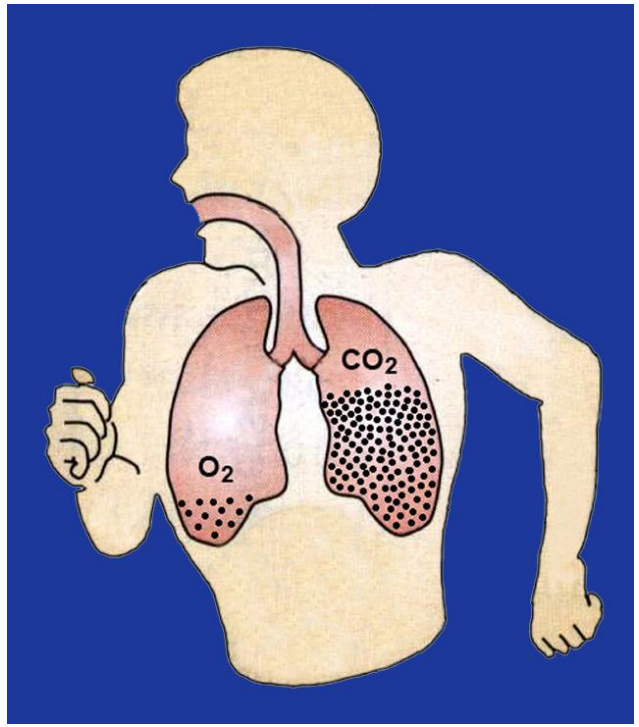
Pathophysiology of the respiratory system II – **Pulmonary gas exchange**

Physiological principles – alveolar ventilation and alveolar gas equations
Oxygen cascade
Respiratory insufficiency
Hypoxemia – classification of possible causes
(1) hypoventilation / (2) diffusion impairment / (3) shunt / (4) VQ mismatch
Ventilation – perfusion mismatch/(in)equality in detail



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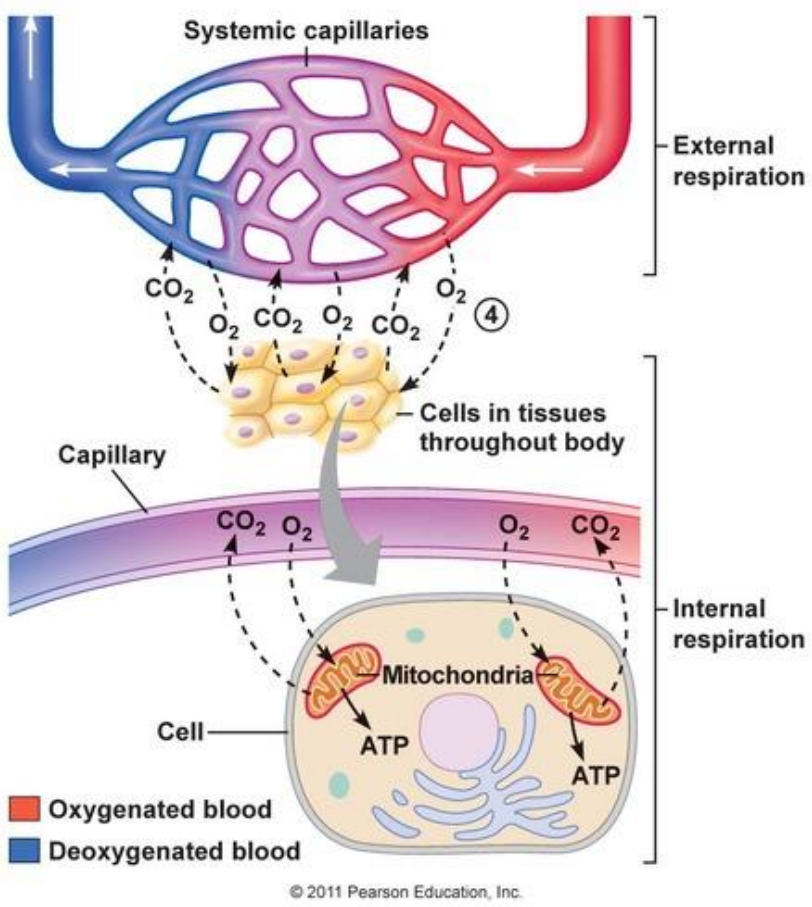
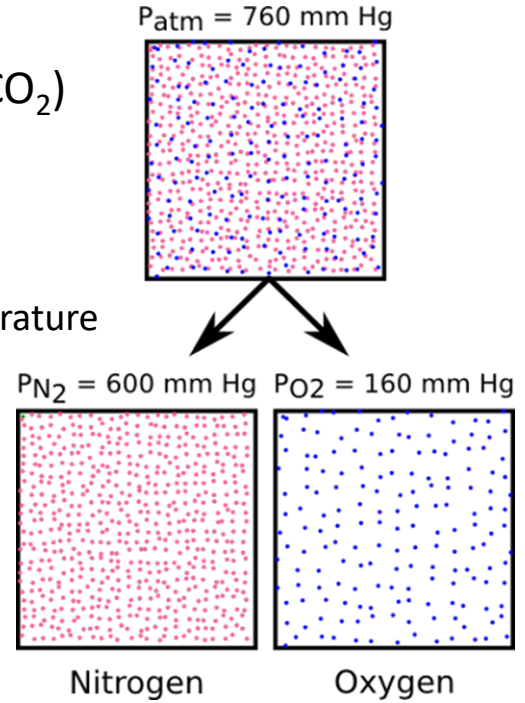
Gas exchange in lungs



- main function of respiratory system – **gas exchange between blood and outside environment** – is governed by temporally changing requirements of organism to maintain a stable pH (by excretion CO_2) and for O_2
  - maintained in optimum by regulation of intensity of ventilation (see control of ventilation further)
- requirements defined mainly by consumption of **ATP** and its replenishing by **mitochondria**
  - oxidative phosphorylation
  - other O_2 consuming processes
- driving force for O_2 exchange (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
- solubility of the gas matters
  - very high for CO_2 = there are **no biological barriers in the body to block CO_2 diffusion**
- tidal volume exchanged by each resting breathing cycle ads only 0.5L to FRC = meaning a composition of the alveolar air is more or less constant



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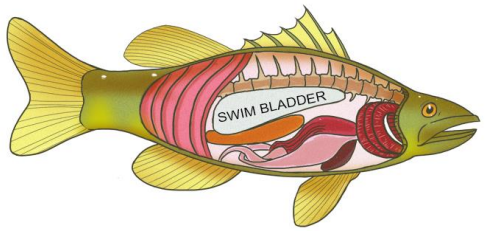
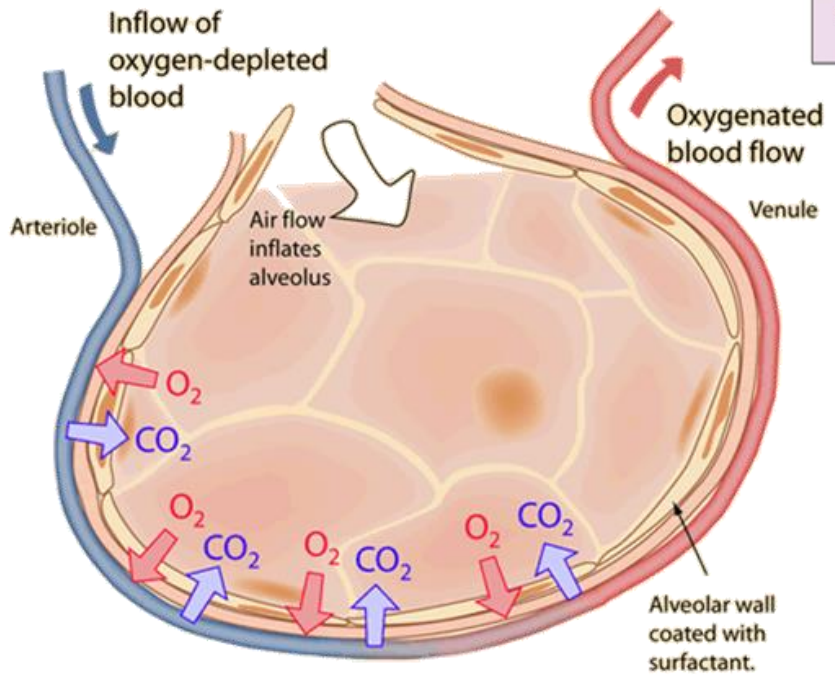
Gas exchange in lungs

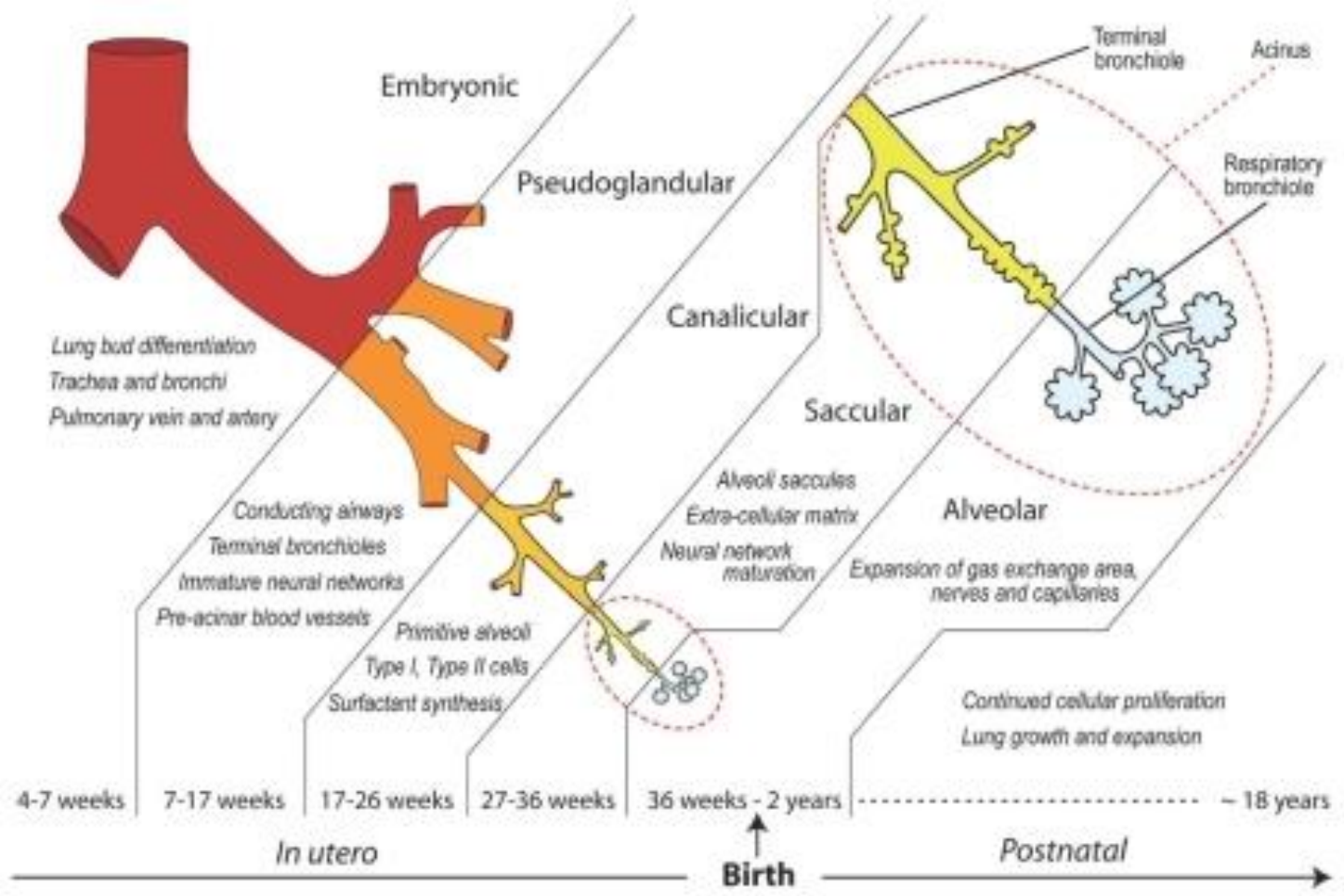
- alveolo-capillary gas exchange takes place in respiratory zone, i.e. between alveolus and blood by **simple diffusion** through alveolar septum, lung interstitium and capillary wall
  - in the past physiologist believed it was an active transport
    - fish, bird lung

	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	
Exchange surface	Bronchioles	12-23	0.5-1	2×10^4 – 8×10^7	100 – 5×10^3
	Alveoli	24	0.3	$3\text{-}6 \times 10^8$	$>1 \times 10^6$





Lung development in humans (from birth until maturity ~20-fold increase in gas-exchange surface area)



(Kajekar R. 2007. Environmental factors and developmental outcomes in the lung. Pharmacol Therap 114:129–145)

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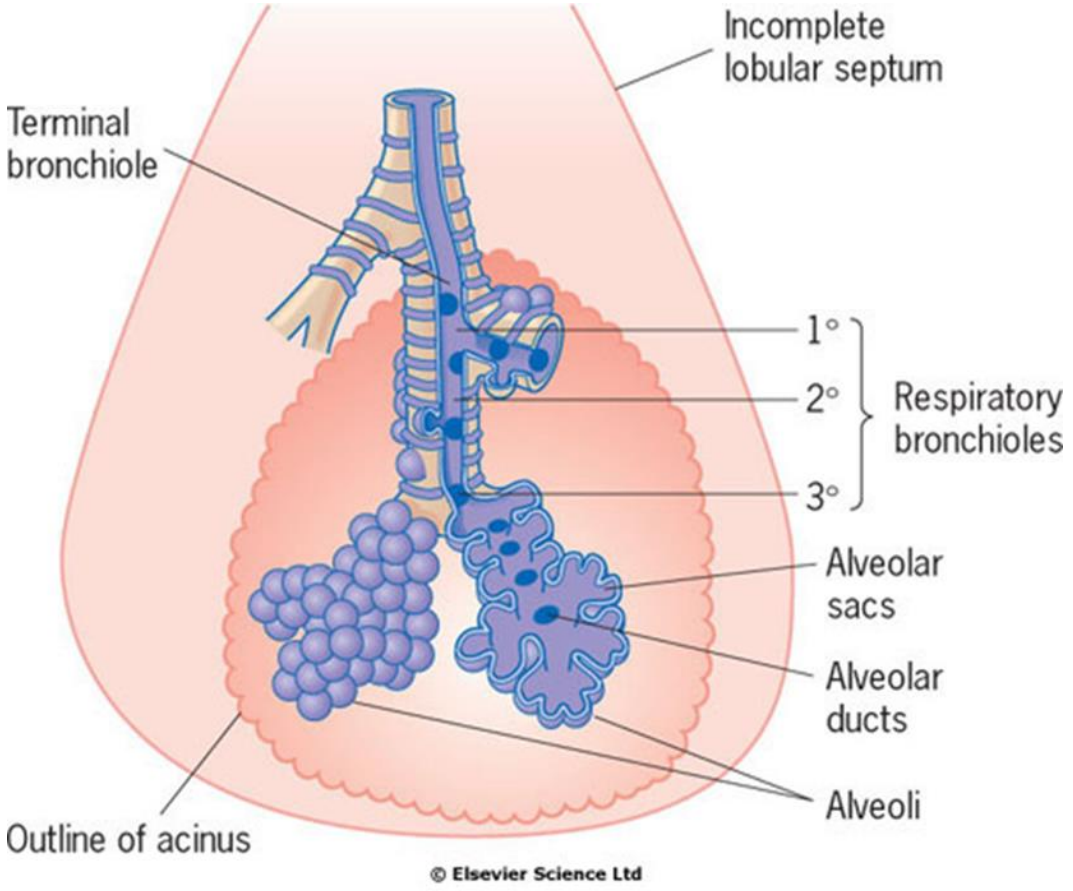
Functional classification of airways

- Conducting airways (= **anatomical dead space**)
  - nose (mouth)
  - larynx
  - trachea
  - main bronchi & bronchioles
  - humidification & warming, defence
- Acinar airways (= **respiratory space**)
  - respiratory bronchioles
  - alveolar 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



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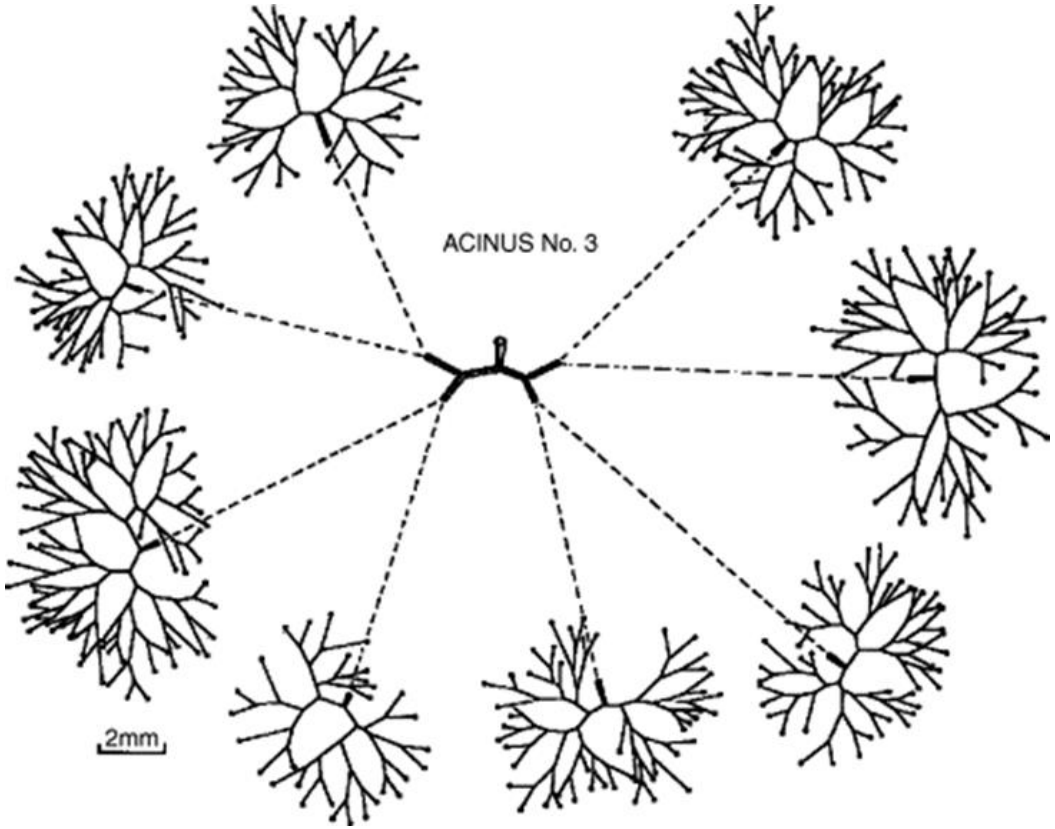
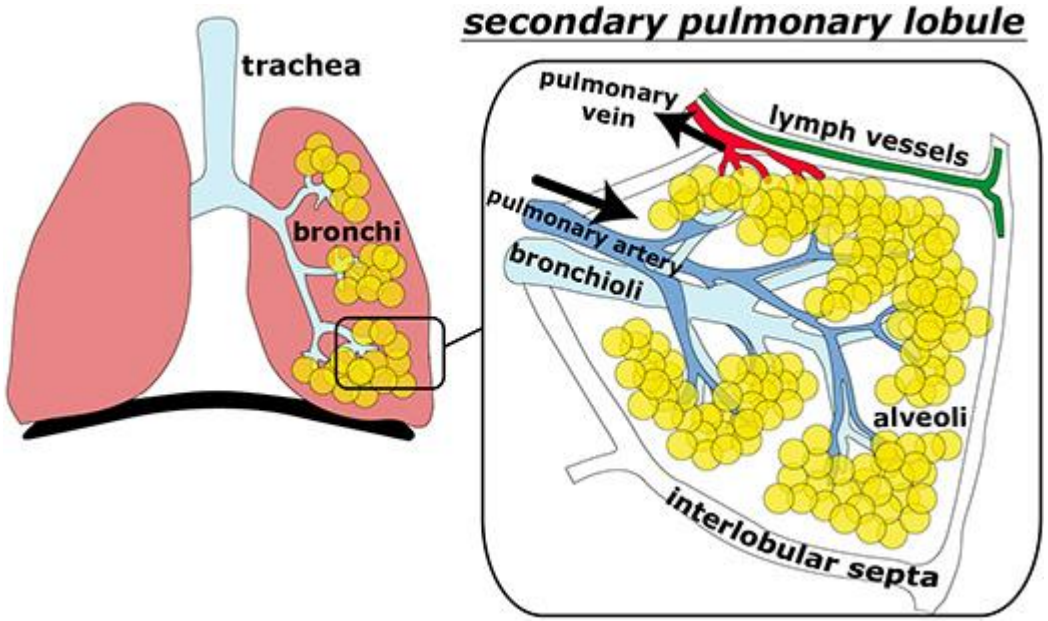
3-D acinus – gas exchange unit



- structure following each individual 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



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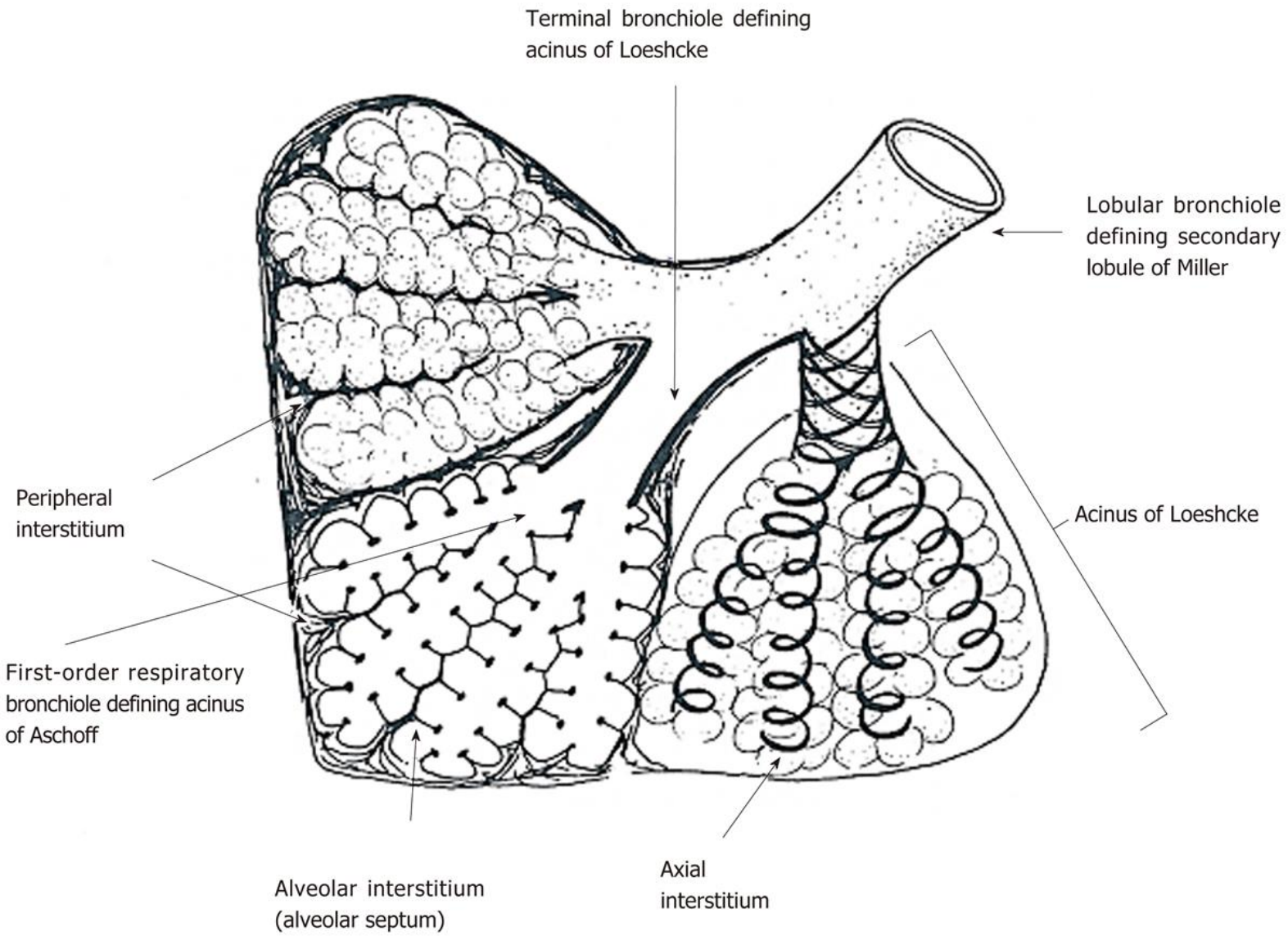
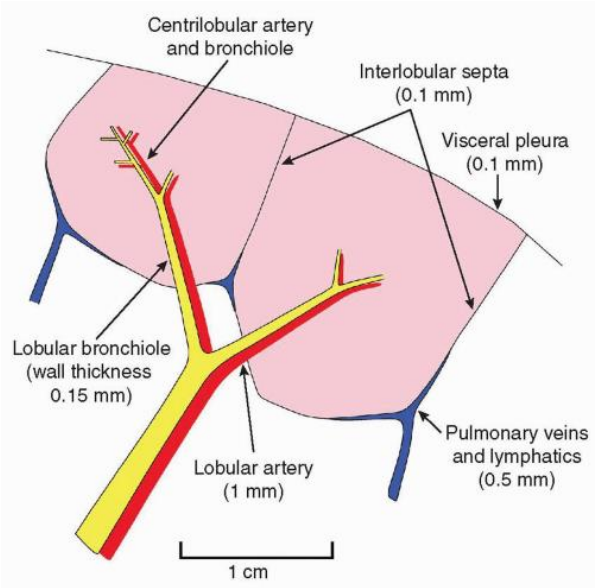
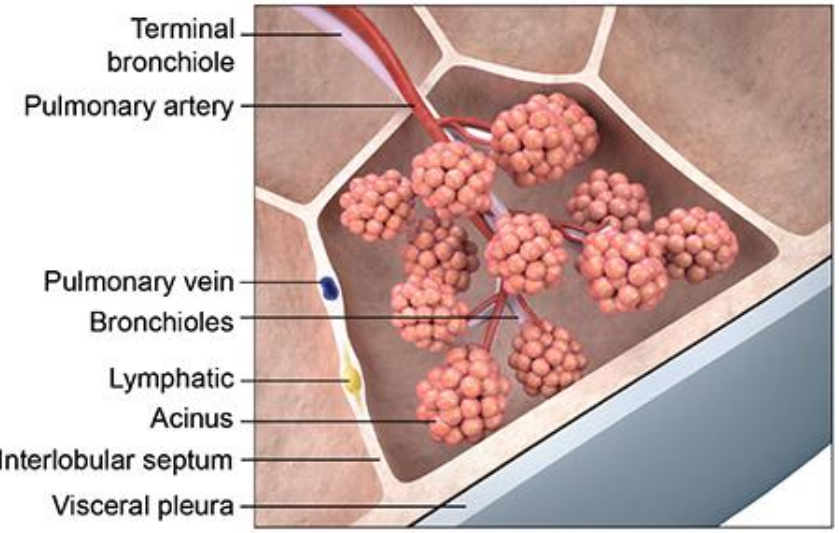
Lobule (= morphological unit, 3-5 acini) vs. acinus (= functional unit)

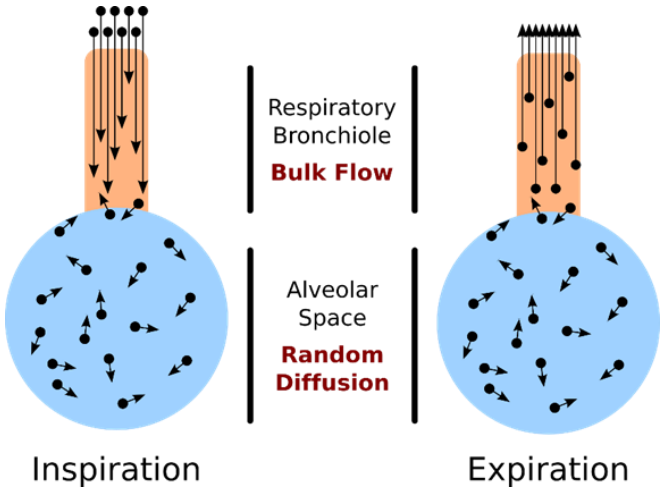




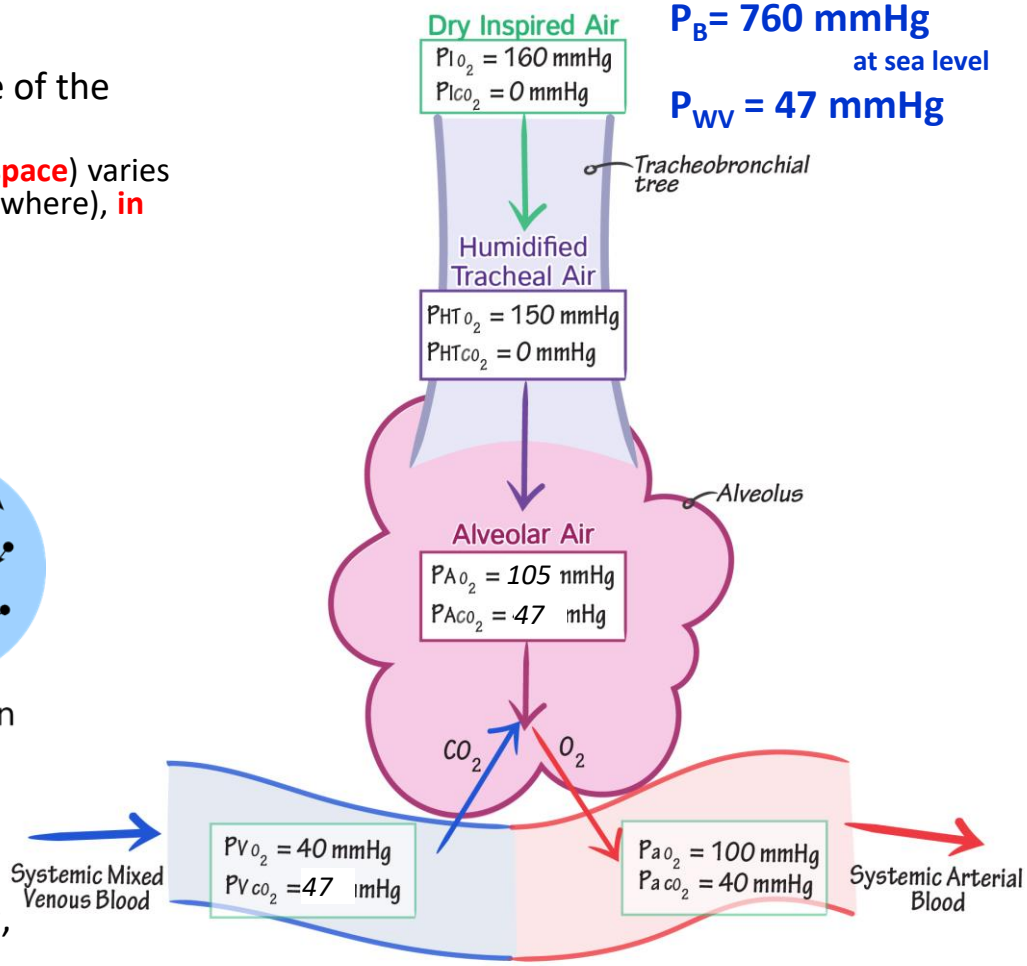


Pulmonary gas exchange as an ultimate purpose of breathing

- **Alveolar ventilation ($V_A = V_T - V_D$)**
  - at rest there is a constant rate of carbon dioxide generation in the body and rate of the diffusion in the lungs
    - while pattern of flow in conductive airways (both upper and lower airways, i.e. **dead space**) varies between turbulent / transitional / laminar (depending on Reynolds number – see elsewhere), **in alveoli gas moves across by diffusion**



