptide subunits (2 α and 2 β) and exists in 2 forms:
  - T (taut; deoxygenated) form has low affinity for O_2, thus promoting release/unloading of O_2. Taut in Tissues.
  - R (relaxed; oxygenated) form has high affinity for O_2. Relaxed in Respiratory area (lung).
- Hb exhibits positive cooperativity:
  - An Hb molecule has four sites that bind oxygen.
  - Each site has a different affinity for oxygen.
  - When oxygen binds to a site, all four sites gain affinity (cooperative binding).
- Oxyhemoglobin (O_2Hb or OxyHb) is the only significant form in which O_2 is delivered to the tissues.
- Carrying capacity = Maximum oxygen that can be carried in a given volume of blood attached to Hb.
- The Hb in systemic arterial blood is about 97% saturated with oxygen, which means slightly less than 20 vol% is carried by Hb.

Site 4 – O_2 attached when the minimal $PO_2 \cong 100$ mm Hg	systemic arterial blood = 97% saturated
Site 3 – O_2 attached when the minimal $PO_2 \cong 40$ mm Hg	systemic venous blood = 75% saturated (resting state)
Site 2 – O_2 attached when the minimal $PO_2 \cong 26$ mm Hg	P_{50} for arterial blood. P_{50} is the PO_2 required for 50% saturation
Site 1 – O_2 usually remains attached under physiologic conditions.	Under physiologic conditions, only sites 2, 3, and 4 need to be considered.

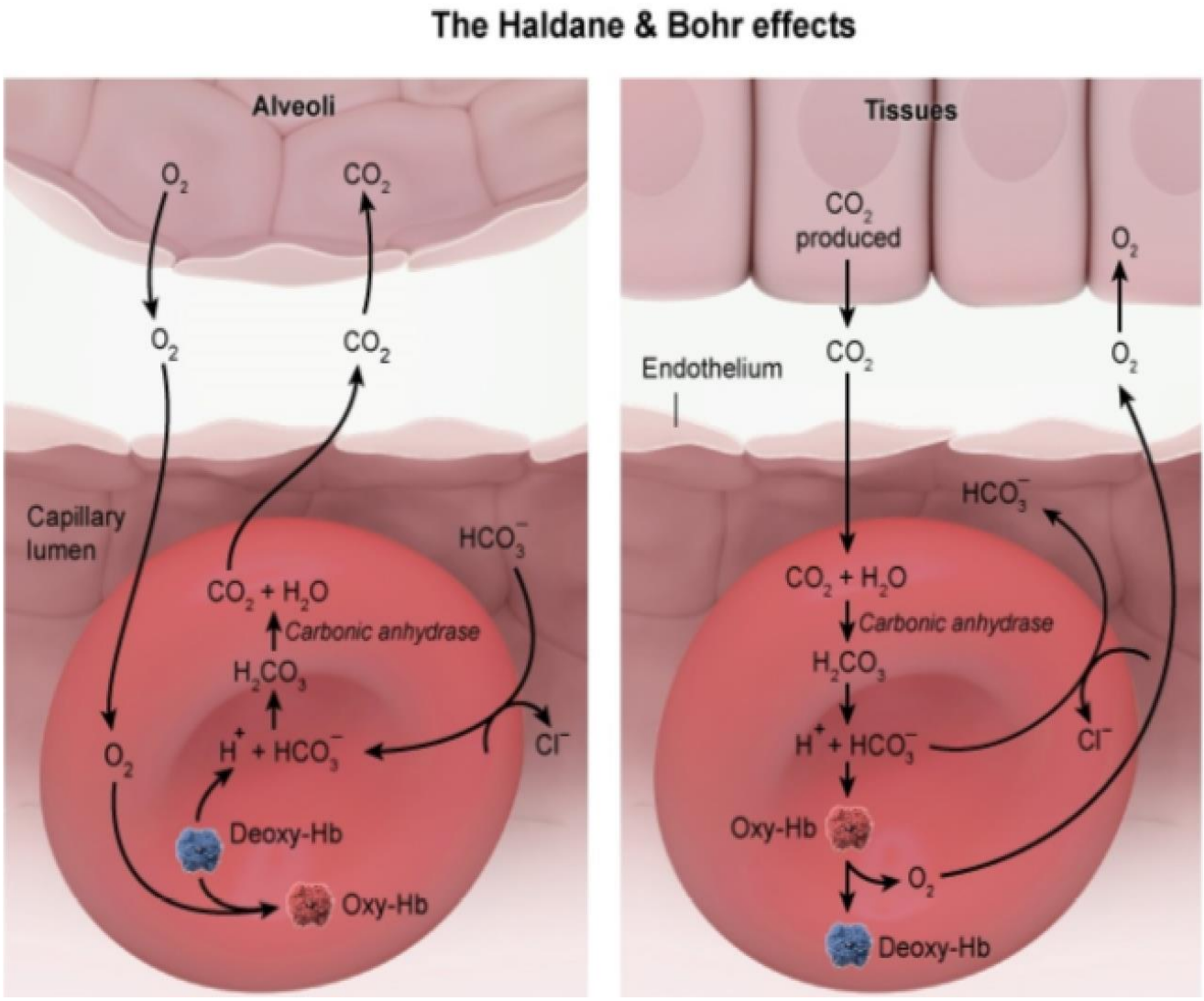
Bohr and Haldane effect

- Bohr effect: In peripheral tissue, ↑ H from tissue metabolism shifts curve to right, unloading O_2.

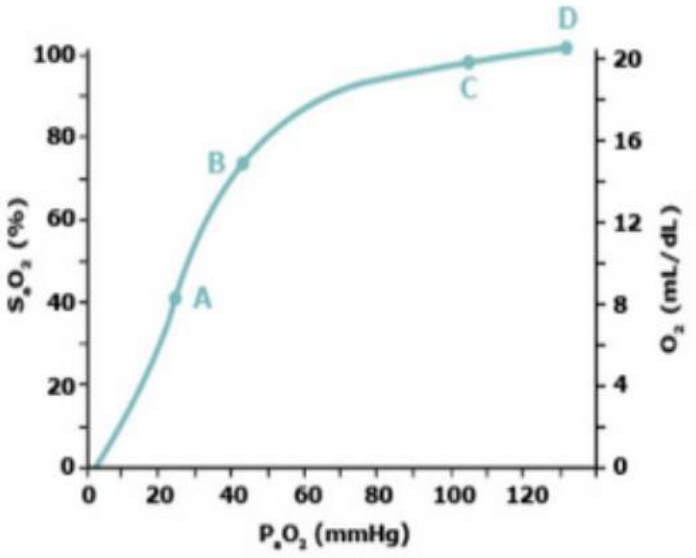
- Haldane effect:

- In lungs, oxygenation of Hb promotes dissociation of H from Hb.

- This shifts equilibrium toward CO_2 formation; therefore, CO_2 is released from RBCs.



Oxygen-Hb Dissociation Curves



A = P_{50}, PO_2 = 26 mmHg
B = systemic venous blood, PO_2 = 40 mmHg, O_2 content 15 vol%
C = systemic arterial blood, PO_2 = 100 mmHg, O_2 content 20 vol%
D = systemic arterial blood with hyperventilation,
PO_2 = 130 mmHg, O_2 content 20.1 vol%

Shift to the Right

- <u>The following factors shift the curve to the right:</u>

- Increased CO_2 (Bohr effect).
- Increased hydrogen ion (decrease pH).
- Increased temperature.
- Increased 2,3-bisphosphoglycerate (2,3-BPG).

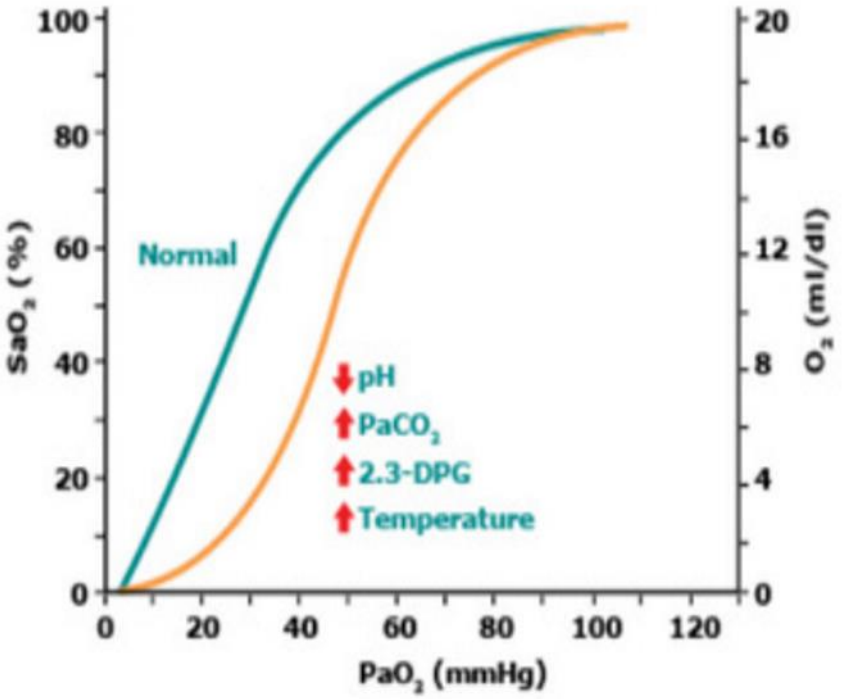
- Decreased Hb affinity.

- Favors unloading to the tissues over loading in the lung.

- P_{50} ↑ (higher PO_2 required to maintain 50% saturation).

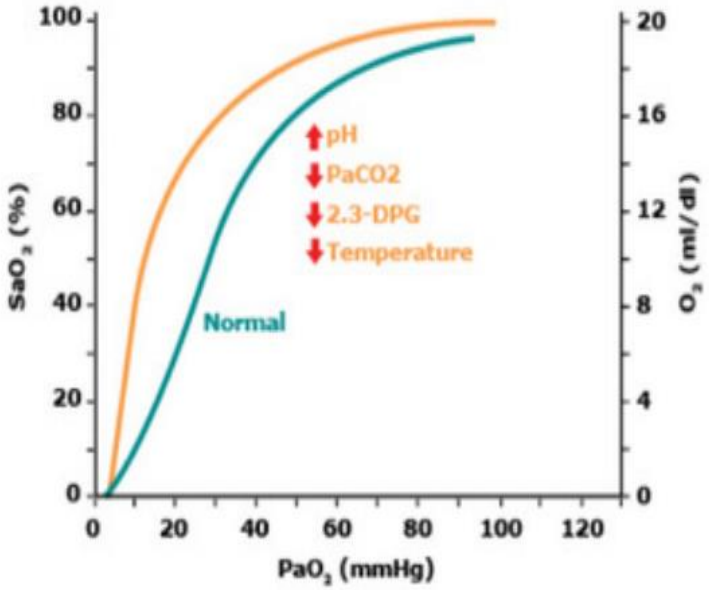
- Carrying capacity unchanged (plateau unchanged).

- Systemic arterial blood at a PO_2 of 100 mm Hg is still close to 100% saturation.



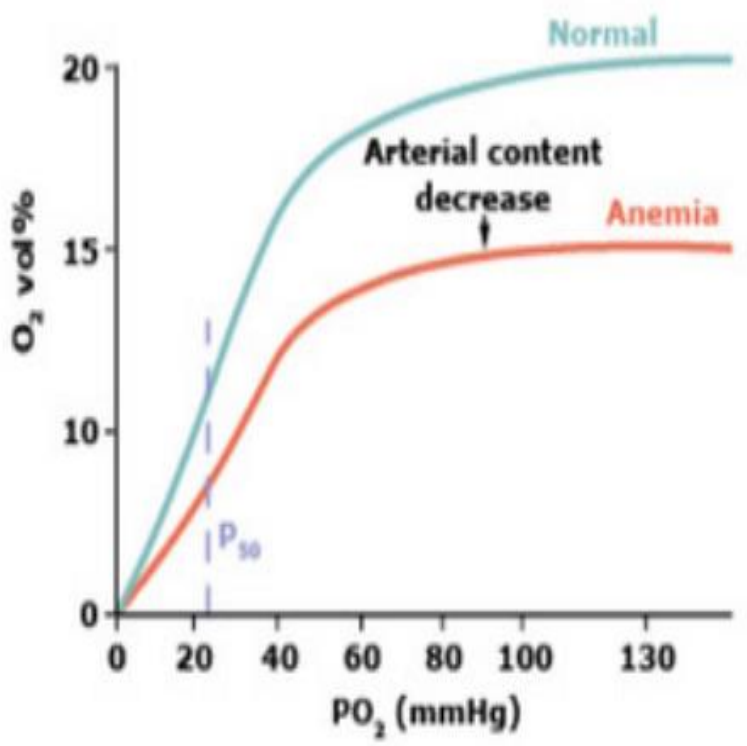
Shift to the Left

- The opposite chemical changes shift the curve to the left.
- Increased Hb affinity.
- A tendency toward loading in the lung over unloading to the tissues.
- P_{50} ↓.
- Carrying capacity unchanged (plateau unchanged)



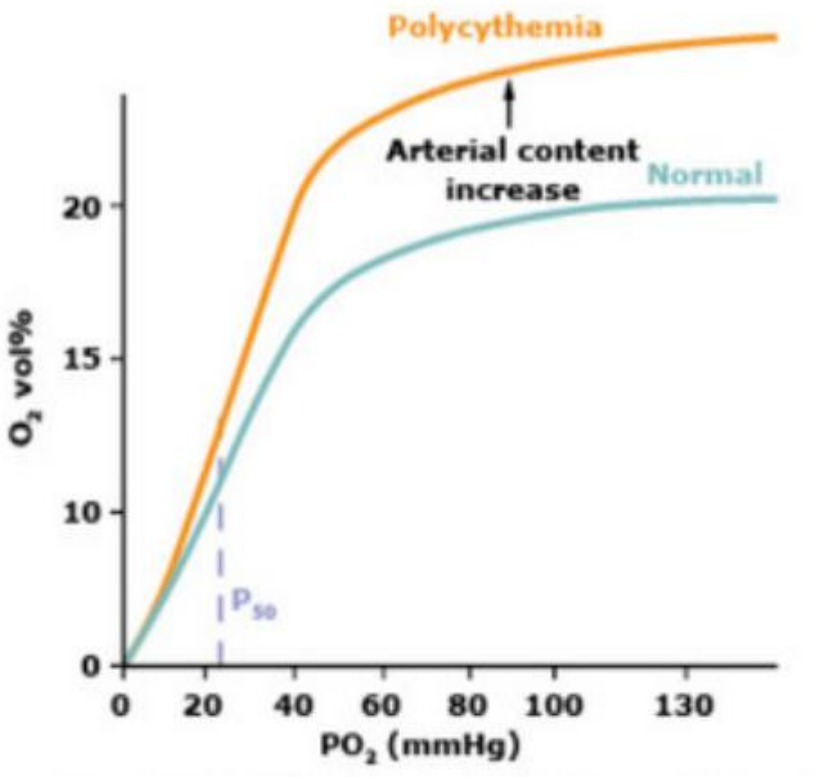
Anemia

- Decreased Hb concentration in the blood.
- Arterial PO_2 normal (100 mmHg).
- Saturation normal (O_2 per g Hb).
- O_2 content ↓.
- Carrying capacity ↓ (less oxygen carried attached to Hb per ml of blood).

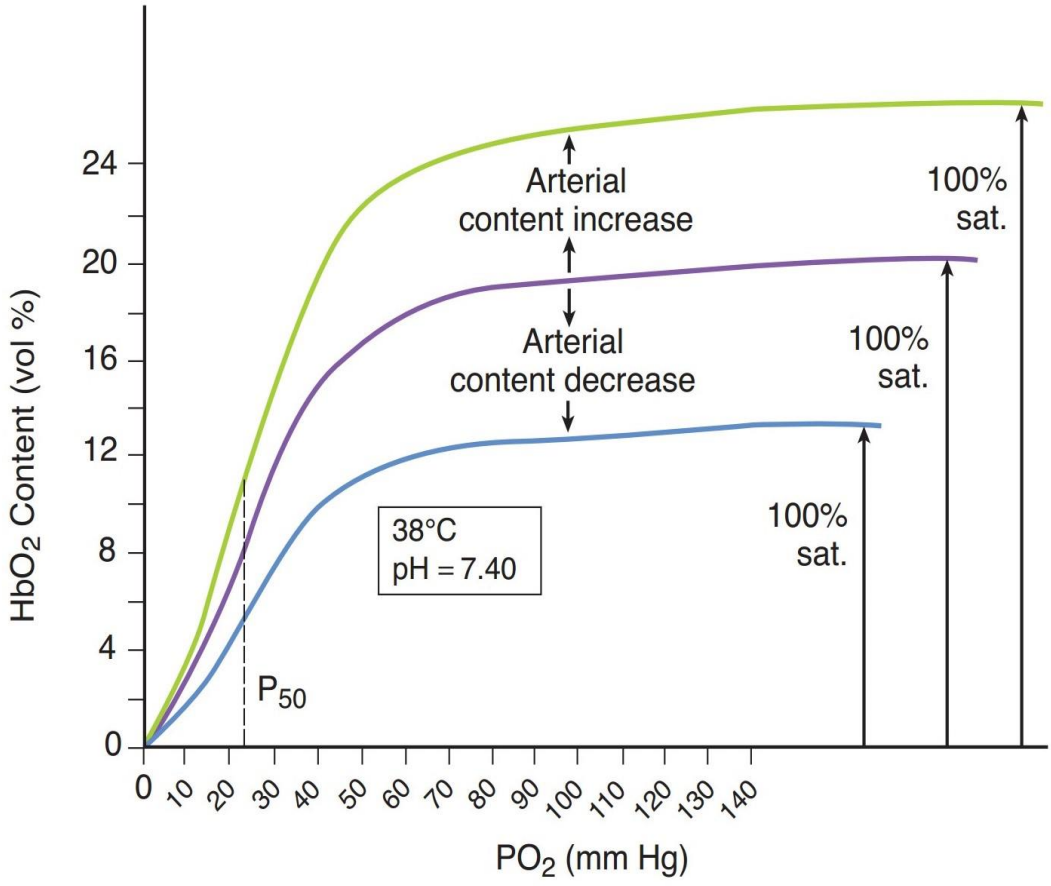


Polycythemia

- Increased Hb concentration in the blood.
- Arterial PO_2 normal.
- Saturation normal (O_2 per g Hb).
- O_2 content ↑.
- Carrying capacity ↑ (more oxygen carried attached to Hb per ml blood).

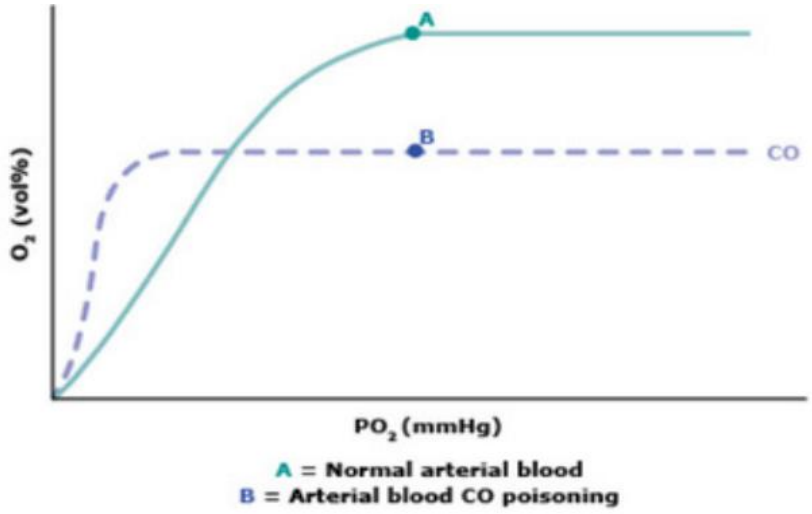


- Note that the point halfway up each curve, the P_{50}, is still close to 26 mm Hg.



Carbon Monoxide Poisoning

- CO is Odorless gas from fires, car exhaust, or gas heaters.
- If CO (200 x the affinity for Hb vs. O_2) attaches to site 4 In the pulmonary capillary, O_2 on the remaining Hb sites is bound more strongly (cooperative binding).
- This causes a shift in the curve to the left, and the O_2 on those sites is essentially not available to tissues.
- Left shift in curve → ↑ affinity for O_2 → ↓ O_2 unloading in tissues.
- Binds competitively to Hb with 200× greater affinity than O2 to form carboxyhemoglobin → ↓ O_2 saturation of Hb.
- Normal Hb concentration (acute poisoning).
- Normal arterial PO_2 (on room air).
- ↓ O_2 content.
- Giving 100% oxygen increases the force of O_2 (PO_2 ↑) and more quickly displaces the CO.
- In a hyperbaric chamber (PO_2 ↑↑↑) CO is displaced even quicker and at the extremely elevated plasma PO_2, it becomes a significant form delivered to the tissues.



❖ N.B:

1. ↑ Cl, H, CO2, 2,3-BPG, and temperature favor taut form over relaxed form (shifts dissociation curve right → ↑ O2 unloading).
2. Fetal Hb (2α and 2γ subunits) has a higher affinity for O_2 than adult Hb, driving diffusion of oxygen across the placenta from mother to fetus.

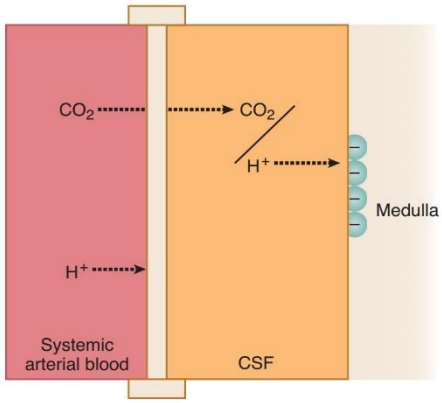
- ↑ O_2 affinity results from ↓ affinity of HbF for 2,3-BPG → dissociation curve is shifted to the left.

Neural regulation of alveolar ventilation

- The inherent rhythm for breathing originates within the medulla of the brain stem.
- The input from the chemoreceptors determines the overall output and the level of alveolar ventilation.
- The greater the stimulation of the chemoreceptors, the greater the level of alveolar ventilation.
- The chemoreceptors that respond to pH, PCO_2, and PO_2, are located within the central nervous system and in the periphery.

Central Chemoreceptors

- These receptors are located in the central nervous system, more specifically, close to the surface of the medulla.
- Stimulation of central chemoreceptors increases ventilation.
- The receptors directly monitor and are stimulated by cerebrospinal fluid H and CO_2.
- There are no central PO_2 receptors.
- The stimulatory effect of increased CO_2 may be due to the local production of H from CO_2 through carbonic anhydrase enzyme.
- Because the blood-brain barrier is freely permeable to CO_2, the activity of these receptors changes with increased or decreased systemic arterial PCO_2.
- These receptors are very sensitive and represent the main drive for ventilation under normal resting conditions at sea level.
- Therefore, the main drive for ventilation is CO_2 (H) on the central chemoreceptors.
- H does not easily penetrate the blood-brain barrier. Thus, an acute rise in arterial H, not of CO_2 origin, does not stimulate central chemoreceptors.



Peripheral Chemoreceptors

- These receptors are found within small bodies at 2 locations:

- Carotid bodies: near carotid sinus, afferents to CNS in glossopharyngeal nerve (IX).
- Aortic bodies: near aortic arch, afferents to CNS in vagus nerve (X).

- The peripheral chemoreceptors are bathed in arterial blood, which they monitor directly. These bodies have 2 different receptors:

A. H/CO_2 receptors:

- These receptors are less sensitive than the central chemoreceptors, but they still contribute to the normal drive for ventilation.

- Therefore, under normal resting conditions at sea level, for all practical purposes, the total drive for ventilation is CO_2, mainly via the central chemoreceptors but with a small contribution via the peripheral chemoreceptors.

B. PO_2 receptors:

- The factor monitored by these receptors is PO_2, not oxygen content.

- Because they respond to PO_2, they are actually monitoring dissolved oxygen and not oxygen on Hb.

- When systemic arterial PO_2 is close to normal (100 mm Hg) or above normal, there is little if any stimulation of these receptors.

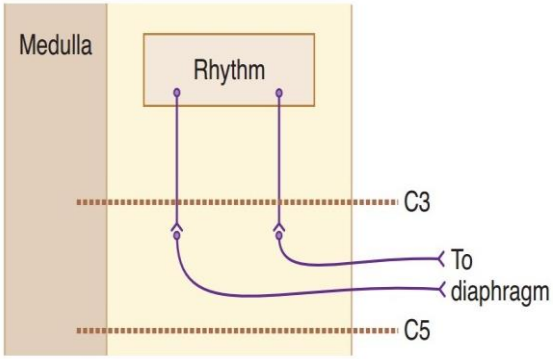
- They are strongly stimulated only by a dramatic decrease in systemic arterial PO_2.

- Sensitivity to hypoxia increases with CO_2 retention.

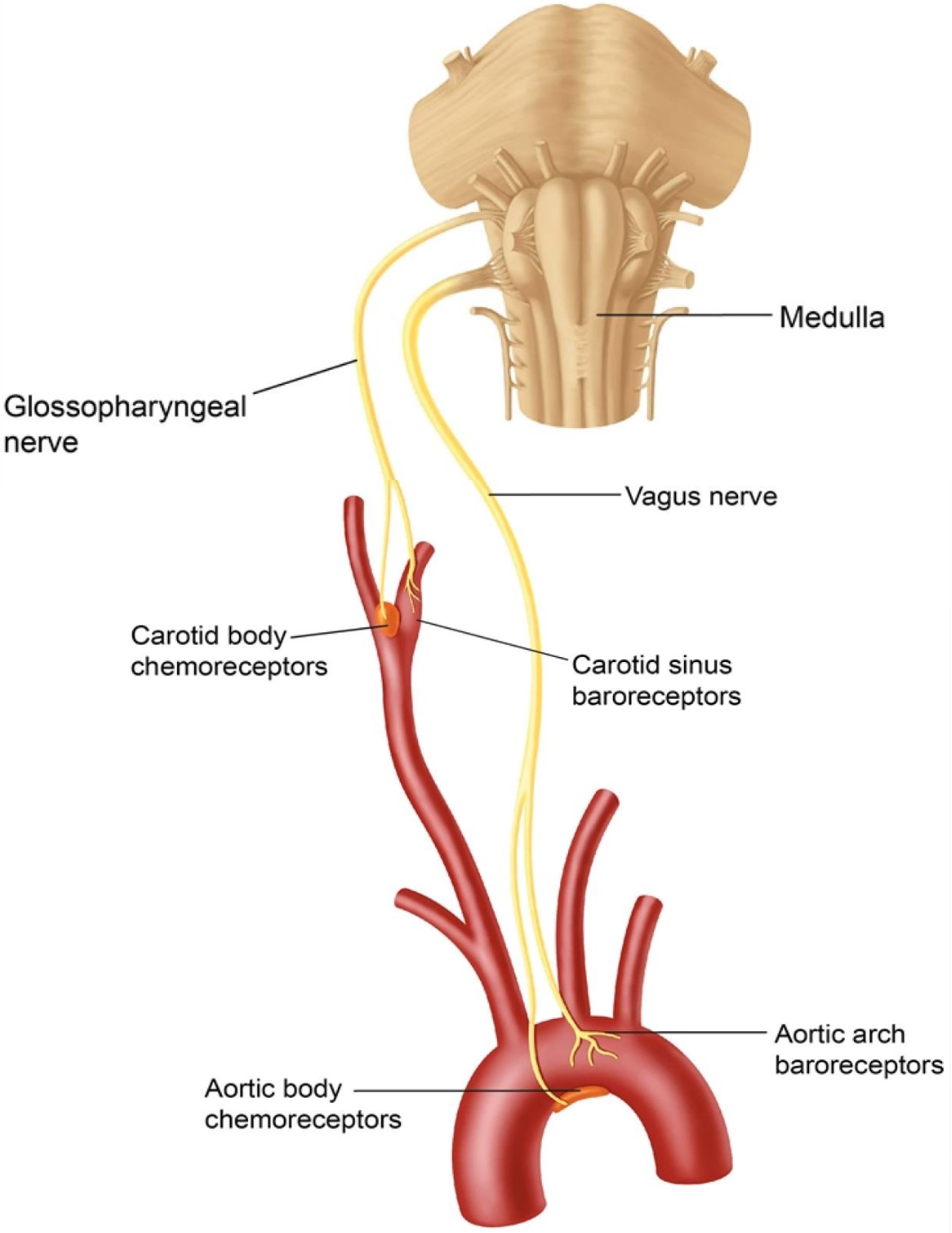
Central Respiratory Centers

- For spontaneous breathing, an intact medulla must be connected to the diaphragm (via the phrenic nerve).

- Thus, a complete C1 or C2 lesion will prevent diaphragmatic breathing but not a complete C6 or lower lesion.

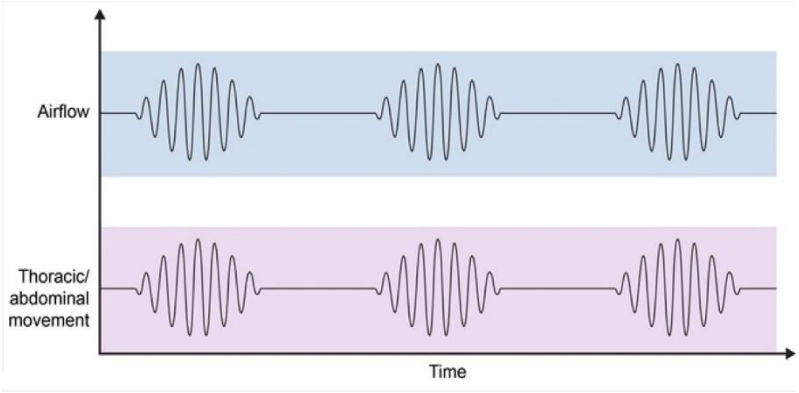


Baroreceptors & peripheral chemoreceptors



❖ N.B:

- Cheyne-Stokes breathing describes cyclic breathing in which apnea is followed by gradually increasing then decreasing tidal volumes until the next apneic period It is commonly seen in the setting of advanced congestive heart failure.
- Patients with CHF have chronic hyperventilation with hypocapnia, which induces apnea during sleep when the partial pressure of carbon dioxide ($PaCO_2$) falls below a certain level (apneic threshold).
- Apnea causes excessive buildup of CO_2 (hypercapnia); this stimulates a ventilatory response that overshoots (hyperpnea), causing the $PaCO_2$ to again fall below the apneic threshold.



