Pathophysiology of the respiratory system I

Structural properties of airways and lungs
Defense mechanisms of the respiratory system
Respiration and gas exchange
- ventilation & diffusion & perfusion

Pulmonary mechanics
Ventilation – perfusion (in)equality
Control of ventilation

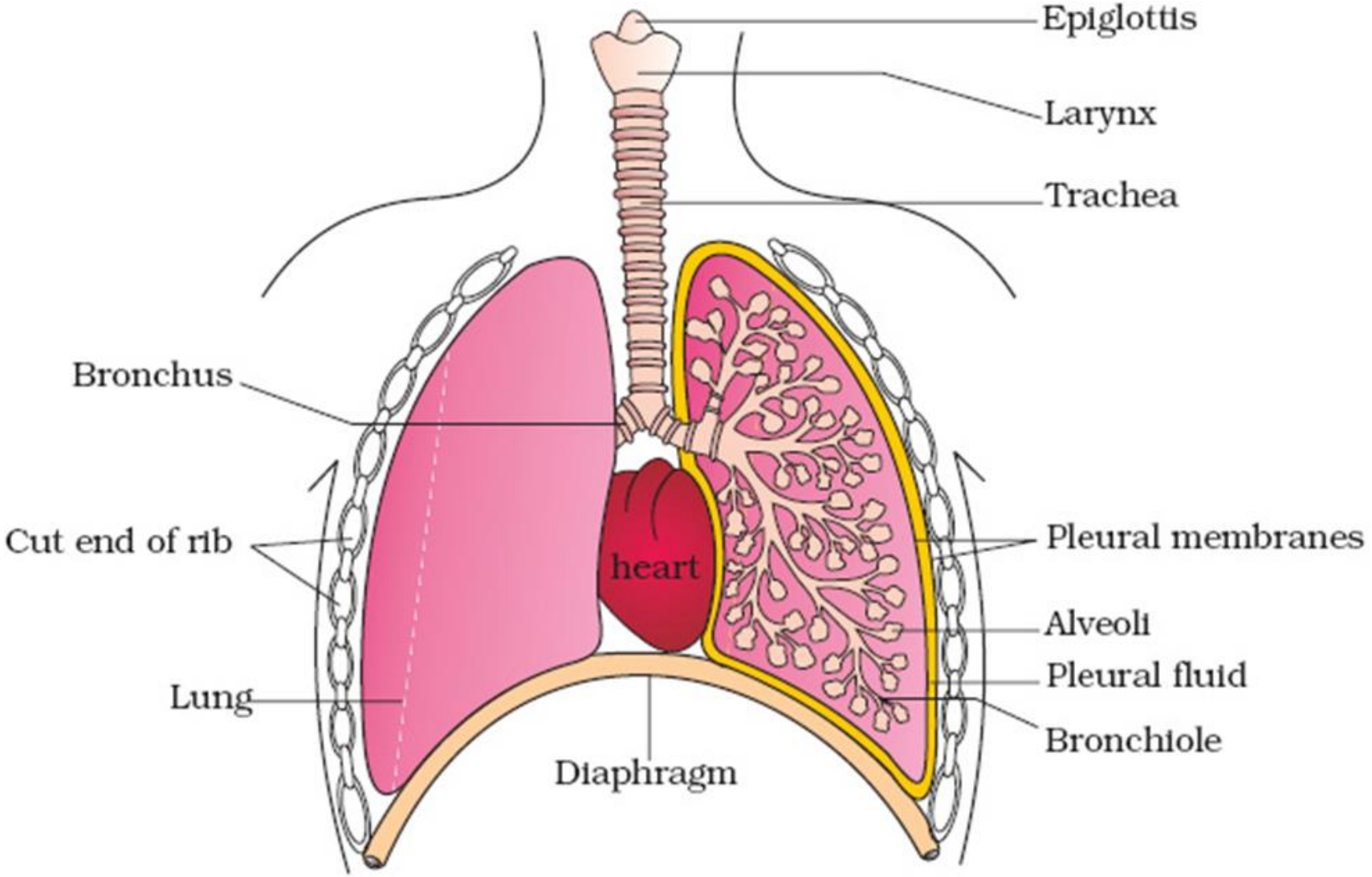
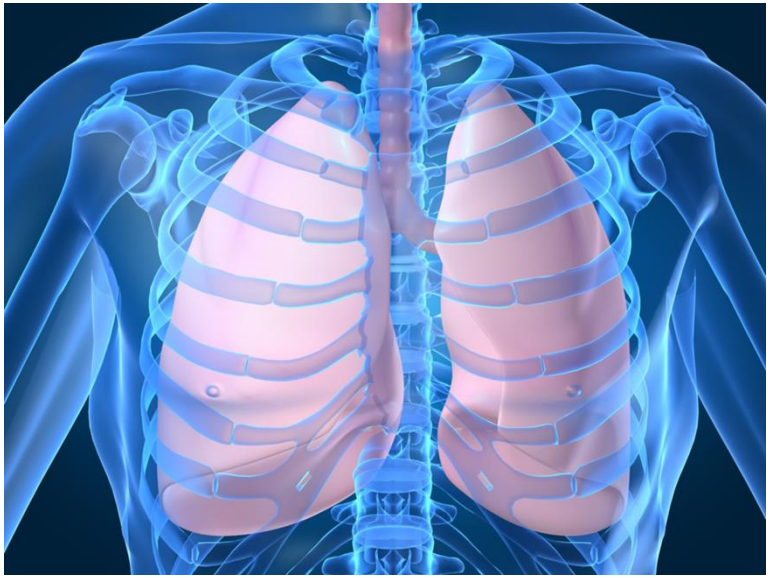


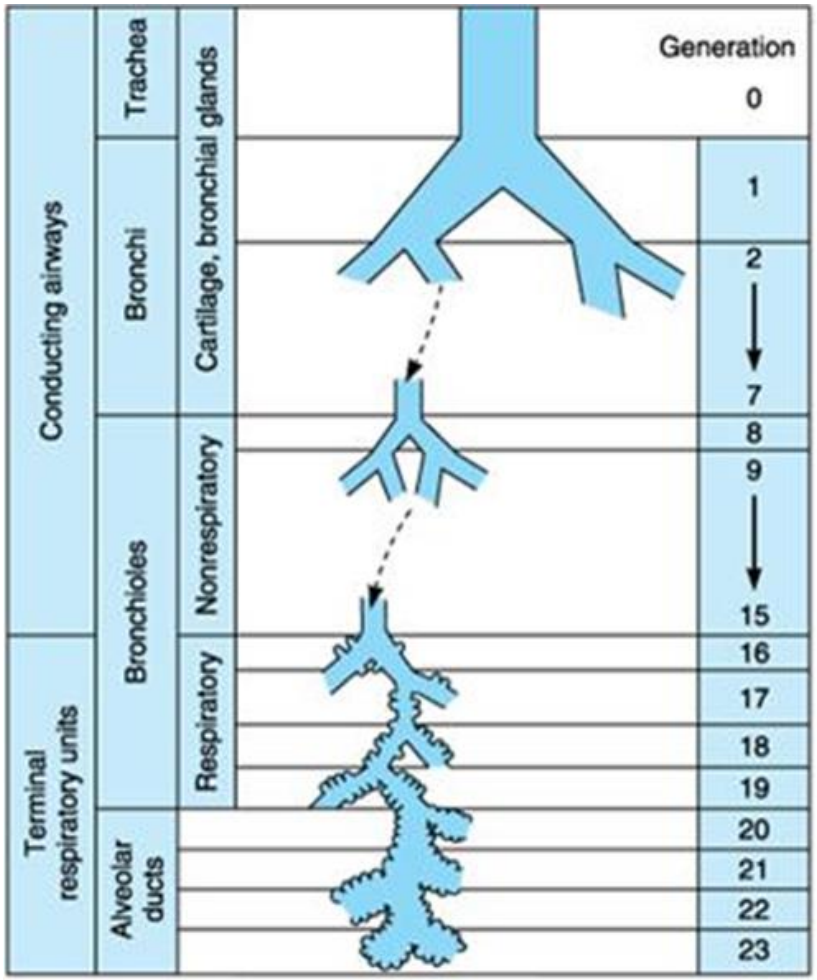
Figure 17.1 Diagrammatic view of human respiratory system (Sectional view of the left lung is also shown)

The delicate structure-function coupling of lungs

- The main role of the respiratory system is to **extract oxygen from the external environment** and **dispose of** waste gases, principally **carbon dioxide**
  - at the end of deep breath 80% of lung volume is air, 10% blood and 10% tissue
    - lung tissue spreads over an enormous area !
- The lungs have to provide
  - a **large surface area** accessible to the environment (~tennis court area) for gas exchange
  - alveoli walls have to present **minimal resistance to gas diffusion**
- Close contact with the external environment means lungs can be damaged by dusts, gases and infective agents
  - **host defense** is therefore a key priority for the lung and is achieved by a combination of structural and immunological means



Structure of airways



Source: McPhee SJ, Ganong WF: *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 5th Edition: http://www.accessmedicine.com

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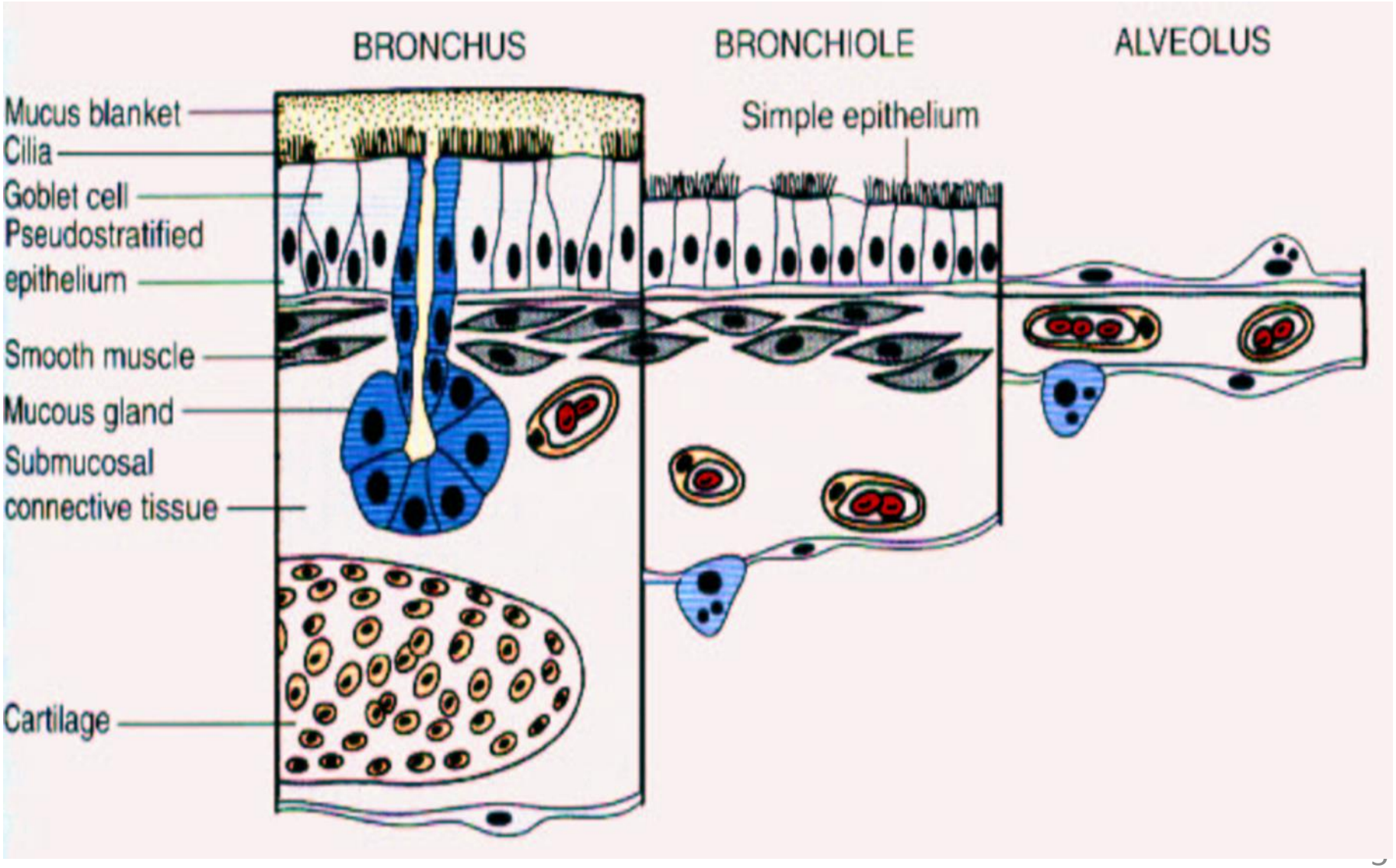
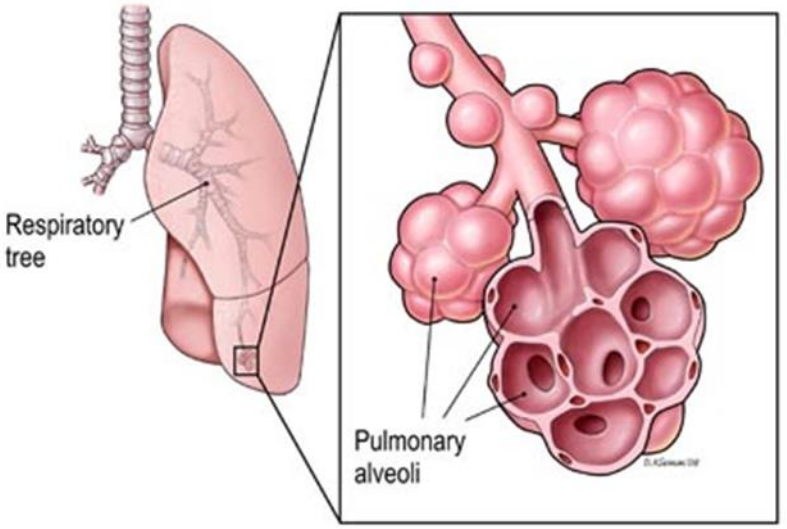
- There are about 23 (18-30) divisions (2^{23} i.e. approx. 8 millions of sacs) between the trachea and the alveoli
  - the first seven divisions, the bronchi have:
    - walls consisting of cartilage and smooth muscle
    - epithelial lining with cilia and goblet cells
    - submucosal mucus-secreting glands
    - endocrine cells - Kulchitsky or APUD (amine precursor and uptake decarboxylation) containing 5-hydroxytryptamine
  - the next 16-18 divisions the bronchioles have:
    - no cartilage
    - muscular layer progressively becomes thinner
    - a single layer of ciliated cells but very few goblet cells
    - granulated Clara cells that produce a surfactant-like substance

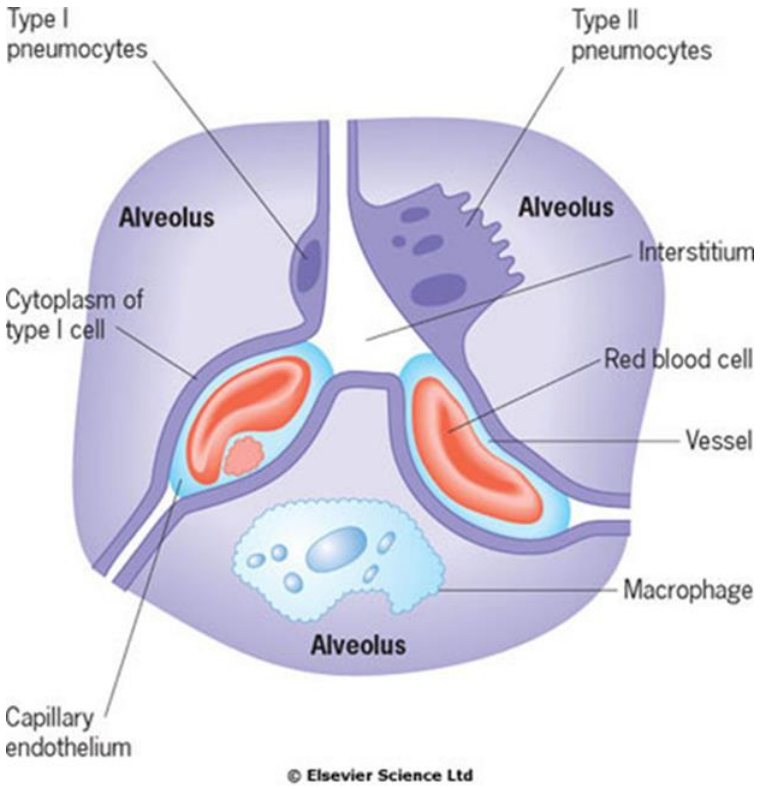
Wall structure of conducting conducting airways and alveolar region



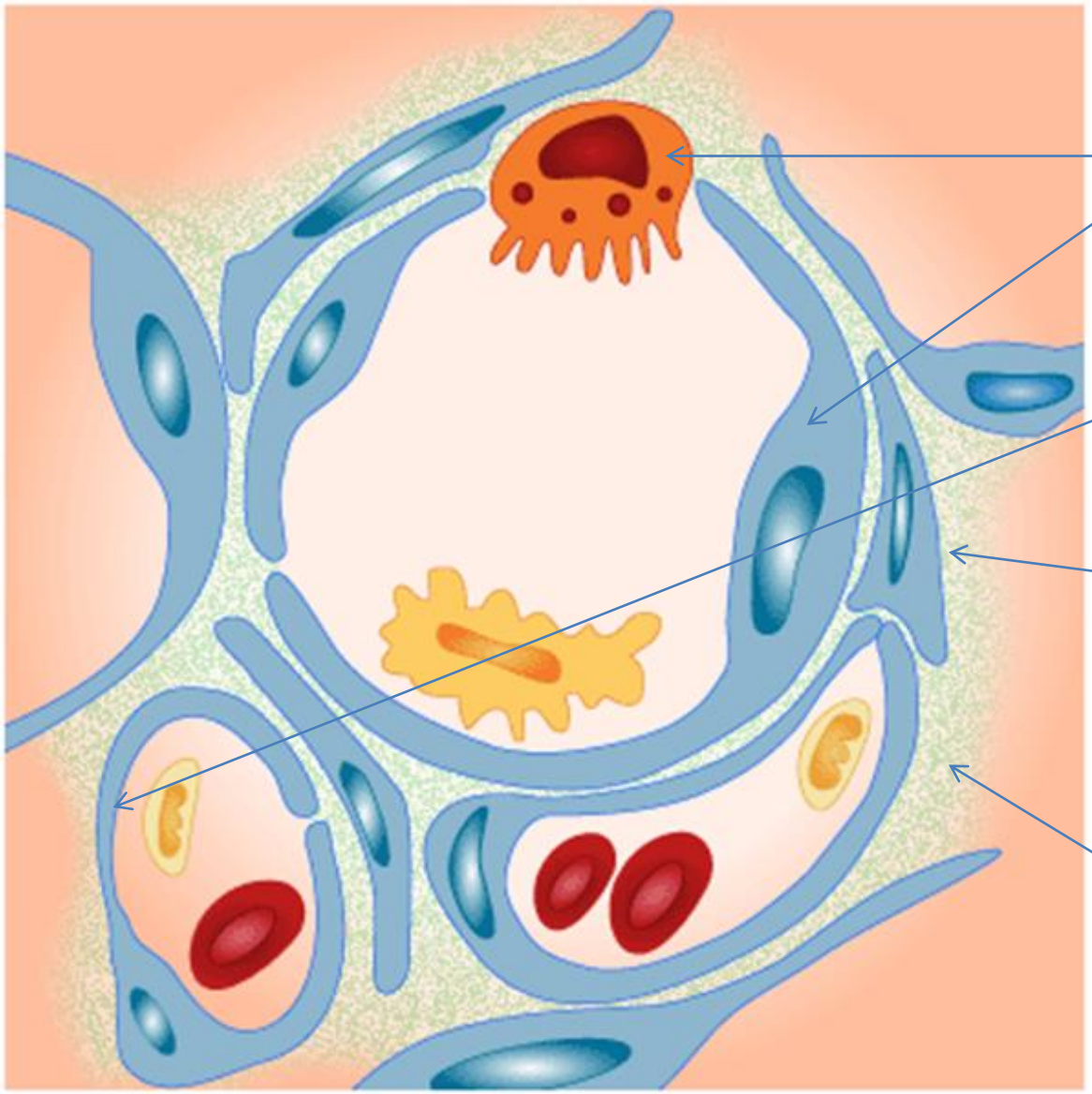
Alveoli

- There are approximately 300-400 million alveoli in each lung with the total surface area is 40-80m^2
- Cell types of the epithelial lining
  - type I pneumocytes
    - an extremely thin cytoplasm, and thus provide only a thin barrier to gas exchange, derived from type II pneumocytes
    - connected to each other by tight junctions that limit the fluid movements in and out of the alveoli
    - easily damageable, but cannot divide!
  - type II pneumocytes
    - slightly more numerous than type I cells but cover less of the epithelial lining
    - the source of type I cells and surfactant
  - macrophages





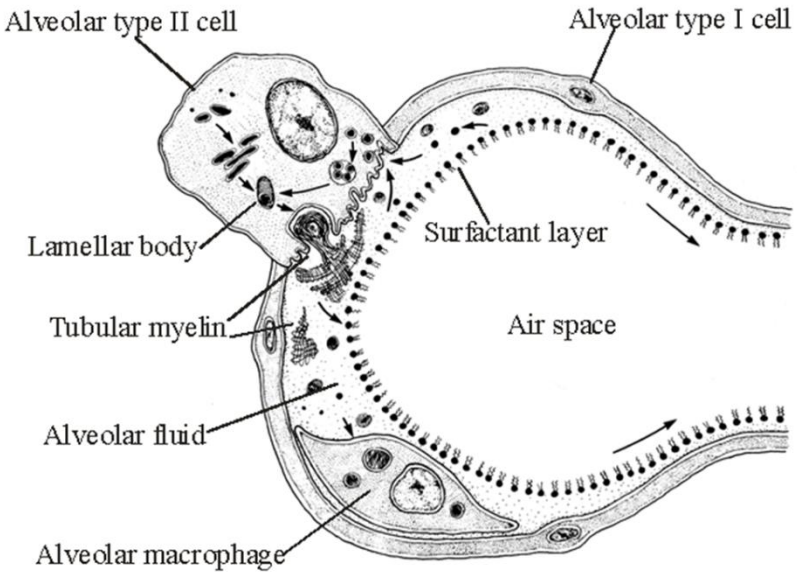
Alveolo - capillary barrier



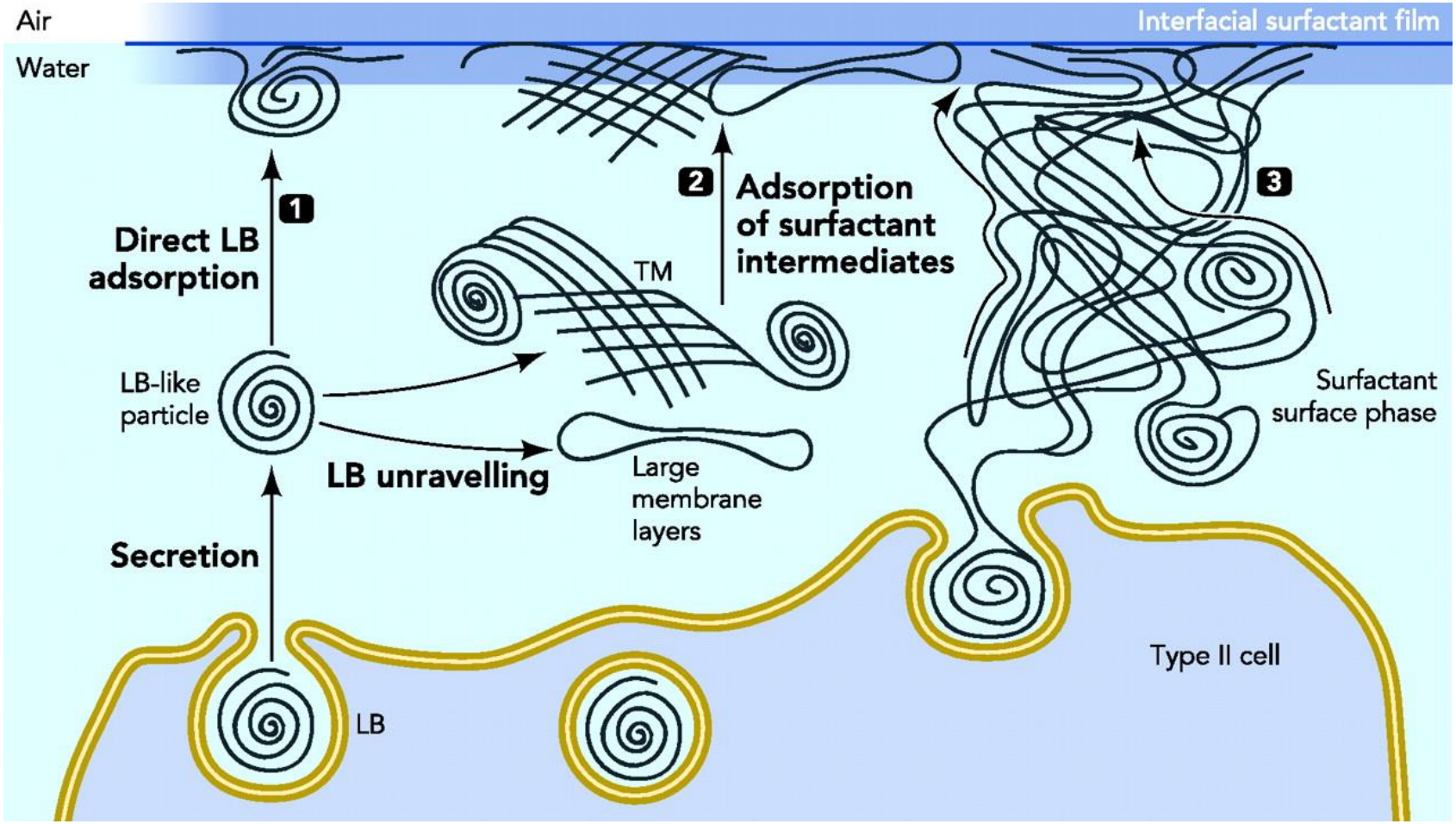
- Alveolar epithelia
  - type I and II cells
- Capillary endothelium
  - non-fenestrated
- Intersticium
  - cells (very few!)
    - fibroblasts
    - contractile cells
    - immune cells (intersticial macrophages, mast cells, …)
  - ECM
    - elastin and collagen fibrils

Pulmonary surfactant

- Complex mixture of lipids and proteins at the alveolar cell surface (liquid – gas interface) reducing surface tension
  - superficial layer made of phospholipids (dipalmitoyl lecithin)
  - deeper layer (hypophase) made of proteins (SP-A, -B, -C, -D)
- Surfactant maintains lung volume at the end of expiration
- Continually recycles
  - influenced by many hormones incl. glucocorticoids
    - lung maturation in pre-term newborns



Pulmonary surfactant adsorption to the interface and surface film formation Processes that may contribute to transport of surface active surfactant species to the interface include 1) direct cooperative transfer of surfactant from secreted lamellar body-like particles touching the interface, 2) unravelling of secreted lamellar bodies to form intermediate structures such as tubular myelin (TM) or large surfactant layers that have the potential to move and transfer large amounts of material to the interface, and 3) rapid movement of surface active species through a continuous network of surfactant membranes, a so-called surface phase, connecting secreting cells with the interface.



