Pathophysiology of the respiratory system II

Pulmonary gas exchange
Oxygen cascade
Hypoxemia – classification of possible causes
(1) hypoventilation / (2) diffusion impairment / (3) shunt / (4) VQ mismatch
Ventilation – perfusion mismatch/(in)equality in detail
Pulmonary circulation – hypoxic pulmonary vasoconstriction
Respiratory insufficiency
Control of ventilation
Restrictive diseases – examples of gas exchange limiting ones

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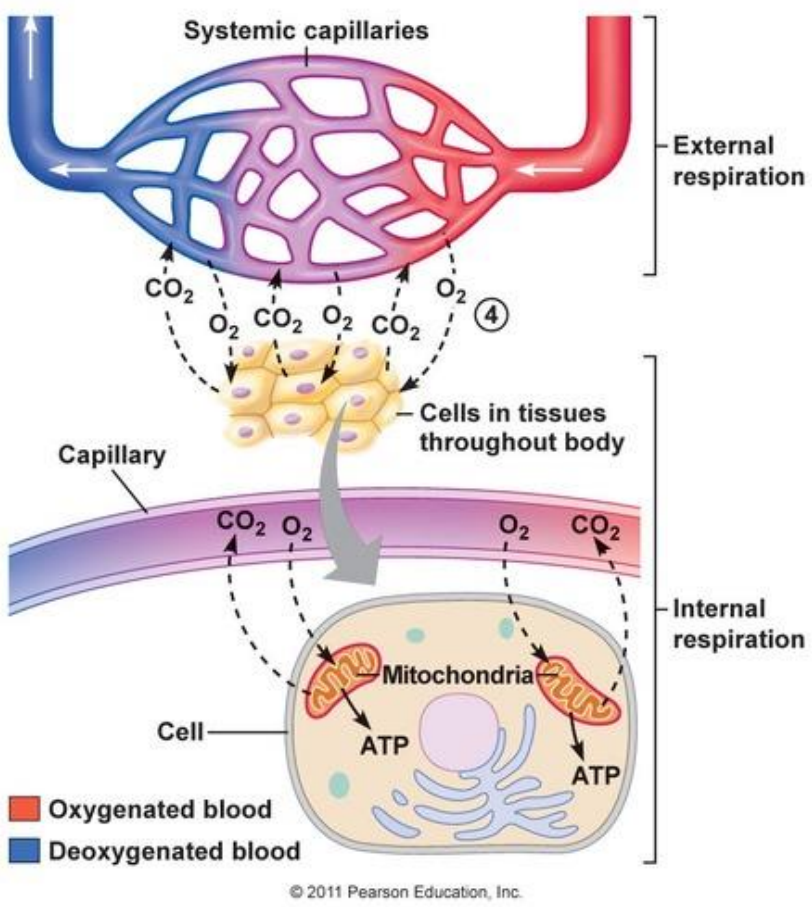
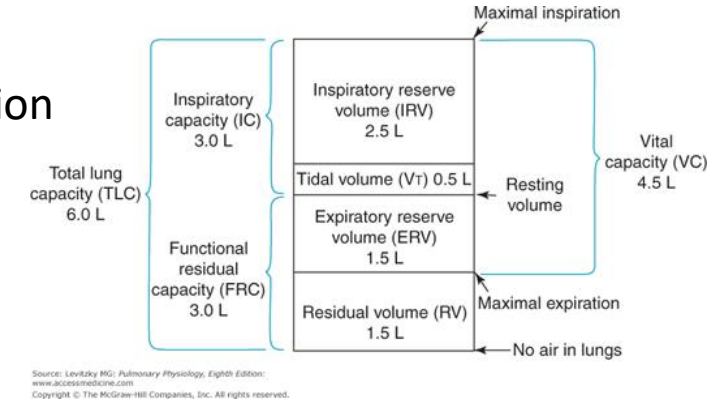
Gas exchange in lungs



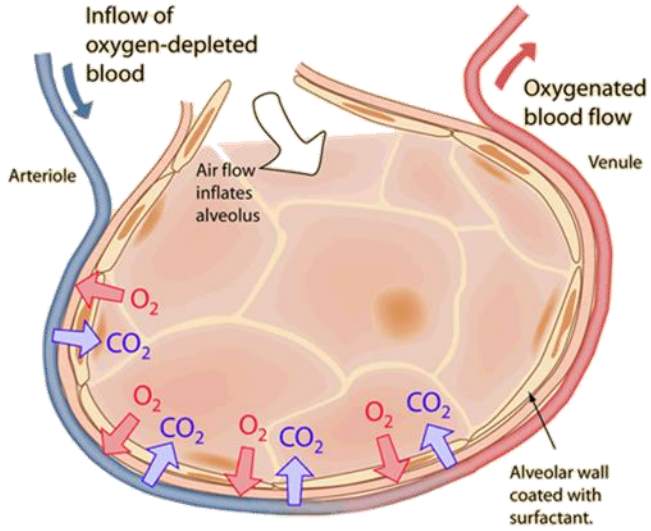
- main function of respiratory system – **gas exchange between blood and outside environment** – is governed by temporally changing requirements of organism for O_2
  - maintained in optimum by regulation of intensity of ventilation (see control of ventilation further)
- requirements defined mainly by 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 exchange by each resting breathing cycle ads only 0.5L to FRC = meaning a composition of the alveolar air is more or less constant



Gas exchange in lungs

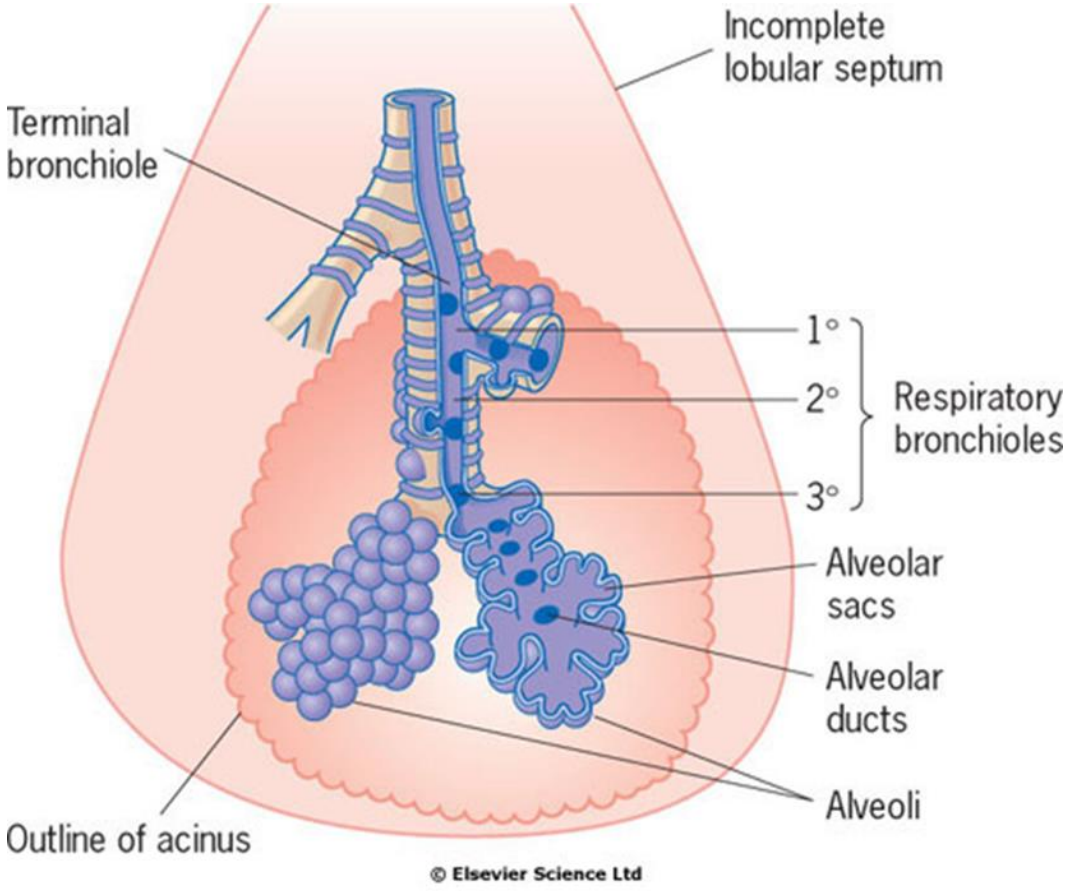
- alveolo-capillary gas exchange takes place from alveolus to blood by **simple diffusion** through alveolar septum, lung intersticium and capillary wall
  - in the past physiologist believed
    it was an active transport
    - fish, bird lung

	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	$3\text{-}6 \times 10^8$	$>1 \times 10^6$



Functional classification of airways

- Conducting airways (= **anatomical dead space**)
  - nose (mouth)
  - larynx
  - trachea
  - main bronchi & bronchioles
  - gas conduction, humidification & warming, defense
- 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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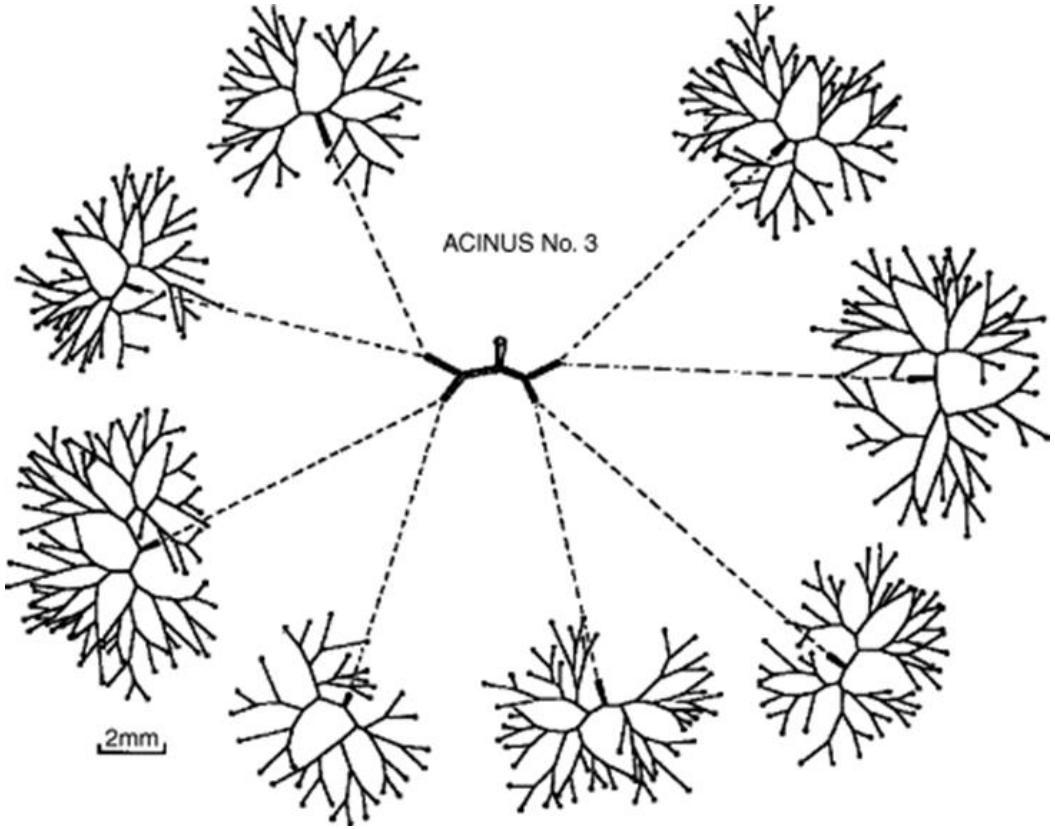
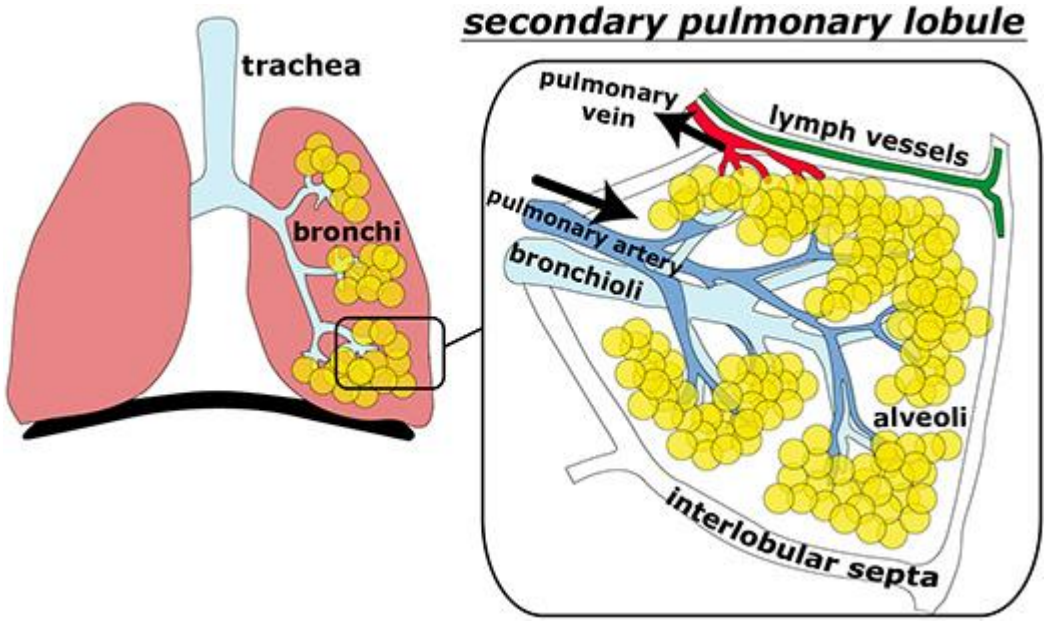
3-D acinus – gas exchange unit