Muscles of Respiration

Inspiration

- Diaphragm:

- The main muscle of inspiration.
- Shaped as a dome, it is flattened by contraction, which intensifies negative intrapleural pressure.
- Motor neurons arise from the cervical region of the spinal cord (C3, 4, 5).

- Intercostal muscles:

- Contraction raises the rib cage and increases the anteroposterior dimension of the chest wall.
- Motor neurons arise from the thoracic region.

Expiration

- Under resting conditions, achieved by simply a relaxation of the muscles of inspiration.

- Active expiration (and coughing) is produced by the contraction of the abdominal muscles. The accompanying increased pressure in the abdominal cavity forces the diaphragm in a rapid central direction.

- All the abdominal muscles contribute: Rectus abdominal, obliques, and transverse abdominal. The obliques are considered the main muscles of expiration and cough.

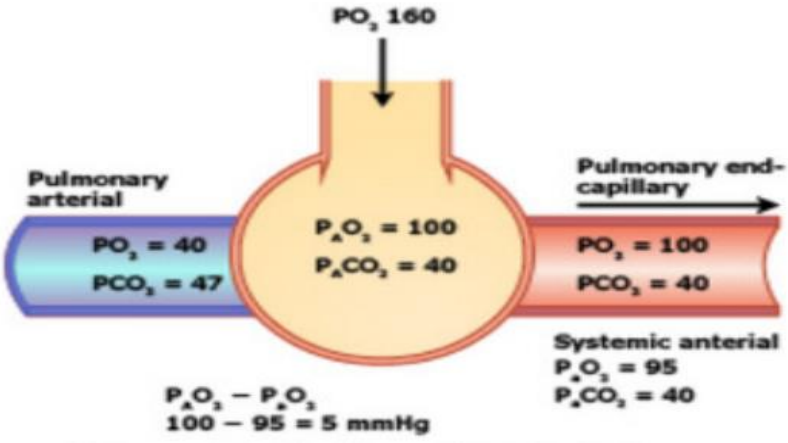
Major causes of hypoxemia

- Hypoxia and hypoxemia are two terms that refer to decreased oxygen availability. Although they sound similar, and one can cause the other, they are different.
- Hypoxemia refers specifically to low levels of dissolved oxygen in the blood (↓PO_2).
- This can lead to the development of hypoxia: decreased oxygen supplies to various organs and tissues.

1- High Altitude

A. Normal Individual at Sea Level:

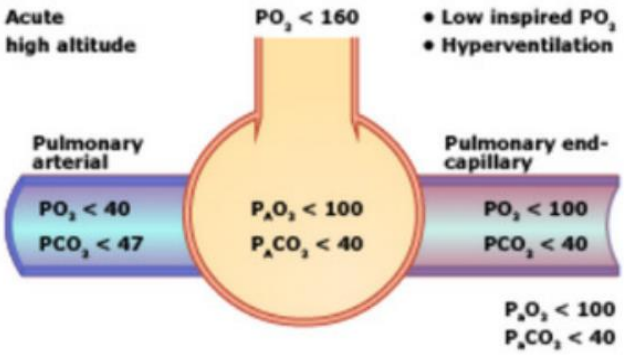
- In a normal individual at sea level, the alveolar compartment, pulmonary end-capillary, and systemic arterial blood have approximately the same PO_2 and PCO_2.
- The natural shunting of blood through the lungs causes a slight drop in systemic arterial PO_2.



B. Acute Changes at High Altitude:

- At high altitude, there is a reduction in barometric pressure and a concomitant reduction in the inspired partial pressure of oxygen.
- PaO_2 correspondingly declines to 60 mm Hg or less. The resulting hypoxemia stimulates the carotid and aortic body chemoreceptors, which increases ventilatory drive.
- Consequently $P_AO_2 < 100$ mmHg, $P_aO_2 < 100$ mmHg.
- The low P_aO_2 stimulates the peripheral chemoreceptors, initiating a hyperventilation and a $P_ACO_2 < 40$ mmHg and a $PCO_2 < 40$ mmHg.
- Thus, acutely at high altitude the main drive for ventilation is the low PO_2 on the peripheral receptors.

- Acute respiratory alkalosis: Arterial pH > 7.4, P_ACO_2 < 40 mmHg, HCO_3 slightly depressed but usually still in the normal range.



C. Adaptation to High Altitude:

- PO_2: P_AO_2 and P_aO_2 are permanently depressed unless supplemental O_2 administrated.

- PCO_2: ↓ due to further increase in alveolar ventilation.

- pH:

- The kidney compensates for the alkalosis. In this case there is a complete or almost complete compensation.

- Arterial pH returns to the normal range after a few days through HCO_3 loss and an alkaline urine are present only during compensation. Once compensation is complete, urine pH returns to its normal value, which is usually in the acidic range.

- Hb:

- Within the first day, hypoxia elevates the circulating levels of erythropoietin, which increases the production of RBCs and their rate of maturation, making polycythemia evident about three weeks later.

- ↑ 2,3-BPG (binds to Hb causing rightward shift of the ODC so that Hb releases more O_2).

- Hb sat: Since the inspired PO_2 remains depressed, Hb saturation remains depressed unless supplemental O_2 is administered.

- Arterial O_2 content:

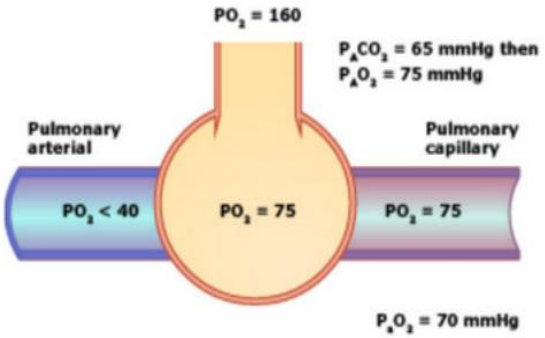
- Acutely depressed due to decreased saturation of a normal Hb concentration.
- Oxygen content returns toward normal not because of a change in Hb saturation, but because of an increase in the Hb concentration.

- Additional compensatory changes such as increases in capillary density, myoglobin concentration, and cellular mitochondria counts contribute to long-term high-altitude acclimatization.

- Chronic hypoxic pulmonary vasoconstriction results in pulmonary hypertension and RVH.

2- Hypoventilation

- Hypoventilation (heroin overdose) elevates the P_Aco_2.
- The increase in P_Aco_2 decreases the P_Ao_2. An increase in P_Aco_2 produces an equivalent decrease in P_Ao_2.
- So, with hypoventilation, there will be equal changes in the alveolar and systemic arterial systems, and thus no widening of the A-a gradient.
- Supplemental O_2 returns P_AO_2 and P_aO_2 to normal.



❖ N.B:

1. The alveolar-arterial oxygen gradient (A-a gradient) is the difference between the partial pressure of oxygen in the alveoli and the partial pressure of oxygen in the arterial blood. Calculating this value helps to determine the cause of hypoxemia.

$$\text{A-a gradient} = P_AO_2 - P_aO_2$$

- Pao_2 is the partial pressure of oxygen in the arterial blood. It is a measured value determined with an arterial blood gas analysis. In a normal individual, P_aO_2 is > 92 mm Hg.
- P_AO_2 is the partial pressure of oxygen in the alveolar air. In a healthy individual at sea level, the P_AO_2 is usually about 100 mm Hg. This value is calculated using the alveolar gas equation:

$$PAO_2 = (Patm - 47)FIO_2 - \frac{PACO_2}{RQ}$$

- Normally, the A-a gradient does not exceed 10-15 mmHg.
- High altitude and hypoventilation are the two causes of hypoxemia that originate from a low alveolar PO_2 and both of them have a normal A-a gradient.
- The only difference between them is P_Aco_2 which decreases in high altitude due to hyperventilation.

2. The 3 variables that affect the total oxygen content of blood are hemoglobin concentration, oxygen saturation of hemoglobin (SaO_2), and the partial pressure of oxygen dissolved in blood (PaO_2).

- Anemia is characterized by decreased hemoglobin concentration in the setting of normal SaO_2 and PaO_2.

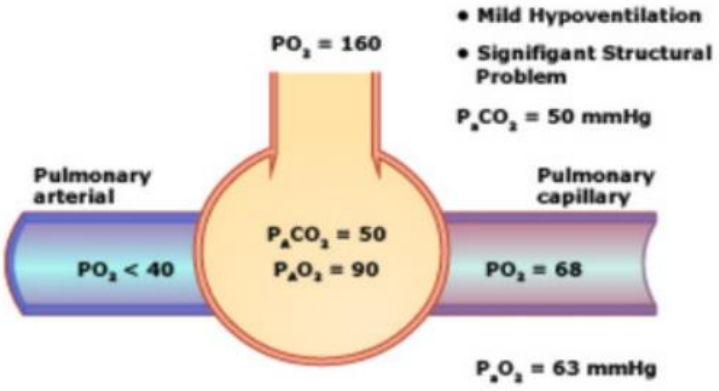
	PaO_2	SaO_2	Oxygen content
CO poisoning	Normal	Decreased*	↓
Cyanide poisoning	Normal	Normal	Normal
Anemia (↓ Hgb)	Normal	Normal	↓
Polycythemia (↑ Hgb)	Normal	Normal	↑
High altitude	↓	↓	↓

*Detected as normal using standard probes.

CO = carbon monoxide; **Hgb** = hemoglobin; **PaO_2** = arterial oxygen tension; **SaO_2** = arterial oxygen saturation.

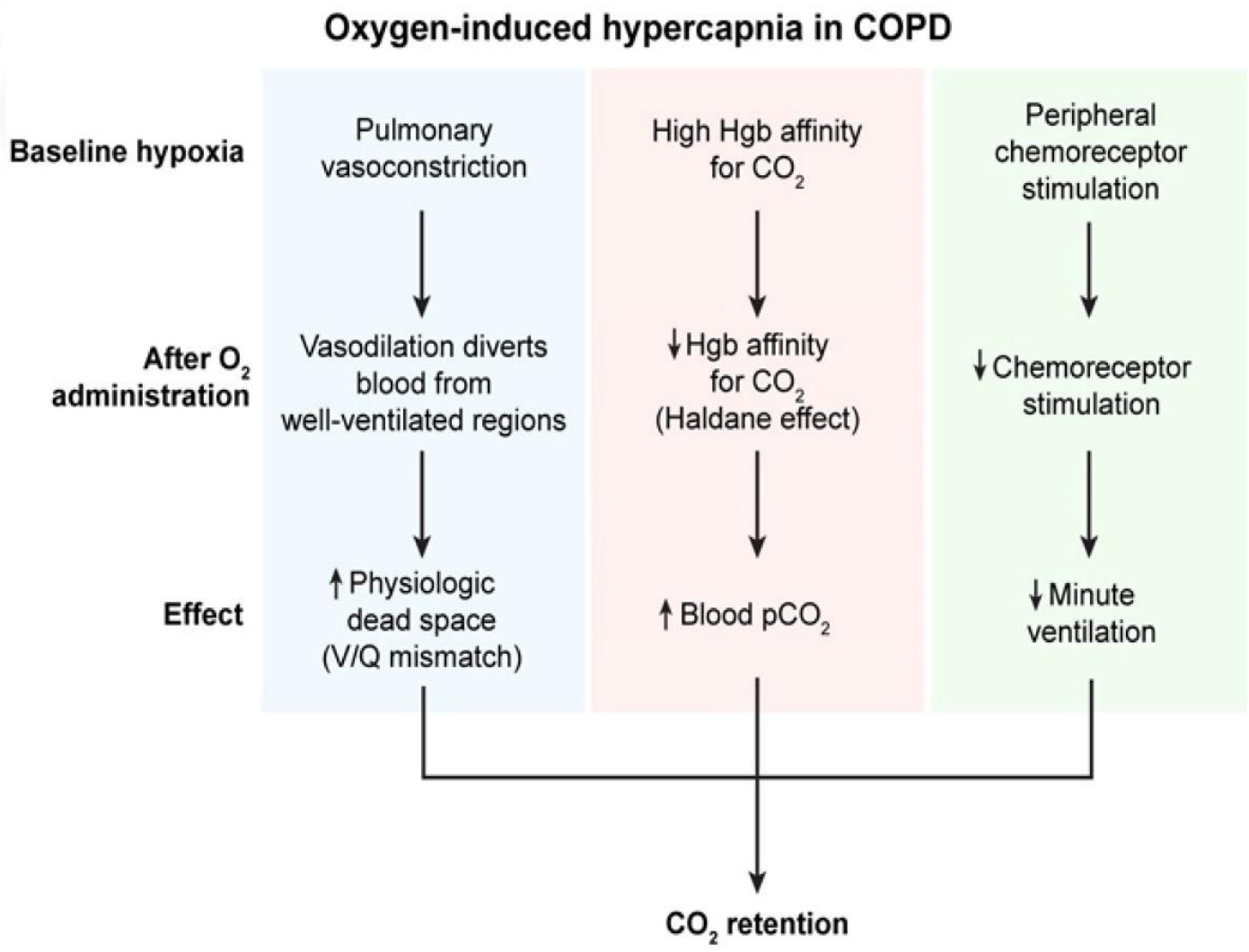
3- Diffusion Impairment

- Diffusion impairment is equivalent to a structural problem in the lung tissue that affects gas exchange.
- It can be a loss of surface area, as occurs in emphysema, and/or an increase in the thickness of the membranes, as occurs in fibrosis. A significant structural problem is a diffusion-limited situation.
- In many cases, a structural problem produces mechanical problems, and there are degrees of hypoventilation.
- In marked diffusion impairment, pulmonary end capillary PO_2 is less than alveolar PO_2.
- There is an increase in A-a oxygen gradient.
- Supplemental oxygen can relieve the hypoxemia.



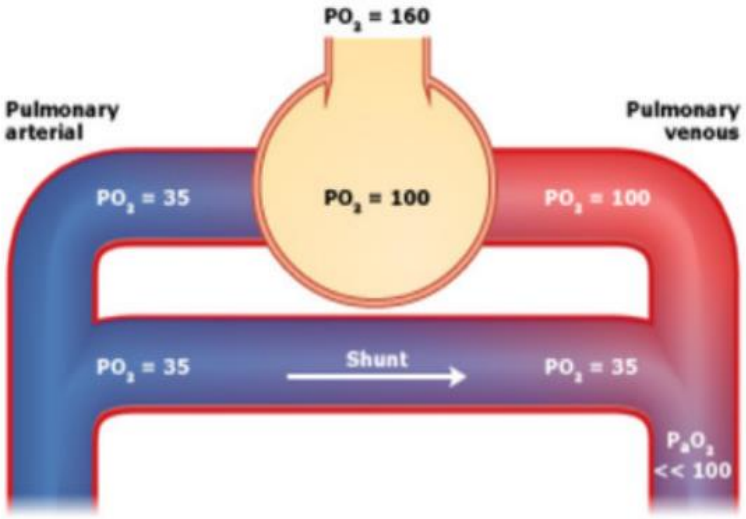
❖ N.B:

- Elevated CO_2 reduces the sensitivity of the CO_2 receptors, and the main drive for ventilation can then be the depressed arterial PO_2 acting on the peripheral chemoreceptors.
- Supplemental oxygen may be warranted in patients with COPD who have significant hypoxemia; however, administration of excessively high oxygen concentrations can lead to increased CO_2 retention (oxygen-induced hypercapnia), resulting in confusion and a depressed level of consciousness (lethargy).
- Several mechanisms contribute to oxygen-induced hypercapnia, but the major cause is increased ventilation-perfusion mismatch.
- Hypoxia causes vasoconstriction of the pulmonary arterioles, which acts to shunt blood toward alveoli with the highest ventilation, thereby minimizing physiologic dead space.
- Providing high-concentration supplemental oxygen allows lung regions with relatively poor ventilation to have higher oxygen levels, reversing pulmonary vasoconstriction.
- The redistribution of blood flow away from well-ventilated alveoli leads to an increase in physiologic dead space (well-ventilated alveoli are less perfused) with a corresponding reduction in CO_2 excretion.



4- Pulmonary Shunt

- A pulmonary shunt is blood passing through the pulmonary circulation and entering the left heart without changing its chemical composition (without gas exchange).
- In the shunted region, pulmonary arterial PO_2 equals pulmonary venous PO_2.
- A pulmonary shunt is also referred to as a right-to-left shunt.
- A regional atelectasis created by a pneumothorax is an example of a pulmonary shunt.



- PaO_2 is below pulmonary end-capillary and PAO_2 in the well-ventilated lung regions.
- If pulmonary end capillary PO_2 is listed as normal with hypoxemia, pulmonary shunt is the most likely possibility.
- Widening of the A-a gradient.
- The most significant characteristic of a pulmonary shunt is that giving supplemental O_2 raises P_AO_2, but there is no significant increase in P_aO_2.

5- Ventilation-Perfusion mismatch

- Blood entering the pulmonary circulation under resting conditions has a PO_2 of about 40 mmHg. Oxygen is added to the pulmonary capillary blood via alveolar ventilation until ideally the Hb is saturated with oxygen (PO_2 100 mmHg).
- The alveolar ventilation (V_A) necessary to supply the oxygen to saturate the Hb as the blood passes through the capillaries is about 4L/min.

- At rest, pulmonary blood flow (Q) is 5L/min (CO).

$$V/Q = 4000\ ml/5000ml = 0.8$$

- In the upright position, regional differences in ventilation and perfusion occur vertically in the lungs due to gravity:

A. Ventilation:

- Apex:
  - At FRC, pleural pressure is about - 10 cmH_2O.
  - This expanding force results in larger, less-compliant, stiffer alveoli at the apex.
  - The less-compliant nature of these alveoli means that less air flows into the apical alveoli during inspiration.
- Base:
  - At FRC, pleural pressure due to Gravity is about - 2 cmH_2O.
  - This smaller expanding force results in smaller, more compliant alveoli at the base.
  - The greater compliance at the base means more air flows into the base alveoli during inspiration.
  - They are smaller than the apical alveoli during the entire respiratory cycle, but have a greater change in size, and overall alveolar ventilation is greater at the base than at the apex.

B. Blood Flow:

- The regional variance in perfusion of the lungs is also determined by gravity and can be divided into 3 zones based on the continuity of blood flow.
- Because of gravity, more pressure in artery and veins at base compared to apex of the lung.
- Alveolar pressure is the same throughout the lung.

A. Zone 1:

- In this zone, alveolar pressure > arterial pressure > venous pressure:
  - This compress vessels.
  - Less perfusion.
  - High V/Q.
  - The major contributor of alveolar dead space.
- The arterial pressure is low in this region as the heart must pump blood "uphill" against the force of gravity.
- Because arterial pressure is lower than alveolar pressure, the pulmonary capillaries are collapsed and there is no blood flow (zone 1 represents alveolar dead space).

B. Zone 2:

- Here, arterial pressure > alveolar pressure > venous pressure.

- As arterial pressure rises during systole, capillary pressure becomes high enough to overcome alveolar pressure. For this reason, blood flows through zone 2 in a pulsatile fashion.

C. Zone 3:

- Here, arterial pressure >venous pressure > alveolar pressure.

- Arterial and venous pressures are both greater than alveolar pressure, and therefore blood flows continuously through the pulmonary capillaries.

- Although both ventilation and perfusion increase from apex to base, perfusion increases to a greater degree.

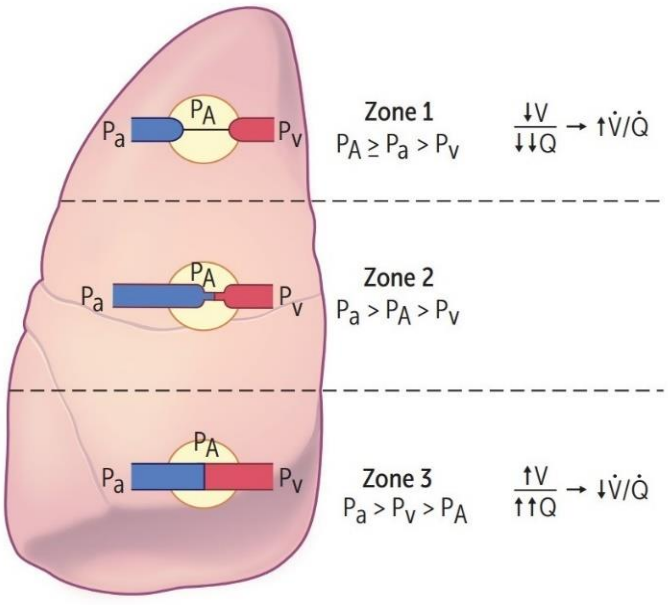
- Perfusion greatly increases from the apex of the lung to the base; ventilation increases slightly from the apex to the base.

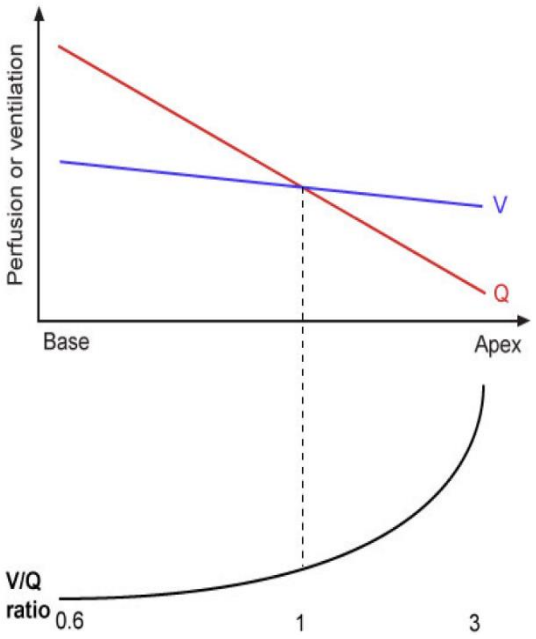
- For this reason, the ventilation/perfusion ratio decreases in the lung from apex to base.

- Ideally, ventilation is matched to perfusion ($\dot{V}/\dot{Q} = 1$) for adequate gas exchange.

- $\dot{V}/\dot{Q}$ at apex of lung = 3 (wasted ventilation).

- $\dot{V}/\dot{Q}$ at base of lung = 0.6 (wasted perfusion).

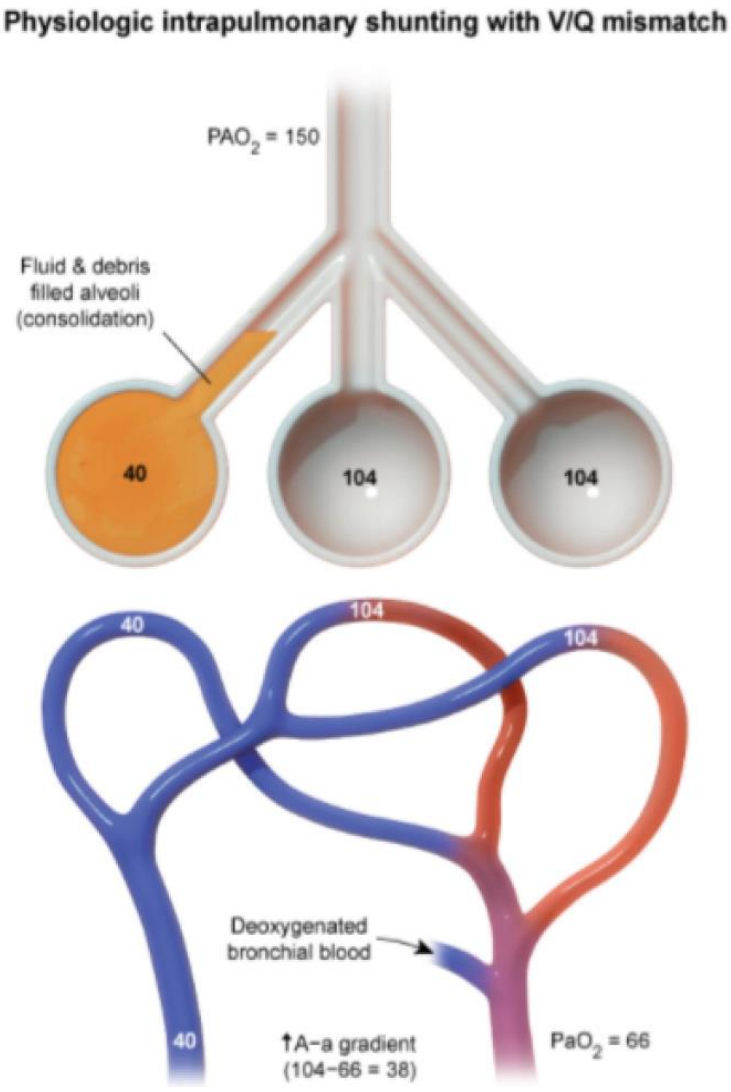




V_A/Q Mismatches

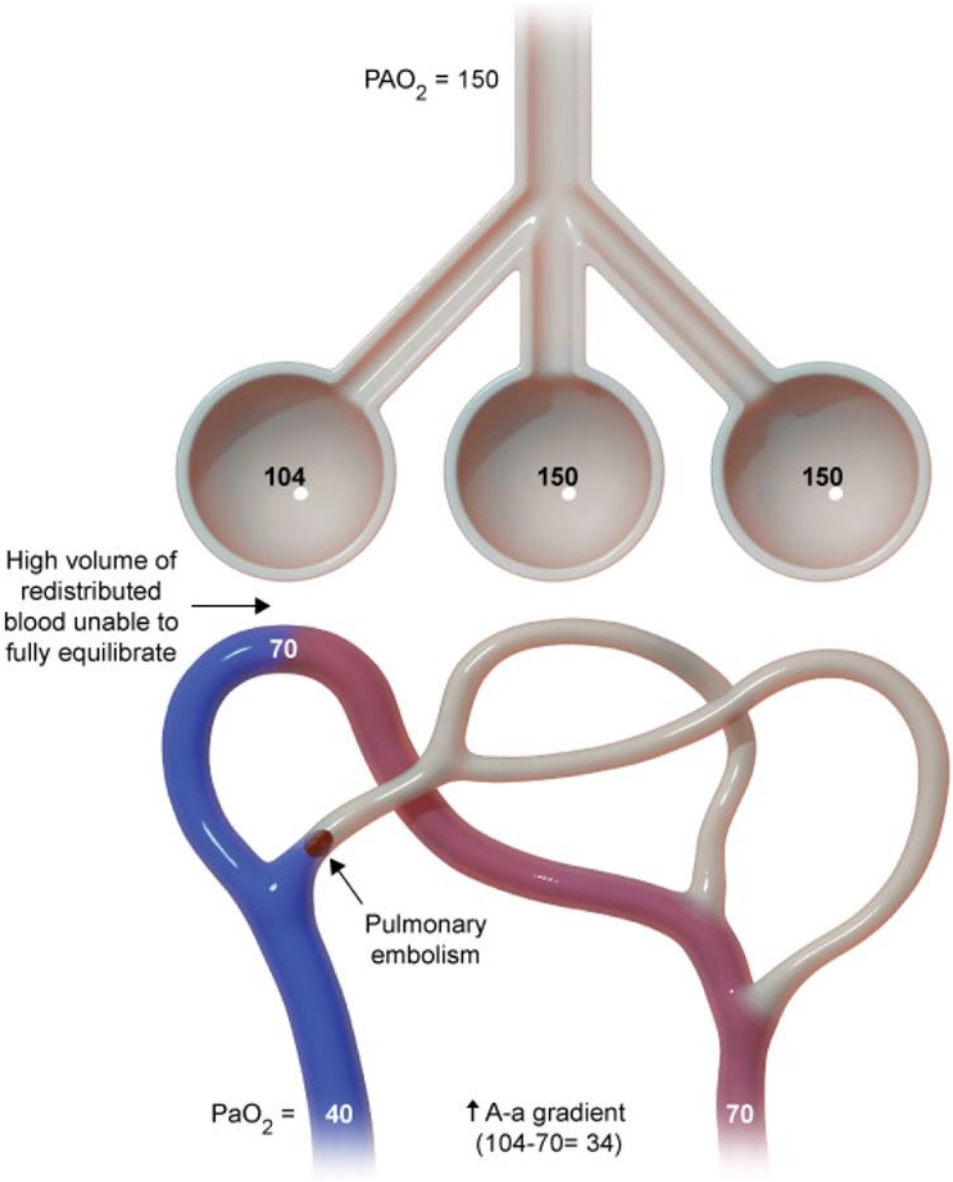
A. $V_A/Q < .8$ (airway obstruction):

- An intrapulmonary shunt is the extreme of ventilation-perfusion mismatch that occurs when blood perfuses alveoli that are not ventilated (pneumonia, pulmonary edema).
- Lung unit underventilated ($PCO_2 > 40$ mmHg, $PO_2 < 100$ mmHg).
- As the ratio decreases, it approaches zero.
- If ratio = zero → blood flow, but no ventilation (pulmonary shunt).
- As the ratio decreases below .8, it has a shunt component.
- 100% O_2 does not improve Pao_2.