Perez-Gil J , Weaver T E Physiology 2010;25:132-141

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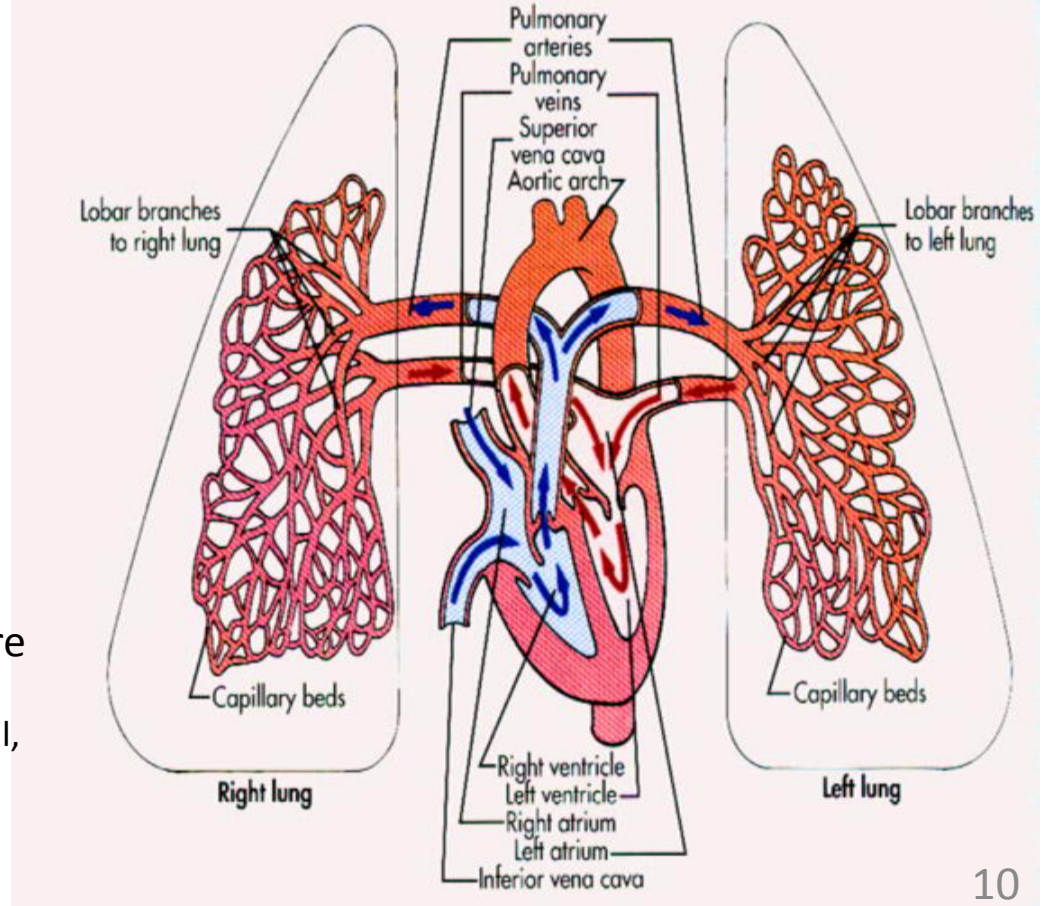
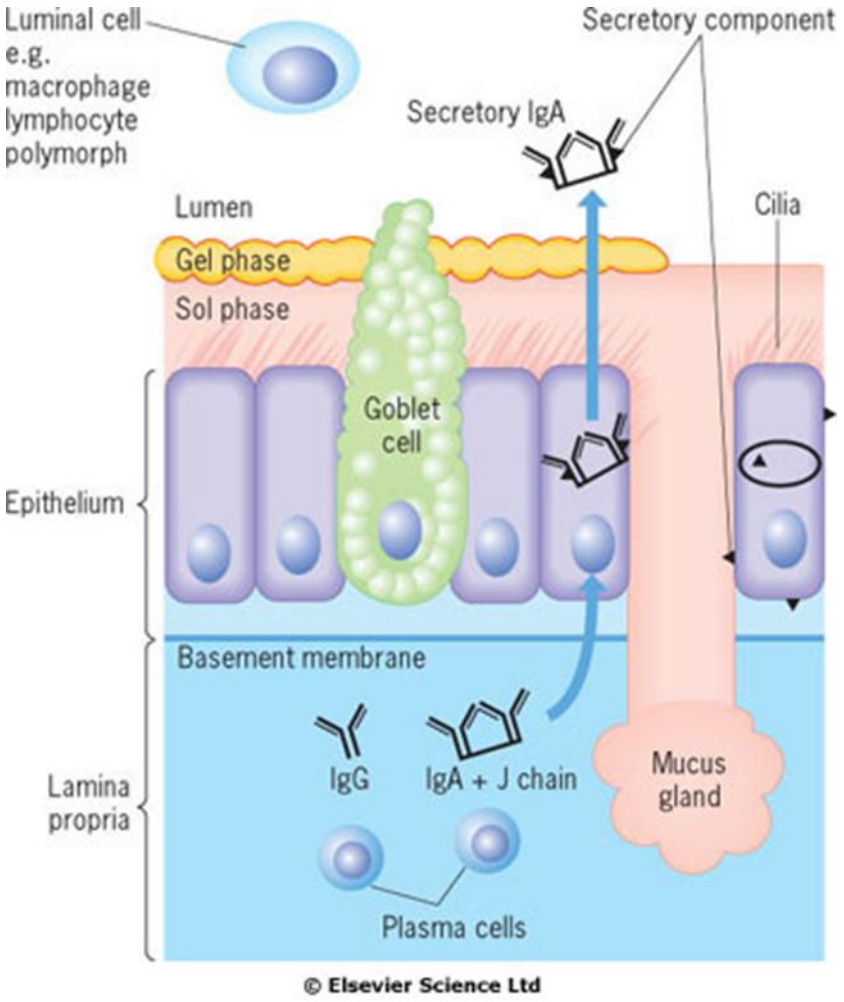
Pulmonary vasculature and lymphatics

- Lungs are the only organ through which **all the blood** (CO) has to pass!!!
- Lungs have a **dual blood supply**
  - deoxygenated blood from the right ventricle via the pulmonary artery
  - systemic (nutritional) supply throughout the bronchial circulation
    - arises from the descending aorta
    - bronchial arteries supply tissues down to the level of the respiratory bronchiole
    - bronchial veins drain into the pulmonary vein, forming part of the physiological shunt observed in normal individuals
- Drainage is provided by the four main pulmonary veins (into the left atrium)
- Lymphatics start in the interstitial space between the alveolar cells and the capillary endothelium of the pulmonary arterioles
  - the tracheobronchial lymph nodes are arranged in five main groups:
    - paratracheal, superior tracheobronchial, subcarinal, bronchopulmonary and pulmonary



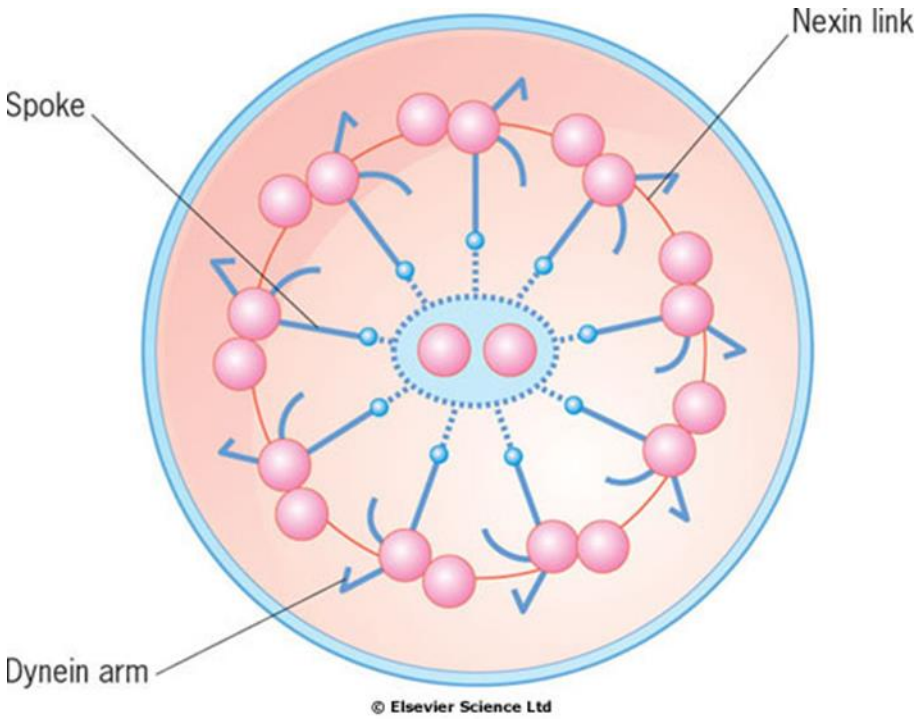
Defense mechanisms of the resp. tract

- These can be divided into two kinds of mechanisms:
  - physical
    - humidification
    - particle removal
      - over 90% of particles greater than 10 µm diameter are removed in the nostril or nasopharynx (incl. most pollen grains which are typically >20 microns in diameter)
      - particles between 5-10 microns become impacted in the carina
      - particles smaller than 1 micron tend to remain
    - mucus
    - particle expulsion
      - by coughing, sneezing or gagging
  - immunological
    - humoral
    - cellular
- Pulmonary disease often results from a failure of the many defense mechanisms that usually protect the lung in a healthy individual



The ciliated epithelium

- Very important defense mechanism
- Each cell contains approximately 200 cilia beating at 1000 beats per minute in organized waves of contraction
- Each cilium consists of nine peripheral pairs and two inner longitudinal fibrils in a cytoplasmic matrix
  - nexin links join the peripheral pairs
  - dynein arms consisting of ATPase protein project towards the adjacent pairs.
- Bending of the cilia results from a sliding movement between adjacent fibrils powered by an ATP-dependent shearing force developed by the dynein arms
  - absence of dynein arms leads to immotile cilia.
- Mucus, which contains macrophages, cell debris, inhaled particles and bacteria, is moved by the cilia towards the larynx at about 1.5 cm/min (the '**mucociliary escalator**,)



Respiratory tract secretions - mucus

- gelatinous substance (~5 mm thick) consisting chiefly of acid and neutral polysaccharides
- relatively impermeable to water
  - mucus floats on a liquid or sol layer that is present around the cilia of the epithelial cells
- secreted from **goblet cells** and **mucous glands** as distinct globules that coalesce increasingly in the central airways to form a more or less continuous mucus blanket
- under normal conditions the tips of the cilia are in contact with the under surface of the gel phase and coordinate their movement to push the mucus blanket upwards
  - it may only take 30-60 minutes for mucus to be cleared from the large bronchi
  - there may be a delay of several days before clearance is achieved from respiratory bronchioles
- reduction in mucociliary transport
  - one of the major long-term effects of **cigarette smoking**
    - contributes to recurrent infection and in the larger airways it prolongs contact with carcinogens
  - air pollutants, local and general anaesthetics
  - bacterial and viral **infections**
  - congenital defects in mucociliary transport (characterized by recurrent infections and eventually with the development of bronchiectasis)
    - the 'immotile cilia' syndrome there is an absence of the dynein arms in the cilia themselves
    - **cystic fibrosis**: an abnormal mucus composition is associated with ciliary dyskinesia

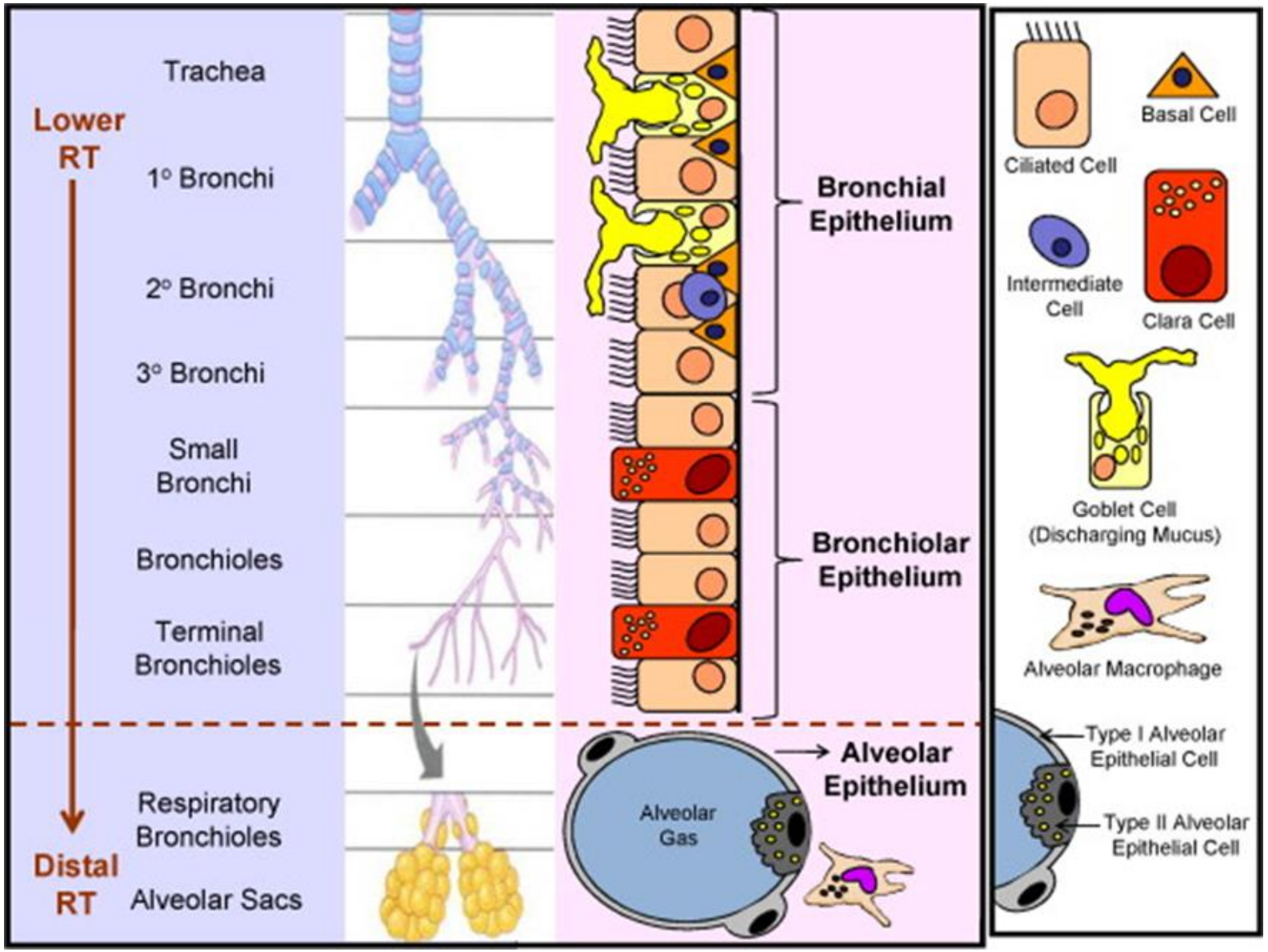
Humoral defense mechanisms

- Non-specific soluble factors
  - characteristic for lungs
    - α-Antitrypsin (α-antiprotease)
      - present in lung secretions derived from plasma
      - inhibits chymotrypsin and trypsin and neutralizes proteases and elastase
    - Surfactant protein A (SPA)
      - one of four species of surfactant proteins which opsonizes bacteria/particles, enhancing phagocytosis by macrophages
  - generally found on biological barriers
    - Lysozyme
      - an enzyme found in granulocytes that has bactericidal properties
    - Lactoferrin
      - synthesized from epithelial cells and neutrophil granulocytes and has bactericidal properties.
    - Interferon (produced by most cells in response to viral infection)
      - a potent modulator of lymphocyte function. It renders other cells resistant to infection by any other virus.
    - Complement
      - present in secretions and is derived by diffusion from plasma
      - in association with antibodies, it plays an important cytotoxic role
    - Defensins
      - bactericidal peptides present in the azurophil granules of neutrophils

Cellular defense mechanisms

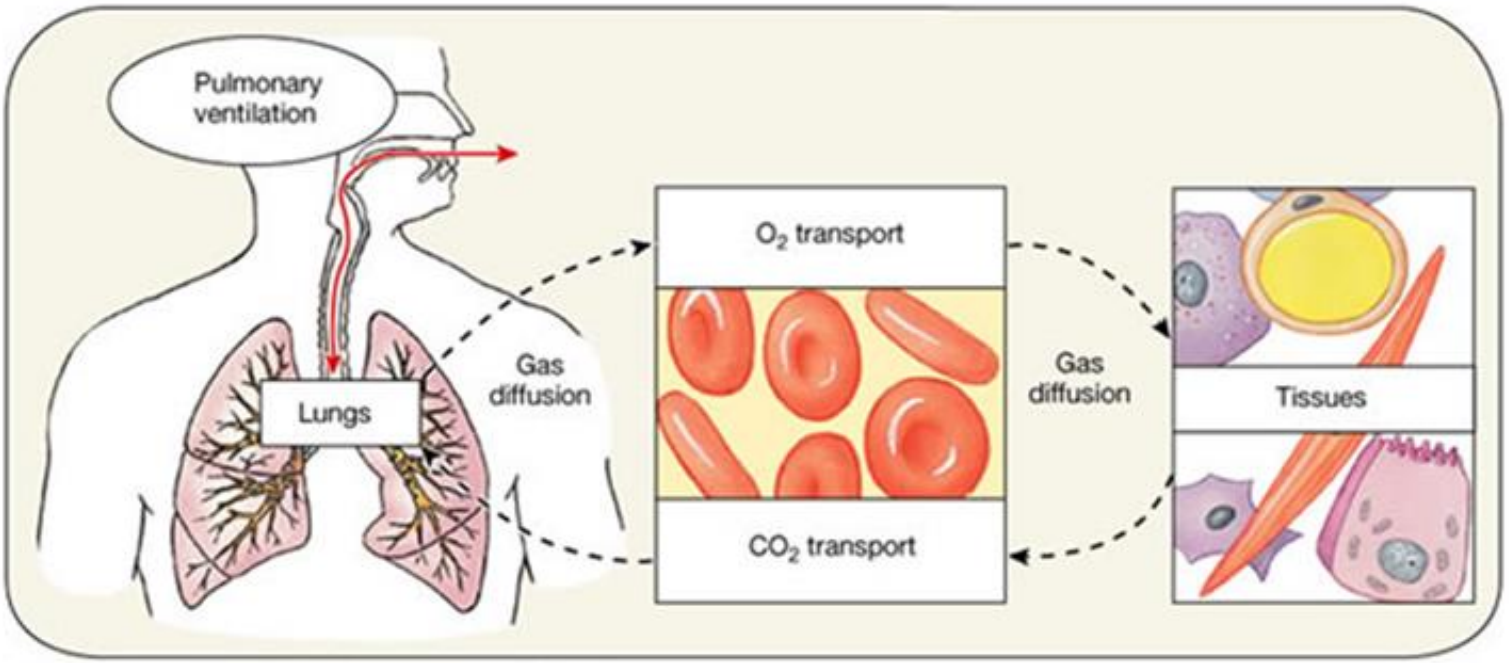
- Pulmonary alveolar macrophages
  - derived from precursors in the bone marrow and migrate to the lungs via the bloodstream
  - phagocytose particles, including bacteria, and are removed by the mucociliary escalator, lymphatics and bloodstream
  - dominant cell in the airways at the level of the alveoli
    - comprise 90% of all cells obtained by bronchoalveolar lavage
  - work principally as scavengers and are not particularly good at presenting antigens to the immune system
- Dendritic cells
  - form a network throughout the airways and are thought to be the key antigen-presenting cell in the airway
- Lymphoid tissue
  - the lung contains large numbers of lymphocytes which are scattered throughout the airways. Sensitized lymphocytes contribute to local immunity through differentiation into IgA-secreting plasma cells. IgG and IgE are found in low concentrations in airway secretions from a combination of local and systemic production.
  - In addition to these resident cells, the lung has the usual range of acute inflammatory responses and can mobilize neutrophils promptly in response to injury or infection and play a major part in inflammatory conditions such as asthma.