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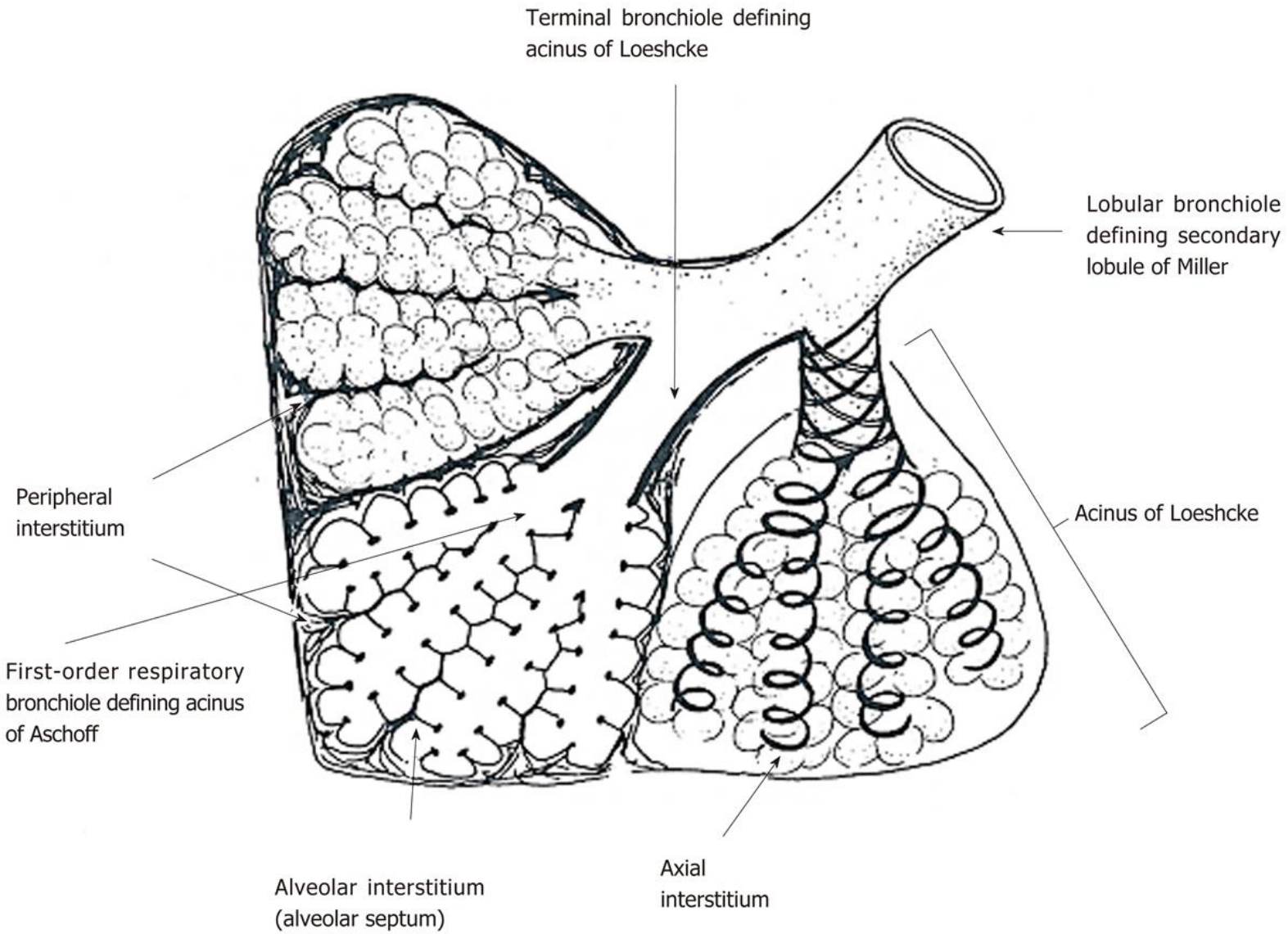
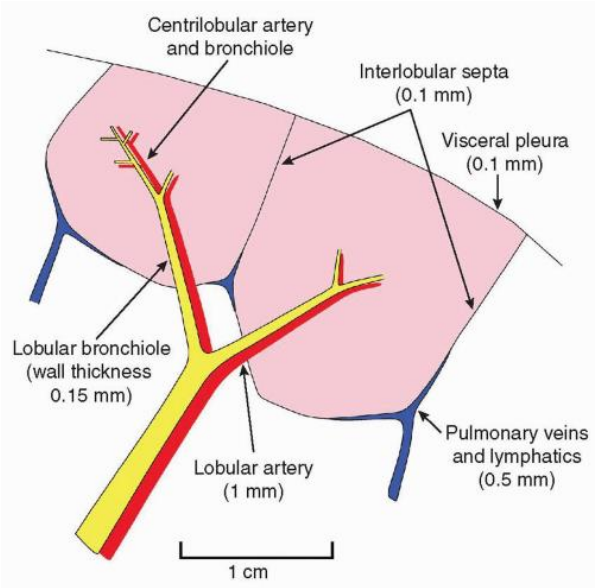
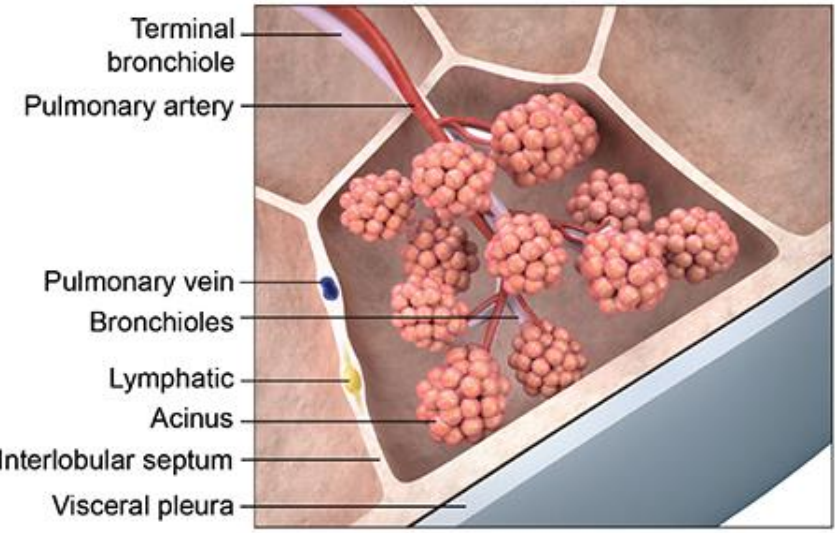
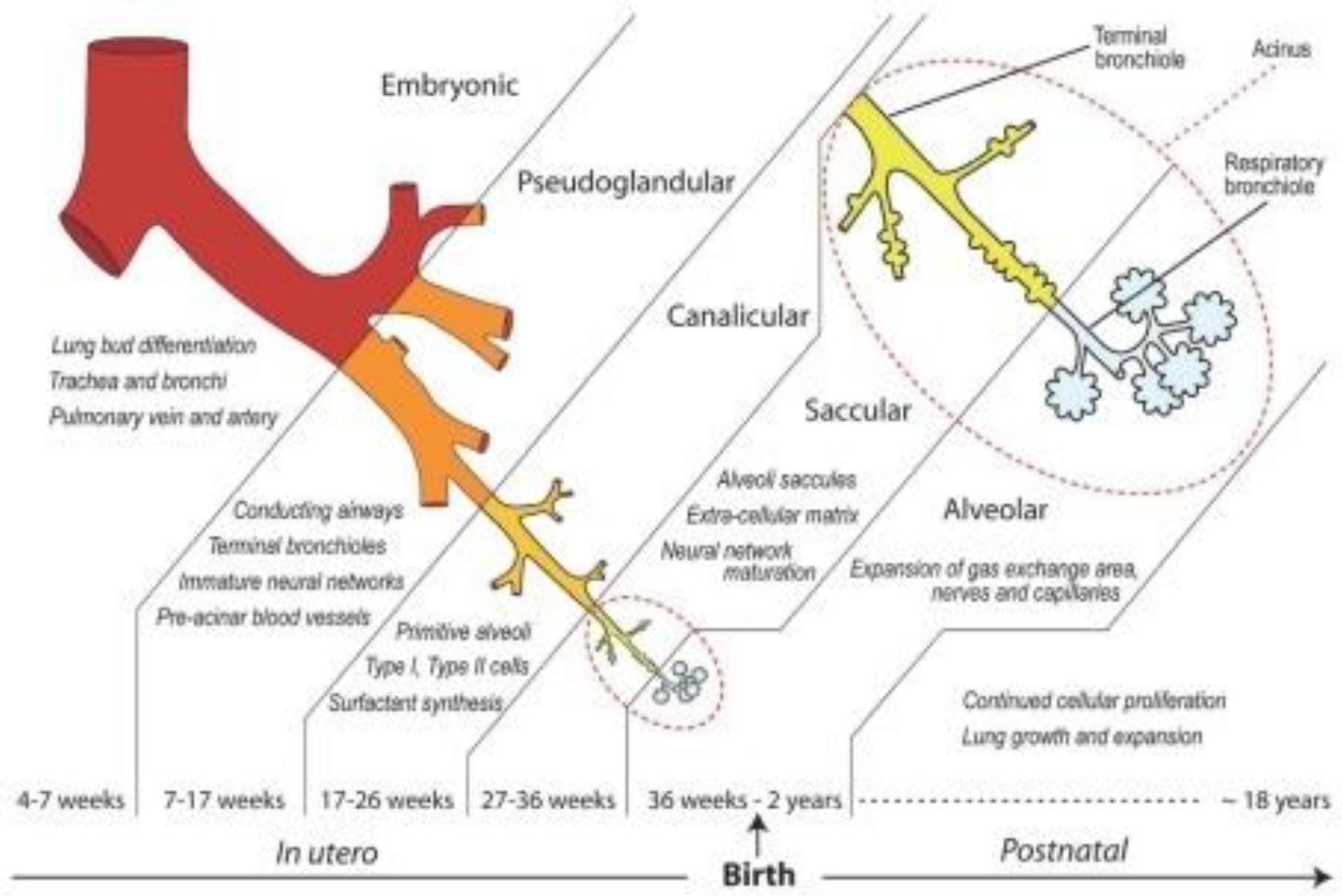
Lobule (= morphological unit, 3-5 acini) vs. acinus (= functional unit)







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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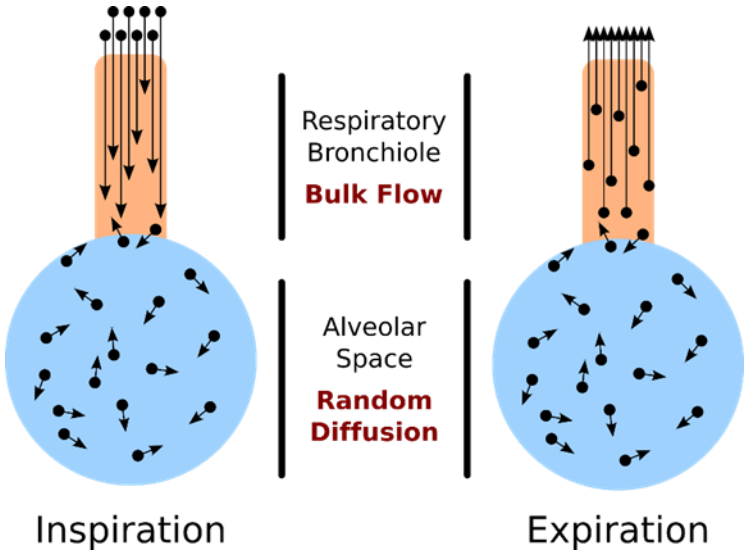
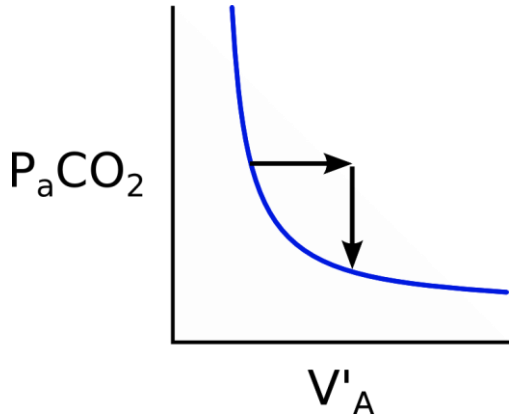
Pulmonary gas exchange as an ultimate purpose of breathing

- **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**
    - CO_2 production can be lowered by cooling the body
    - CO_2 production increases by exercise or in pathology
  - therefore $PACO_2$ is more ore less constant (or fluctuates very little)
  - all of the CO_2 exhaled by the body comes from gas exchanging areas of the lung, that is ventilated alveoli
  - the $PACO_2$ is equivalent to the $PaCO_2$ (complete diffusion)



- **(1) The alveolar ventilation equation** – describes the 'mechanics'
  - allows us to calculate alveolar ventilation rate
  - **$V'_A = (V'CO_2/PaCO_2) * K =$ ~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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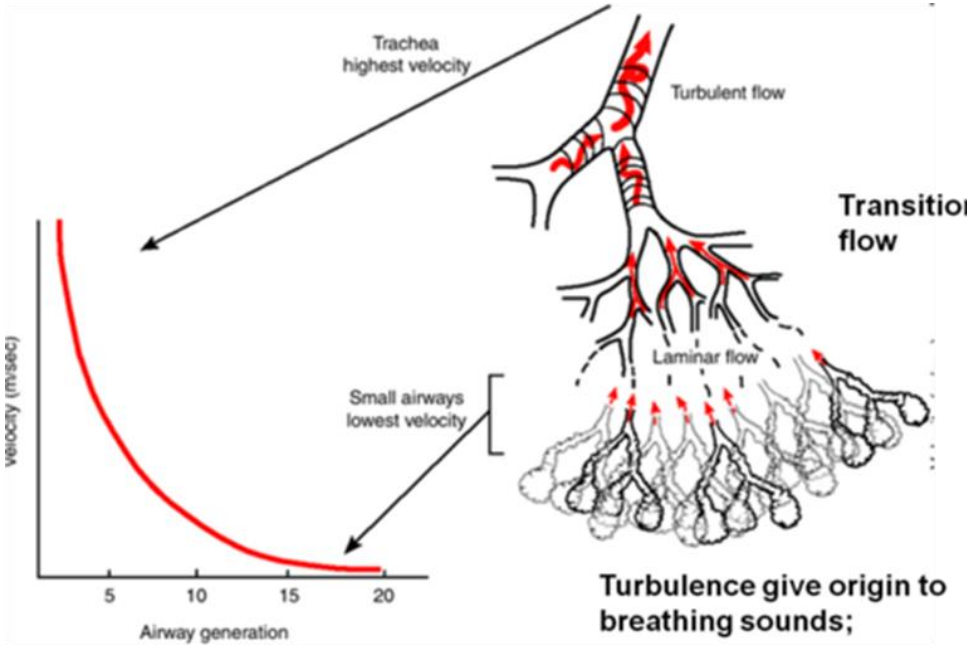
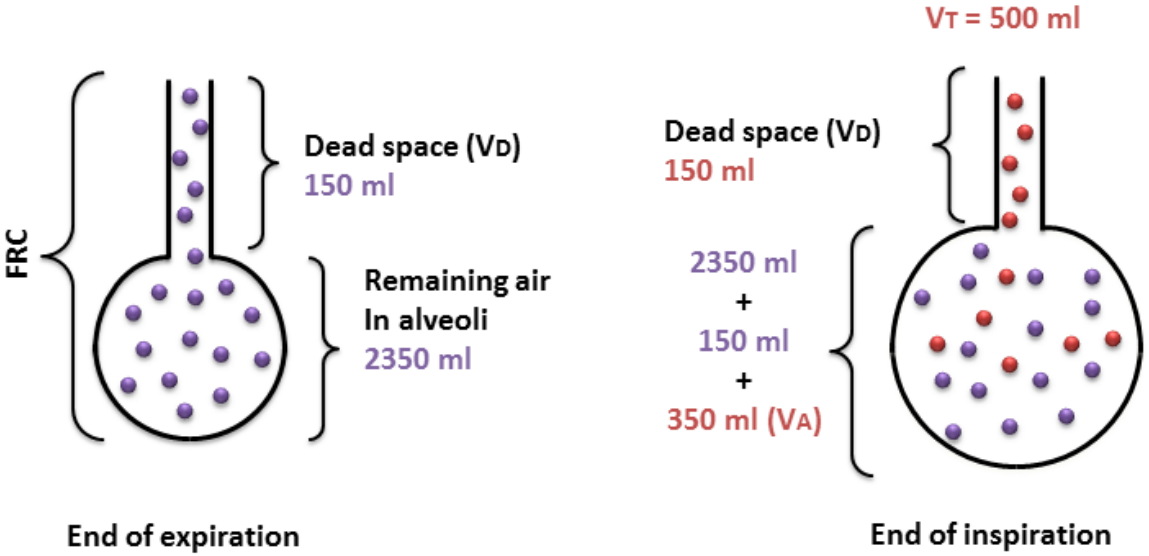
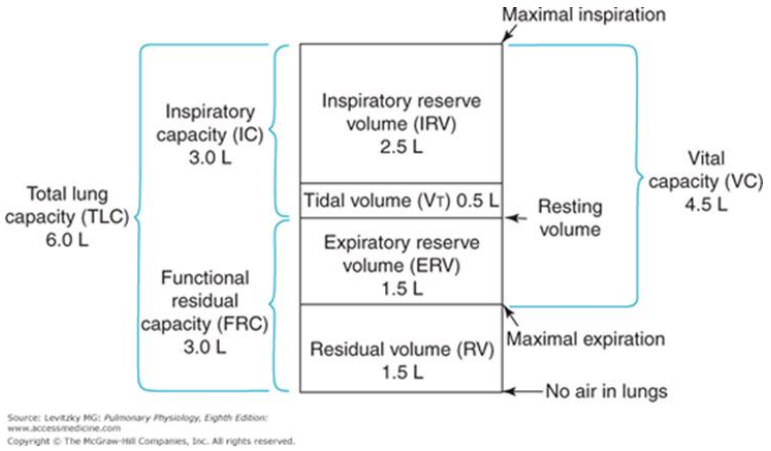
Exchange of gas between the alveolus and the respiratory bronchiole occurs purely by random diffusion







- There are minimal changes 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 VT (the depth of each breath) of around 500 ml, 150 ml is lost in dead space (VD), 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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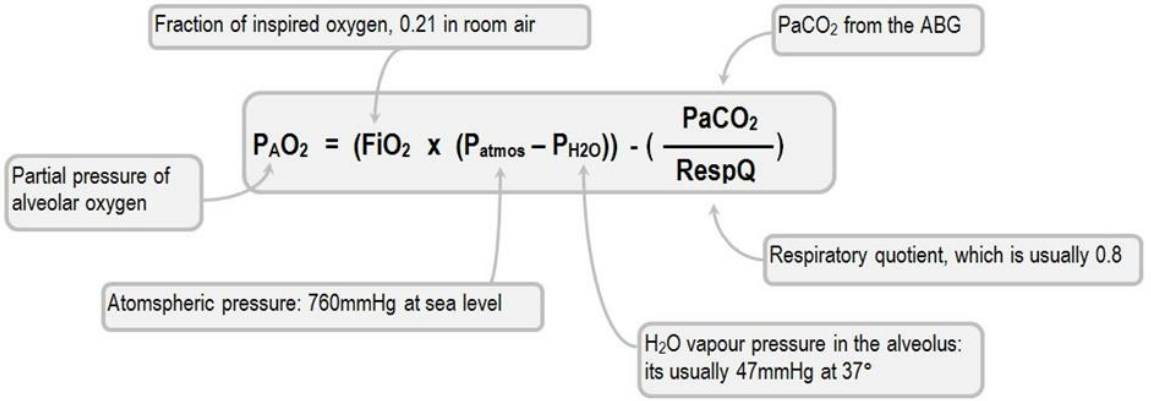
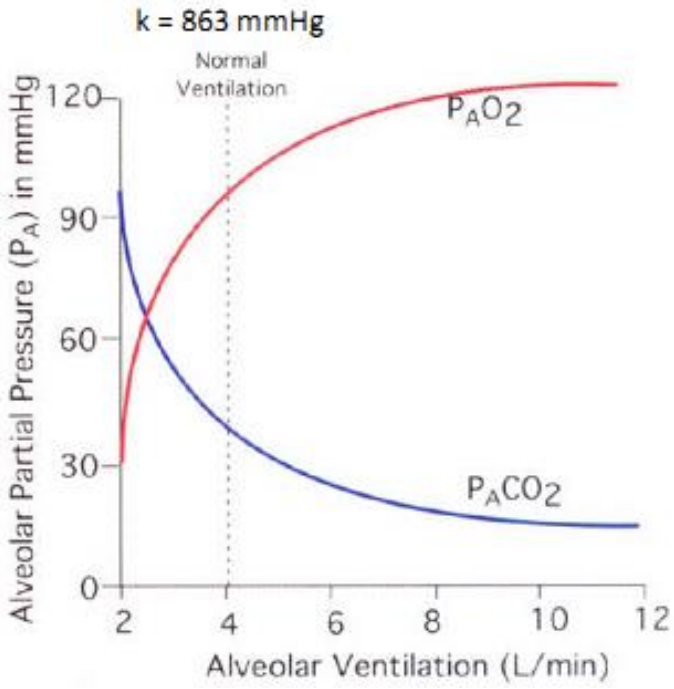
Pulmonary gas exchange as an ultimate purpose of breathing

- **(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
  - **PAO_2 = (0.21 x (760 - 47)) - ($PaCO_2$ x 1.25) = ~100 mmHg**
    - basically the two gases compete for partial pressures
      - if one increases, other must decrease
      - nitrogen does not change
    - normally $PaCO_2$ in mixed venous blood (i.e. pulmonary artery and the same in alveolus) is 40 mmHg
    - if $PaCO_2$ doubles (e.g. hypoventilation) then PAO_2 falls in half, i.e. 50 mmHg





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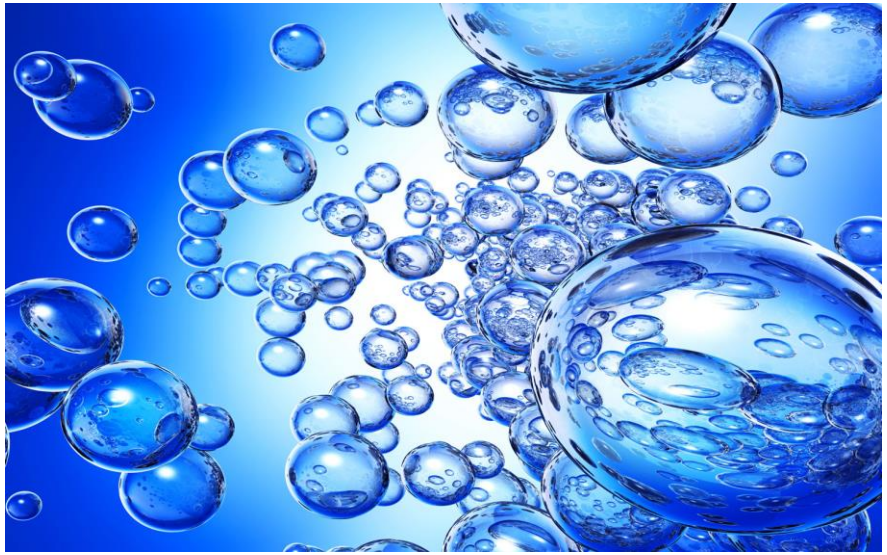