B. $V_A/Q > .8$ (blood flow obstruction):

- Dead space ventilation is one extreme of ventilation-perfusion mismatch that occurs when the alveoli are adequately ventilated, but there is no alveolar perfusion (pulmonary embolism).
- Lung unit overventilated ($PCO_2 < 40$ mmHg, $PO_2 > 100$ mmHg).
- As the ratio increases, it approaches infinity.
- If ratio = ∞ → Ventilation, but no blood flow (alveolar dead space).
- As the ratio increases above .8, it has a dead space component.
- 100% O_2 improves Pao_2.



❖ N.B:

1. Pulmonary embolism typically arises when a thrombus from the lower extremity embolizes the arterial blood supply of one of the lungs, causing hypoperfusion of the pulmonary parenchyma.

- Although the distribution of alveolar ventilation remains the same, the amount of blood passing through the alveoli is reduced in the affected areas and increased in the remainder of the lung.
- A significant pulmonary embolism causes an acute pulmonary V/Q imbalance, which results in hypoxemia.
- The hypoxemia leads to hyperventilation and respiratory alkalosis.
- An arterial blood gas in an individual with acute respiratory alkalosis would include an increased pH and reductions in PaO_2 and $PaCO_2$.
- The combination of acute onset dyspnea, calf swelling, obesity, and a history of prolonged immobility is strongly suggestive of pulmonary embolism.

2.

Oxygen deprivation

Hypoxia (↓ O_2 delivery to tissue)	Hypoxemia (↓ Pao_2)	Ischemia (loss of blood flow)
↓ cardiac output	Normal A-a gradient	Impeded arterial flow
Hypoxemia	▪ High altitude	↓ venous drainage
Ischemia	▪ Hypoventilation (eg, opioid use, obesity hypoventilation syndrome)	
Anemia	↑ A-a gradient	
CO poisoning	▪ V/Q mismatch	
	▪ Diffusion limitation (eg, fibrosis)	
	▪ Right-to-left shunt	

Response to exercise

- Long distance running and other forms of aerobic exercise cause increased oxidative metabolism of glucose and fatty acids in skeletal muscle.
- The active skeletal muscles increase their rate of both oxygen consumption and carbon dioxide production.
- These increases are balanced by increases of the cardiac output/skeletal muscle perfusion and ventilation, respectively.
- Heart rate and cardiac output increase to meet increased tissue oxygen demands, and the respiratory rate increases to eliminate excess CO_2 produced.
- V /Q ratio from apex to base becomes more uniform.
- Homeostatic mechanisms maintain arterial O_2 and CO_2 contents and arterial pH near normal resting values, but there are significant changes in the venous blood O_2 and CO_2 contents and pH.

- Because exercising muscles extract additional O_2, the venous blood O_2 content is decreased. The venous blood CO_2 content is increased due to increased CO_2 production. The venous blood pH is decreased (2° to lactic acidosis).

- Right shift of ODC.

- No change in Pao_2 and $Paco_2$ but ↑ in venous CO_2 content and ↓ in venous O_2 content.

Hyperbaric Environment

- PO_2 and PN_2 increases in the alveoli and the systemic arterial blood.

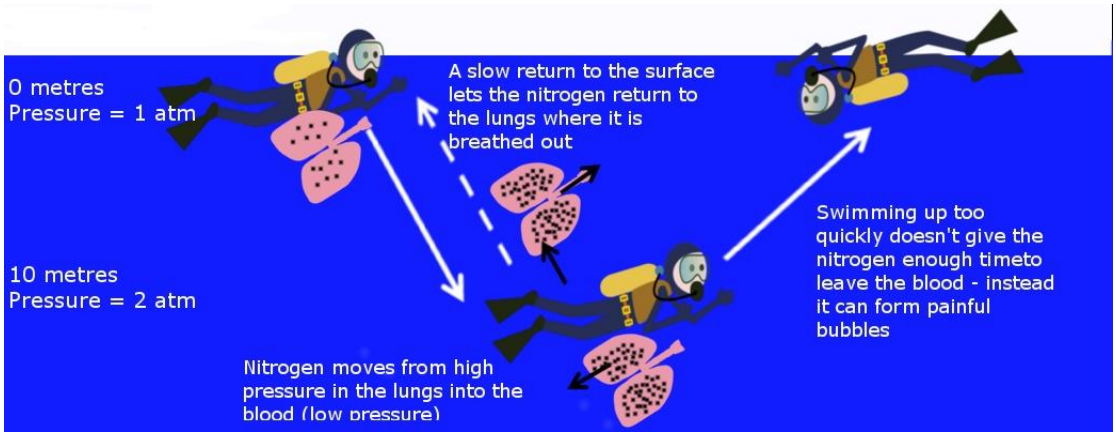
- Increased PO_2 can cause oxygen toxicity, and increased PN_2 can cause nitrogen narcosis. In addition, a scuba diver who suddenly decompresses can suffer the bends, or Caisson disease.

- Nitrogen bubbles can form in the tissues and blood.

- These bubbles may expand and injure tissue, or they may block blood vessels in many organs. This blood vessel blockage causes pain and various other symptoms. Nitrogen bubbles also cause inflammation, causing swelling and pain in muscles, joints, and tendons.

- Treatment is a recompression and a slow decompression or breathing 100% oxygen.

- This replaces the nitrogen in the inspired air and accelerates the nitrogen washout.



CHAPTER 3

Pathology

Nasopharynx

Rhinosinusitis

- Causes:

- The paranasal sinuses (maxillary, frontal, ethmoidal, sphenoid) are air-filled cavities within the bones of the skull that surround the nasal cavity. The nose and the paranasal sinuses provide resonance to the voice and humidify and warm inhaled air.

- Inflammation of the sinuses due to infection → inflammation and pain over affected area (typically maxillary sinuses, which drain into the middle meatus, in adults).

- Most common acute cause is viral upper respiratory infection.

- Contaminating bacteria cannot be cleared by mucociliary clearance due to mucosal inflammation from viral infection, leading to secondary bacterial infection.

- May cause superimposed bacterial infection, most commonly S pneumoniae, H influenzae, M catarrhalis.

- Presentation: Patients complain of facial pain, headache, postnasal drainage, and purulent nasal drainage. Headache is common and is worse when the patient leans forward.

- Diagnosis:

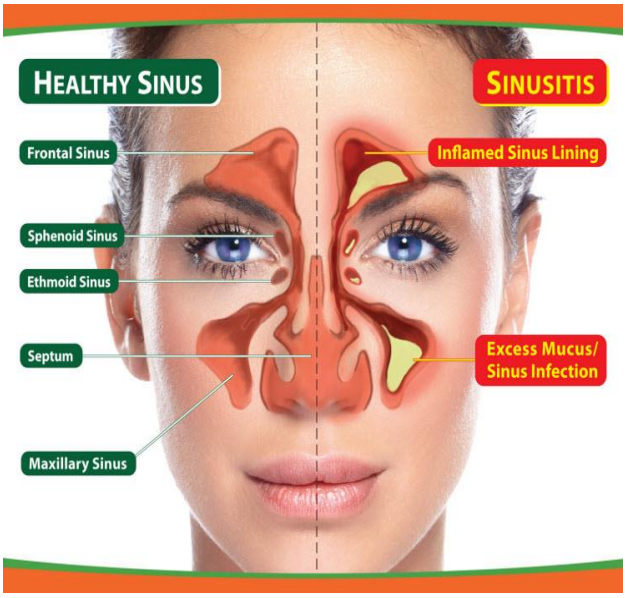
- Obvious cases of sinusitis do not always need radiologic confirmation prior to treatment.

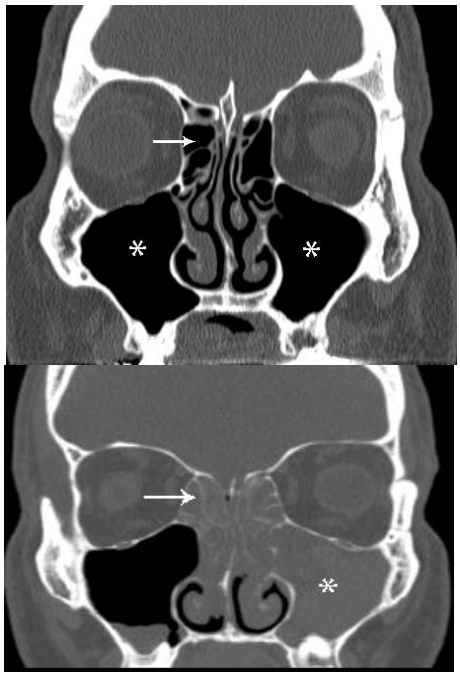
- If imaging is required because of concern for complications, uncertain diagnosis, or lack of response to treatment, CT scan of the sinuses is the test of choice since it provides greater details to evaluate for complications such as orbital cellulitis or intracranial extension.

- Treatment:

- Most cases of viral rhinosinusitis resolve in 7-10 days with management (antihistamines, NSAIDS, and decongestants such as oral pseudoephedrine or oxymetazoline sprays).

- If symptoms persist beyond that point or get worse, antibiotics should be considered. Streptococcus pneumoniae and nontypeable Haemophilus influenzae are the most common causes of acute bacterial rhinosinusitis. Due to increasing beta-lactamase resistance, the treatment of choice is amoxicillin-clavulanic acid.





Epistaxis

- Nose bleed.

- Etiology:

- Digital trauma (nose picking; most common).
- Dry air.
- Nasal steroid sprays.
- Congenital vascular anomalies.
- Clotting disorders, hypertension.
- Nasal angiofibromas (common in adolescent males)

- Types:

- 90-95% are anterior, venous bleeds of the Kiesselbach venous plexus. Management is directed at stopping the bleeding from Kiesselbach plexus, preferably by direct compression of the nasal alae. Cautery (silver nitrate) at the anterior nasal septum may be necessary for persistent bleeding.

- 5% are posterior, arterial bleeds (sphenopalatine artery, a branch of maxillary artery). These are very dangerous and need packing or balloon.

Nasal polyps

- Protrusion of edematous, inflamed nasal mucosa.

- Usually secondary to repeated bouts of rhinitis; also occurs in cystic fibrosis and aspirin -intolerant asthma.

- Aspirin-intolerant asthma is characterized by the triad of asthma, aspirin-induced bronchospasms, and nasal polyps; seen in 10% of asthmatic adults.

Angiofibroma

- Benign tumor of nasal mucosa composed of large blood vessels and fibrous tissue; classically seen in adolescent males.
- Presents with profuse epistaxis.

Nasopharyngeal carcinoma

- Squamous cell carcinoma arising from the epithelial cells of the nasopharynx.
- Associated with EBV; classically seen in African children and Chinese adults (rare in the United States).
- Risk is thought to be higher in these locations due to diet (salt-cured food, early exposure to salted fish) and genetic predisposition.
- Biopsy usually reveals pleomorphic keratin-positive epithelial cells (poorly differentiated squamous cell carcinoma) in a background of lymphocytes.
- NPC tumors obstruct the nasopharynx and invade adjacent tissues, often resulting in nasal congestion with epistaxis, headache, cranial nerve palsies (facial numbness), and/or serous otitis media (eustachian tube obstruction).
- Often presents with involvement of cervical lymph nodes.

Larynx

Acute epiglottitis

- Epiglottitis is an inflammation and swelling of the epiglottis (Usually caused by a bacterial infection). Isolated pathogens are usually nasopharyngeal bacteria, most commonly Haemophilus influenzae type b (Hib). Due to widespread vaccination against Hib, the incidence of epiglottitis has diminished. However, the proportion of epiglottitis caused by other pathogens, such as other strains of H influenzae, Streptococcus species (S pneumoniae, S pyogenes), and Staphylococcus aureus, has increased.

- <u>Presentation:</u>

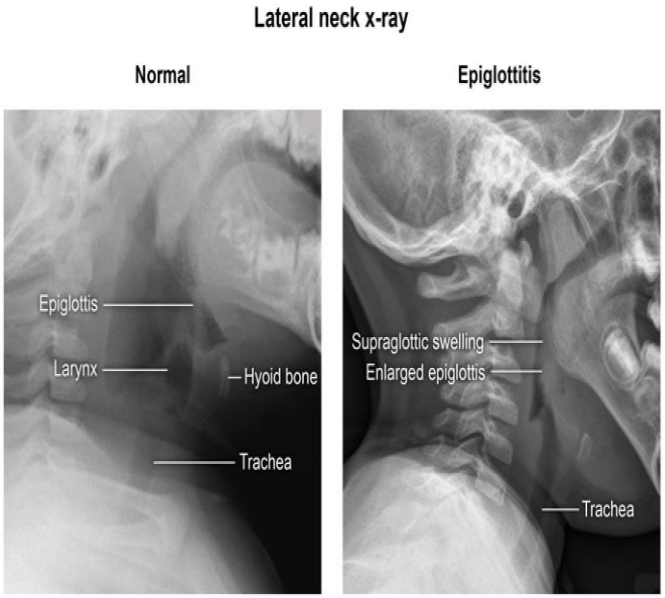
- Epiglottitis is an uncommon but potentially fatal infection that presents with acute onset of fever with dysphagia, drooling, and respiratory distress.
- Signs of impending airway obstruction include restlessness, anxiety, worsening inspiratory stridor, and a muffled "hot potato voice".
- Patients may hyperextend the neck and maintain a tripod position (upright/forward positioning with neck hyperextension) to maximize airway diameter when significant airway swelling is present.

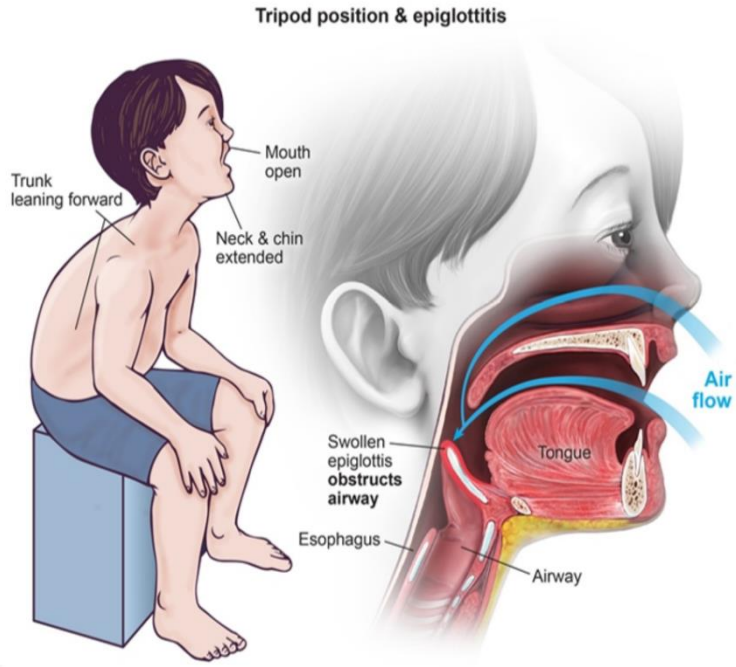
- Diagnosis and treatment:

- X-ray is not required for diagnosis if clinical suspicion is high, but lateral view shows an enlarged epiglottis "thump sign", suggestive of edema.

- The first step in management of epiglottitis is to secure the airway, usually via endotracheal intubation.

- Once the airway is secured, broad-spectrum antibiotic therapy with is needed.





Laryngotracheobronchitis (croup)

- Croup, or laryngotracheitis, is a viral respiratory illness most commonly caused by parainfluenza virus and typically presents in children aged 3 months to 3 years.

- Presentation:

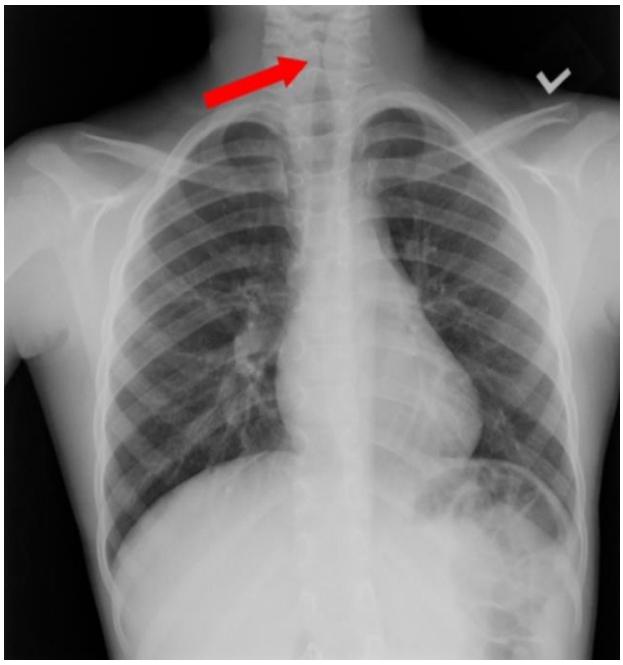
- The virus spreads from the nasopharyngeal mucosa to the larynx and trachea, causing edema and narrowing of proximal trachea (subglottis). Inflammation of the cricoid cartilage creates a partial upper airway obstruction.

- The illness usually begins with nonspecific symptoms (rhinorrhea, congestion, fever); classic croup then presents with a dry, "barky," seal-like cough, hoarseness, and inspiratory stridor due to upper airway obstruction.

- Diagnosis and treatment:

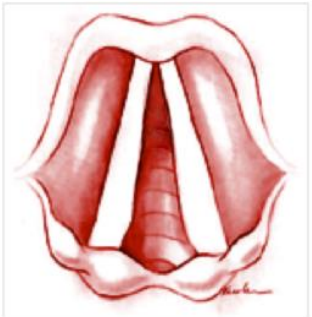
- Croup is typically a clinical diagnosis. If the diagnosis is unclear, anteroposterior neck radiographs will reveal subglottic edema known as the "steeple sign" (red arrow).

- Patients with moderate to severe croup (respiratory distress, stridor at rest) should be treated with corticosteroids and nebulized epinephrine, which constricts mucosal arterioles in the upper airway and alters capillary hydrostatic pressure, leading to decreased airway edema and reduced secretions.

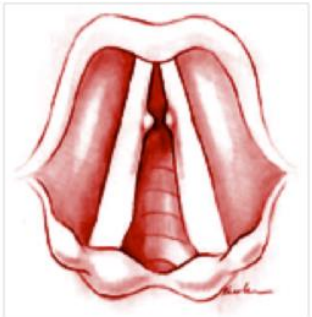


Vocal cord nodules (singer's nodules)

- Nodule that arises on the true vocal cord.
- Due to excessive use of vocal cords; usually bilateral.
- Composed of degenerative (myxoid) connective tissue.
- Presents with hoarseness; resolves with resting of voice.



Normal

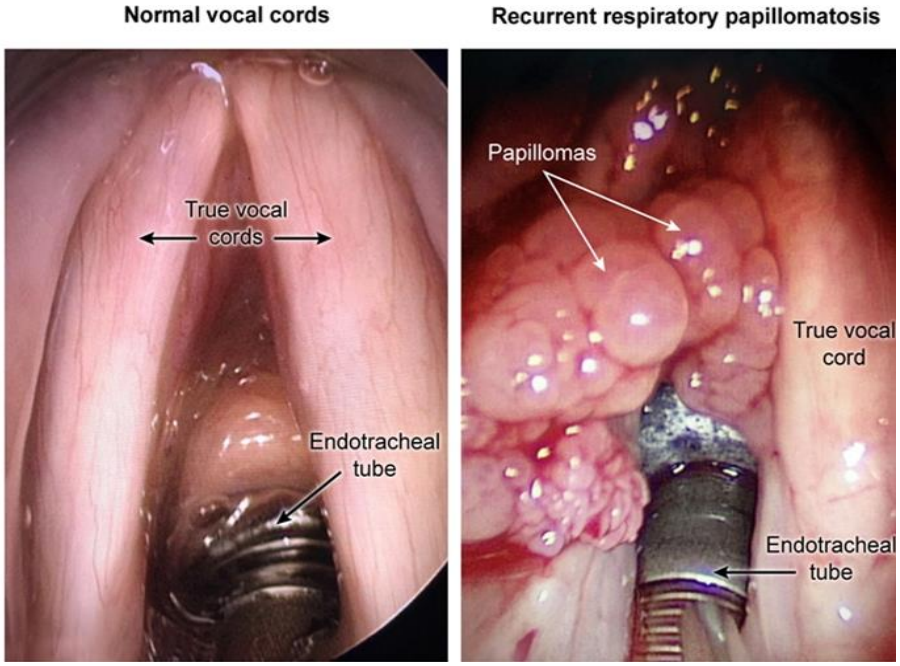


Vocal Nodules

Laryngeal papilloma

- Benign papillary tumor of the vocal cord.
- Due to HPV 6 and 11; papillomas are usually single in adults and multiple in children.
- Human papilloma virus, which has affinity for stratified squamous epithelium, can cause warty growths (papillomas) on the true vocal cords, producing hoarseness and possible stridor (upper airway obstruction).

- Constant (>1 month) or progressive hoarseness is often related to a vocal cord lesion and requires evaluation by laryngoscopy.
- Irregular, exophytic, warty or grapelike growths in clusters on the surfaces of vocal cords suggest laryngeal papillomas due to recurrent respiratory papillomatosis (RRP).
- Although benign, RRP is associated with significant morbidity (voice outcomes, airway obstruction, repeated operative interventions).
- Medical therapy (interferon, cidofovir) has limited efficacy; therefore, the mainstay of treatment remains surgical debridement, and patients often require many procedures.



Laryngeal carcinoma

- Squamous cell carcinoma usually arising from the epithelial lining of the vocal cord.
- Risk factors are alcohol and tobacco; can rarely arise from a laryngeal papilloma.
- Presents with hoarseness; other signs include cough and stridor.

Pulmonary infections

- Infection of the lung parenchyma.

- It is the 6th leading cause of death in the United States.

- Occurs when normal defenses are impaired (impaired cough reflex, damage to mucociliary escalator, or mucus plugging).

- Clinical features:

- Fever and chills, productive cough with yellow-green (pus) or rusty (bloody) sputum, tachypnea with pleuritic chest pain is because of localized inflammation of the pleura by the infection, decreased breath sounds, dullness to percussion, and elevated WBC count.

- The sputum with S. pneumoniae is described as rusty. The "rust" is simply hemoptysis. As the blood oxidizes, it becomes brownish-red color.

- The sputum with Klebsiella pneumoniae is described as currant jelly. This is simply hemoptysis with mucoid characteristics from a combination of the necrotizing nature of Klebsiella with the organism's thick mucopolysaccharide coating.

- Interstitial infections such as those caused by Pneumocystis pneumonia (PCP), viruses, Mycoplasma, and sometimes Legionella often give a nonproductive or "dry" cough.

- Diagnosis:

- It is made by chest x-ray, sputum gram stain and culture, and blood cultures.

- Three patterns are classically seen on chest x-ray (lobar pneumonia, bronchopneumonia, and interstitial pneumonia):

A. Lobar pneumonia:

- Characterized by intra-alveolar exudate → consolidation of an entire lobe of the lung.

- Typical organisms:

- Usually bacterial; most common causes are Streptococcus pneumoniae (95%), Legionella, Klebsiella pneumoniae.

- Classic gross phases of lobar pneumonia:

A. Congestion:

- Days: 0-2.

- Findings:

  - Neutrophils respond to bacterial components (peptidoglycan) by releasing cytokines that increase the permeability of the pulmonary capillary endothelium, which allows circulating immune cells to more easily migrate to the area.
  - Increased capillary permeability also leads to the accumulation of erythrocytes and abundant proteinaceous fluid in the alveolar space, resulting in the affected lobe becoming heavy and congested.

B. Red hepatization:

- Days: 2-4.

- Findings:
  - The proteinaceous fluid transforms into fibrin strands, resulting in a confluent exudate of fibrin, neutrophils, and erythrocytes.
  - On gross examination, the lobe appears liver-like: Red, firm, and airless.

C. Gray hepatization:

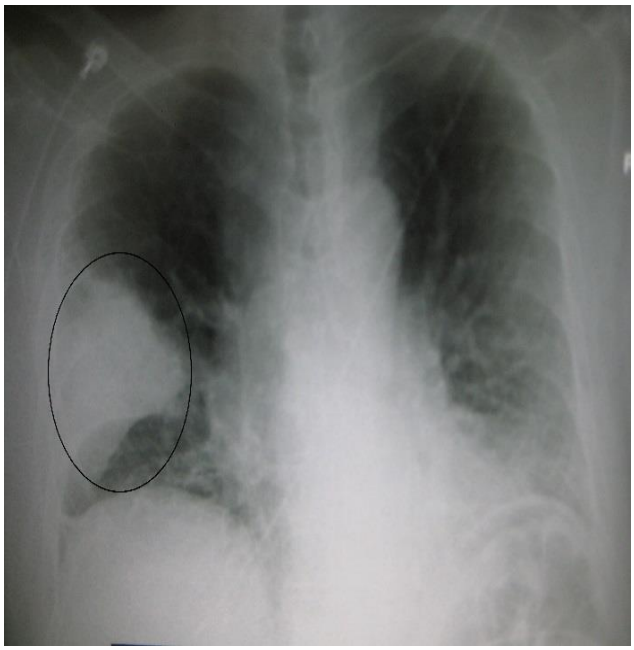
- Days: 4-7 days.

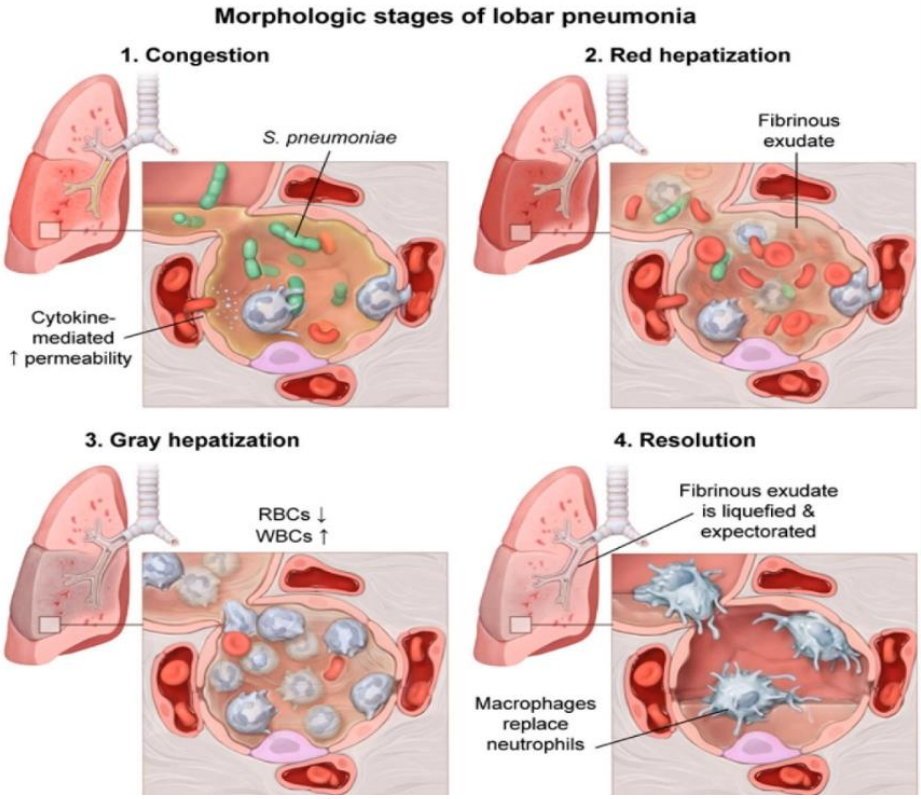
- Findings:
  - Red cell disintegration along with increased leukocyte infiltration causes the lung to appear gray rather than red.
  - Neutrophils begin to be replaced by macrophages that begin the repair process.

D. Resolution:

- Days: >7.

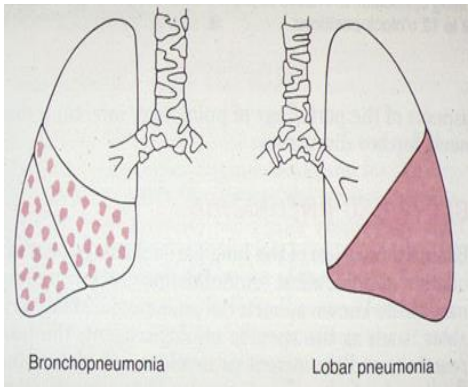
- Findings: Enzymatic digestion of exudate by macrophages.





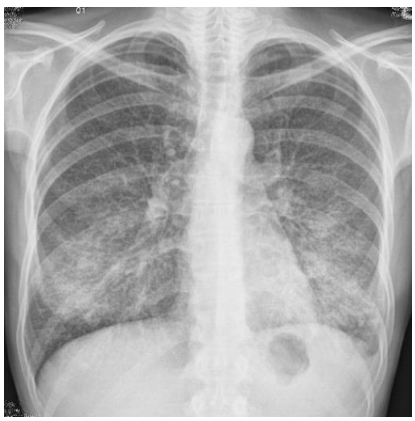
B. Bronchopneumonia:

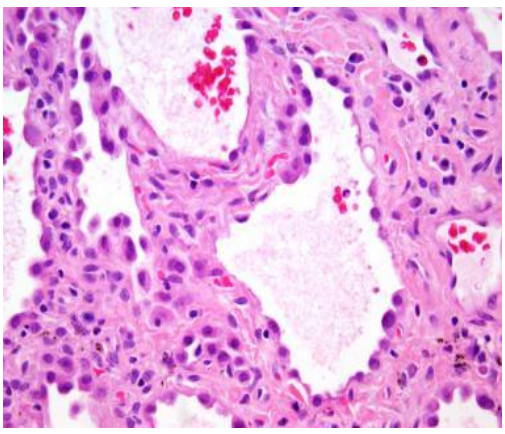
- Acute inflammatory infiltrates from bronchioles into adjacent alveoli.
- Characterized by scattered patchy consolidation centered around bronchioles; often multifocal and bilateral.
- Caused by a variety of bacterial organisms.
- Presents with relatively mild upper respiratory symptoms (minimal sputum and low fever).
- Typical organisms: S pneumoniae, S aureus, H. influenzae, Klebsiella.