  - therefore P_ACO_2 is more or less **constant** (or fluctuates very little)
    - A = alveolar × a = arterial
  - all of the **CO_2 exhaled** by the body **comes from** gas exchanging areas of the lung, that is **ventilated alveoli**
    - no CO_2 comes from a dead space, because there is an atmospheric air there with negligible CO_2 content
  - the **P_ACO_2 is equivalent to the P_vCO_2** (complete diffusion) and proportional to **P_aCO_2**
    - the „excess“ (A-a difference) of CO_2 produced is determined by respiratory quotient (RQ)



hypothetical perfect lung

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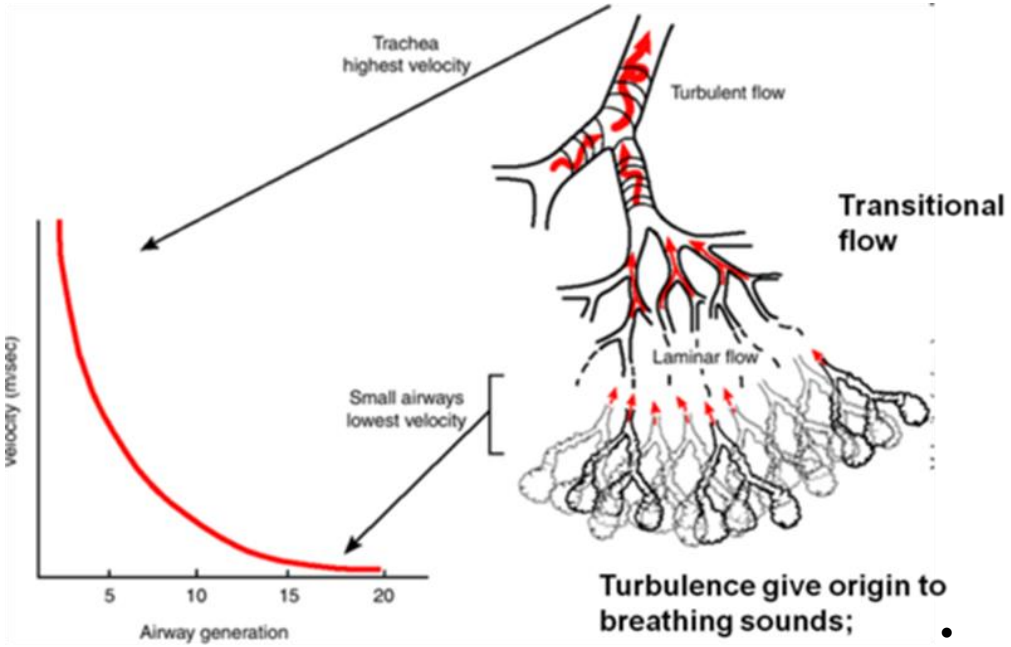
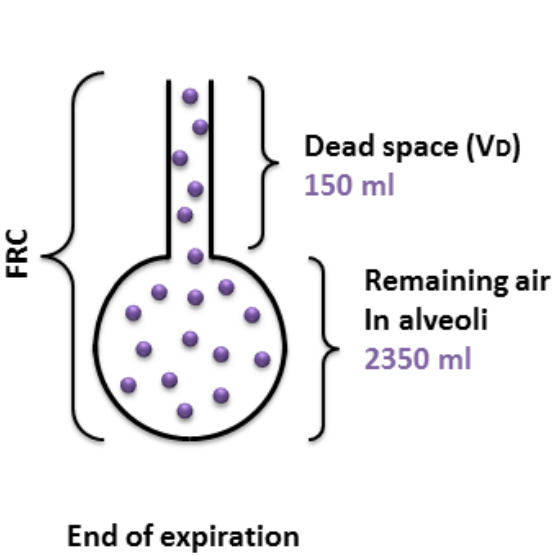
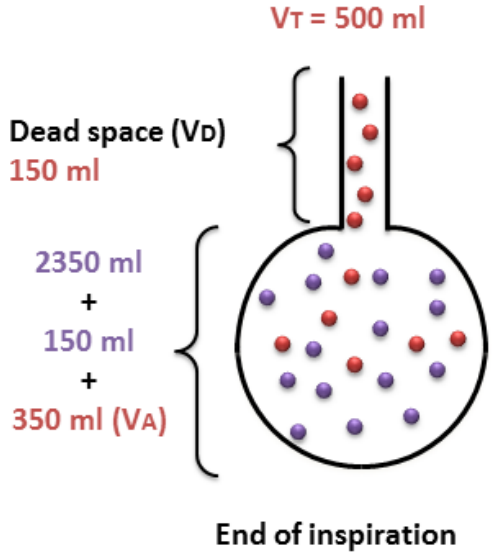
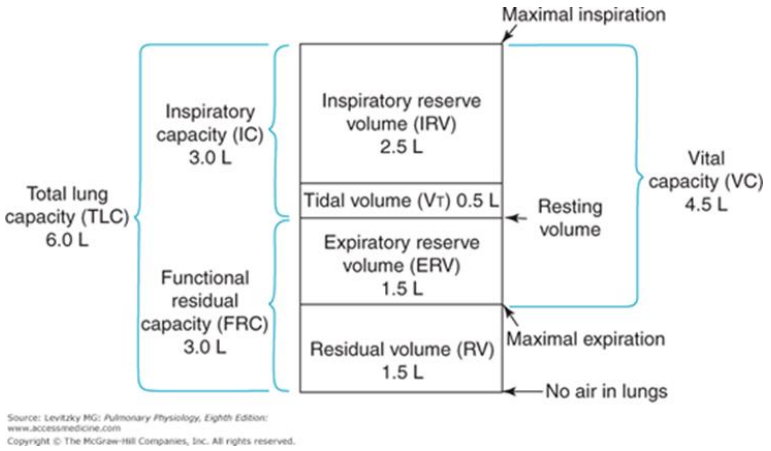
Exchange of gas between the alveolus and the respiratory bronchiole occurs purely by random diffusion









- There are minimal changes in volume between inspirium and expirium
  - breathing in and out doesn't completely replenish the stale air in the lungs
  - in fact **most of the volume of the lungs stays in the lungs, and each breath dilutes fresh air in the functional residual capacity (FRC) of the lung**
- At rest, with a typical tidal volume V_T (the depth of each breath) of around 500 ml, 150 ml is lost in dead space (V_D), and the remaining 350 mL is mixed into the much larger ~3,000 mL of existing FRC
  - so, it's not a matter of breathing in, exchanging gases and breathing out
- The process of **gas exchange goes on continuously**, and breathing is just the mechanism for removing a little stale air and adding a little fresh stuff
- Therefore, **V_A is a tidal volume (V_T) minus the dead space (V_D)**

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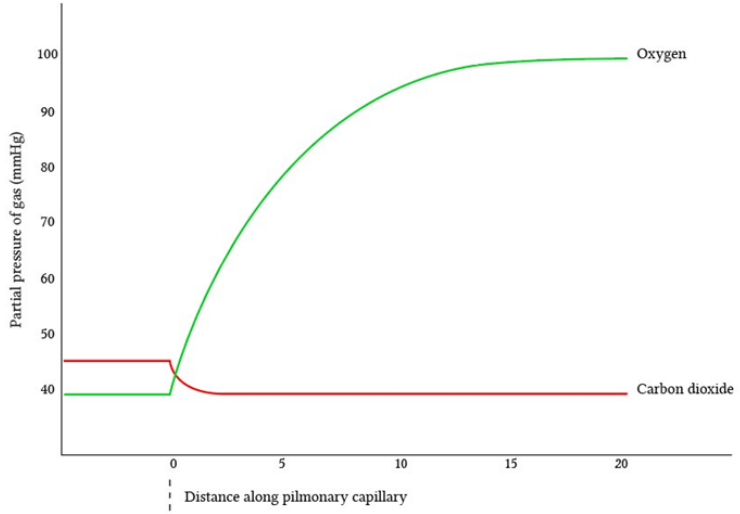
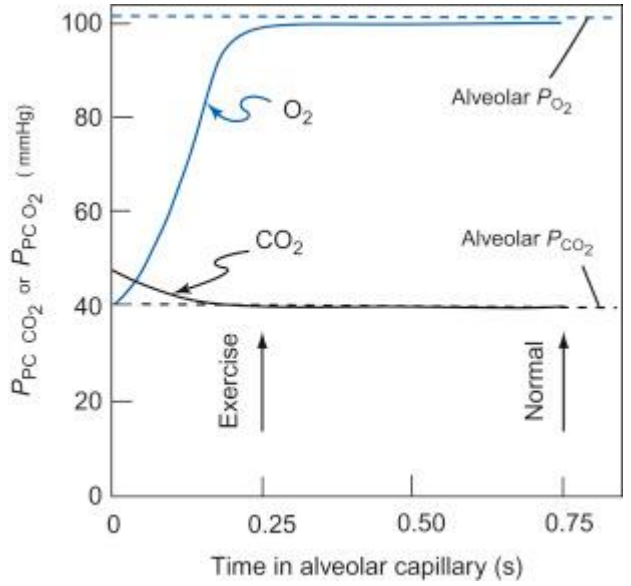
Blood is in the lungs for less than a second—but that is long enough to equilibrate the gases (normally!)



the total length of pulmonary capillary



- Cardiac Output (CO) of RV equals to that of LV, i.e. CO ~5L/min [CO = SV (~70mL) × f (~72 bpm)]
  - the total amount of blood in the lung capillaries is normally about 70 mL (= one stroke volume of the heart
  - at a heart rate of 72 bpm, the blood is in the lungs only 60 s min^{-1}/72 min^{-1} = 0.83 s
  - in literature this value is often 0.75s
- during this short time, venous blood entering the lungs equilibrates nearly completely with the alveolar air so that the exiting blood has nearly the same PCO_2 and PO_2 as alveolar air
  - blood actually equilibrates faster than its dwell time, indicating that there is some reserve in the diffusing capacity to accommodate the increased cardiac output and higher needs for gas exchange during exercise

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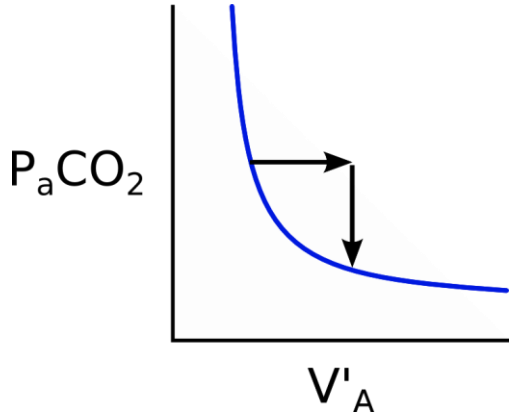
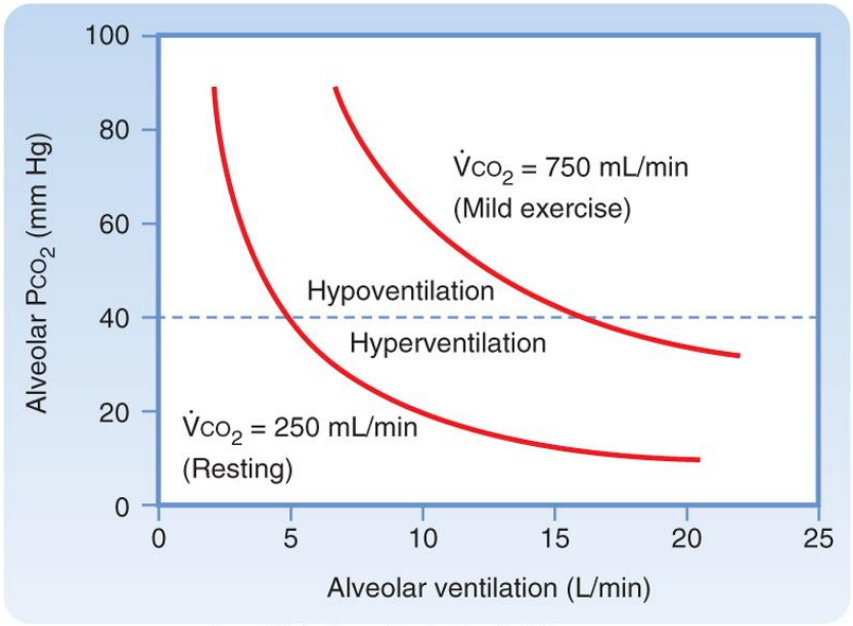
Pulmonary gas exchange as an ultimate purpose of breathing

- **Alveolar ventilation ($V_A = V_T - V_D$)**
  - at rest there is a constant rate of carbon dioxide generation in the body and rate of the diffusion in the lungs
    - **CO_2** production can be **lowered** by cooling the body
    - **CO_2** production **increases** by exercise or in pathology
  - therefore P_ACO_2 is more or less constant (or fluctuates very little)
  - all of the CO_2 exhaled by the body (**$V'CO_2$**) comes from gas exchanging areas of the lung, that is ventilated alveoli (not from a dead space)
  - the P_ACO_2 equivalent to the $PvCO_2$ (complete diffusion with very short equilibration time) and proportional to **$PaCO_2$**



- **(1) The alveolar ventilation equation** – describes the 'mechanics' = is (alveolar) ventilation sufficient to maintain gas exchange?
  - allows us to calculate alveolar ventilation rate
  - **$V'_A = (V'CO_2/PaCO_2) * K = \sim 4.2$ L/min**
    - thus the alveolar ventilation is proportional to the rate of carbon dioxide exhaled by the body ($V'CO_2$) and inversely proportional to the $PaCO_2$
    - instructive in understanding the influence of alveolar ventilation on the partial pressure of arterial carbon dioxide
      - **for example, if V'_A is doubled, the $PaCO_2$ is halved**
      - **if alveolar ventilation (V'_A) is halved, the $PaCO_2$ will double**



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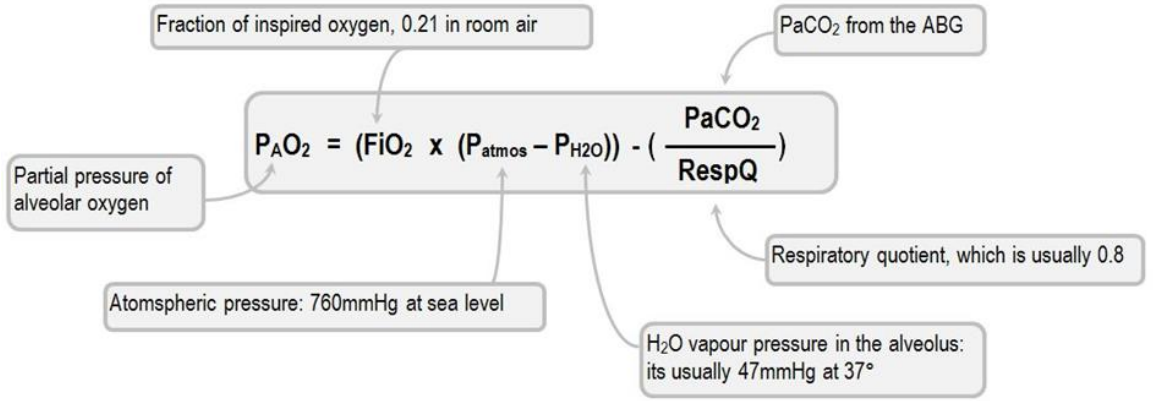
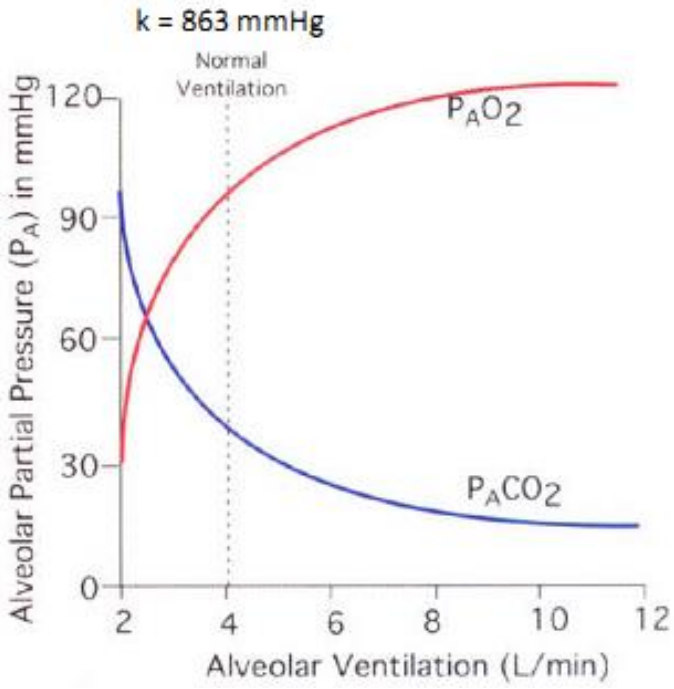
Pulmonary gas exchange as an ultimate purpose of breathing

- **(2) The alveolar gas equation** – describes the interdependency of alveolar gases and derives P_AO_2
  - describes the concentration of gases in the alveolus and demonstrates, that their dynamic is interconnected
  - answers the question: is alveolar oxygen sufficient and how much is needed to maintain arterial oxygen normal
    - allows to derive an „**A-a difference**“ as a measure of diffusion efficiency
  - **P_AO_2 = inspired value (= 0.21 x (760 - 47)) – pressure taken by CO_2 (= $PaCO_2$ / RQ (0.8) = ~ 105 mmHg**
    - basically the two gases (in fact all gases) compete for partial pressures
      - if one increases, others must decrease
      - nitrogen irrelevant
    - normally P_ACO_2 in mixed venous blood (i.e. in pulmonary artery is the same as in alveolus) is 45 mmHg and is proportional to $PaCO_2$
    - if $P_ACO_2/PaCO_2$ doubles (e.g. hypoventilation) then P_AO_2 falls in half, i.e. 50 mmHg





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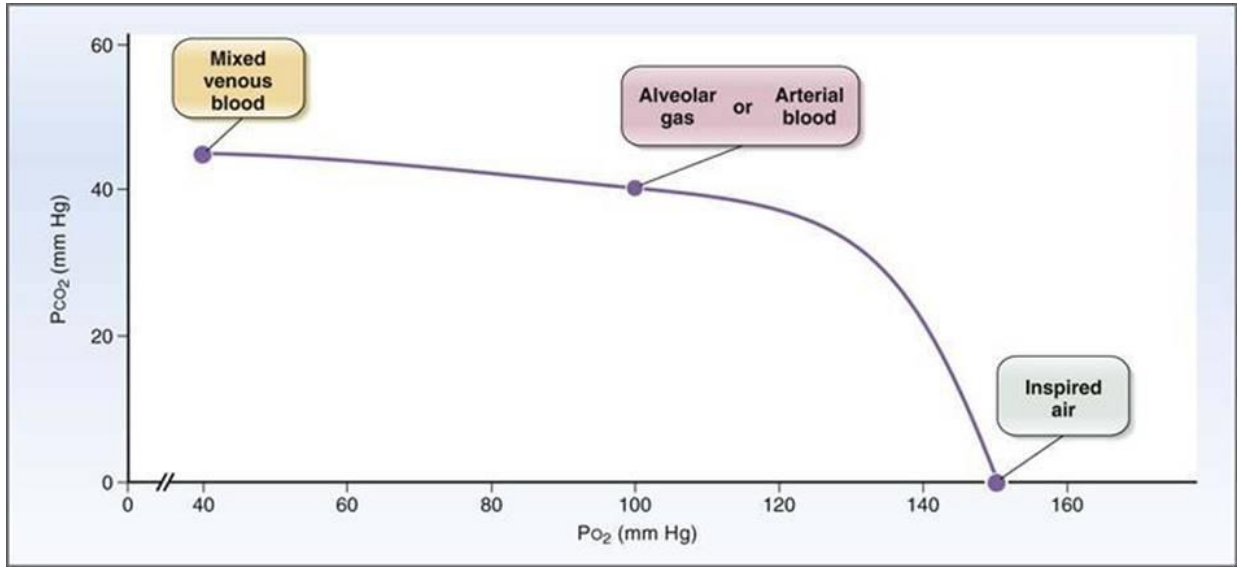
Example: why I need to be aware of the two equations?

- alveolar gases are very difficult/impossible to measure directly
- on the contrary, we can relatively easily measure arterial blood gases (ABG), i.e. PaO_2 and $PaCO_2$

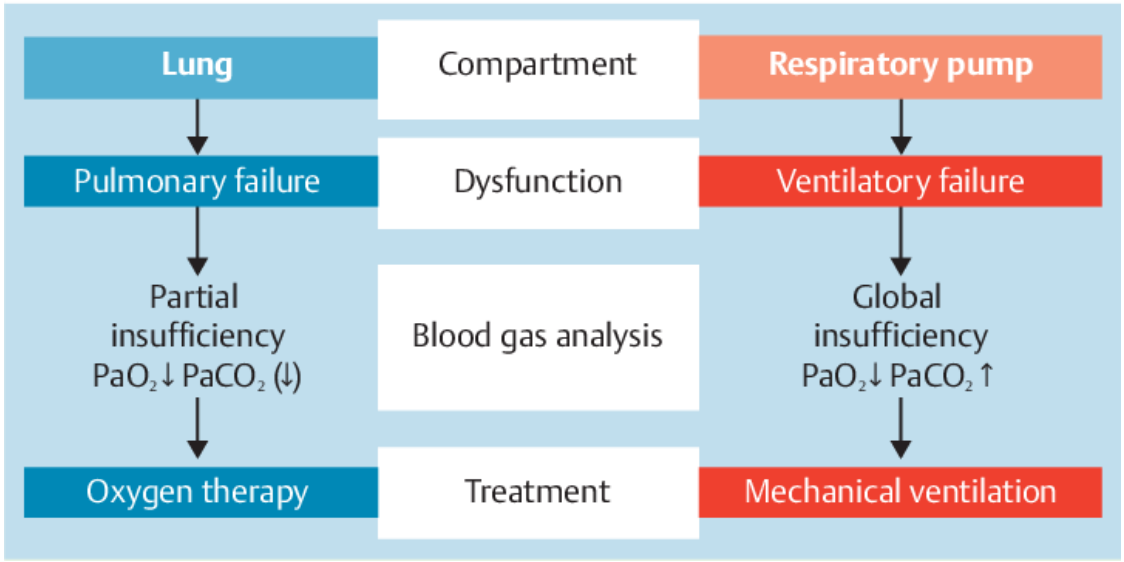
- **(1) The alveolar ventilation equation**
  - is (alveolar) ventilation sufficient to maintain normal gas exchange?
    - NO - patient has a two-fold increase of $PaCO_2$ (80 mmHg) → he hypoventilates (V_A is inversely related, therefore halved)
- **(2) The alveolar gas equation**
  - is alveolar oxygen sufficient?
    - NO – they are mutually interconnected/dependent
    - normally $P_AO_2 = PiO_2$ (= 0.21 x (760 - 47) = 150) – P_ACO_2 (= $PaCO_2$ 40 mmHg/ RQ 0.8 = 45 mmHg) = 105 mmHg
    - hypoventilation **P_AO_2** = PiO_2 (= 0.21 x (760 - 47) = 150) – P_ACO_2 (= **$PaCO_2$ 80mmHg** / RQ 0.8 = 45 mmHg = 100 mmHg) = **50 mmHg**
  - and how much is needed to maintain arterial oxygen
    - to maintain **P_AO_2** normal, i.e. **105 mmHg** we have to change the fractional concentration of O_2 in inspired air
      - PiO_2 (= 0.21 x (760 - 47) has to be ~200 mmHg (i.e. SiO2 = 200/(760-47)) = 28%)
    - **PiO_2** (= **0.28** x (760 - 47) = 200) – P_ACO_2 (= **$PaCO_2$ 80mmHg** / RQ 0.8 = 45 mmHg = 100 mmHg) = **100 mmHg**



Respiratory insufficiency/failure (= abnormality of pulmonary gas exchange as an ultimate purpose of breathing)

hypoxemia = PaO_2 decreased (<60 mmHg/8.0 kPa)
normocapnia = $PaCO_2$ normal or low (<50 mmHg/6.7 kPa)
$P_{A-a}O_2$ increased

Causes:
(1) low ambient oxygen (e.g. at high altitude)
(2) mild alveolar hypoventilation
(3) diffusion problem
(4) R-L shunt
(5) ventilation-perfusion mismatch leading to pathological dead space
(parts of the lung receive oxygen but not enough blood)



Causes:
(1) severe alveolar hypoventilation
(2) ventilation-perfusion mismatch leading to pathological shunting (parts of the lung receive blood but not air – such as in obstructive diseases)

hypoxemia PaO_2 decreased (<60 mmHg/8.0 kPa)
hypercapnia $PaCO_2$ increased (>50 mmHg/6.7 kPa)
$P_{A-a}O_2$ normal
pH<7.35

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FOUR (4) CAUSES OF HYPOXEMIA (I.E. ABNORMALITY DEFINING RESPIRATORY FAILURE)

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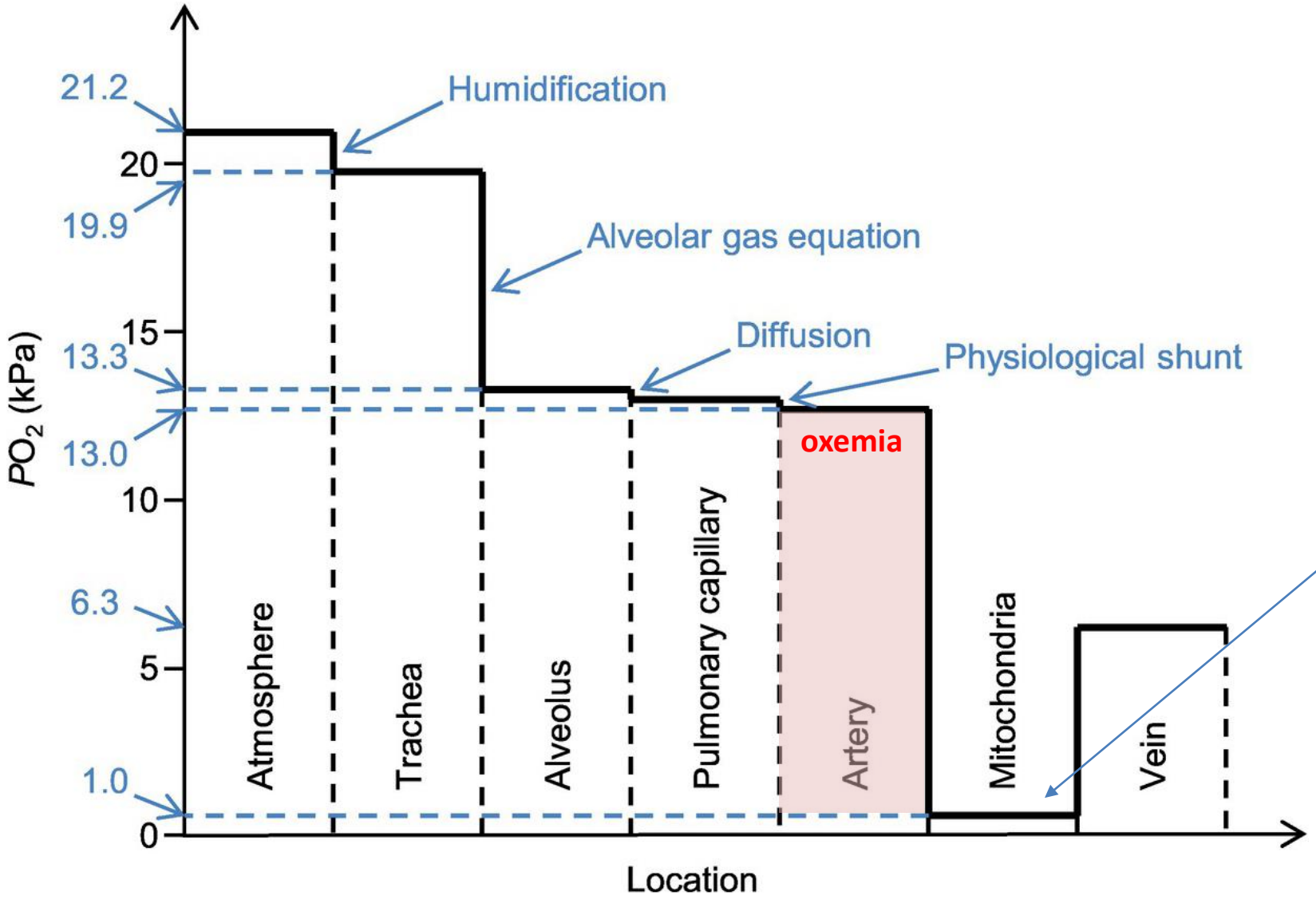
Oxygen cascade



any interference with this physiological cascade (fall in P_AO_2/PaO_2 will result in tissue hypoxia

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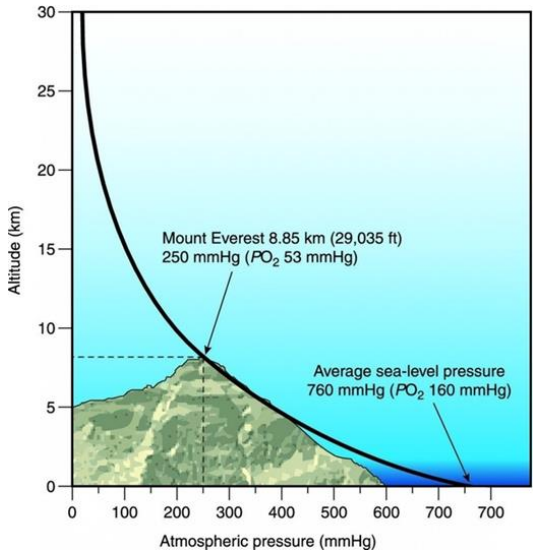
Hypoxemia (low PaO_2) - classification

- (1) Hypoventilation (low $\dot{V}'_A$)
  - low PaO_2 due to low PAO_2 with normal atmospheric pressure and normal FiO_2
- (2) Diffusion impairment
  - (a) low inspired oxygen or atmospheric pressure
    - e.g. high altitude hypoxemia
      - low PaO_2 due to low PAO_2 with low atmospheric pressure and normal FiO_2
    - or gas mixture with low FiO_2
  - (b) shortening of time spent by blood in the capillary
  - (c) thickening of alveolo-capillary barrier
    - low PaO_2 with normal PAO_2 with normal atmospheric pressure and normal FiO_2 (increased $P(A\text{-}a)O_2$)
- (3) R-L shunt
  - low PaO_2 with normal PAO_2 with normal atmospheric pressure and normal FiO_2 (increased $P(A\text{-}a)O_2$)
- (4) Ventilation perfusion inequality
  - low PaO_2 with variable PAO_2 with normal atmospheric pressure and normal FiO_2



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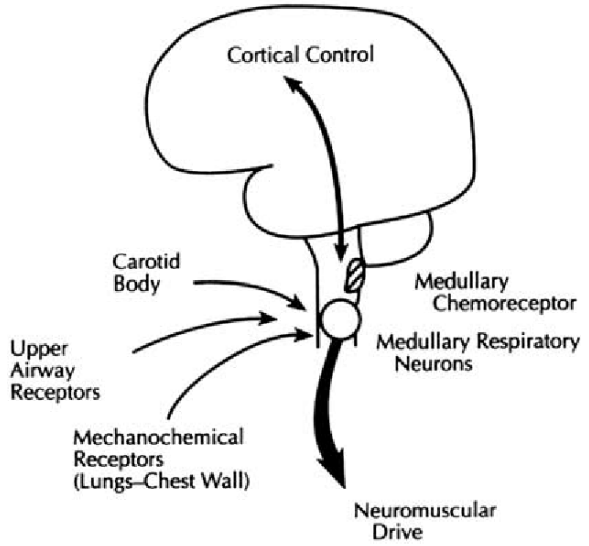
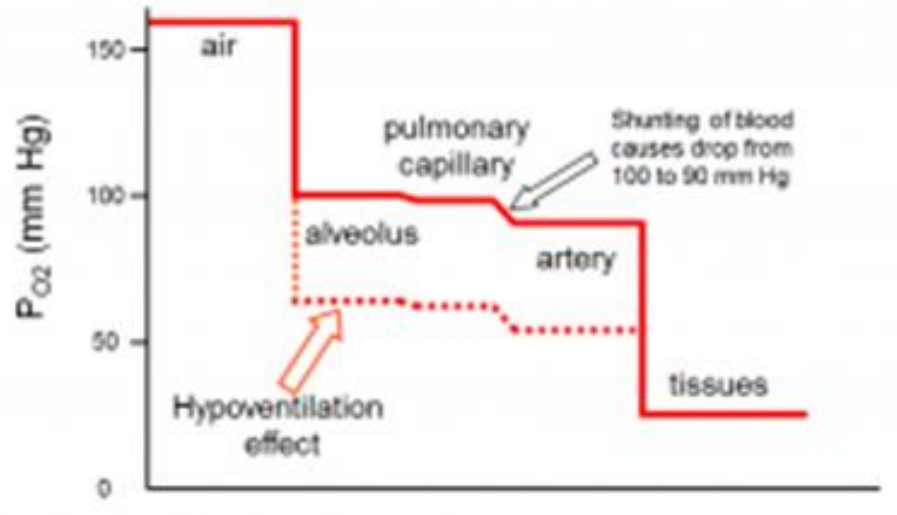
(1) Hypoventilation as a cause of hypoxemia