OXYGEN CASCADE IN THE BODY

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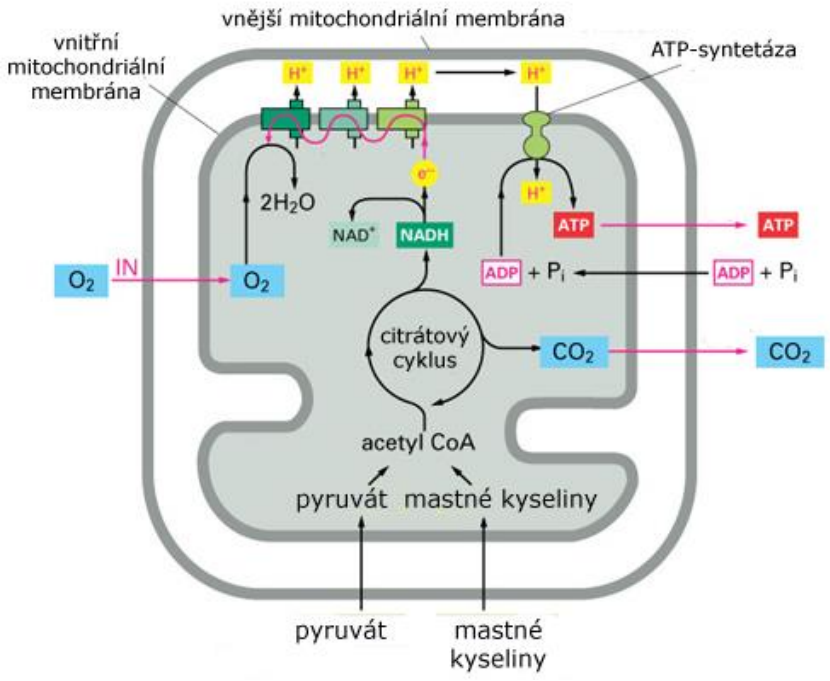
Oxygen in the body



- 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 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

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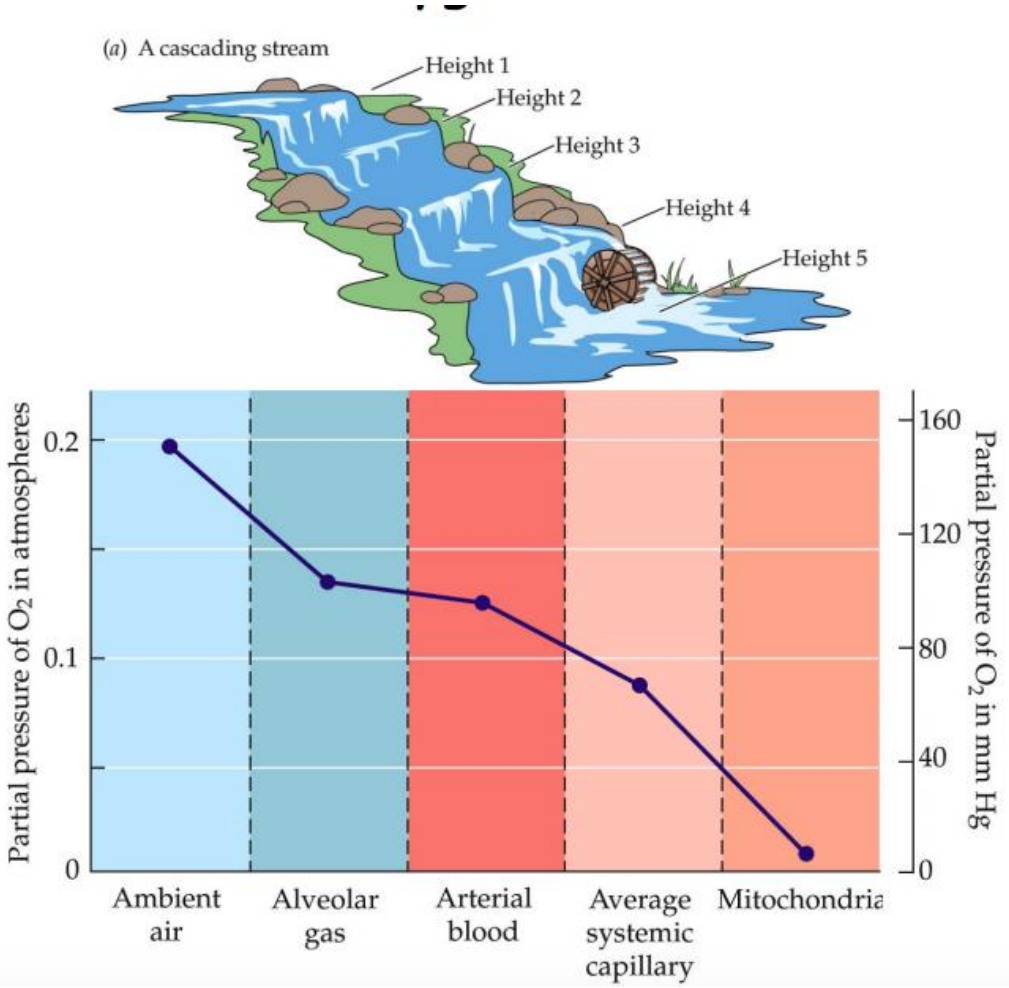
Oxygen cascade – progressive drop of oxygen content



- 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
    - 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
  - phyiological ventilation-perfusion inequality
  - 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 (= hypoxemia)
  - anemic
  - circulatory
  - histiotoxic

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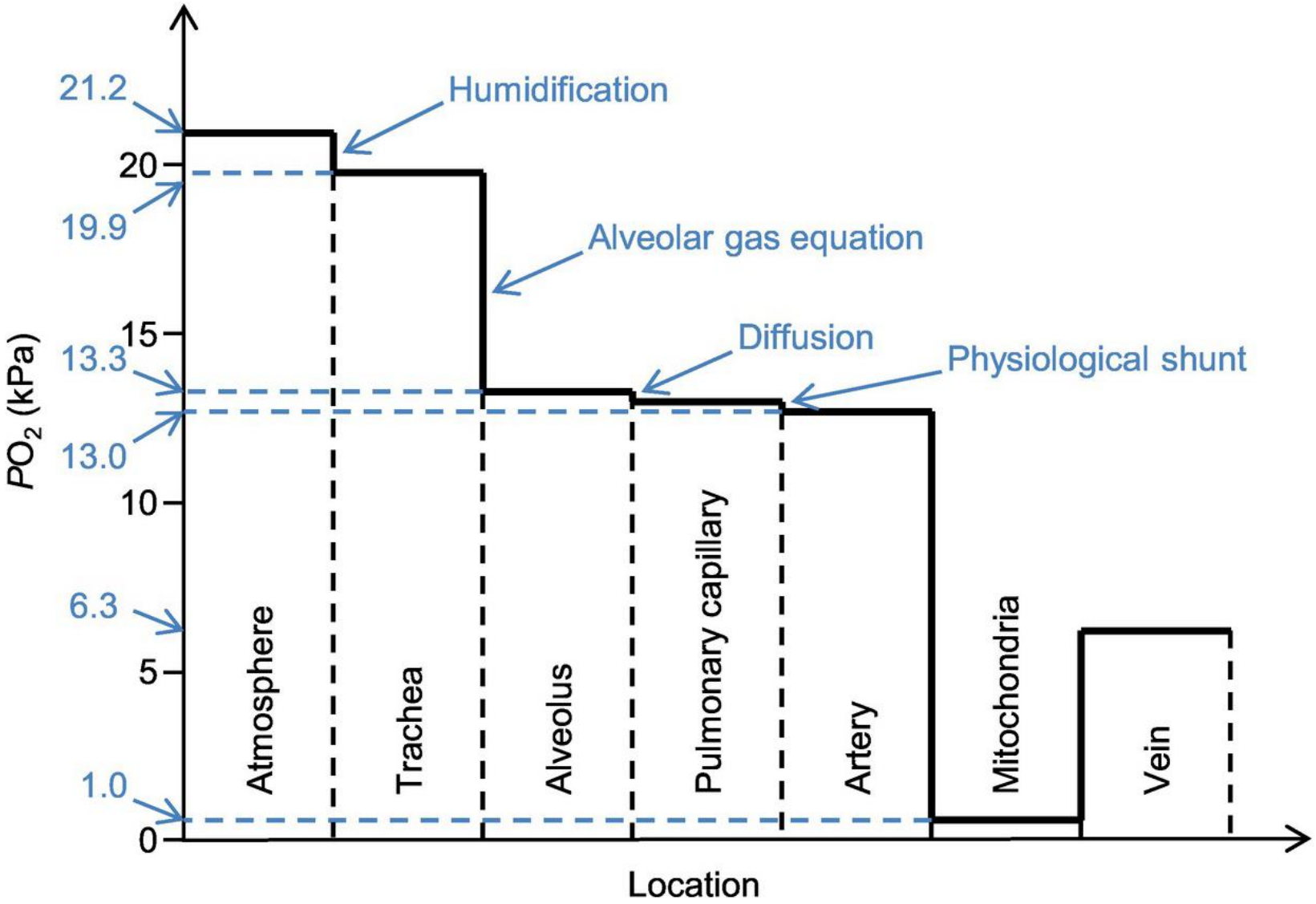
Oxygen cascade



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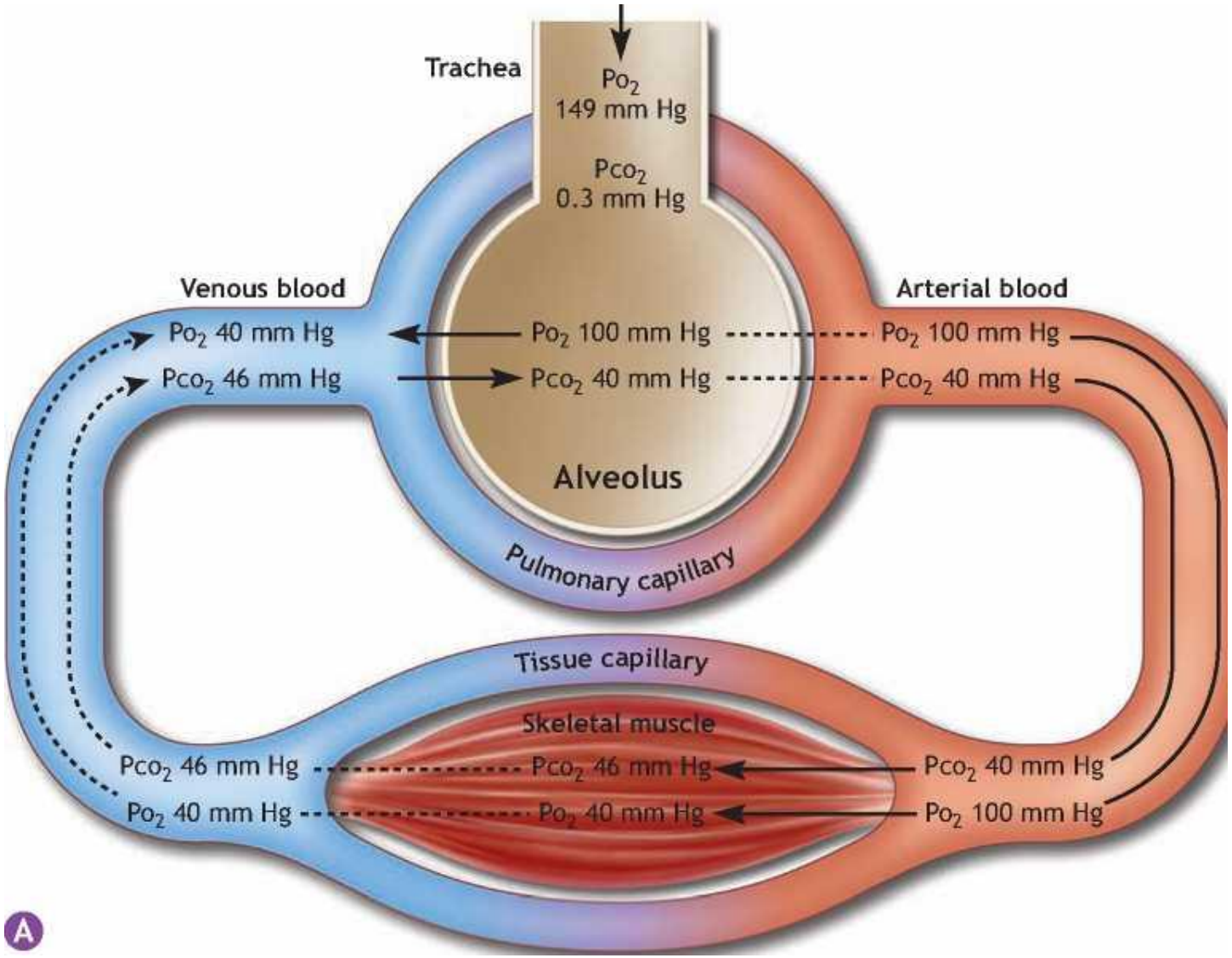
Normal values of blood gases in various parts of circulation



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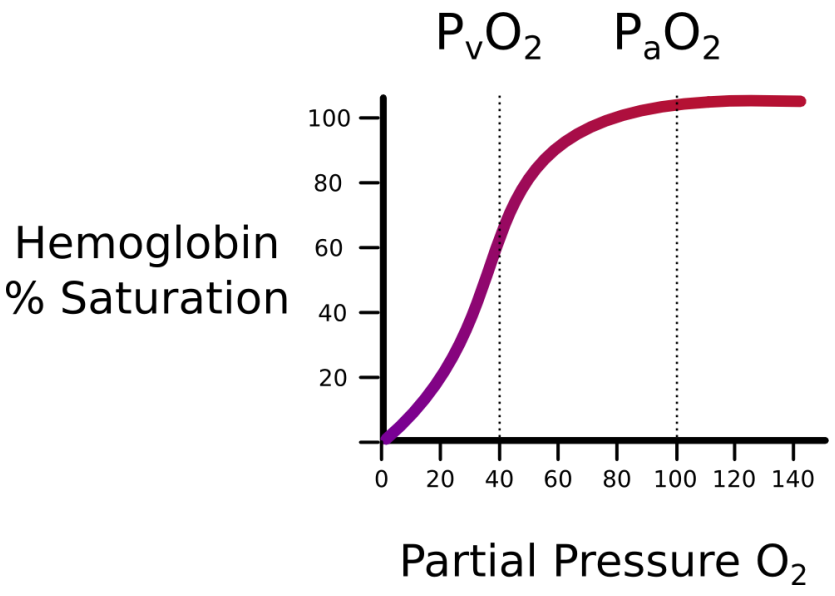
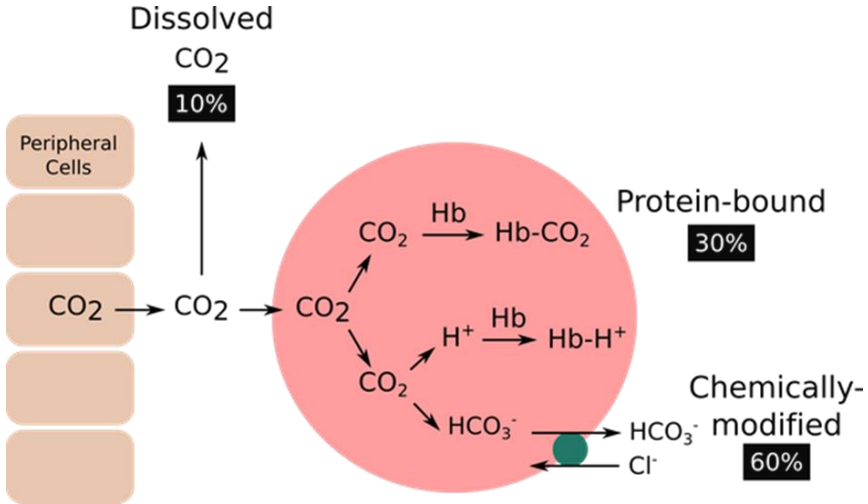
Transport of gases in blood





- 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 > 10kPa/60 mmHg, 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 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

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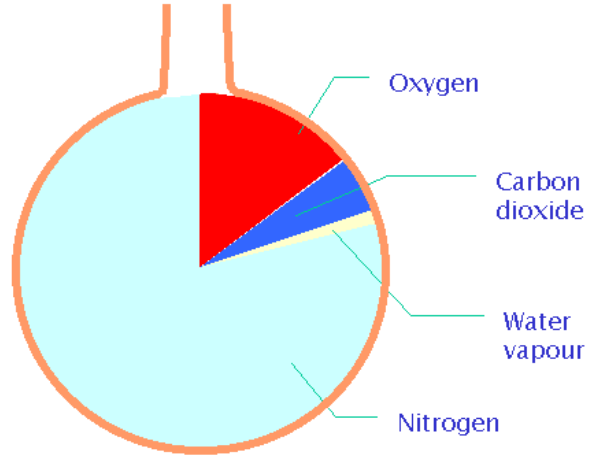
Quantitatively

- (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

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CAUSES OF HYPOXEMIA (I.E. RESPIRATORY FAILURE)

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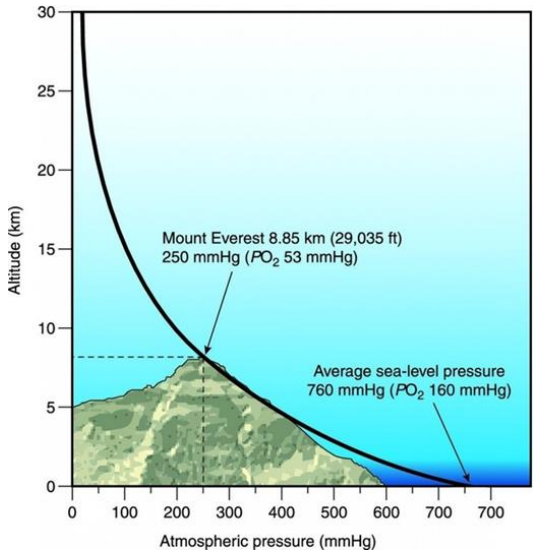
Hypoxemia (low PaO_2) - classification