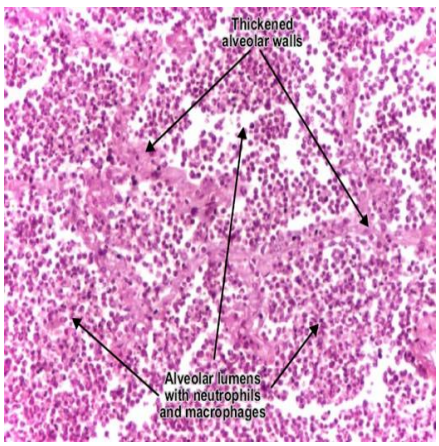


C. Interstitial (atypical) pneumonia:

- Diffuse patchy inflammation localized to interstitial areas at alveolar walls; diffuse distribution involving ≥ 1 lobe.
- Generally, follows a more indolent course ("walking" pneumonia).
- CXR shows bilateral multifocal opacities.
- Typical organisms: Mycoplasma, Chlamydia, Legionella, viruses (RSV, CMV, influenza, adenovirus).







❖ Cryptogenic organizing pneumonia:

- Noninfectious pneumonia characterized by inflammation of bronchioles and surrounding structure.
- Secondary organizing pneumonia is caused by chronic inflammatory diseases (rheumatoid arthritis) or medication side effects (amiodarone).
- Etiology unknown. ⊖ sputum and blood cultures, often responds to steroids but not to antibiotics.

❖ N.B:

- The green discoloration of pus or sputum noted during bacterial infections is associated with the release of myeloperoxidase (MPO) from neutrophil azurophilic granules.
- Myeloperoxidase is a blue-green heme-based pigmented molecule contained within the azurophilic granules of neutrophils that catalyzes the production of hypochlorous acid (HOCl) from chloride and hydrogen peroxide during the phagocytic respiratory burst.

Aspiration pneumonia

- Aspiration pneumonia is due to inhalation of oropharyngeal secretions colonized by pathogenic bacteria.
- Aspiration pneumonia is most commonly caused by anaerobic bacteria normally found in the oral cavity. Fusobacterium, Prevotella, Peptostreptococcus and Bacteroides species are the most frequent pathogens.
- Aspiration risk factors include the following:

- Altered consciousness impairing cough reflex/glottic closure (dementia, seizure, drug intoxication).
- Dysphagia due to neurologic deficits (stroke, neurodegenerative disease).
- Mechanical compromise of aspiration defenses (nasogastric & endotracheal tubes).

- Heavy alcohol users are at risk of aspiration if they have impaired consciousness.
- Patients usually present with indolent symptoms (days to weeks) and foul-smelling sputum.
- Progression to lung abscess is quite common.
- Broad-spectrum antibiotics with good anaerobic coverage (clindamycin, amoxicillin-clavulanate) are the mainstay of treatment.

Lung abscess

- Pulmonary abscesses are local suppurative collections within lung parenchyma that result in necrosis of the surrounding lung tissue.

- Tissue damage and resultant abscess formation is primarily caused by lysosomal enzyme release from neutrophils and macrophages.

- 90% have at least some anaerobes involved. The most commonly implicated anaerobes are Peptostreptococcus, Fusobacterium, and Bacteroides species, which are oral anaerobes found in the gingival crevices.

- Lung abscesses are usually caused by one of the following:

A. Aspiration of oral bacteria into the lower airways (most common):

- These abscesses are usually composed of a combination of anaerobic oral flora (Peptostreptococcus, Prevotella, Bacteroides, Fusobacterium) and aerobic organisms (Streptococcus).

- Risk is greatest in those who have conditions associated with loss of consciousness or impaired swallowing, such as alcoholism, drug abuse or neurologic disease (seizures, stroke).

B. Bacterial pneumonia:

- Lung abscess can occur in the setting of certain bacterial pneumonias such as those due to Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, or Pseudomonas aeruginosa.

- Most cases arise in the hospital setting and occur in patients with immunosuppression, older age, or underlying lung disease.

C. Bacteremia and/or infectious endocarditis:

- Hematogenous spread of an infection to the lung usually causes multiple, monomicrobial lung abscesses.

- The most common causative agents are Staphylococcus and Streptococcus species.

- If the abscess cavity communicates with an air passage, the semiliquid exudate within will partially drain, creating an air-containing cavity that can be identified on chest radiograph (Air-fluid levels often seen on CXR).

- Clinical features:

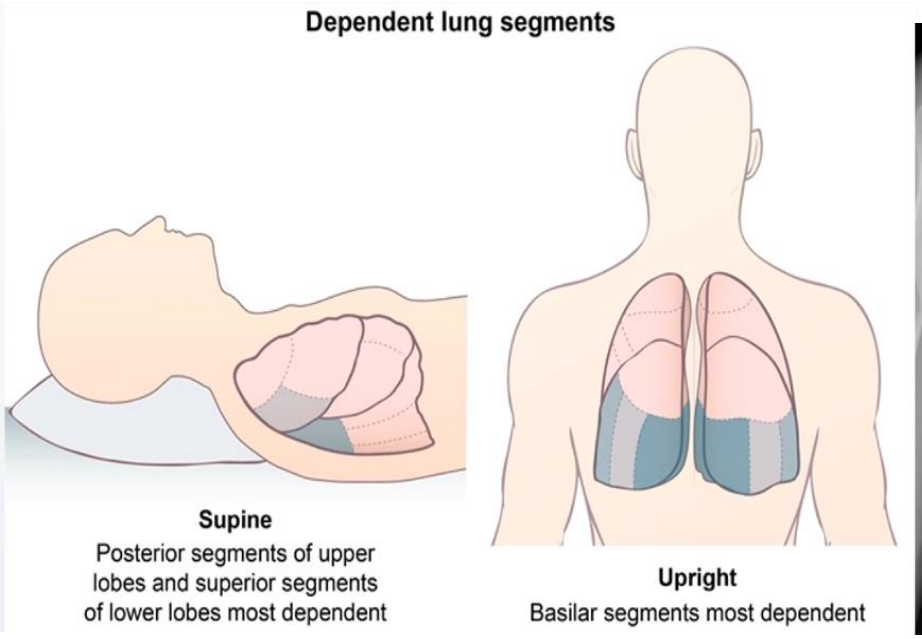
- Clinically, a lung abscess will cause fever, malaise, weight loss, clubbing and leukocytosis lasting a few weeks.

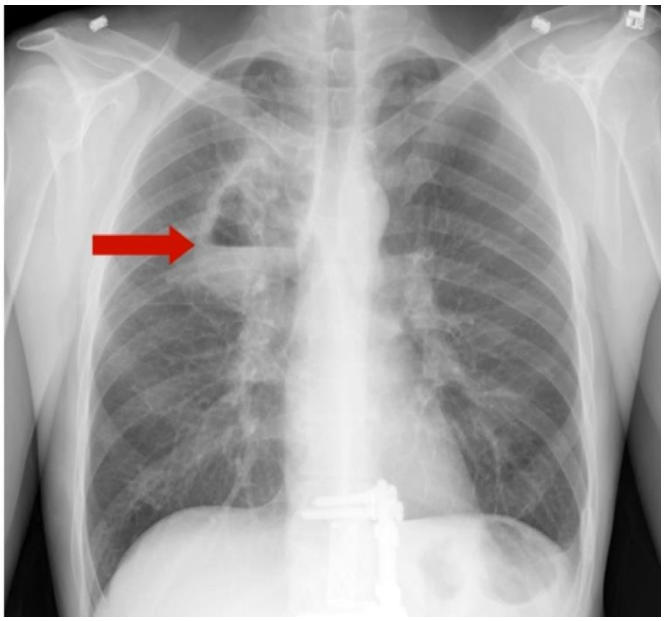
- Patients complain of cough with copious production of foul-smelling sputum.

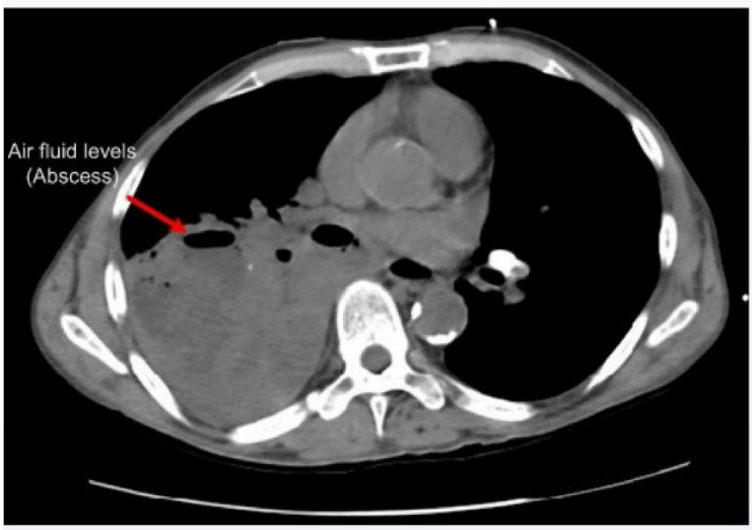
- Lung abscess 2° to aspiration is most often found in right lung because the right bronchus is shorter, wider, and straighter than the left bronchus (the right main stem bronchus branches at a less acute angle than the left).

- Location depends on patient's position during aspiration
  - Upright → basal segments of right lower lobe.
  - Supine → posterior segments of right upper lobe or superior segment of right lower lobe.

- Treatment: In the absence of specific microbiologic diagnosis, clindamycin is good empiric coverage for the "above the diaphragm" anaerobes most often found.



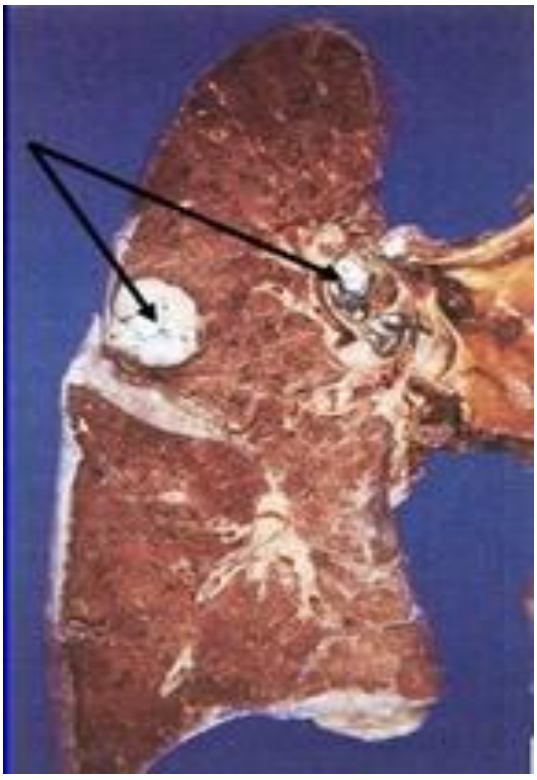




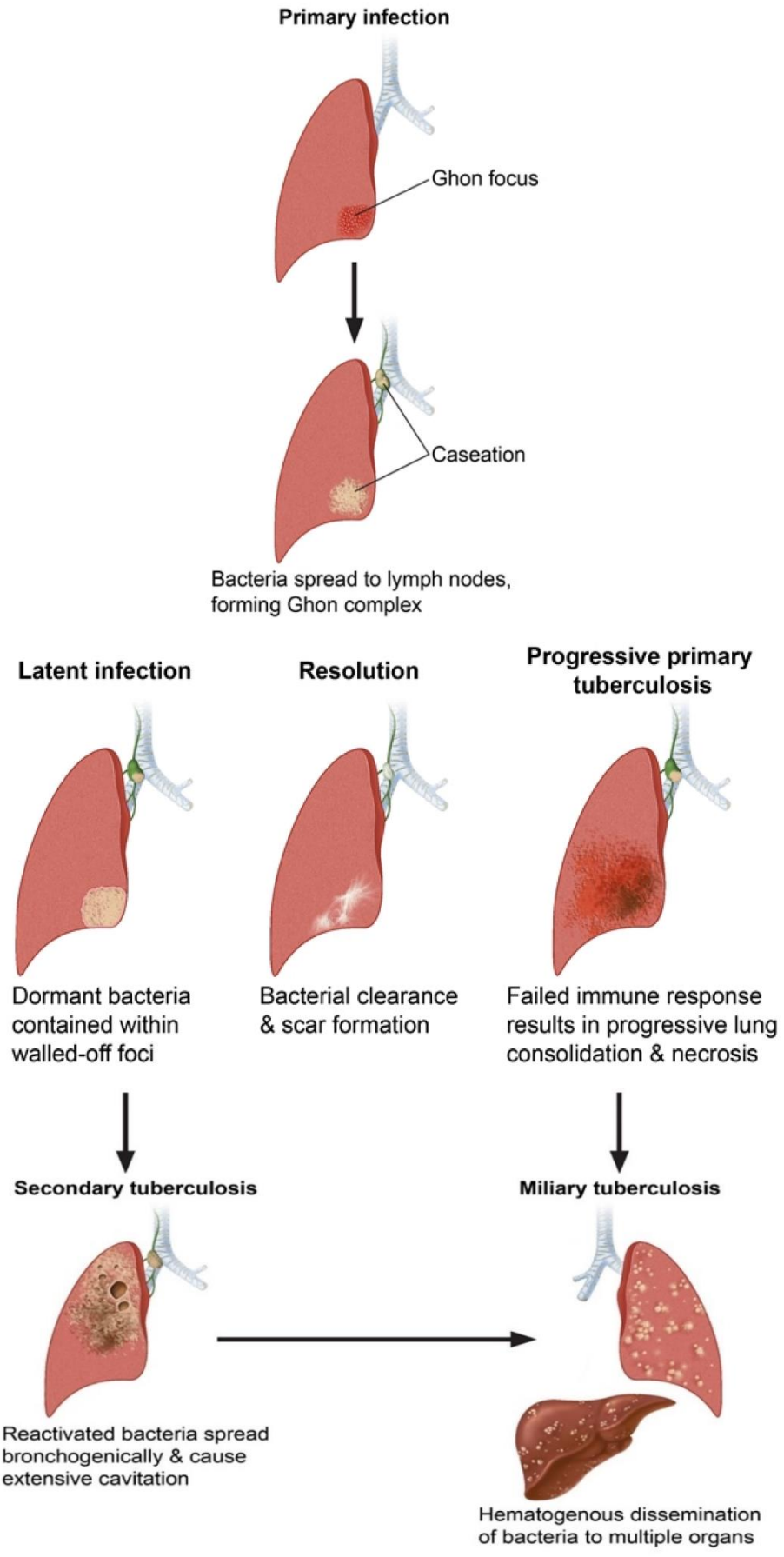
Tuberculosis (TB)

- Tuberculosis (TB) is an infection with Mycobacterium tuberculosis.
- TB is spread exclusively by person-to-person transmission by means of respiratory droplet infection.
- Primary TB arises with initial exposure:

- Primary tuberculosis infection occurs following inhalation of aerosolized Mycobacterium tuberculosis.
- The organisms are deposited in the lower lungs and phagocytosed by alveolar macrophages and the sulfatide virulence factor expressed by M. tuberculosis allows for intracellular bacterial proliferation until the macrophages are activated by Th_1 lymphocytes.
- Granuloma formation assists in disease containment and occurs mainly through an interaction among macrophages, multinucleated giant cells, and CD4 T lymphocytes.
- Although eliminated in 95% of cases, dormant M. tuberculosis bacilli are still present within the larger granulomas of many patients, able to later cause secondary tuberculosis during periods of immunosuppression.
- Primary TB is generally asymptomatic, but leads to a positive PPD.
- In initial M. tuberculosis infection, a lower lobe lung lesion (Ghon focus) accompanied by ipsilateral hilar adenopathy is described as a Ghon complex.



Pathogenesis of pulmonary tuberculosis infection



- Secondary TB arises with reactivation of Mycobacterium tuberculosis:

- Later in life (usually following immunosuppression by drugs or HIV) the bacteria can be reactivated and establish infection in the upper lungs (particularly the apex).

- The predilection for upper lung regions may be related to decreased lymphatic flow or increased oxygen tension.

- The organisms multiply in the apices, causing caseous and liquefactive necrosis and extensive cavitary disease.

- Clinical features:

- Clinical features include fevers and night sweats, cough with hemoptysis, and weight loss. AFB stain reveals acid-fast bacilli.

- Erosion into the pulmonary vessels can result in severe hemoptysis.

- Biopsy reveals caseating granulomas. The tissue destruction caused by M. tuberculosis infection is the direct result of host immune activation and inflammation through a type IV delayed-type hypersensitivity reaction.

- Hematogenous dissemination may also occur, causing miliary or extrapulmonary tuberculosis. Systemic spread often occurs and can involve any tissue; common sites include meninges (meningitis), cervical lymph nodes, kidneys (sterile pyuria), and lumbar vertebrae (Pott disease).

Deep venous thrombosis

- Blood clot within a deep vein → swelling, redness, warmth, pain.

- Homan sign: dorsiflexion of foot → calf pain.

- Predisposed by Virchow triad (SHE):

- Stasis (post-op, long drive/flight).

- Hypercoagulability (defect in coagulation cascade proteins, such as factor V Leiden, oral contraceptive use; pregnancy). Elderly individuals who undergo hip surgery are at very high risk of developing postoperative deep venous thrombosis and pulmonary embolism. The predominant pathophysiological cause of DVT in this setting is thought to be stasis of the deep veins that drain the immobilized leg.

- Endothelial damage (exposed collagen triggers clotting cascade).

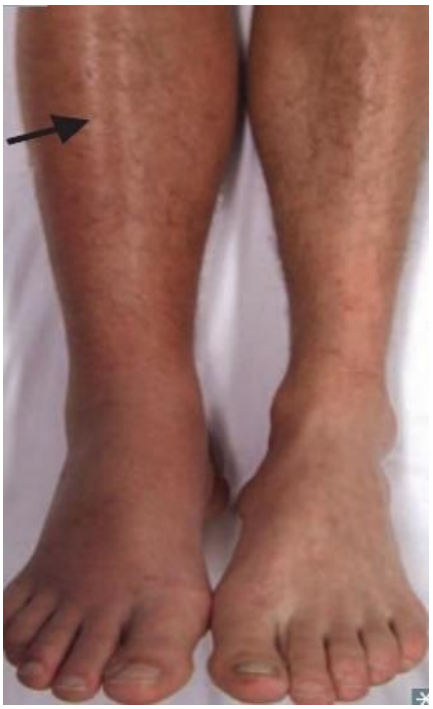
- Pulmonary emboli derive from DVT of the large vessels of the legs in 70% and pelvic veins in 30%, but since the risks and treatment are the same, they can be discussed at the same time.

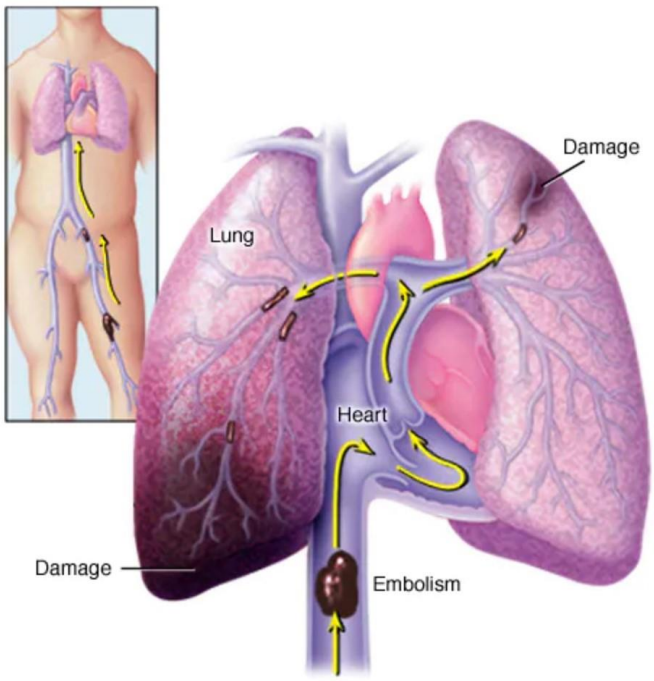
- Diagnosis and treatment:

- Imaging test of choice is compression ultrasound with doppler.

- Unfractionated heparin or low-molecular weight heparins (enoxaparin) are used for prophylaxis and acute management.

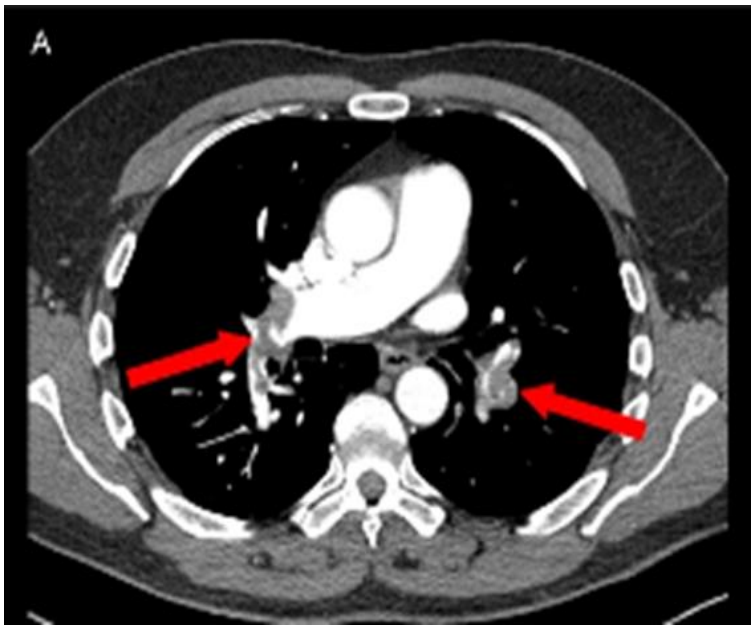
- Use oral anticoagulants (apixaban, rivaroxaban) for treatment and long-term prevention.

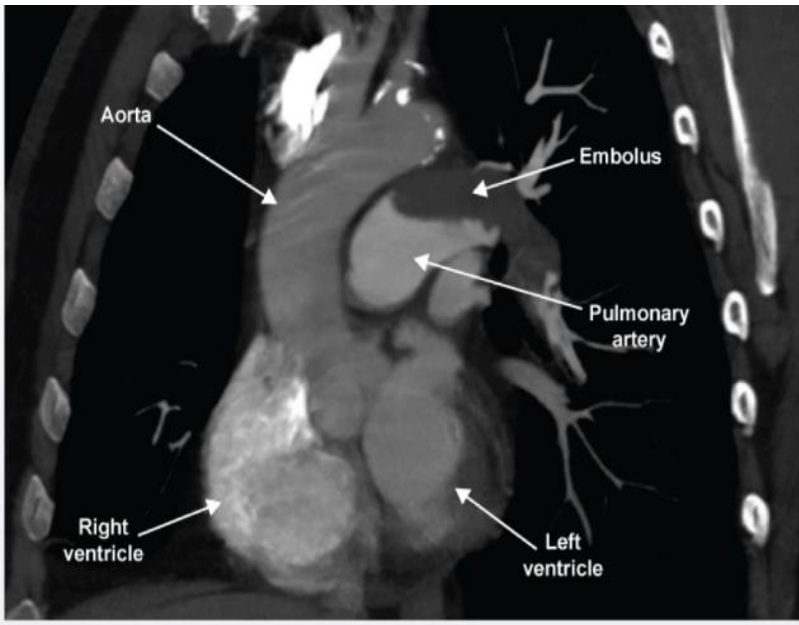




Pulmonary emboli

- V˙/Q˙ mismatch → hypoxemia with (A-a gradient) → respiratory alkalosis.
- Clinical presentation: Sudden-onset dyspnea, pleuritic chest pain, tachypnea, tachycardia.
- Most patients with PE have underlying lower-extremity deep venous thrombosis (DVT), a condition that often goes unrecognized.
- Thromboemboli originate in the deep veins of the lower extremities and travel through the right atrium and ventricle to reach the pulmonary circulation.
- Large emboli lodge in the pulmonary artery bifurcation (saddle emboli), while smaller emboli occlude peripheral branches (wedge-shaped emboli). Large emboli or saddle embolus may cause sudden death.
- Spiral CT, also called a CT angiogram has become the standard of care in terms of diagnostic testing to confirm the presence of a PE.
- D-dimer is the answer when the pretest probability of PE is low and you need a simple, noninvasive test to exclude thromboembolic disease. A negative test excludes a clot, but a positive test doesn't mean anything (elevated D-dimer may be due to a thromboembolism, but it may also be due to a recent surgery, infection, trauma, pregnancy, and DIC).
- V/Q scans are helpful in evaluating patients in whom angiography is contraindicated (contrast allergy, renal failure, pregnancy). A pulmonary embolus will typically cause perfusion defects with normal ventilation.





- Types:

- Fat, Air, Thrombus, Bacteria, Amniotic fluid, Tumor. An embolus moves like a FAT BAT.

A. Fat emboli:

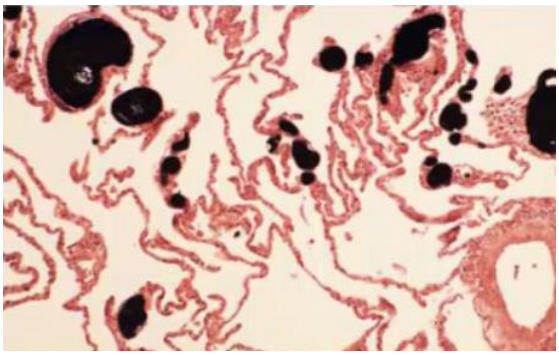
- Associated with long bone fractures and liposuction.

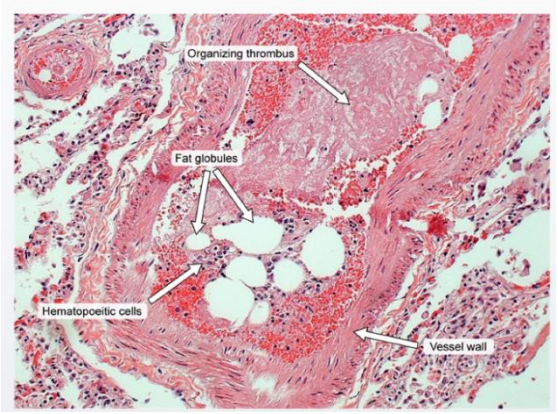
- The development of the classic triad respiratory distress, diffuse neurological impairment (confusion), and an upper body petechial rash (due to thrombocytopenia) within days of severe long bone fractures is characteristic of the fat embolism syndrome. The underlying mechanism involved widespread inflammation.

- The condition arises when a traumatic event dislodges fat globules from the bone marrow, allowing them to travel through the marrow vascular sinusoids and into the pulmonary microvessels.

- Occlusion of these microvessels impairs pulmonary gas exchange and induces hypoxemia.

- The multiple fat emboli occluding the pulmonary microvasculature stain black with osmium tetroxide.





B. Amniotic fluid emboli:

- Amniotic fluid embolism (AFE) is a rare and catastrophic pregnancy complication that results from amniotic fluid entering the maternal circulation → anaphylactoid reaction (caused by the metabolites).

- Common signs of AFE include hypoxia, hypotensive shock, and disseminated intravascular coagulation (Tissue factor thromboplastin is also released from amniotic fluid).

- For years, some researchers believed that the amniotic fluid and fetal cells cause obstruction within the mother's blood vessels, but now most researchers believe that the mother's immune system reacts to the amniotic fluid and fetal cells causing an overwhelming immune system response

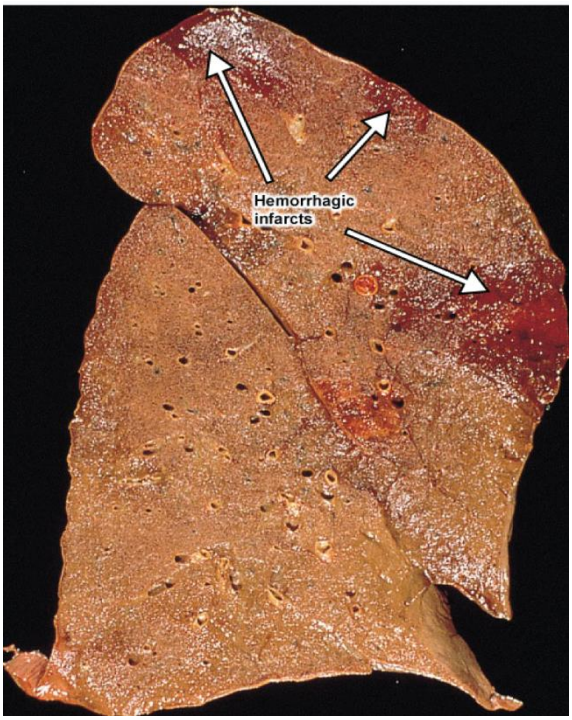
- Fetal squamous cells are seen in the pulmonary vasculature during histologic evaluation.

C. Air emboli: Nitrogen bubbles precipitate in ascending divers (caisson disease, decompression sickness); treat with hyperbaric O_2; or can be iatrogenic 2° to invasive procedures (central line placement).