Summary – lung defense



Respiration and gas exchange in the lungs

- **ventilation** = mechanical process
  - breathing in narrower meaning
- **diffusion** = chemical process
  - through alveolo-cappilary barrier
- **perfusion** = circulatory process
  - circulation of blood in lungs



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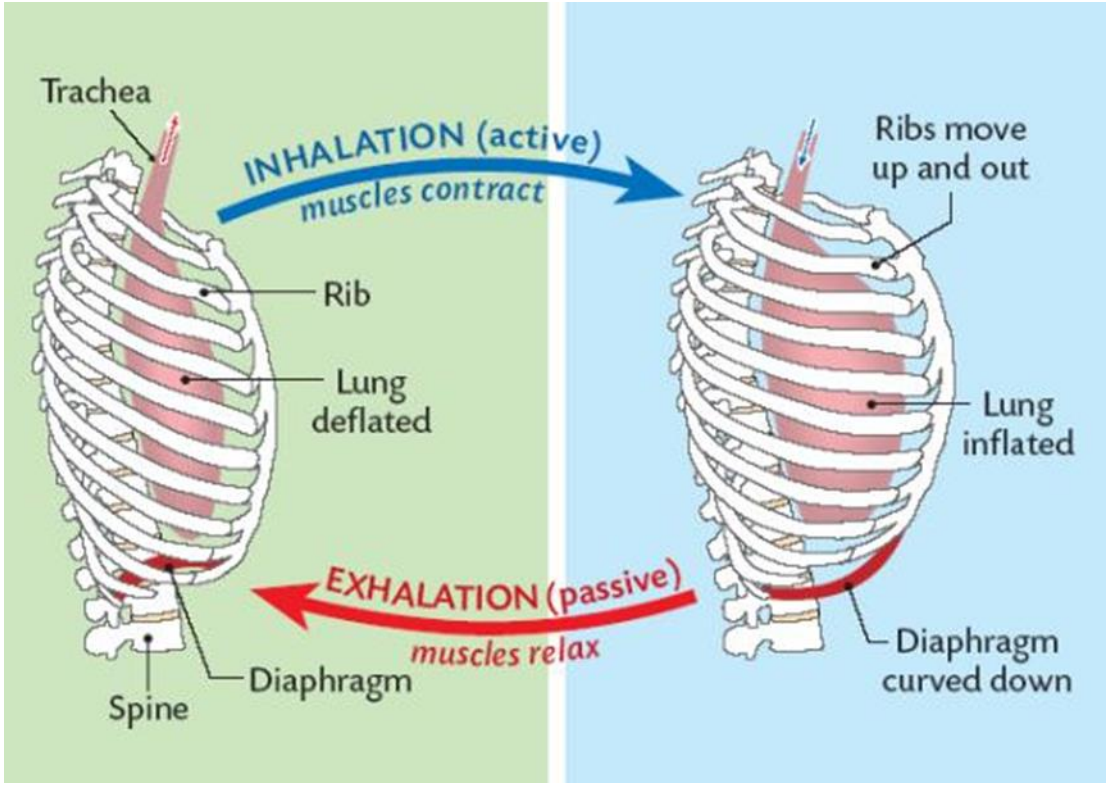
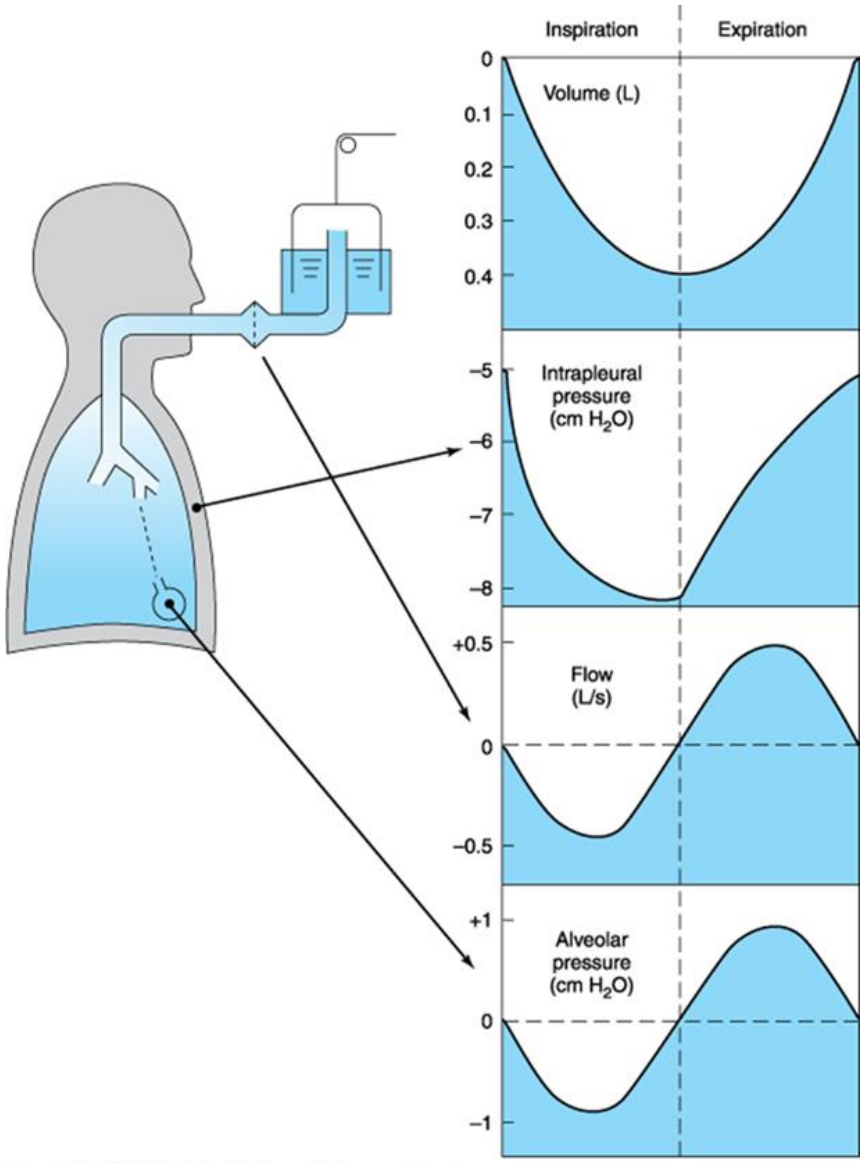


VENTILATION & PULMONARY MECHANICS

Mechanics of ventilation



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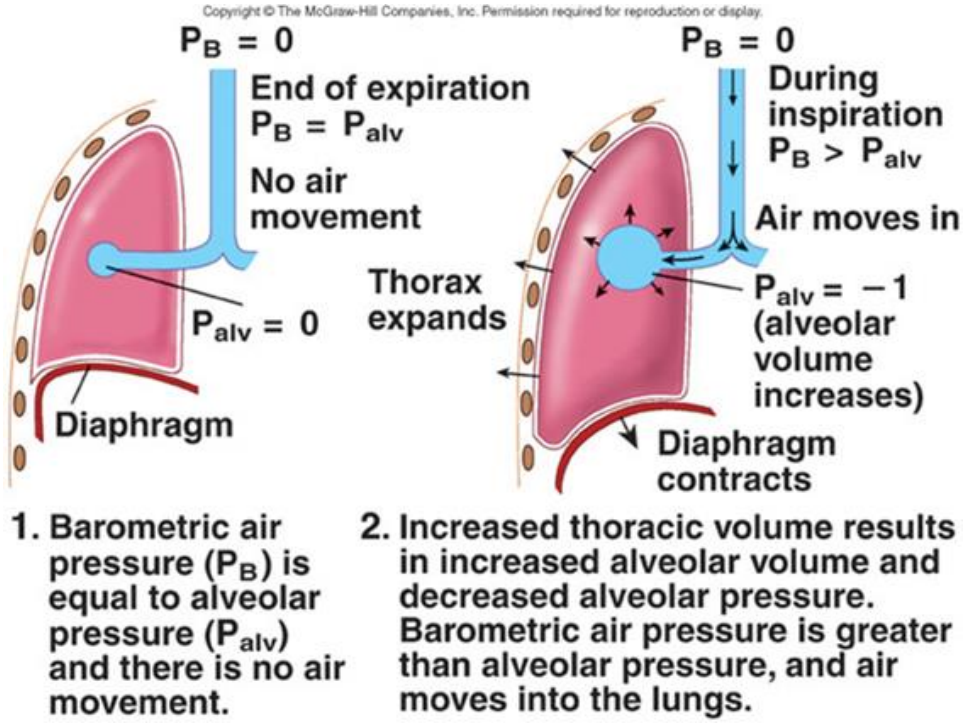
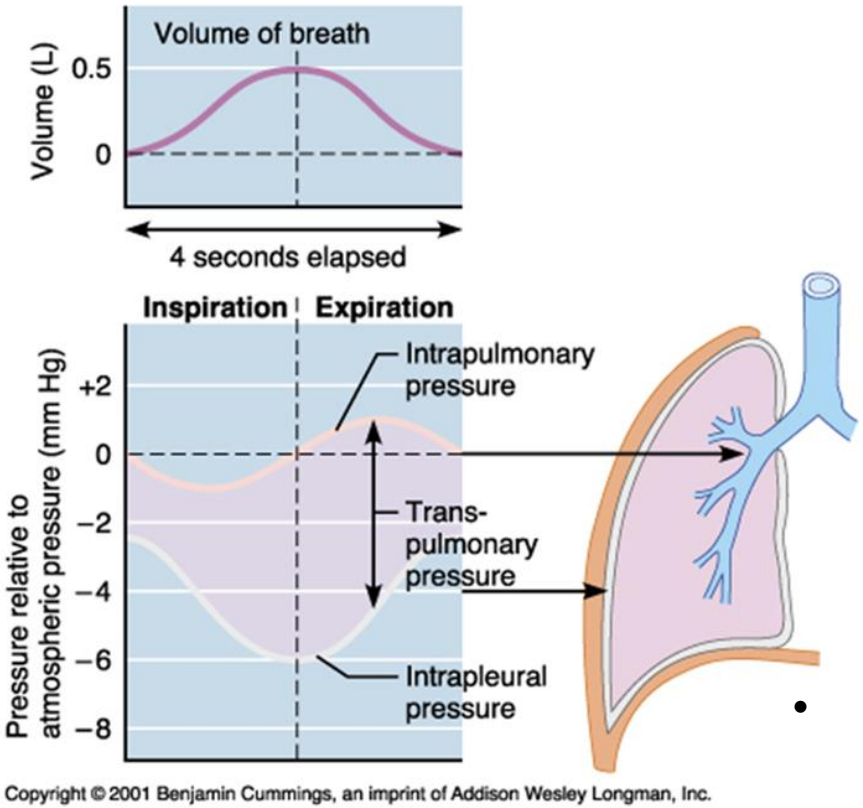
- pressures and pressure gradients
  - pressure on the body surface(P_{bs}),
    - usually equal to atmospheric (P_{ao})
  - alveolar pressure (P_{alv})
  - „elastic“ pressure (P_el)
    - generated by lung parenchyma and surface tension
  - pressure in pleural cavity (P_{pl})
  - trans-pulmonary pressure (P_L)
    - pressure difference between alveolus and pleural cavity
    - $P_L = P_{alv} - P_{pl}$
  - trans-thoracic pressure (P_{rs})
    - pressure difference between alveolus and body surface
    - determines actual phase of ventilation, i.e. inspirium or expirium
    - $P_{rs} = P_{alv} - P_{bs}$

Ventilation



- pressure necessary to distend lungs has to overcome two kinds of resistances
  - **DYNAMIC = airway resistance** (in the convection part of airways)
  - **STATIC = elastic recoil** (in the respiratory part of airways and lung parenchyma)
- energy requirements for respiratory muscles to overcome these resistances in normally quite low (2-5% of a total O_2 consumption) but increases dramatically when resistance increases (up to 30%)

Ventilation (breathing) as a mechanical process



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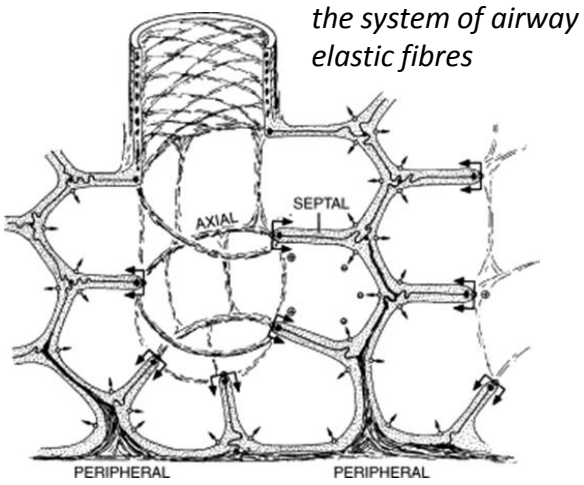
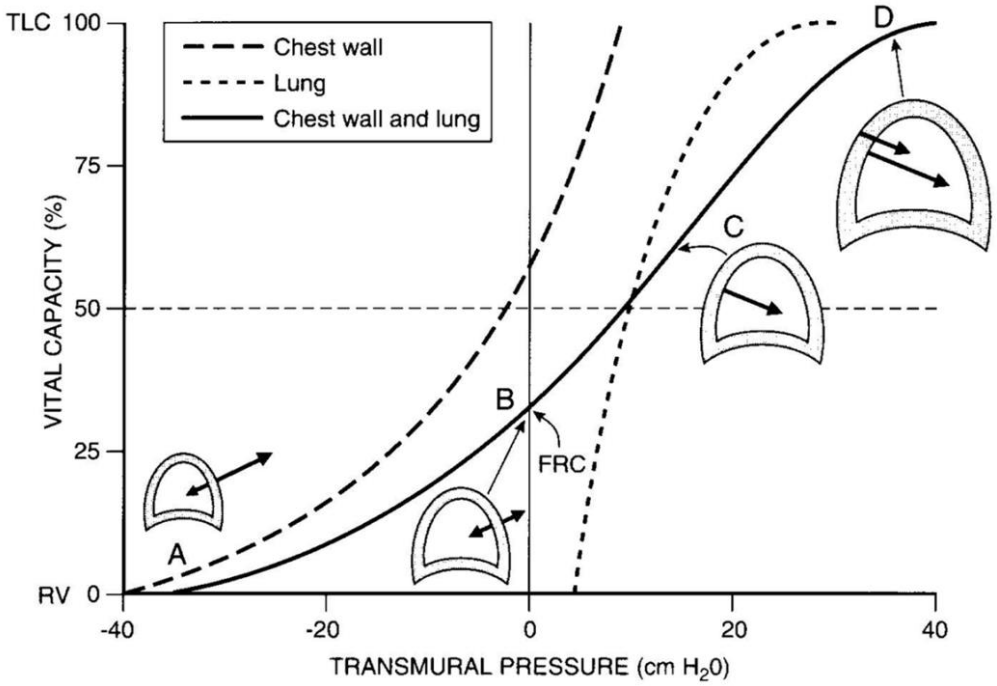
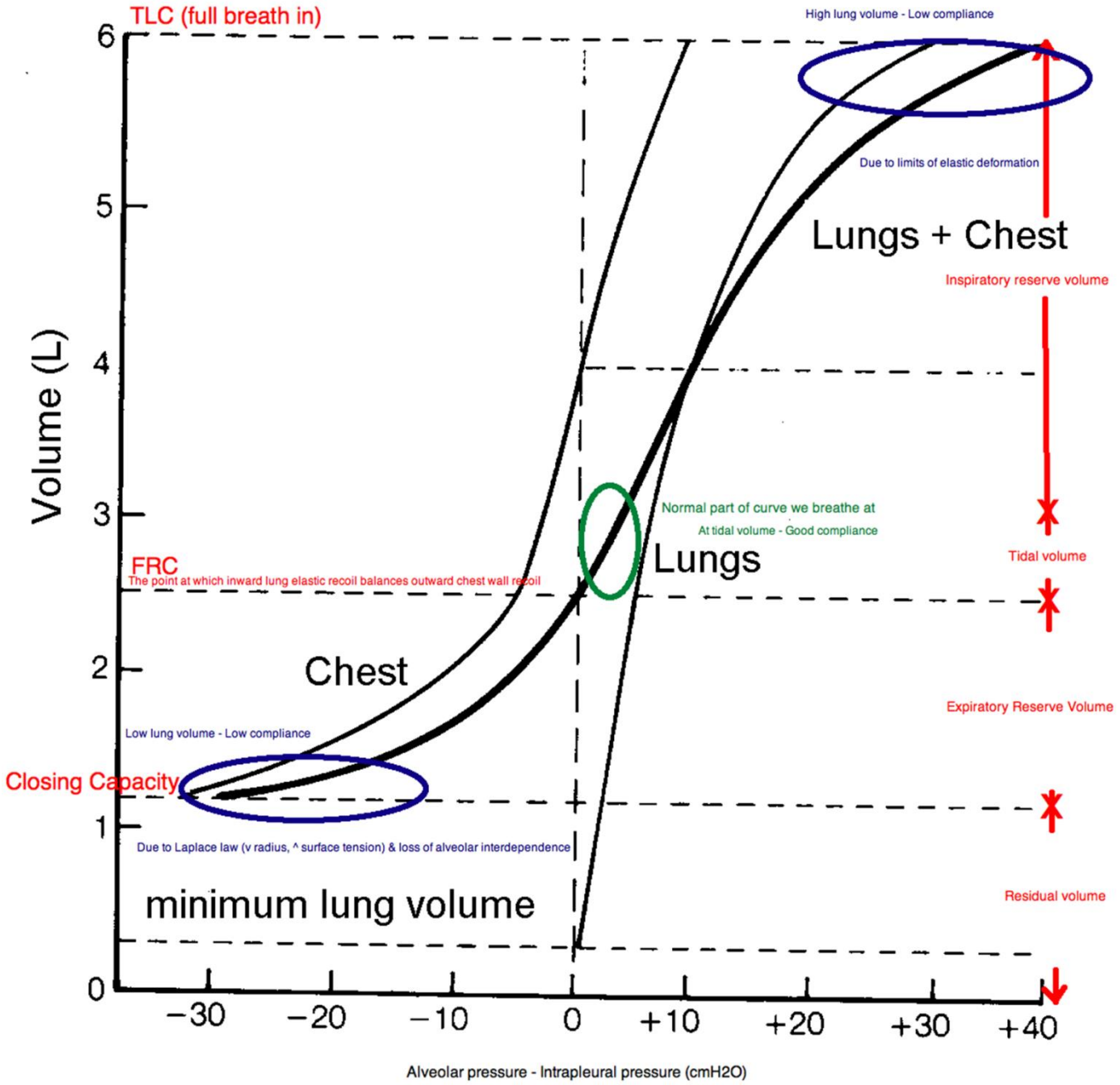
- Inspiration
  - an active process that results from the descent of the **diaphragm** and movement of the ribs upwards and outwards under the influence of the **intercostal muscles**
    - in resting healthy individuals, contraction of the diaphragm is responsible for most inspiration
  - respiratory muscles are similar to other skeletal muscles but are less prone to fatigue
    - weakness may play a part in respiratory failure resulting from neurological and muscle disorders and possibly with severe chronic airflow limitation
  - inspiration against increased resistance may require the use of the accessory muscles of ventilation
    - sternocleidomastoid and scalene muscles
- Expiration
  - follows passively as a result of gradual lessening of contraction of the intercostal muscles, allowing the lungs to collapse under the influence of their own elastic forces (**elastic recoil**)
  - forced expiration is also accomplished with the aid of accessory muscles
    - abdominal wall

Elastic properties of the lung

- lungs have an inherent elastic property that causes them to tend to collapse generating a negative pressure within the pleural space
  - the strength of this retractive force relates to the volume of the lung; for example, at higher lung volumes the lung is stretched more, and a greater negative intrapleural pressure is generated
  - at the end of a quiet expiration, the retractive force exerted by the lungs is balanced by the tendency of the thoracic wall to spring outwards
    - at this point, respiratory muscles are resting and the volume of the lung is known as the **functional residual capacity** (FRC)

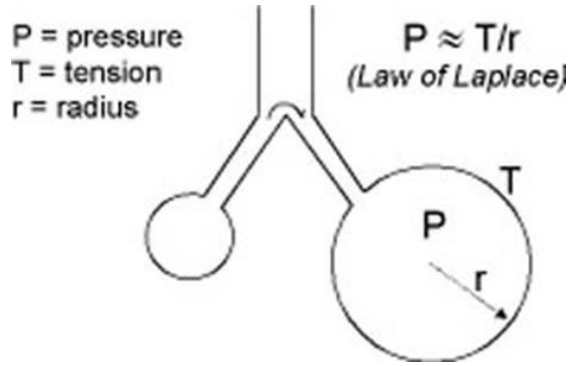




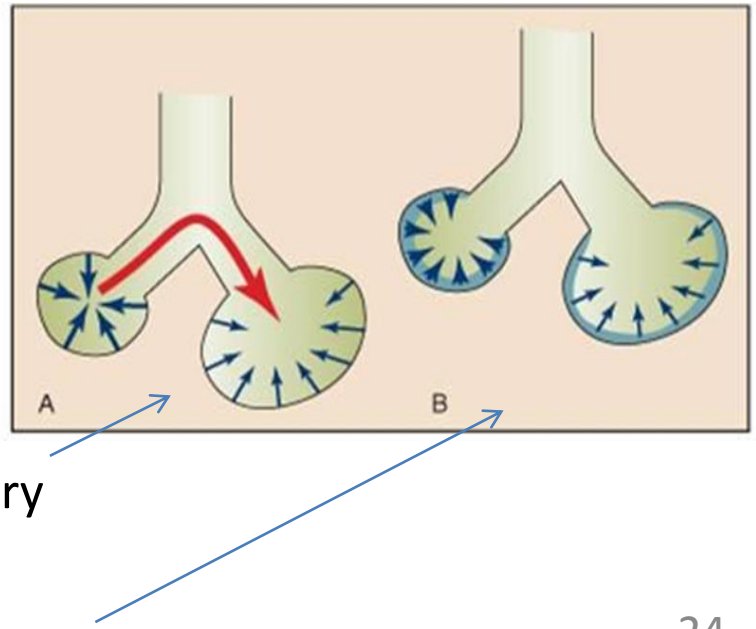

TLC (full breath in)
High lung volume - Low compliance
Due to limits of elastic deformation
Lungs + Chest
Inspiratory reserve volume
Volume (L)
6
5
4
3
2
1
0
Normal part of curve we breathe at
At tidal volume - Good compliance
Lungs
Tidal volume
FRC
The point at which inward lung elastic recoil balances outward chest wall recoil
Chest
Expiratory Reserve Volume
Low lung volume - Low compliance
Closing Capacity
Due to Laplace law (v radius, ^ surface tension) & loss of alveolar interdependence
minimum lung volume
Residual volume
−30
−20
−10
0
+10
+20
+30
+40
Alveolar pressure - Intrapleural pressure (cmH2O)

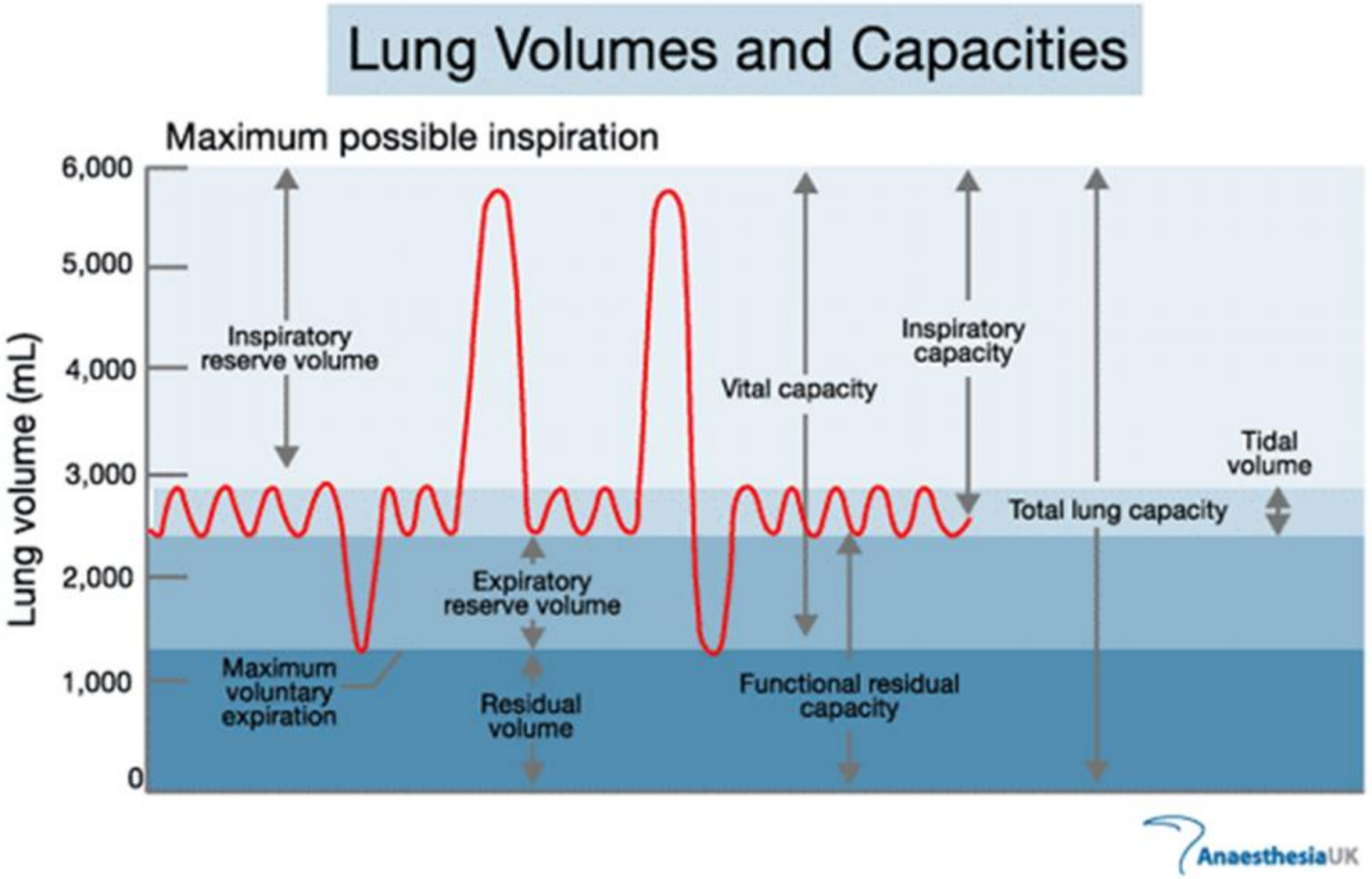
Elastic recoil is determined by two kinds of forces

- **lung compliance** ("distensibility")
  - a measure of the relationship between this retractive force and lung volume
  - defined as the change in lung volume brought about by unit change in transpulmonary (intrapleural) pressure (L/kPa)



- **surface tension** produced by the layer of fluid that lines the alveoli
  - determined by the cohesive (binding together) forces between molecules of the same type
    - on the inner surface of the alveoli is fluid that can resist lung expansion
    - there would be a lot of surface tension because there is an air-water interface in every alveolus
    - if surface tension remained constant, decreasing r during expiration would increase P and smaller alveolus would empty into large one (A)
  - this collapsing tendency is offset by pulmonary surfactant which significantly lowers surface tension (B)