- (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
    - 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 O_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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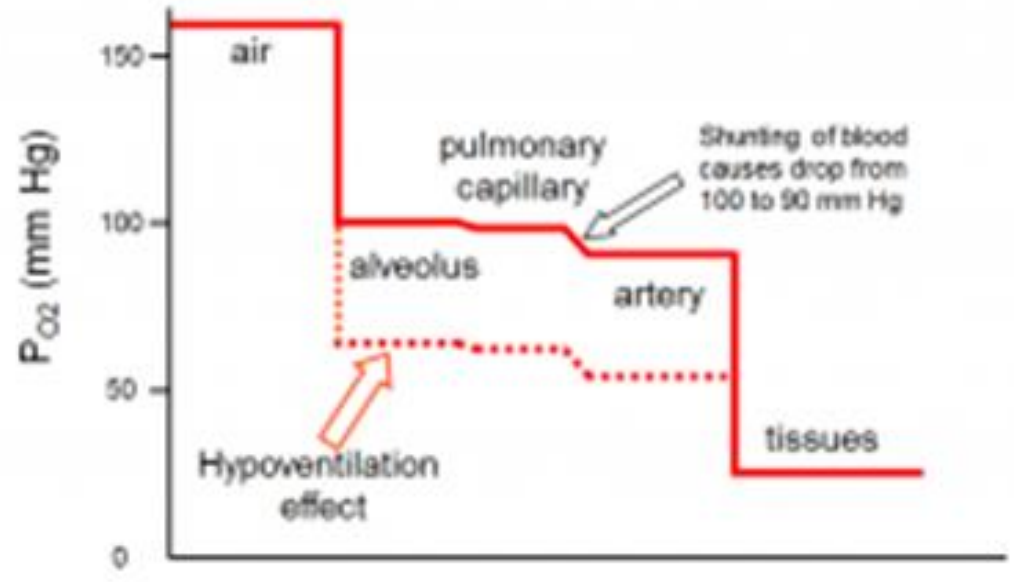
(1) Hypoventilation as a cause of hypoxemia

(results in low PaO_2 + hypercapnia)

- normally $PaCO_2$ in mixed venous blood (i.e. pulmonary artery and the same in alveolus) is 40 mmHg
- if $PaCO_2$ doubles (e.g. hypoventilation) then PAO_2 falls in half, i.e. 50 mmHg (more than $PaCO_2$ rise since RQ is 0.8)
- can we restore the PAO_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 100mmHg** = (**FiO2 ??** x (760 - 47)) - (**$PaCO_2$ 80mmHg** x 1.25**) = ~0.28, i.e. 28%**
- examples – **typically extra-pulmonary**
  - respiratory CNS generator
    - congenital, drug overdose, CNS injury, metab. alkalosis, encephalitis, …
  - neuromuscular
    - myasthenia gravis, ALS, muscular dystrophy, cervical spinal cord injury, …
  - chest wall
    - deformities, injury, obesity, …



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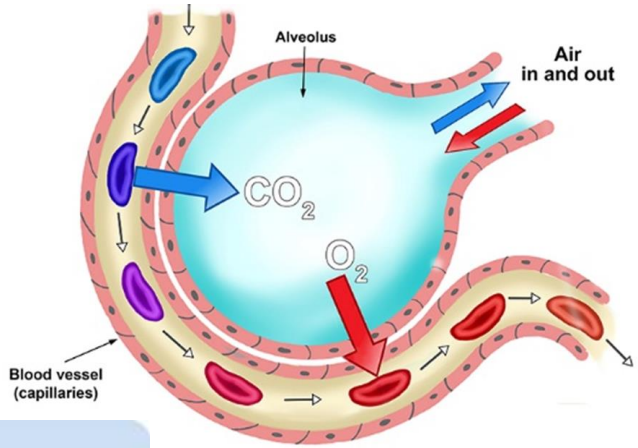
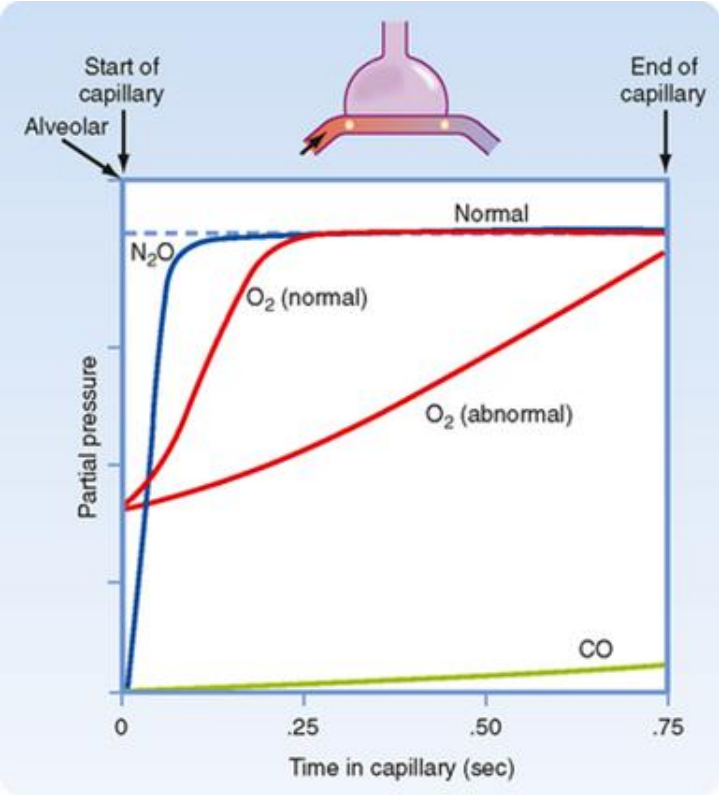
(2) Diffusion impairment as a cause of hypoxemia

(low PaO_2 + normocapnia)

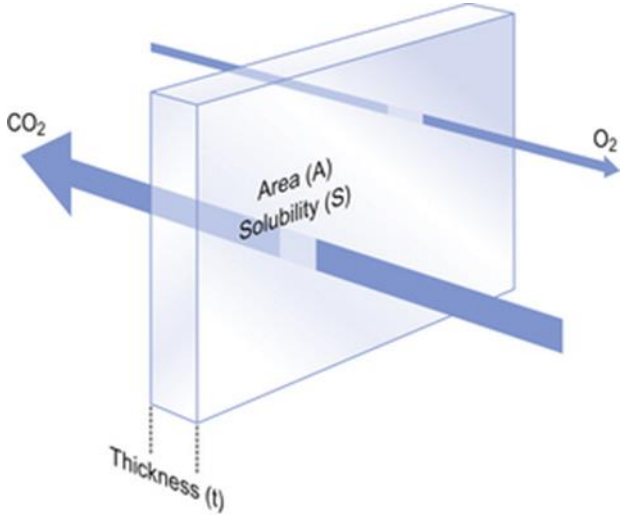


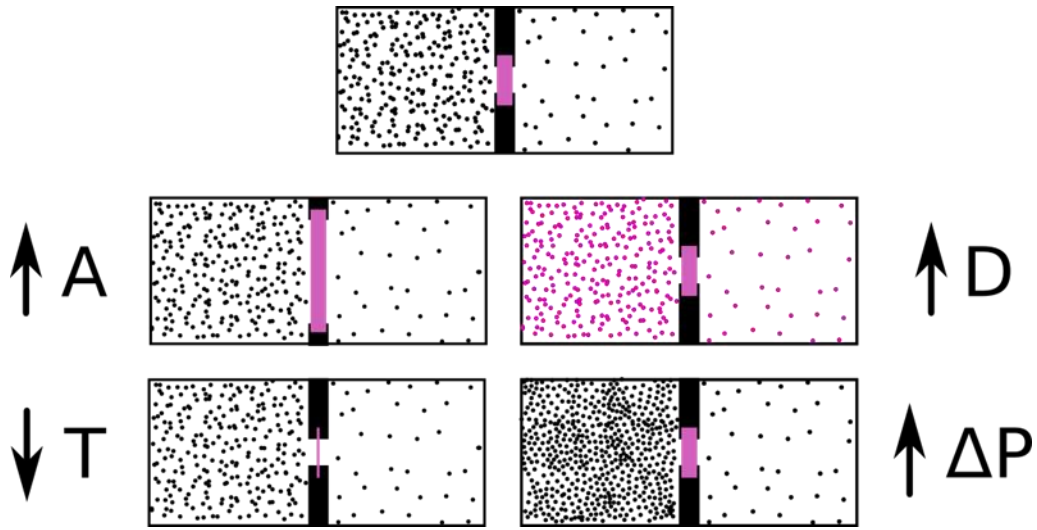
- due to
  - low inspired oxygen
  - shortening of the time blood spends in pulmonary capillary
    - oxygen is perfusion limited
      - extreme exercise
      - hyperkinetic circulation
      - increased velocity of pulmonary circulation
  - thickened alveolo-capillary barrier
    - PaO_2 typically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



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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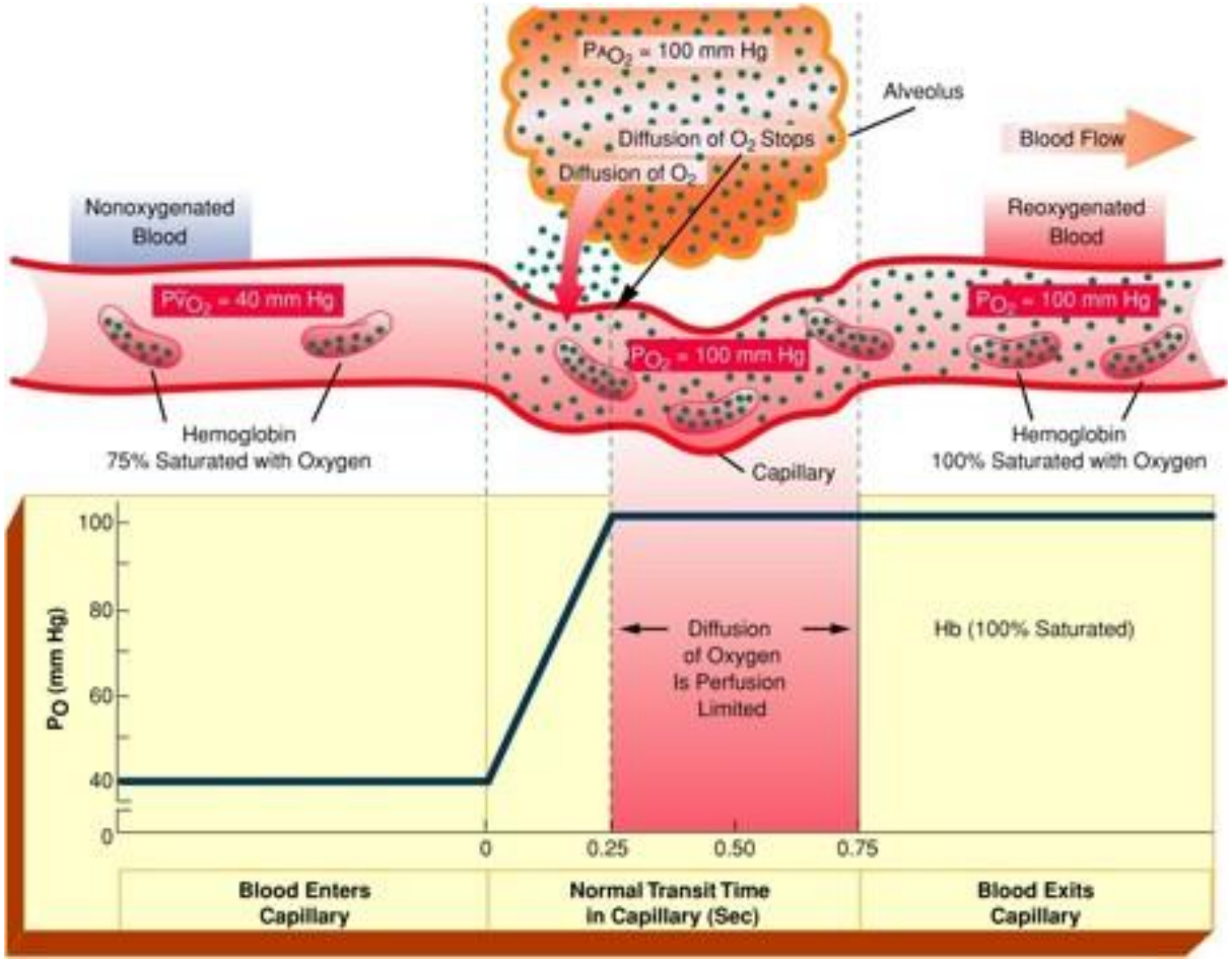
Oxygen is perfusion-limited



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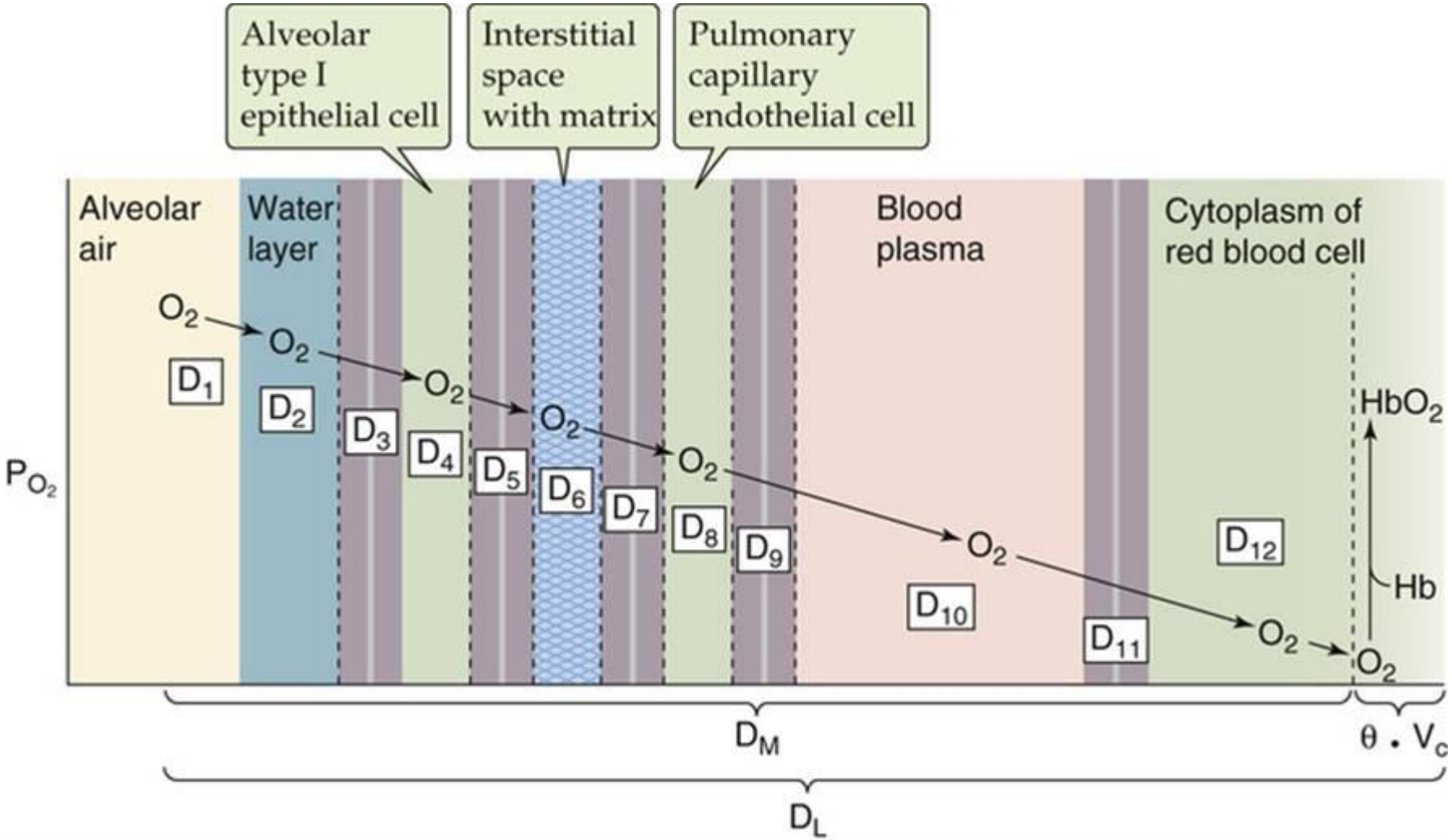
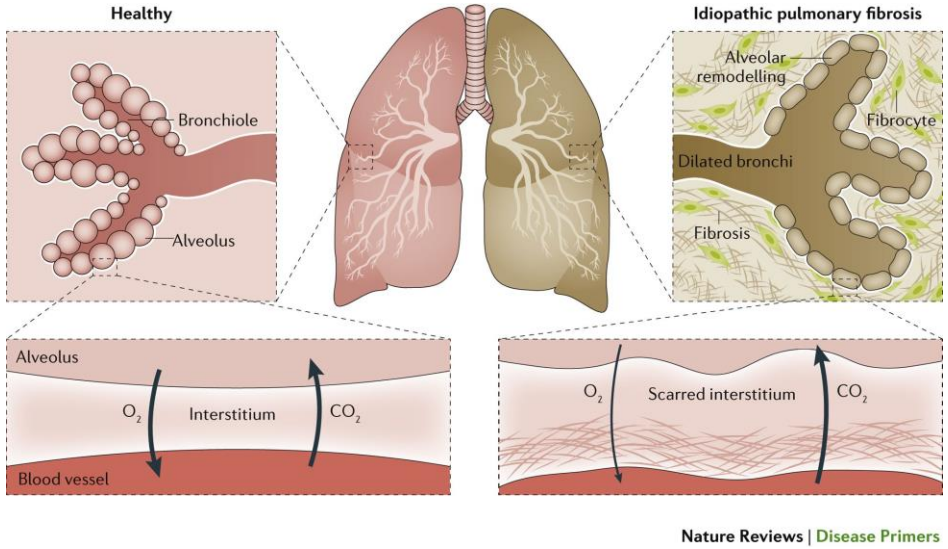
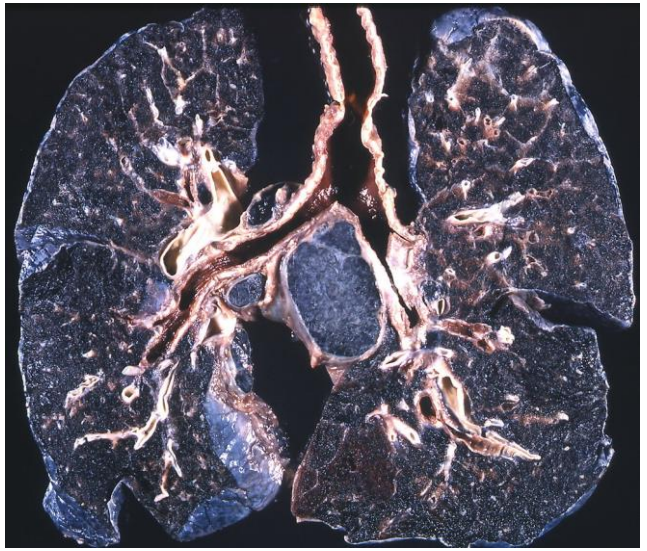
Gases do not diffuse across a homogeneous barrier