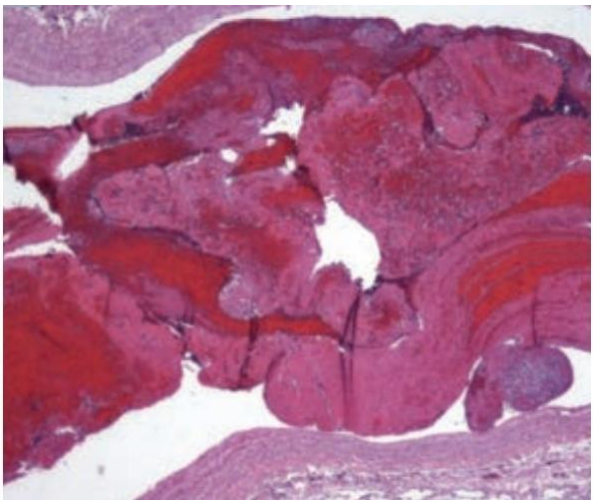
❖ N.B:

1. The lung specimen below shows multiple wedge-shaped hemorrhagic infarcts in the periphery of the lung due to septic pulmonary emboli.

- Patients with intravenous drug use are at increased risk of developing tricuspid valve endocarditis, most commonly due to Staphylococcus aureus.
- The infarcts are typically wedge-shaped due to the triangular perfusion field of small arteries at the lung periphery.
- Due to dual blood supply of the lung (pulmonary and bronchial arteries), pulmonary infarcts are typically hemorrhagic (red) rather than ischemic.



2. Lines of Zahn are interdigitating areas of pink (platelets, fibrin) and red (RBCs) found only in thrombi formed before death; help distinguish pre- and postmortem thrombi.

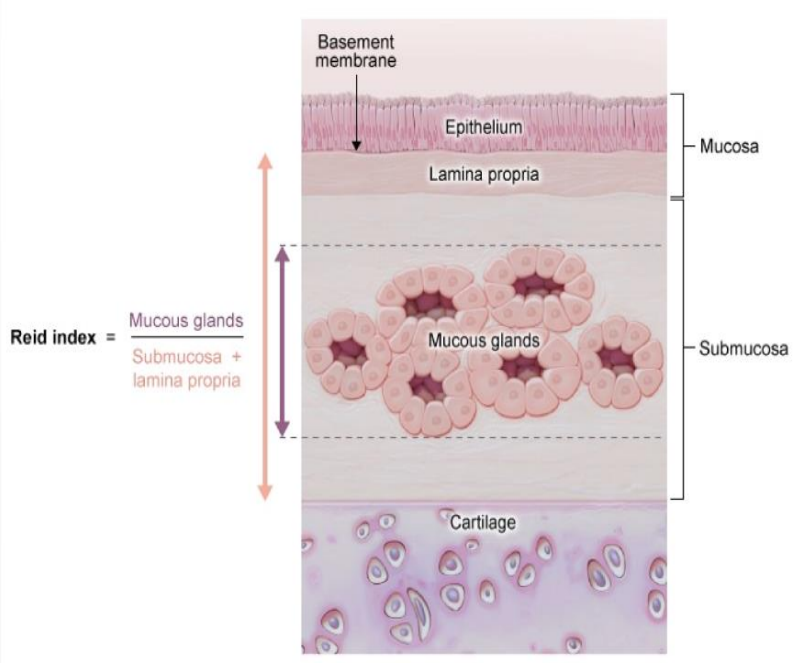


Chronic pulmonary obstructive diseases

- Group of diseases characterized by airway obstruction; lung does not empty, and air is trapped.
- Volume of air that can be forcefully expired is decreased (↓ FVC), especially during the first second of expiration (↓↓FEV_1); results in ↓ FEV_1: FVC ratio.
- Total lung capacity (TLC) is usually increased due to air trapping.

Chronic bronchitis (blue bloaters)

- Chronic productive cough lasting ≥ 3 months (not necessarily consecutive) per year for > 2 consecutive years; highly associated with smoking.
- The leading cause of chronic bronchitis is cigarette smoking.
- The severity of chronic bronchitis is largely dependent upon the extent to which the luminal diameter of the bronchi and bronchioles is decreased.
- The major contributor to this wall thickening is hypertrophy and hyperplasia of submucosal mucous gland, which can be quantified by the ratio of the thickness of the mucous gland layer to the thickness of the wall between the epithelium and the cartilage (Reid index).
- Reid index increases to > 50%; normal is < 40%.
- DLCO usually normal.
- As chronic bronchitis progresses, both the total bronchial wall thickness and the Reid index increase.



- Findings:
- Wheezing, crackles, cyanosis (early onset hypoxemia due to shunting), late-onset dyspnea, CO_2 retention (hypercapnia), 2° polycythemia.

- Hypoxia is sensed by cells in the renal cortex that synthesize and release erythropoietin in response. Erythropoietin stimulates erythrocyte production → Polycythemia.

- Clinical features:
- Productive cough due to excessive mucus production.

- Cyanosis (blue bloaters): Mucus plugs trap carbon dioxide; ↑ $Paco_2$ and ↓ Pao_2.

- Increased risk of infection and cor pulmonale.

- Chronic complications: pulmonary hypertension, cor pulmonale.

Emphysema (pink puffer)

- Destruction of interalveolar air sacs septa → Loss of elastic property of the lung and collapse of airways during exhalation results in obstruction and air trapping.

- ↓ diffusion capacity (DLCO) due to destruction of alveoli and adjoining capillary beds.

- Due to imbalance of proteases and antiproteases:
- Inflammation in the lung normally leads to release of proteases by neutrophils and macrophages.

- Antitrypsin (A_1AT) neutralizes proteases.

- Excessive inflammation or lack of A_1AT leads to destruction of the alveolar air sacs.

- There are two types of emphysema:

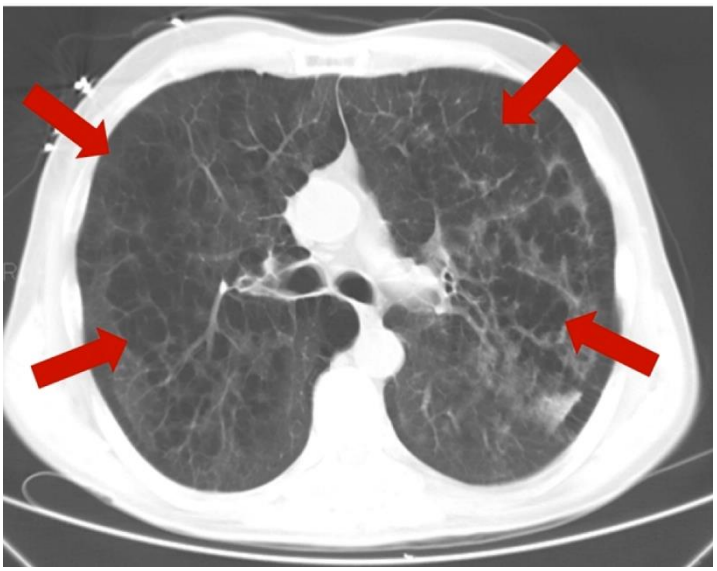
A. Centriacinar emphysema:

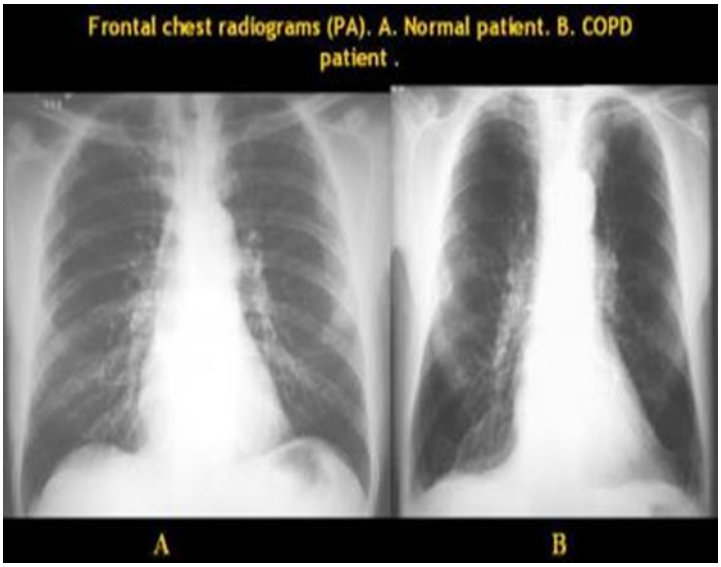
- The pathogenesis of centriacinar emphysema associated with chronic, heavy smoking predominantly involves intra-alveolar release of proteases, especially elastase, from infiltrating neutrophils and from alveolar macrophages.

- Smoking is the most common cause of emphysema.

- Centriacinar emphysema is most severe in the upper lobes.

- A heavy smoker with exertional dyspnea and airspace enlargement on CT likely has centriacinar emphysema.





B. Panacinar emphysema:

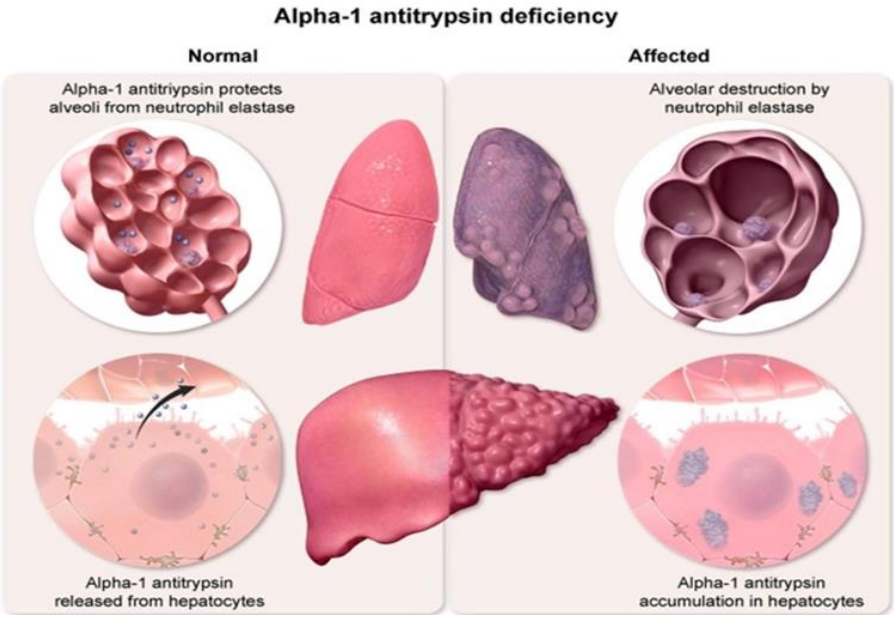
- Associated with A_1AT deficiency which is a rare cause of emphysema.
- A_1-AT deficiency is due to misfolding of the mutated protein and associated with panacinar emphysema and liver cirrhosis.
- Neutrophil elastase is the major protease of extracellular elastin degradation. It is released by neutrophils and macrophages.
- The major serum inhibitor of extracellular elastase is alpha 1-antitrypsin (A_1AT).
- Panacinar emphysema results from the unopposed action of neutrophil elastase on alveolar walls.
- Because alpha-1 antitrypsin is deficient throughout the acinus, the entirety of the acinus is affected, resulting in panacinar emphysema.
- Mutant A1AT accumulates in the endoplasmic reticulum of hepatocytes, resulting in liver damage.
- Panacinar emphysema is most severe in the lower lobes. Lower lung fields may be affected most severely because they receive relatively greater perfusion, allowing a greater rate of neutrophil infiltration.
- Biopsy reveals pink-PAS-positive globules in hepatocytes.
- Smoking dramatically increases the risk of panacinar emphysema in patients with A_1AT deficiency.

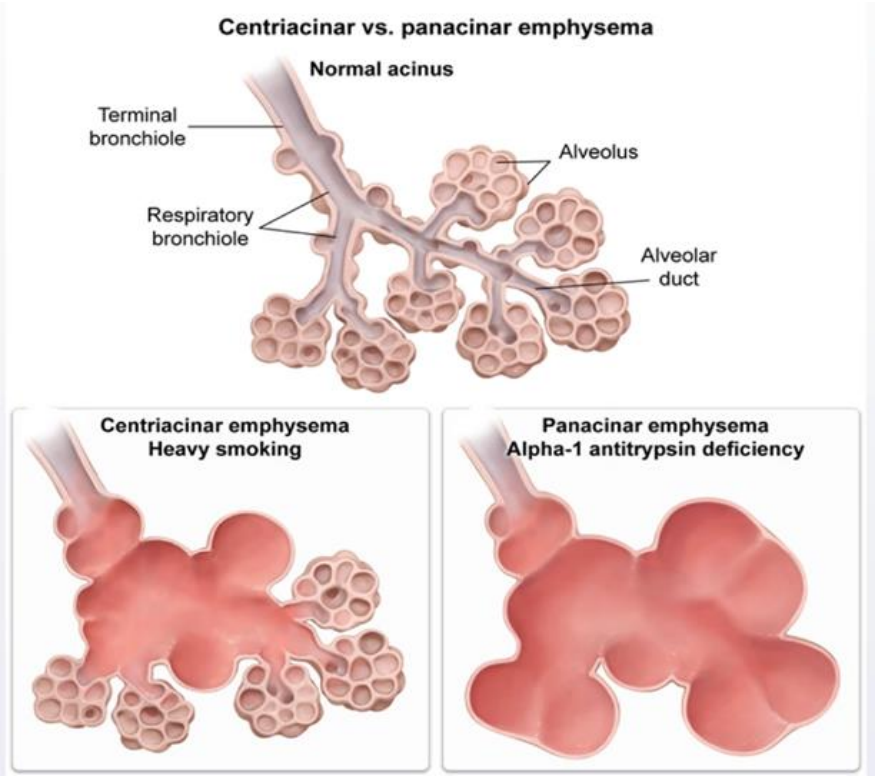
▪ Clinical features of emphysema include:

- Dyspnea and cough with minimal sputum.
- Prolonged expiration with pursed lips ('pink-puffer') to ↑ airway pressure and prevent airway collapse during respiration.

- Increased anterior-posterior diameter of chest (barrel-chest), flattened diaphragm, ↑ lung field lucency.

- Hypoxemia (due to destruction of capillaries in the alveolar sac) and cor pulmonale are late complications.





Asthma

- Pathogenesis:

- Asthma is an obstructive airway disease (Reversible airway bronchoconstriction) that occurs due to type I hypersensitivity of the conducting airways to various stimuli, including physical, chemical, and allergenic irritants.

- Clinical features are episodic and related to allergen exposure.

- Presents in childhood; often associated with allergic rhinitis, eczema, and a family history of atopy.

- Flares occur following exposure to airborne allergens that interact with IgE bound to pulmonary mast cells. Allergen avoidance is an important preventive measure in these patients. Common inciting allergens include animal dander, feathers, dust mites, mold and pollens.

- Asthma may also arise from nonallergic causes such as exercise, viral infection, aspirin (aspirin intolerant asthma), and occupational exposures.

- Children exposed to second-hand smoke are at increased risk for developing asthma over the long-term. Similarly, infants of mothers who smoked during pregnancy have heightened airway responsiveness compared to the infants of non-smoking mothers.

- Diagnosis:

- Clinical diagnosis can be supported by spirometry and methacholine challenge test.

- Patients with asthma will demonstrate a decreased FEV_1 and peak expiratory flow rate on spirometry.

- These changes are typically reversible with the use of a bronchodilator, typically an inhaled beta-adrenergic agonist, like albuterol.

- Airway challenge testing with methacholine is a highly sensitive but nonspecific measure that can detect the degree of bronchial hyperreactivity in patients suspected of having asthma.

- When a patient presents with a history consistent with asthma, but has normal spirometry values, agents such as methacholine can be used to provoke asthma symptoms.

- Methacholine is a muscarinic cholinergic agonist that causes bronchoconstriction and increased airway secretions; a decrease in FEV_1 by more than 20% after a methacholine challenge indicates the diagnosis of bronchial asthma.

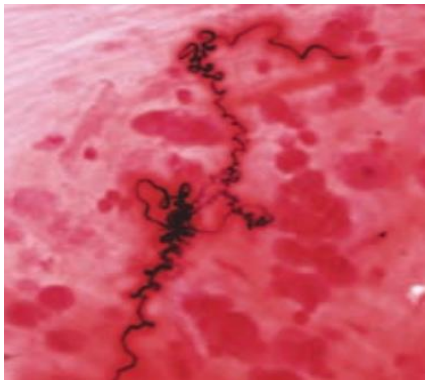
- A negative methacholine challenge test can help to exclude (rule out) the diagnosis.

- Clinical features:

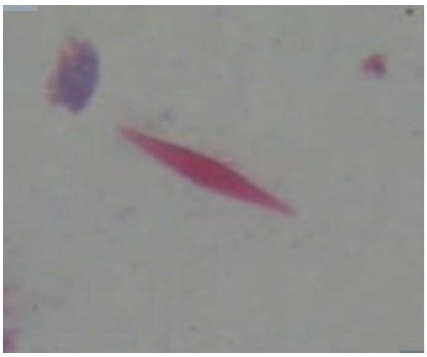
- Dyspnea, cough and wheezing.

- Severe, unrelenting attack can result in status asthmaticus and death.

- Productive cough, classically with Curschmann spirals (shed epithelium forms whorled mucus plugs).



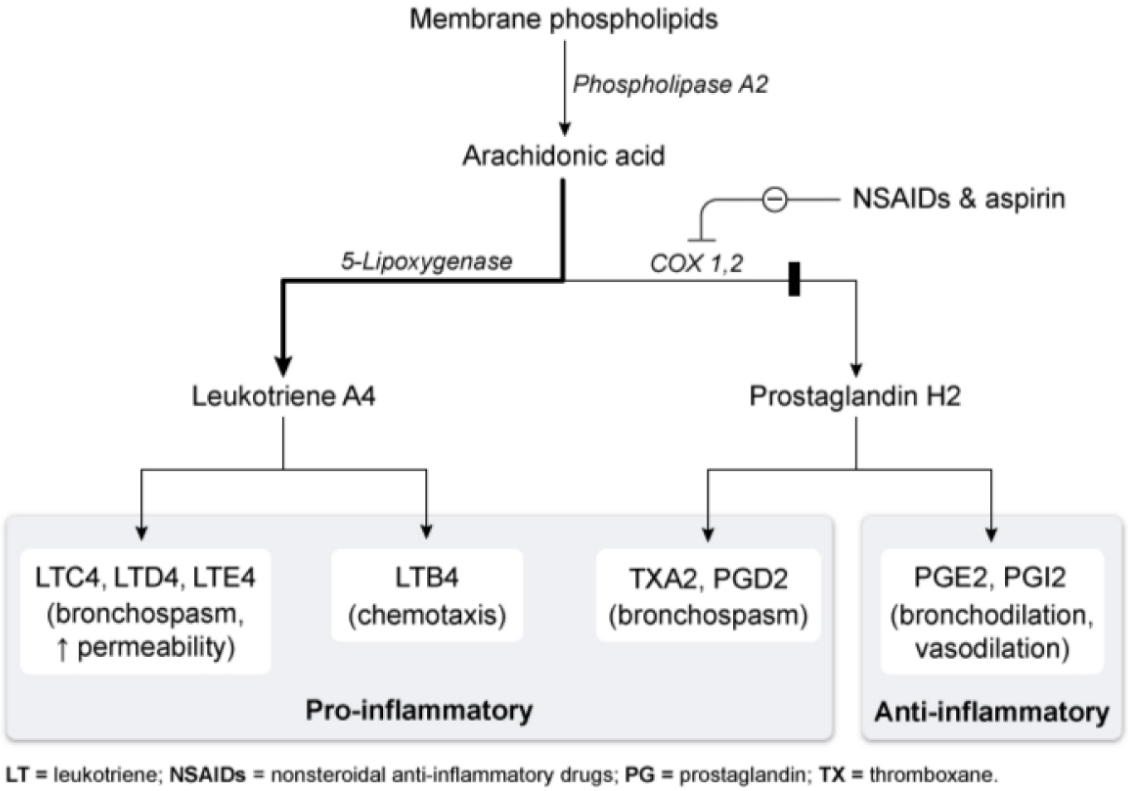
- Classic sputum findings include eosinophils and Charcot-Leyden crystals (eosinophilic, hexagonal, double-pointed, needle-like crystals formed from breakdown of eosinophils in sputum).



❖ N.B:

1. Under the influence of inflammatory stimuli, cell membrane phospholipids release arachidonic acid.

- The arachidonic acid is a precursor to three families of biologically active substances collectively called eicosanoids.



LT = leukotriene; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **PG** = prostaglandin; **TX** = thromboxane.

- The most potent chemotactic eicosanoid is leukotriene B_4.
- It plays an important role in the pathogenesis of bronchial asthma because they cause bronchospasm and increase bronchial mucus secretion.
- Leukotriene B_4 stimulates neutrophil migration to the site of inflammation.

2. Eosinophils are important in allergic disease and defense against parasitic infection (ascaris).

- The eosinophilic granules predominantly contain major basic protein, which, once released, acts as a potent antihelminthic toxin.
- Major basic protein also damages epithelial and endothelial cells and is a major cause of chronic lung damage in asthma.
- This is called Loeffler syndrome (eosinophilic invasion of the lungs due to parasitic infection).

Bronchiectasis

- Chronic necrotizing infection of bronchi → Permanent dilatation of bronchioles and bronchi; loss of airway tone results in air trapping.
- Development of the disease requires an infectious insult in combination with impaired bacterial clearance (impaired immune defenses, structural airway defect).
- Chronic bacterial infection ensues, leading to enhanced neutrophil recruitment and excessive release of elastase, which contributes to bronchial airway damage.
- This is a permanent anatomic abnormality that cannot be reversed or cured.
- Causes include:

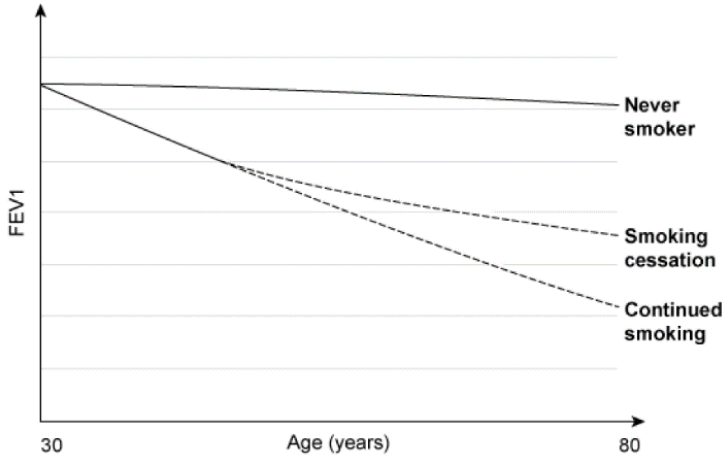
- Cystic fibrosis.
- Kartagener syndrome: inherited defect of the dynein arm, which is necessary for ciliary movement.
- Tumor or foreign body.
- Allergic bronchopulmonary aspergillosis: Hypersensitivity reaction to Aspergillus leads to chronic inflammatory damage; usually seen in individuals with asthma or cystic fibrosis

- Clinical features:

- Cough, dyspnea, and foul-smelling sputum.
- Complications include hypoxemia with cor pulmonale and secondary (AA) amyloidosis.

❖ N.B:

- Smoking is the strongest risk factor for chronic obstructive pulmonary disease (COPD) and is responsible for accelerated decline in forced expiratory volume in 1 second (FEV1) in patients with COPD.
- Smoking cessation will slow the accelerated decline in FEV1, but FEV1 will not return to the level it would have been had the patient never smoked.



Restrictive diseases

- Restricted lung expansion causes ↓ lung volumes (↓ FVC and TLC). FEV1/FVC ratio ≥ 80%.

- Most commonly due to interstitial diseases of the lung; may also arise with chest wall abnormalities (massive obesity).

- Types:

A. Poor breathing mechanics (extrapulmonary, normal D_{LCO}, normal A-a gradient):

- Poor muscular effort: polio, myasthenia gravis, Guillain-Barré syndrome.
- Poor structural apparatus: scoliosis, morbid obesity.

❖ N.B:

- Obesity, particularly morbid, central obesity, can cause a pattern of extrinsic restrictive pulmonary function tests.
- Obesity alters respiratory compliance, which is the ability of the lung and chest wall to stretch in response to increased lung pressures.
- Obesity has minimal effect on residual volume (RV), but functional residual capacity, which is the sum of RV and ERV, is reduced due to the marked reduction in ERV.
- The most common indicator of obesity-related disease is a reduction in expiratory reserve volume and functional residual capacity, but forced expiratory volume in 1 second, forced vital capacity, and total lung capacity are also typically decreased.

B. Interstitial lung diseases (pulmonary, ↓ D_{LCO}, ↑ A-a gradient):

- Idiopathic pulmonary fibrosis.
- Pneumoconiosis (anthracosis, silicosis, asbestosis).
- Hypersensitivity pneumonitis.
- Acute respiratory distress syndrome (ARDS).
- Neonatal respiratory distress syndrome (NRDS; hyaline membrane disease).
- Sarcoidosis: bilateral hilar lymphadenopathy, noncaseating granuloma; ↑ ACE and Ca.
- Goodpasture syndrome.
- Granulomatosis with polyangiitis (Wegener).
- Pulmonary Langerhans cell histiocytosis (eosinophilic granuloma).
- Drug toxicity (bleomycin, busulfan, amiodarone, methotrexate).

Pulmonary fibrosis

- Fibrosis of lung interstitium.

- Etiology is unknown:

- Likely related to cyclical lung injury; TGF-β from injured pneumocytes induces fibrosis.

- Many cases (approximately 15%) have no known cause and therefore classified as idiopathic pulmonary fibrosis (IPF). Insidious-onset progressive exertional dyspnea, pulmonary function tests showing a restrictive profile, and surgical biopsy showing extensive interstitial fibrosis together with paraseptal and subpleural cystic airspace enlargement (honeycomb lung) are characteristic of idiopathic pulmonary fibrosis. Repetitive injury and disordered healing are implicated as potential causes; lung injury results in focal loss of type 1 pneumocytes and hyperplasia of type 2 pneumocytes.

- The most common causes are environmental exposures (approximately 25%), sarcoidosis (approximately 20%), and collagen vascular diseases (approximately 10%).

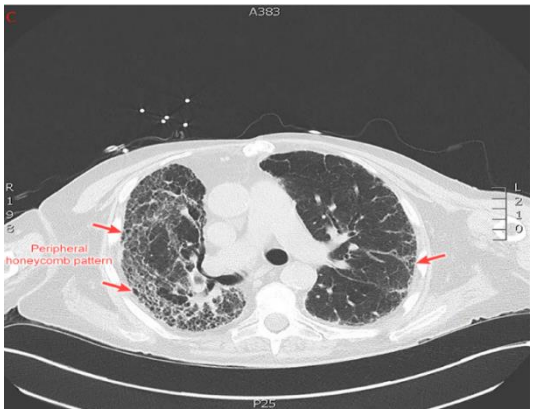
- Secondary causes of interstitial fibrosis such as drugs (bleomycin and amiodarone) and radiation therapy must be excluded.

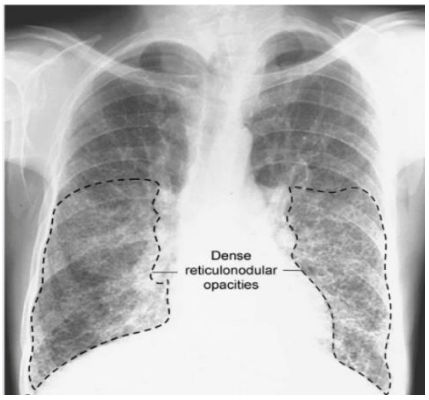
- Clinical features:

- Progressive dyspnea, cough and bilateral reticulonodular opacities on chest x-ray.

- Fibrosis on lung CT; initially seen in subpleural patches, but eventually results in diffuse fibrosis with end-stage 'honeycomb' lung.

- Treatment: lung transplantation.





❖ N.B:

- Rheumatoid arthritis can cause a variety of pulmonary manifestations; the most common is a form of interstitial lung disease similar to idiopathic interstitial pneumonia.
- Methotrexate is a drug frequently used for rheumatoid arthritis treatment that can also cause interstitial pneumonitis and fibrosis.

Pneumoconiosis

- Interstitial fibrosis due to occupational exposure; requires chronic exposure to small particles that are fibrogenic.
- Alveolar macrophages engulf foreign particles and induce fibrosis.
- Dust particles are constantly being inhaled and cleared by the respiratory tract.
- The clearance mechanisms utilized by the lung vary depending on the size of the particles:

- Particles 10-15 µm in size are trapped in the upper respiratory tract.
- Particles 2.5-10 µm in size enter the trachea and bronchi and are cleared by mucociliary transport.
- The finest particles (diameter less than 2 µm) reach the terminal bronchioli and alveoli and are phagocytized by macrophages.
- Alveolar macrophages that take up dust particles become activated and release a number of cytokines.
- Some of these cytokines induce injury and inflammation of alveolar cells, which stimulate fibroblasts to proliferate and produce collagen.
- Inflammation with subsequent fibrosis results.

- Coal workers' pneumoconiosis, silicosis, and asbestosis → ↑ risk of cor pulmonale, cancer, and Caplan syndrome (rheumatoid arthritis and pneumoconioses with intrapulmonary nodules).