(results in low PaO_2 + hypercapnia + normal A-a gradient)

- normally $PaCO_2$ in mixed venous blood (i.e. pulmonary artery) is about 47 mmHg and nearly the same in alveolus (47 mmHg)
- if $PaCO_2$ doubles due to hypoventilation (i.e. V_A halves– see alveolar ventilation equation) then P_AO_2 falls in half (see alveolar gas equation), i.e. 50 mmHg (more than $PaCO_2$ rise since RQ is 0.8)
- can we restore the P_AO_2?
  - using alveolar gas equation you can calculate what the inspired fraction of oxygen should be to bring it back to normal
    - i.e. **PAO_2 100 mmHg** = (**FiO2 ??** x (760 - 47)) - (**$PaCO_2$ 80 mmHg** x 1.25**) = 0.28, i.e. 28% oxygen**
- examples – **typically extra-pulmonary (the lung itself is typically normal)**
  - respiratory CNS generator
    - drug overdose (barbiturates, narcotics, …), CNS trauma, brainstem disease, metab. alkalosis, encephalitis, congenital apnoea syndromes, …
  - neuromuscular
    - myasthenia gravis, ALS, Guillain-Barre, muscular dystrophy, cervical spinal cord injury (phrenic nerve), polio, botulism, …
  - chest wall
    - deformities, injury (flail chest), obesity, …
  - upper airway obstruction
    - croup, epiglottitis, OSA,





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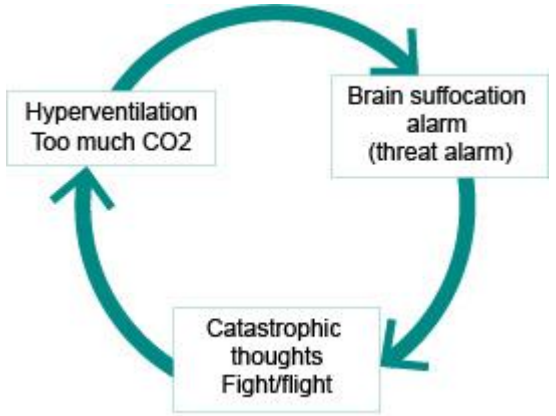
The opposite situation is bad too: Hyperventilation

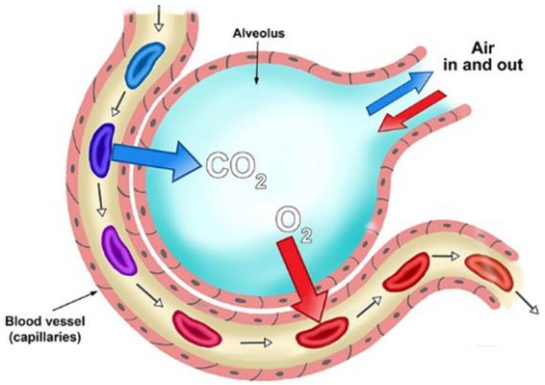
- Common causes:
  - anxiety, panic attack, nervousness, or stress
- Other causes include:
  - bleeding
  - use of stimulants/drug overdose (e.g. salicylates - aspirin)
  - severe pain
  - pregnancy (to increase PaO_2)
  - lung infection
  - lung diseases (COPD or asthma, pulmonary embolism)
  - heart conditions (e.g. heart attack)
  - diabetic ketoacidosis
  - head injuries
  - anemia
  - high altitude (over 6,000 feet)
  - septic shock
  - hyperventilation syndrome
- Symptoms (of $\downarrow PaCO_2 \rightarrow \uparrow$pH (respiratory alkalosis)):
  - peripheral vasoconstriction incl. brain!!!
  - decreased ionised calcium $\rightarrow$ tetany
    - tingling in the lips, hands or feet, headache, weakness, fainting, and seizures
    - in extreme cases carpo-pedal spasms (a flapping and contraction of the hands and feet)

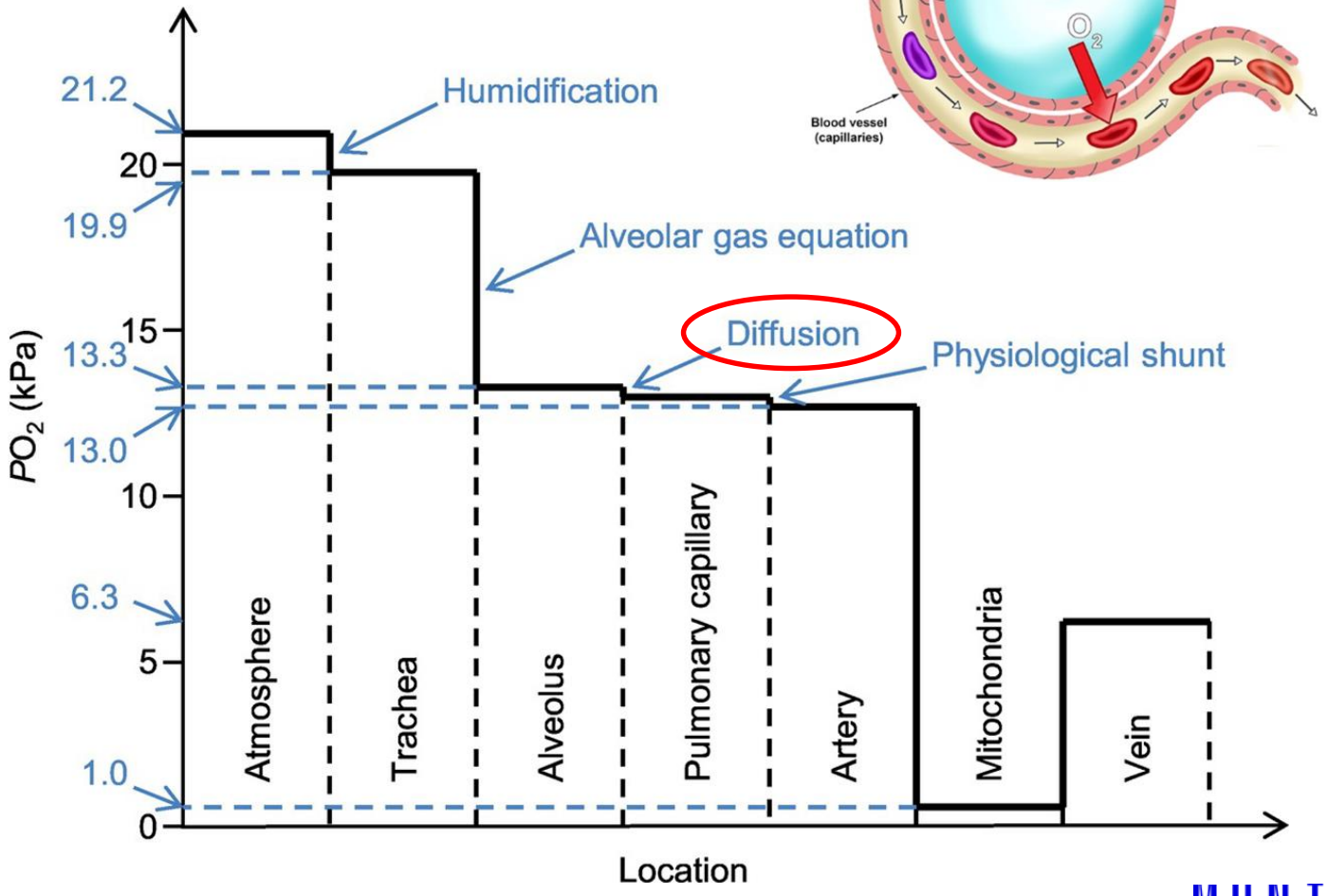


(2) Diffusion impairment as a cause of hypoxemia

(low PaO_2 + normocapnia + large A-a gradient)

- due to
  - low inspired oxygen or high altitude
  - shortening of the time blood spends in pulmonary capillary
    - **oxygen is normaly perfusion limited**
      - extreme exercise
      - hyperkinetic circulation
      - increased velocity of pulmonary circulation
  - thickened alveolo-capillary barrier
    - **oxygen might become pathologically diffusion limited**
      - PaO_2 typically normal at rest, but hypoxemia appears in exercise





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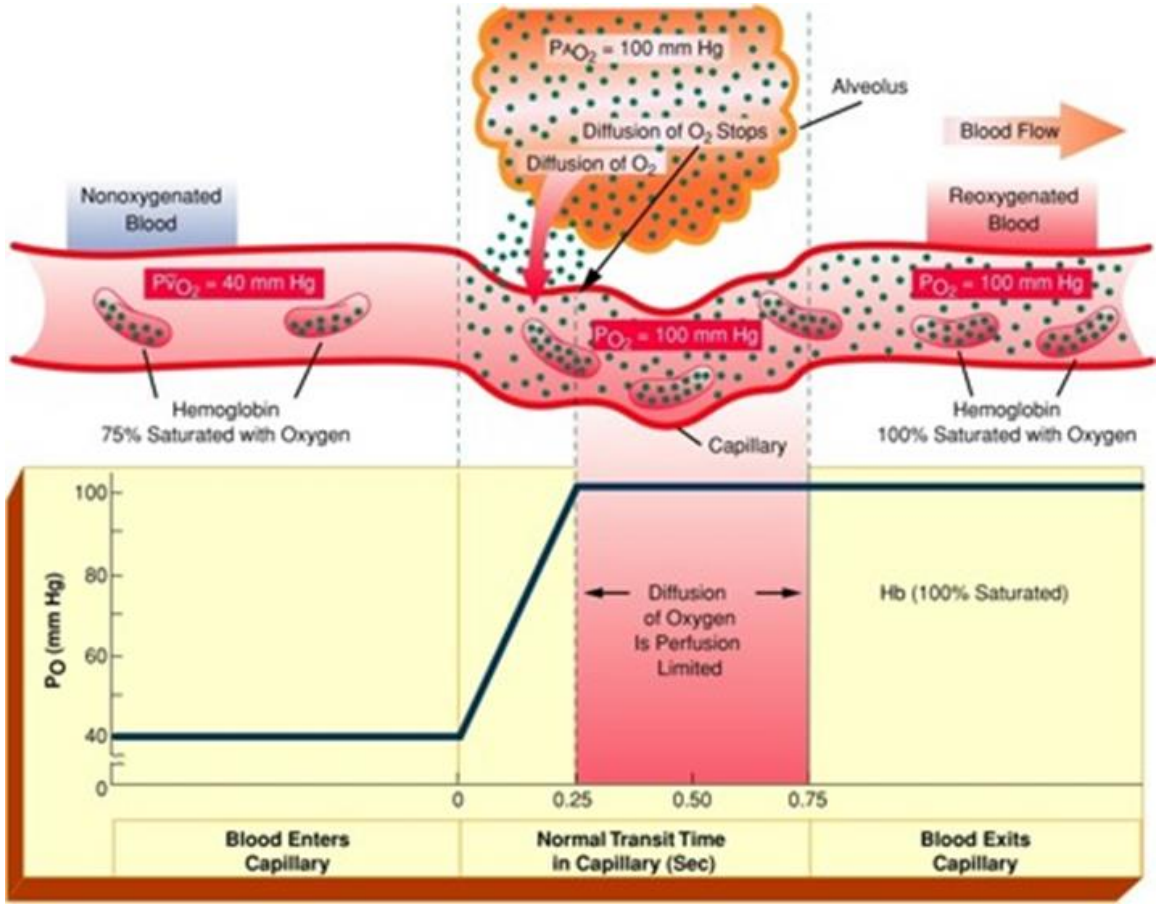
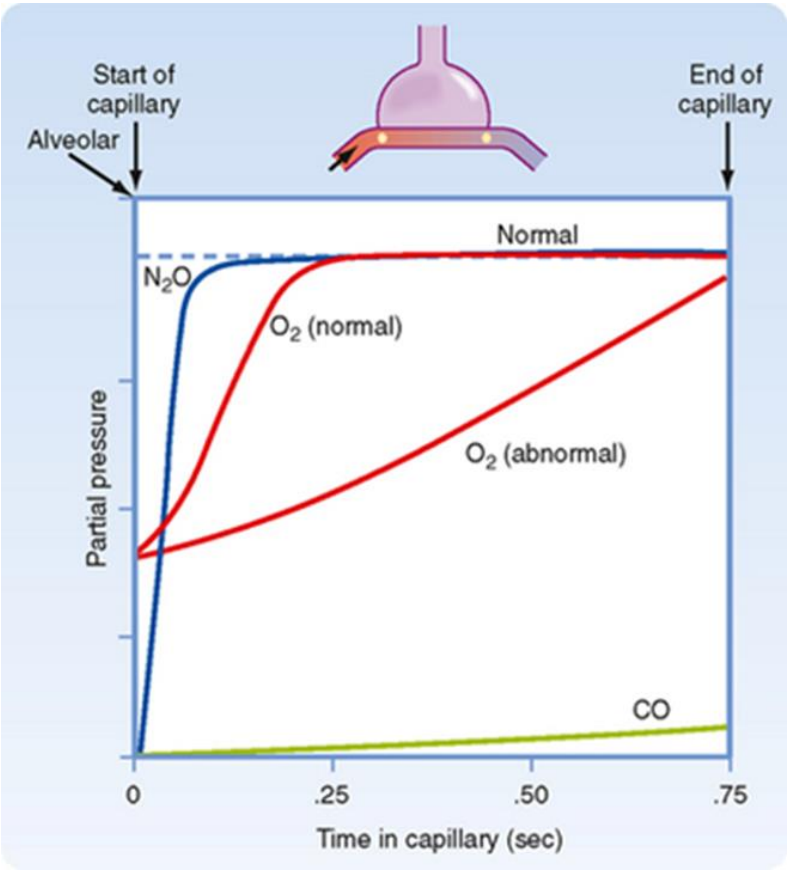
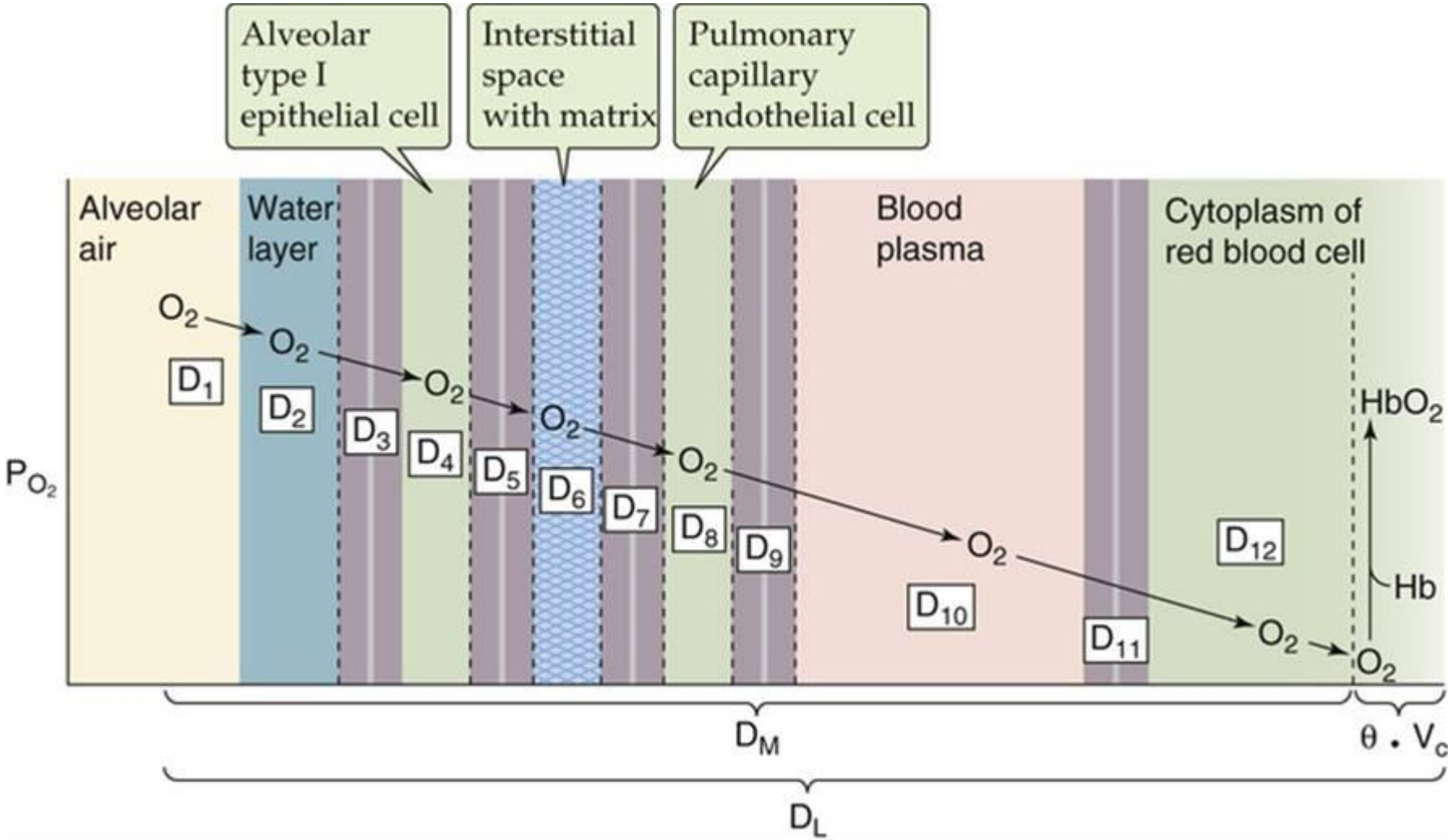
Oxygen is normally perfusion-limited

- blood entering the pulmonary capillary has plenty of time to equilibrate
  - blood is in the lungs for less than a second—but juts one third of this time is long enough to equilibrate the oxygen (normally!)



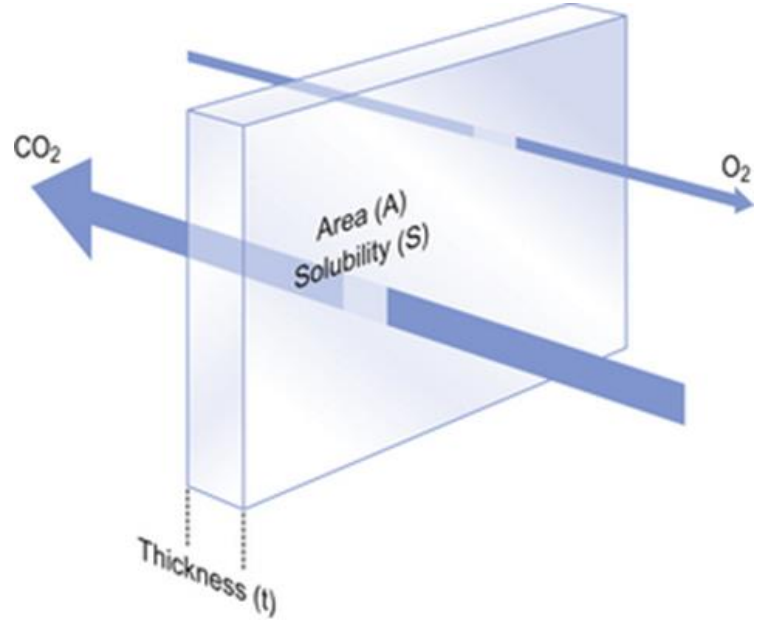


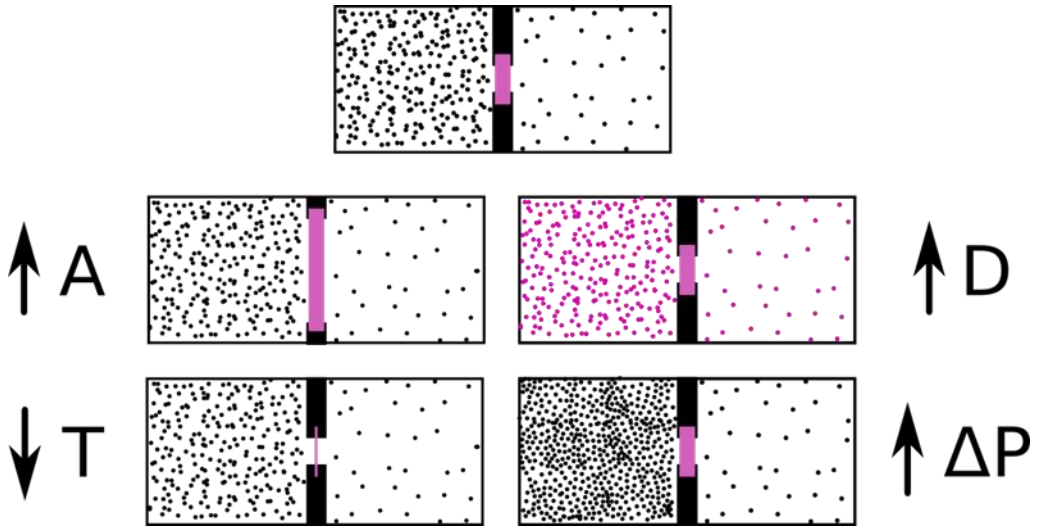
Gases do not diffuse across a homogeneous barrier



Determinants of diffusion

- Fick's Law: V'gas = D * A * ΔP/T
  - V'gas = Rate of gas diffusion across permeable membrane
  - D = Diffusion coefficient of that particular gas for that membrane
  - A = Surface Area of the membrane
  - ΔP = Difference in partial pressure of the gas across the membrane
  - T = Thickness of the membrane





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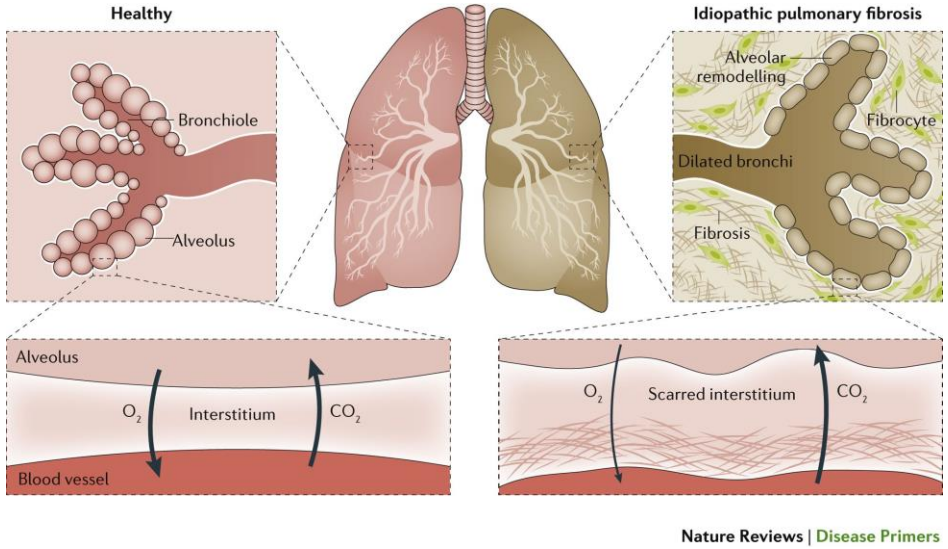
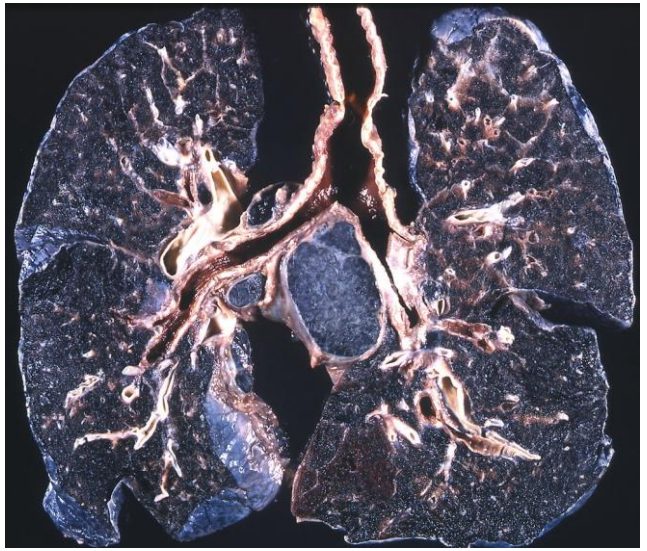
Examples of disease leading to diffusion impairment

- pathologically oxygen can be diffusion-limited
- typically in interstitial lung diseases
  - idiopathic pulmonary fibrosis
  - associated with autoimmune diseases
    - i.e. rheumatoid arthritis, scleroderma, …
  - sarcoidosis
  - drug-induced
  - acute hypersensitivity pneumonitis
  - inhalation of substances and subsequent scarring = pneumoconiosis
    - i.e. silicosis, asbestosis, coal-miner lung, …
- manifest typically with exertional dyspnea, dry cough and clubbing
- NOTE, very often the diffusion impairment combines with **dominant V/Q mismatch**
  - because diffusion impairing disease are typically intrinsic **restrictive** diseases from the point of view of ventilation





O_2 might become diffusion limited- hence the A-a difference importance

- normally 5-15 mmHg
- increases with age
  - A-a diff ≤ age/4 + 4, e.g. in 100 yrs/4 + 4 ~ 30 → age related hypoxemia
- massively increased in intrinsic restrictive pulmonary disease
  - spirometry:↓ FVC, ↓FEV1, ↑FEV1/FVC ratio
  - ABG: ↓PaO_2, ↓ SaO_2 Hb
  - A-a difference **– high!!!**
    - P_AO_2 – from alveolar gas equation
      - **P_AO_2 = inspired value (= 0.21 x (760 - 47)) – pressure taken by CO_2 (= $PaCO_2$ / RQ (0.8) = ~ 105 mmHg**
    - PaO_2 – from ABG

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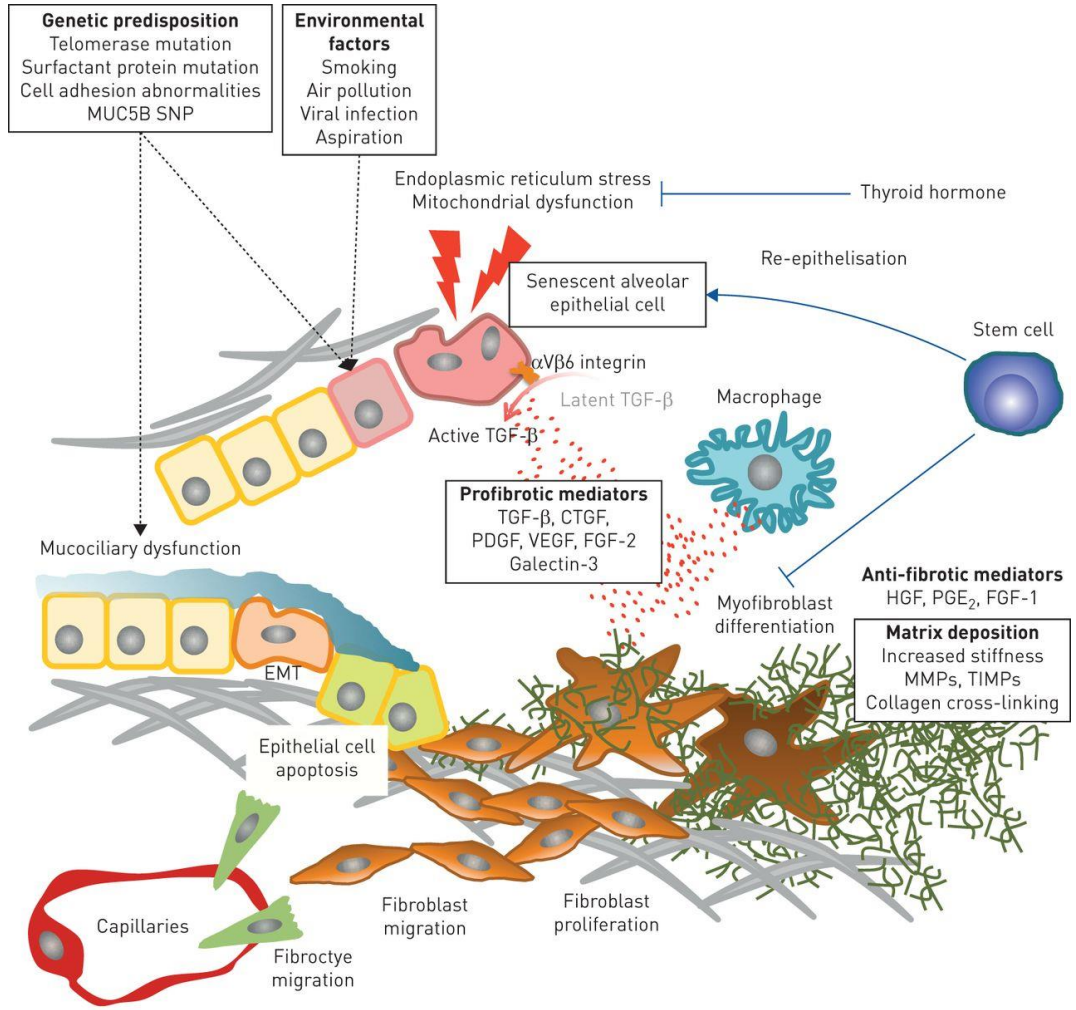
Idiopathic pulmonary fibrosis (IPF)

- an age-related disease, with the vast majority of individuals being diagnosed at >60 years of age
- median survival time of 3–5 years after diagnosis
- pathogenesis of IPF not fully understood
  - the current hypothesis is that subclinical alveolar epithelial injury imposed on ageing of epithelial cells in genetically susceptible individuals leads to aberrant wound healing, secretion of high levels of growth factors, cytokines, chemokines, accumulation of fibroblasts and differentiation into myofibroblasts, and deposition of the extracellular matrix (ECM)
  - genes – examples
    - surfactant protein (SP)-C, mucin 5B, other genes involved in cell adhesion, integrity and mechano-transduction



Proposed pathophysiological features of IPF: Recurrent epithelial cell injury in genetically susceptible individuals causes senescence of epithelial cells and epithelial mesenchymal transition (EMT), releasing profibrogenic mediators induces fibrocytes/fibroblasts migration and differentiation into profibrotic macrophages/myofibroblasts, resulting in aberrant matrix deposition with destructing lung architecture. SNP: single nucleotide polymorphism; TGF: transforming growth factor; HGF: hepatocyte growth factor; PGE_2: prostaglandin E2; FGF-1: fibroblast growth factor-1; FGF-2: fibroblast growth factor-2; CTGF: connective tissue growth factor; PDGF: platelet-derived growth factor; VEGF: vascular endothelial growth factor; MMP: matrix metalloproteinases; TIMP: tissue inhibitors of metalloproteinases.

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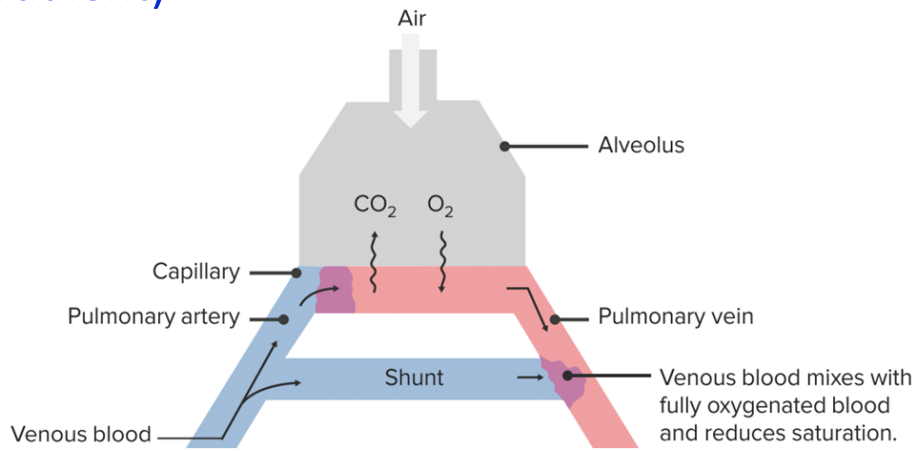
(3) Pathological right to left shunt as a cause of hypoxemia

(low PaO_2 + normocapnia + large A-a gradient)

- fraction of the RV cardiac output that bypasses pulmonary circulation (a. pulmonaris capillary network around respiratory airways)
  - oxygen-poor blood from the right heart flows in the left heart without passing through functional, ventilated alveoli
- **physiological** shunts
  - (1) bronchial circulation
    - a. bronchialis capillary network around conductive airways – anatomical dead space
  - (2) thebesian veins draining coronary vessels into the left ventricle
    - majority of the coronary capillary network drains into coronary sinus, a large vein returning the deoxygenated blood from the heart muscle to the right atrium so that it can be replenished with oxygen via pulmonary circulation.