Examples of disease leading to diffusion impairment

- Interstitial lung diseases
  - Idiopathic pulmonary fibrosis
  - Hypersensitivity Pneumonitis
  - Sarcoidosis
  - Pneumoconiosis
  - TBC
- Note, very often the diffusion impairment combines with V/Q mismatch

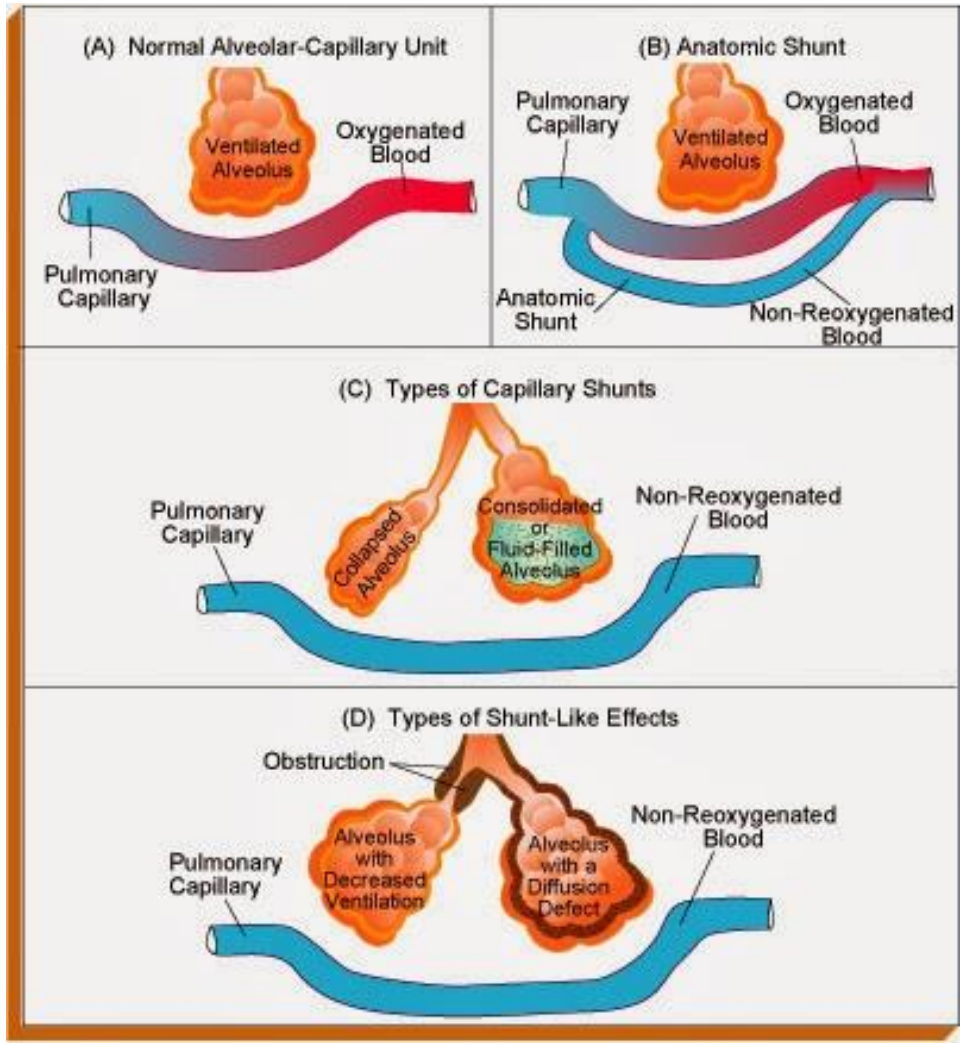




(3) Right to left shunt as a cause of hypoxemia

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

- fraction of the cardiac output that bypasses normal circulatory pathways
  - oxygen-poor blood from the right heart flows in the left heart without passing through functional, ventilated alveoli
- physiologically this happens due to bronchial circulation and thebesian veins draining into left ventricle
- **Anatomical causes** of increased right-to-left shunting
  - intrapulmonary: pulmonary arteriovenous malformations
  - extrapulmonary: right-to-left intracardiac shunts
    - patent ductus arteriosus
    - septal defects
- Pathological causes of increased right-to-left shunting
  - poorly ventilated alveoli
  - fluid filled alveoli
- Hypoxemia caused by right-left shunts prototypically cannot be corrected by oxygen therapy



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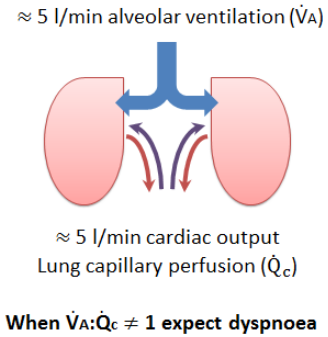
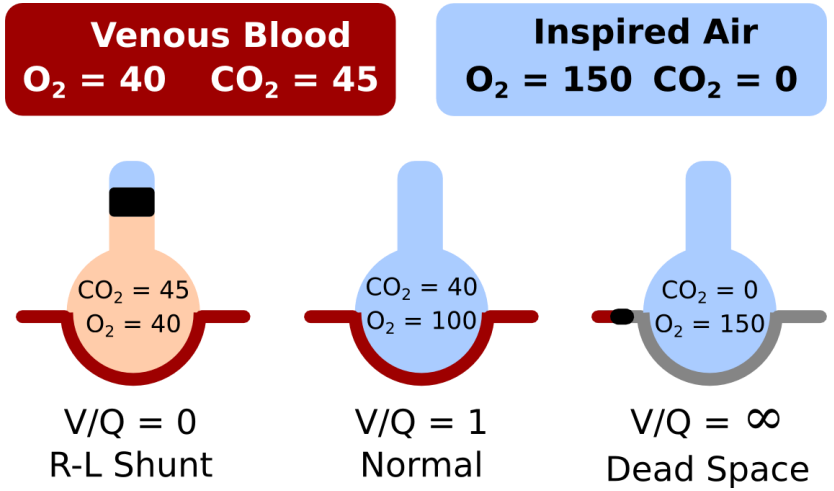
(4) Ventilation-perfusion inequality as a cause of hypoxemia

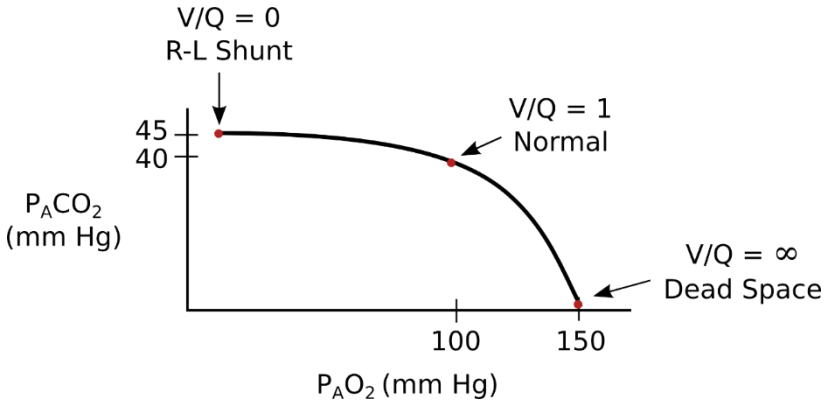
(low PaO2 + hypercapnia)

- 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
- Ventilation-perfusion mismatch is by far the most common cause of arterial hypoxaemia
- 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/Q ratio = 1





- **Effect of the V/Q ratio on Alveolar Gas Tensions**
- **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
    - athough 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
- The effect of an increased **dead space** (V/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 **R-L shunting** (VA/Q ratio < 1) results in arterial hypoxaemia that cannot be effectively compensated for by hyperventilation
- In advanced disease with V/Q mismatch this compensation cannot occur, leading to increased alveolar and arterial PCO2, together with hypoxaemia which cannot be compensated by increasing ventilation



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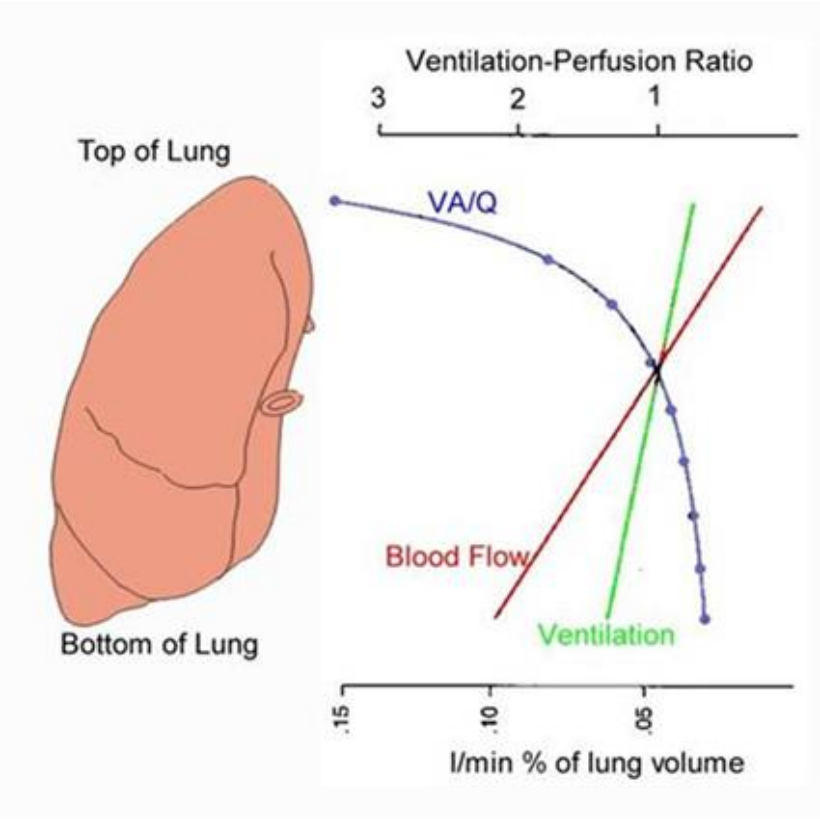
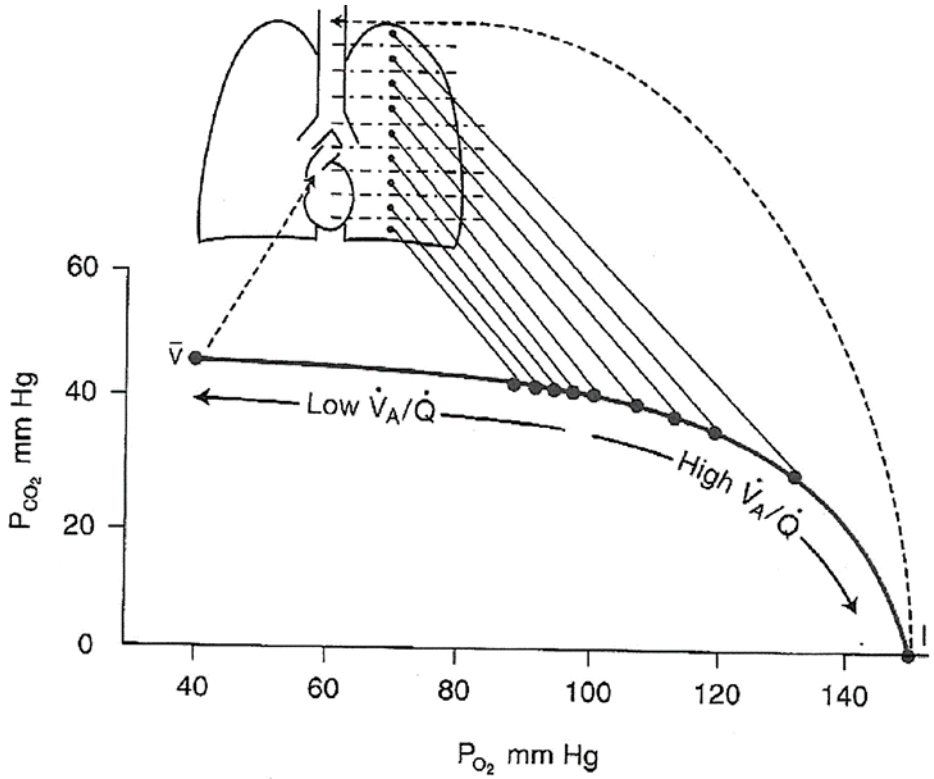
Normal lung - relationship between ventilation and perfusion



- There is a wide variation in the **V_A/Q ratio** to some extent already in healthy subjects
  - 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 ($V_A/Q = 0.7$) – lower PAO2, higher PACO2 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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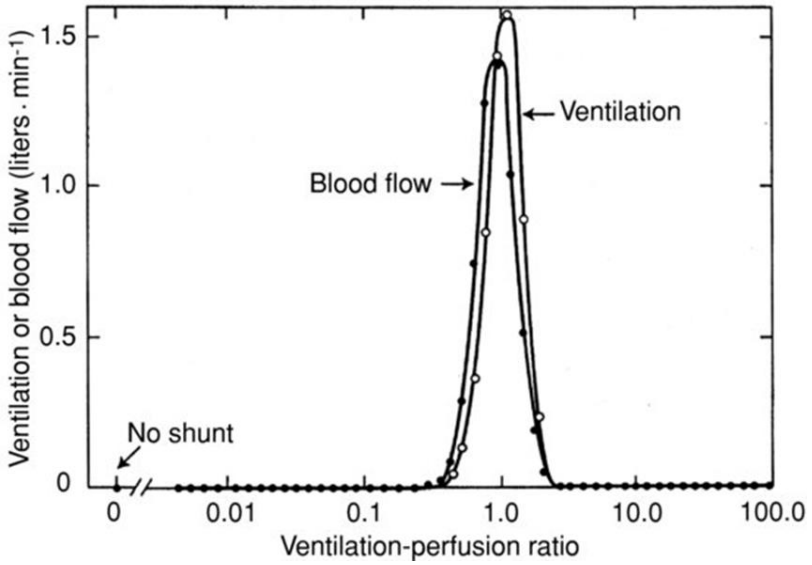
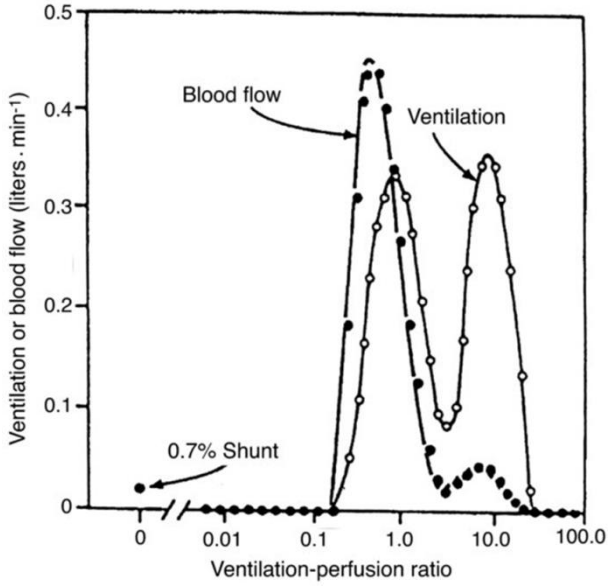
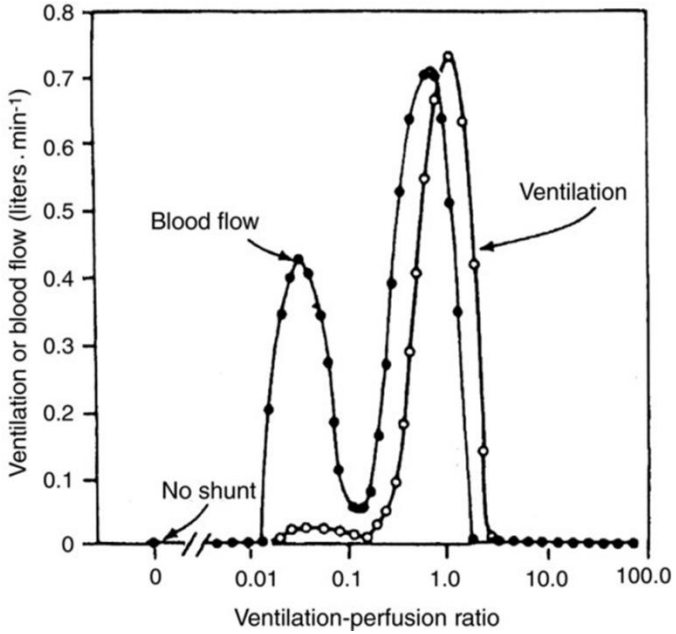
Example of a distribution of ventilation-perfusion ratios