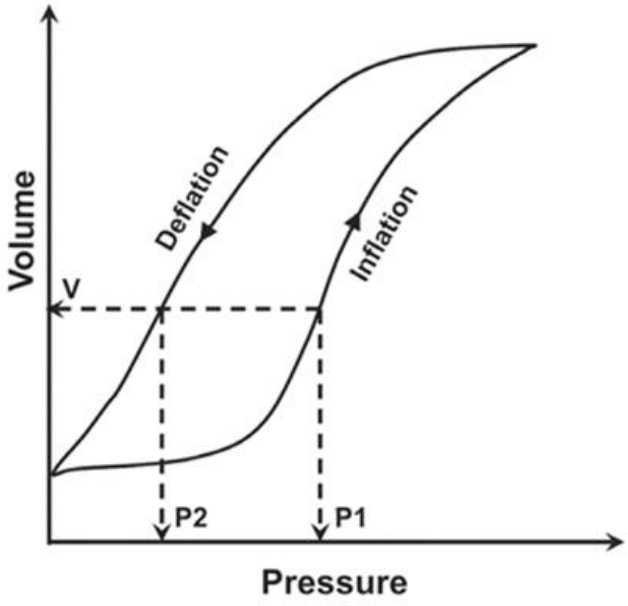


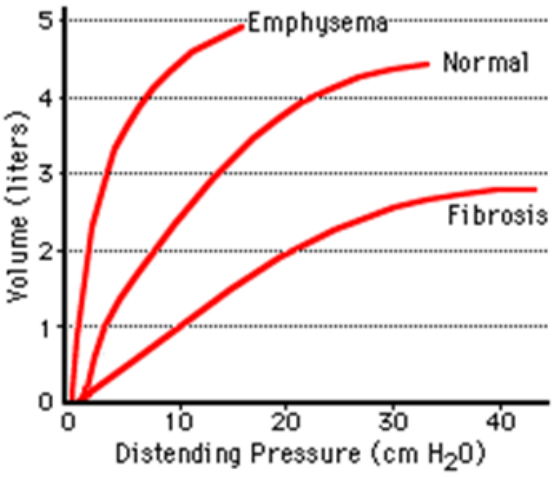


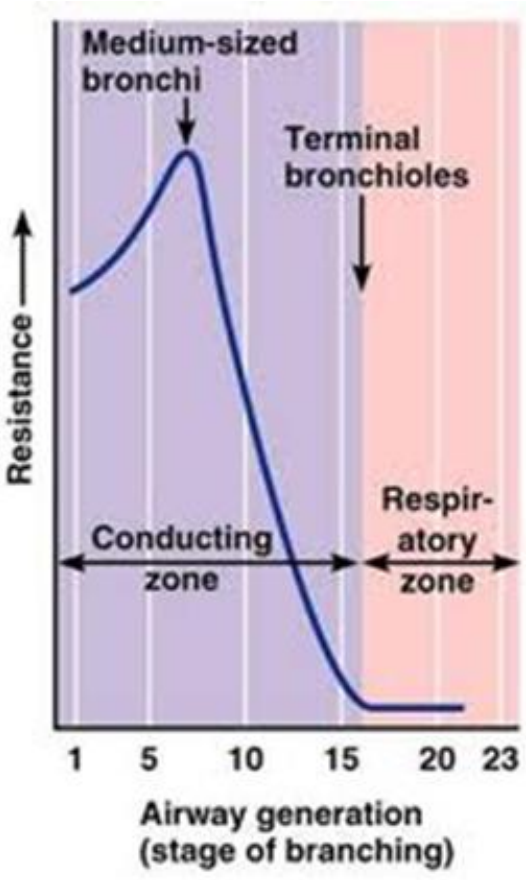
set by opposing recoil forces of the chest and lungs and the effort of respiratory muscles

Abnormalities of elastic properties

- change of lung compliance (TLC, FRC, RV)
  - ↑ pulmonary **emphysema**, aging (↑ TLC, ↑ FRC, ↑ RV)
  - ↓ **interstital disease** (↓TLC, ↓ FRC, ↓ RV), e.g. pulmonary fibrosis or bronchopneumonia
- lack of surfactant (↓TLC, ↓ FRC, ↓ RV)
  - infant or adult **respiratory distress syndromes** (IRDS or ARDS, resp.), i.e. lung collapse
  - alveolar lung **edema** (damages surfactant)
- diseases that affect the movement of the thoracic cage and diaphragm
  - marked obesity
  - diseases of the thoracic spine
    - ankylosing spondylitis and kyphoscoliosis
  - neuropathies
    - e.g. the Guillain-Barré syndrome)
  - injury to the phrenic nerves
  - myasthenia gravis





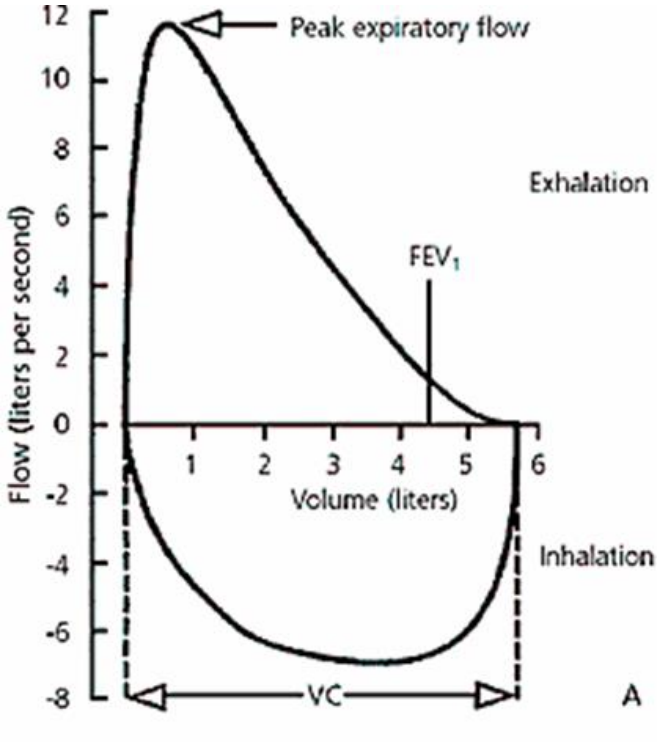


Airflow

- From the trachea to the periphery, the airways become smaller in size (although greater in number)
  - the cross-sectional area available for airflow increases as the total number of airways increases
  - the flow of air is greatest in the trachea and slows progressively towards the periphery (as the velocity of airflow depends on the ratio of flow to cross-sectional area)
    - in the terminal airways, gas flow occurs solely by diffusion
- The **resistance to airflow** is very low (0.1-0.2 kPa/L in a normal tracheobronchial tree), **steadily increasing from the small to the large airways**
- Airway tone is under the control of the autonomic nervous system
  - bronchomotor tone is maintained by **vagal efferent nerves**
  - many **adrenoceptors** on the surface of bronchial muscles respond **to circulating catecholamines**
    - sympathetic nerves do not directly innervate them!

Airflow

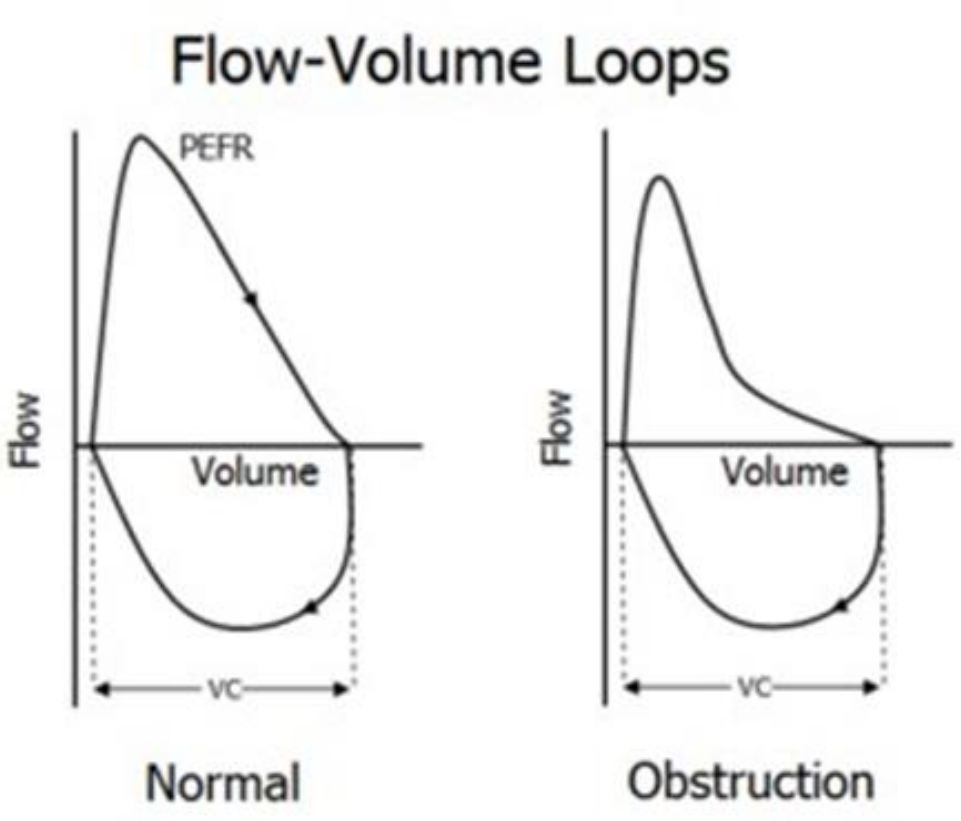
- Movement of air through the airways results from a **difference between the pressure in the alveoli and the atmospheric pressure**
  - alveolar pressure (P_{ALV}) is equal to the elastic recoil pressure (P_{EL}) of the lung plus the pleural pressure (P_{PL})
  - positive P_{ALV} occurs in expiration and a negative pressure occurs in inspiration
- During quiet breathing the sub-atmospheric pleural pressure throughout the breathing cycle slightly distends the airways
  - during vigorous expiratory efforts (e.g. cough) the central airways are compressed by positive pleural pressures exceeding 10 kPa
  - the airways do not close completely because the driving pressure for expiratory flow (alveolar pressure) is also increased
- When there is no airflow (i.e. during a pause in breathing) the tendency of the lungs to collapse (the positive P_{EL}) is exactly balanced by an equivalent negative P_{PL}



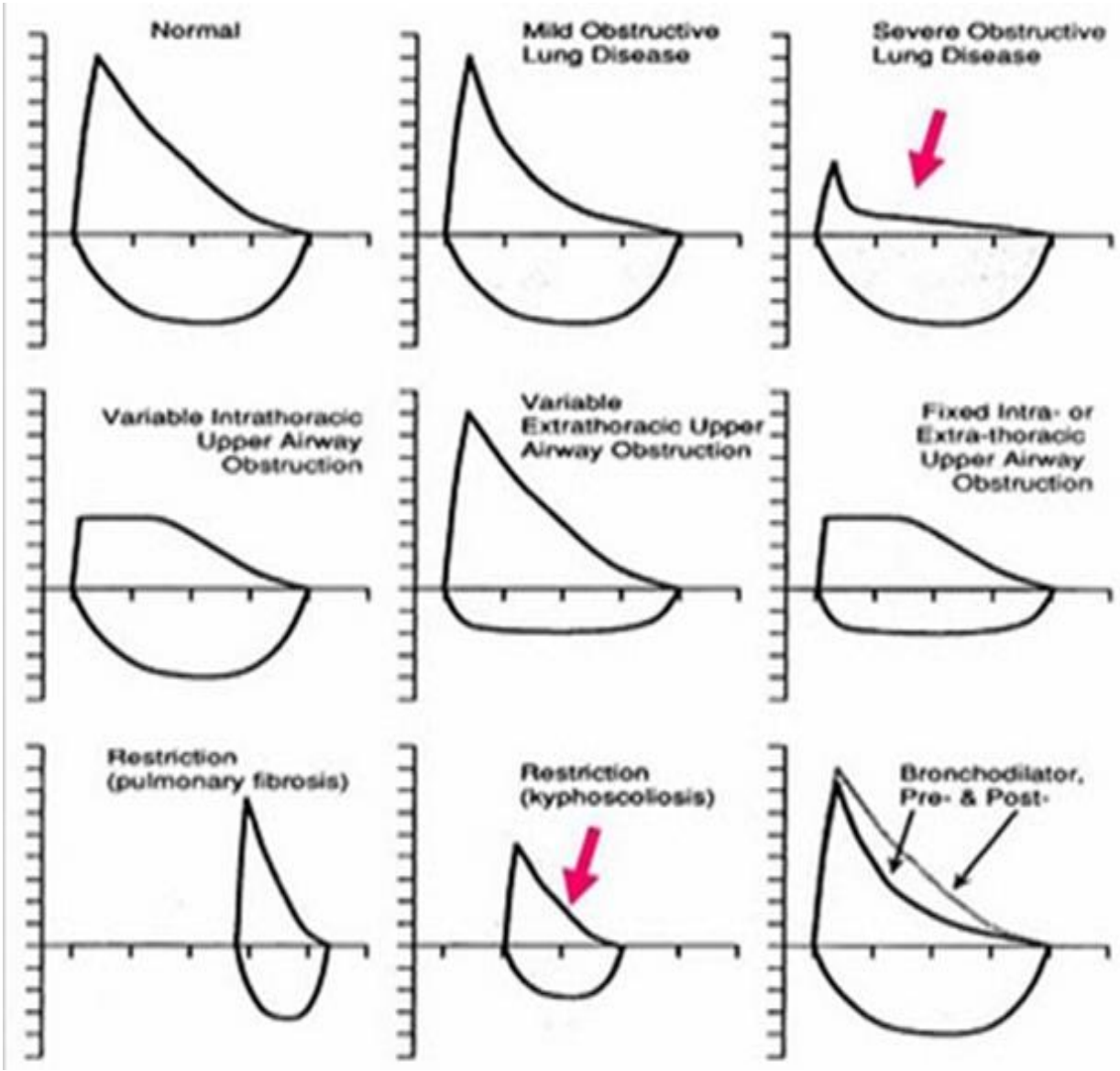
The relationship between maximal flow rates on expiration and inspiration is demonstrated by the maximal flow-volume (MFV) loops

Airflow obstruction

- In patients with severe COPD, limitation of expiratory flow occurs even during tidal breathing at rest
- To increase ventilation these patients have to breathe at higher lung volumes and also allow more time for expiration by increasing flow rates during inspiration, where there is relatively less flow limitation
- Thus patients with severe airflow limitation have a prolonged expiratory phase to their respiration

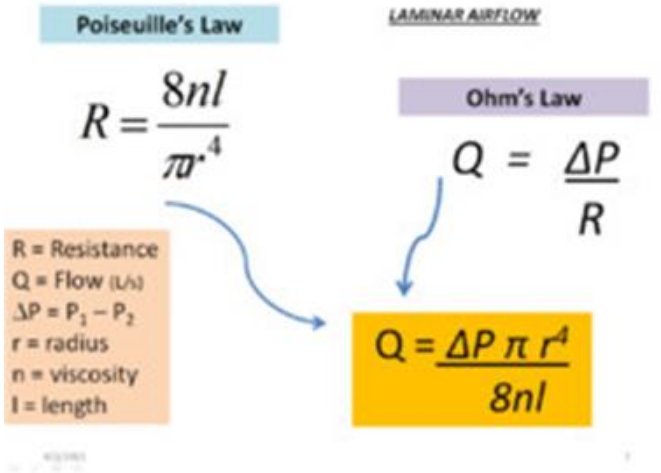


Other examples of flow-volume loops



Airway resistance

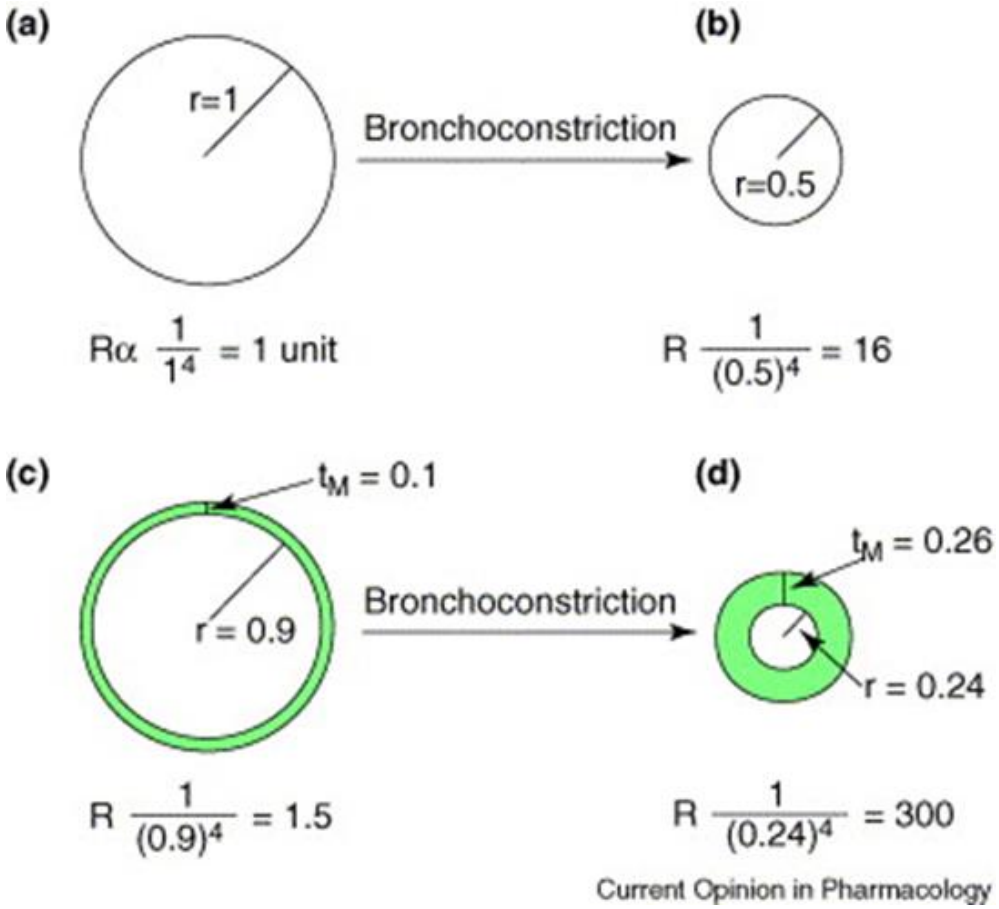
- Poiseuille's law for pressure states that pressure is directly proportional to flow, tube length, and viscosity, and it is inversely proportional to tube radius
- Overcoming increased resistance requires **forced expiration**



Q	Flow rate
P	Pressure
r	Radius
η	Fluid viscosity
l	Length of tubing

$$Q = \frac{\pi \mathrm{Pr}^4}{8\eta l}$$

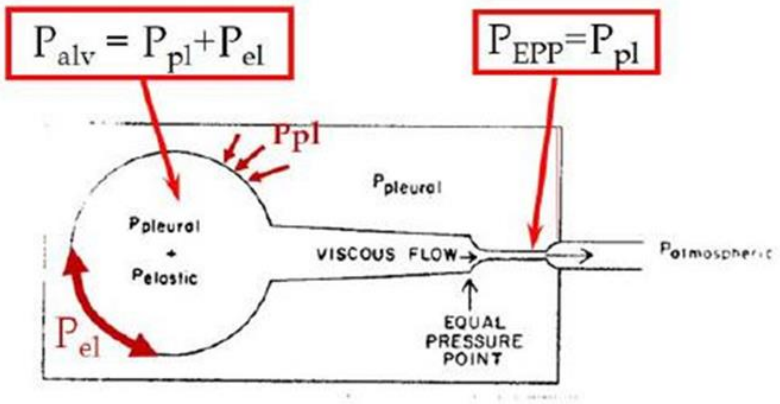
Airflow resistance - bronchoconstriction

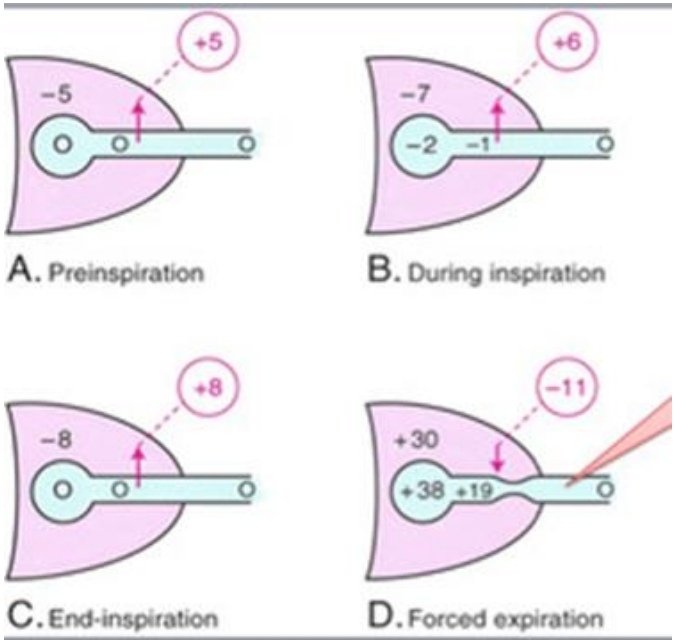


- theoretical amplifying effect of luminal mucus on airflow resistance in asthma. **(a)** According to Poiseuille's law, resistance to flow (R) is proportional to the reciprocal of the radius (r) raised to the fourth power. **(b)** Without luminal mucus, bronchoconstriction to reduce the airway radius by half increases airflow resistance 16-fold. **(c)** A small increase in mucus thickness (t_M), which reduces the radius of the airway by only one-tenth, has a negligible effect on airflow in the unconstricted airway (compare with panel **a**). **(d)** With bronchoconstriction, the same amount of luminal mucus markedly amplifies the airflow resistance of this airway

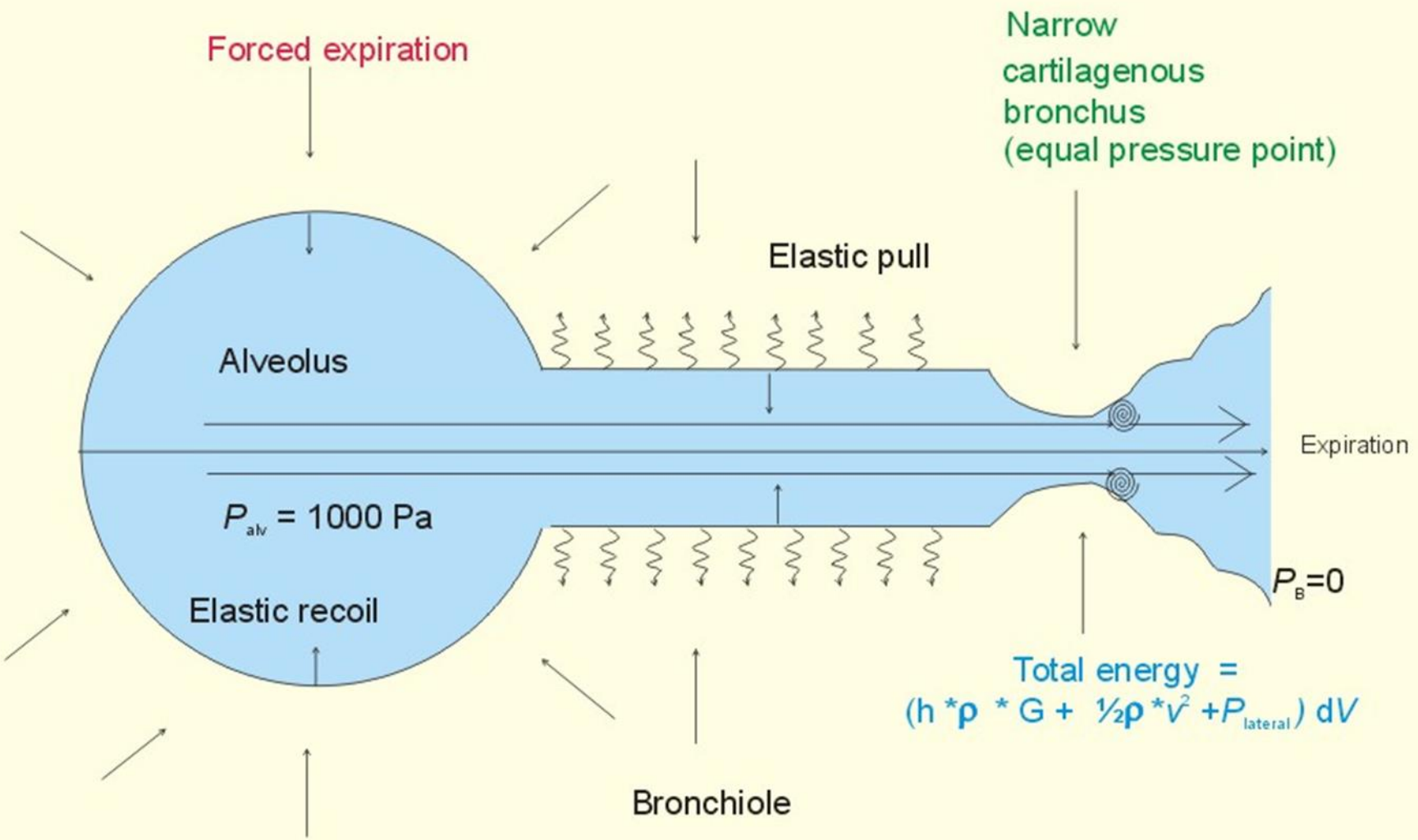
Dynamic compression

- In forced expiration, the driving pressure raises both the P_{ALV} and the P_{PL}
  - between the alveolus and the mouth, a point will occur (C) where the airway pressure will equal the intrapleural pressure, and airway compression will occur
  - however, this compression of the airway is temporary, as the transient occlusion of the airway results in an increase in pressure behind it (i.e. upstream) and this raises the intra-airway pressure so that the airways open and flow is restored
    - the airways thus tend to vibrate at this point of 'dynamic compression'