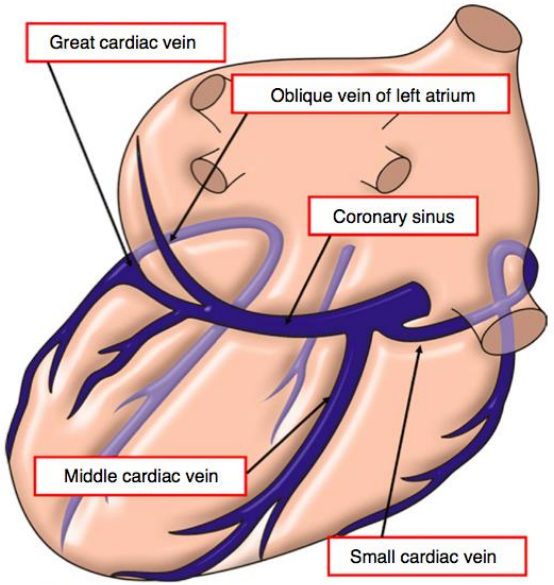
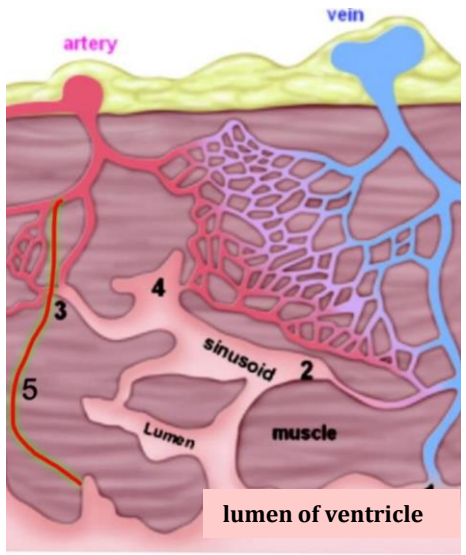
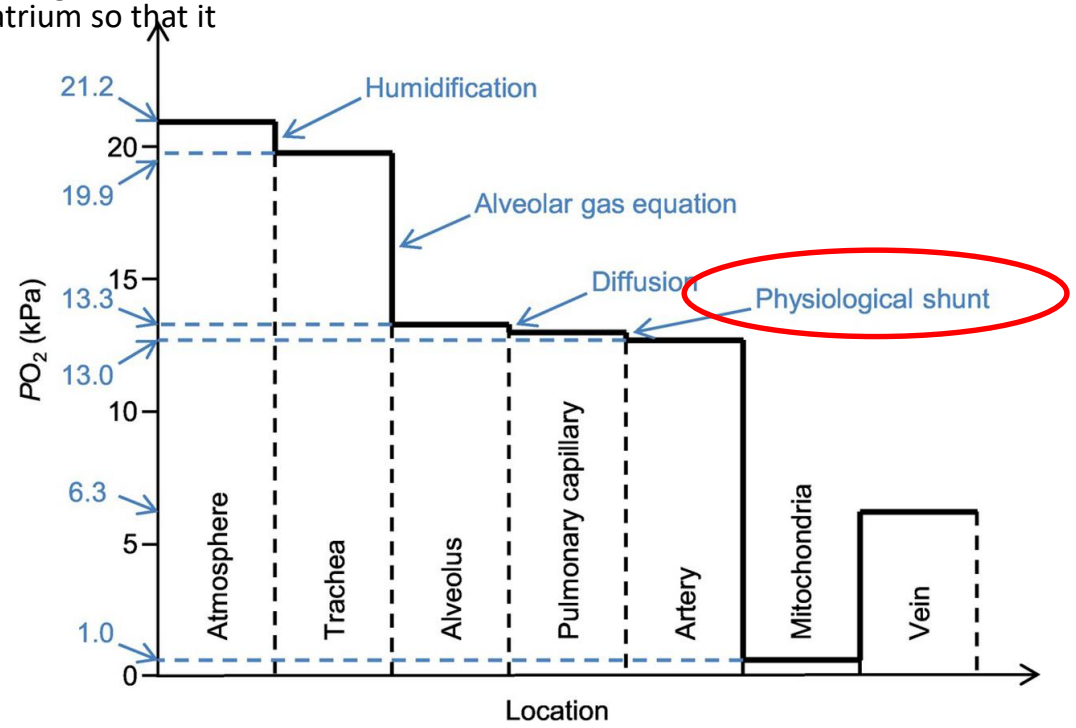


Figure 2-51 The cartoon, showing the heart viewed from behind, illustrates the arrangement of the coronary veins.



(1) Thebesian vein; (2) Venule entering Sinusoid; (3) Arteriosinusoidal vessel entering Sinusoid; (4) Capillary entering Sinusoid; (5) Arterioluminal vessel



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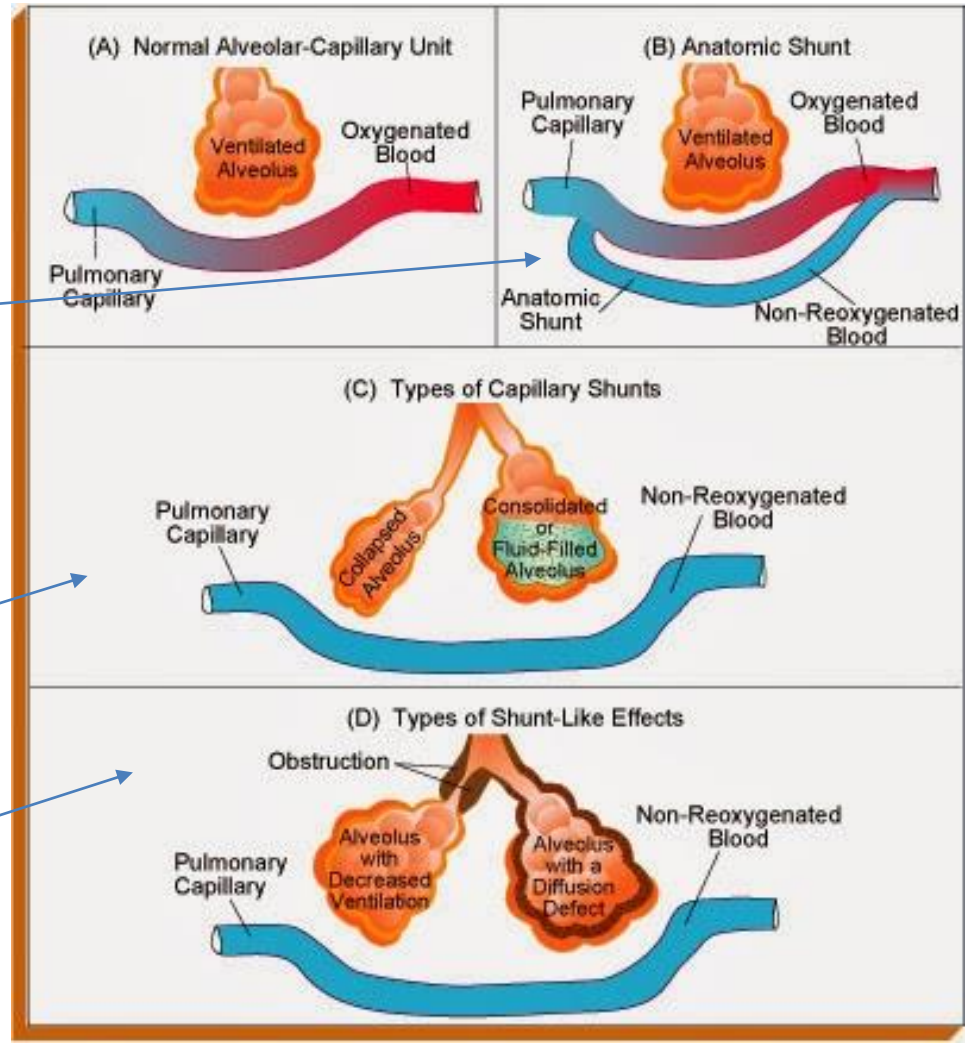
(3) Pathological R-L shunts as a cause of hypoxemia

(low PaO_2 + normocapnia + large A-a gradient)

- **(A) pathological anatomical** (pre-existing) shunts aggravating normal right-to-left shunting
  - intrapulmonary: pulmonary arteriovenous malformations (PAVMs)
    - usually congenital direct communications between pulmonary artery and vein by-passing the capillary network
      - can be single or multiple, unilateral or bilateral, and simple or complex
      - clinical consequences
        - » hypoxemia
        - » increased the risk of paradoxical embolism (air bubbles, bacteria or clot from systemic venous blood going to systemic circulation) resulting in stroke or brain abscess
        - » increased the risk of rupture (manifesting as haemoptysis or haemothorax)
  - extrapulmonary: right-to-left intra-cardiac shunts
    - typically the pressure gradient favours left-to-right shunting, however, when combined with other conditions increasing resistance, the shunt goes form right-to-left
      - patent ductus arteriosus (PDA)
      - atrial septal defect – patent foramen ovale
      - ventricular septal defects
- **(B) pathological functional (cappilary)** causes of increased right-to-left shunting
  - fluid filled alveoli
  - atelectasis, ARDS
- **(C) shunt-like V/Q mismatch** - poorly ventilated alveoli (obstruction)
- Hypoxemia caused by right-left shunts prototypically **cannot be corrected by oxygen therapy**



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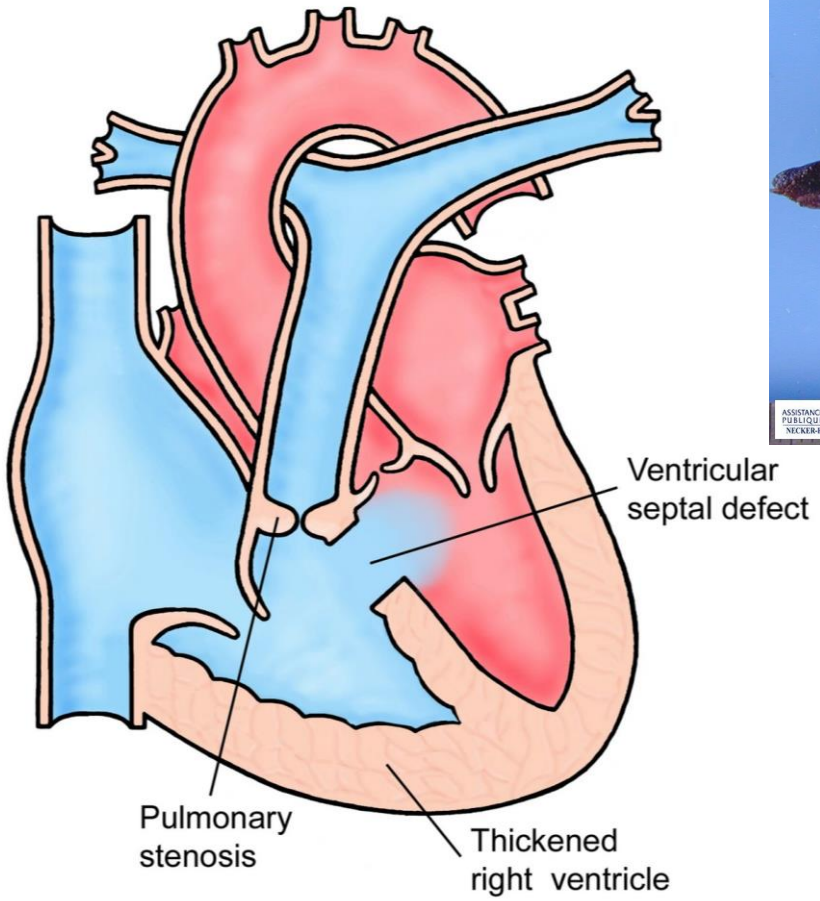
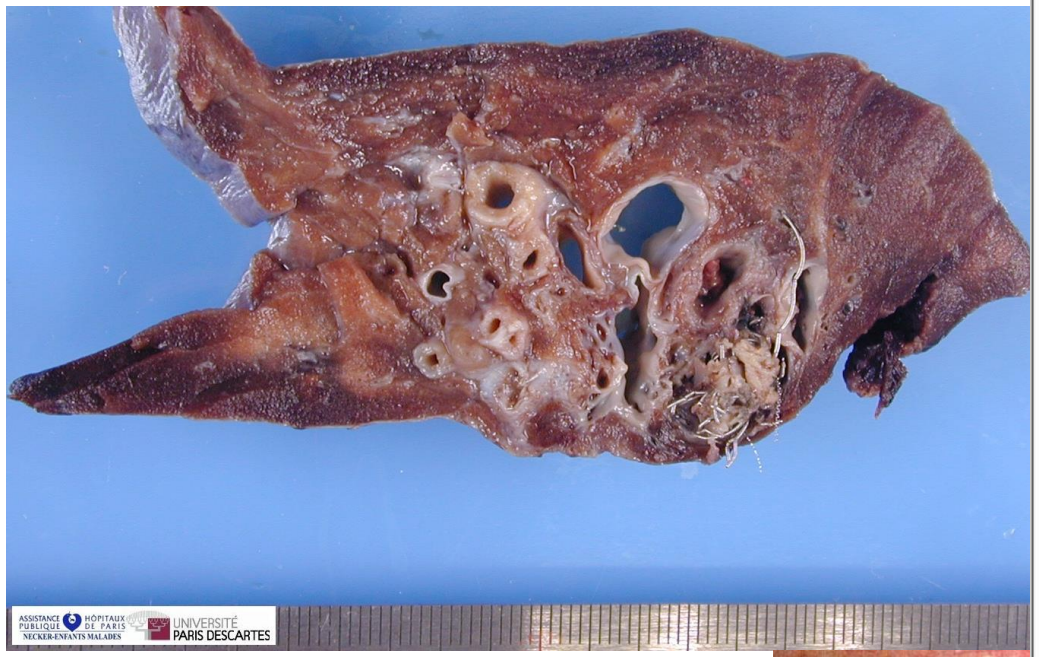
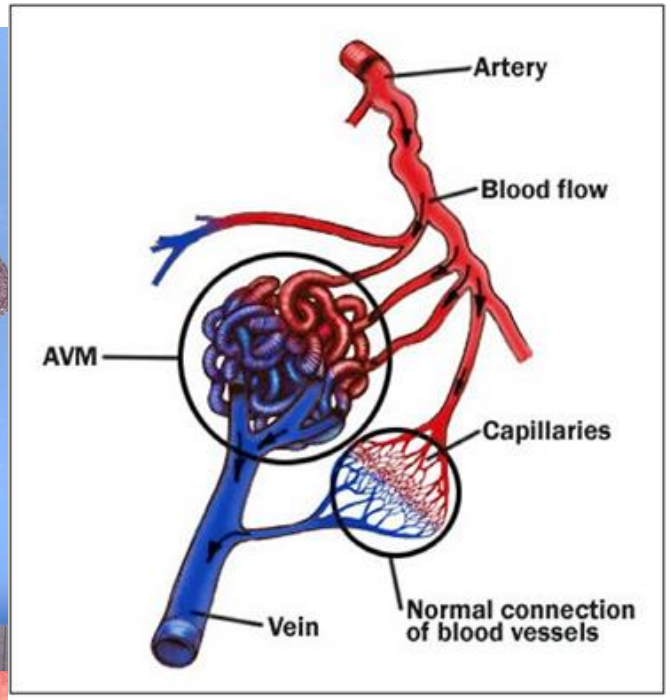
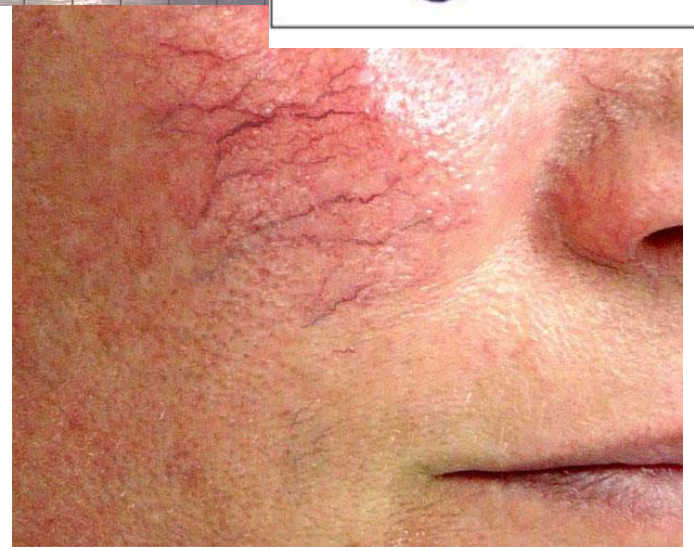
Examples of pathological anatomical shunts









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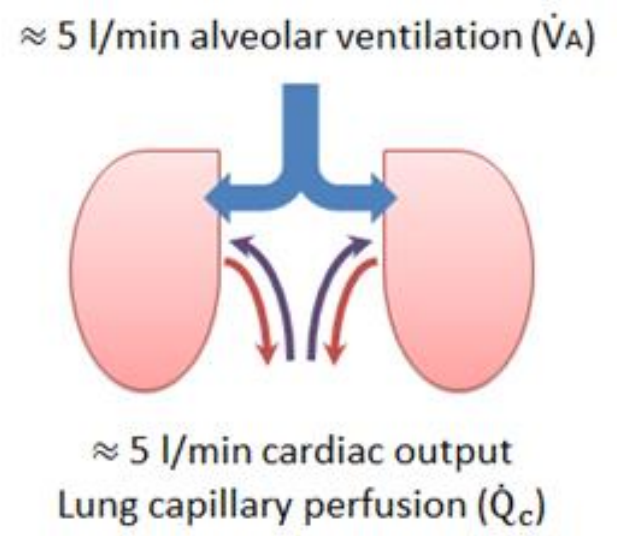
(4) Ventilation-perfusion inequality as a cause of hypoxemia

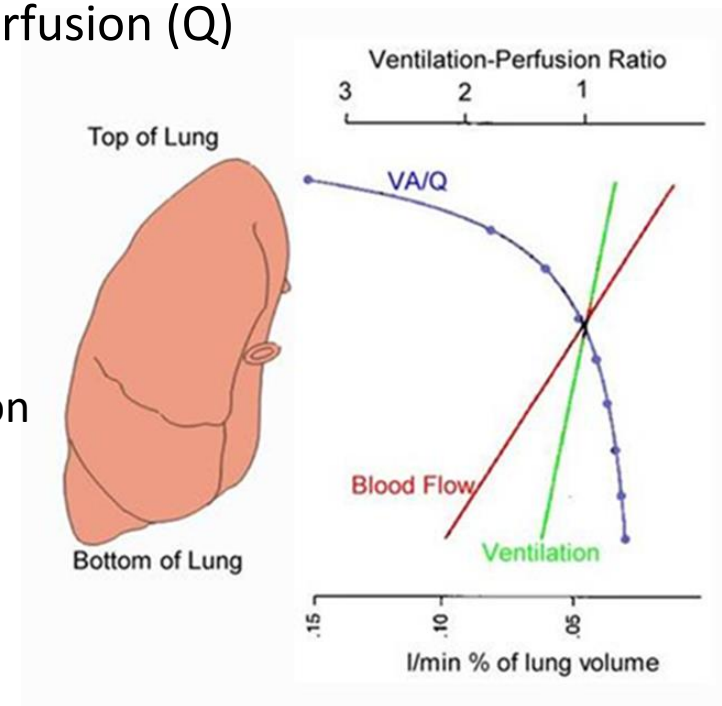
(low PaO_2 + variable normo/hypercapnia)

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

(500mL – 150mL) × 15 = 5L



- Alveolar air composition
  - the partial pressures of oxygen and carbon dioxide in any given alveolar unit are largely determined by the relative rates of ventilation and perfusion of that alveolus
- For efficient gas exchange it is important that there is a match between ventilation of the alveoli (V_A) and their perfusion (Q)
  - in ideal alveolus V_A /Q ratio = 1
- **However, V'/Q' ratio of alveoli within even a healthy lung is not uniform**
  - regional variation within the lung when an individual is standing upright
  - the action of gravity results in a vertical gradient of both blood flow and ventilation in the upright lung
    - although both blood flow and ventilation are lowest at the lung apex and highest in the base, the vertical gradient for blood flow is wider than that for ventilation



$SV \times f = CO$

70mL × 75 bpm = 5L

- **Ventilation-perfusion mismatch is by far the most common cause of arterial hypoxaemia**, because many lung diseases aggravate the physiological V/Q mismatch

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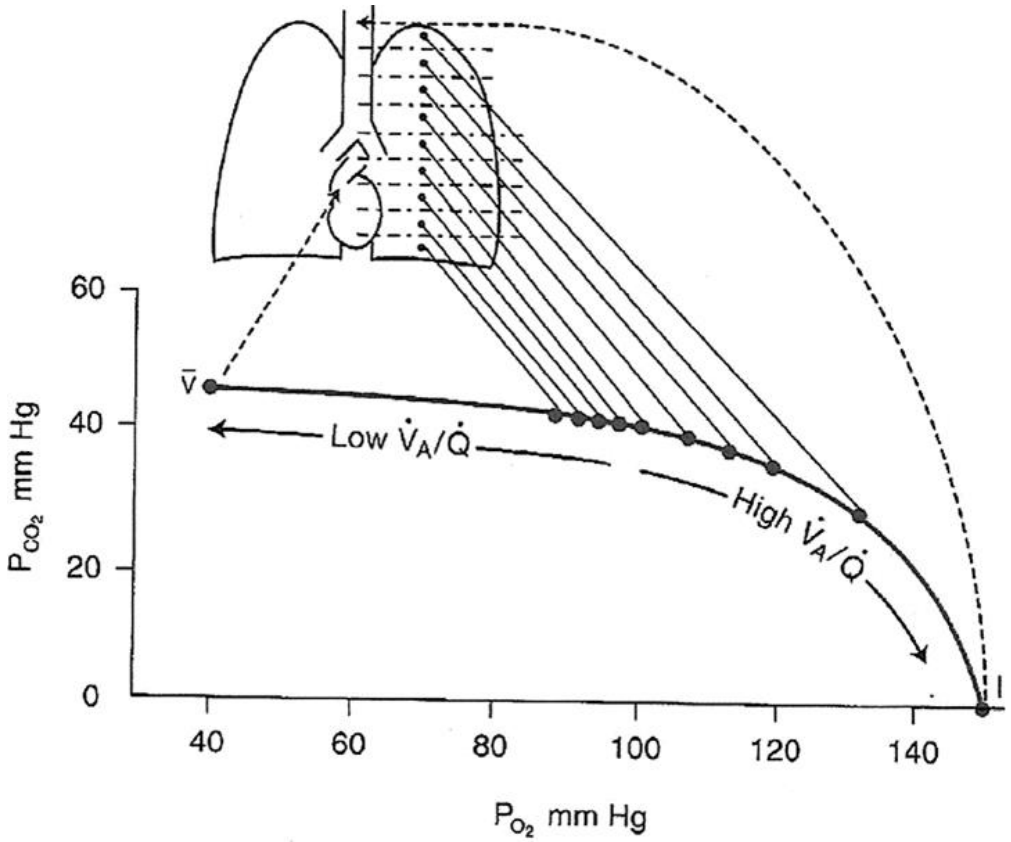
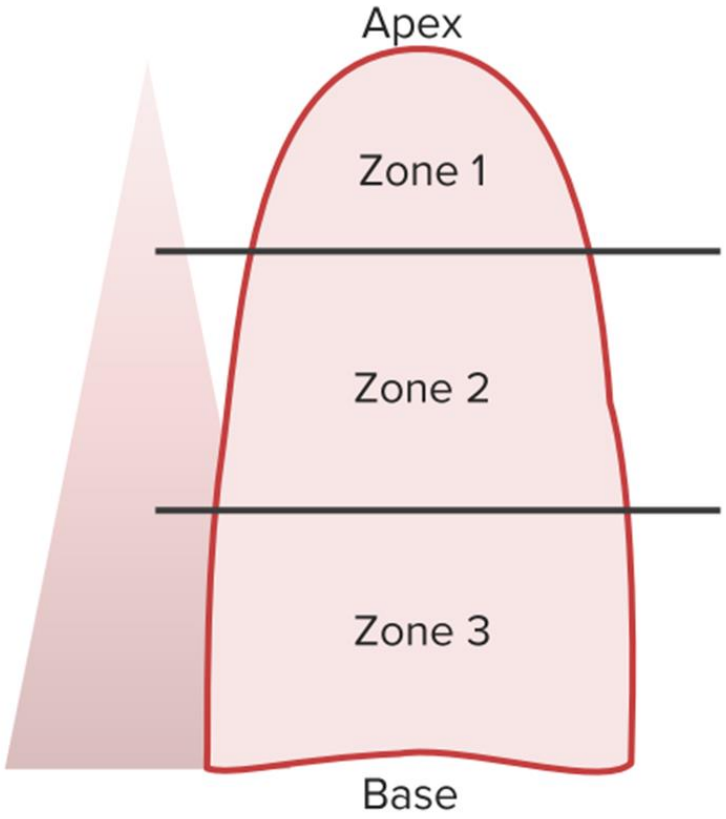
Normal lung - relationship between ventilation and perfusion

- There is a wide variation in the **V_A/Q ratio** to some extent already in healthy subjects, however, it does not represent a serious health problem in healthy man
  - tendency for ventilation not to be matched by perfusion towards the apices, with the reverse occurring at the bases
    - **kind of physiological dead space** in apexes ($V_A/Q = 3.3$)
    - **kind of physiological shun**t in bases ($V_A/Q = 0.7$) – lower P_AO_2, higher P_ACO_2 and lower pH
- All the blood from various lung regions mixes, however, quantitative contribution of the blood from bases of the lungs is much greater!





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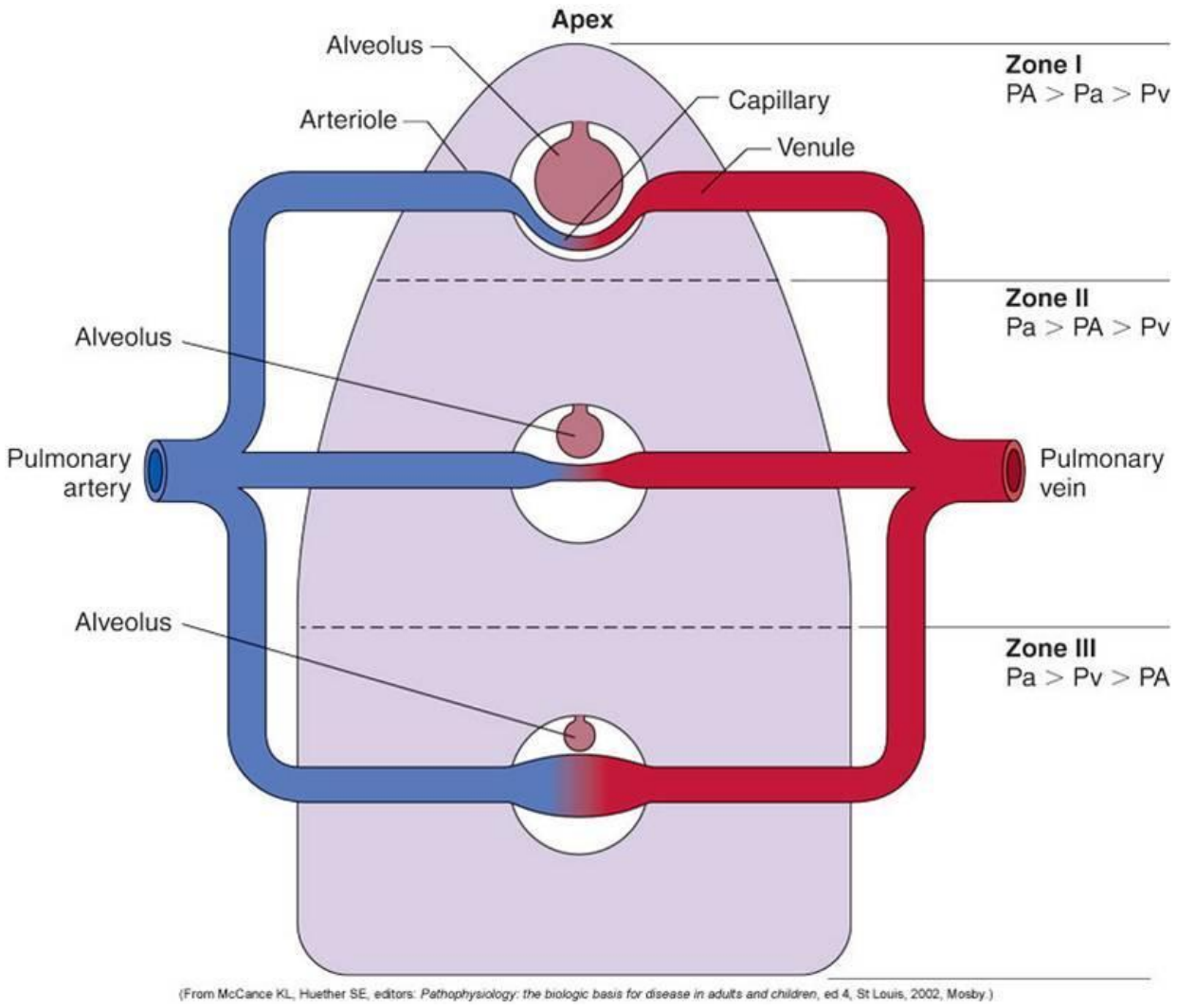
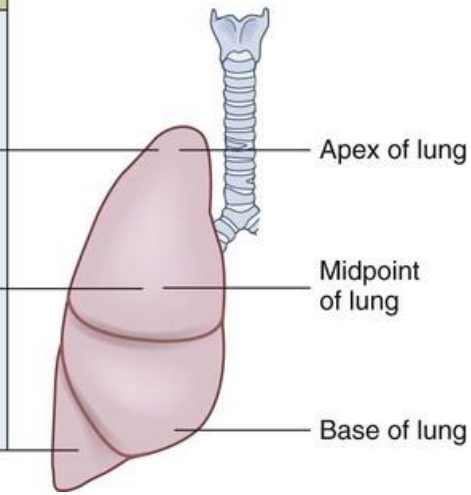
Distribution of V_A/Q mismatch largely contributes to the A-a difference of oxygen



(From McCance KL, Huether SE, editors: *Pathophysiology: the biologic basis for disease in adults and children*, ed 4, St Louis, 2002, Mosby.)