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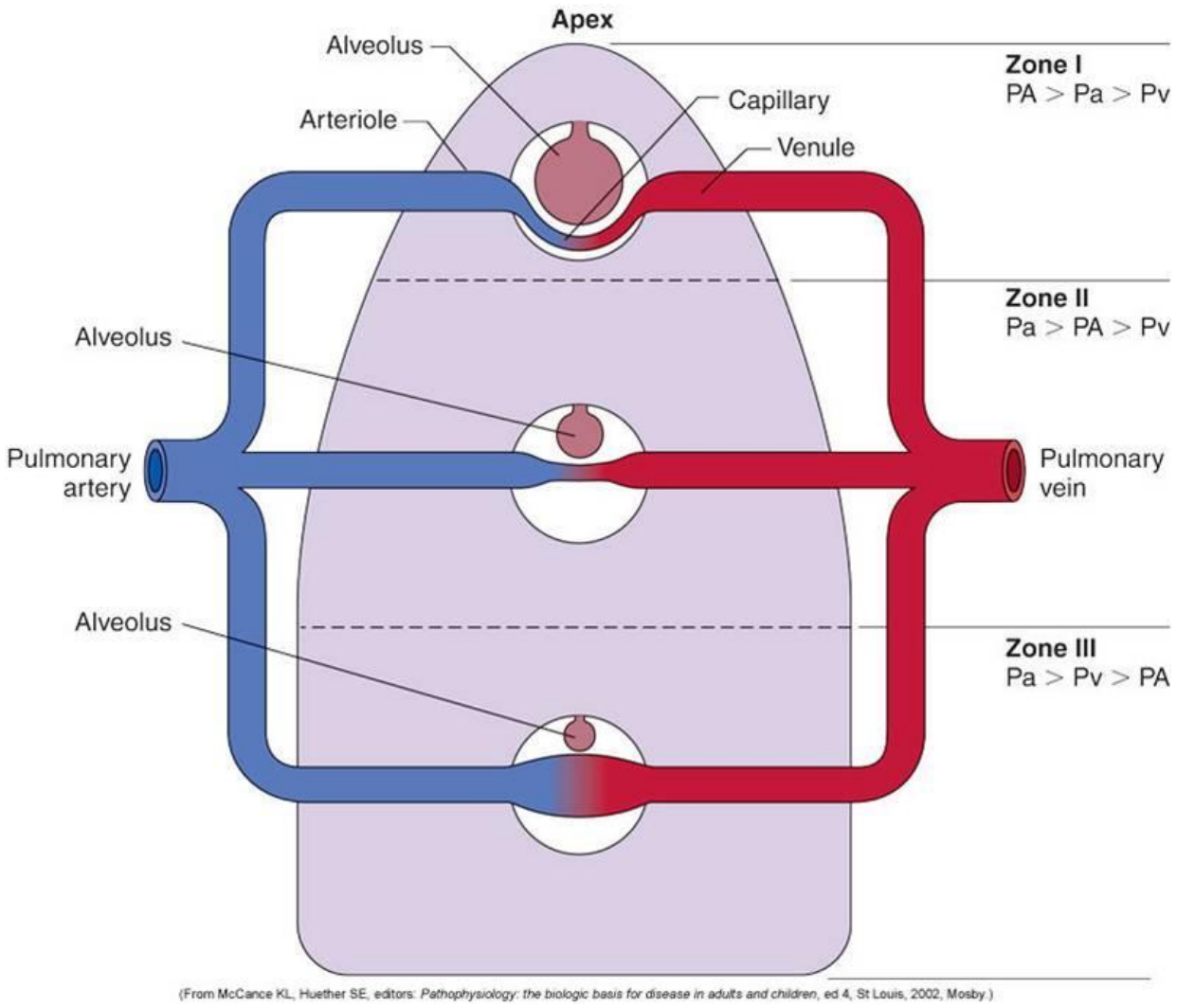
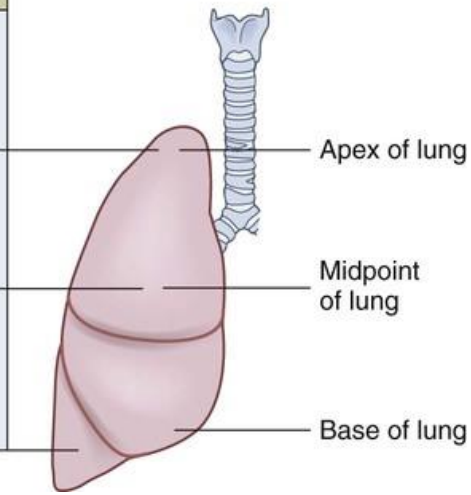
V/Q mismatch largely contributes to the A-a difference of oxygen



(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/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 expired 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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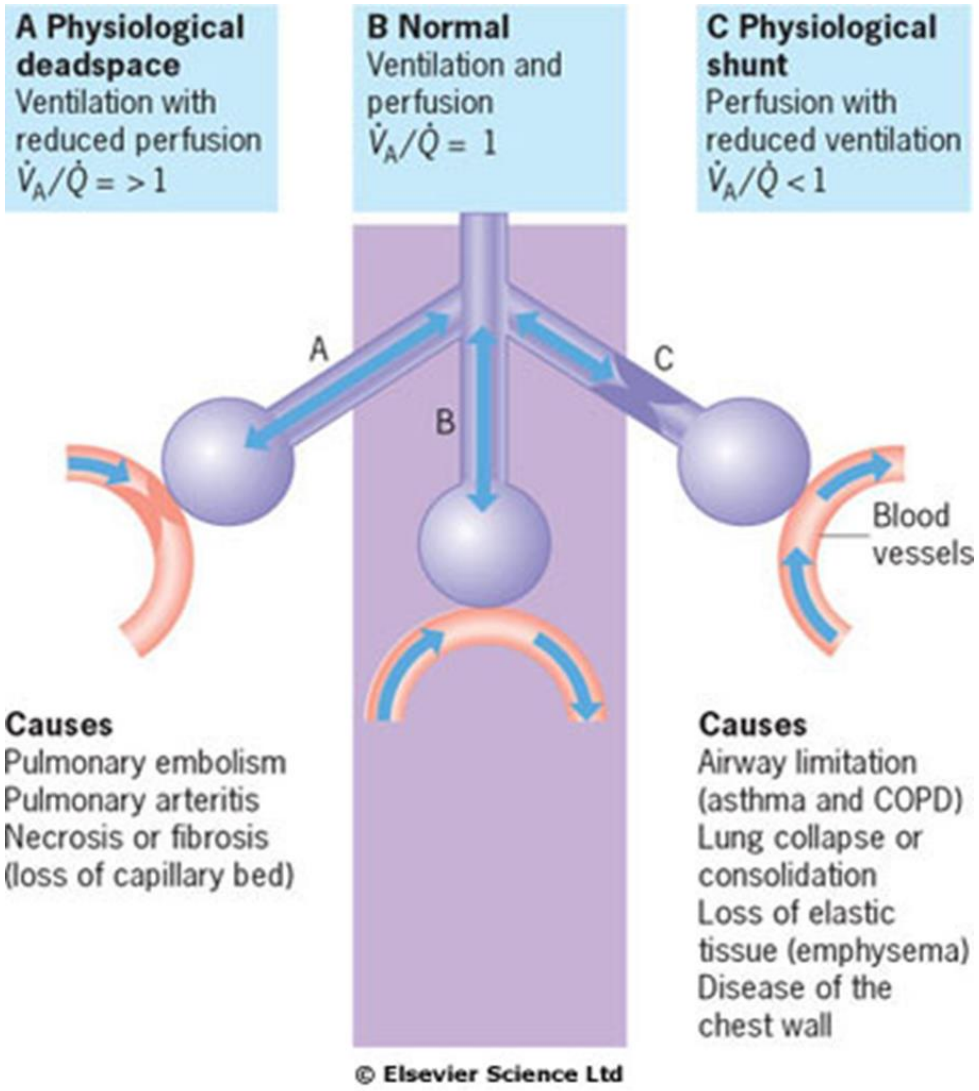
Ventilation-perfusion inequality (mismatch)



- 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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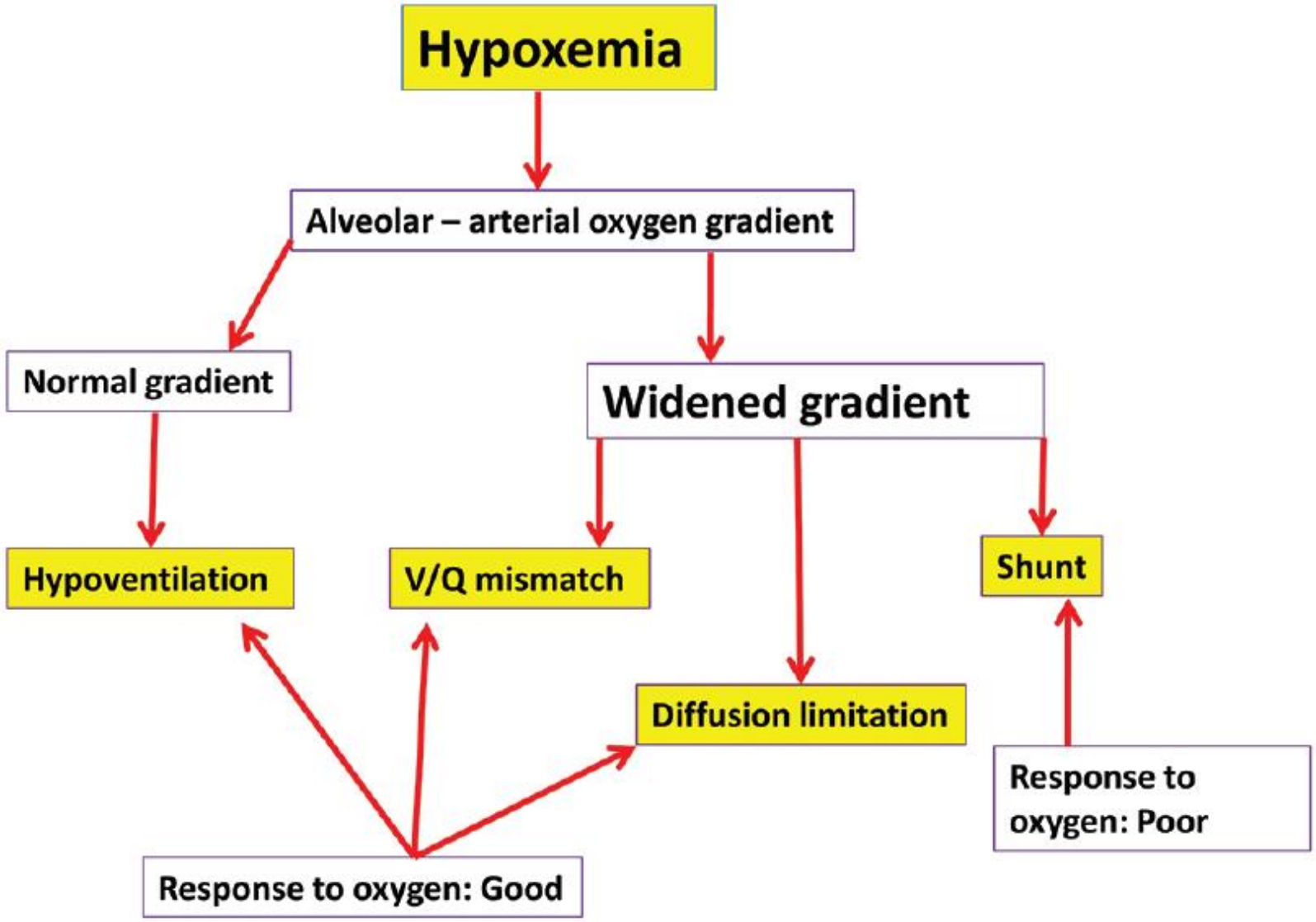
Hypoxemia dif. dg.



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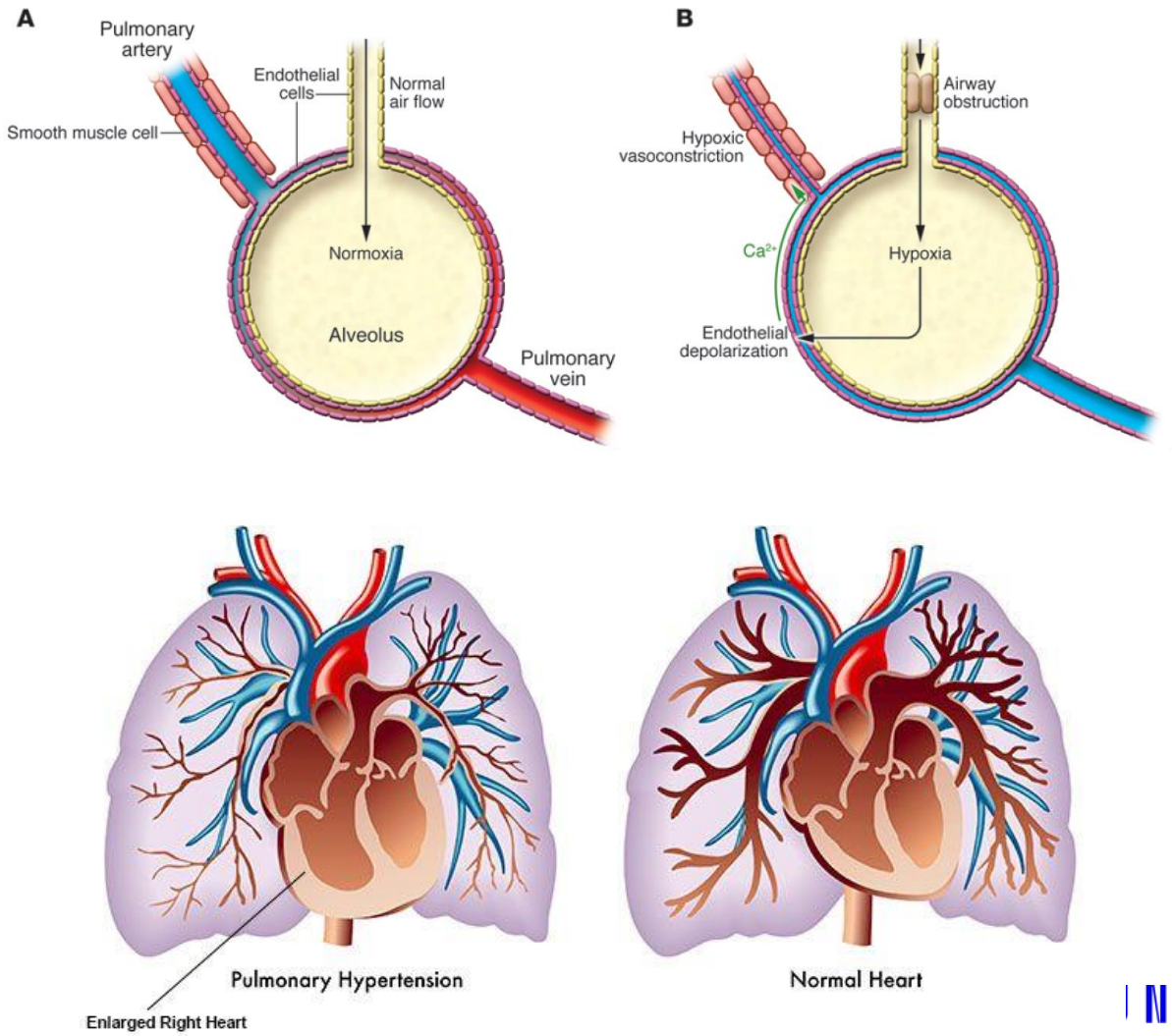
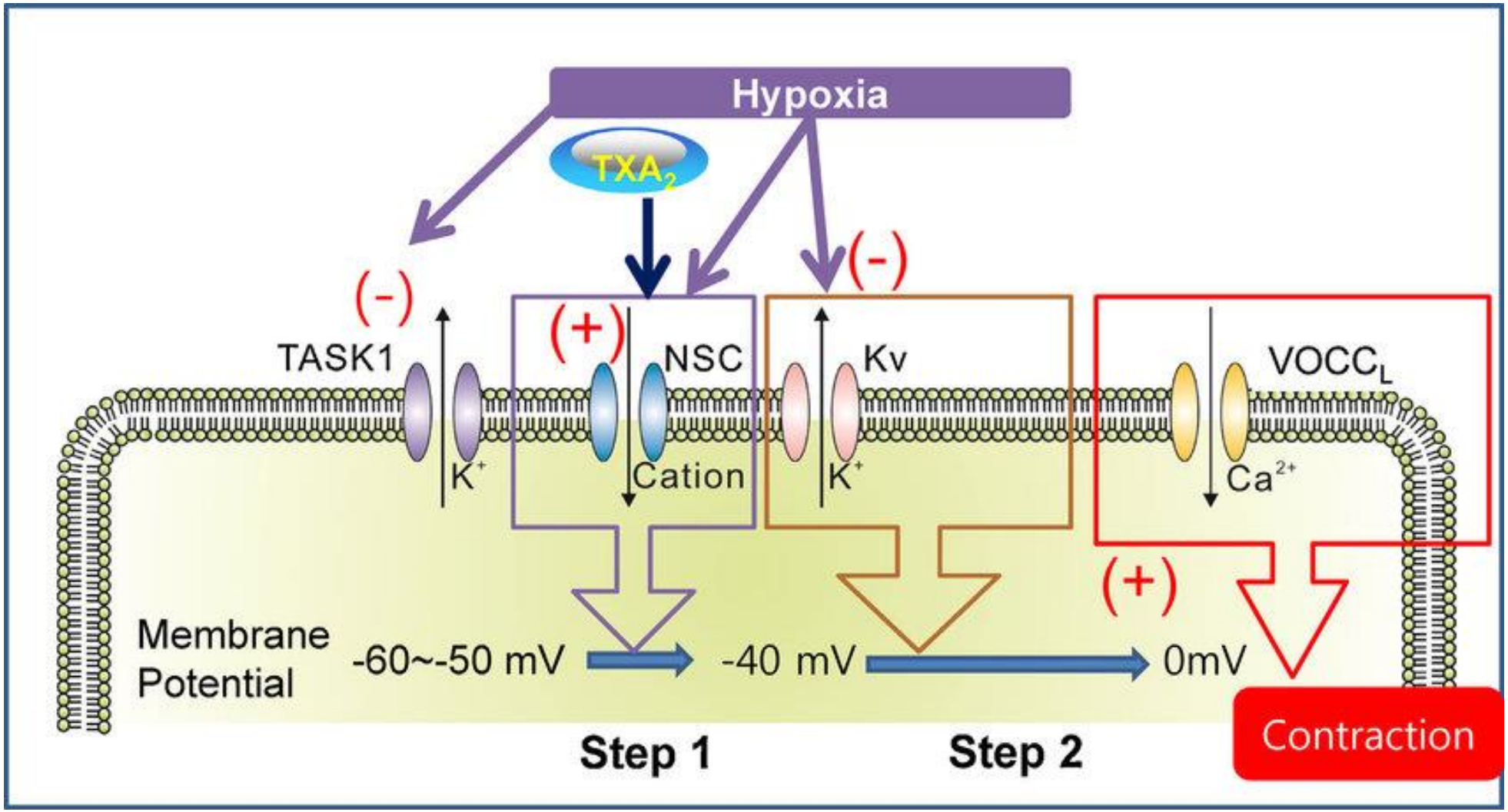
Hypoxic pulmonary vasoconstriction (HPV)

- a physiological phenomenon in which small pulmonary arteries constrict in the presence of **alveolar hypoxia** (low oxygen levels)
- 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



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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RESPIRATORY INSUFFICIENCY