A. Asbestosis:

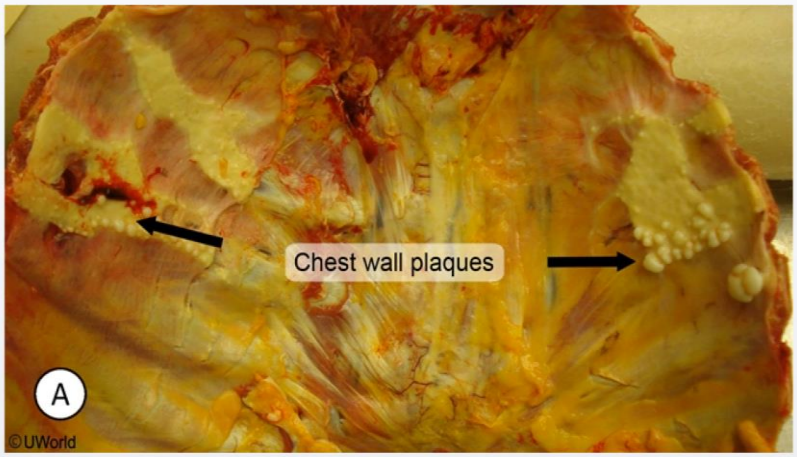
- Asbestos is a material with insulating properties used in shipbuilding, construction, and textile industries.
- Inhalation of fine asbestos fibers leads to epithelial cell injury, activation of macrophages, interstitial inflammation and fibrosis.
- Affects lower lobes.
- The main health sequelae of asbestos exposure are:

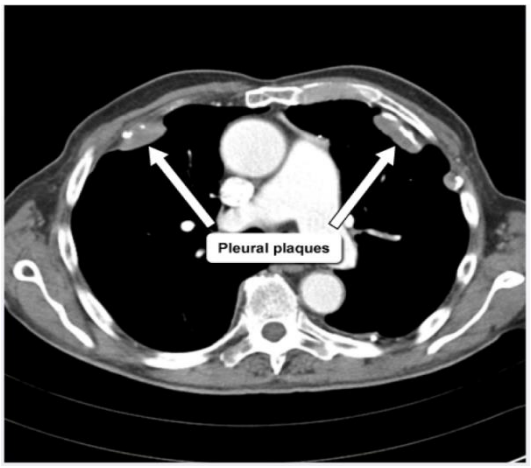
A. Pleural disease:

- Asbestos-related pleural disease presents with pleural thickening, calcified lesions (pleural plaques), and occasionally benign pleural effusions.
- Many patients are asymptomatic despite visible disease on imaging.

- Fibrocalcific plaques on the parietal pleura are a hallmark of asbestos exposure that typically affect the parietal pleura along the lower lungs and diaphragm.

- The plaques are composed of discrete circumscribed areas of dense collagen that frequently become calcified.

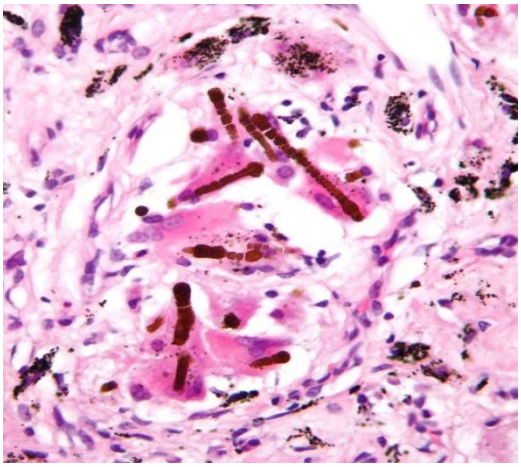




B. Pulmonary fibrosis:

- Asbestosis is characterized by progressive pulmonary fibrosis that is most predominant in the lower lobes and by the presence of asbestos bodies.

- Asbestos bodies (also called ferruginous bodies) are golden-brown fusiform rods resembling dumbbells, found in alveolar septum sputum sample, visualized using Prussian blue stain, often obtained by bronchoalveolar lavage.



C. Bronchogenic carcinoma:

- Bronchogenic carcinoma (malignant neoplasm arising from bronchial epithelium) develops in 25% of heavily exposed asbestos workers and is the most common cause of death in this population.

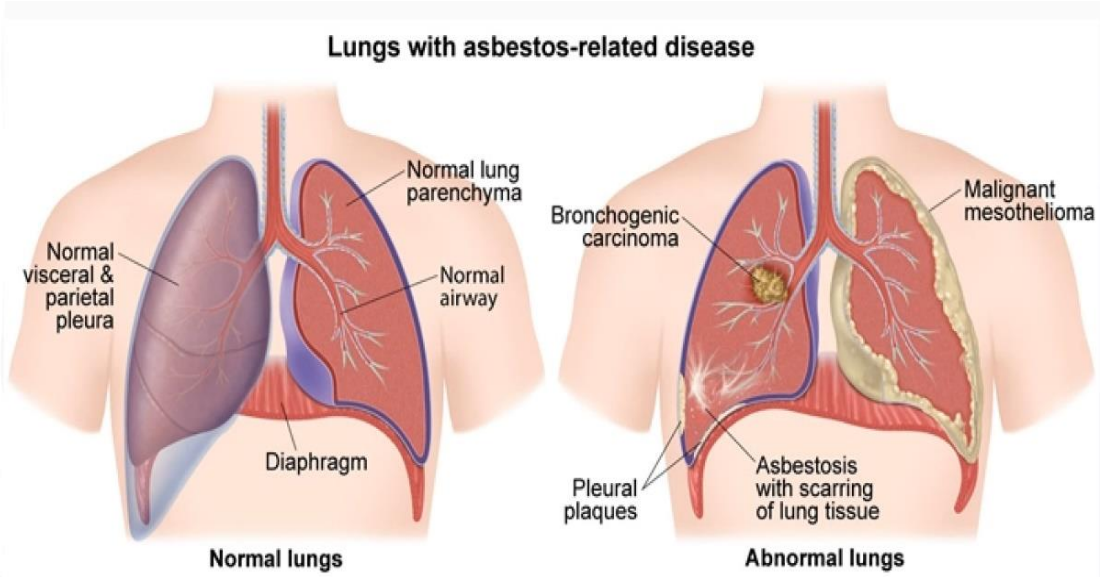
- Smoking and asbestos exposure have a synergistic effect on the development of lung carcinoma, increasing the risk from 6-fold in nonsmoking patients with asbestos exposure to 60-fold in asbestos-exposed patients who smoke regularly.

D. Malignant mesothelioma:

- It is a rare malignancy of the pleura for which asbestos is the only known environmental risk factor. Histopathology shows tumor cells with numerous long, slender microvilli and abundant tonofilaments.

- Immunohistochemistry is important for diagnosis; nearly all mesotheliomas stain positive for cytokeratins and may also stain positive for calretinin.

- It is less common than bronchogenic carcinoma in asbestos-exposed patients. However, mesothelioma is more specific for heavy asbestos exposure.



B. Berylliosis:

- Associated with exposure to beryllium in aerospace and manufacturing industries.

- Granulomatous on histology (noncaseating granuloma) and therefore occasionally responsive to steroids.

- Affects upper lobes.

C. Coal workers' pneumoconiosis:

- Prolonged coal dust exposure → macrophages laden with carbon → inflammation and fibrosis.

- Also known as black lung disease.

- Affects upper lobes.

- Anthracosis: asymptomatic condition found in many urban dwellers exposed to sooty air.

D. Silicosis:

- Associated with foundries, sandblasting, mines.

- Macrophages respond to silica and release fibrogenic factors, leading to fibrosis.

- It is thought that silica may disrupt phagolysosomes and impair macrophages, increasing susceptibility to TB.
- Affects upper lobes.
- Silicosis is distinguished by eggshell calcification of hilar nodes and birefringent silica particles surrounded by fibrous tissue.

❖ Mnemonic:

- Asbestos is from the roof (was common in insulation), but affects the base (lower lobes)
- Silica, beryllium, and coal are from the base (earth), but affect the roof (upper lobes).

Hypersensitivity pneumonitis

- Mixed type III/IV hypersensitivity reaction to environmental antigen → dyspnea, cough, chest tightness, headache.
- Often seen in farmers and those exposed to birds.
- Granulomatous reaction (noncaseating) to inhaled organic antigens (pigeon breeder's lung).
- Presents with fever, cough, and dyspnea hours after exposure; resolves with removal of the exposure.
- Chronic exposure leads to interstitial fibrosis.

❖ In a nutshell:

- Of the pneumoconioses that can cause exertional dyspnea and interstitial densities on chest x-ray:

- Silicosis is the only one that produces eggshell calcifications of hilar nodes and birefringent particles surrounded by fibrous tissue on histologic exam.
- Asbestosis is associated with calcified pleural plaques and ferruginous bodies.
- Berylliosis and hypersensitivity pneumonitis may produce noncaseating granulomas.
- Coal miner's lung is associated with perilymphatic accumulations of coal dust-laden macrophages.

Sarcoidosis

- Sarcoidosis is an inflammatory disease of unknown etiology that leads to development of non-caseating granulomas in many organs and tissues.

- It typically presents in young adults (women > men) and occurs more commonly in African Americans presenting with cough, night sweats, and bilateral hilar adenopathy (red arrows).

- Etiology is unknown; likely due to CD4' helper T-cell response to an unknown antigen.

- Sarcoidosis is a CD4 T-cell mediated disease, in which large numbers of CD4 lymphocytes release interferon-gamma and tumor necrosis factor-alpha to drive macrophage activation and granuloma formation.

- Bronchoalveolar lavage fluid in pulmonary sarcoidosis demonstrates a lymphocytic predominance with a high CD4/CD8 ratio.

- In sarcoidosis, non-caseating granulomas consist of aggregates of epithelioid cells (activated macrophages) and multinucleated giant cells consistent with chronic granulomatous inflammation.

- Granulomas most commonly involve the hilar lymph nodes and lung, leading to restrictive lung disease.

- Clinical features:

- Commonly, sarcoidosis is discovered in a completely asymptomatic patient, usually in the form of hilar adenopathy on chest x-ray.

- Lung involvement in sarcoidosis occurs in 90% of patients at some time in their course.

- In addition to pulmonary symptoms (cough, chest pain, dyspnea), constitutional symptoms (including fever, weight loss, fatigue, night sweats, and arthralgias) are common.

- Associated with Bell palsy, Uveitis, Granulomas (noncaseating epithelioid, containing microscopic Schaumann and asteroid bodies), Lupus pernio (skin lesions on face resembling lupus), Interstitial fibrosis (restrictive lung disease), Erythema nodosum, Rheumatoid arthritis-like arthropathy. A facial droop is UGLIER.

- Elevated serum ACE.

- Hypercalcemia (α_1 hydroxylase activity of epithelioid histiocytes converts vitamin D to its active form).

- Liver biopsy shows changes in up to 75% of cases, they are rarely symptomatic. Scattered granulomas are the most common liver pathology finding. Liver granulomas affect the portal triads to a greater degree than the lobular parenchyma.

- Diagnosis and treatment:

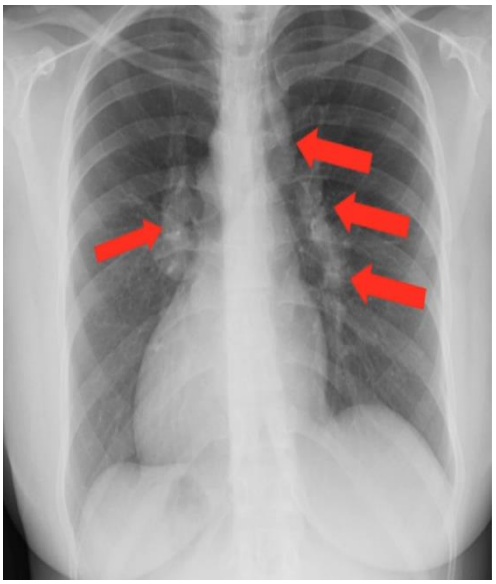
- Chest X-ray is essential for diagnosis.

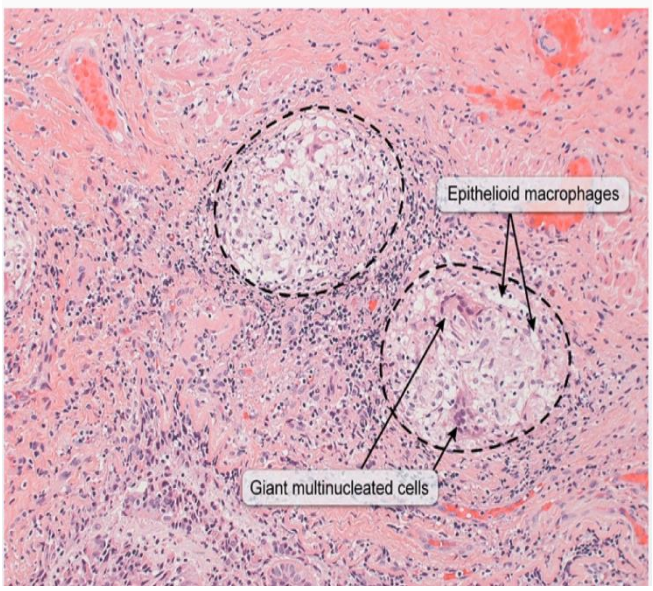
- Treatment is steroids; often resolves spontaneously without treatment.

❖ In a nutshell:

- An African American presenting with constitutional symptoms, bilateral hilar adenopathy (arrows), and pulmonary complaints is concerning for sarcoidosis.

- Histologically, non-caseating granulomas are seen, helping to distinguish sarcoidosis from tuberculosis infection.





Respiratory distress syndrome

Acute respiratory distress syndrome

- Causes: It can occur due to direct pulmonary trauma (pulmonary contusions, inhaled irritants) or indirect non-pulmonary insults (sepsis, burns, pancreatitis) that result in pulmonary epithelial and/or endothelial injury.

- Pathophysiology:
- Diffuse damage to the alveolar-capillary interface (diffuse alveolar damage).

- ARDS is characterized by bilateral pulmonary infiltrates and hypoxemia in the absence of heart failure.

- In ARDS, Endothelial damage → ↑ alveolar capillary permeability (leaky alveolocapillary membrane) → protein-rich leakage into alveoli → diffuse alveolar damage and noncardiogenic pulmonary edema (PCWP within the normal range 6-12).

- One of the minor diagnostic criteria for ARDS is absence of cardiogenic pulmonary edema, which means that the pulmonary capillary wedge pressure is usually normal.

- An elevated wedge pressure would be more suggestive of a cardiogenic (hemodynamic) cause of pulmonary edema, such as pulmonary venous hypertension.

- More severe involvement and/or atelectasis of regional alveoli can cause V/Q mismatch (decreased ventilation with maintained perfusion).

- Clinical features: Hypoxemia and cyanosis with respiratory distress: due to thickened diffusion barrier and collapse of air sacs (increased surface tension).

- Diagnosis:
- Diagnosis of exclusion with the following criteria (ARDS):
  - Abnormal chest X-ray (bilateral lung opacities). White-out' on chest x-ray.

  - Respiratory failure within 1 week of alveolar insult.

  - Decreased Pao_2/Fio_2 (ratio < 300, hypoxemia due to ↑ intrapulmonary shunting and diffusion abnormalities).

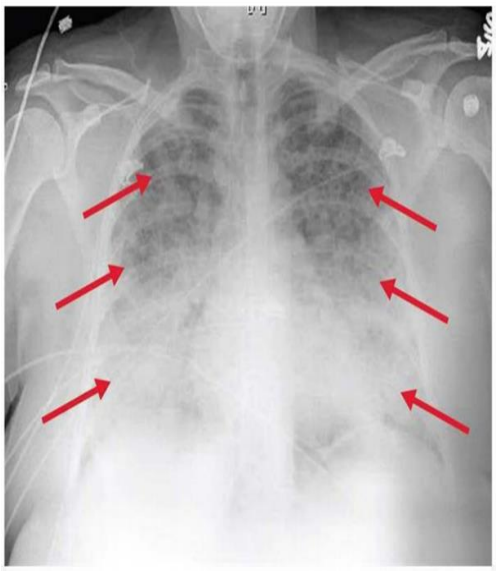
  - Symptoms of respiratory failure are not due to HF/fluid overload.

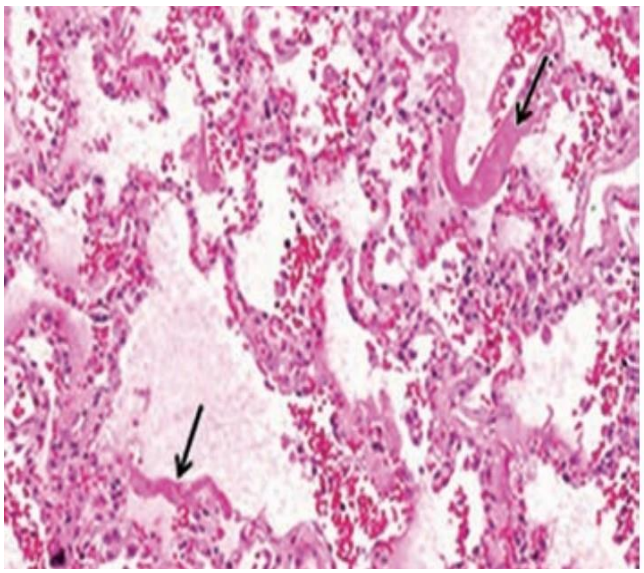
- Treatment:

- Address underlying cause.

- Mechanical ventilation with low tidal volumes and high PEEP.

- Recovery may be complicated by interstitial fibrosis; damage and loss of type 1 pneumocytes leads to scarring and fibrosis.





Acute respiratory distress syndrome	
Risk factors	• Sepsis, pneumonia • Trauma • Pancreatitis
Pathophysiology	• Cytokine release, endothelial activation • Neutrophil recruitment & degranulation in lung • ↑ Capillary permeability, alveolar fluid accumulation • Formation of hyaline membrane
Clinical features	• Hypoxia • Bilateral pulmonary infiltrates • Normal pulmonary capillary wedge pressure (6-12 mm Hg)

❖ N.B:

- Common consequences of left ventricle infarction include left ventricular failure, cardiogenic acute pulmonary edema, pulmonary venous hypertension (congestion), and transudate of plasma into the lung interstitium and alveoli.
- Histologically, cardiogenic acute pulmonary edema is represented by increased filtration of plasma water and electrolytes into the lung interstitium and alveoli.
- The fluid that accumulates is a transudate (an ultrafiltrate of plasma caused by hemodynamic changes) rather than an exudate (an extravasation not only of plasma water and small ions but also plasma protein components and circulating leukocytes, as seen in inflammatory states).

Neonatal respiratory distress syndrome

- Respiratory distress due to inadequate surfactant levels.

- Surfactant which is produced in type II pneumocytes, works to decrease the surface tension in alveoli, facilitating lung expansion during respiration.

- When there is insufficient surfactant, as in neonatal respiratory distress syndrome, the result is collapse of alveoli (atelectasis) due to increased surface tension and formation of hyaline membranes.

- Associated with:

- Prematurity:
  - Surfactant production begins at 28 weeks; adequate levels are not reached until 34 weeks.
  - Amniotic fluid lecithin to sphingomyelin ratio is used to screen for lung maturity.
  - Phosphatidylcholine (lecithin) levels increase as surfactant is produced; sphingomyelin remains constant. A ratio > 2 indicates adequate surfactant production.

- Caesarian section delivery: Due to lack of stress-induced steroids; steroids increase synthesis of surfactant.

- Maternal diabetes: Insulin decreases surfactant production.

- Clinical features:

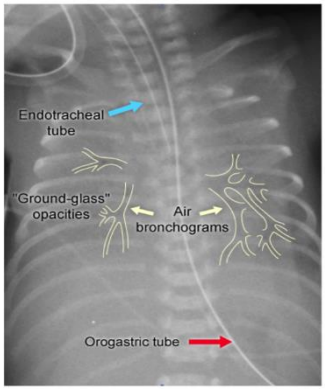
- Increasing respiratory effort after birth, tachypnea with use of accessory muscles, nasal flaring, and grunting.

- Hypoxemia with cyanosis.

- Diffuse granularity of the lung ('ground-glass' appearance) on x-ray.

- Prevention: Betamethasone or dexamethasone is administered to pregnant women at risk of premature delivery (before 34 weeks of gestation) to prevent neonatal respiratory distress syndrome.

- Treatment: Treatment involves administration of supplemental oxygen at high concentrations, nasal continuous positive airway pressure, and/or mechanical ventilation with intratracheal surfactant.



- Complications: Hypoxemia increases the risk for persistence of patent ductus arteriosus and necrotizing enterocolitis.

- Therapeutic supplemental O_2 can result in (RIB):

A. Retinopathy of prematurity:

- Temporary local hyperoxia in the retina is thought to induce changes that cause up-regulation of proangiogenic factors such as vascular endothelial growth factor (VEGF) upon return to room air ventilation.

- Retinal vessel proliferation (neovascularization) and possible retinal detachment with blindness may result.

- This complication of neonatal respiratory distress syndrome is referred to as retinopathy of prematurity.

B. Intraventricular hemorrhage.

C. Lung damage leads to bronchopulmonary dysplasia:

- Results from repeated insult to the neonatal lung from factors such as mechanical ventilation, prolonged oxygen exposure, and inflammation.

- Persistent oxygen requirement with tachypnea, rhonchi, and radiographic findings of haziness and decreased lung volumes.

- Surfactant therapy does not prevent BPD development but may reduce mortality from it. Most patients with BPD improve over 2-4 months; some develop pulmonary arterial hypertension

Pulmonary hypertension

- High pressure in the pulmonary circuit (mean arterial pressure > 25 mm Hg; normal is 10 -14 mm Hg)
- Characterized by atherosclerosis of the pulmonary trunk, smooth muscle hypertrophy of pulmonary arteries, and intimal fibrosis; plexiform lesions are seen with severe, long-standing disease.
- Leads to right ventricular hypertrophy with eventual cor pulmonale which can present elevated jugular venous pressure, hepatic congestion, and peripheral edema.
- Course: severe respiratory distress → cyanosis and RVH → death from decompensated cor pulmonale.
- Subclassified as primary or secondary based on etiology.

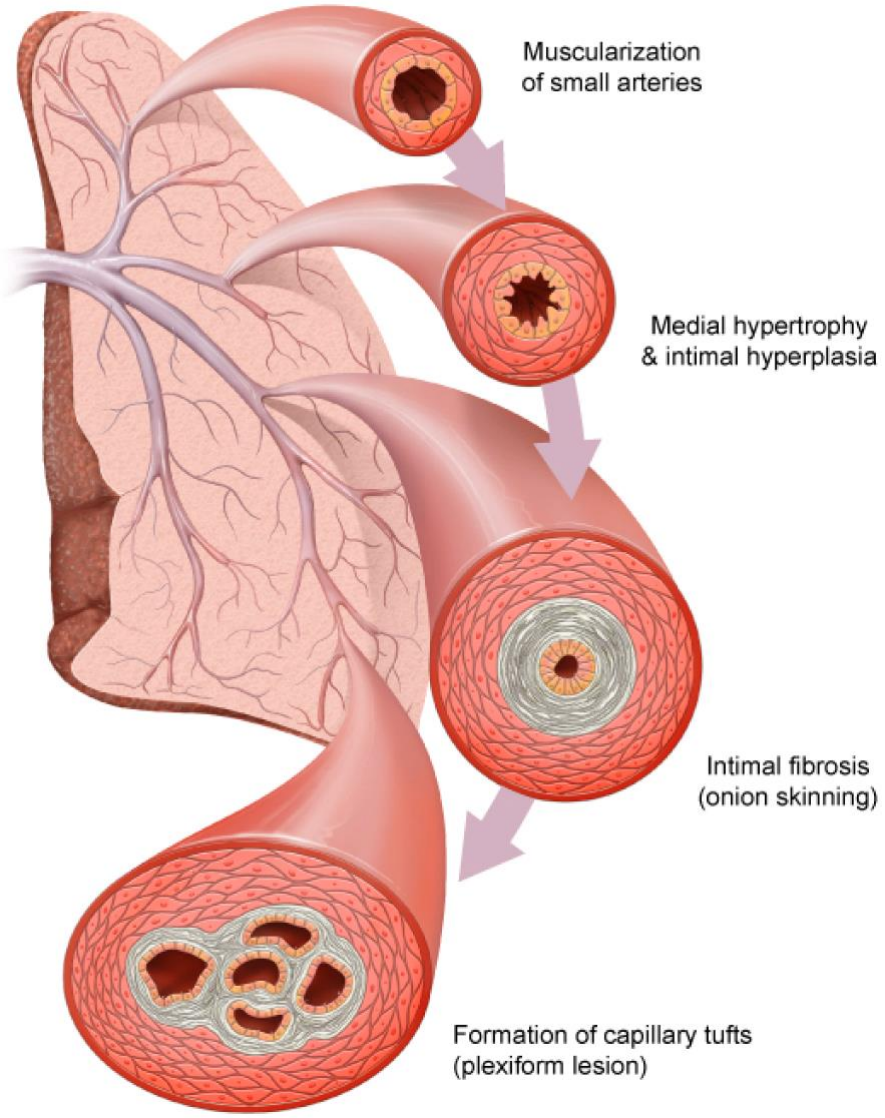
Primary pulmonary hypertension

- Classically seen in young adult females.
- It is thought to be due to an inherited (autosomal dominant with variable penetrance) inactivating mutation of bone morphogenetic protein receptor type 2 (BMPR2) as the first insult, which predisposes patients to pulmonary vascular disease.
- A second insult (infection, drugs, and ion channel defects) then activates the disease process, increasing endothelin (vasoconstrictor), decreasing nitric oxide (vasodilator), and decreasing prostacyclin (vasodilator and platelet inhibitor).
- The result is vasoconstriction, vascular smooth muscle proliferation, fibrosis, thrombosis of pulmonary arteries and arterioles, endothelial cell growth, and elevated pulmonary pressures.

Secondary pulmonary hypertension

- Due to hypoxemia (COPD and interstitial lung disease) or increased volume in the pulmonary circuit (congenital heart disease); may also arise with recurrent pulmonary embolism.
- Other causes include drugs (amphetamines, cocaine), connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis.
- Ingestion of fenfluramine, dexfenfluramine, and phentermine (appetite suppressants) for more than three months' duration has been associated with the development of secondary pulmonary hypertension.
- Pulmonary hypertension is a common complication of CREST syndrome. Microvascular injury of pulmonary arterioles leads to narrowing of the lumen and increased pressure in pulmonary circulation.

Pathogenesis of pulmonary arterial hypertension



Sleep apnea

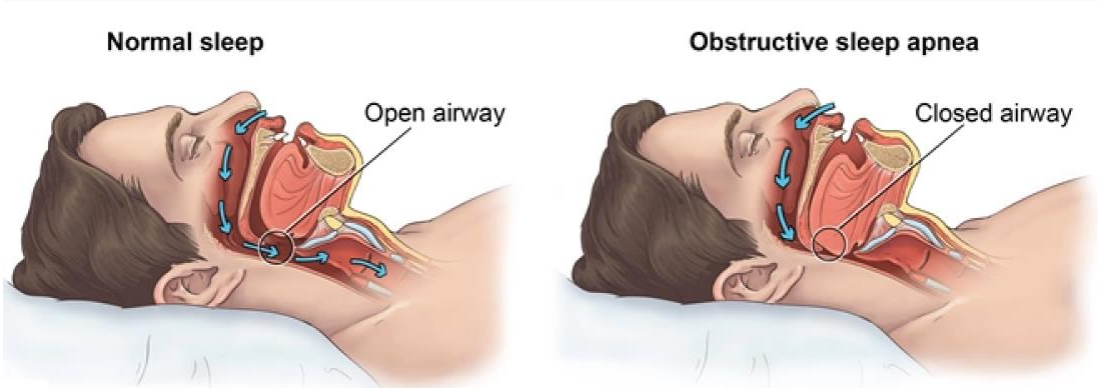
- Repeated cessation of breathing > 10 seconds during sleep → disrupted sleep → daytime somnolence.
- Nocturnal hypoxia → systemic/pulmonary hypertension, arrhythmias (atrial fibrillation/flutter), sudden death.
- Hypoxia → ↑ EPO release → ↑ erythropoiesis.

Obstructive sleep apnea

- Respiratory effort against airway obstruction.
- Normal PaO_2 during the day.
- Anatomical and neuromuscular mechanisms have been implicated in OSA:

- Anatomical mechanism is caused by excess parapharyngeal tissue in adults, adenotonsillar hypertrophy in children.
- Neuromuscular weakness as a pathogenic mechanism in OSA is supported by the fact that apneas occur only during sleep, a time of muscle relaxation. The upper airway dilator muscles weaken during the transition from wake to sleep, leading to airway narrowing and ultimately collapse in individuals with OSA.
- Stimulation of the hypoglossal nerve using an implantable nerve stimulator causes the tongue to move forward slightly, increasing the anteroposterior diameter of the airway.

- Associated with obesity, loud snoring.
- Signs and symptoms of recurrent nocturnal upper airway obstruction (snoring) and apnea (daytime sleepiness, poor energy) are characteristic of obstructive sleep apnea syndrome.
- Each nocturnal episode of reduced ventilation causes transient hypercapnea and hypoxemia in the patient.



- These blood gas derangements result in reflexive systemic and pulmonary vasoconstriction as well as sympathetic cardiac stimulation:

- Prolonged, untreated obstructive sleep apnea can cause pulmonary hypertension and right heart failure.

- More than 50% of patients with obstructive sleep apnea will eventually develop systemic hypertension, which is thought to be a consequence of chronic sympathetic cardiovascular stimulation and elevated plasma norepinephrine levels→ arrhythmias (atrial fibrillation/flutter), sudden death.

- Hypoxia → ↑ EPO release → ↑ erythropoiesis.

- Diagnosis confirmed by sleep study.

- Treatment: weight loss, CPAP, surgery.

Central sleep apnea

- No respiratory effort due to CNS injury/toxicity, HF, opioids.

- Treat with positive airway pressure.

Obesity hypoventilation syndrome

- Also known as Pickwickian syndrome.

- Obesity (BMI ≥ 30 kg/m^2) → hypoventilation (↓ respiratory rate) → ↑ $Paco_2$ during waking hours (retention), ↓PaO_2 and ↑ $PaCO_2$ during sleep.

- Obstructive sleep apnea (OSA) can exist alone or in combination with obesity hypoventilation syndrome (OHS).