- Blood form various zones mixes with **largest contribution of that from lung bases**
  - therefore alveoli with lower V_A/Q (from lung bases with more perfusion) affect the arterial PaO_2 more (**PaO_2 ~97 mmHg**)
  - on the contrary, ventilation does not differ that much, therefore PO_2 in the expired alveolar air is ~100 mmHg

V/Q	PaO_2	$PaCO_2$
3.3	132	28
1.0	108	39
0.63	89	42



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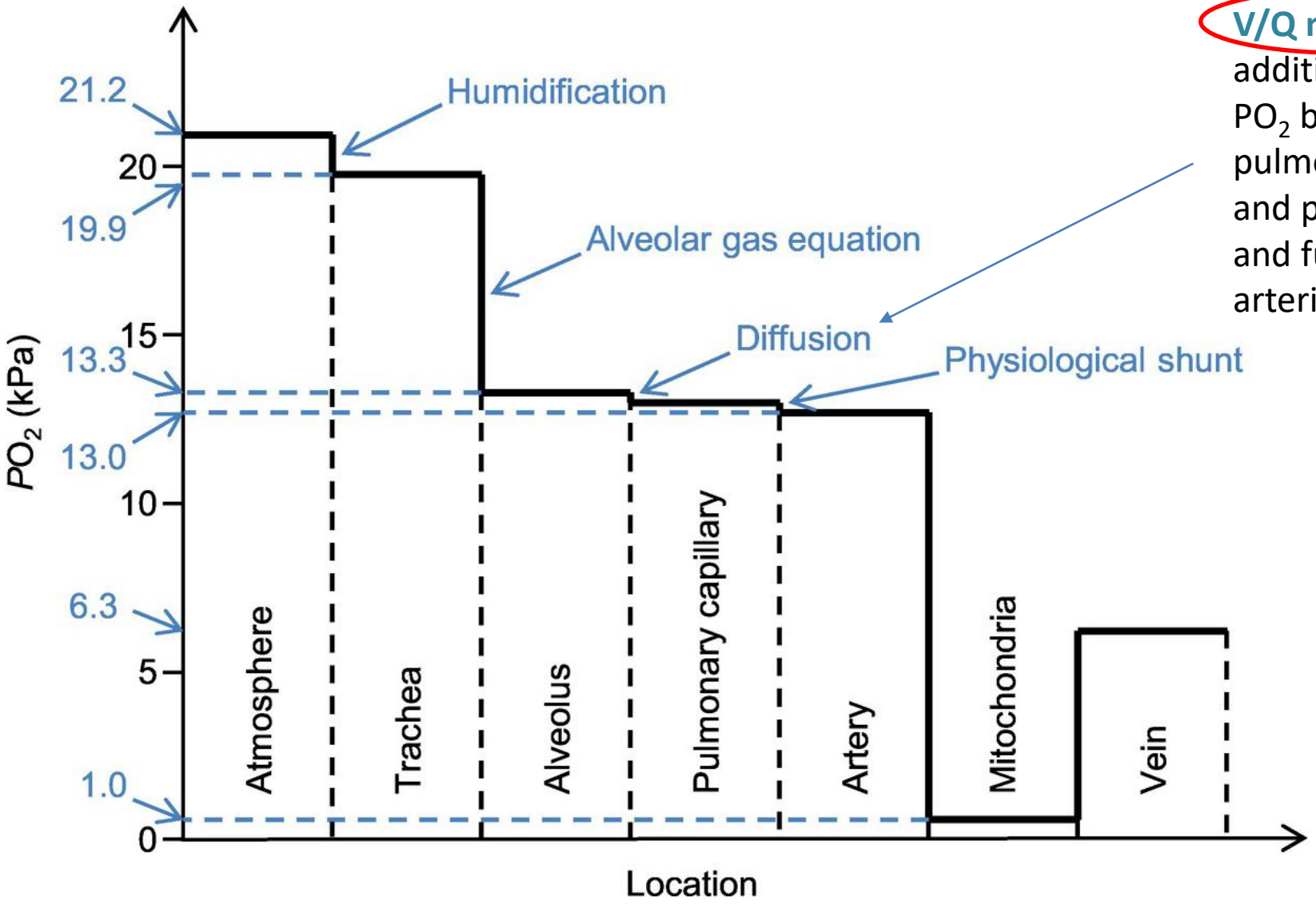
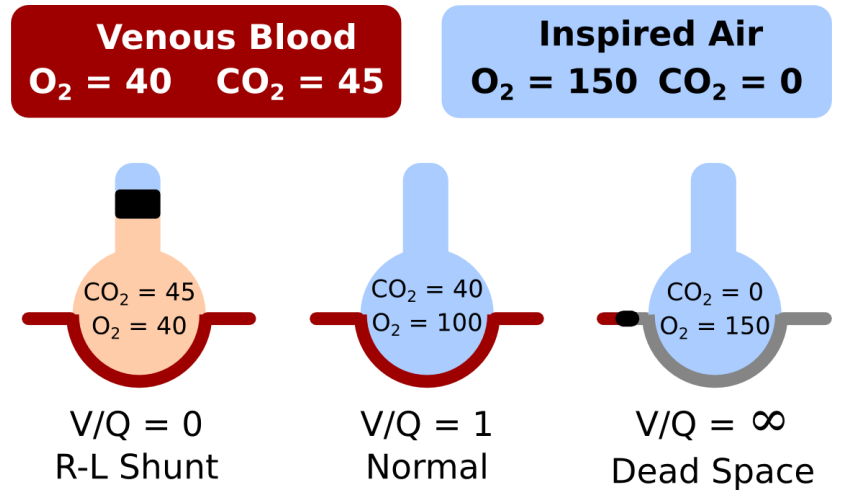
Physiological V/Q inequality contributes to the O_2 cascade

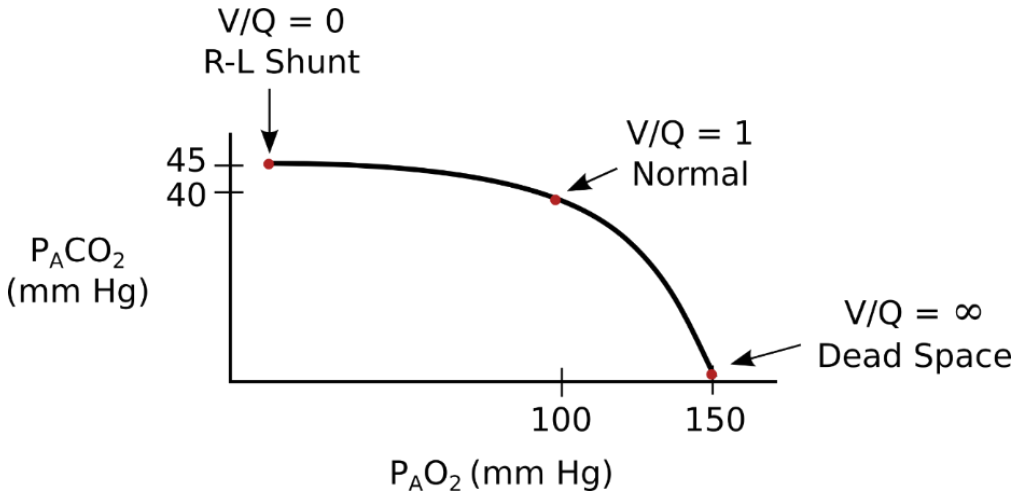


V/Q mismatch – causes additional difference in PO_2 between pulmonary capillaries and pulmonary vein and further systemic arteries

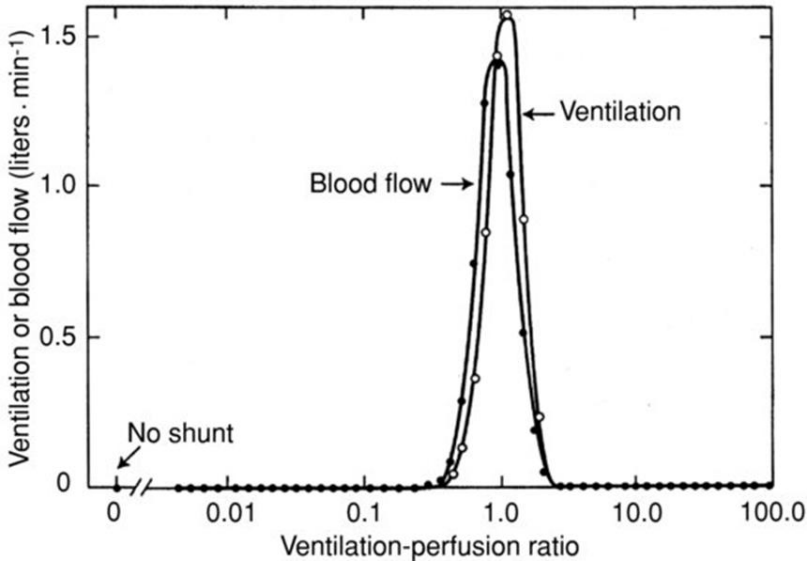
Effect of the V/Q ratio on Alveolar Gas Tensions

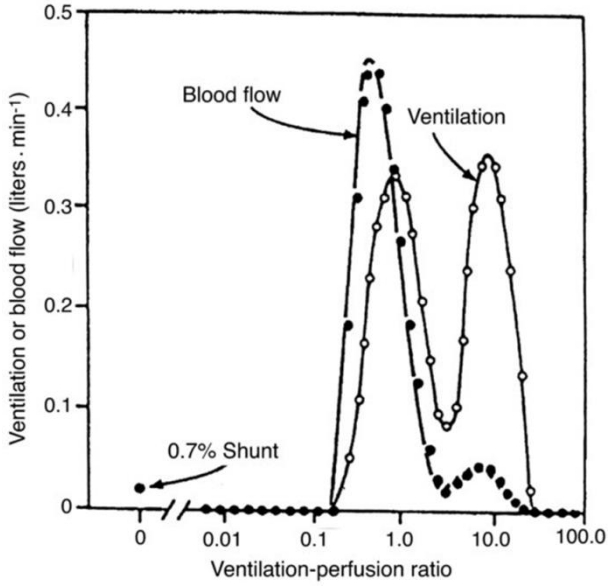
- There are limits in the V_A/Q ratio
- The effect of diseases leading to an increased **dead space** (V_A/Q ratio > 1) can usually be overcome by a compensatory hyperventilation of normally perfused alveoli
  - alveolar hyperventilation reduces the alveolar P_ACO_2 and considerable diffusion of CO_2 leads to a proportional fall in the carbon dioxide content of the blood
- An increased **R-L shunting** (V_A/Q ratio < 1) results in arterial hypoxaemia that cannot be effectively compensated for by hyperventilation
- In advanced disease with large V_A/Q mismatch this compensation cannot occur, leading to increased alveolar and arterial P_{CO2}, together with hypoxaemia which cannot be compensated by increasing ventilation

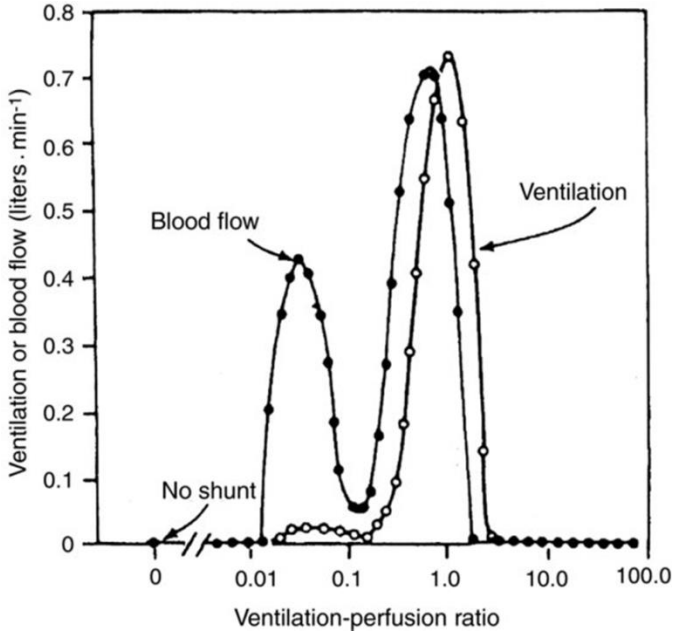




Example of a distribution of ventilation-perfusion ratios







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).

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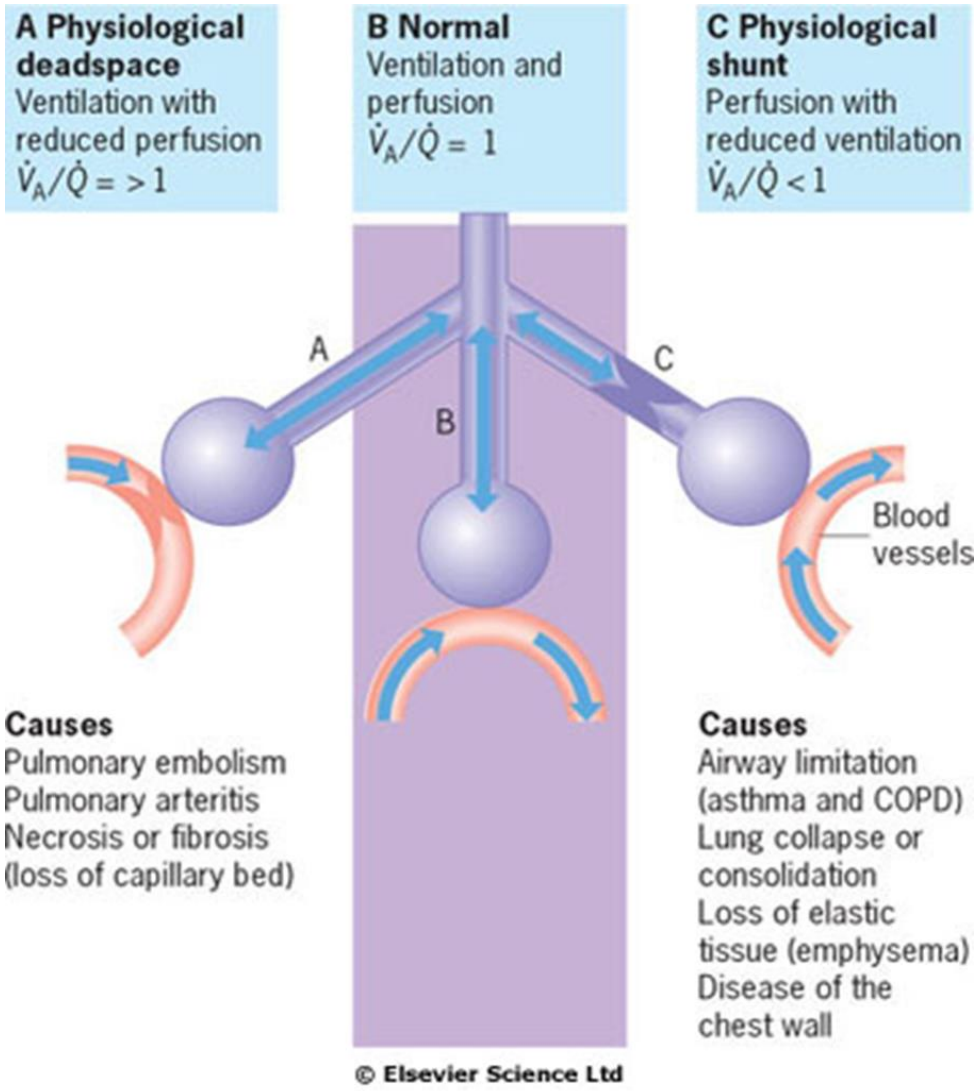
Ventilation-perfusion inequality (mismatch)



- 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

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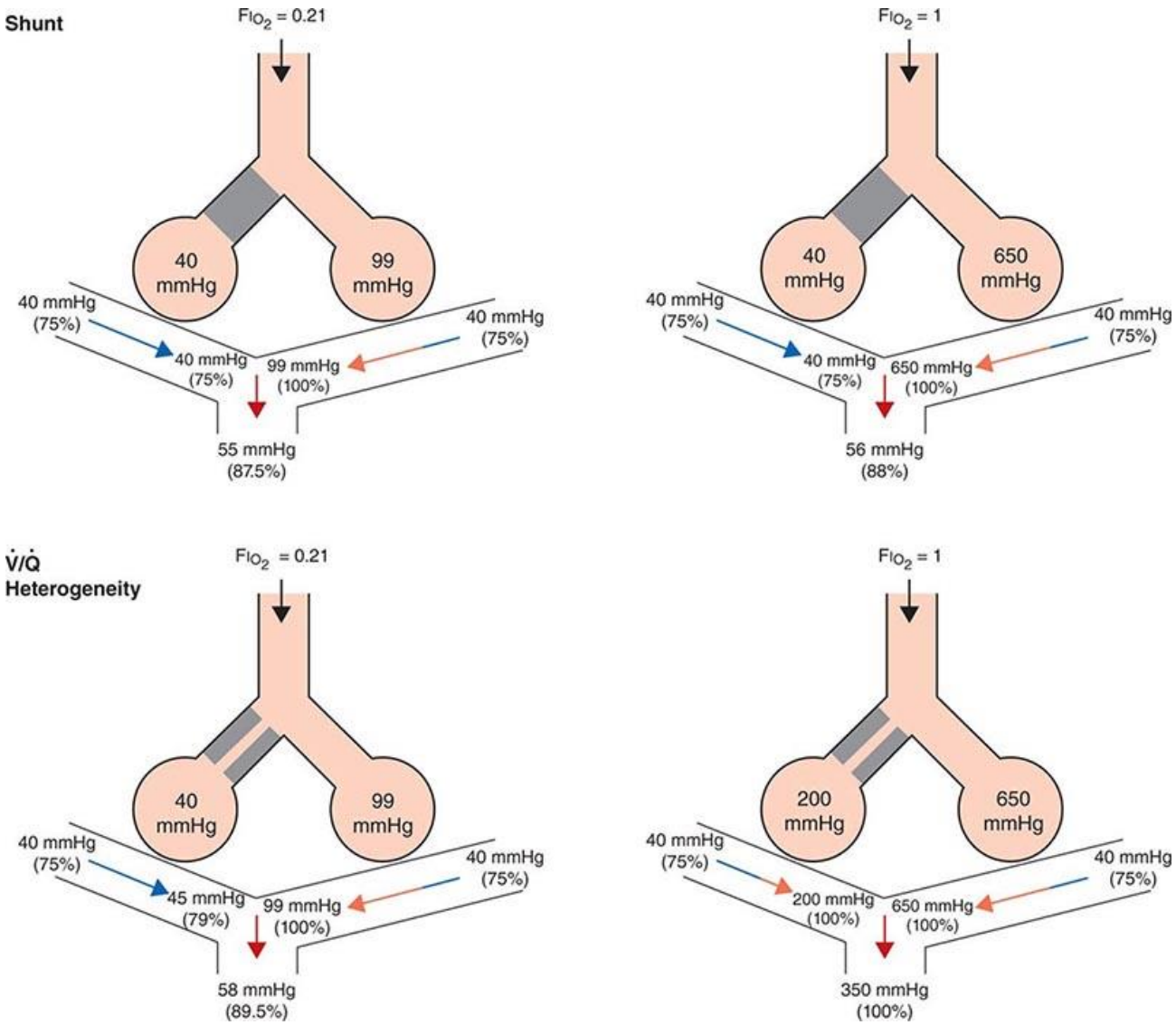
Arterial hypoxemia refractory to supplemental inspired O_2



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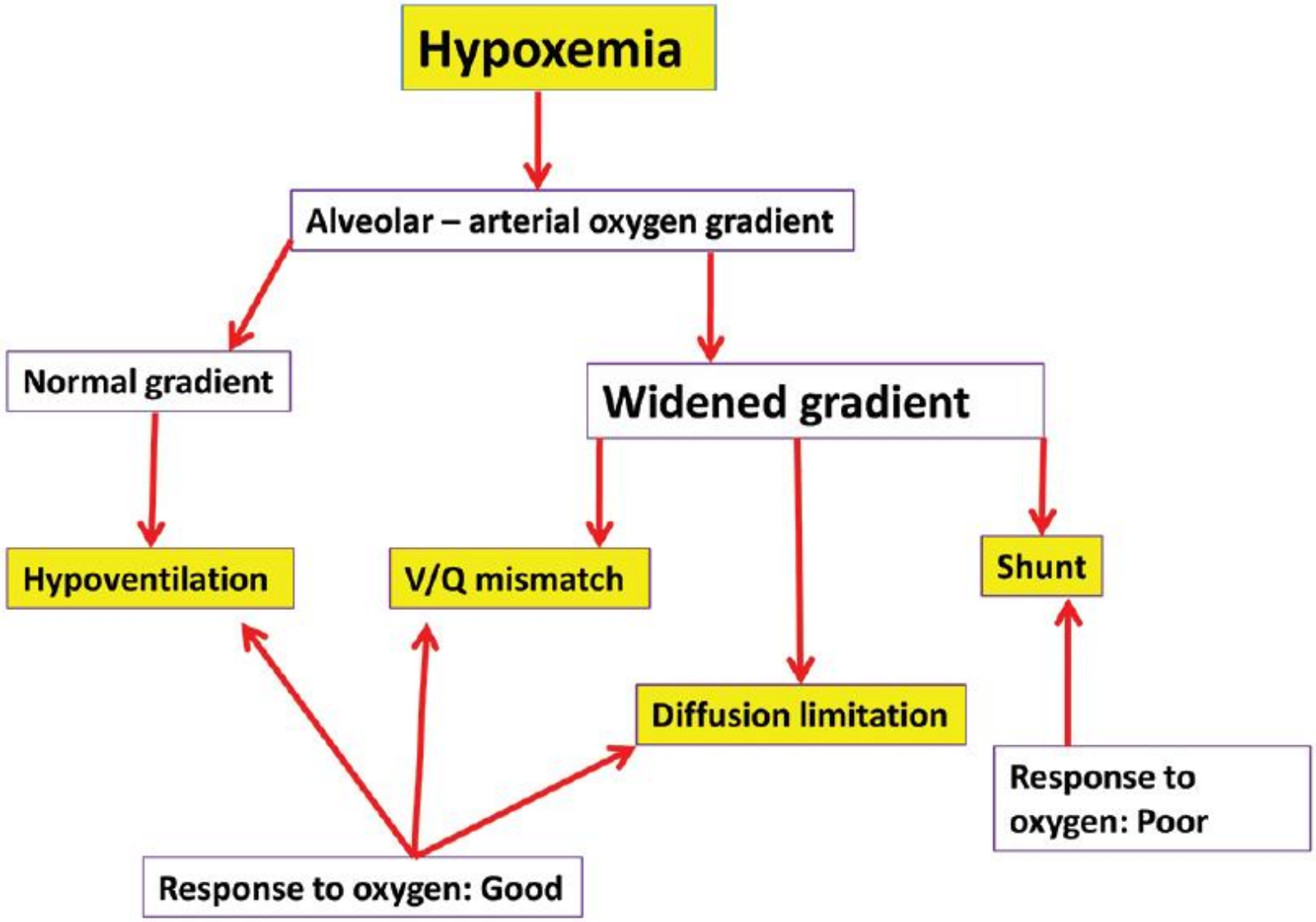
Hypoxemia dif. dg.



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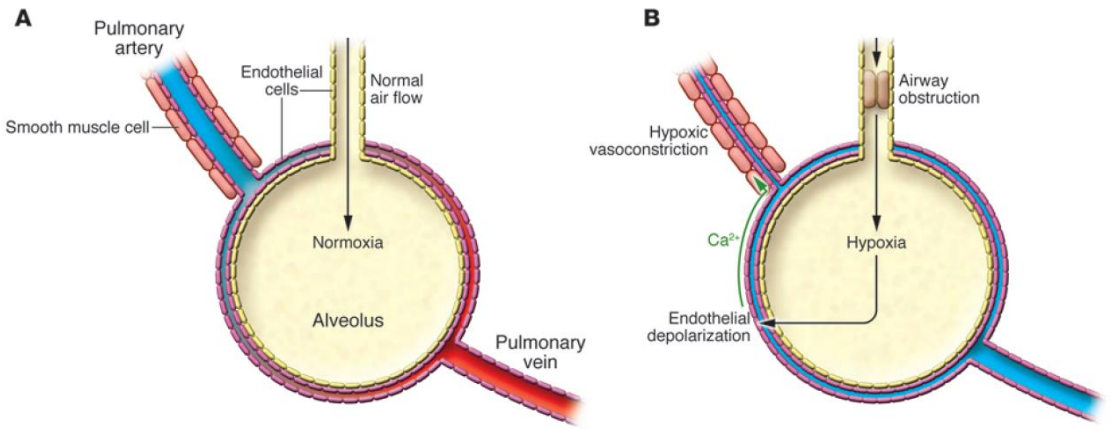
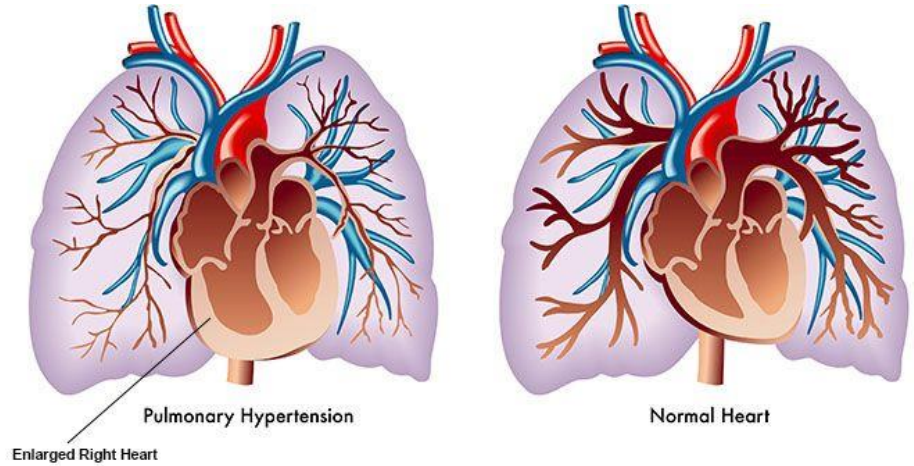
Hypoxic pulmonary vasoconstriction (HPV)

- a physiological phenomenon in which small pulmonary arteries constrict in the presence of **alveolar hypoxia** (low oxygen levels)
  - as in hypoventilation and **low V_A/Q ratio**
    - typically in obstructive diseases resistant to compensatory hyperventilation such as chronic bronchitis
- a homeostatic mechanism that is intrinsic to the pulmonary vasculature
  - intrapulmonary arteries constrict in response to alveolar hypoxia, diverting blood to better-oxygenated lung segments, thereby **optimizing ventilation/perfusion matching and systemic oxygen delivery**
    - chronically happens with low V/Q ratio (and event. in long-lasting hypoventilation)
- mechanisms
  - in response to alveolar hypoxia, a mitochondrial sensor dynamically changes reactive oxygen species and redox couples in pulmonary artery smooth muscle cells (PASMC)
  - this inhibits potassium channels, depolarizes PASMC, activates voltage-gated calcium channels, and increases cytosolic calcium, causing vasoconstriction
  - sustained hypoxia activates rho kinase, reinforcing vasoconstriction, and hypoxia-inducible factor (HIF)-1α, leading to adverse pulmonary vascular remodeling and **pulmonary hypertension** (PH)
  - this pre-capillary PH leads to right heart remodelling – **cor pulmonale**
- primary role is in the non-ventilated fetal lung, HPV diverts blood to the systemic vasculature





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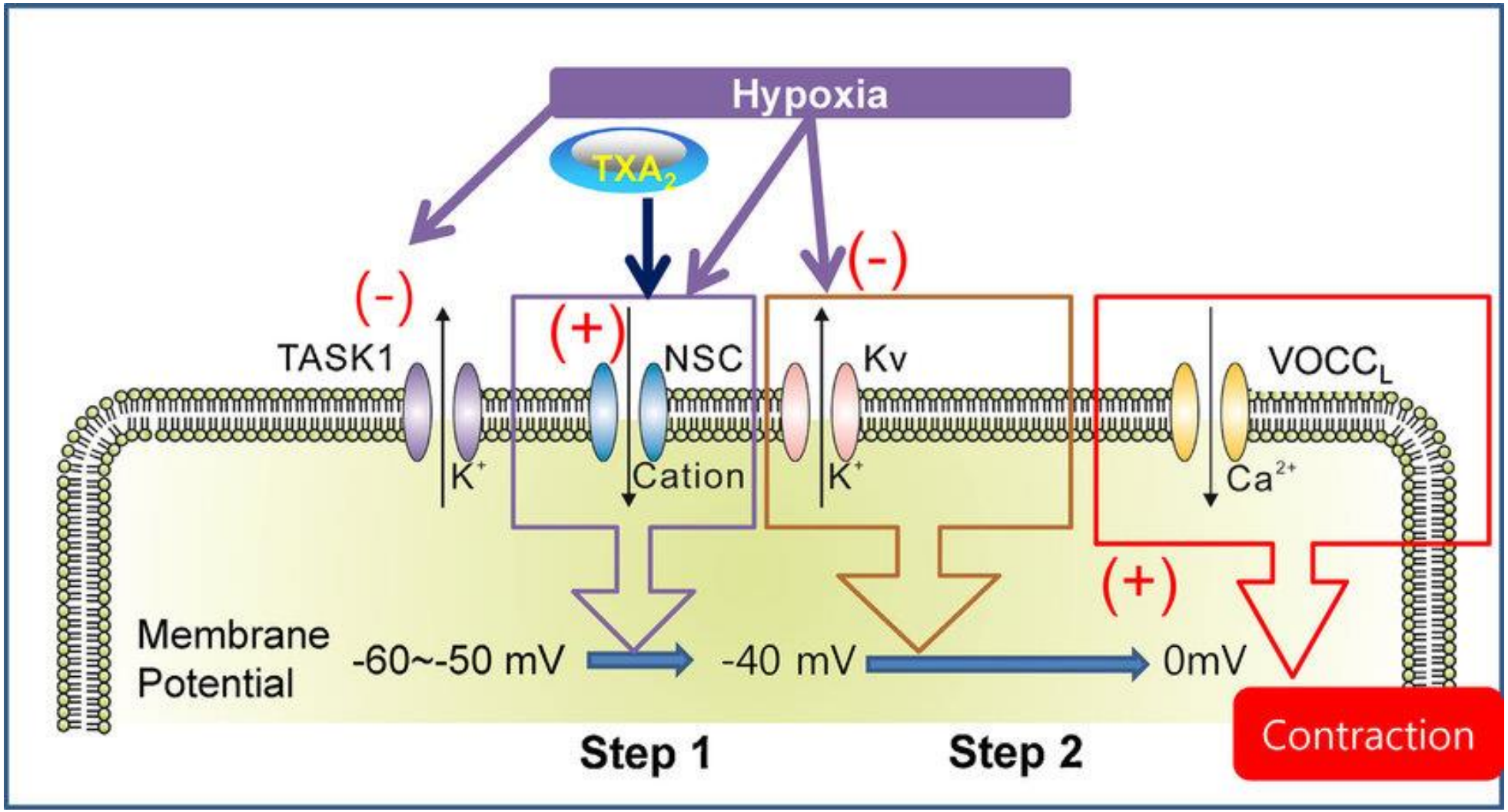
Mechanism of HPV



The current model of the cellular mechanism of hypoxic pulmonary vasoconstriction in a rat pulmonary artery (PA). Relevant ion channels are displayed. Under normoxia, the membrane potential of the smooth muscle of the PA is held at approximately −50 mV because of the TASK-like background current of a K + channel. Hypoxic conditions initially decrease TASK activity. When combined with TXA 2 , activation of NSC induces membrane depolarization up to the threshold voltage for activation of K v channels (Step 1). In addition to the NSC activation, hypoxic inhibition of the K v current further depolarizes the membrane potential (Step 2). As the membrane potential depolarizes above −40 mV, the activation of VOCC L eventually allows for Ca 2+ influx for contraction of smooth muscles. K v , voltage-gated K + channel; NSC, nonselective cation channel; TASK-1, background-type K + channel with a two-pore domain (K2P); TXA 2 , thromboxane A 2 ; VOCC L , voltage-gated L-type Ca 2+ channels.