Dynamic Airway Collapse

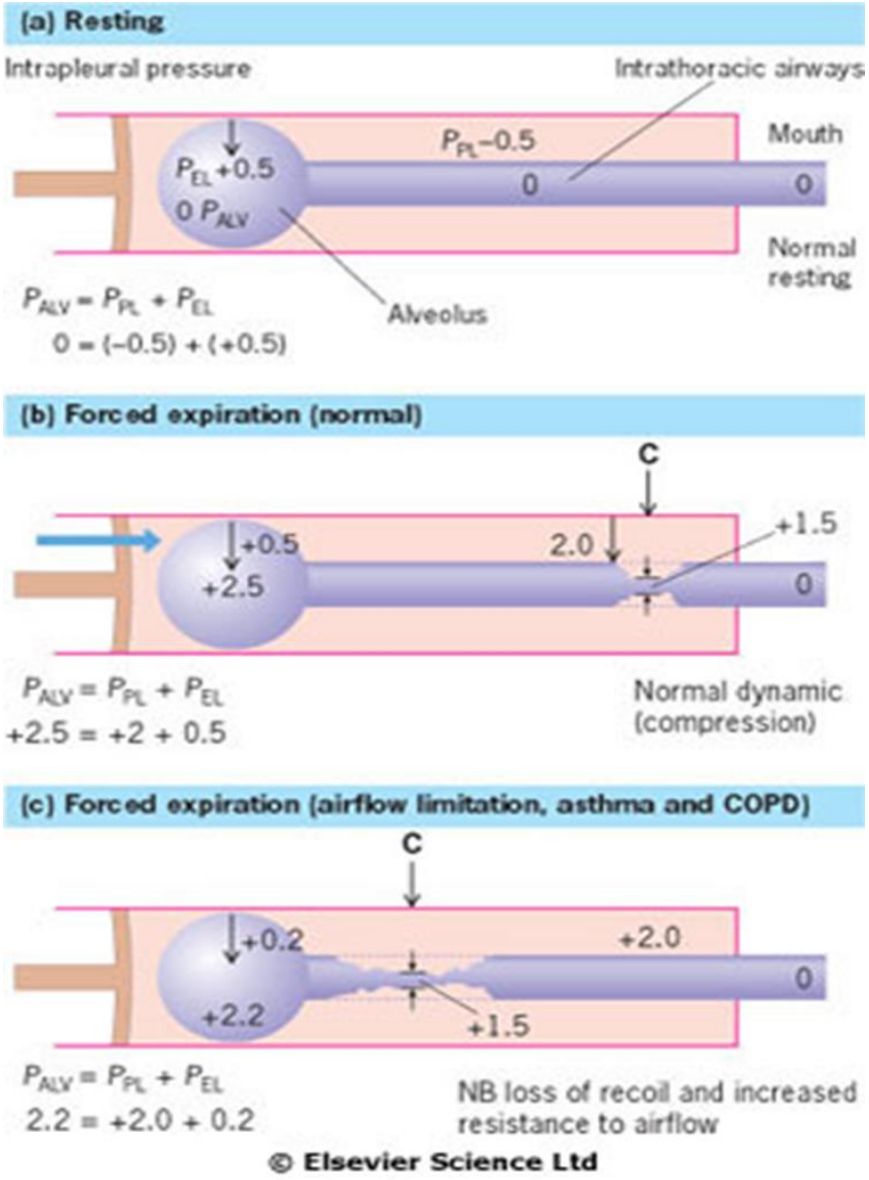


Expiratory effort --- Increased kinetic energy --- Reduced lateral pressure --- Dynamic Airway Collapse

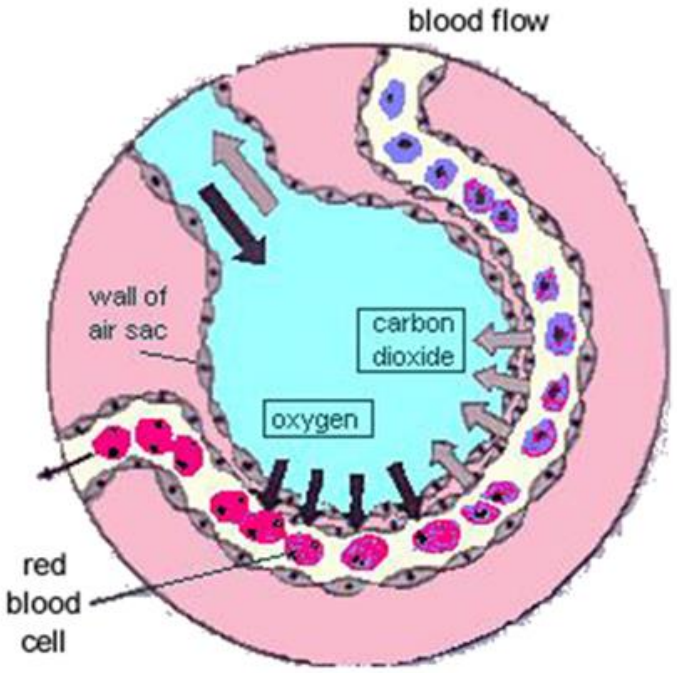
Fig. 13-5

KMc

Dynamic compression in various situations



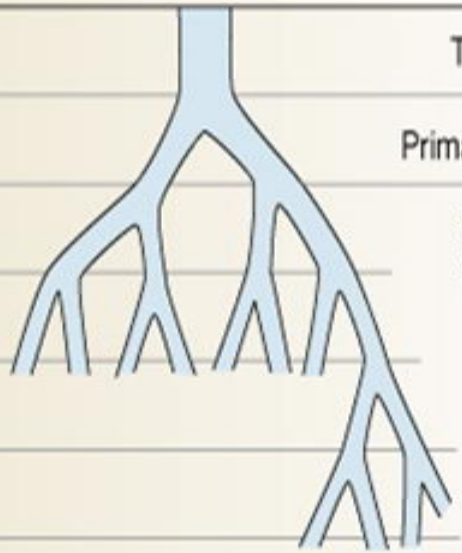
- The respiratory system is represented as a piston with a single alveolus and the collapsible part of the airways within the piston
  - C, compression point; PALV, alveolar pressure; PEL, elastic recoil pressure; PPL, pleural pressure.
  - (a) at rest at functional residual capacity
  - (b) forced expiration in normal subjects
  - (c) forced expiration in a patient with COPD



GAS EXCHANGE IN LUNGS & VENTILATION-PERFUSION MATCHING

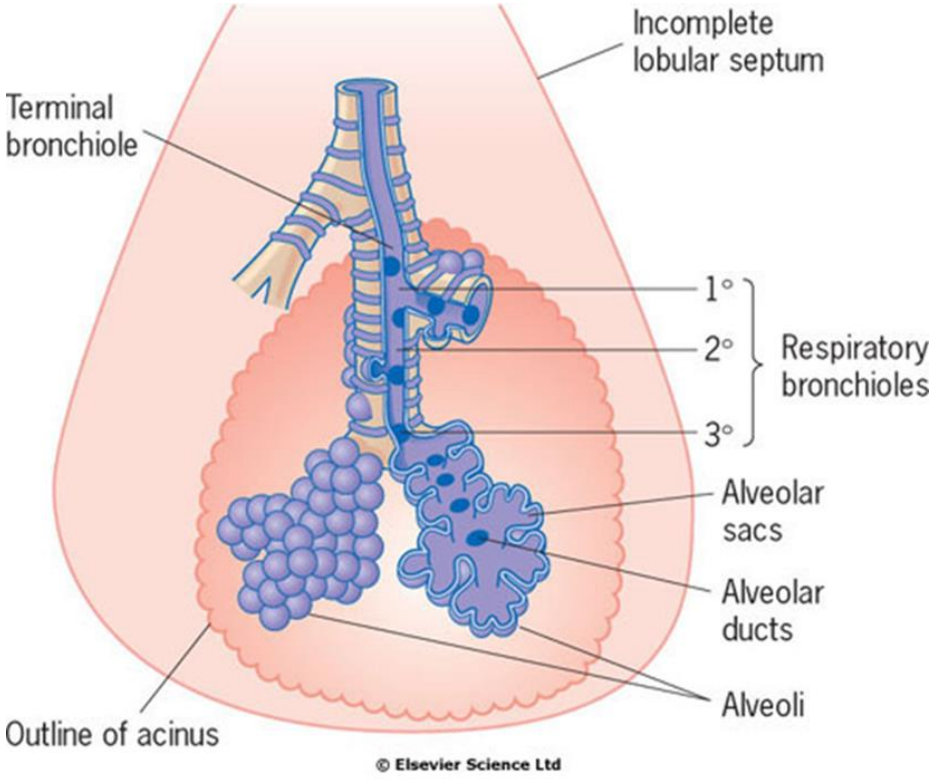
Functional classification of airways

	Name	Division	Diameter (mm)	How many?	Cross-sectional area (cm)
Conducting system	Trachea	0	15-22	1	2.5
	Primary bronchi	1	10-15	2	
	Smaller bronchi	2	1-10	4	
		3			
		4			
		5			
		6-11		1×10^4	
	Bronchioles	12-23	0.5-1	2×10^4 → 8×10^7	100 → 5×10^3
Exchange surface	Alveoli	24	0.3	$3\text{-}6 \times 10^8$	$>1 \times 10^6$

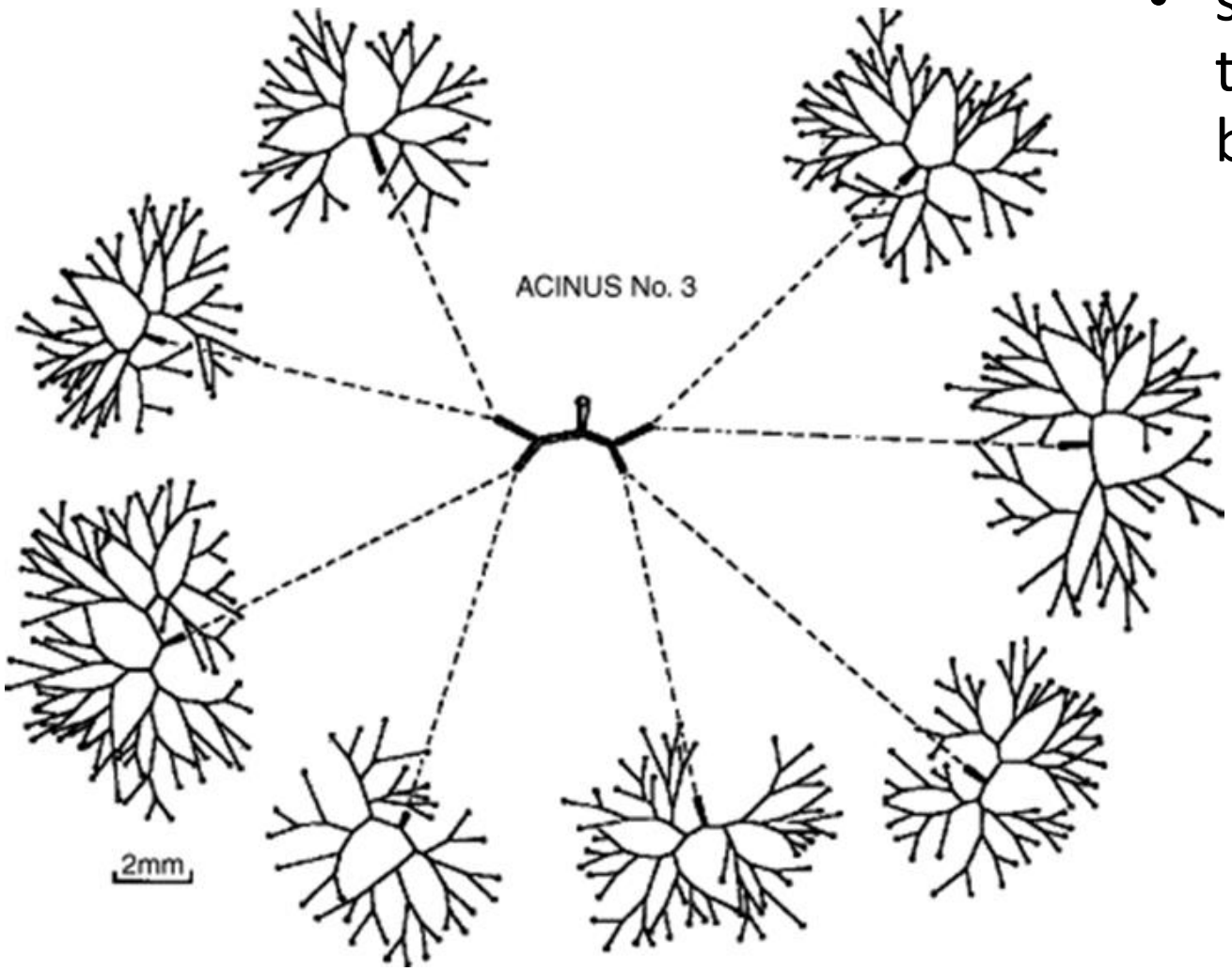


Functional classification of airways

- Conducting airways (= **anatomical dead space**)
  - nose (mouth)
  - larynx
  - trachea
  - main bronchi & bronchioles
  - gas conduction, warming
- Acinar airways (= **respiratory space**)
  - respiratory bronchioles
  - alv. ducts & sacs
  - alveoli
  - gas exchange
- The concept of acinus
  - the functional 3-D unit - part of parenchyma - in which all airways have alveoli attached to their wall and thus participating in gas exchange

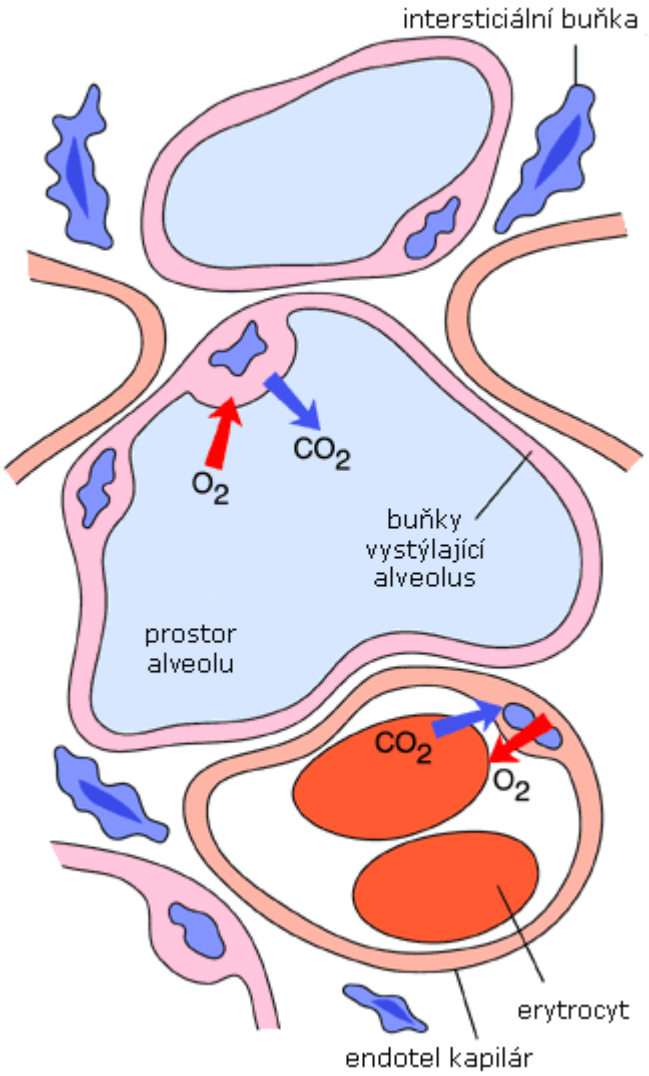


3-D acinus



- structure following terminal bronchiole
  - 3 generations of branching of resp. bronchiole and subsequent approx. 8 generations of branching of alveolar dusts
  - every pulmonary lobule (= anatomical term) contains 10 - 30 acini

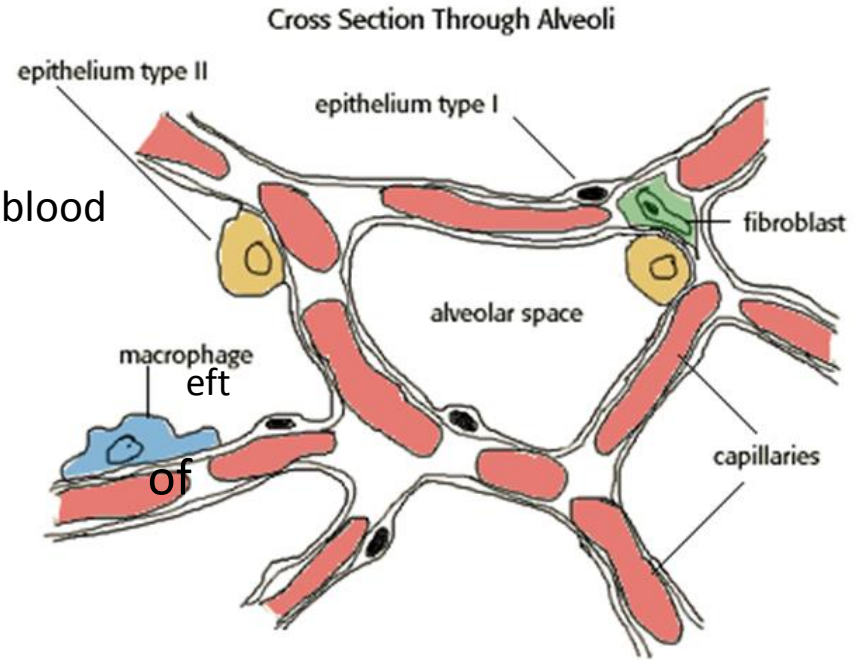
Gas exchange in lungs



- main function of respiratory system – **gas exchange between blood and outside environment** – is governed by temporally changing requirements of organism for O_2
  - maintained in optimum by regulation of intensity of ventilation (see further)
- requirements defined mainly by consumption of **ATP** and its replenishing by **mitochondria**
  - oxidative phosphorylation
  - other O_2 consuming processes
- alveolo-capillary gas exchange takes place from alveolus to blood by **simple diffusion** through alveolar septum, lung intersticium and capillary wall
- driving force for O_2 (and reciprocally for CO_2) is the gradual decrease of its partial pressure, i.e. **concentration gradient** between inhaled air, blood and tissues:
  - partial pressure = the pressure that the gas would have if it alone occupied the same volume at the same temperature

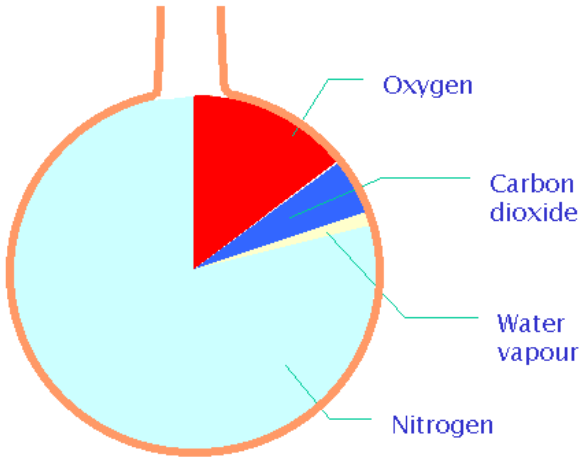
Gas exchange in lungs

- reasons for normal gradual decrease of PO_2 between air and blood:
  - competition with CO_2 in alveoli
    - up to the atmospheric pressure
      - alveolar gas equation $P_{AO_2} = P_{IO_2} - (P_{aCO_2}/R)$
  - less that 100% diffusion across alveolo-capillary membrane
    - irregularity of its thickness
    - lower solubility of O_2 compared to CO_2
  - physiological right-left shunt
    - mixing of oxygenated and deoxygenated blood
      - nutritional supply of large airways by aa. bronchiales and their drainage to v. pulmonalis
      - drainage of vv. coronarie into l atrium
  - physiologically a small fraction abnormal Hb
    - Met-Hb
    - COHb
  - gradual consumption of O_2 along acinus



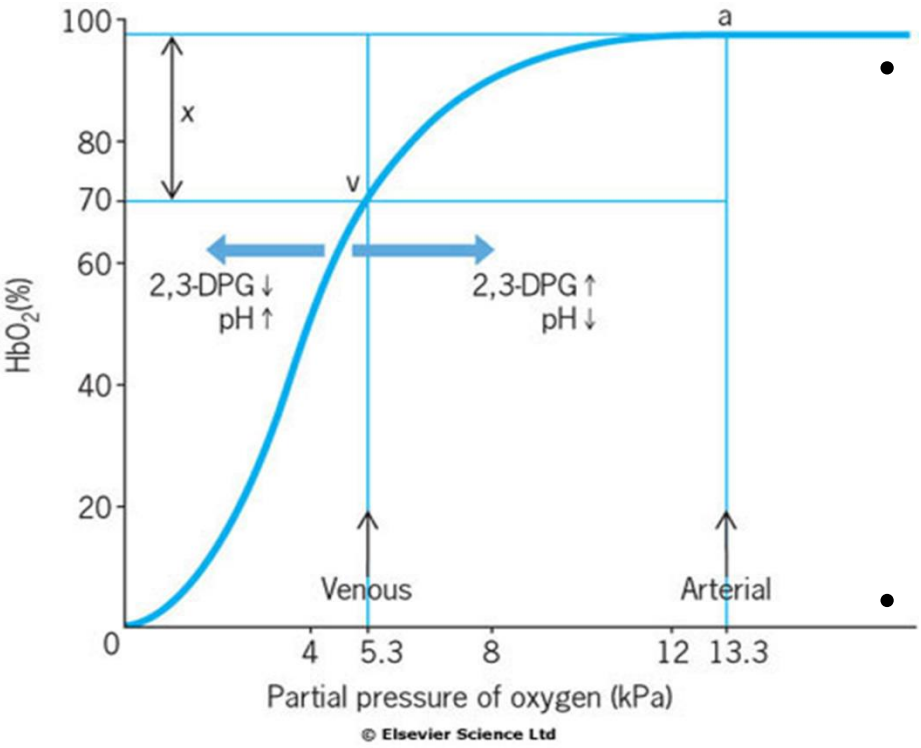
Quantitatively

- (1) inhaled **atmospheric** air
  - 21% O_2, 0.03% CO_2, 78% N_2, water gases 0.6% and the rest other gases (argon, helium, ..)
    - atm. pressure 760 mmHg (101 kPa)
    - PO_2: 0.21 x 760 = 160 mmHg
    - analogically PCO_2 = 0.3mmHg
- (2) **alveolar** air (mixture of inhaled and exhaled air)
  - P_AO_2 = 100mmHg (13.3kPa), P_ACO_2 = 40 mmHg (5.3kPa)
    - P_AO_2 in alveolus slightly lower than atmospheric due to higher CO_2 content in alveolus (diffusion from blood)
- (3) **arterial** blood
  - PaO_2 = 90mmHg (12kPa), $PaCO_2$ = 45 mmHg
    - diffusion of oxygen not 100% and there is also physiological shunt
- (4) **venous** blood
  - PvO_2 = 30 - 50mmHg



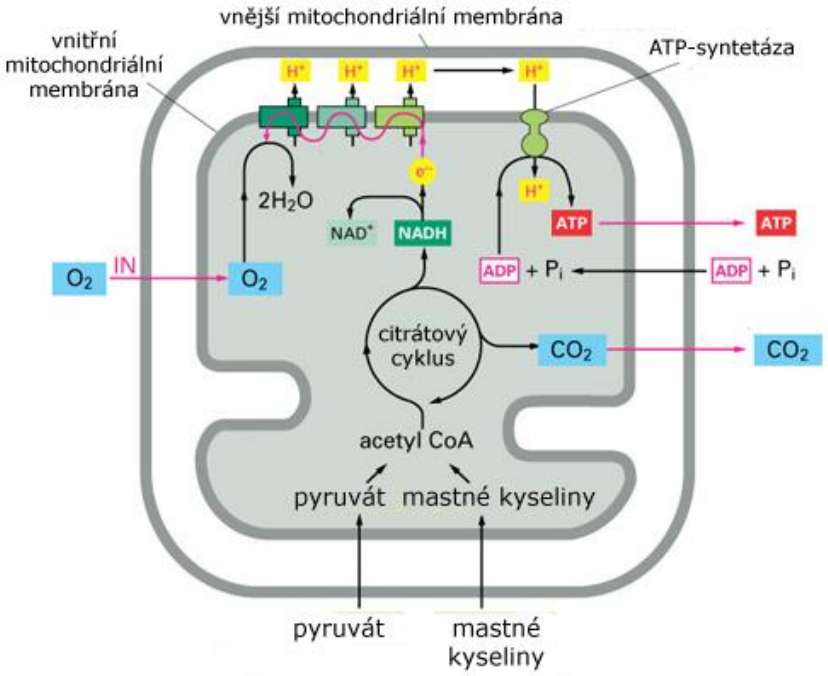
	air (P)	alveolar (P_A)	arterial (Pa)	venous (Pv)
O_2	21kPa/150mmHg	13.3 kPa/100mmHg	12kPa/90mmHg	5.3kPa/40mmHg
CO_2	0.03kPa/0.3mmHg	5.3kPa/40mmHg	5.3kPa/40mmHg	6.0kPa/45mmHg