- Patients with OSA in the absence of OHS experience hypoventilation only at night with transient hypoxia and hypercapnia that resolve while awake.

- However, in those with OHS, the physical restriction of the thoracic cavity caused by excess thoracic tissue continues throughout the day, resulting in chronic hypoxia and hypercapnia. In an effort to maintain a normal pH, the kidneys increase bicarbonate retention and decrease chloride reabsorption to create a compensatory metabolic alkalosis.

Lung cancer

- Most common cause of cancer mortality in the US; average age at presentation is 60 years.
- Risk factors include smoking, second-hand smoke, radon, asbestos, family history.
- Cancer risk is directly related to the duration and amount of smoking (pack/years).
- In the lung, metastases (usually multiple lesions) are more common than 1° neoplasms. Most often from breast, colon, prostate, and bladder cancer.
- Sites of metastases from lung cancer: adrenals, brain, bone (pathologic fracture), liver (jaundice, hepatomegaly).
- Benign lesions, which often occur in younger patients, can also produce a coin lesion. Examples include:

- Granuloma: often due to TB or fungus (especially Histoplasma).
- Bronchial hamartoma:
  - The most common benign lung tumor is a hamartoma (also called pulmonary chondroma).
  - A hamartoma is an excessive disorganized growth of a tissue type native to the organ of involvement.
  - The lung is the most common location.
  - Lung hamartomas often contain disorganized islands of mature hyaline cartilage, fat, smooth muscle and clefts lined by respiratory epithelium.
  - Hamartomas usually present as incidental findings on chest x-ray, with the appearance of a well-defined coin lesion with "popcorn calcifications."
  - This incidentally discovered solitary lung nodule (or "coin lesion") is probably benign, but malignant and metastatic disease must be ruled out via tissue biopsy.

- Presentation:

- Cough, hemoptysis, bronchial obstruction, wheezing, unexplained weight loss, pneumonic “coin” lesion on CXR or noncalcified nodule on CT.
- Imaging often reveals a solitary nodule (coin-lesion); biopsy is necessary for a diagnosis of cancer.

- Lung cancers are broadly divided into small cell and non-small cell carcinomas:

1. Small cell lung carcinoma:

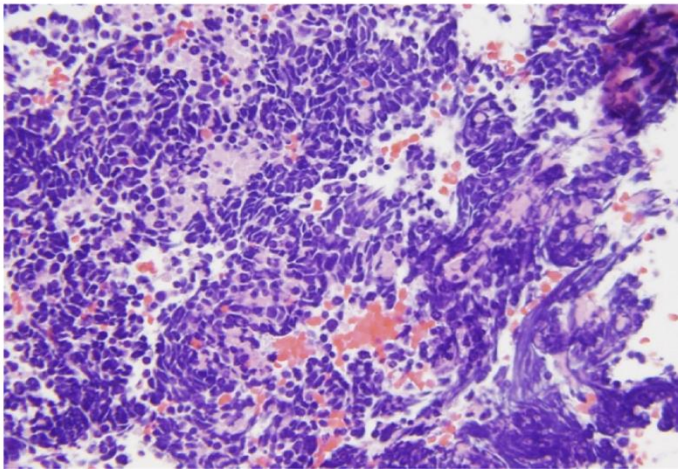
- Small cell lung carcinoma is also called undifferentiated or oat cell carcinoma arises from neuroendocrine (Kulchitsky) cells.

- On light microscopy, it is composed of round or oval dark blue cells with scant cytoplasm and large hyperchromatic nuclei. Abundant mitoses are usually seen.

- Small cell carcinomas can display varying degrees of neuroendocrine differentiation. These tumors stain for neuroendocrine markers, such as neural cell adhesion molecule (NCAM, also known as CD56), neuron-specific enolase, chromogranin, and synaptophysin.

- It comprises 15% of all malignant lung tumors.

- Small cell lung carcinoma is strongly associated with Smoking and is usually Sentral (centrally) located.



- Small cell carcinomas frequently synthesize hormones or hormone-like substances:

- ACTH leading to Cushing syndrome.

- ADH leading to syndrome of inappropnate antidiuretic hormone secretion.

- Antibodies against presynaptic Ca channels (Lambert Eaton myasthenic syndrome) or neurons (paraneoplastic myelitis, encephalitis, subacute cerebellar degeneration).

- Amplification of myc oncogenes also common.

- Small cell carcinoma is the most aggressive type of lung cancer. It is highly invasive; the majority of patients have distant metastases at the time of diagnosis.

- For this reason, there is no role for surgery in the treatment of small cell carcinomas, even when the disease is localized.

- These tumors are sensitive to chemotherapy and radiation. Even with treatment, however, the 5-year survival is very low (< 10%).

- All other lung cancer subtypes can be treated with surgery when the disease is localized.

2. Non-small cell:

- Non-small cell carcinoma is far more common than small cell carcinoma.

- Non-small cell lung cancers are further divided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

- Non-small cell carcinomas can be treated with surgery if they are localized; small cell carcinoma is treated with chemotherapy and radiation.

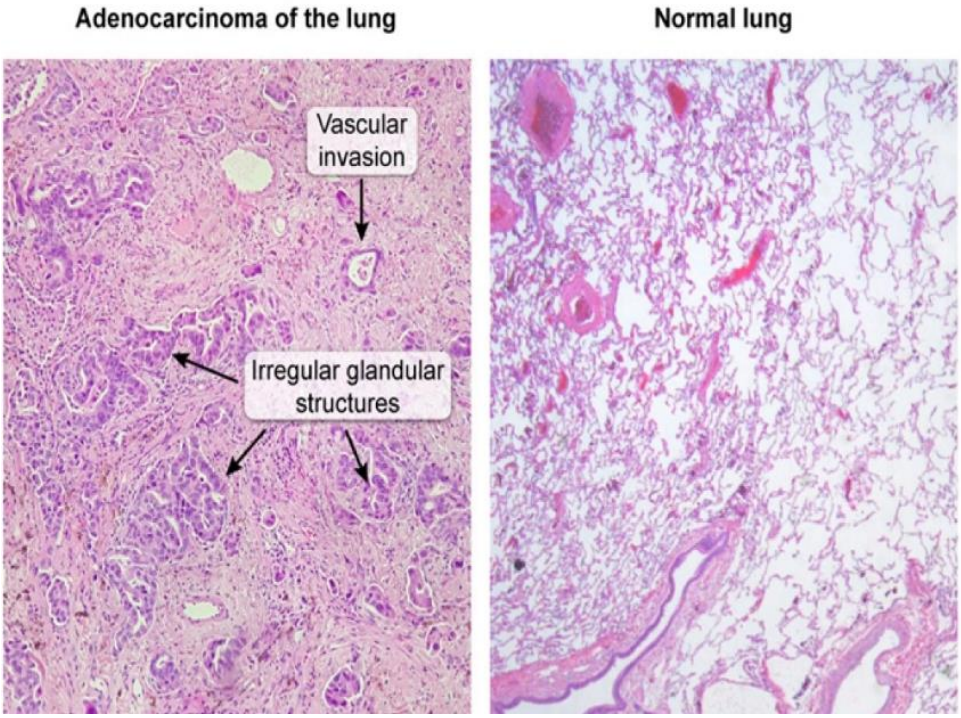
A. Adenocarcinoma:

- Adenocarcinoma is the most common primary lung cancer overall, occurring most frequently in women and nonsmokers.

- It is located peripherally and consists of tumor cells that form glandular or papillary structures.

- Associated with hypertrophic osteoarthropathy and clubbing.

- Adenocarcinoma arises from the alveolar epithelium and is characterized by invasive cells with abundant cytoplasm and eccentrically placed nuclei that form irregular glandular elements; mucin production is common. often stains mucin ⊕



- Adenocarcinoma in situ (bronchioloalveolar carcinoma):

- Adenocarcinoma in situ (formerly known as bronchioloalveolar carcinoma) is one of the major subtypes of lung adenocarcinoma.

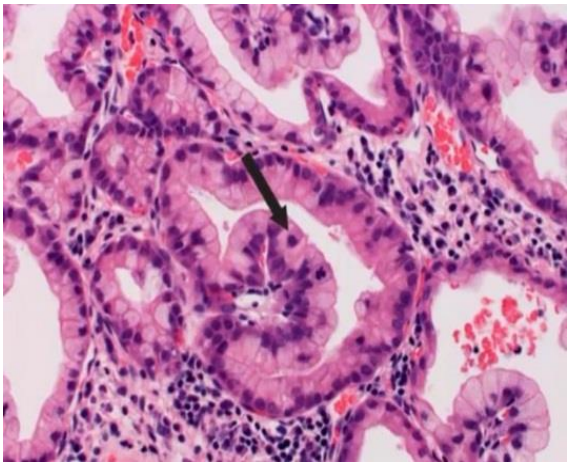
- This uncommon tumor occurs in non-smoker.

- The tumor arises from the alveolar epithelium and is located at the periphery of the lung. It is considered a preinvasive lesion characterized by growth along Intact alveolar septa without vascular or stromal invasion.

- Microscopic examination reveals well-differentiated, dysplastic columnar cells with or without intracellular mucin (compare to normal lung).

- The tumor has a tendency to undergo aerogenous spread (along the airways) and can progress to invasive disease if not resected.

- Imaging shows a discrete mass or pneumonia-like consolidation.

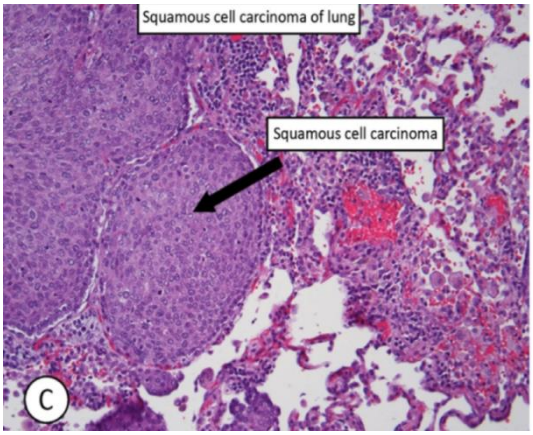


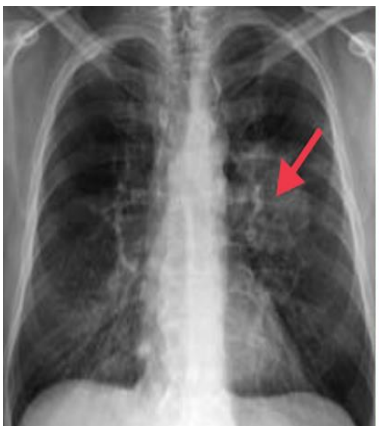
B. Squamous cell carcinoma:

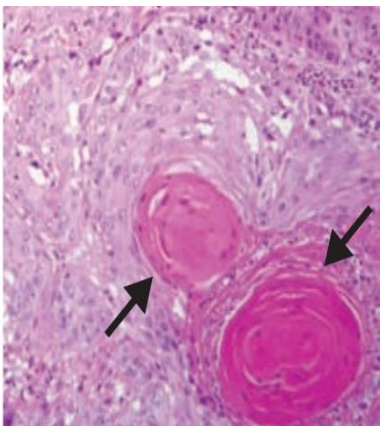
- Hilar mass arising from bronchus; Cavitation; Cigarettes; hyperCalcemia (produces PTHrP).

- Microscopic examination reveals Keratin pearls and intercellular bridges.

- Central.







C. Large cell carcinoma:

- Highly anaplastic undifferentiated tumor (no keratin pearls, or intercellular bridges, or glands, or mucin).
- Poor prognosis.
- Microscopic examination reveals Pleomorphic giant cells.
- Can secrete β-hCG → Gynecomastia and galactorrhea.
- Peripheral.
- Less responsive to chemotherapy; removed surgically.

3. Bronchial carcinoid tumor:

- Excellent prognosis; metastasis rare.
- Symptoms due to mass effect or carcinoid syndrome (flushing, diarrhea, wheezing).
- Nests of neuroendocrine cells; chromogranin ⊕.
- SPHERE of complications of lung cancer:

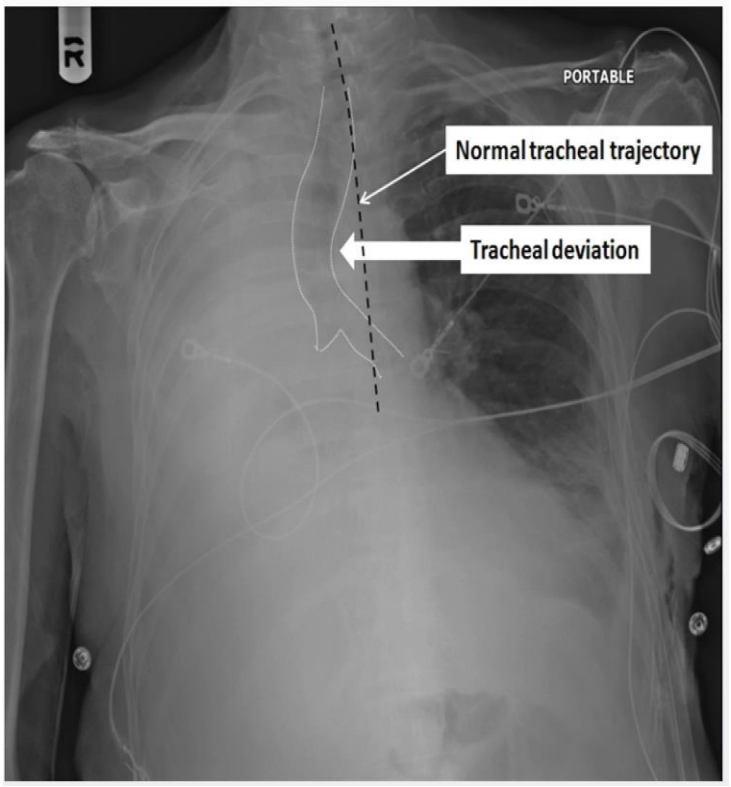
- Superior vena cava syndrome.
- Pancoast tumor.
- Horner syndrome (Compression of sympathetic chain).
- Endocrine (paraneoplastic).
- Recurrent laryngeal nerve compression (hoarseness).
- Effusions (pleural or pericardial).

Type of tumor	Incidence	Location	Clinical associations
Adenocarcinoma	40%-50%	• Peripheral	• Clubbing • Hypertrophic osteoarthropathy
Squamous cell carcinoma	20%-25%	• Central • Necrosis & cavitation	• Hypercalcemia
Small cell carcinoma	10%-15%	• Central	• Cushing syndrome • SIADH • Lambert-Eaton syndrome
Large cell carcinoma	5%-10%	• Peripheral	• Gynecomastia • Galactorrhea

SIADH = syndrome of inappropriate antidiuretic hormone.

❖ N.B:

- An obstructive lesion in a mainstem bronchus due to central lung tumors can prevent ventilation of an entire lung, leading to obstructive atelectasis and complete lung collapse.
- Characteristic findings on chest x-ray include unilateral pulmonary opacification and deviation of the mediastinum toward the opacified lung.
- Other mediastinal structures (heart, esophagus, great vessels) may also shift in the same direction.
- The loss of radiolucent air, combined with shifting of organs into the hemithorax appears as a completely opacified hemithorax on chest x-ray.



Pancoast syndrome (superior sulcus tumor)

- Pancoast syndrome is caused by a tumor at the lung apex.

- Tumors of the lung apex most often arise in the superior sulcus (the groove formed by the subclavian vessels). The apical location allows an extensive local tumor spread.

- This neoplasm can invade the multiple neck structures and cause the following symptoms:

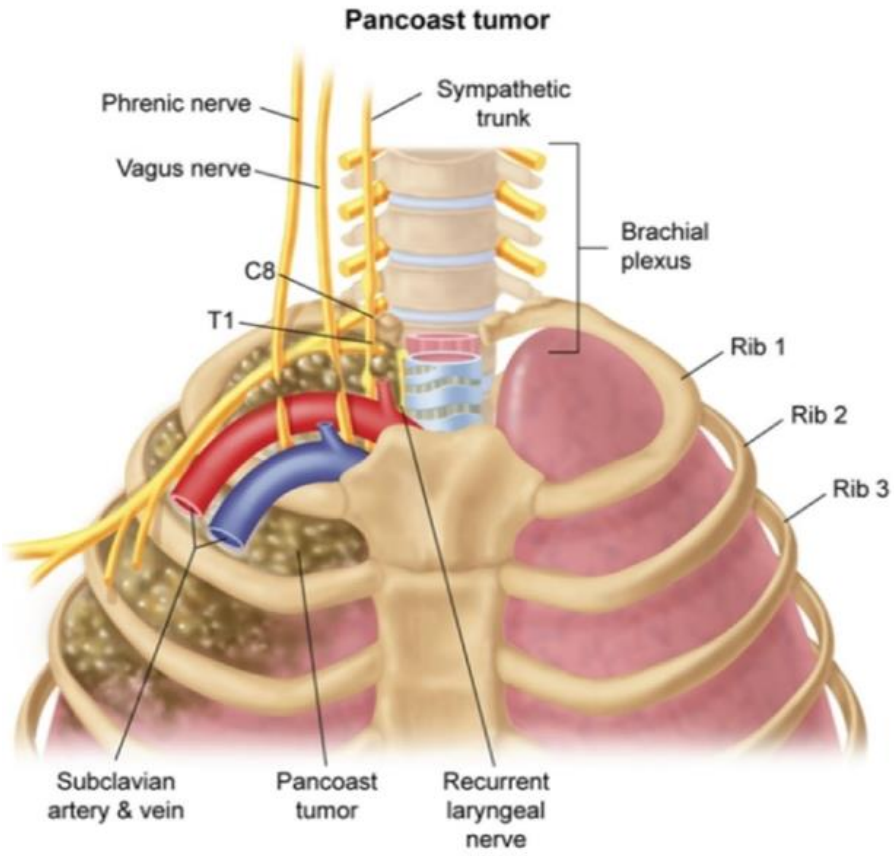
1. Severe pain in the shoulder region that radiates toward the axilla and scapula is the most common presenting symptom. It occurs due to involvement of the lower brachial plexus. Other associated symptoms include arm paresthesia, weakness, and muscle atrophy.

2. Homer's syndrome occurs due to involvement of the cervical sympathetic ganglia. Symptoms include ipsilateral ptosis, miosis and anhydrosis.

3. Compression of the subclavian vessels may cause edema of the upper extremity.

4. Extension of the tumor into the intervertebral foramina may lead to spinal cord compression and paraplegia.

5. Involvement of recurrent laryngeal (hoarseness) or phrenic (diaphragmatic paralysis) nerve.



Superior vena cava syndrome

- Causes:

- Compression of the superior vena cava causes a combination of symptoms called superior vena cava syndrome.

- Lung cancer, followed by non-Hodgkin lymphoma (Mediastinal mass), is the most common cause of superior vena cava syndrome.

- The superior vena cava provides venous drainage for the head, neck, upper trunk, and upper extremities.

- It is formed by the union of the right and left brachiocephalic veins behind the 1st costal cartilage on the right. It extends inferiorly for 6-8 cm and drains directly into the right atrium.

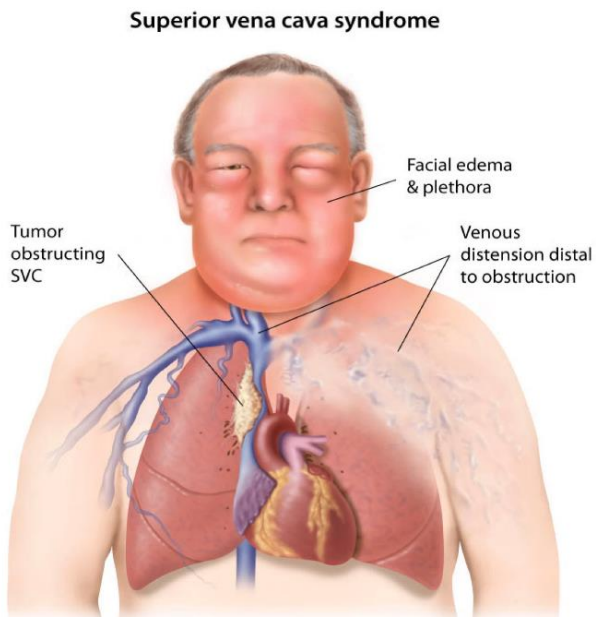
- It is surrounded by the sternum, trachea, right bronchus, aorta, and pulmonary artery. The vein also lies in close proximity to the perihilar and paratracheal lymph nodes. It has thin walls and is easily compressed by mediastinal masses.

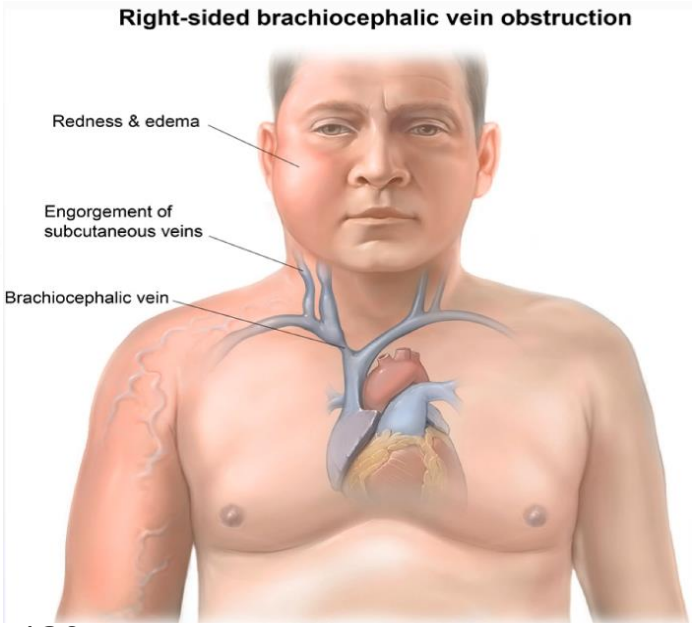
- Presentation:

- Affected patients complain of dyspnea, cough, and swelling of the face (facial plethora), neck (jugular venous distention), and upper extremities.

- Headaches, dizziness, and confusion may occur due to cerebral edema and elevated intracranial pressure. ↑ risk of aneurysm/rupture of intracranial arteries

- The brachiocephalic vein drains the ipsilateral jugular and subclavian veins. The bilateral brachiocephalic veins combine to form the superior vena cava (SVC). Brachiocephalic vein obstruction causes symptoms similar to those seen in SVC syndrome, but only on one side of the body.

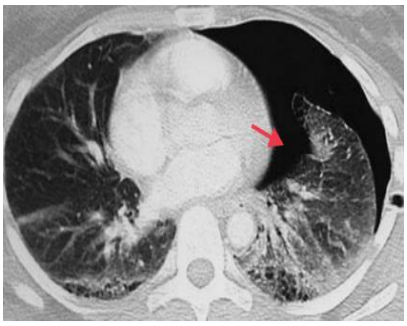




Pleura

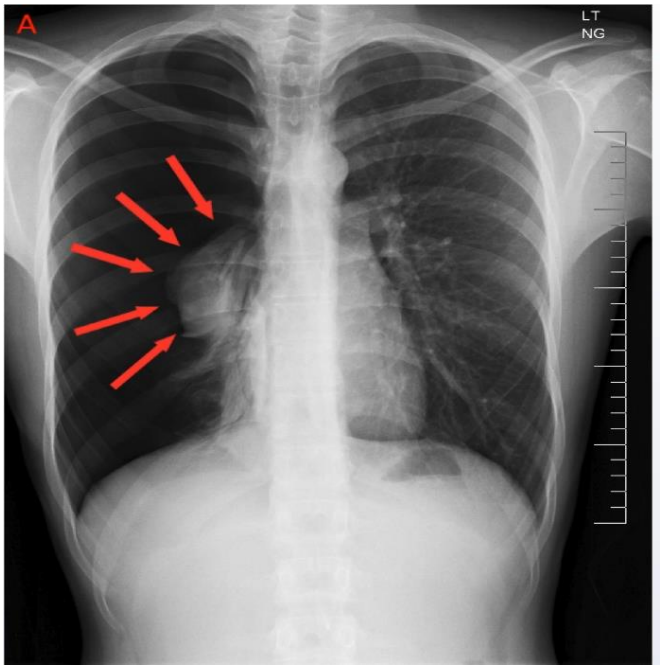
Pneumothorax

- Accumulation of air in the pleural space.
- Unilateral chest pain and dyspnea, ↓ tactile fremitus, hyperresonance, diminished breath sounds, all on the affected side.



A. Primary spontaneous pneumothorax:

- Primary spontaneous pneumothorax is defined as a pneumothorax in someone without pre-existing pulmonary disease and not caused by trauma or barotrauma.
- Rupture of apical subpleural blebs is the most common cause of primary spontaneous pneumothorax.
- Occurs most frequently in tall, thin, young males.
- Results in collapse of a portion of the lung; trachea shifts to the side of collapse.

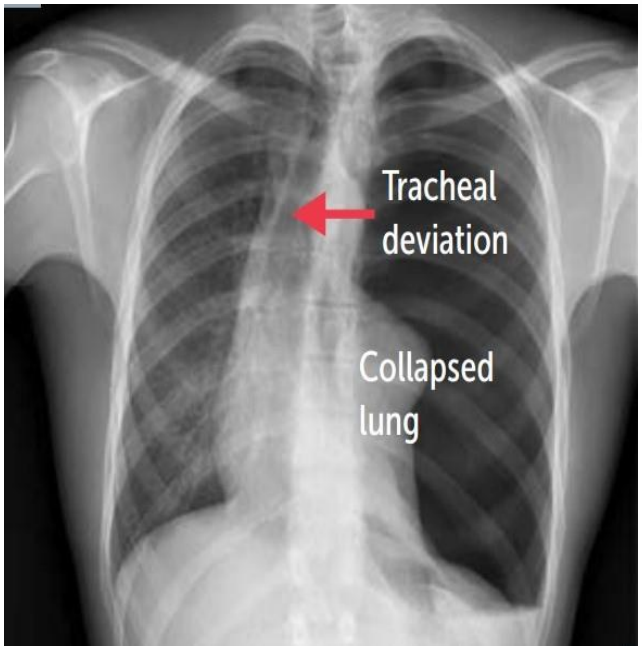


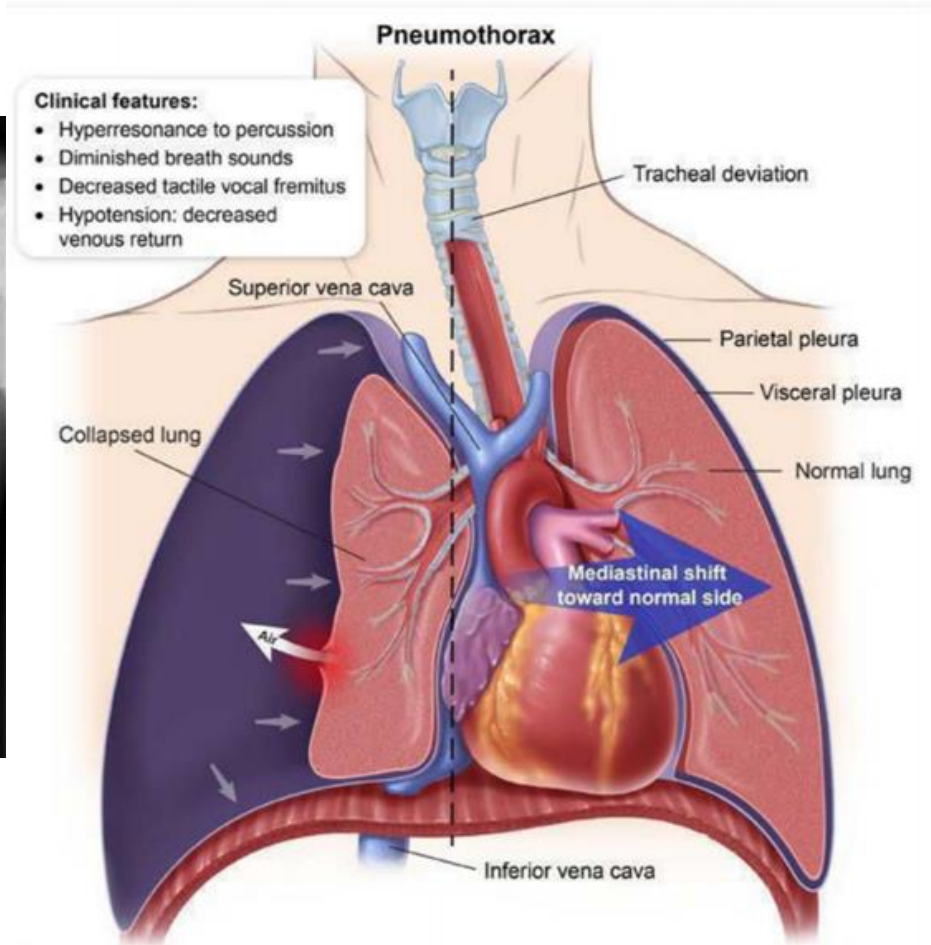
B. Secondary spontaneous pneumothorax: Due to diseased lung (bullae in emphysema, infections), mechanical ventilation with use of high pressures → barotrauma.

C. Traumatic pneumothorax: Caused by blunt (rib fracture) or penetrating (gunshot) trauma.

D. Tension pneumothorax:

- Can be any of the above.
- It develops when injured tissue forms a one-way valve allowing air to enter the pleural space but preventing it from escaping naturally.
- Increasing trapped air → tension pneumothorax.
- Trachea deviates away from affected lung.
- May lead to increased intrathoracic pressure → mediastinal displacement → kinking of IVC → ↓ venous return → ↓ cardiac output.
- Needs immediate needle decompression and chest tube placement.