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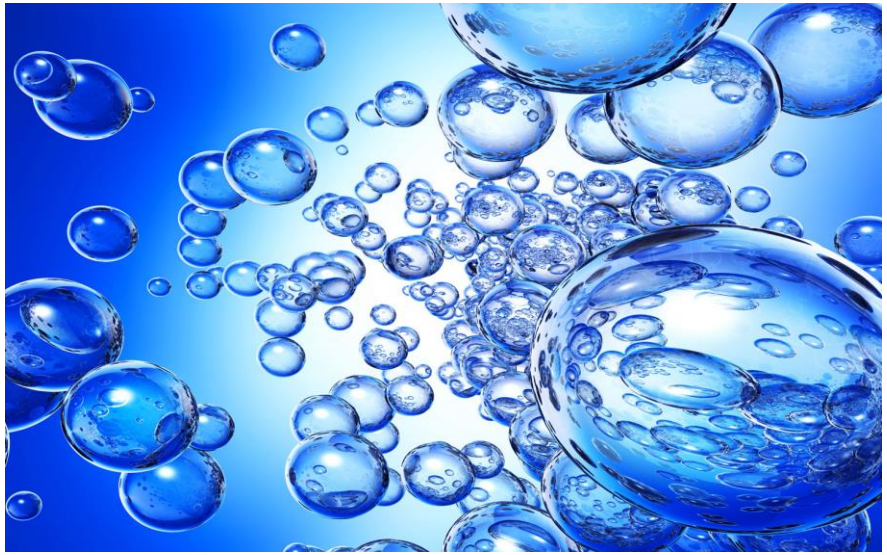

OXYGEN CASCADE IN THE BODY

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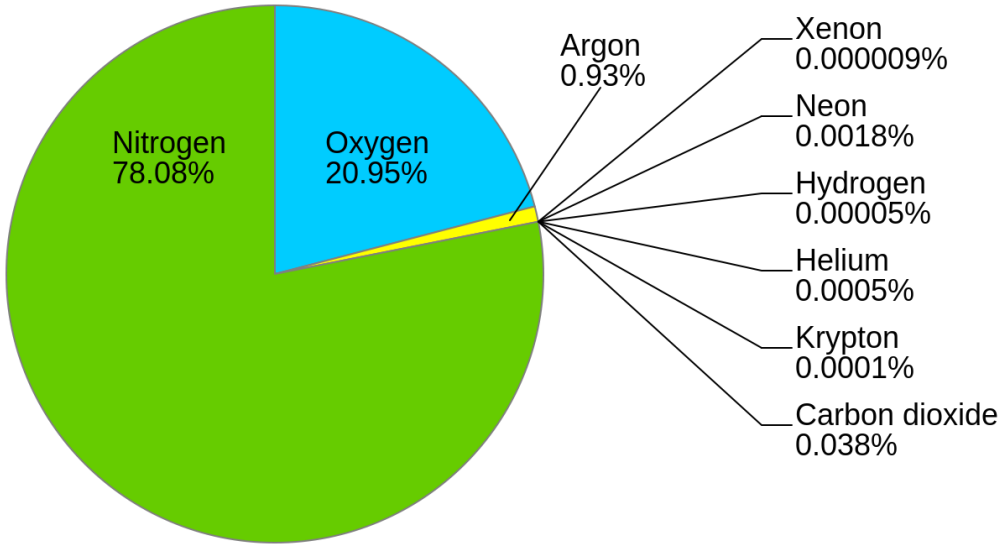
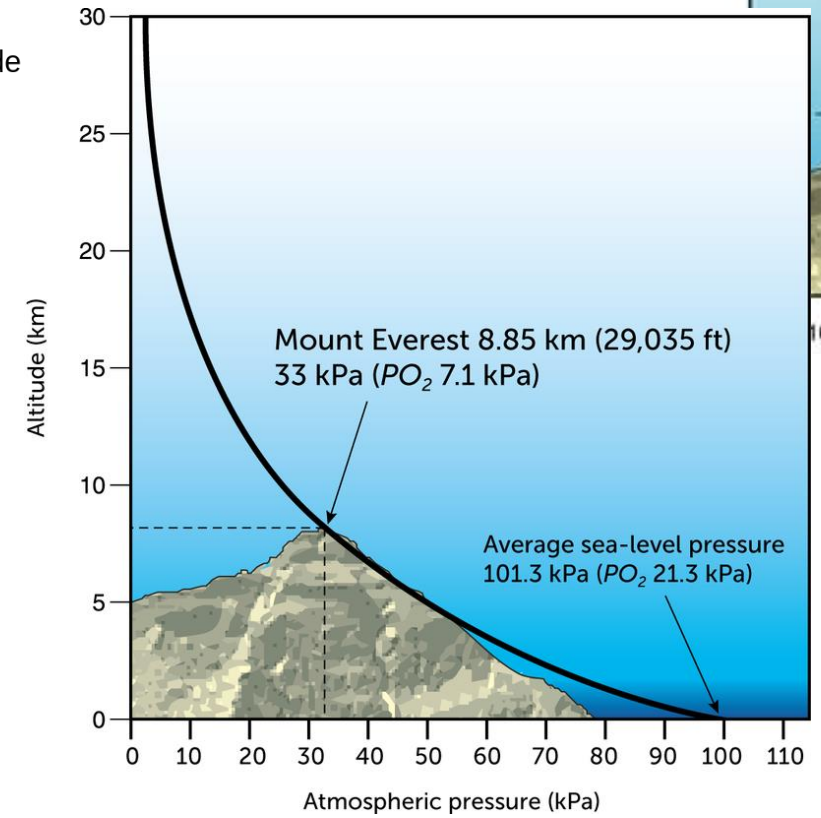
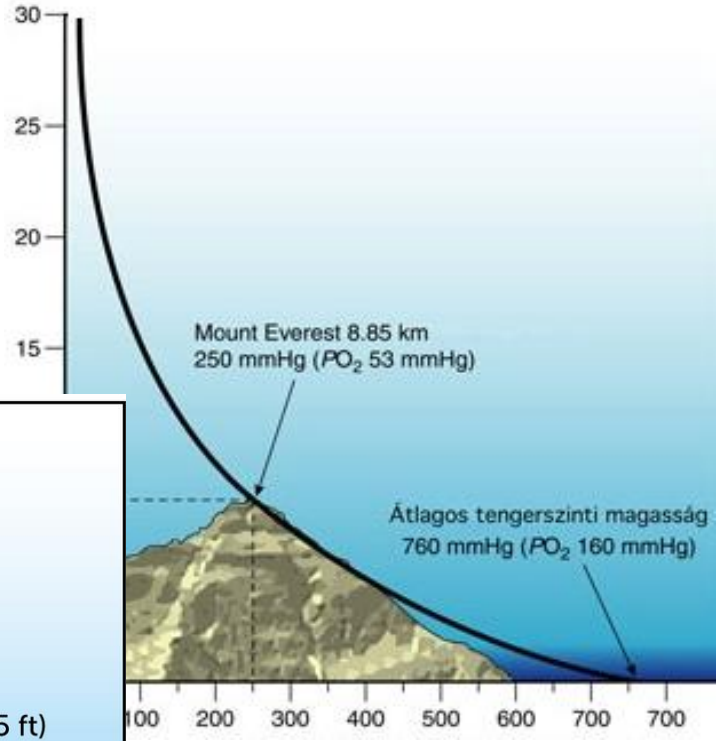
What are we breathing?







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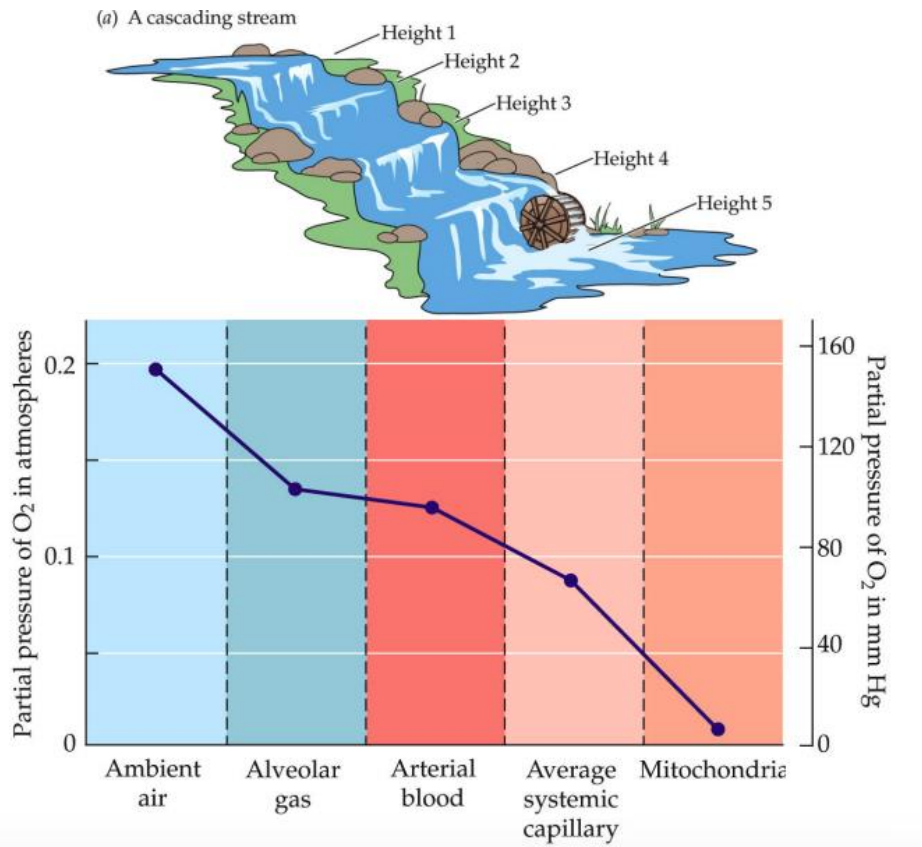
Oxygen cascade – progressive drop of oxygen content



gas	atmospheric air	alveolar air
nitrogen	78%	79.6%
oxygen	21%	15% (14.8%)
carbon dioxide	0.04%	6% (5.6%)

- reasons for normal gradual decrease of PO_2 between air and blood:
  - „competition“ with CO_2 in alveoli
    - up to the atmospheric pressure
      - see alveolar gas equation
  - less that 100% diffusion across alveolo-capillary membrane
    - irregularity of its thickness and change in the rate of lung perfusion
      - diffusion & perfusion limitation
    - 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 and thebesian veins into left atrium and other chambers
  - physiological ventilation-perfusion inequality
- other contributing factors to drop of oxygen content
  - physiologically a small fraction of abnormal Hb
    - Met-Hb
    - COHb
  - various oxygen extraction by tissues
- pathological aggravation in any if these steps contributing to drop of oxygen tension can **cause hypoxia**
  - hypoxic (= hypoxemic!!!!)
  - anaemic
  - circulatory
  - histotoxic

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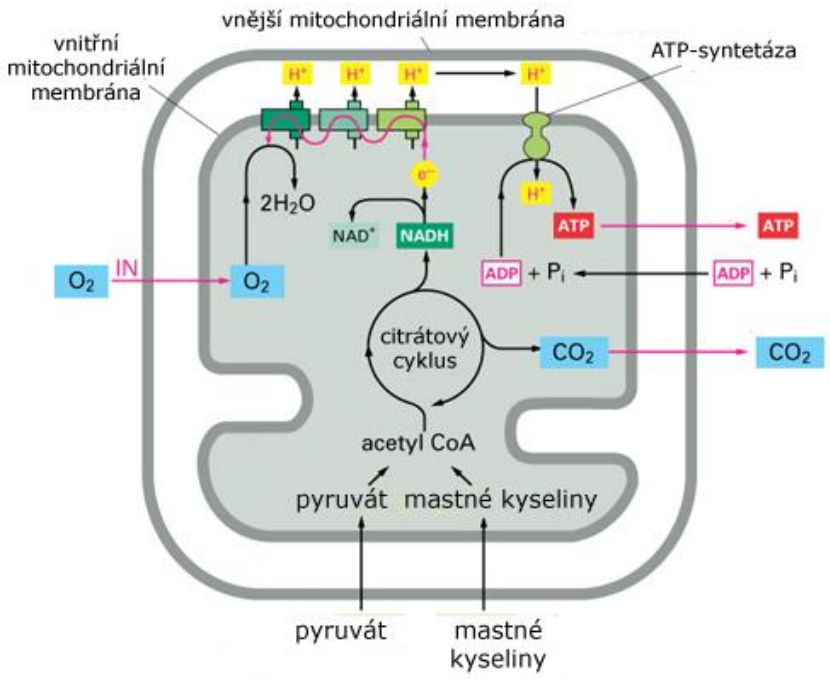
Oxygen in the body



- there are no significant O_2 stores in the body
  - available oxygen 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 coupled with 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

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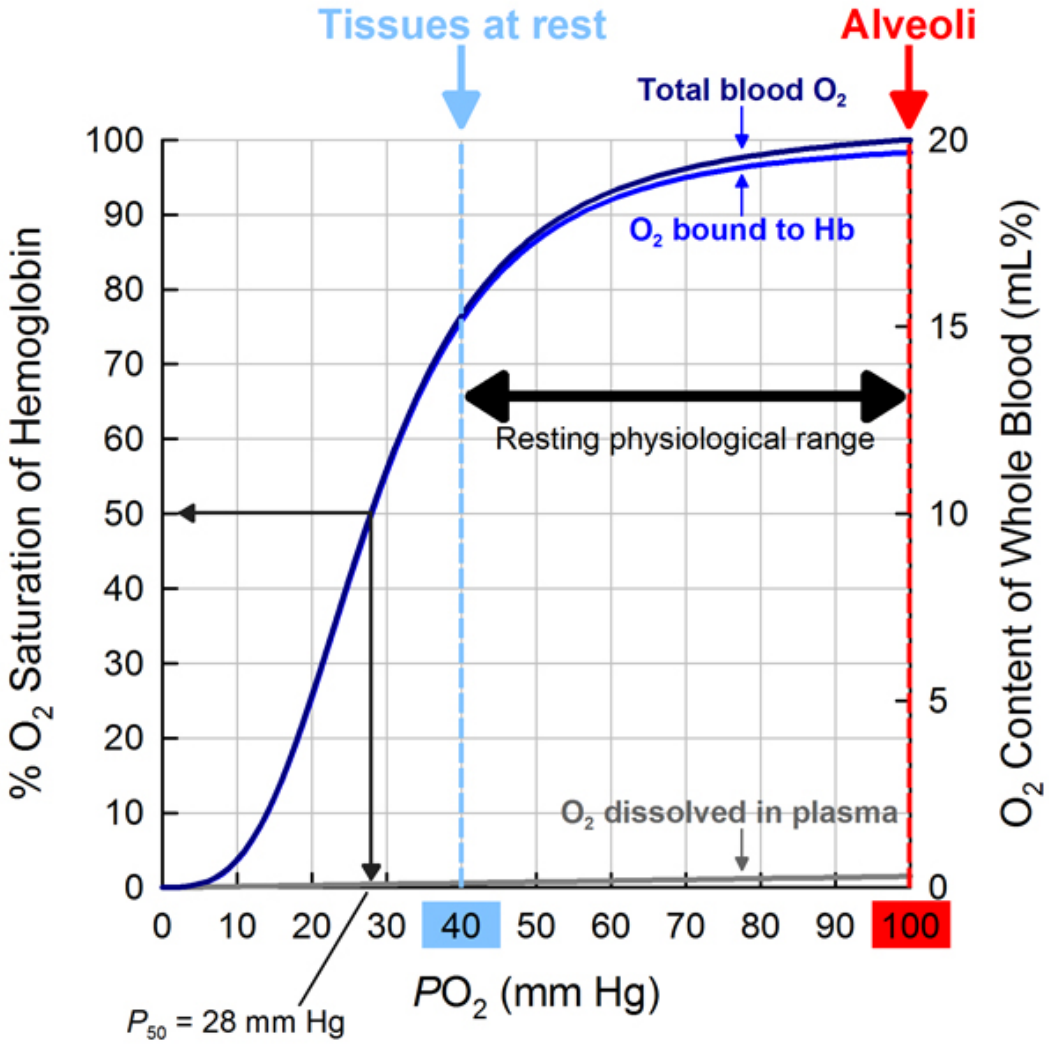
Transport of oxygen in the blood

- 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 > 10kPa/60 mmHg, saturation do not significantly decreases**
      - advantage when being in high altitude
      - saturation measured by pulsion oxymetry
- O_2 diffuses to tissues according to demands of mitochondria
  - for adequate production of ATP in mitochondria O_2 in tissues have to be > 0.13kPa/**1mmHg = critical oxygen tension**
- organism needs oxygen:
  - ~ 250 mL/min → 350 L/day in rest
  - much more (10x) during exercise
- total O_2 in the blood
  - total $[O_2] = 1.39 \times [Hb] \times \%\ saturation / 100 + 0.003 \times PO_2 = 20.5$ ml/dl



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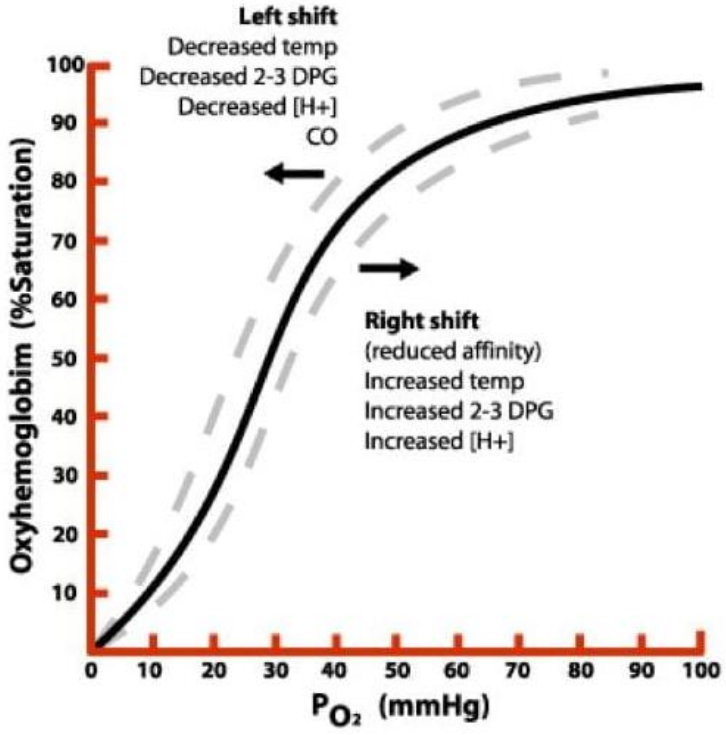
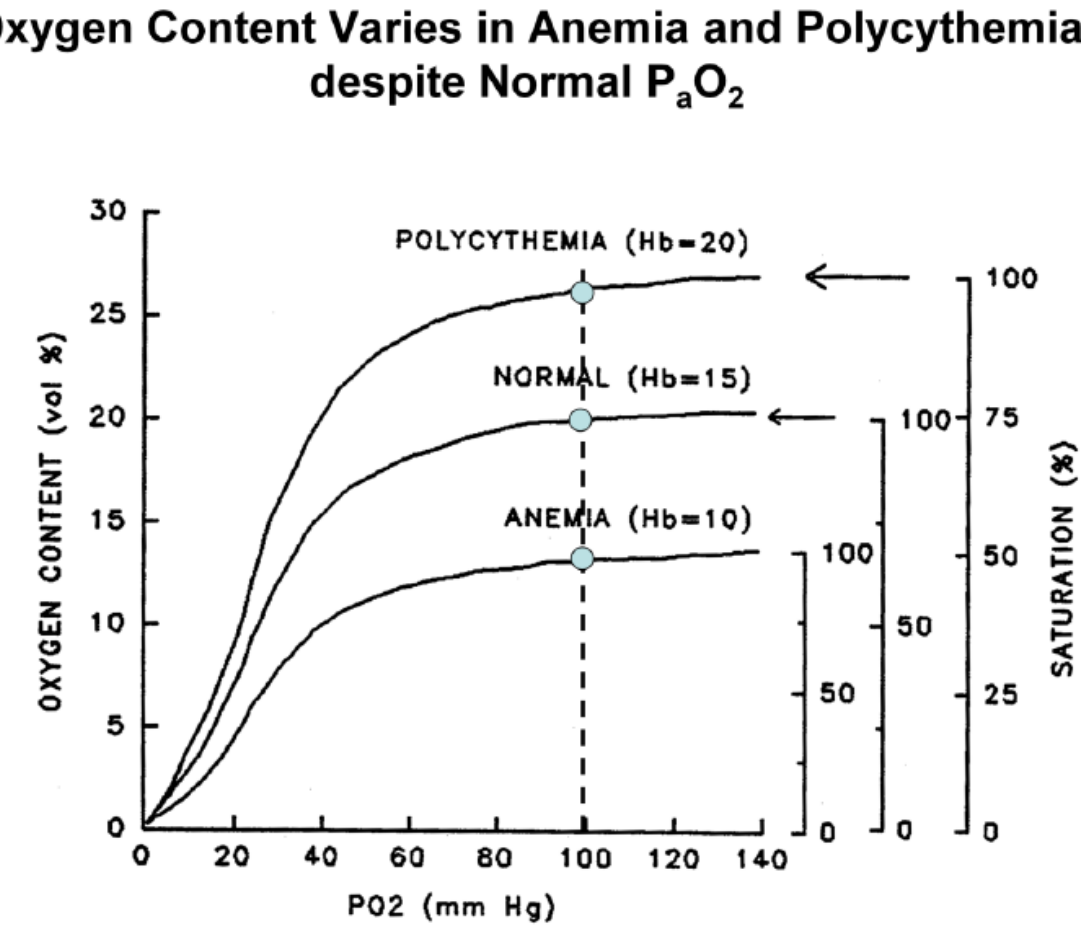
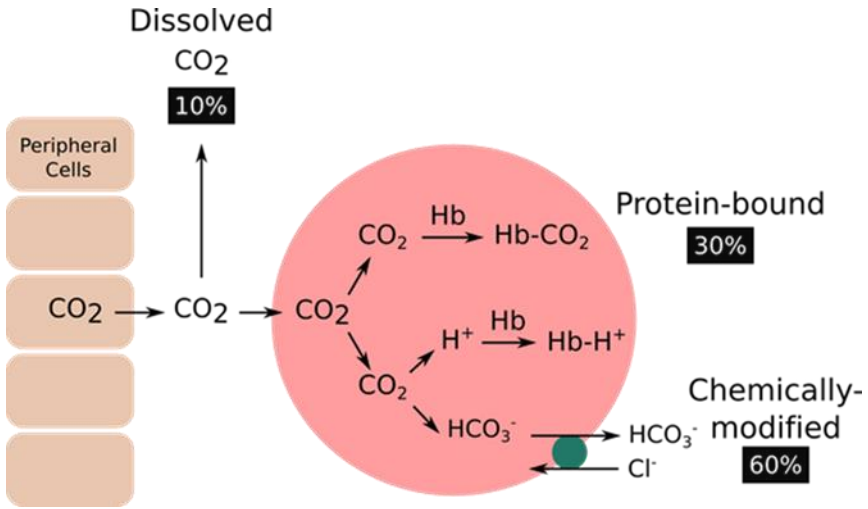
Shifting of Hb dissociation curve and the effect of [Hb]

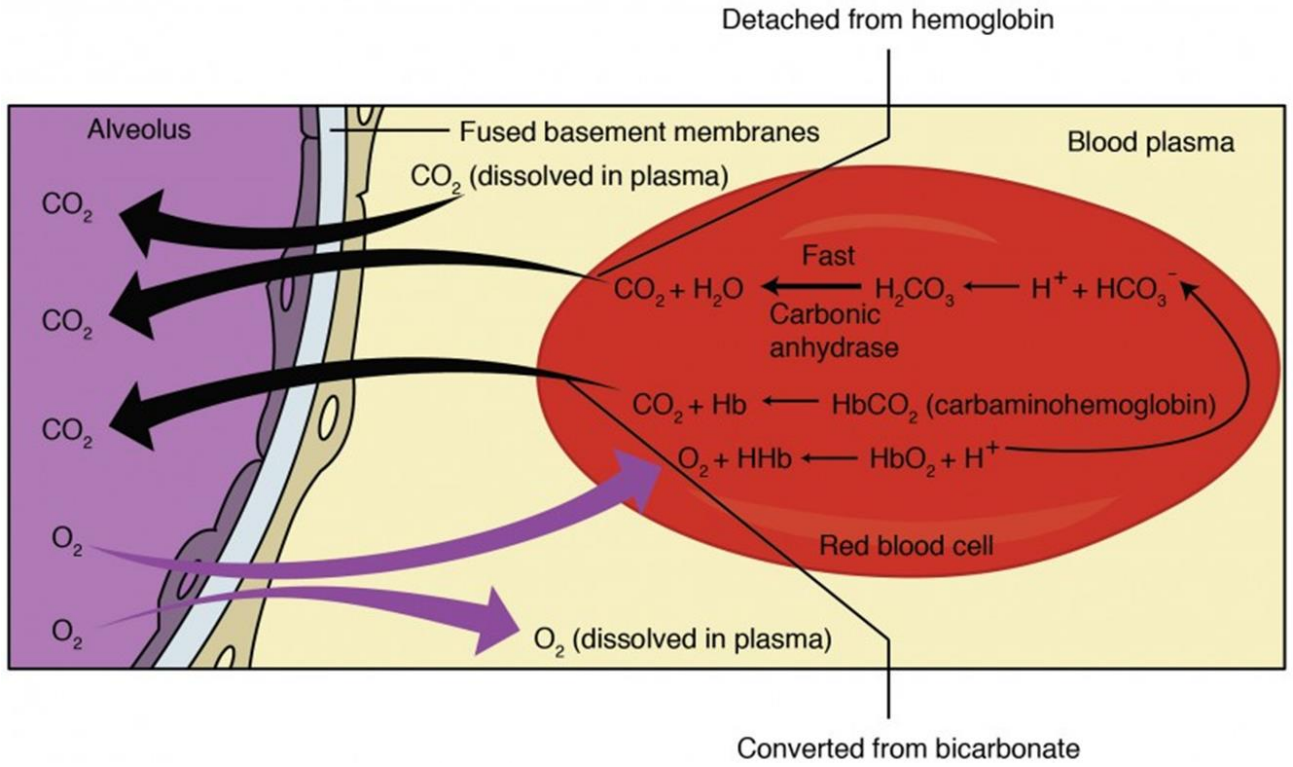




Transport of CO_2 in the blood

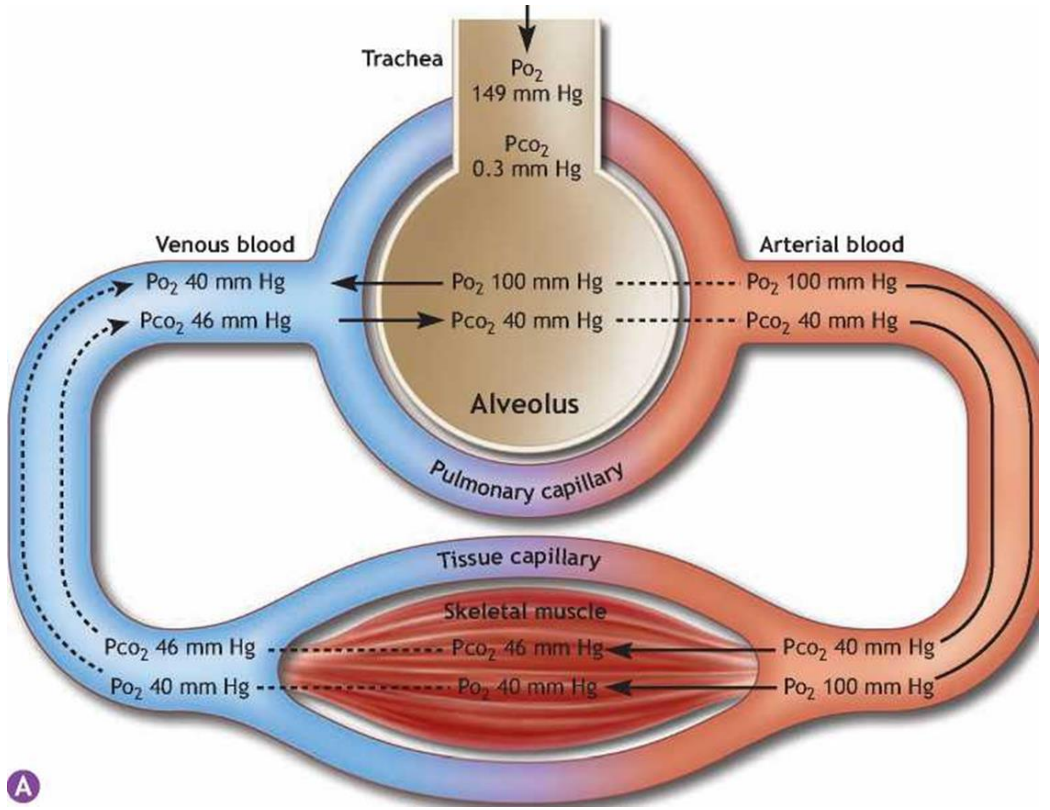
- CO_2 can be considered to be in simple solution in the plasma, the volume carried being proportional to its partia pressure (physically dissolved)
- solubility of carbon dioxide is much higher (20×) than that of oxygen, therefore physically dissolved CO_2 is much more important than for O2





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), $P_{water\ vapour}$ = 47 mmHg
    - 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

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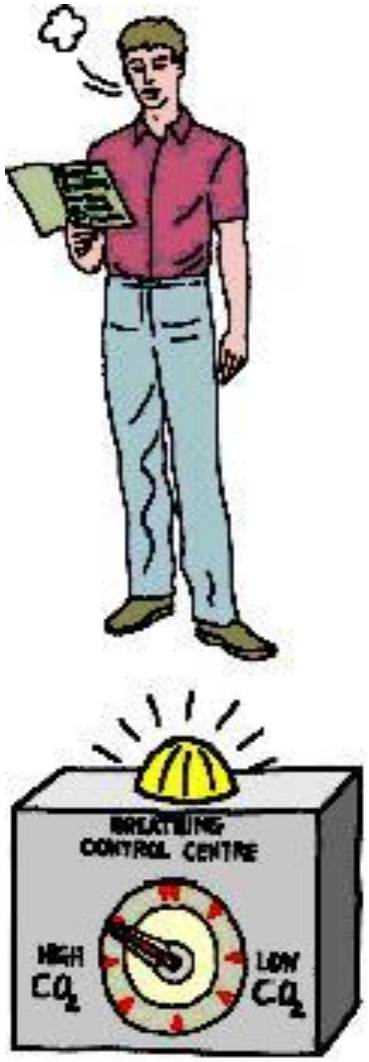
CONTROL OF RESPIRATION & ITS DISORDERS



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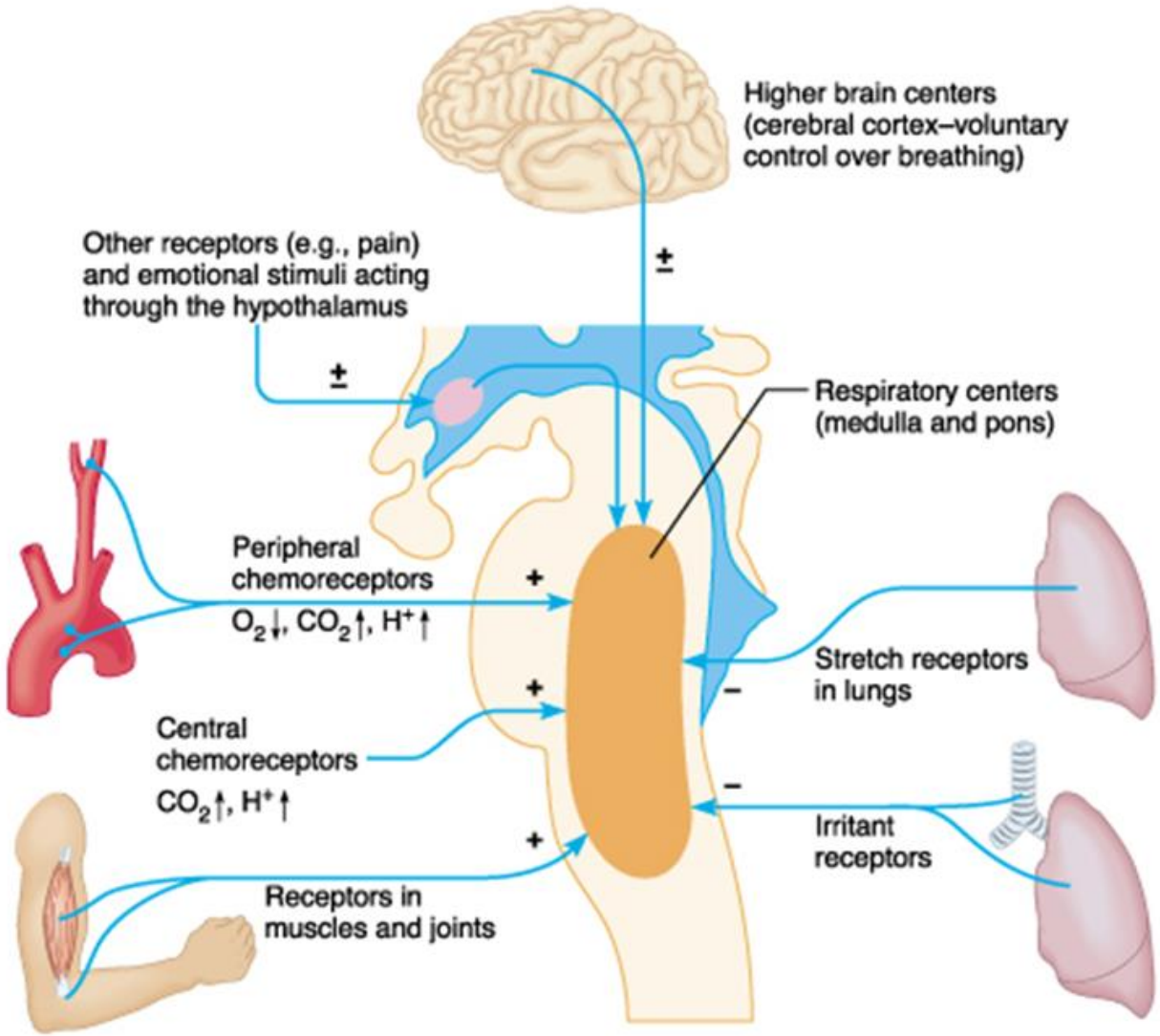
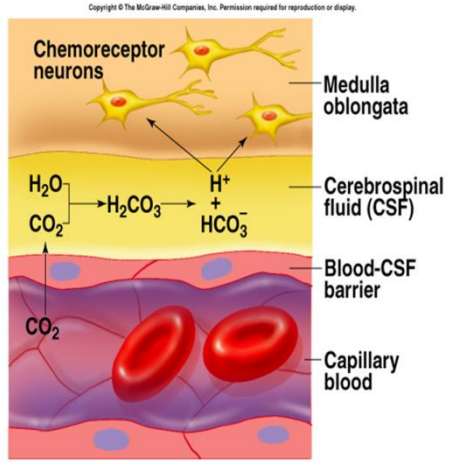
Control of respiration