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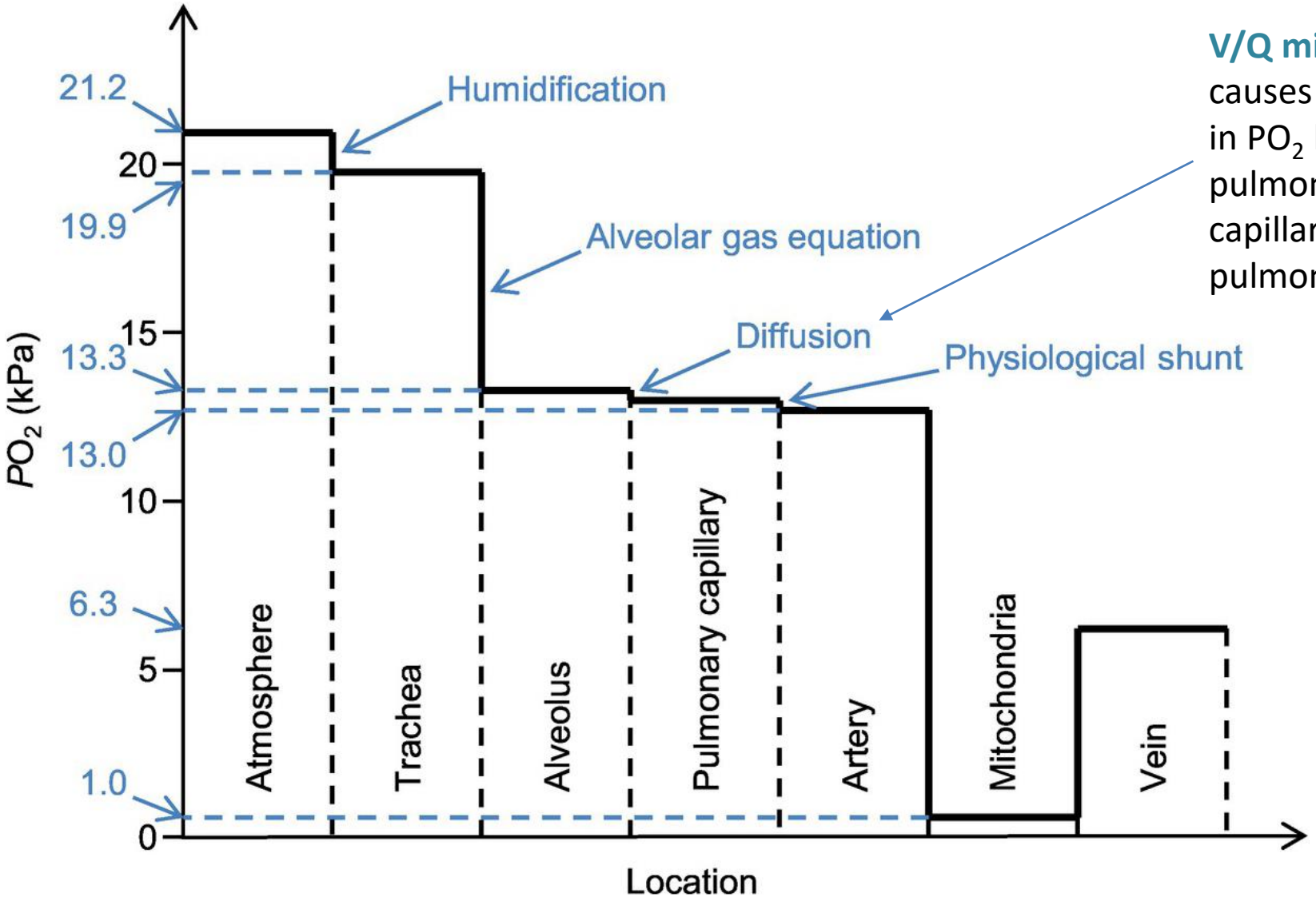
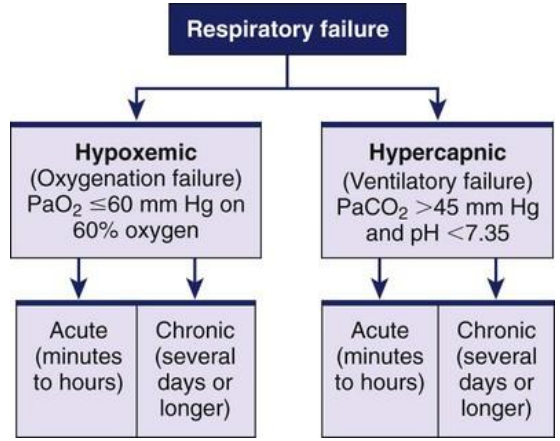
Oxygen cascade completed – 4 causes of hypoxemia

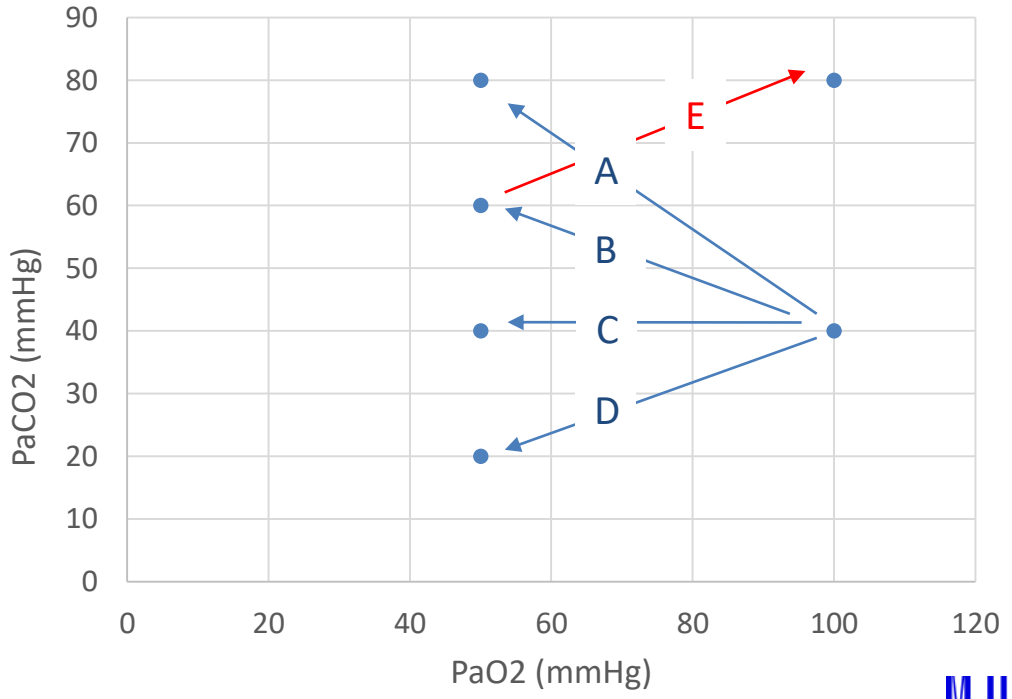


V/Q mismatch – causes difference in PO_2 between pulmonary capillaries and pulmonary vein

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		Type II-Hypoxemic, Hypercapnic Respiratory Failure	
	Acute Hypoxemic Respiratory Failure (Acute Hypoxemia)	Chronic Hypoxemic Respiratory Failure (Chronic Hypoxemia)	Acute Hypoxemic, Hypercapnic Respiratory Failure (Acute Hypoventilation, Acute Ventilatory 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		Type II-Hypoxemic, Hypercapnic Respiratory Failure	
	Acute Hypoxemic Respiratory Failure (Acute Hypoxemia)	Chronic Hypoxemic Respiratory Failure (Chronic Hypoxemia)	Acute Hypoxemic, Hypercapnic Respiratory Failure (Acute Hypoventilation, Acute Ventilatory 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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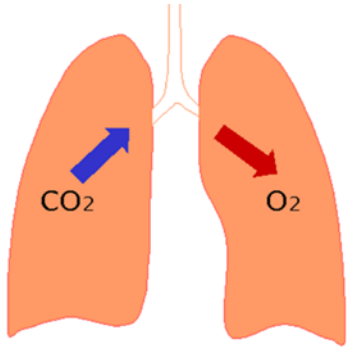
Respiratory insufficiency (RI)

- 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 (↓paO_2 <10kPa/75mm Hg)
- types:
  - (1) hypox(emi)c hypoxia = ↓ **arterial PO_2** - leads to central cyanosis
    - causes of hypoxemia
      - ↓ 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**
    - ↓ 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** , ↑ venous PO_2
    - Intoxication with cyanides, cobalt, …)

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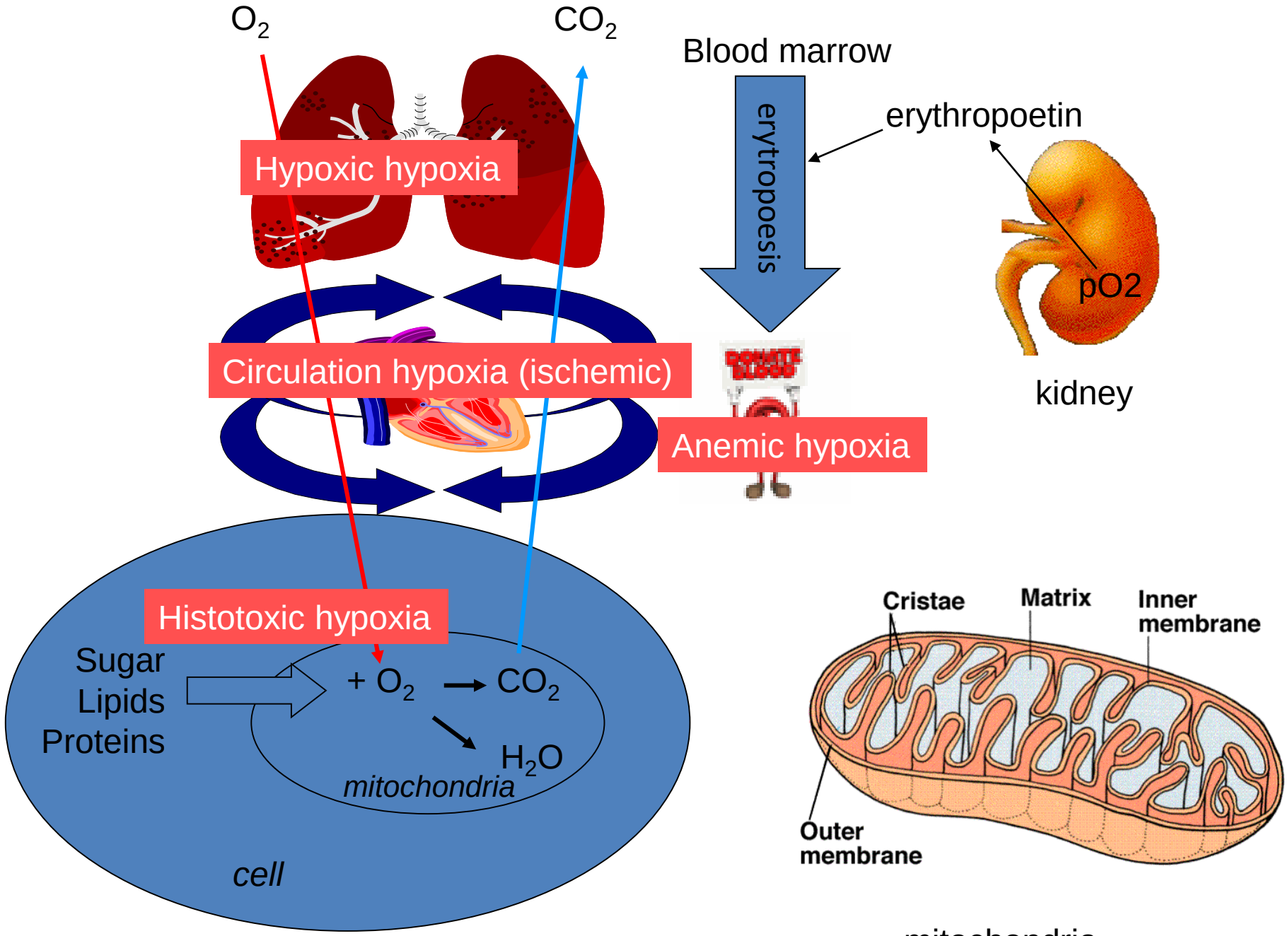
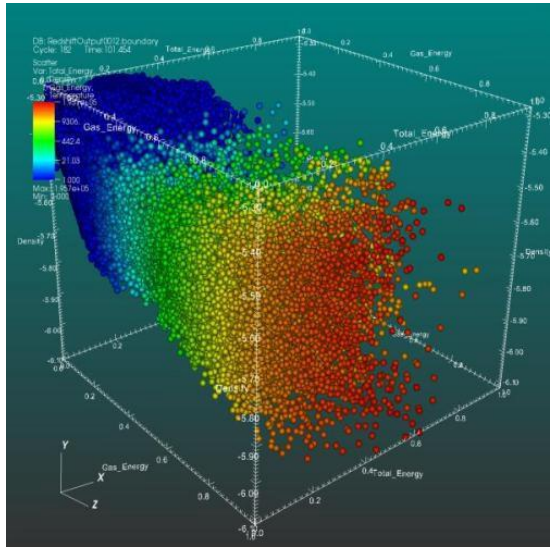

O_2
CO_2
Hypoxic hypoxia
Circulation hypoxia (ischemic)
Histotoxic hypoxia
Sugar
Lipids
Proteins
+ O_2
CO_2
H_2O
mitochondria
cell
Blood marrow
erythropoetin
erytropoesis
pO2
kidney
Anemic hypoxia
Cristae
Matrix
Inner membrane
Outer membrane
mitochondria

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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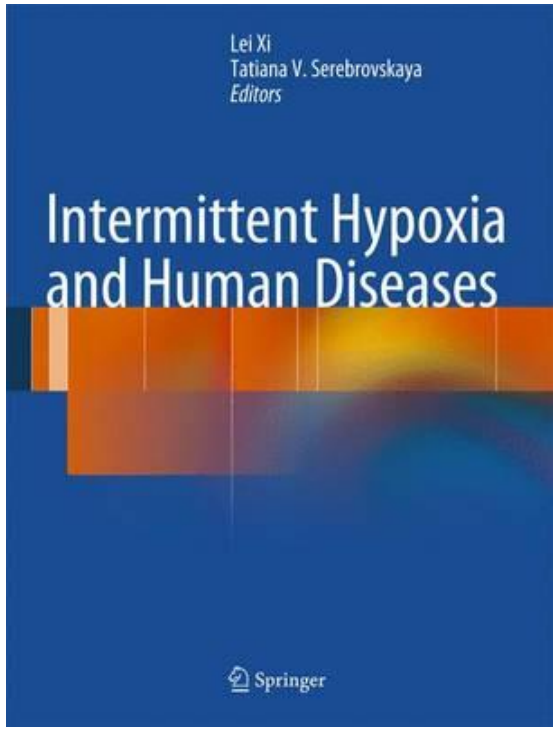
Intermittent, chronic intermittent and chronic hypoxia

- **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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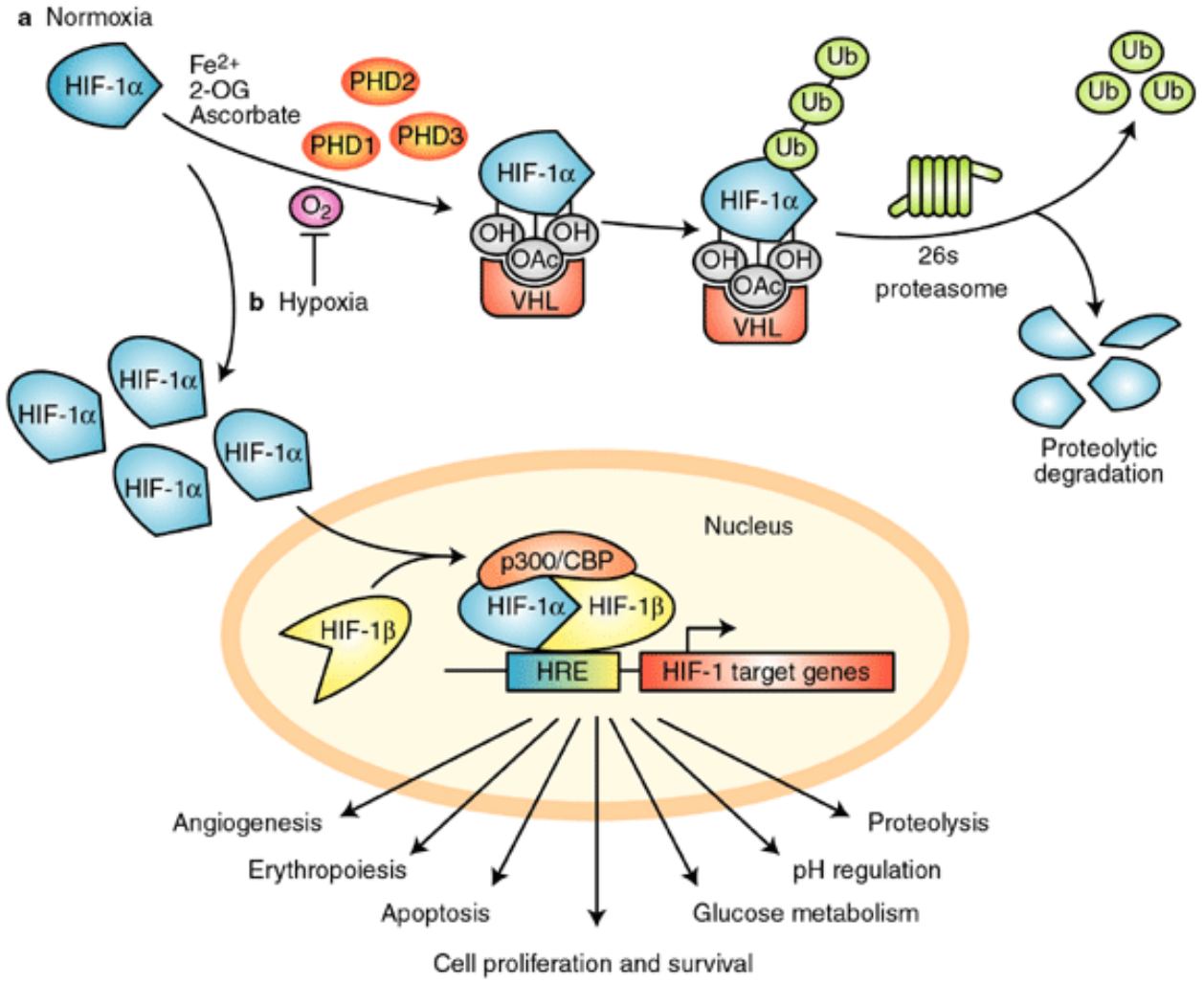
Hypoxia and gene transcription