Transport of gases in blood



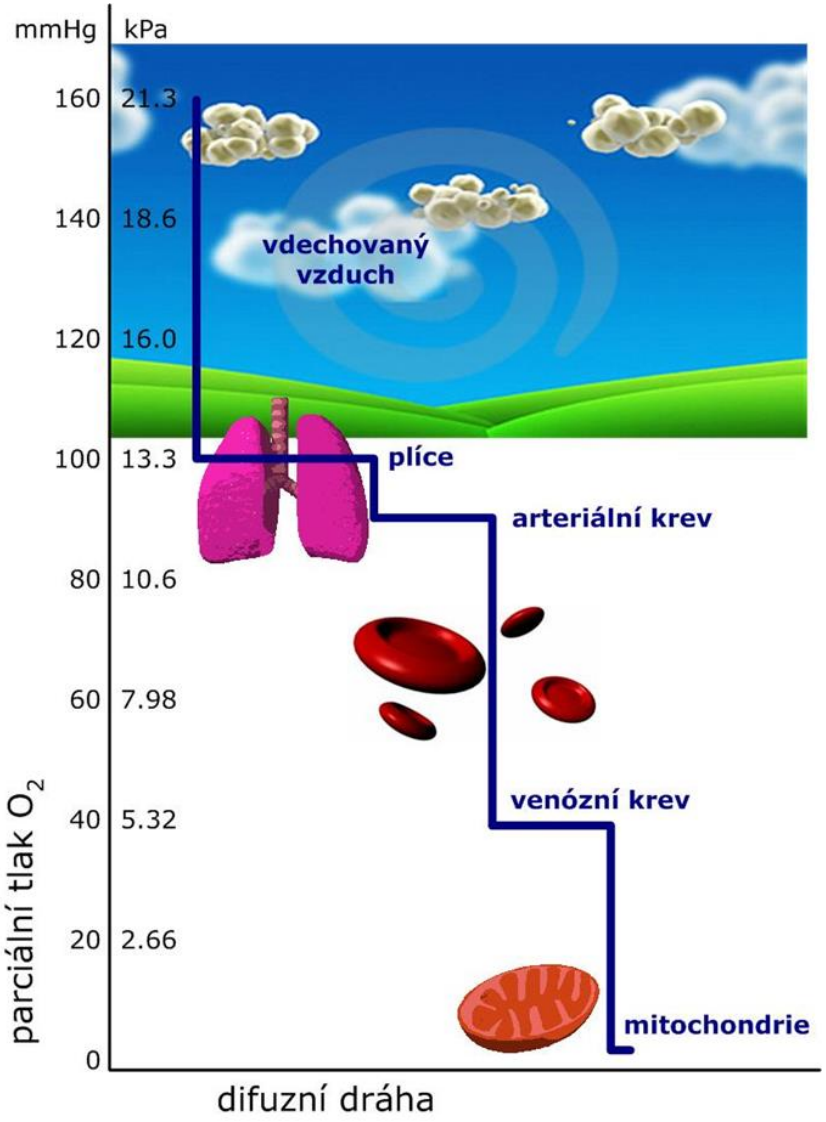
- CO_2 can be considered to be in simple solution in the plasma, the volume carried being proportional to its partial pressure (physically dissolved)
- O_2 is carried in chemical combination with hemoglobin in the red blood cells, and the relationship between the volume carried and the partial pressure (physically dissolved fraction) is not linear
  - in physiological PaO_2 (90mmHg/12kPa) and normal hemoglobin there is nearly 100% Hb saturation
    - if PaO2 > 1OkPa saturation do not significantly decreases
      - saturation measured by pulsion oxymetry
- O_2 diffuses to tissues according to demands of mitochondria
  - for adequate production of ATP jpO2 in tissues have to be > 0.13kPa (1mmHg) = critical oxygen tension
- organism needs oxygen:
  - ~ 250ml/min → 350l/day in rest
  - much more during exercise

Oxygen in the body

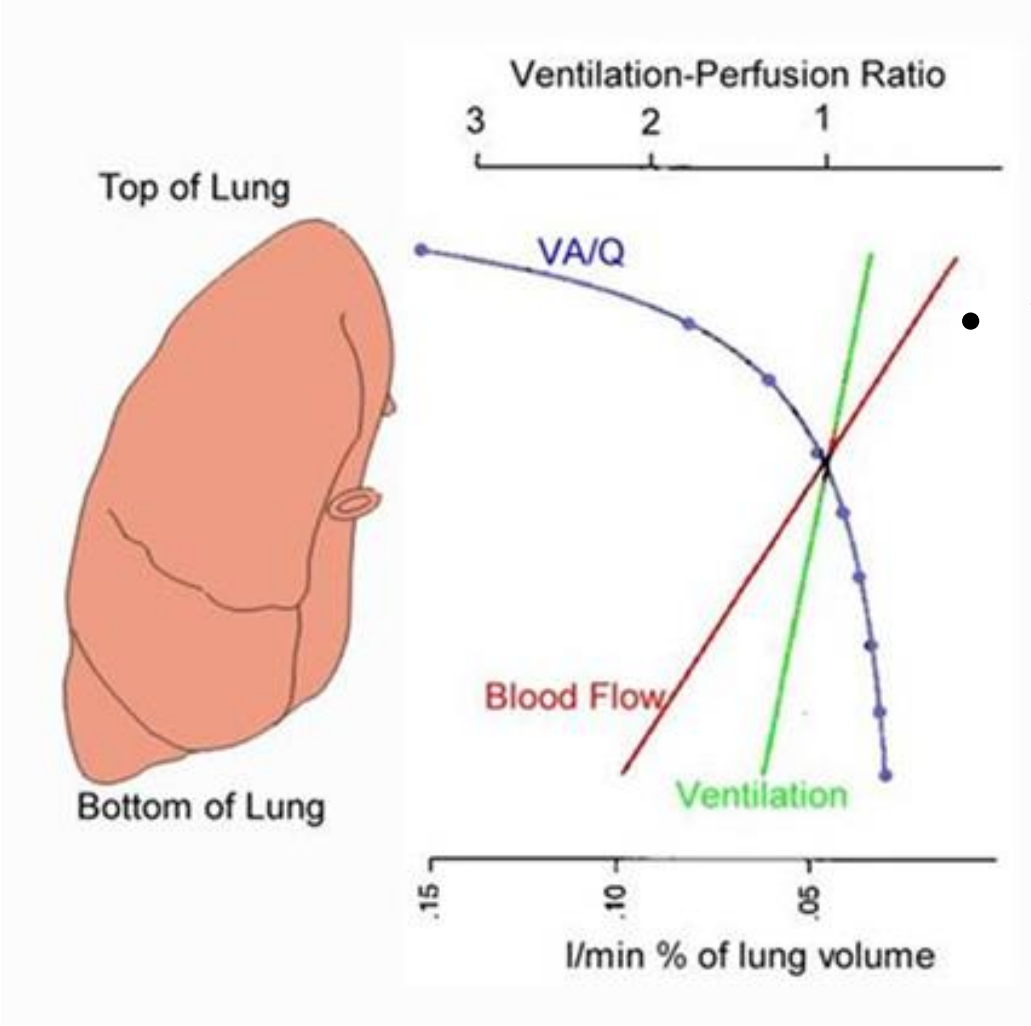


- there are no significant O_2 stores in the body
  - lasts for ~ 5min
  - therefore breathing has to be continuous process
  - disruption means
    - life-threatening emergency (<5min)
      - reversible vision loss in~7s, unconsciousness in ~10s
    - clinical death (~5-7min), event. brain death
    - death of the whole organism (>10min)
- 85-90% used in aerobic metabolism in ATP production
  - maintenance of ion gradients
  - muscle contraction
  - chemical synthetic reactions
- remaining processes are less sensitive to ↓PaO_2
  - hydroxylation of steroids
  - detoxification of xenobiotics in liver
  - synthesis of NO (→ vasodilation)
  - degradation of haem by hemoxygenase

Summary: The lung as a part of the "O_2 pathway"

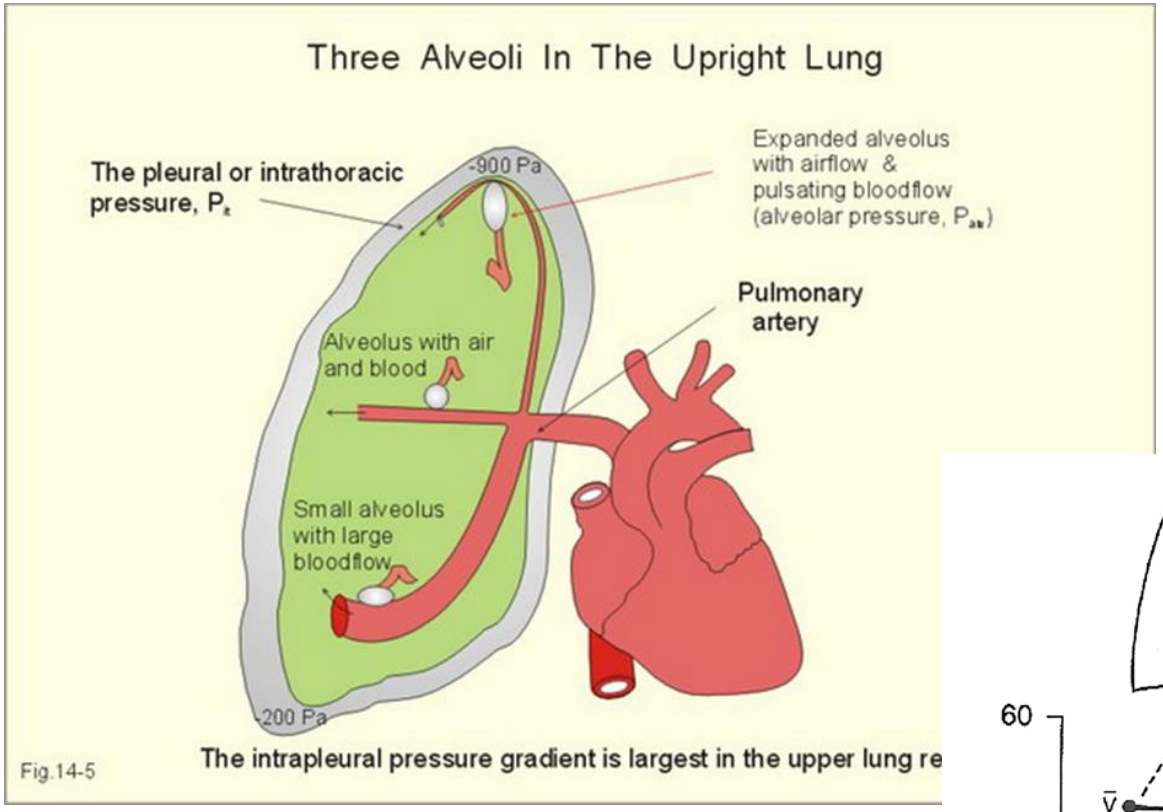


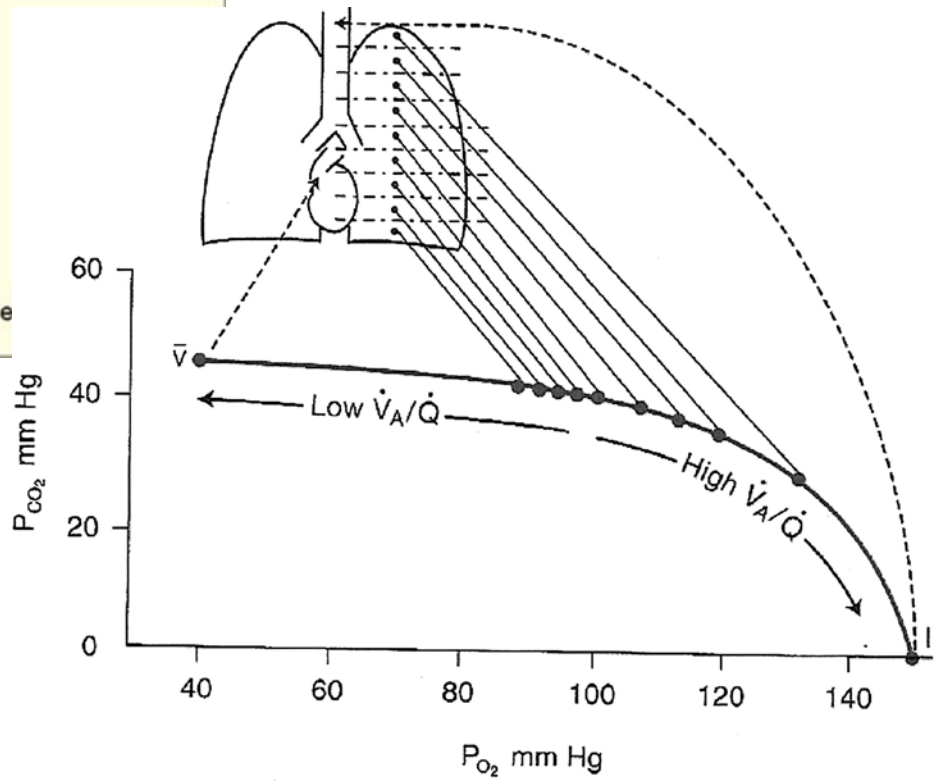
Relationship between ventilation and perfusion



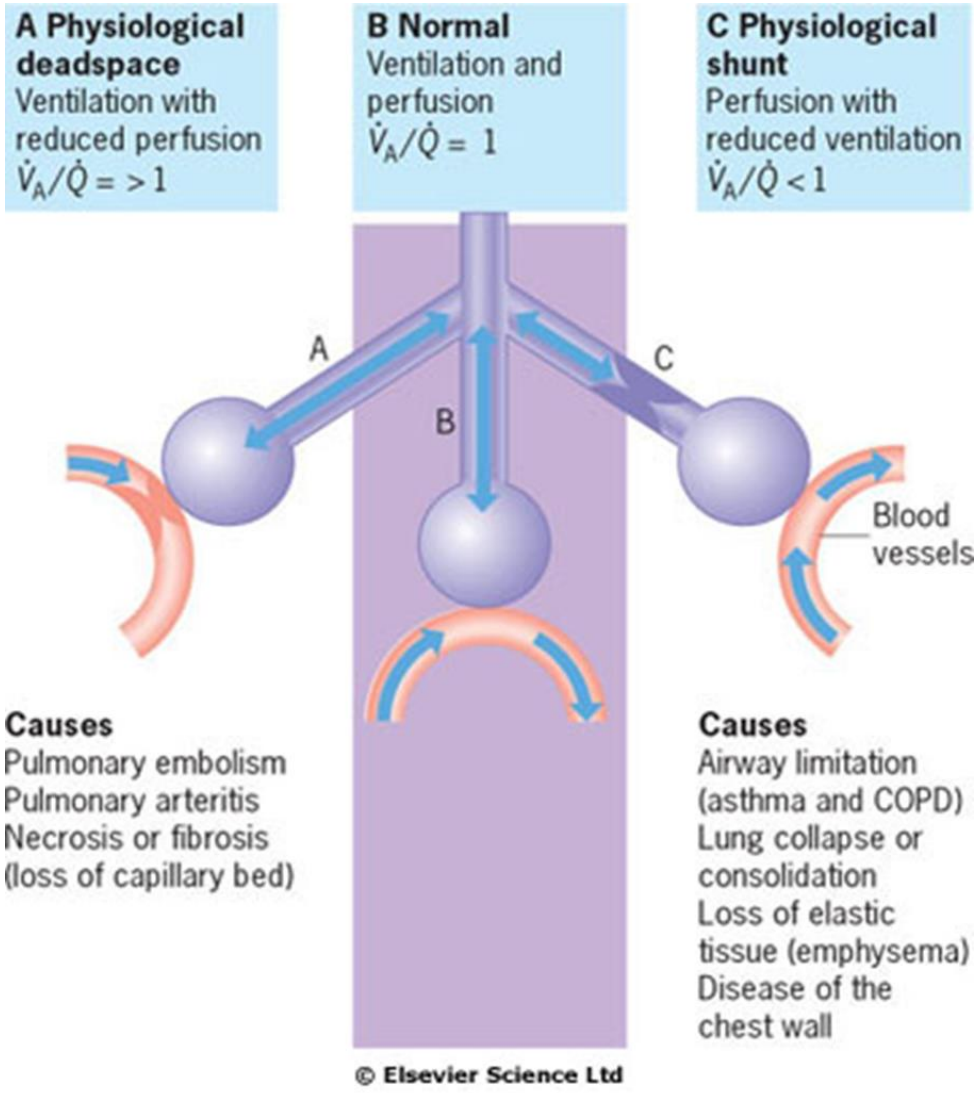
- For efficient gas exchange it is important that there is a match between ventilation of the alveoli (V_A) and their perfusion (Q)
- There is a wide variation in the **V_A/Q ratio** to some extent already in healthy subjects
  - tendency for ventilation not to be matched by perfusion towards the apices, with the reverse occurring at the bases
    - **physiological dead space** in apexes (V_A/Q = 3.3))
    - **physiological shunt** in bases (V_A/Q = 0.7)

Normal lung

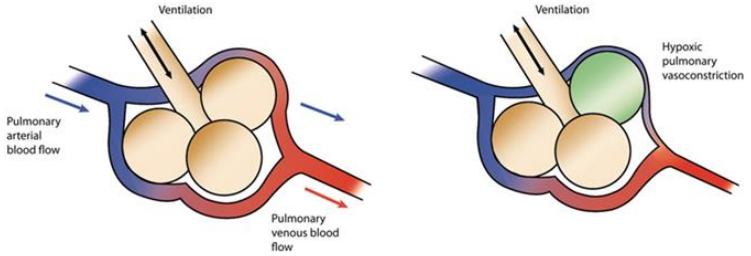

Three Alveoli In The Upright Lung
The pleural or intrathoracic pressure, P_{pl}
-900 Pa
Expanded alveolus with airflow & pulsating bloodflow (alveolar pressure, P_{alv})
Pulmonary artery
Alveolus with air and blood
Small alveolus with large bloodflow
-200 Pa
Fig.14-5
The intrapleural pressure gradient is largest in the upper lung re


60
40
20
0
P_{CO_2} mm Hg
$\bar{V}$
Low $\dot{V}_A/\dot{Q}$
High $\dot{V}_A/\dot{Q}$
40
60
80
100
120
140
P_{O_2} mm Hg

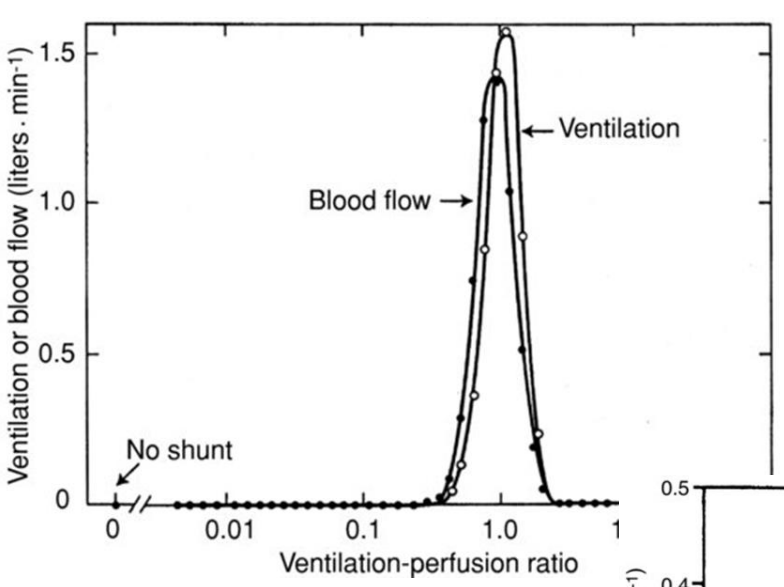
Ventilation-perfusion inequality (mismatch)

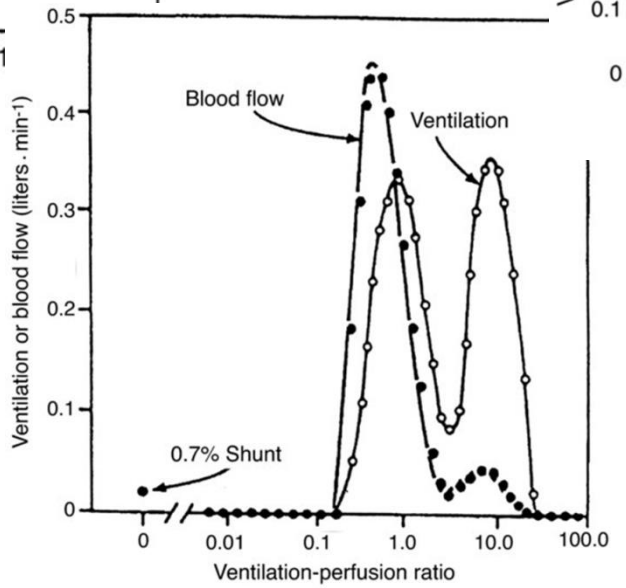


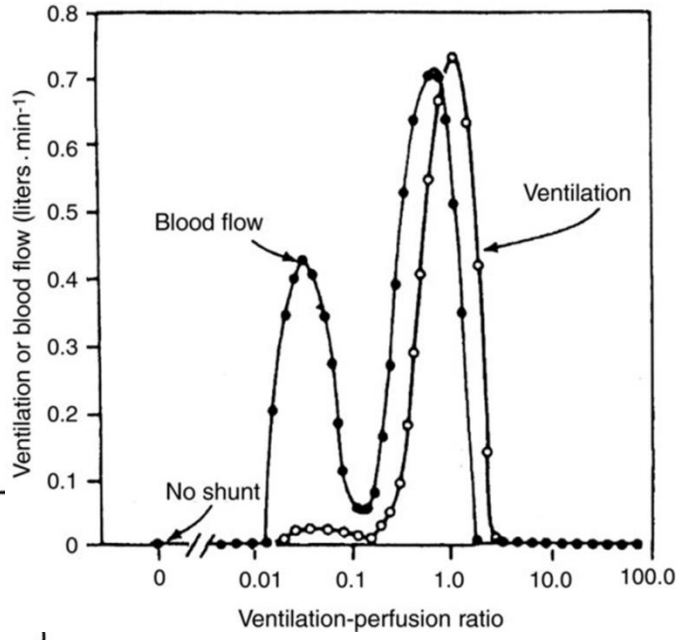
- V_A/Q inequality (mismatch) is significantly increased in many lung diseases and contributes to their pathophysiology
  - ↑ V_A/Q ratio (i.e. ↑ **dead space**)
    - e.g. pulmonary embolism
  - ↓ V_A/Q ratio (tj. ↑ **pulmonary shunt**)
    - obstructive diseases
    - lung collapse
- optimalisation of ↓ V_A/Q - **vasoconstriction reflex**
  - vessels around hypoventilated part of the lung contract
  - but!!! see obstructive diseases → development of pulmonary hypertension



Example of a distribution of ventilation-perfusion ratios



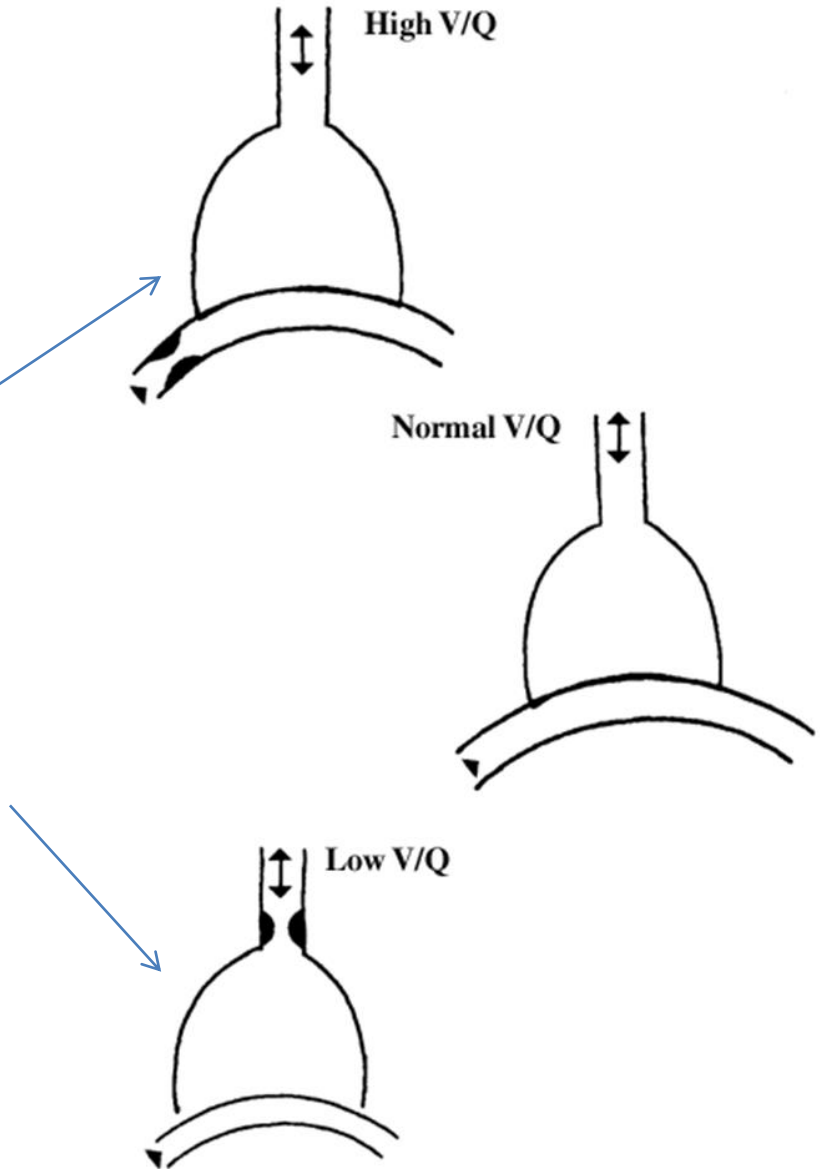




V_A and Q measured with the multiple inert gas infusion technique. [Left] healthy subject, [Middle] COPD type A (i.e. emphysema), [Right] COPD type B (i.e. chronic bronchitis).