- 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

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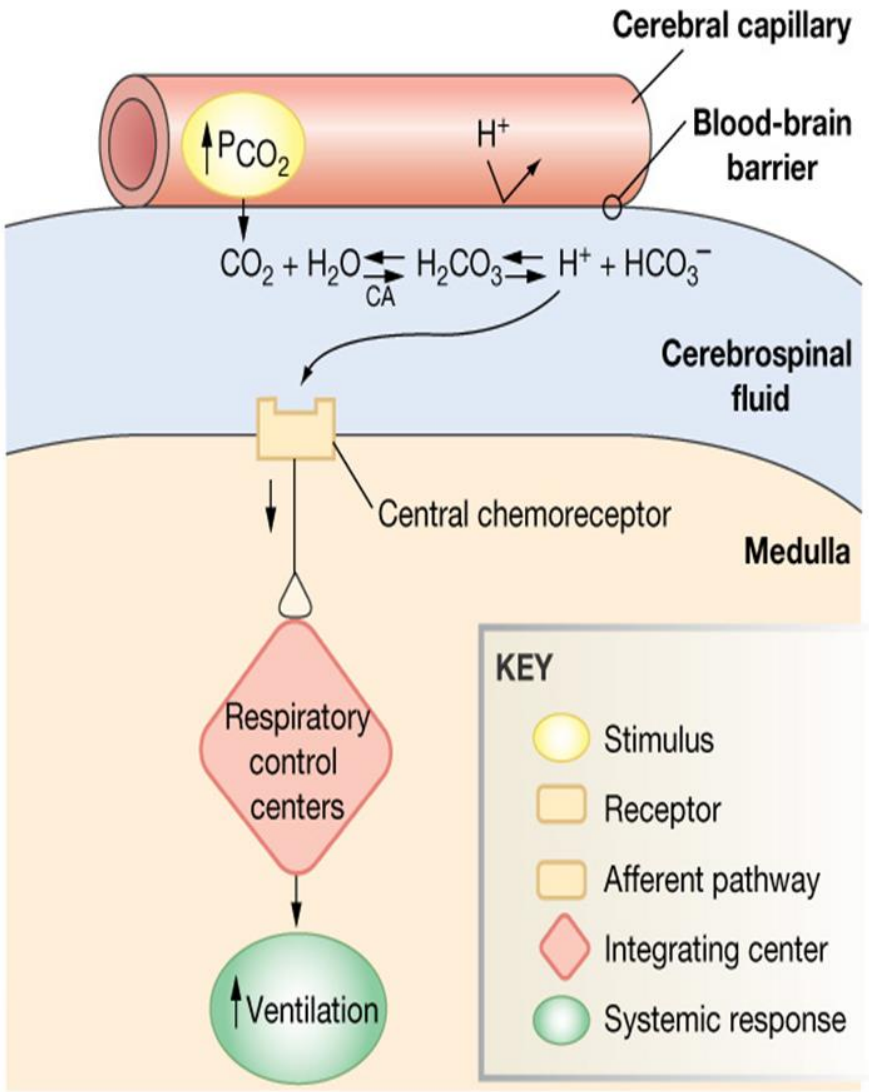
Central chemoreceptors



- sensitive to ↑$PaCO_2$ (and subsequent formation of H^+ in CF)
- H^+ cannot go through hematoencephalic barrier therefore response to other 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
    - they adjust to hypercapnia and hyperventilation ceases
    - -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 $PaCO_2$

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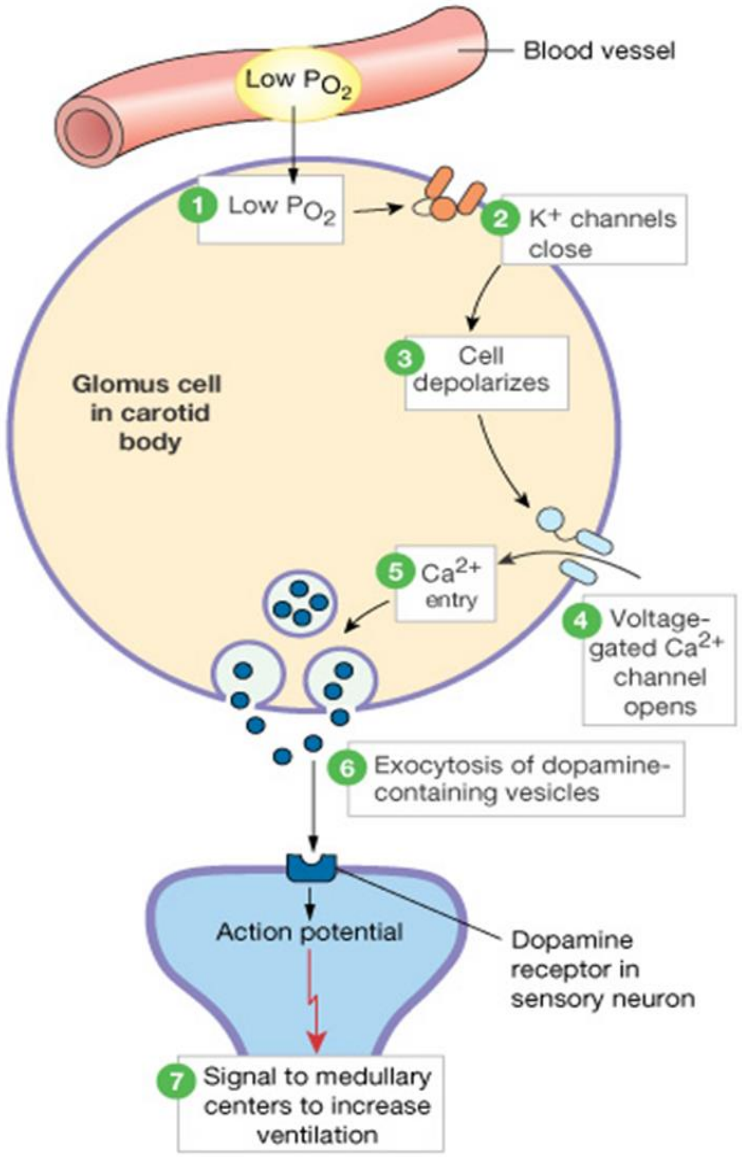
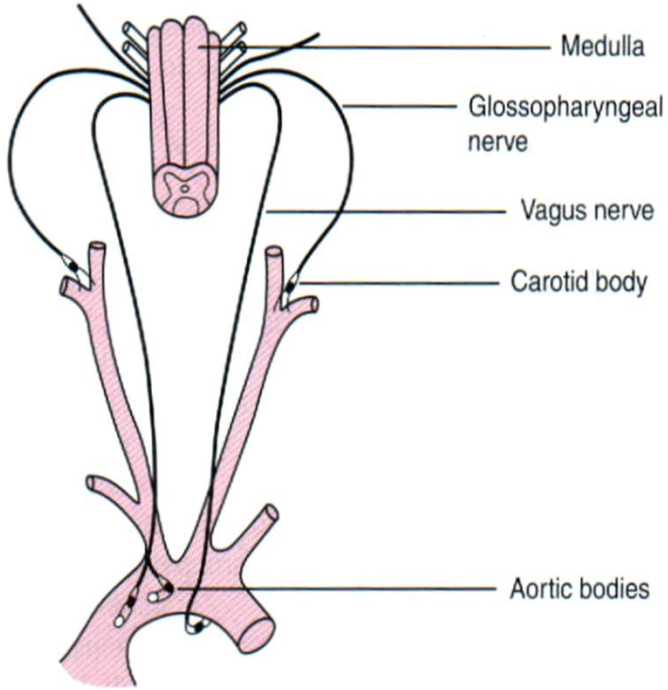
Peripheral chemoreceptors - oxygen senzors





- Glomus caroticus and aortic bodies - sensitive to change of PaO_2 and pH chgange
  - 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)

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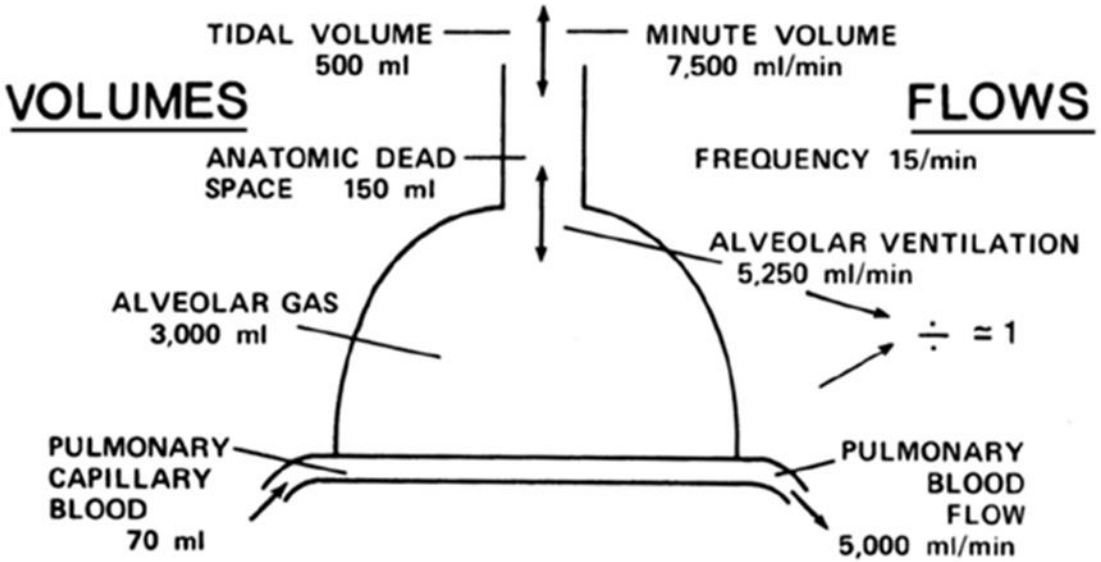
Respiratory stimuli

- 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 auxiliary 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)

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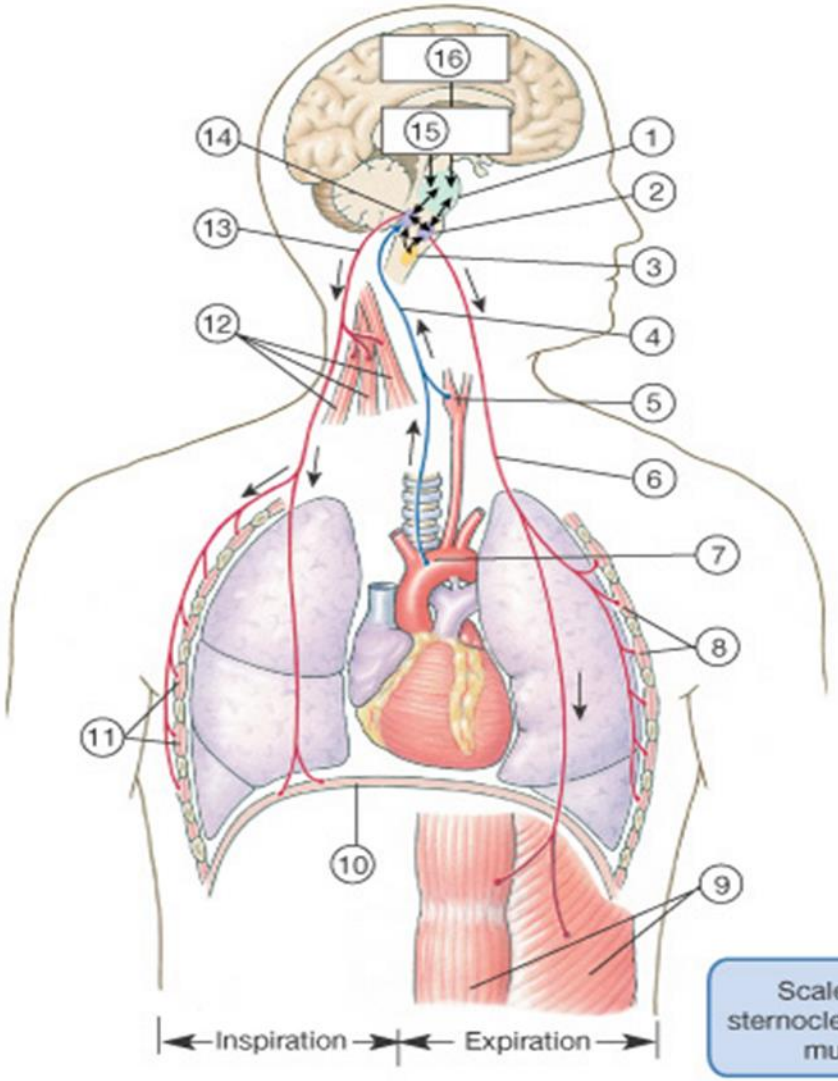
16
15
14
1
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12
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7
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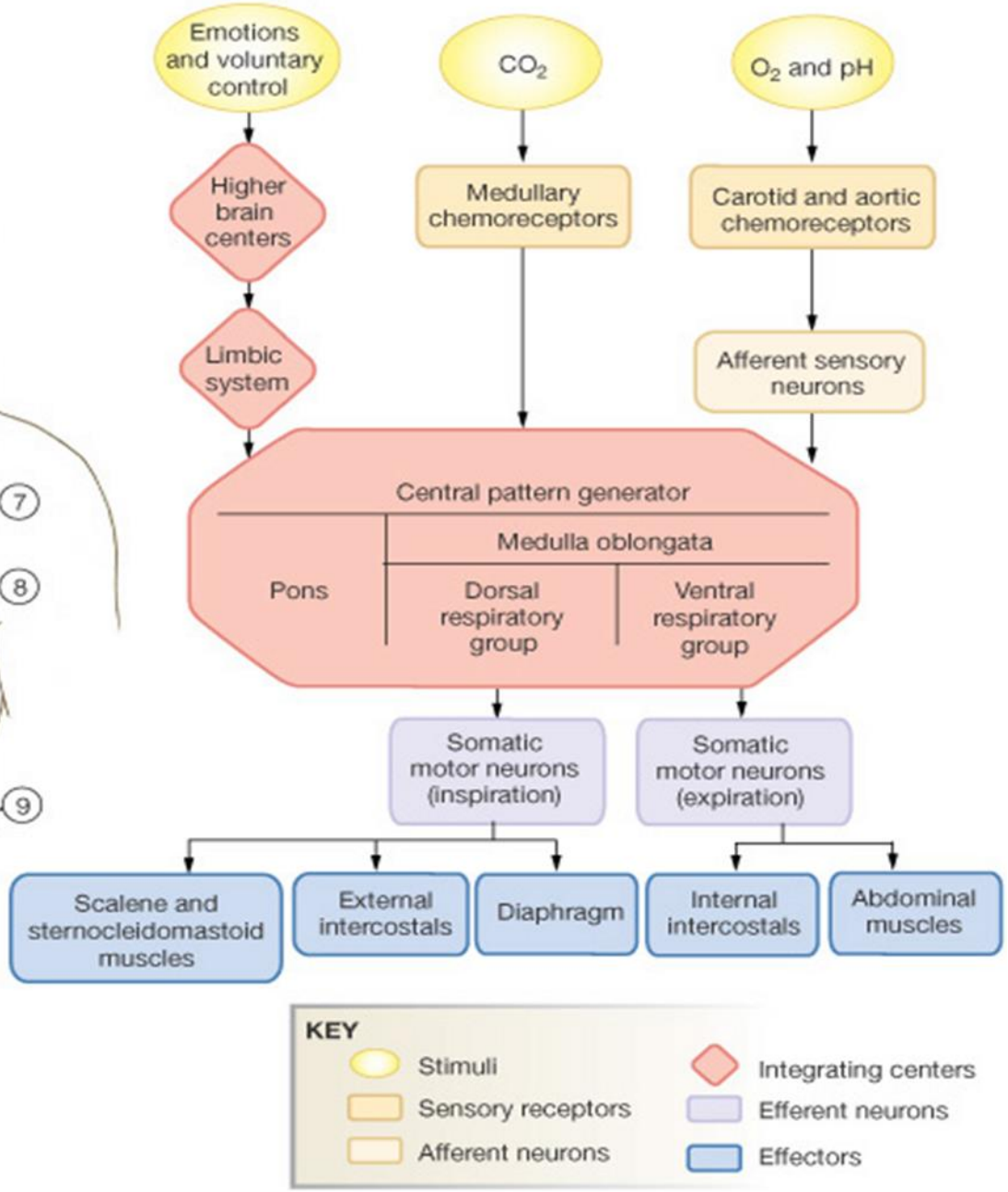
11
10
9
Inspiration
Expiration


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

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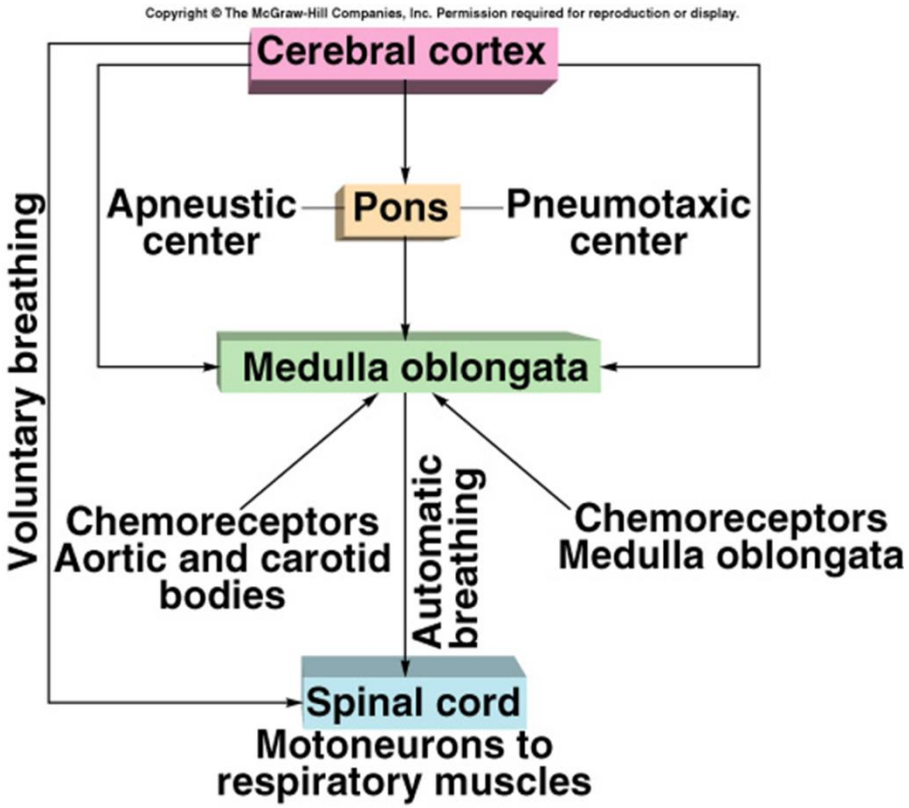
Respiratory centres



- 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

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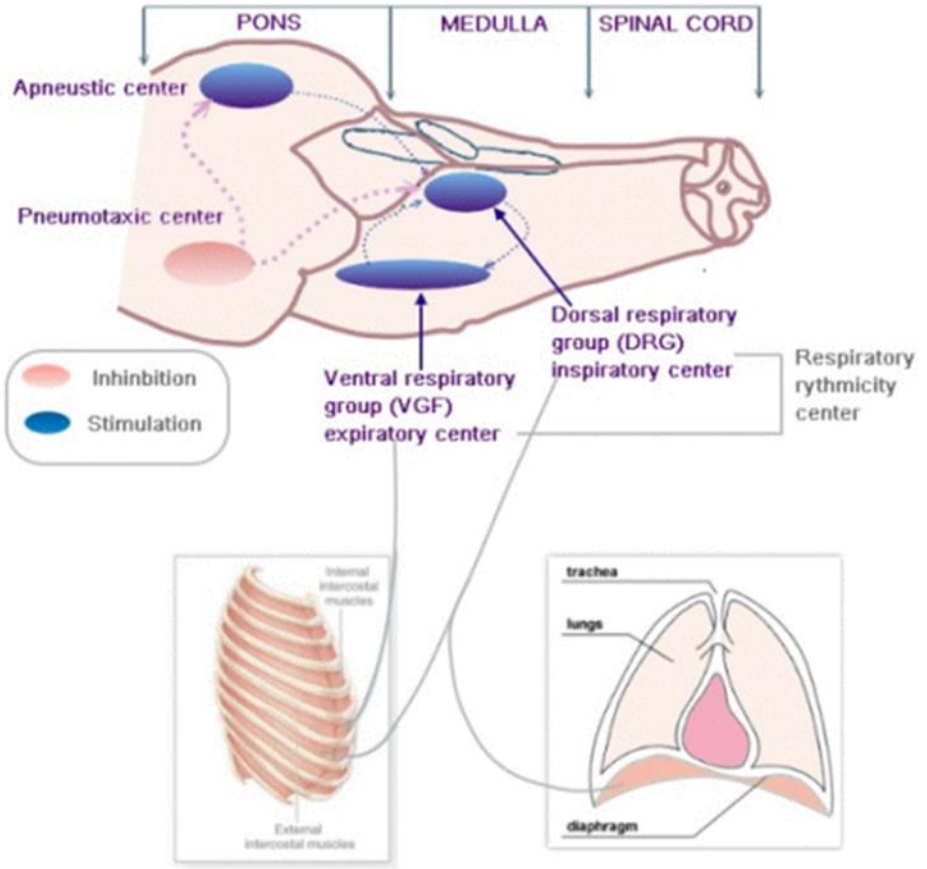
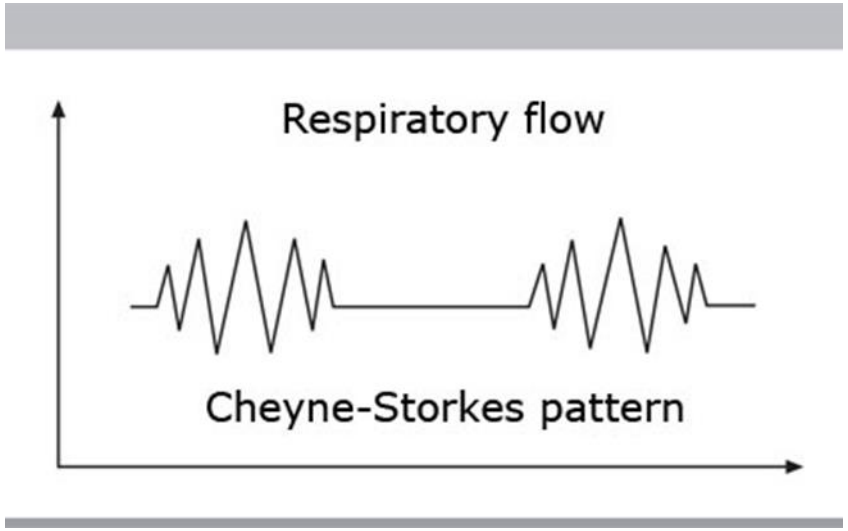
Higher respiratory centres

- 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).



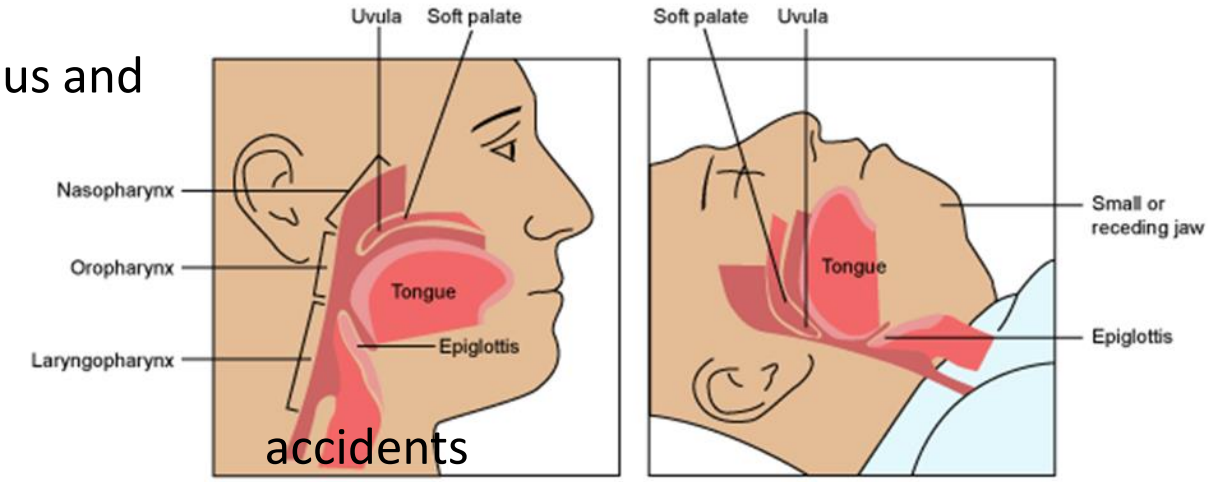
Apnea

- 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



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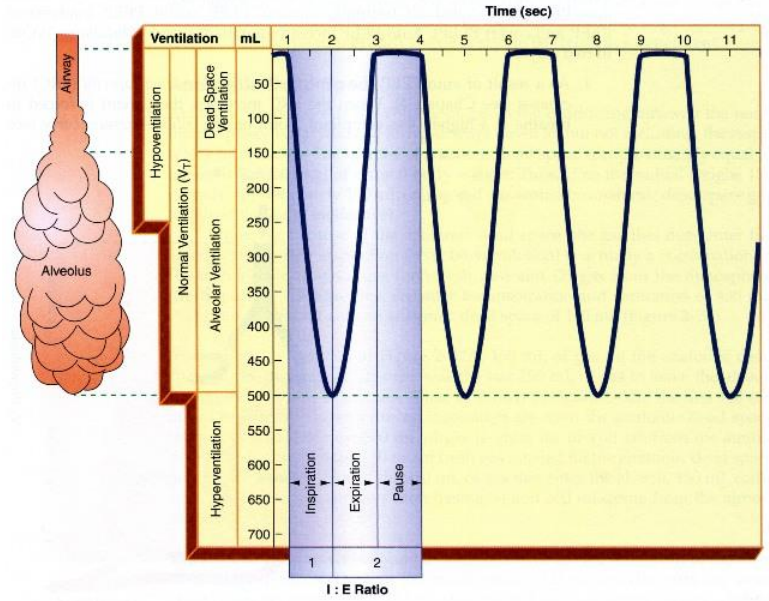

Figure 2–30. *Normal, spontaneous breathing (eupnea). The I:E ratio typically is 1:2.*

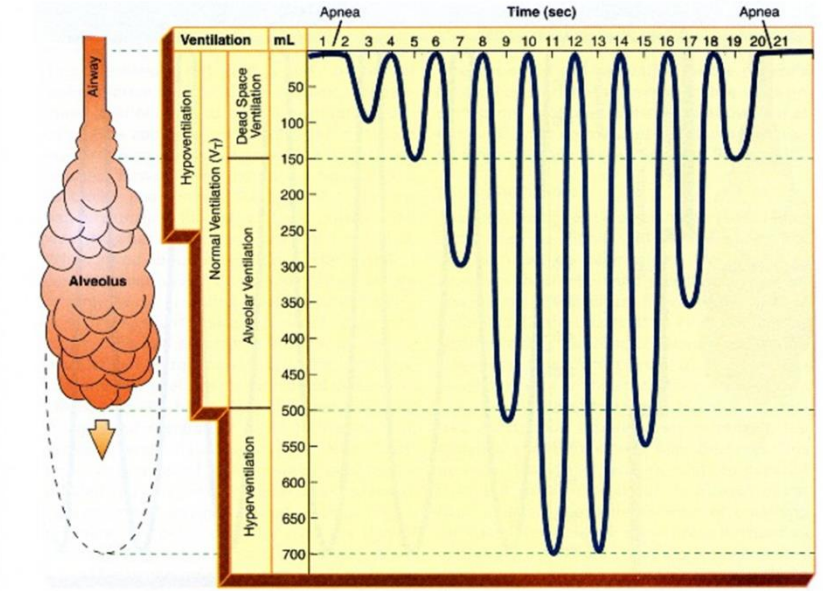

Figure 2–39. *Cheyne-Stokes respiration: A gradual increase and decrease in the volume and rate of breathing, followed by 10 to 30 seconds of apnea.*

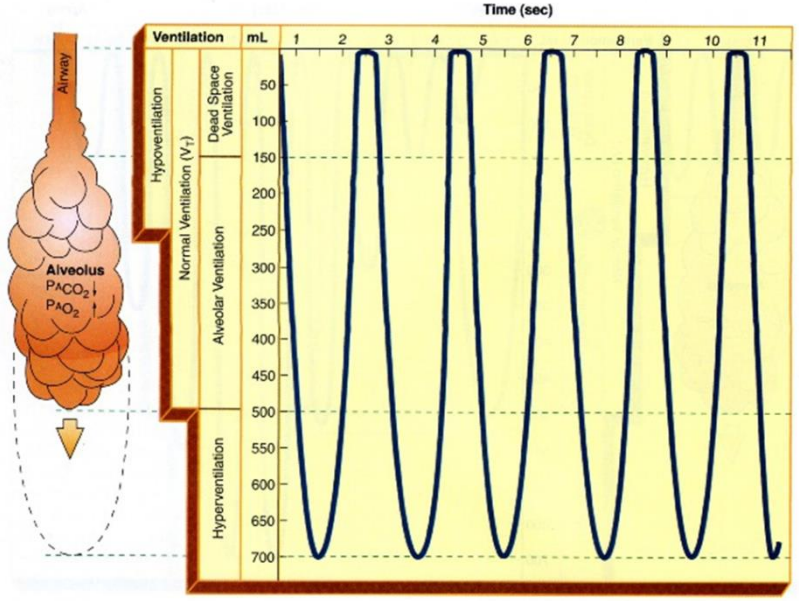

Figure 2–40. *Kussmaul's respiration: Increased rate and depth of breathing. This breathing pattern causes the $P_{A_{CO_2}}$ and Pa_{CO_2} to decrease and $P_{A_{O_2}}$ and Pa_{O_2} to increase.*