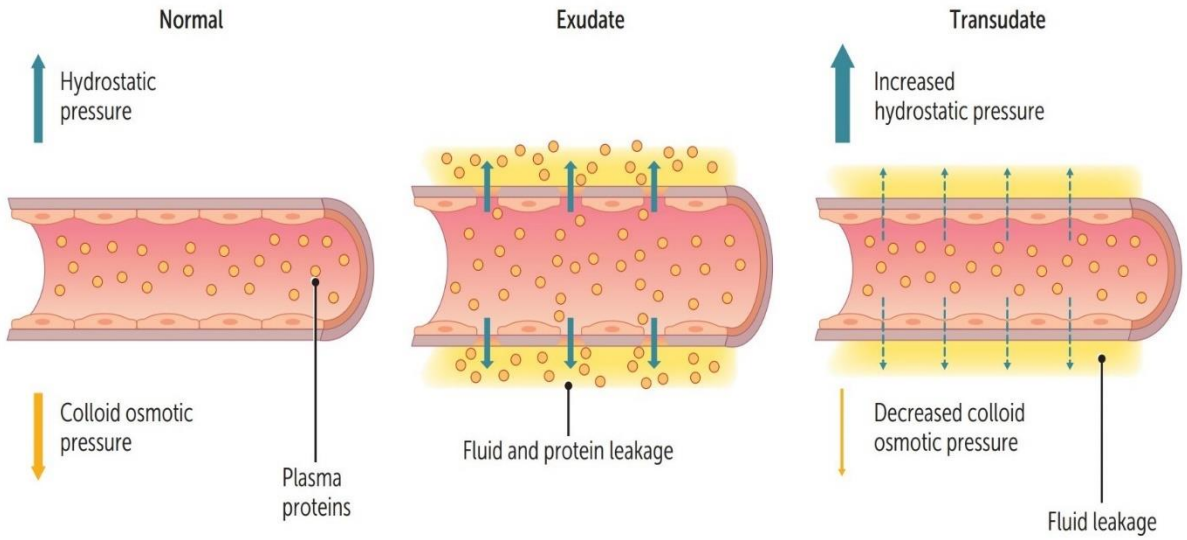
Pleural effusions

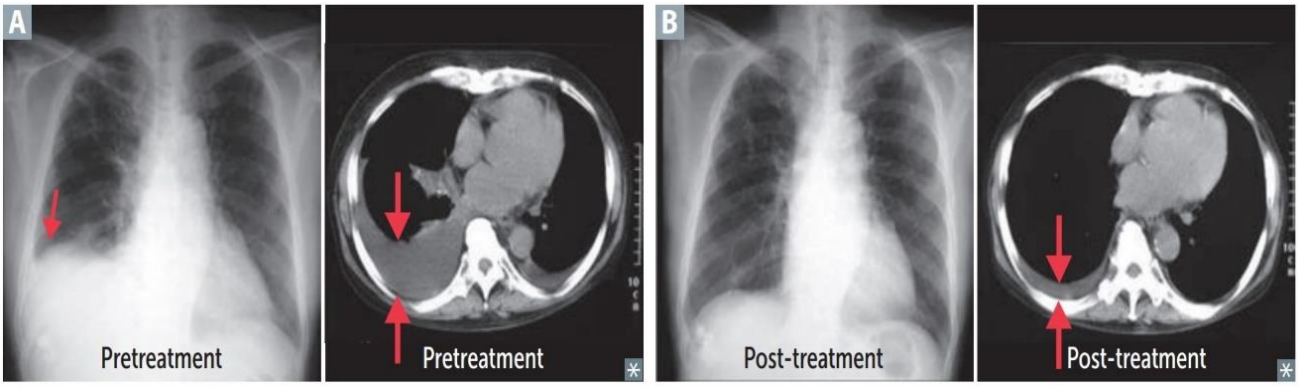
- Excess accumulation of fluid between pleural layers → restricted lung expansion during inspiration.
- Under normal physiologic conditions, pleural fluid enters the pleural space from parietal pleural microvessels and is removed by lymphatics at a constant rate.
- Pathologic states that disrupt pleural capillary hydrostatic or oncotic pressure, decrease pleural space pressure, reduce lymphatic drainage, or increase vascular membrane permeability can lead to pleural effusion.
- Can be treated with thoracentesis to remove fluid.

A. Transudate:
- ↓ protein content, clear (hypocellular).
- Due to ↑ hydrostatic pressure (HF) or ↓ oncotic pressure (nephrotic syndrome, cirrhosis).

B. Exudate:
- ↑ protein content, cloudy (cellular).
- Develop due to inflammation and consequent increased vascular membrane permeability (malignancy, pneumonia, collagen vascular disease, trauma).
- Must be drained due to risk of infection.

C. Lymphatic:
- Also known as chylothorax.
- Due to thoracic duct injury from trauma or malignancy.
- Milky appearing fluid; ↑ triglycerides.





❖ N.B:

1. The Light criteria are used to differentiate transudative and exudative pleural effusions and aid in the differential diagnosis.

- Transudative effusions have a low fluid-to-serum ratio of total protein and lactate dehydrogenase and low absolute levels of lactate dehydrogenase.
- In contrast, exudative effusions have a high fluid-to-serum ratio of total protein (>0.5) or lactate dehydrogenase (>0.6) or high absolute levels of lactate dehydrogenase (>2/3 the serum upper limit of normal).

Exudative & transudative pleural effusions

	Exudate	Transudate
Light criteria	• Pleural fluid protein/serum protein ratio >0.5 OR • Pleural fluid LDH/serum LDH ratio >0.6 OR • Pleural fluid LDH >two-thirds upper limit of normal of serum LDH	• Exudate criteria not met
Pathophysiology	• Inflammation	• Hydrostatic or oncotic pressure
Common causes	• Infection (eg, pneumonia) • Malignancy • Rheumatologic disease	• Heart failure • Cirrhosis (hepatic hydrothorax) • Nephrotic syndrome

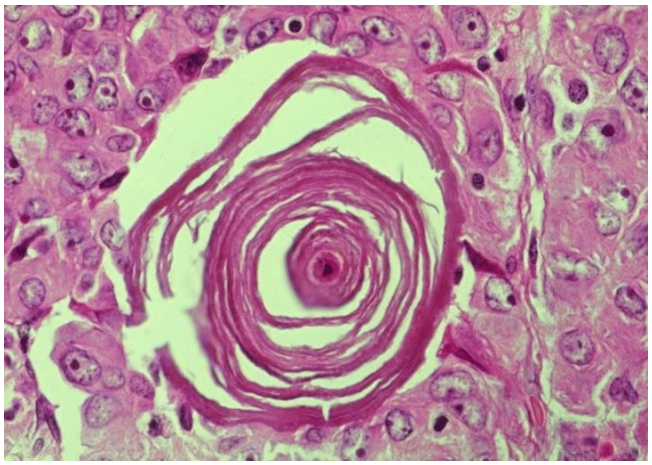
LDH = lactate dehydrogenase.

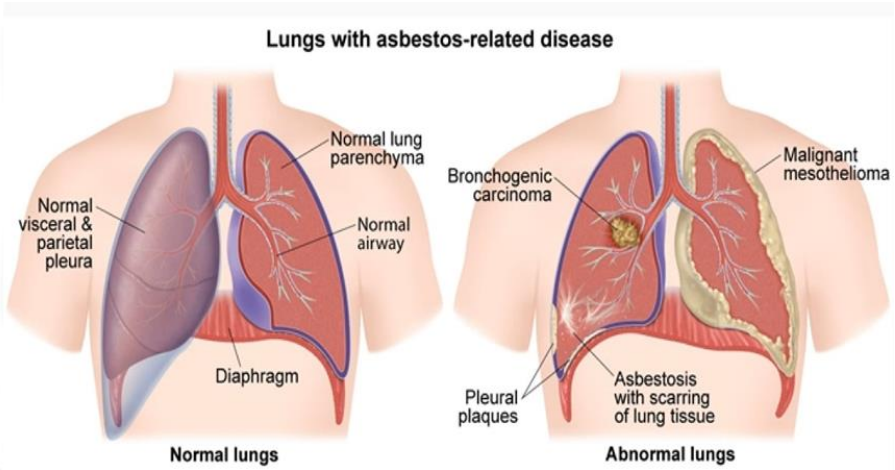
2. Parapneumonic effusions occur frequently in bacterial pneumonia as a result of exudative fluid accumulation within the pleural space.

- Infections and other forms of inflammatory tissue injury cause increased vascular permeability, leading to the formation of protein-rich exudates that contain a variety of biologically active substances.
- Under the influence of inflammatory stimuli, cell membrane phospholipids release arachidonic acid, a precursor to the eicosanoid inflammatory mediators (prostanoids, leukotrienes, lipoxins).
- The most potent chemotactic eicosanoid is leukotriene B_4. Leukotriene B_4 stimulates neutrophil migration to sites of inflammation. Other important chemotactic agents include component C5a, and IL-8.

Mesothelioma

- Malignancy of the pleura associated with asbestosis.
- Body cavities (pleural, peritoneal and pericardial) are lined with mesothelium.
- Mesothelioma is a malignant neoplasm arising from mesothelial cells.
- This tumor is extremely rare.
- Smoking is not a risk factor. Asbestos exposure is the only significant risk factor.
- The symptoms of mesothelioma include dyspnea and chest pain. Hemorrhagic pleural effusions are frequently present.
- Hemorrhagic pleural effusions and pleural thickening are characteristic. Histopathology reveals tumor cells with numerous, long slender microvilli and abundant tonofilaments.
- Psammoma bodies seen on histology.
- Cytokeratin and calretinin ⊕ in almost all mesotheliomas, ⊖ in most carcinomas.





Mediastinal pathology

- Normal mediastinum contains heart, thymus, lymph nodes, esophagus, and aorta.

Mediastinal masses

- Some pathologies (lymphoma, lung cancer, abscess) can occur in any compartment, but there are common associations:

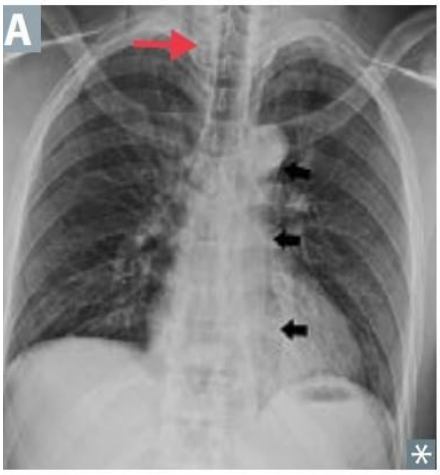
- Anterior (4T's): Thyroid (substernal goiter), Thymic neoplasm, Teratoma, "Terrible" lymphoma.
- Middle: esophageal carcinoma, metastases, hiatal hernia, bronchogenic cysts.
- Posterior: neurogenic tumor (neurofibroma), multiple myeloma.

Mediastinitis

- Inflammation of mediastinal tissues.
- Acute mediastinitis: Commonly due to postoperative complications of cardiothoracic procedures (≤ 14 days), esophageal perforation, or contiguous spread of odontogenic/retropharyngeal infection.
- Chronic mediastinitis:
  - Also known as fibrosing mediastinitis; due to ↑ proliferation of connective tissue in mediastinum.
  - Histoplasma capsulatum is common cause.
- Clinical features: fever, tachycardia, leukocytosis, chest pain, and sternal wound drainage.

Pneumomediastinum

- Presence of gas (usually air) in the mediastinum (black arrows show air around the aorta, red arrow shows air dissecting into the neck).
- Can either be spontaneous (due to rupture of pulmonary bleb) or 2° (trauma, iatrogenic, Boerhaave syndrome).
- Ruptured alveoli allow tracking of air into the mediastinum via peribronchial and perivascular sheaths.
- Clinical features: Chest pain, dyspnea, voice change, subcutaneous emphysema, ⊕ Hamman sign (crepitus on cardiac auscultation).



Atelectasis

- Alveolar collapse.

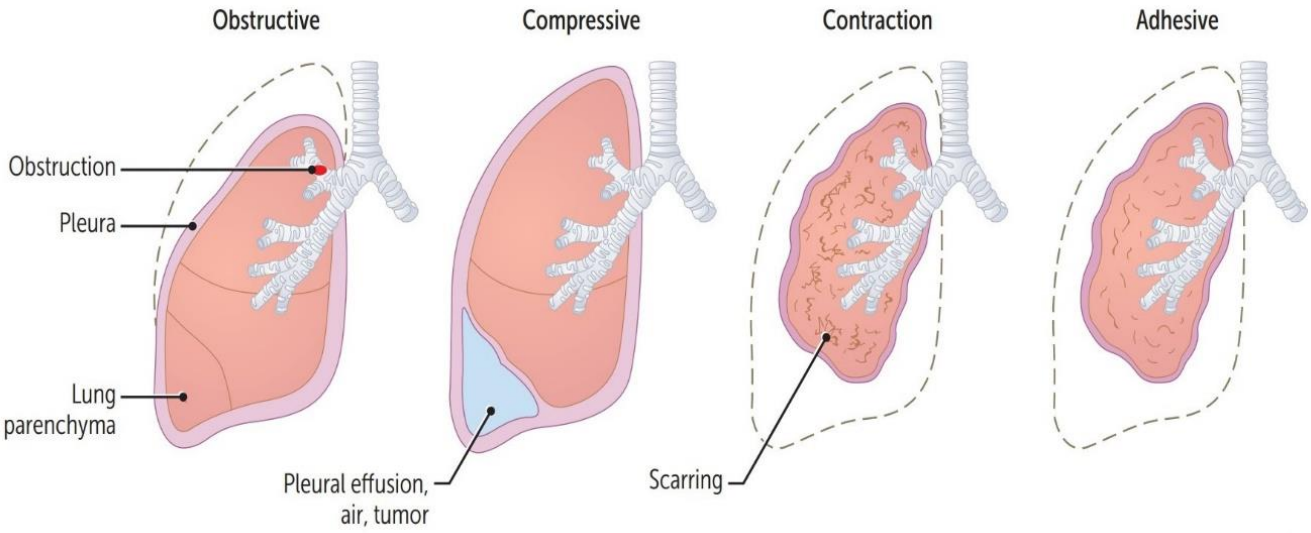
- Multiple causes:

A. Obstructive: airway obstruction prevents new air from reaching distal airways, old air is resorbed (foreign body, mucous plug, tumor).

B. Compressive: external compression on lung decreases lung volumes (space-occupying lesion, pleural effusion).

C. Contraction (cicatrization): scarring of lung parenchyma that distorts alveoli (sarcoidosis).

D. Adhesive: due to lack of surfactant (NRDS in premature babies).



Lung (physical findings)

Abnormality	Breath sound	Percussion	Fremitus	Tracheal deviation
Pleural effusion	↓	Dull	↓	-- or away from side of lesion (if large)
Atelectasis (bronchial obstruction)	↓	Dull	↓	Toward side of lesion
Simple pneumothorax	↓	Hyperresonant	↓	----
Tension pneumothorax	↓	Hyperresonant	↓	Away from side of lesion
Consolidation (lobar pneumonia, pulmonary edema)	Bronchial breath sounds; late inspiratory crackles	Dull	↑	----

- Excess fluid within the pleural space acts to insulate vibrations and breath sounds that originate in the airways of the lungs. Consequently, tactile fremitus, the transmission of vibration from vocalized sound (saying "ninety-nine"), is decreased over a pleural effusion.
- Breath sounds are also decreased or absent.
- The high density of pleural fluid compared to normal lung (alveolus-air composite) causes dullness to percussion over the effusion.

CHAPTER 4

Pharmacology

Antihistamines

- Reversible inhibitors of H_1 histamine receptors.

A. First generation drugs:
- Diphenhydramine, dimenhydrinate, chlorpheniramine. Names contain "-en/-ine" or "-en/-ate".
- Clinical uses: Allergy, motion sickness, sleep aid.
- Adverse effects: Sedation (additive with other CNS depressants), antimuscarinic, anti-α-adrenergic.

B. Second generation drugs:
- Loratadine, fexofenadine, desloratadine, cetirizine, meclizine. Usually end in "-adine".
- Clinical uses: Allergy.
- Adverse effects: Far less sedating than 1st generation because of ↓ entry into CNS.

Expectorants

A. Guaifenesin:
- Expectorant: thins respiratory secretions; does not suppress cough reflex.

B. N-acetylcysteine:
- Mucolytic: N-acetylcysteine is a mucolytic agent that loosens the thick sputum by cleaving disulfide bonds within mucus glycoproteins.
- Also used as an antidote for acetaminophen overdose.

Dextromethorphan

- Mechanism of action: Synthetic codeine analog antagonizes NMDA glutamate receptors.
- Clinical use: Antitussive.
- Side effects:

- Has mild opioid effect when used in excess.
- Mild abuse potential. Naloxone can be given for overdose.
- May cause serotonin syndrome if combined with other serotonergic agents.

Pseudoephedrine, phenylephrine

- Mechanism of action: α-adrenergic agonists, used as nasal decongestants.

- Clinical use: Reduce hyperemia, edema, nasal congestion; open obstructed eustachian tubes. Pseudoephedrine also illicitly used to make methamphetamine.

- Adverse effects:
  - Hypertension.

  - Can also cause CNS stimulation/anxiety (pseudoephedrine).

Treatment of pulmonary hypertension

1. BosENtan:
- Mechanism of action:
  - Competitively antagonizes ENdothelin-1 receptors → ↓ pulmonary vascular resistance.

  - Endothelin is a potent vasoconstrictor and stimulant of endothelial proliferation.

  - Administered orally

- Side effects:
  - Associated with vasodilation (headache, flushing, hypotension).

  - Hepatotoxic (monitor LFTs).

- Contraindication: pregnancy.

2. Sildenafil:
- Mechanism of action: Inhibits cGMP PDE-5 and prolongs vasodilatory effect of nitric oxide.

- Also used to treat erectile dysfunction.

- Contraindicated when taking nitroglycerin or other nitrates (due to risk of severe hypotension).

3. Prostacyclin (PGI_2):
- Drug:
  - Epoprostenol, iloprost.

  - Administered via infusion pumps.

- Mechanism of action:

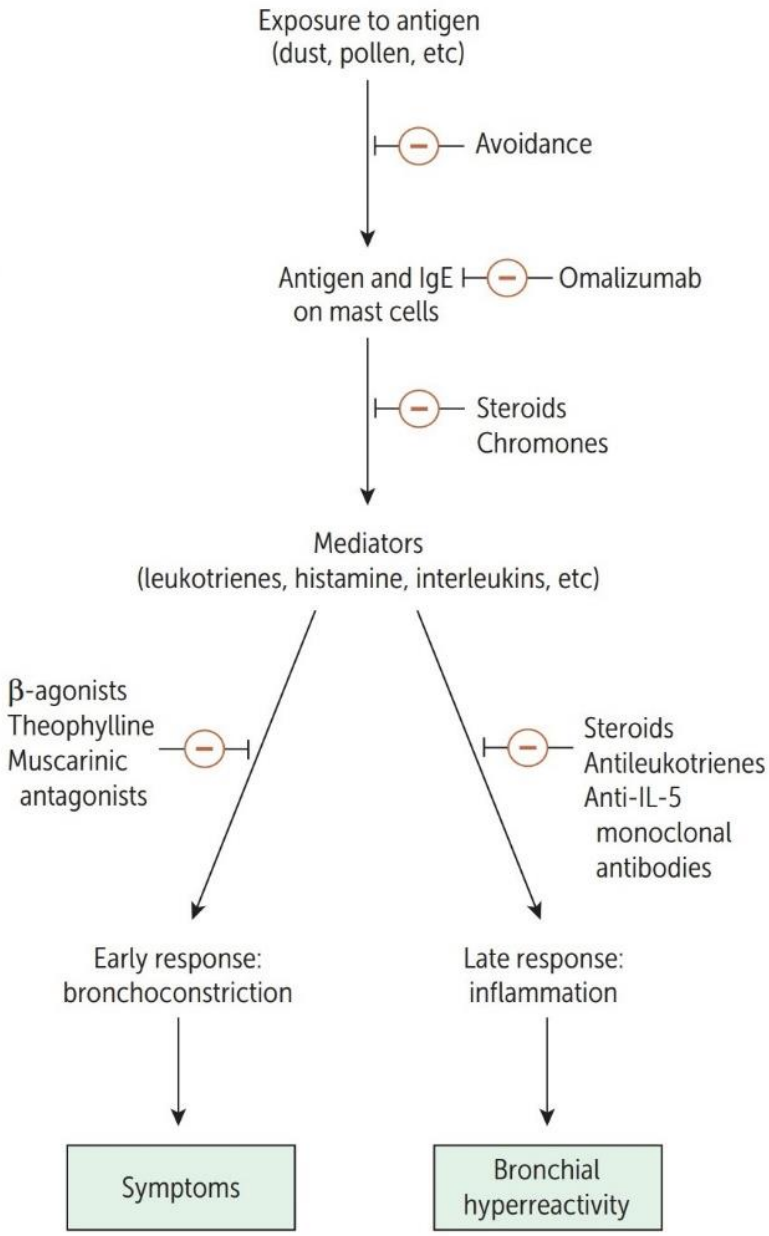
- PGI_2 (prostacyclin) with direct vasodilatory effects on pulmonary and systemic arterial vascular beds.

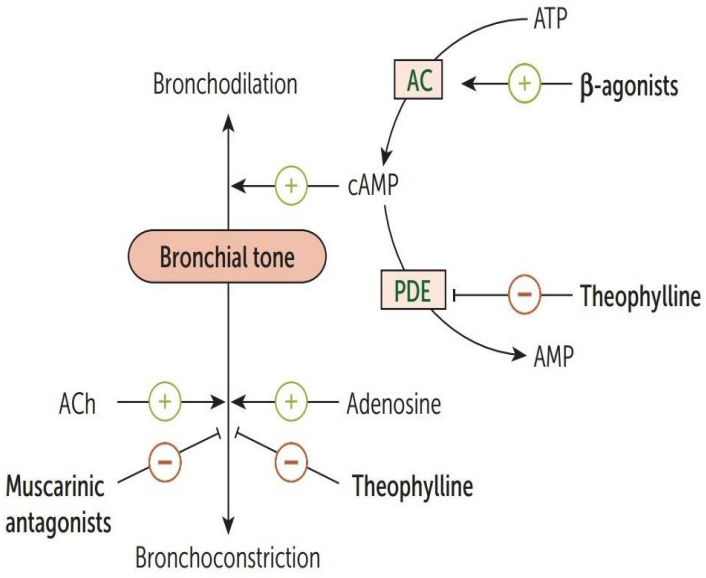
- Inhibits platelet aggregation.

- Side effects: flushing, jaw pain.

Asthma drugs

- Bronchoconstriction is mediated by (1) inflammatory processes and (2) parasympathetic tone; therapy is directed at these 2 pathways.





1. β_2 agonists:

- Drugs:

- Albuterol: relaxes bronchial smooth muscle (short acting β_2-agonist). Used during acute exacerbation.

- Salmeterol, formoterol: long-acting agents for prophylaxis.

- Adverse effects: tremor and arrhythmia.

2. Inhaled corticosteroids:

- Drugs: Fluticasone, budesonide.

- Mechanism of action:

- Glucocorticoids have pronounced anti-inflammatory effects on the respiratory epithelium and are used for both chronic asthma management (inhaled steroids) and during acute exacerbations (systemic steroids).

- They inhibit the formation of inflammatory mediators (cytokines, prostaglandins, leukotrienes) implicated in bronchial asthma.

- They also reduce leukocyte extravasation and induce apoptosis of inflammatory cells (macrophages, lymphocytes, and eosinophils).

- As a result, patients treated with glucocorticoids for a few weeks show significantly reduced airway inflammation.

- In addition, glucocorticoids decrease the amount of mucus produced by goblet cells, further reducing the airway obstruction.

- Clinical use:

- 1st-line therapy for chronic asthma.

- Inhaled glucocorticoids are used to prevent acute exacerbations; they do not have a role in the treatment of acute episodes.

- High-dose systemic glucocorticoids are generally reserved for the initial management of acute asthma exacerbations.

- Side effects:

- The most common side effect of inhaled glucocorticoids is oropharyngeal candidiasis. By using a spacer and rinsing one's mouth after glucocorticoid inhalation, patients can avoid this complication.

- Dysphonia unrelated to oral candidiasis has also been reported; this may be due to myopathy of laryngeal muscles.

- Systemic effects may be seen with higher doses of inhaled glucocorticoids.

- These may include: increased intraocular pressure, cataracts, growth retardation in children, bone loss, and suppression of the hypothalamic-pituitary-adrenal axis.

- Development of Cushing syndrome from inhaled steroids is exceedingly rare.

3. Muscarinic antagonists:

- Drugs: Ipratropium. Tiotropium is long acting.

- Mechanism of action:

- Competitively blocks muscarinic receptors, preventing bronchoconstriction.

- Ipratropium and similar asthma drugs are less effective than β_2 adrenergic agonists. Their effect starts 60 to 90 minutes after initiating treatment.

- Clinical use: Asthma. Also used for COPD.

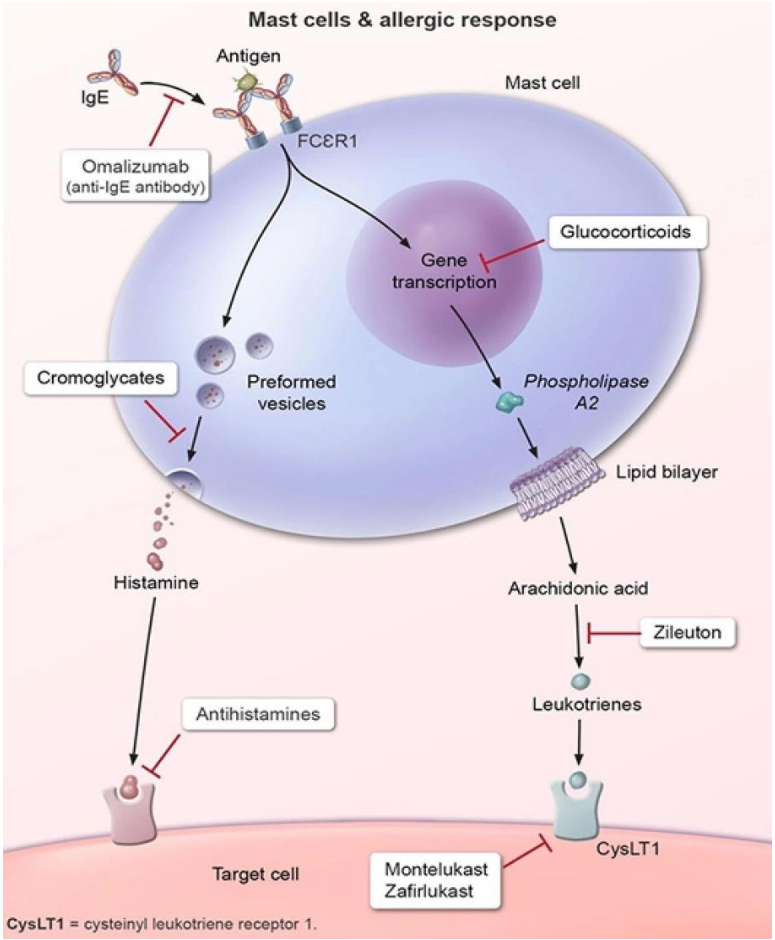
- Side effects: minor atropine like side effects.

4. Antileukotrienes:

- Drugs:

- Montelukast, zafirlukast:
  - Block leukotriene receptors.
  - Especially good for aspirin-induced asthma.

- Zileuton:
  - 5-lipoxygenase pathway inhibitor.
  - Blocks conversion of arachidonic acid to leukotrienes.
  - Hepatotoxic.



5. Anti-IgE monoclonal therapy:

- Drugs: Omalizumab.

- Mechanism of action: binds mostly unbound serum IgE and blocks binding to FcεRI.

- Clinical use: Used in allergic asthma with ↑ IgE levels resistant to inhaled steroids and long-acting β_2-agonists.

6. Methylxanthines:

- Drugs: Theophylline.

- Mechanism of action: Methylxanthines like theophylline and aminophylline cause bronchial dilatation by decreasing phosphodiesterase enzyme activity→ increasing intracellular cAMP, and also by antagonism of adenosine (a bronchoconstrictor).

- Clinical use: Aminophylline IV sometimes used in bronchospasm or status asthmaticus

- Side effects:

- Usage is limited because of narrow therapeutic index (cardiotoxicity, neurotoxicity); metabolized by cytochrome P-450.

- Seizures are the major cause of morbidity and mortality in theophylline intoxication. Tachyarrhythmias are the other major concern.

- Drug interaction: Toxicity ↑ by erythromycin, cimetidine, and fluoroquinolones.

- Treatment of theophylline intoxication:

- It includes gastric lavage followed by administration of activated charcoal (to reduce absorption) and cathartics (to increase elimination via the gastrointestinal tract).

- Beta-blockers are the drugs of choice for theophylline-induced cardiac tachyarrhythmias.

- Theophylline-induced seizures are difficult to treat. Benzodiazepines and barbiturates are the most effective agents.

7. Chromones:

- Drugs: Cromolyn and nedocromil.

- Mechanism of action:

- Prevents acute asthma symptoms. Rarely used. They are less effective than inhaled glucocorticoids, and are considered second-line for the treatment of allergic rhinitis and bronchial asthma.

- The mast cell plays a pivotal role in the pathophysiology of bronchial asthma.

- Cromolyn and nedocromil are mast cell stabilizing agents. They inhibit mast cell degranulation independent of stimuli present.

8. Anti-IL-5 monoclonal therapy:

- Drugs:

- Mepolizumab, reslizumab: against IL-5.

- Benralizumab: against IL-5 receptor α.

- Mechanism of action:

- Prevents eosinophil differentiation, maturation, activation, and survival mediated by IL-5 stimulation.

- For maintenance therapy in severe eosinophilic asthma.