Ventilation-perfusion inequality

- Ventilation-perfusion mismatch is by far the most common cause of arterial hypoxaemia
  - hypoxaemia occurs more readily than hypercapnia because
    - carbon dioxide diffuses more readily than oxygen
    - oxygen and carbon dioxide are carried in the blood differently
      - haemoglobin is already saturated with oxygen, there is no significant increase in the blood oxygen content as a result of increasing the alveolar PO2 through hyperventilation
- The effect of an increased **dead space** (V_A/Q ratio > 1) can usually be overcome by a compensatory hyperventilation of normally perfused alveoli
  - alveolar hyperventilation reduces the alveolar PCO2 and considerable diffusion of CO2 leads to a proportional fall in the carbon dioxide content of the blood
- An increased **shunting** (V_A/Q ratio < 1) results in arterial hypoxaemia
    - cannot be compensated for by hyperventilation
- In advanced disease this compensation cannot occur, leading to increased alveolar and arterial PCO2, together with hypoxaemia which cannot be compensated by increasing ventilation



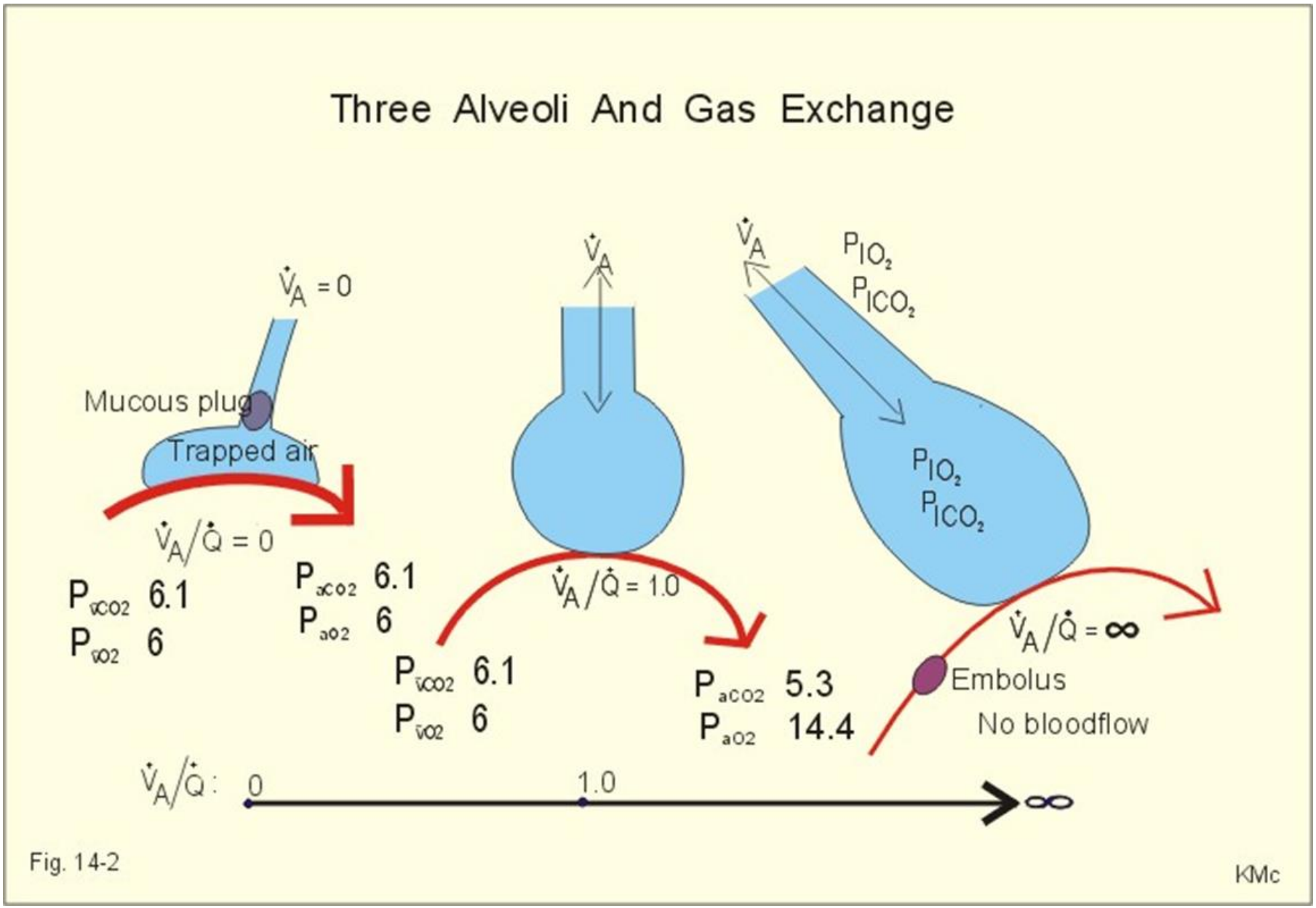
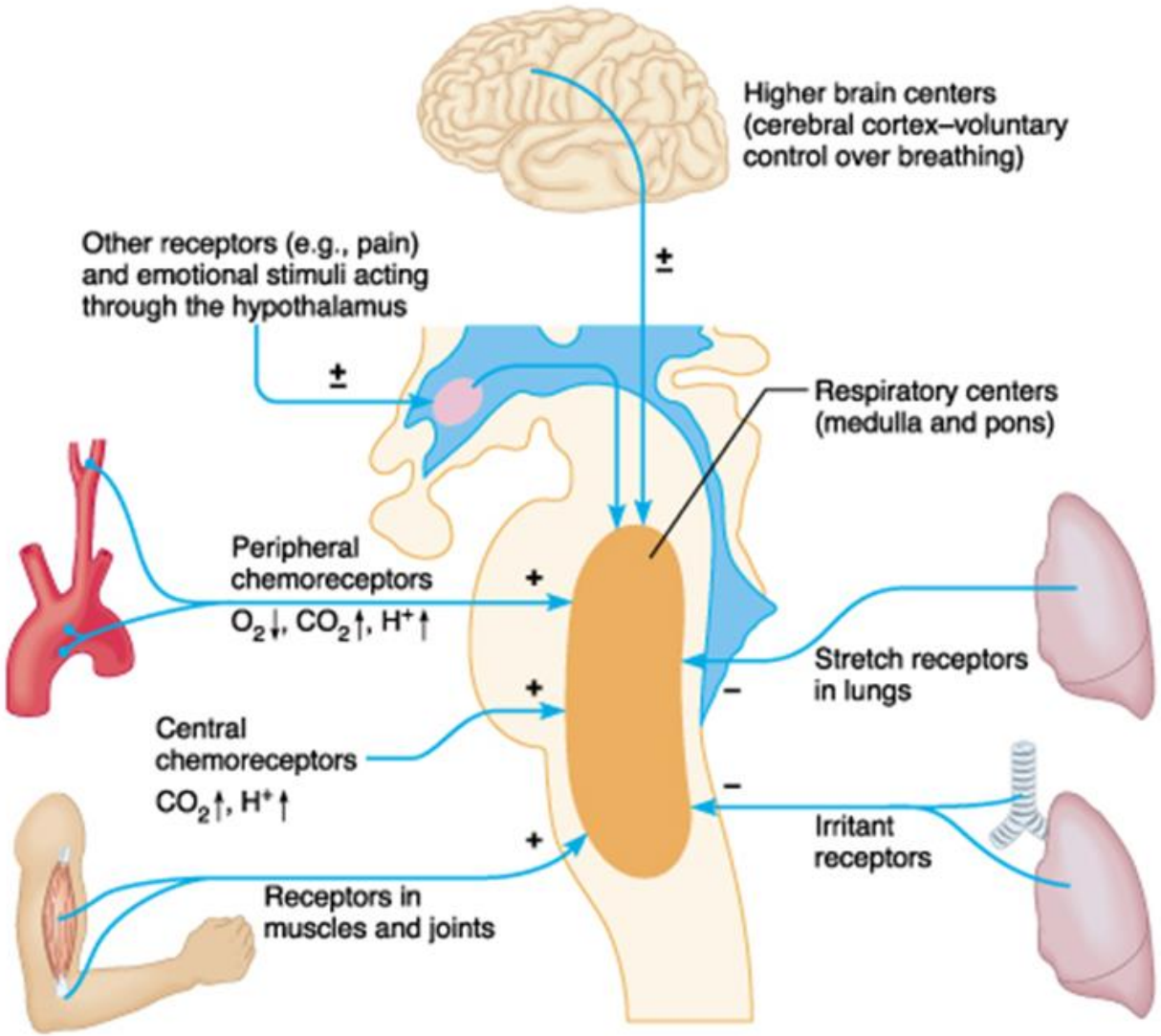

Three Alveoli And Gas Exchange
$\dot{V}_A = 0$
Mucous plug
Trapped air
$\dot{V}_A/\dot{Q} = 0$
$P_{\bar{v}CO2}$ 6.1
$P_{\bar{v}O2}$ 6
P_{aCO2} 6.1
P_{aO2} 6
$\dot{V}_A$
$\dot{V}_A/\dot{Q} = 1.0$
$P_{\bar{v}CO2}$ 6.1
$P_{\bar{v}O2}$ 6
P_{aCO2} 5.3
P_{aO2} 14.4
$\dot{V}_A$
P_{IO_2}
P_{ICO_2}
P_{IO_2}
P_{ICO_2}
$\dot{V}_A/\dot{Q} = \infty$
Embolus
No bloodflow
$\dot{V}_A/\dot{Q}$: 0 1.0 ∞

Fig. 14-2

KMc

CONTROL OF RESPIRATION & ITS DISORDERS

Control of respiration



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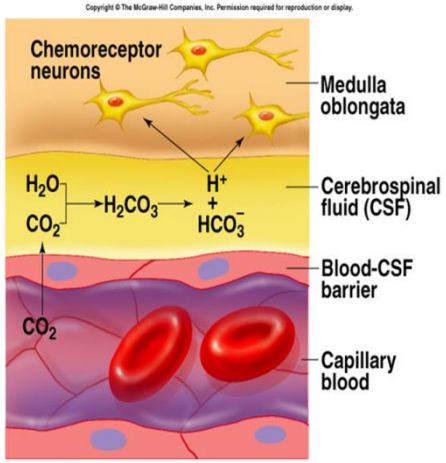
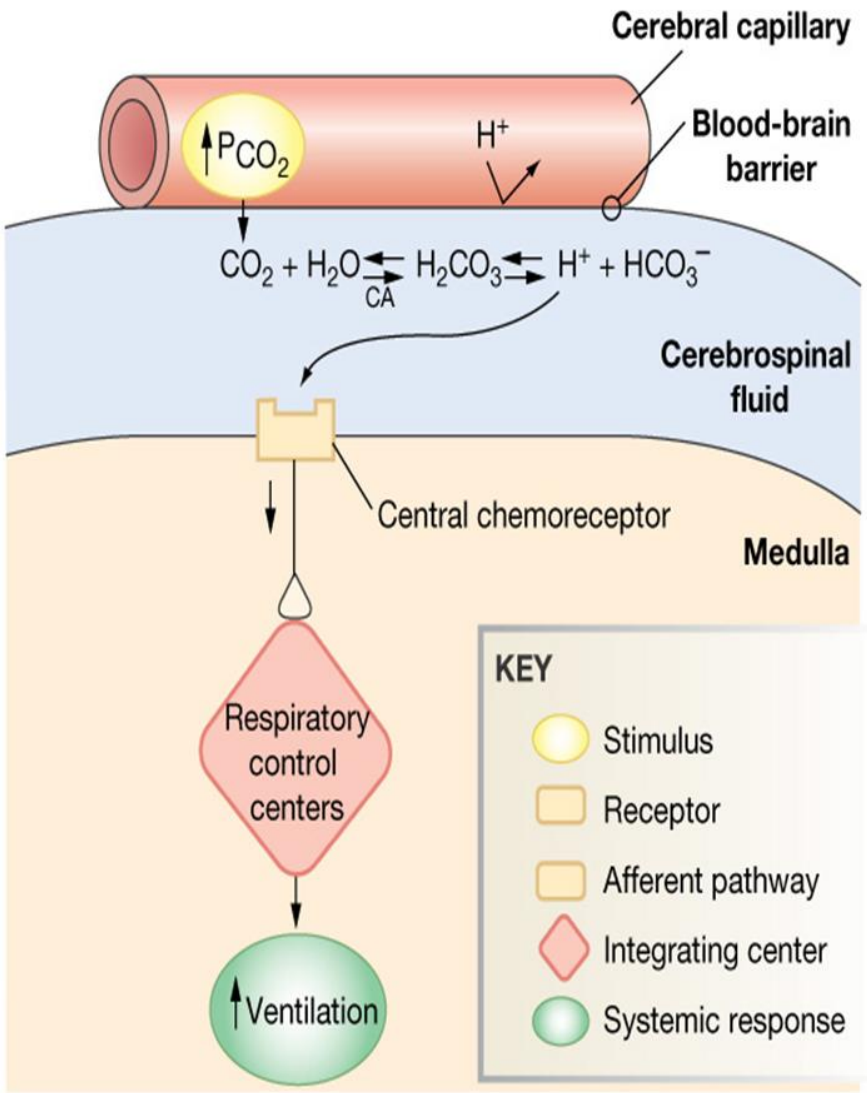
- central chemoreceptors in medulla oblongata



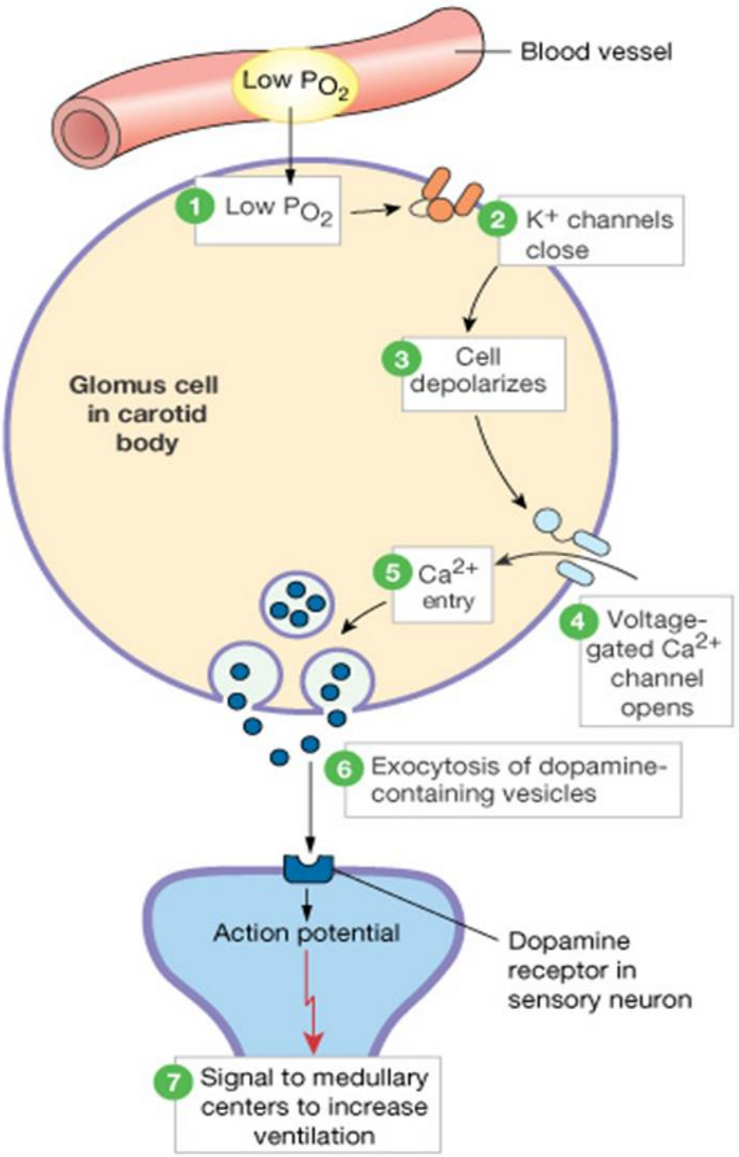
- peripheral chemoreceptors in aorta and glomus caroticum (via n. glossopharyngeus and vagus)
  - active when $\downarrow PaO_2$ below 10kPa
  - activation supported by hypercapnia
- pulmonary mechanoreceptors

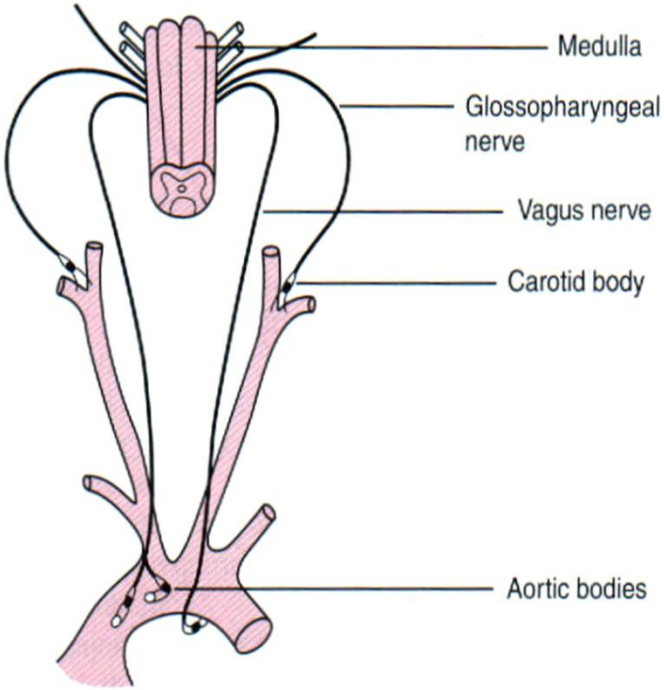
Central chemoreceptors



- sensitive to ↑$PaCO_2$ (and subsequent formation of H^+ in CF)
- H^+ cannot go through hematoencephalic barrier therefore response to olther than respiratory acidosis slower
  - increase in [H+] due to metabolic acidosis (e.g. diabetic ketoacidosis) will subsequently increase ventilation with a fall in $PaCO_2$ causing deep (Kussmaul) respiration
- very quick adaptation to acute or intermittent hypercapnia, however, gets adapted to chronic hypercapnia due to ↑HCO_3- in cerebrospinal fluid
  - problem in COPD - in these patients hypoxaemia is the chief stimulus to respiratory drive
  - oxygen treatment may therefore reduce respiratory drive and lead to a further rise in $PaCO_2$

Peripheral chemoreceptors - oxygen senzors

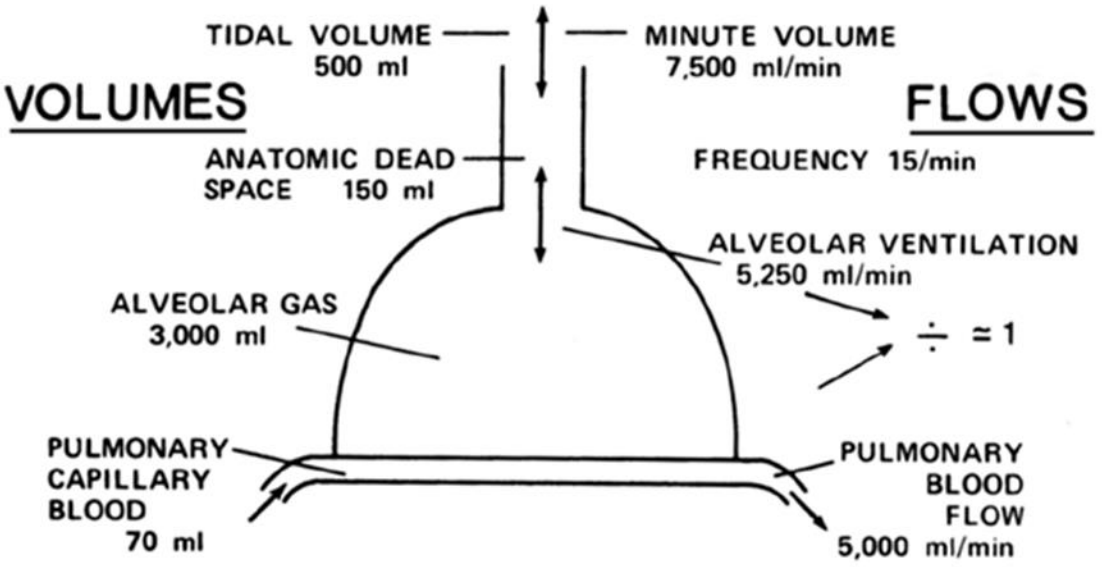




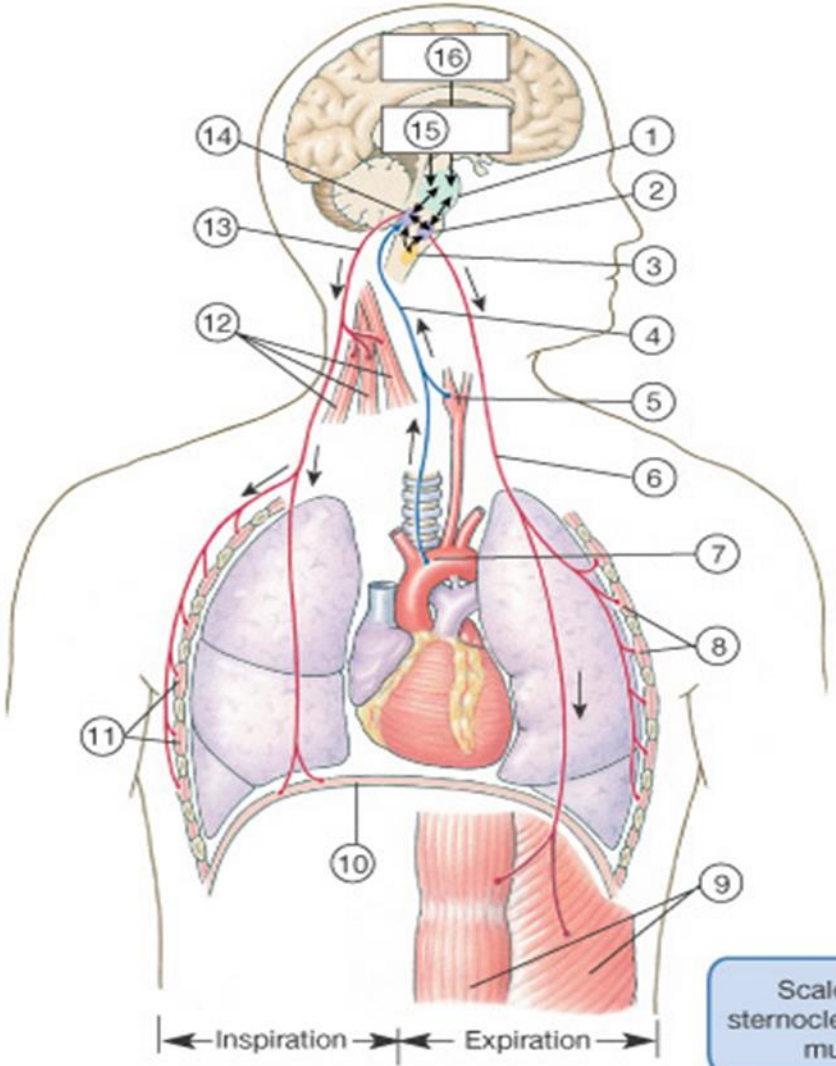
- Glomus caroticus and aortic bodies - sensitive to change of $Pa0_2$
  - decrease of 0_2 in these cells closes K^+ channels → depolarization → ↑ intracellular Ca^{2+} → excitation → activation of the respiratory centre
- When hypoxemia is not accompanied with hypercapnia, activation of this sensors is when PaO_2<7,3 kPa (55 mm Hg)

Respiratory stimuli

- Coordinated respiratory movements result from rhythmical discharges arising in interconnected neurones in the reticular substance of the brainstem (medulla oblongata), known as the **respiratory centre**
  - via the phrenic and intercostal nerves to the respiratory musculature (principal and aucilliary respiratory muscles)



- the pulmonary blood flow of 5 L/min carries 11 mmol/min (250 mL/min) of oxygen from the lungs to the tissues
- ventilation at about 6 L/min carries 9 mmol/min (200 mL/min) of carbon dioxide out of the body
- normal PaO_2 is between 11 and 13 kPa (83 - 98 mmHg)
- normal $PaCO_2$ is 4.8-6.0 kPa (36-45 mmHg)