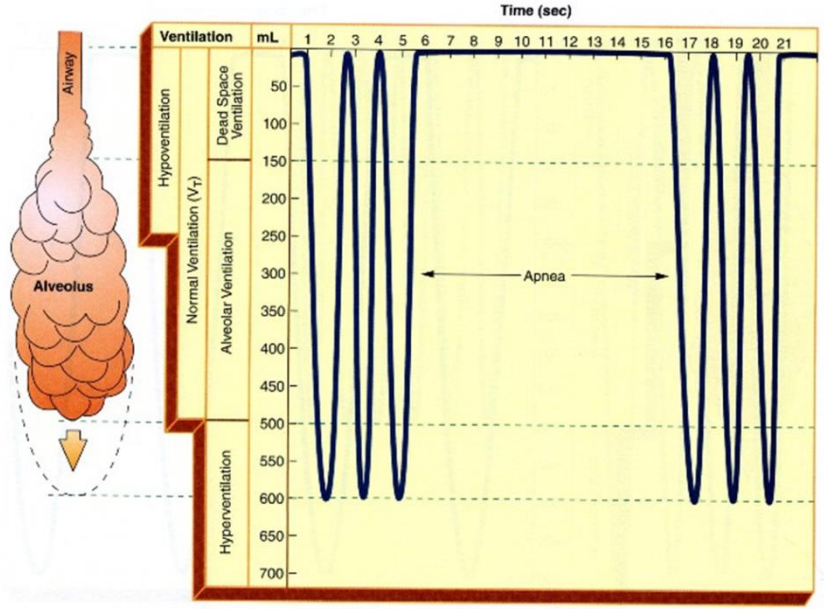

Figure 2–35. *Biot's respiration: Short episodes of rapid, uniformly deep inspirations, followed by 10 to 30 seconds of apnea.*

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RESPIRATORY INSUFFICIENCY

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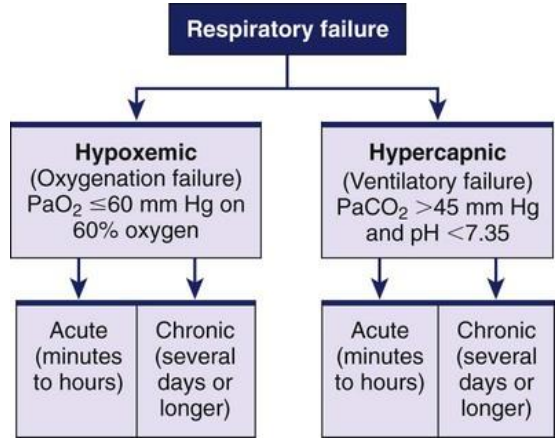
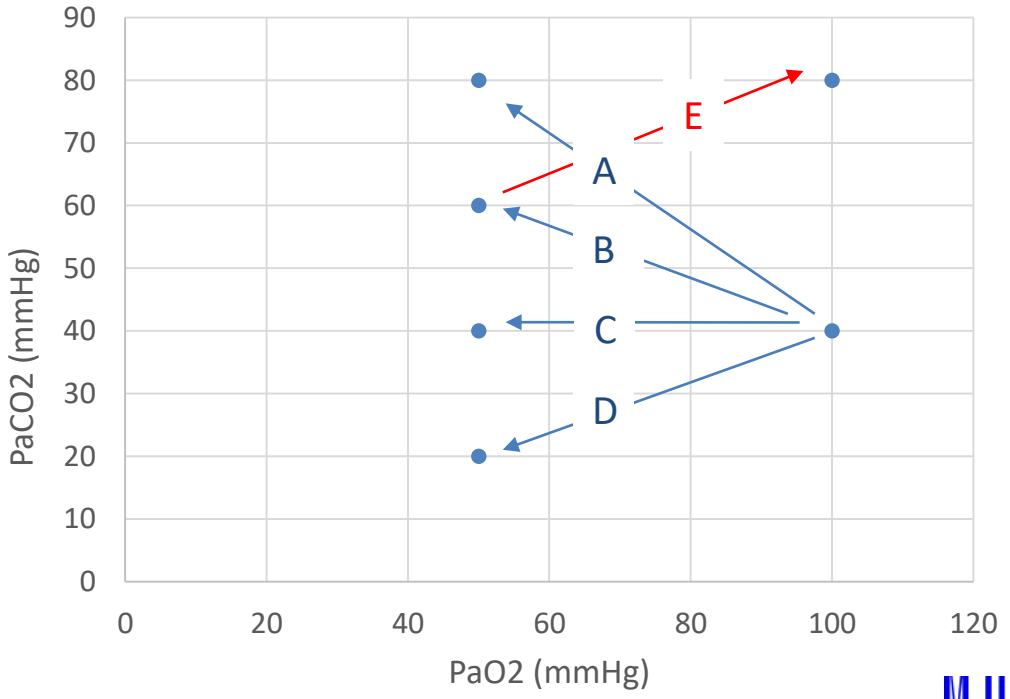
Respiratory insufficiency (RI)

- the aim of the respiration is to maintain optimal values of blood gases by way of their exchange with environment, therefore the main criteria of resp. insufficiency are blood gases values
- **RI is defined as PaO_2 ≤60 mmHg and event. $PaCO_2$ ≥ 50 mmHg**
  - ↓PaO_2 (hypoxemia) is a constant component of RI
    - a dop below 60 mmHg already decrease Hb saturation
      - pulsion oxymetry!
  - ↑$PaCO_2$ (hypercapnia) sometimes, often normo- or even hypocapnia
    - see all 4 causes of hypoxemia and their variable effect on $PaCO_2$
- classification of resp. insufficiency
  - **type I or partial or hypoxemic**
    - ↓PaO_2 <10 kPa and normo or ↓$PaCO_2$)
    - failure of oxygenation
  - type 2 or global or ventilatory
    - ↓PaO_2 <10kPa and $PaCO_2$ >6 kPa)
    - failure of mechanical ventilation
      - compensated – normal blood pH
        - » compensatory increase of hydrogen carbonates
      - decompensated – decrease of blood pH < 7,36 (respiratory acidosis)
- patterns of blood gas abnormality is different in various types of disease – for example:
  - A - pure hypoventilation
  - B - severe V/Q inequality (e.g. bronchial obstruction)
  - C - interstitial lung disease with diffusion impairment
  - D - R-L shunt
  - E - effect of oxygen breathing





Aetiology and consequences of RI

Arterial Blood Gas (ABG)	Type I-Hypoxemic Respiratory Failure: Acute Hypoxemic Respiratory Failure (Acute Hypoxemia)	Type I-Hypoxemic Respiratory Failure: Chronic Hypoxemic Respiratory Failure (Chronic Hypoxemia)	Type II-Hypoxemic, Hypercapnic Respiratory Failure: Acute Hypoxemic, Hypercapnic Respiratory Failure (Acute Hypoventilation, Acute Ventilatory Failure)	Type II-Hypoxemic, Hypercapnic Respiratory Failure: Chronic Hypoxemic, Hypercapnic Respiratory Failure (Chronic Hypoventilation)
pH	Normal	Normal	Decreased	Near Normal
pCO_2	Normal-Decreased	Normal-Decreased	Increased	Increased
pO_2	Decreased (<60 mm Hg)	Decreased (<60 mm Hg)	Decreased (<60 mm Hg)	Decreased (<60 mm Hg)
Bicarbonate	Normal	Normal	Normal	Increased

Type	Type I-Hypoxemic Respiratory Failure: Acute Hypoxemic Respiratory Failure (Acute Hypoxemia)	Type I-Hypoxemic Respiratory Failure: Chronic Hypoxemic Respiratory Failure (Chronic Hypoxemia)	Type II-Hypoxemic, Hypercapnic Respiratory Failure: Acute Hypoxemic, Hypercapnic Respiratory Failure (Acute Hypoventilation, Acute Ventilatory Failure)	Type II-Hypoxemic, Hypercapnic Respiratory Failure: Chronic Hypoxemic, Hypercapnic Respiratory Failure (Chronic Hypoventilation)
Etiology: Decreased Inspired pO_2	Fire in Enclosed Space; High Altitude	Low Inspired pO^2		
Etiology: Low Mixed Venous pO_2	Decreased Cardiac Output; Fever/Anxiety	Increased Work of Breathing		
Etiology: Intrapulmonary Shunt	Acute Respiratory Distress Syndrome (ARDS); Atelectasis; Hepatopulmonary Syndrome	Intralobar Pulmonary Sequestration; Pneumonia; Pulmonary Arteriovenous Malformation (AVM)		
Etiology: Intracardiac Right to Left Shunt	Atrial Septal Defect (ASD); Patent Ductus Arteriosus (PDA)	Patent Foramen Ovale (PFO); Ventricular Septal Defect (VSD)		
Etiology: Ventilation/Perfusion (V/Q) Mismatch	Acute Pulmonary Embolism (PE); Atelectasis; Dialysis-Associated Hypoxemia; Interstitial Lung Disease (ILD)	Pneumonia; Obstructive Lung Disease: Asthma, Chronic Obstructive Pulmonary Disease (COPD), etc; Pulmonary Vascular Disease: Pulmonary Hypertension, Leukostasis, etc		
Etiology: Diffusion Limitation	Heavy Exercise	Severe Interstitial Lung Disease		
Etiology: Decreased Ventilatory Drive			Chemosensitivity Disorders; Brainstem Disease	Chemosensitivity Disorders; Brainstem Disease
Etiology: Decreased Ventilatory Output (Despite Increased Ventilatory Effort) Due to Neuromuscular Disease			Spinal Cord Disease; Motor Neuron Disease; Peripheral Neuropathy; Neuromuscular Junction Disease; Myopathy/Muscle Dysfunction	Spinal Cord Disease; Motor Neuron Disease; Peripheral Neuropathy; Neuromuscular Junction Disease; Myopathy/Muscle Dysfunction
Etiology: Decreased Ventilatory Output (Despite Increased Ventilatory Effort) Due to Excessive Ventilatory Demand			Acute Upper Airway Obstruction; Acute Obstructive Lung Disease; Acute Parenchymal Lung Disease; Acute Pleural/Chest Wall Disease; Increased Dead Space Ventilation; Increased Carbon Dioxide Production; Exogenous Carbon Dioxide Inhalation	Progressive Upper Airway Obstruction; Chronic Obstructive Lung Disease; Chronic Parenchymal Lung Disease; Chronic Pleural/Chest Wall Disease

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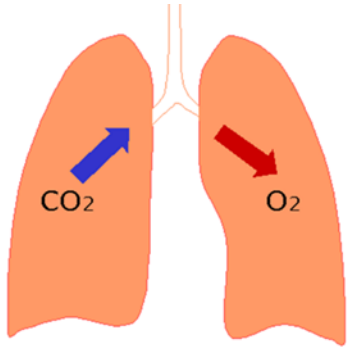
Respiratory insufficiency (RI)

- extra-pulmonary causes of low paO_2 (hypoxemia/hypoxia) are not usually classified as RI
  - cardiovascular (heart disease with right-to-left shunt)
  - circulation hypoxia
- classification of RI
  - latent RI: normal blood gases at rest, abnormal during exercise
  - manifest RI: blood gases pathological in rest
- time course:
  - acute: abrupt onset
    - aspiration of foreign body, pneumothorax, asthma attack
  - chronic: slowly progressing, variable compensation
    - COPD, lung fibrosis, cystic fibrosis
  - chronic with acute exacerbations:
    - COPD



- diagnostics of resp. insufficiency
  - examination of blood gases and acid-base balance (Astrup)
    - arterial blood (a. radialis, a. cubitalis, a. femoralis)
    - arterialised blood (ear lobe)
    - capillary blood (fingers) – imprecise
  - parameters:
    - blood pH – normally 7.36-7.44
      - i.e.[H+] = 35-44 nM
    - paO_2 – partial pressure of oxygen
      - 10-13 kPa (75-95 mmHg)
    - $paCO_2$ – partial pressure of carbon dioxide
      - 4.8-6 kPa (36-45 mmHg)
    - HCO_3 – hydrogen carbonates
      - 22,0-26,0 mmol/l
    - BE – base excess
      - normally 0
    - $SatO_2$ – saturation of Hb (normally > 90%)
    - Mean PvO2
      - 6 kPa (45 mmHg)
    - Mean PvCO2
      - 6.1 kPa (46 mmHg)

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RI is one of the causes of generalized hypoxia

- = deficiency of O_2 in the organism ($\downarrow paO_2$ <10kPa/75mm Hg)
- types:
  - (1) hypox(em)ic hypoxia = **$\downarrow$ arterial PO_2** - leads to central cyanosis
    - causes of hypoxemia
      - $\downarrow$ PO_2 in inspired air (PO_2 (high altitude, low FiO_2)
      - hypoventilation due to damage of respiration center
      - diffusion impairment (fibrosis, emphysema)
      - anatomical shunting of non-oxygenated blood (heart)
      - ventilation-perfusion mismatch
  - (2) anemic hypoxia = **normal arterial PO_2**
    - $\downarrow$ concentration of hemoglobin
      - anemia, leukemias
    - abnormal hemoglobin with low ability to bind oxygen
      - carbonylhemoglogin (COHb)
      - methemoglobin
  - (3) circulatory hypoxia = **normal arterial PO_2** – leads to peripheral cyanosis
    - decreased cardiac output
    - decreased of systemic blood pressure
    - (local tissue ischemia)
    - microcirculation defects
  - (4) histotoxic hypoxia – **normal arterial PO_2** , $\uparrow$ venous PO_2
    - Intoxication with cyanides, cobalt, …)

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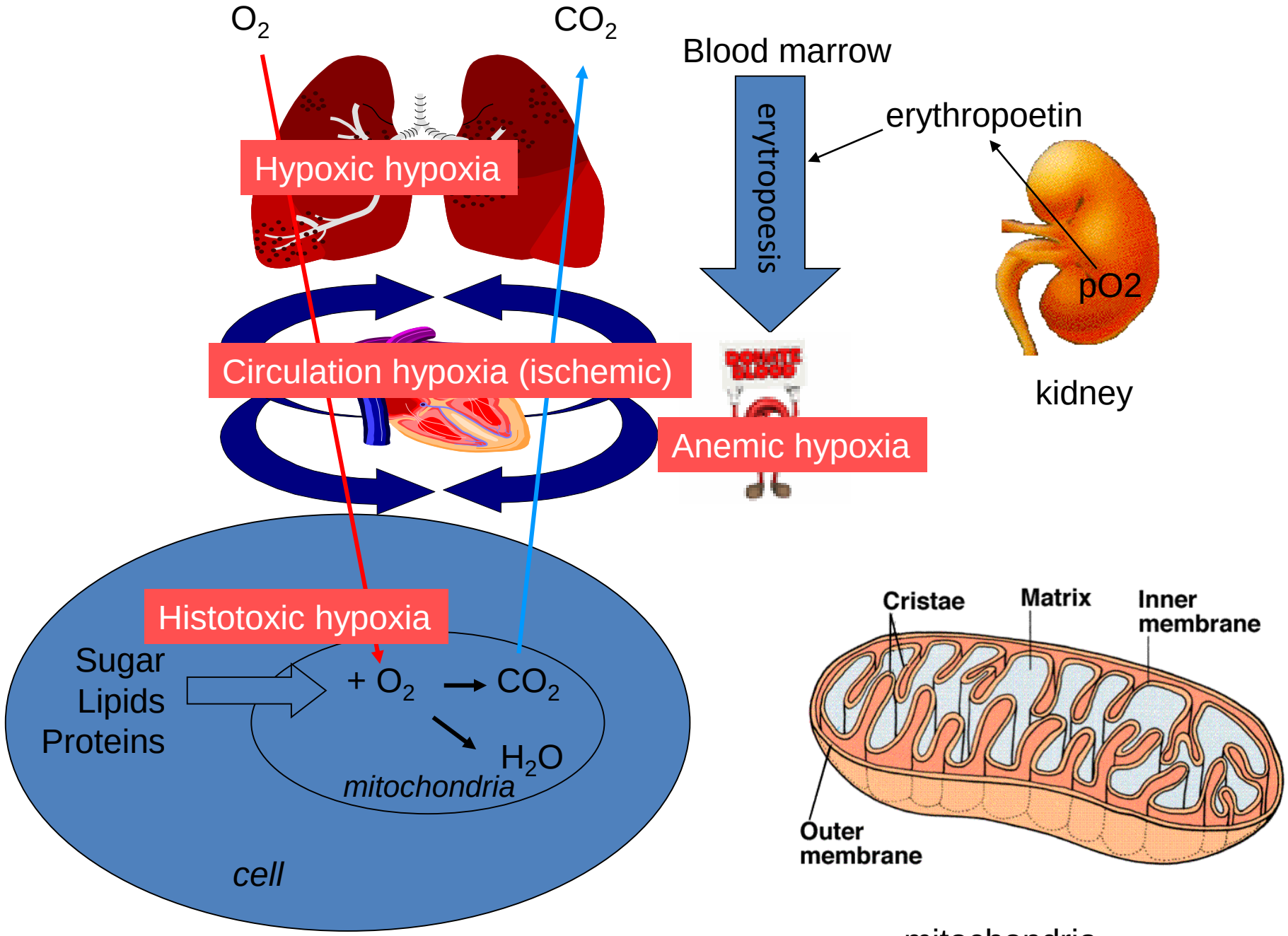
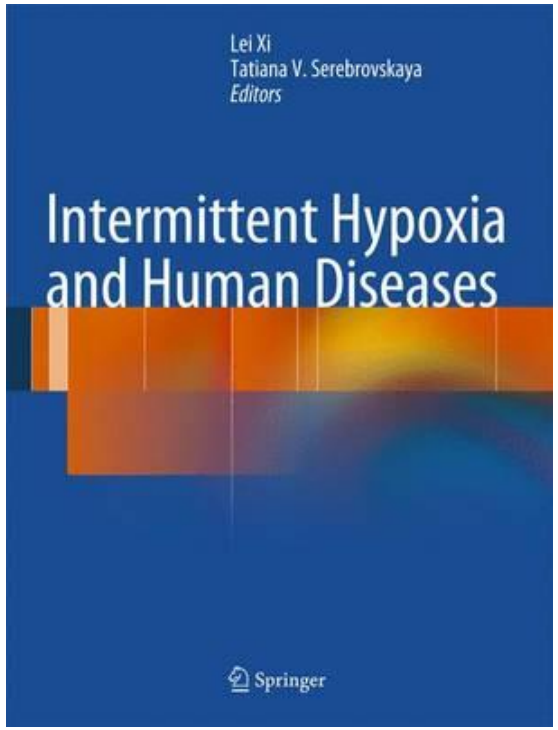

O_2
CO_2
Hypoxic hypoxia
Circulation hypoxia (ischemic)
Histotoxic hypoxia
Sugar
Lipids
Proteins
+ O_2
CO_2
H_2O
mitochondria
cell
Blood marrow
erythropoetin
erytropoesis
pO2
kidney
Anemic hypoxia
Cristae
Matrix
Inner membrane
Outer membrane
mitochondria

Intermittent, chronic intermittent and chronic hypoxia

- **Intermittent** hypoxia
  - an effective stimulus for evoking the respiratory, cardiovascular, and metabolic to some extent beneficial
    - they may provide protection against disease as well as improve exercise performance in athletes
- Long-term consequences of **chronic intermittent** hypoxia (such as OSA) may have detrimental effects
  - hypertension, cerebral and coronary vascular problems
  - ↑ right ventricular heart mass, pulmonary vascular remodeling and pulmonary hypertension
  - developmental and neurocognitive deficits and neurodegeneration
- **Chronic** hypoxia induces proliferation of the vasculature due to angiogenesis (up-regulation of VEGF) but can also change the integrity of vessels, leading to changes in vascular permeability (e.g. contribution to acute mountain sickness)



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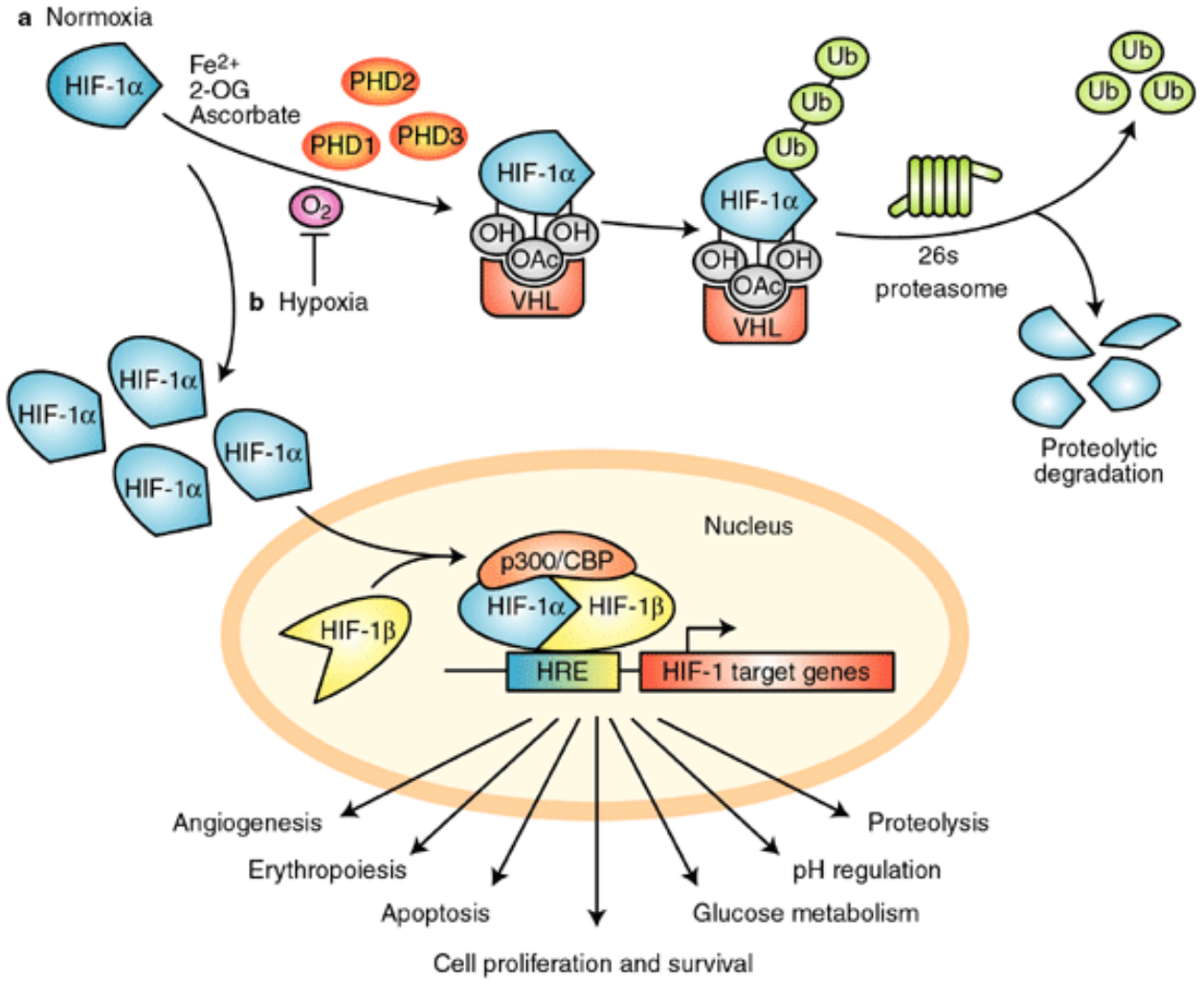
Hypoxia and gene transcription



HIF-1α regulation by proline hydroxylation

- The ability of hypoxia to promote persistent adaptations is due in part to its ability to induce changes in gene transcription
- The regulation of the expression of a wide variety of genes involved in hypoxic adaptations is largely due to activation of a hypoxia-sensitive transcription factor, hypoxia-inducible factor 1 (HIF-1)
  - HIF-1 is a heterodimer of HIF-1 alpha and HIF-1 beta
  - oxygen levels directly regulate the expression of the HIF-1 component in a dose-dependent manner

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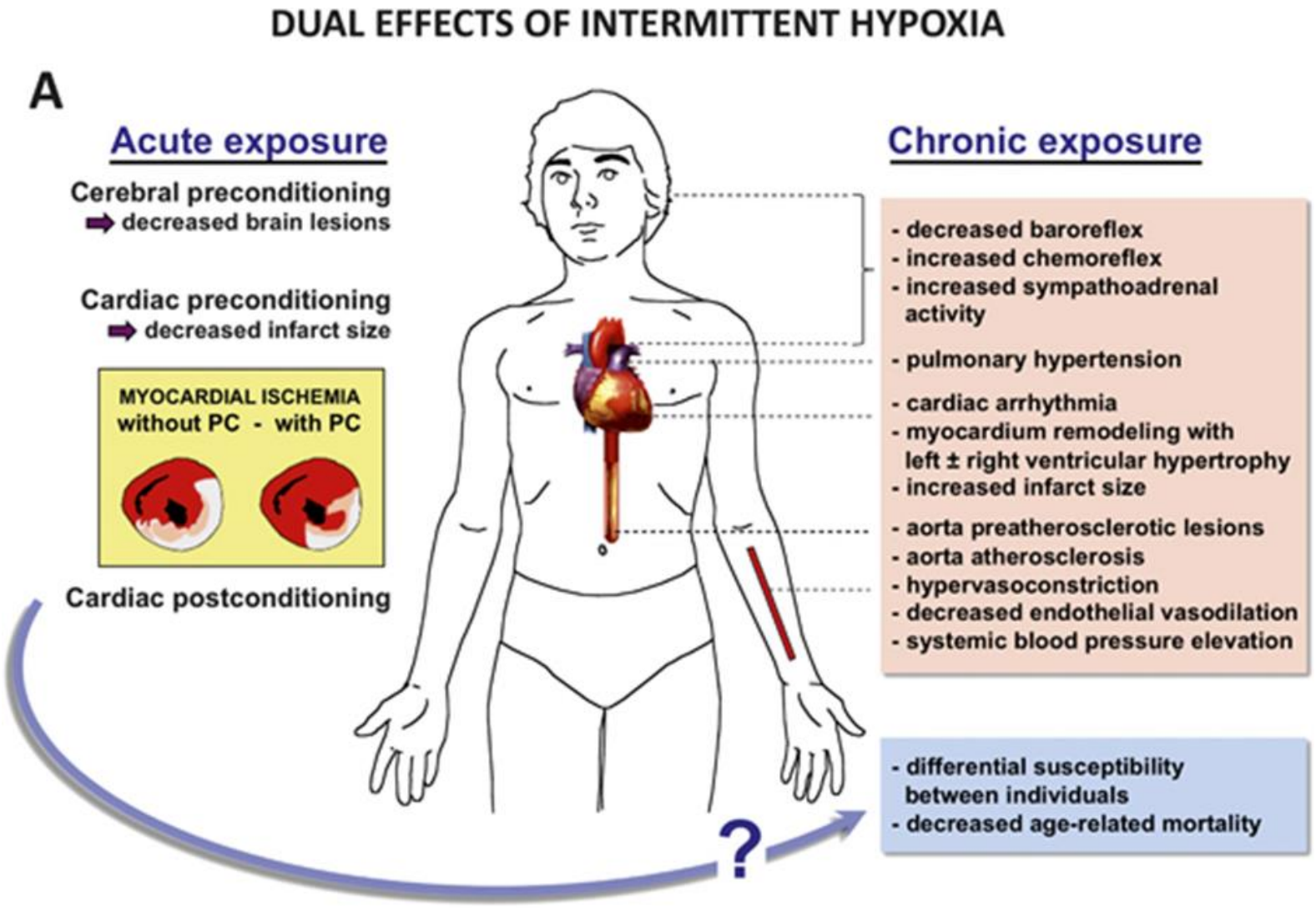

According to the severity and duration of exposure, intermittent hypoxia (IH) may have either beneficial effects, involving pre- and postconditioning, or detrimental effects as in sleep apnea. It is not clear whether pre-/postconditioning-like phenomena occur during chronic exposure and contribute to the differential susceptibility between patients for IH-related consequences and/or to the age-related decline in mortality observed in sleep apnea patients

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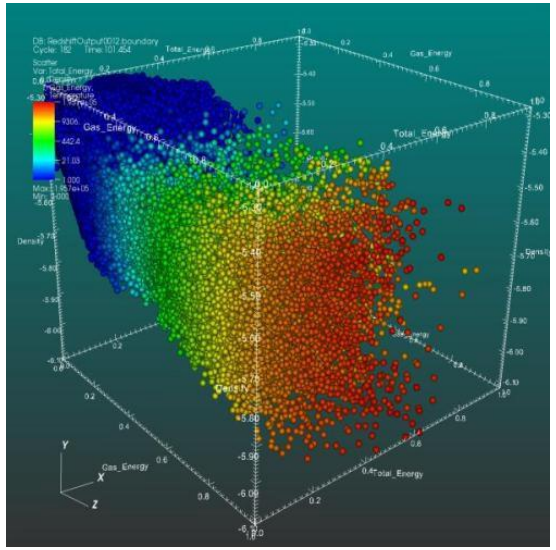
Multidimensional classification of lung diseases

- basically each pulmonary disease can be classified un multiple aspects
  - whether it causes a **ventilator impairment** and of what kind – **spirometry** and other kinds of tests
    - **obstructive (FEV1) vs. restrictive (FVC, TLC)**
  - whether it causes a **gas exchange impairment** and of what kind – **blood gas analysis**
    - **4 causes hypoxemia (hypoventilation, diffusion, R-L shunt, V/Q mismatch)**
  - whether it combines with **CO_2 retention**
    - **hypoxemic** (type 1, partial) vs. **hypercapnic** (type 2, global) **RI**
  - whether it **affects ABB** and which way - ABG
    - **respiratory acidosis vs. alkalosis**
  - what kind of **symptoms** they produce
    - **cough / dyspnea / cyanosis / change of breathing pattern**



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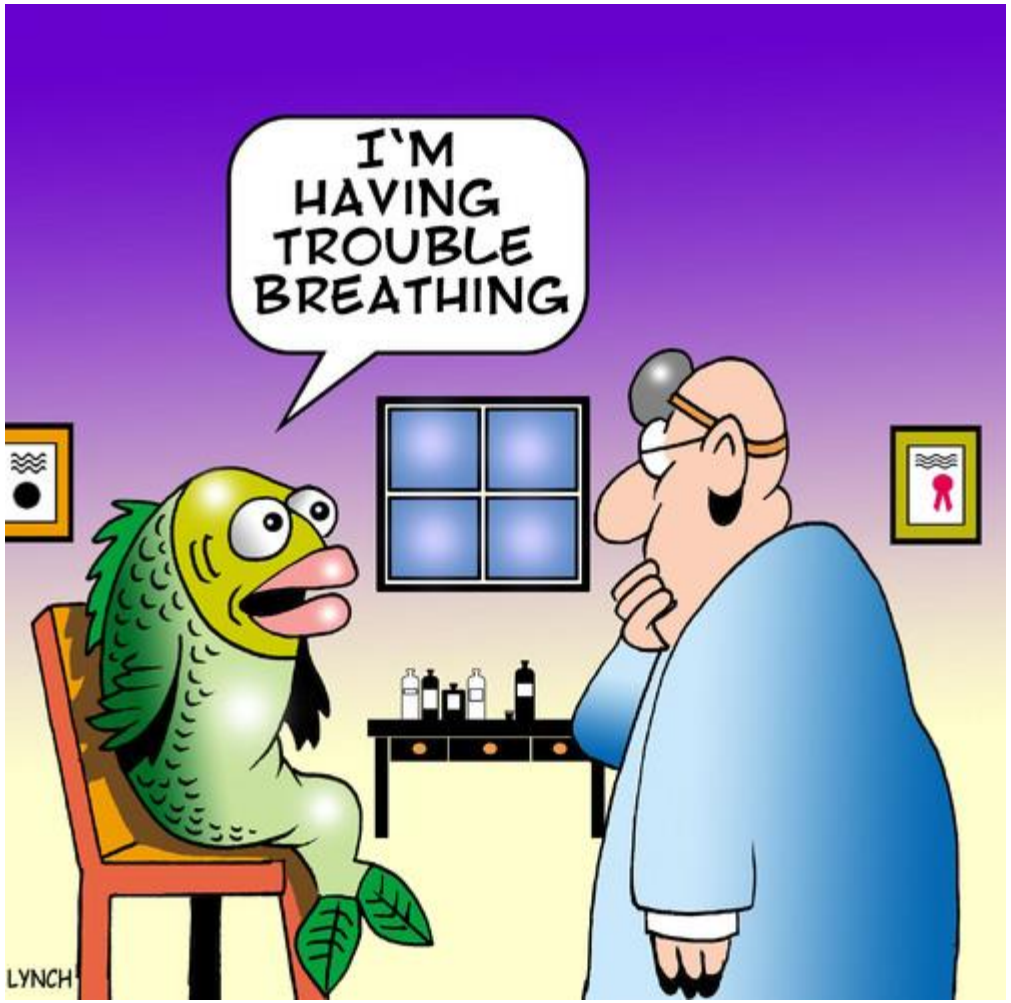

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