16
15
14
1
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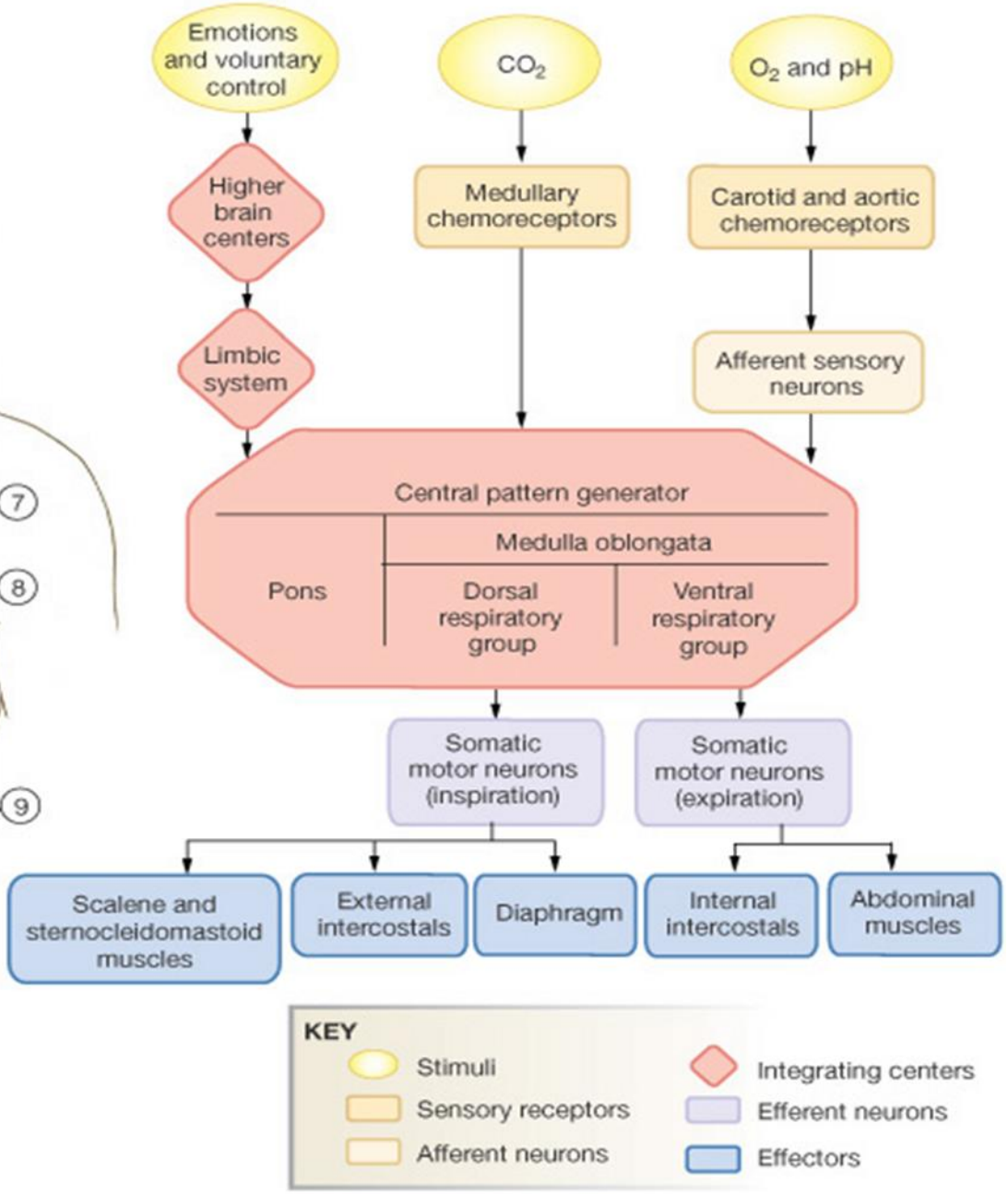
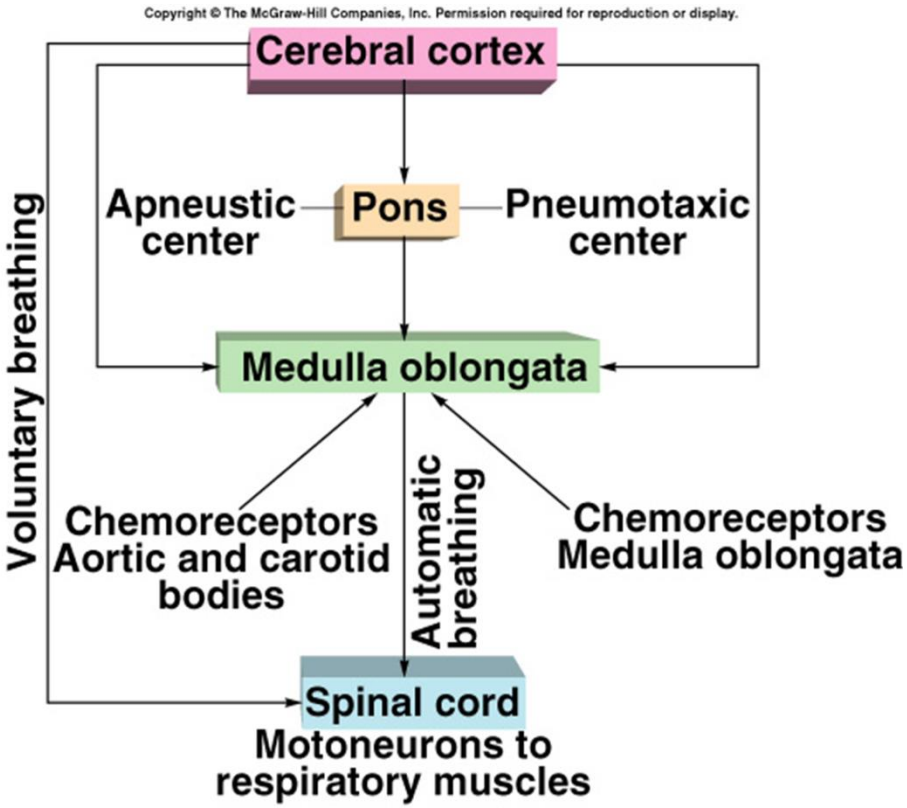
Inspiration
Expiration


Emotions and voluntary control
CO_2
O_2 and pH
Higher brain centers
Medullary chemoreceptors
Carotid and aortic chemoreceptors
Limbic system
Afferent sensory neurons
Central pattern generator
Medulla oblongata
Pons
Dorsal respiratory group
Ventral respiratory group
Somatic motor neurons (inspiration)
Somatic motor neurons (expiration)
Scalene and sternocleidomastoid muscles
External intercostals
Diaphragm
Internal intercostals
Abdominal muscles
KEY
Stimuli
Sensory receptors
Afferent neurons
Integrating centers
Efferent neurons
Effectors

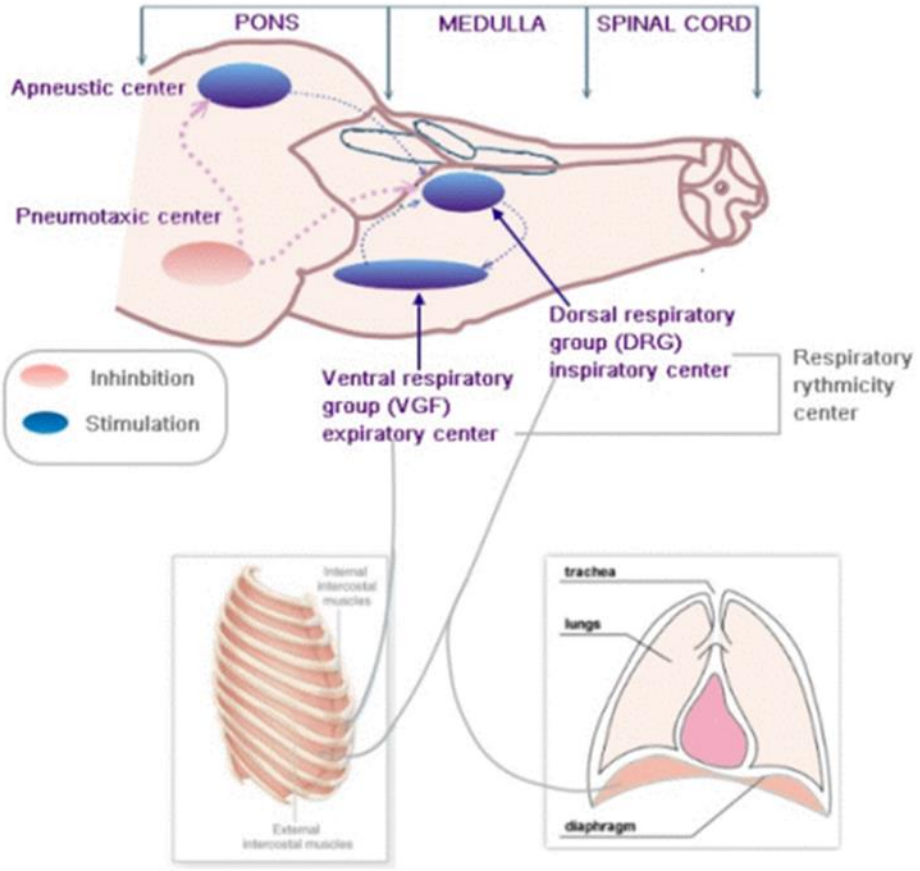
Respiratory centres



- Respiratory centre is formed by several groups of neurons:
  - The basic automatic rhytm of respiration is due to activity of Dorsal Respiratory Group (DRG) — inspiration neurons – efferent impulses go to diaphragma and inspiration intercostal muscles
    - DRG also obtain afferent stimuli from the peripheral chemoreceptors and several pulmonary receptors
  - Ventral Respiratory Group (VRG) contains both inspiration and expiration neurons
    - inactive during to normal ventilation, increased ventilation leads to their activation

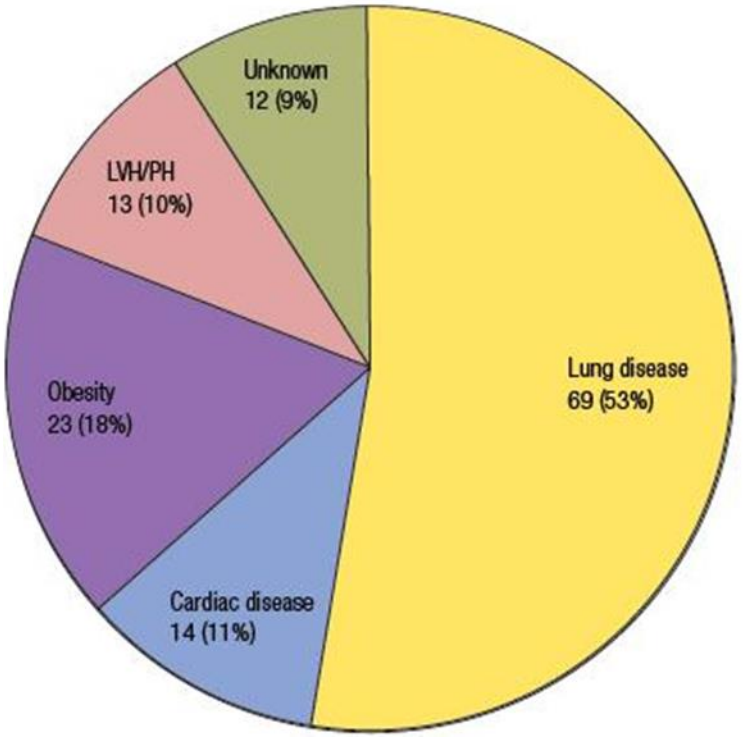
Higher respiratory centres

- Medulla
  - quiet inspiration
  - —effort inspiration and forced expiration
- Pons - Pneumotaxic and apneustic centres can modulate depth of ventilation and its frequency
  - Apneustic centre:
    - supports inspiration by the activity of inspiration neurons
  - Pneumotaxic centre:
    - antagonises apneustic centre
    - inhibition of inspiration
- Ventilation can be modulate by cortex, limbic systém and hypothalamus (emotions and diseases).

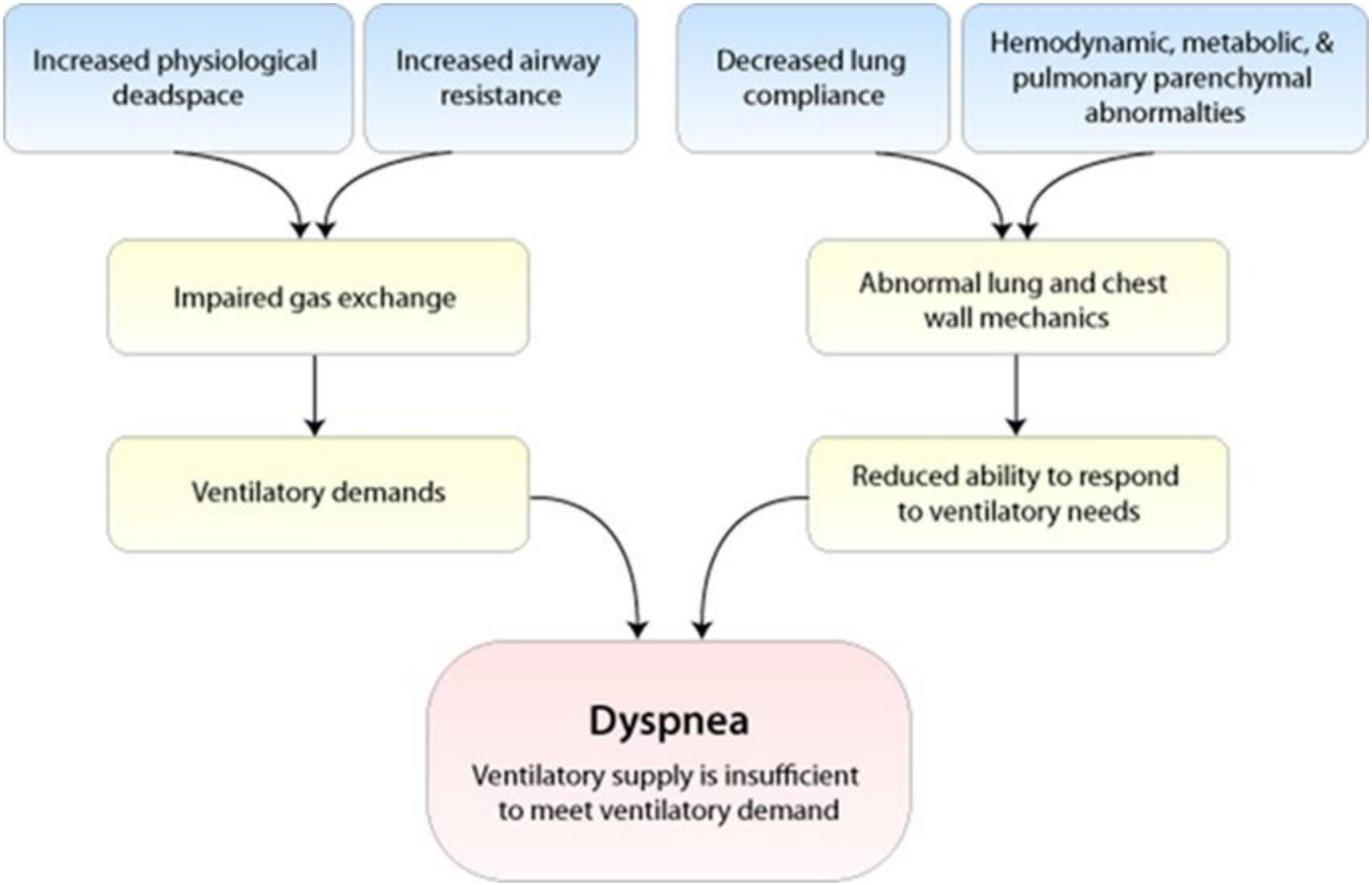


Dyspnea (breathlessness)

- on physical exertion is normal and not considered a symptom unless the level of exertion is very light, such as when walking slowly
- although breathlessness is a very common symptom, the sensory and neural mechanisms underlying it remain obscure
- the sensation of breathlessness is derived from at least three sources:
  - changes in lung volume
    - sensed by receptors in thoracic wall muscles signalling changes in their length
  - the tension developed by contracting muscles
    - this can be sensed by Golgi tendon organs
    - tension developed in normal muscle can be differentiated from that developed in muscles weakened by fatigue or disease
  - central perception of the breathing effort

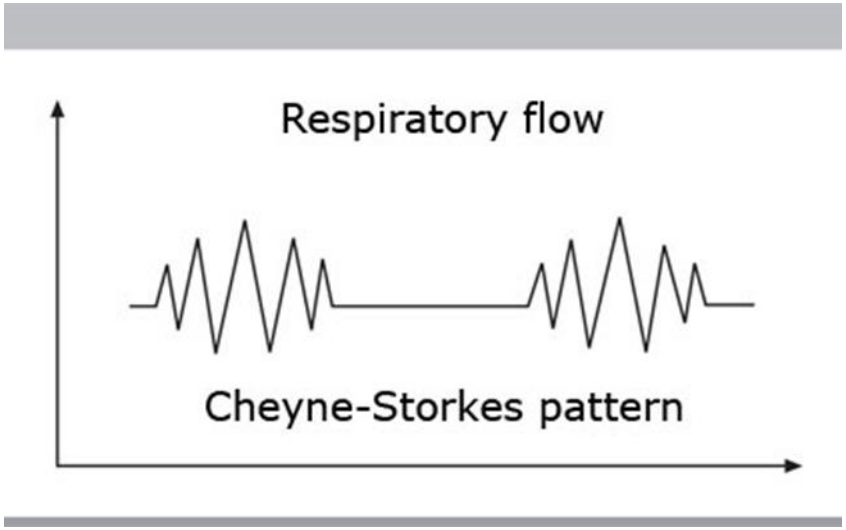


common causes of dyspnea


Increased physiological deadspace
Increased airway resistance
Decreased lung compliance
Hemodynamic, metabolic, & pulmonary parenchymal abnormalties
Impaired gas exchange
Abnormal lung and chest wall mechanics
Ventilatory demands
Reduced ability to respond to ventilatory needs
Dyspnea
Ventilatory supply is insufficient to meet ventilatory demand

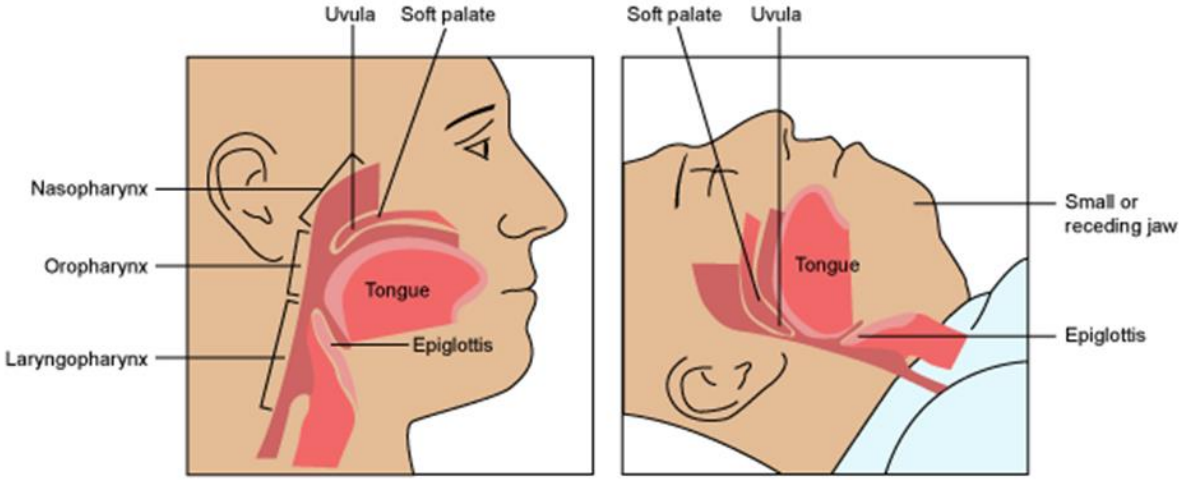
Apnea

- suspension of external breathing
- causes
  - voluntarily achieved (free diving)
  - drug-induced (e.g. opiate toxicity)
  - during sleep
    - mechanically induced (e.g. OSA)
    - infants (sudden death)
  - central apnea syndromes
    - periodical breathing
    - Cheyne-Stokes breathing
      - patients with cardiac failure
  - consequence of neurological disease or trauma



Obstructive sleep apnea (OSA)

- Episodic obstructions of airflow during sleep due to airway blockade
  - breathing pauses can last from a few seconds to minutes
  - may occur 30-60 times or more an hour
  - typically, normal breathing then starts again, sometimes with a loud snort or choking sound
- During apnea deep sleep shifts to light sleep
  - as a result, the quality of sleep is poor, which makes one tired during the day (excessive daytime sleepiness)
- Commonly undiagnosed, typically overweight adults
- Risks – due to intermittent hypoxia with significant Hb desaturation to levels as low as 50%
  - changes in the neurons of the hippocampus and frontal cortex
  - hypertension
  - coronary artery disease
  - type 2 diabetes
  - depression
  - sleepiness-related accidents



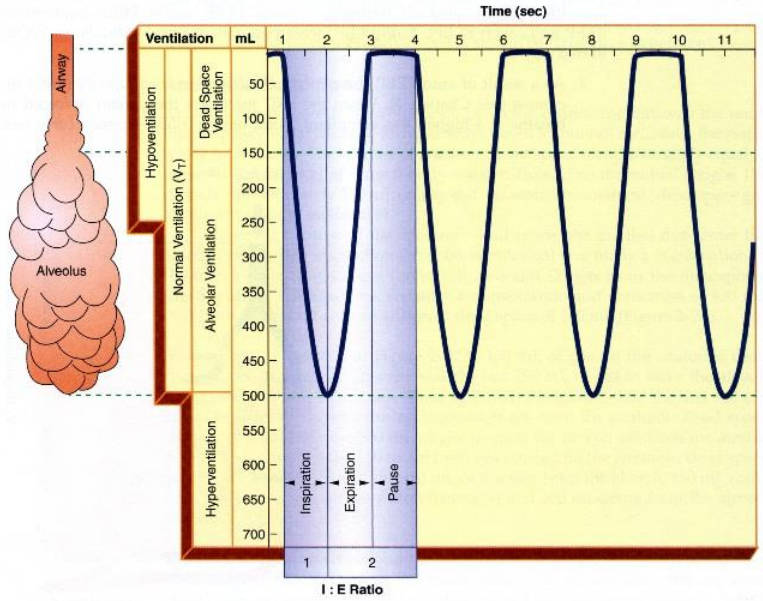


Figure 2–30. *Normal, spontaneous breathing (eupnea). The I:E ratio typically is 1:2.*

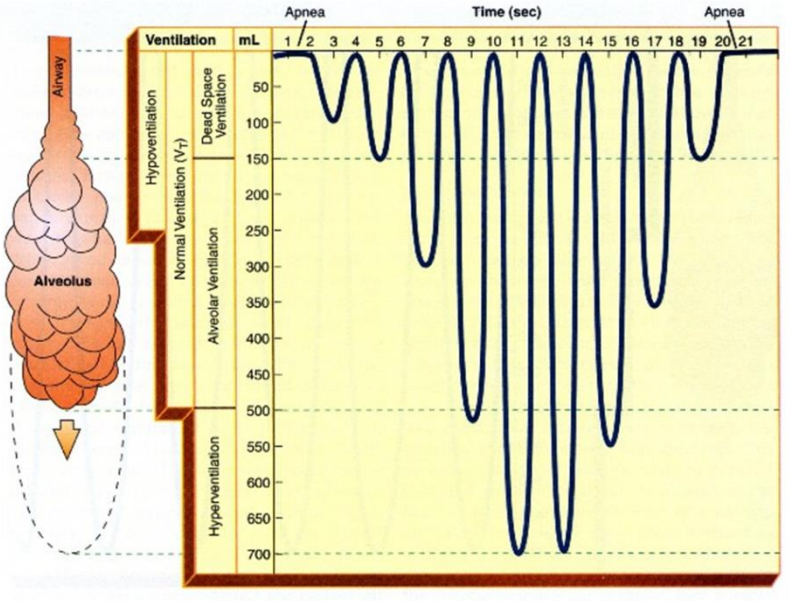


Figure 2–39. *Cheyne-Stokes respiration: A gradual increase and decrease in the volume and rate of breathing, followed by 10 to 30 seconds of apnea.*

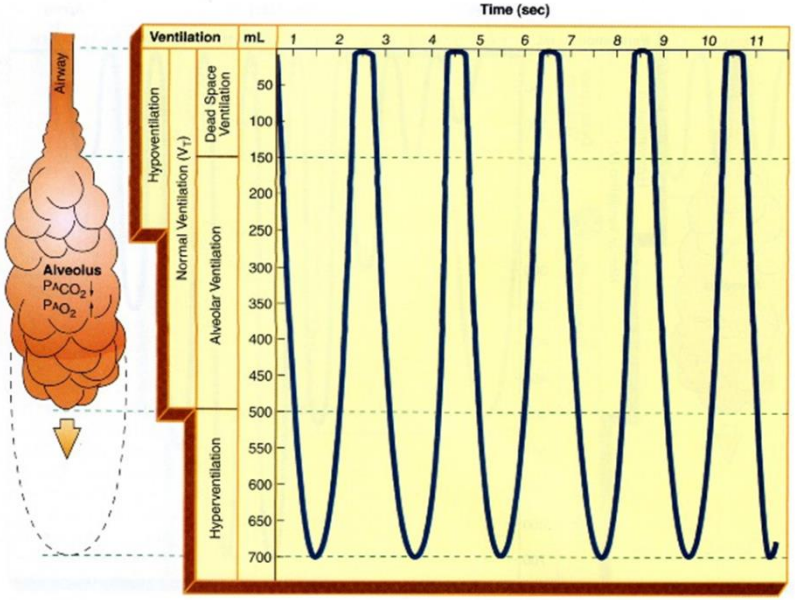


Figure 2–40. *Kussmaul's respiration: Increased rate and depth of breathing. This breathing pattern causes the $P_{A_{CO_2}}$ and Pa_{CO_2} to decrease and $P_{A_{O_2}}$ and Pa_{O_2} to increase.*

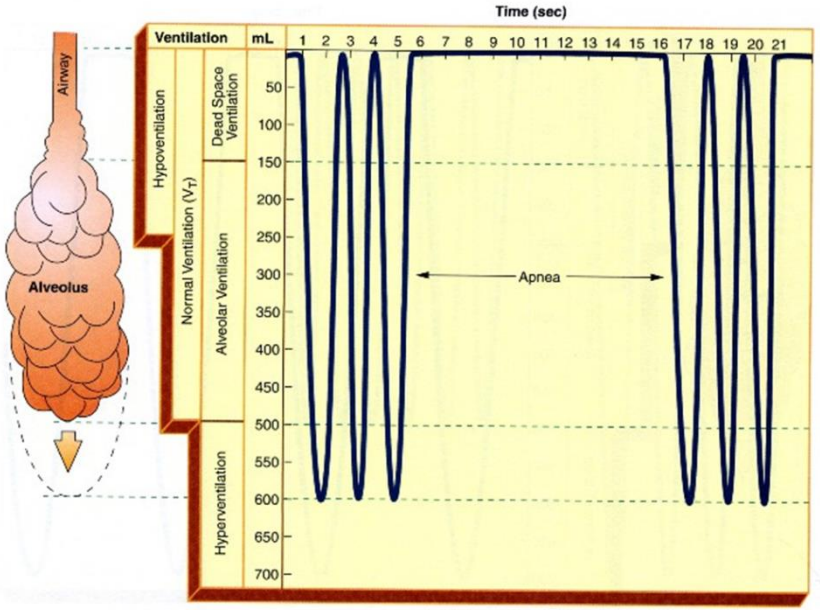


Figure 2–35. *Biot's respiration: Short episodes of rapid, uniformly deep inspirations, followed by 10 to 30 seconds of apnea.*


I'M HAVING TROUBLE BREATHING
LYNCH