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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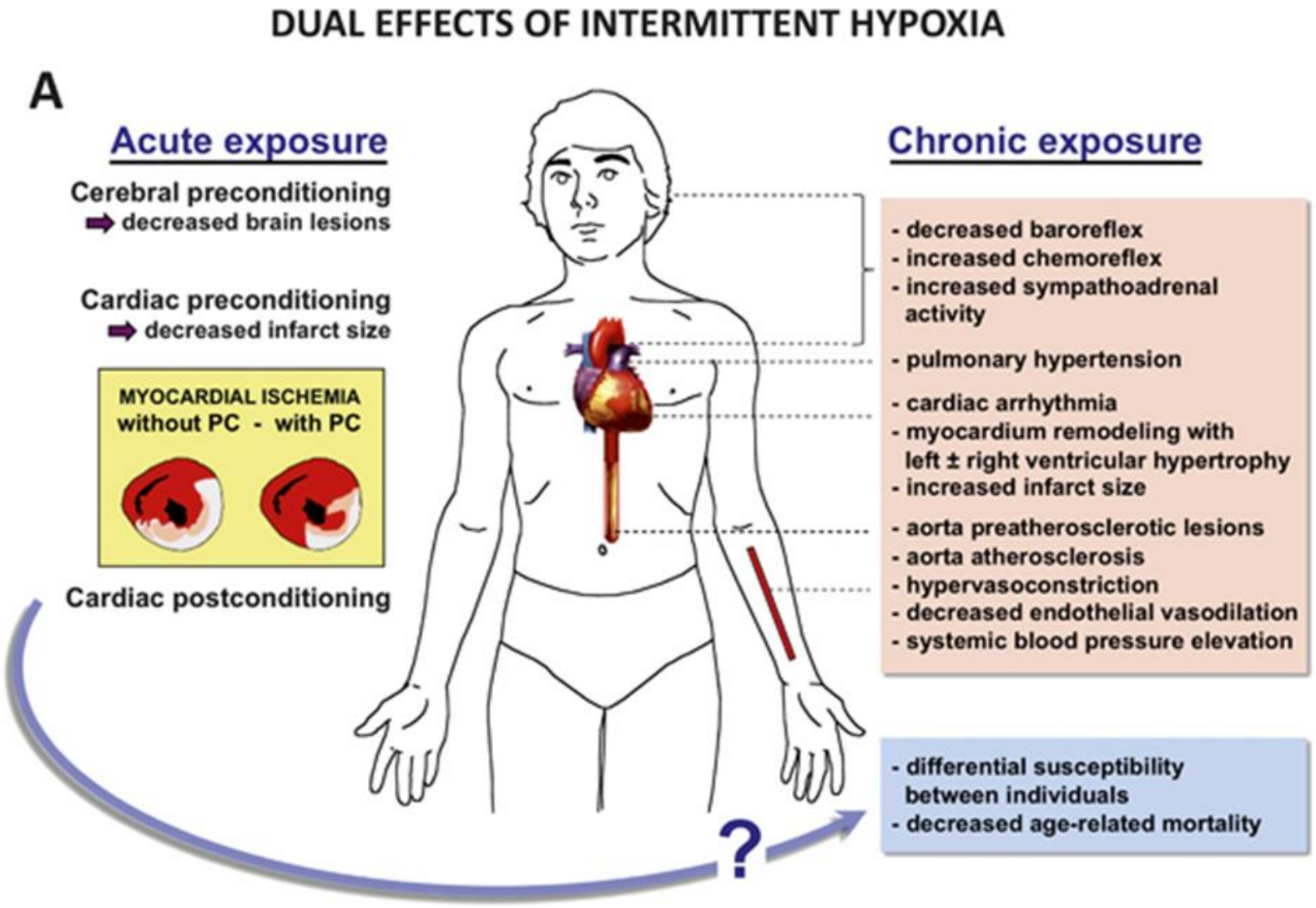

According to the severity and duration of exposure, intermittent hypoxia (IH) may have either beneficial effects, involving pre- and postconditioning, or detrimental effects as in sleep apnea. It is not clear whether pre-/postconditioning-like phenomena occur during chronic exposure and contribute to 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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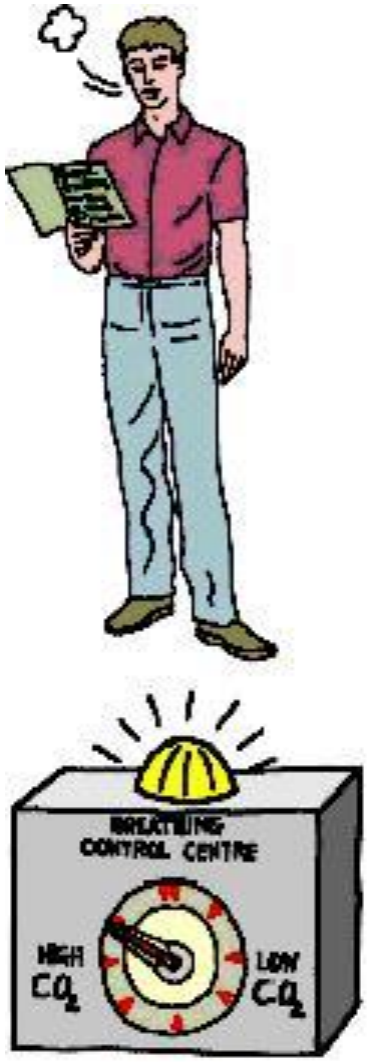
CONTROL OF RESPIRATION & ITS DISORDERS



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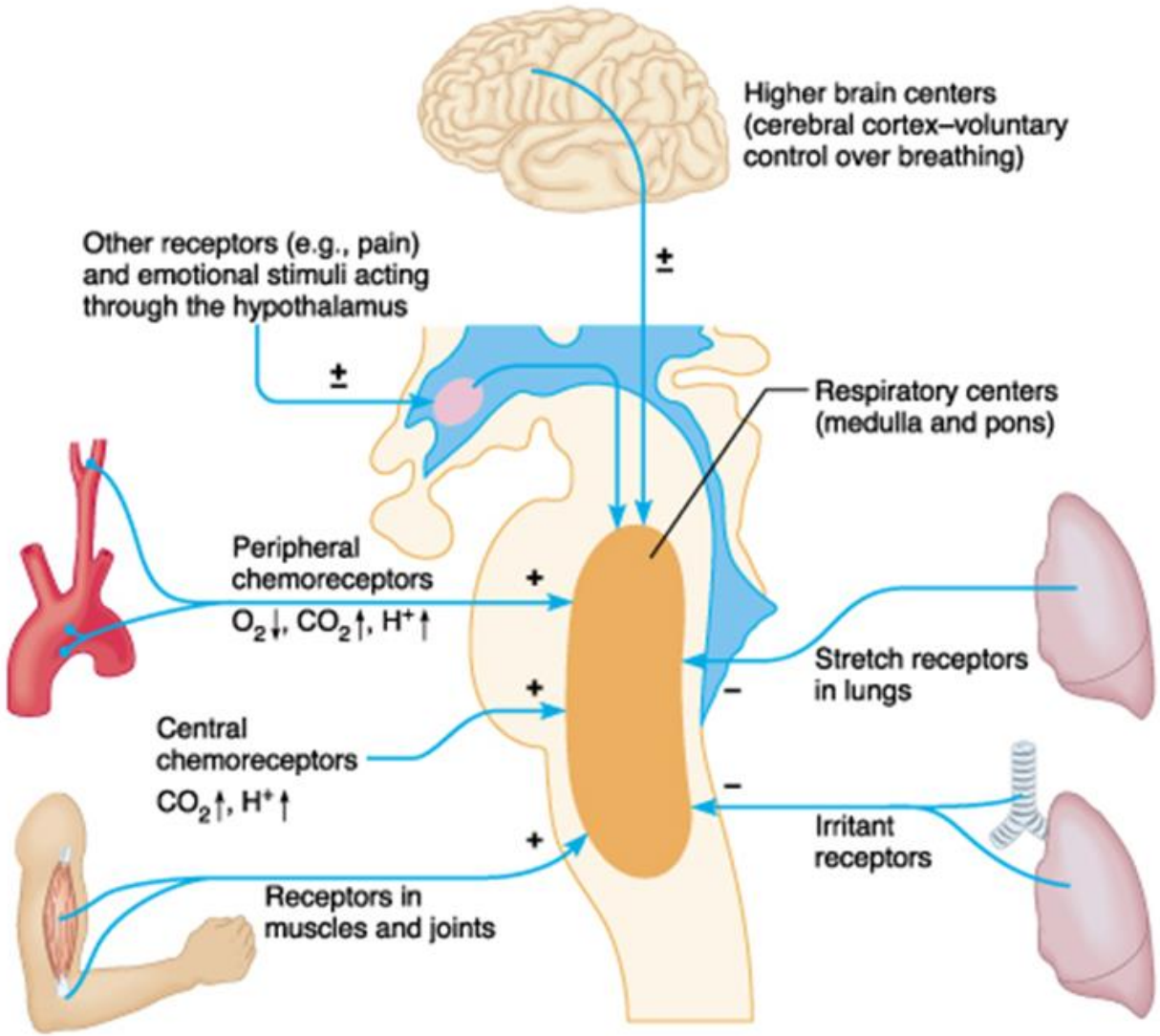
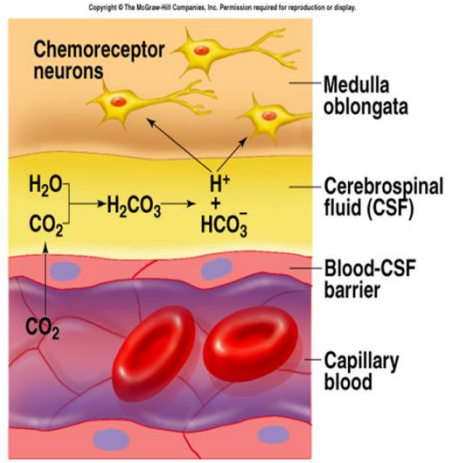
Control of respiration



- 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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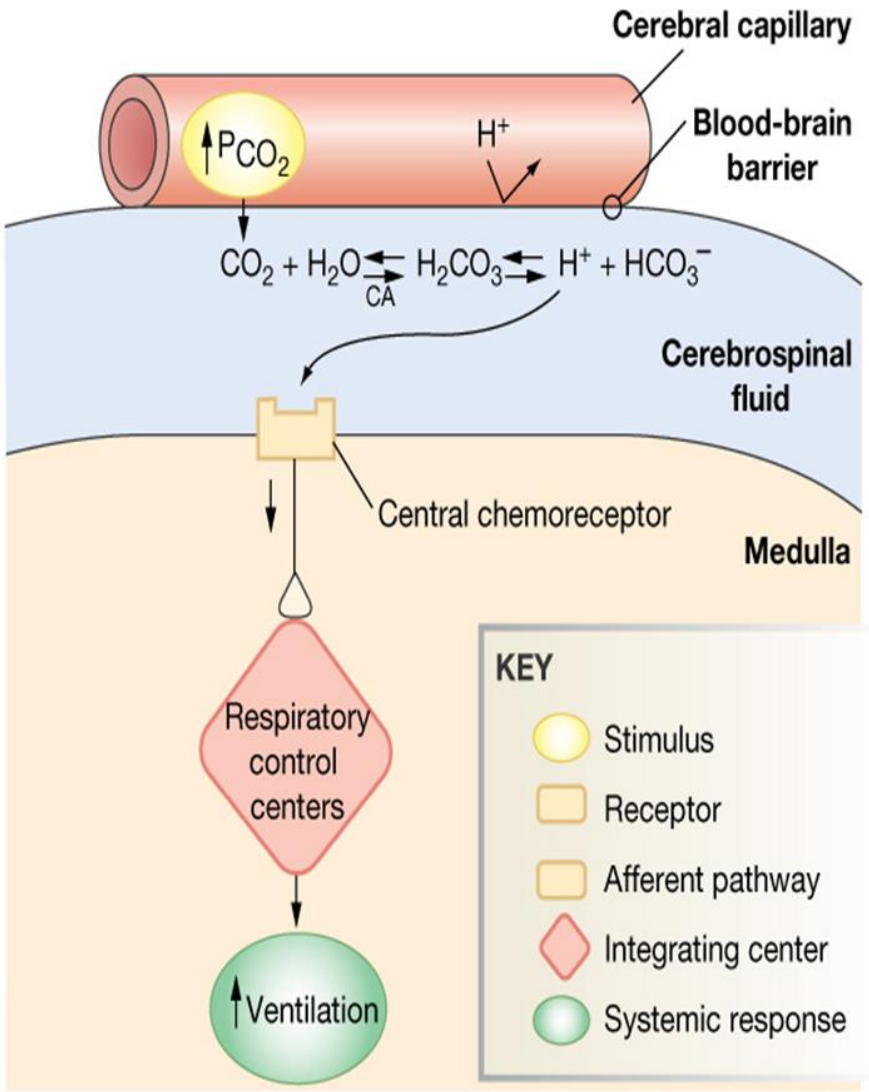
Central chemoreceptors



- sensitive to $\uparrow PaCO_2$ (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 $\uparrow HCO_3$- 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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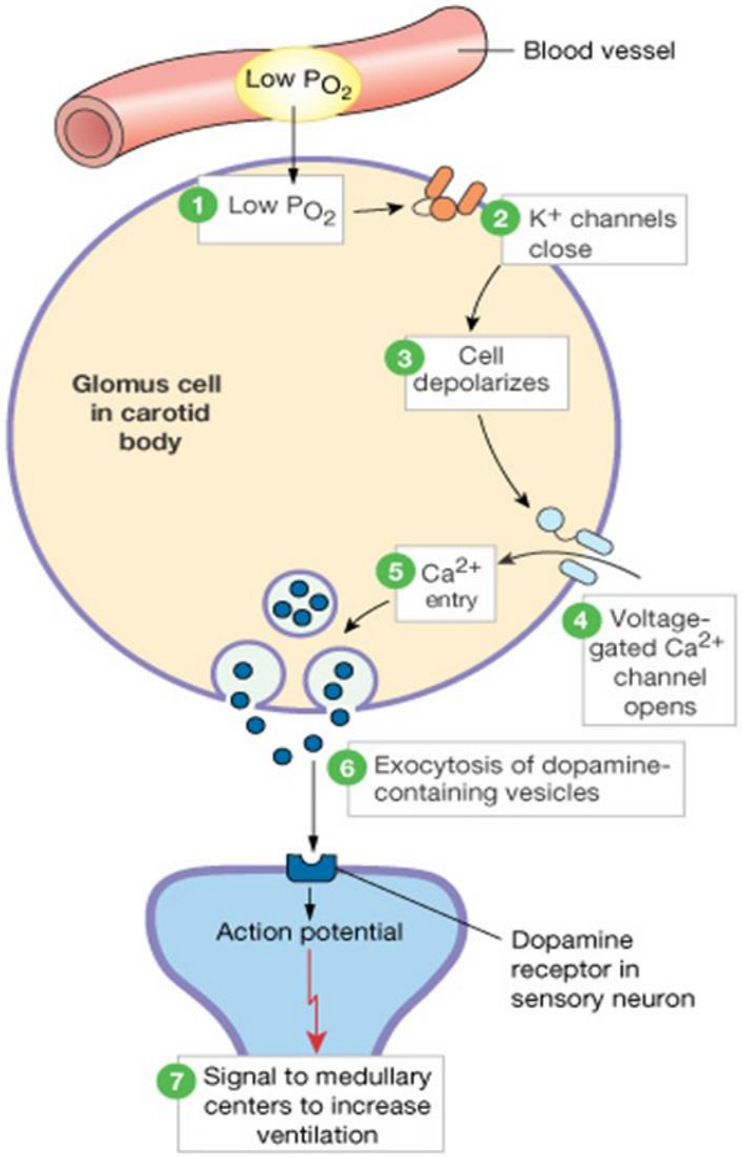
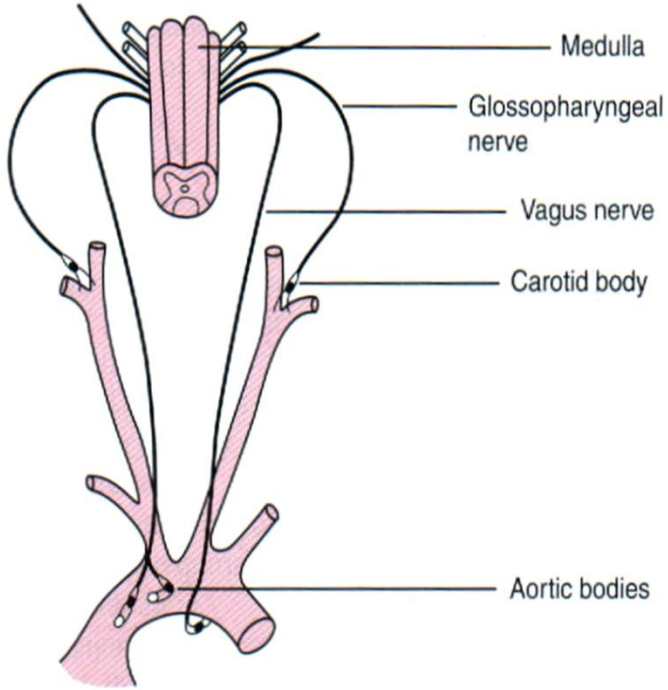
Peripheral chemoreceptors - oxygen senzors





- Glomus caroticus and aortic bodies - sensitive to change of PaO_2
  - 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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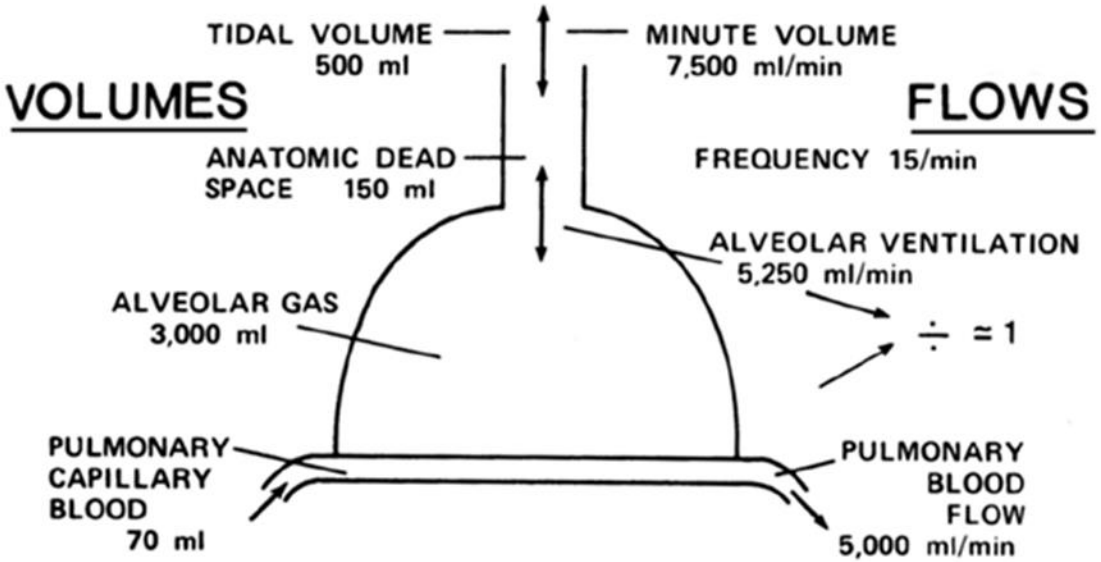
Respiratory stimuli

- 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 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)

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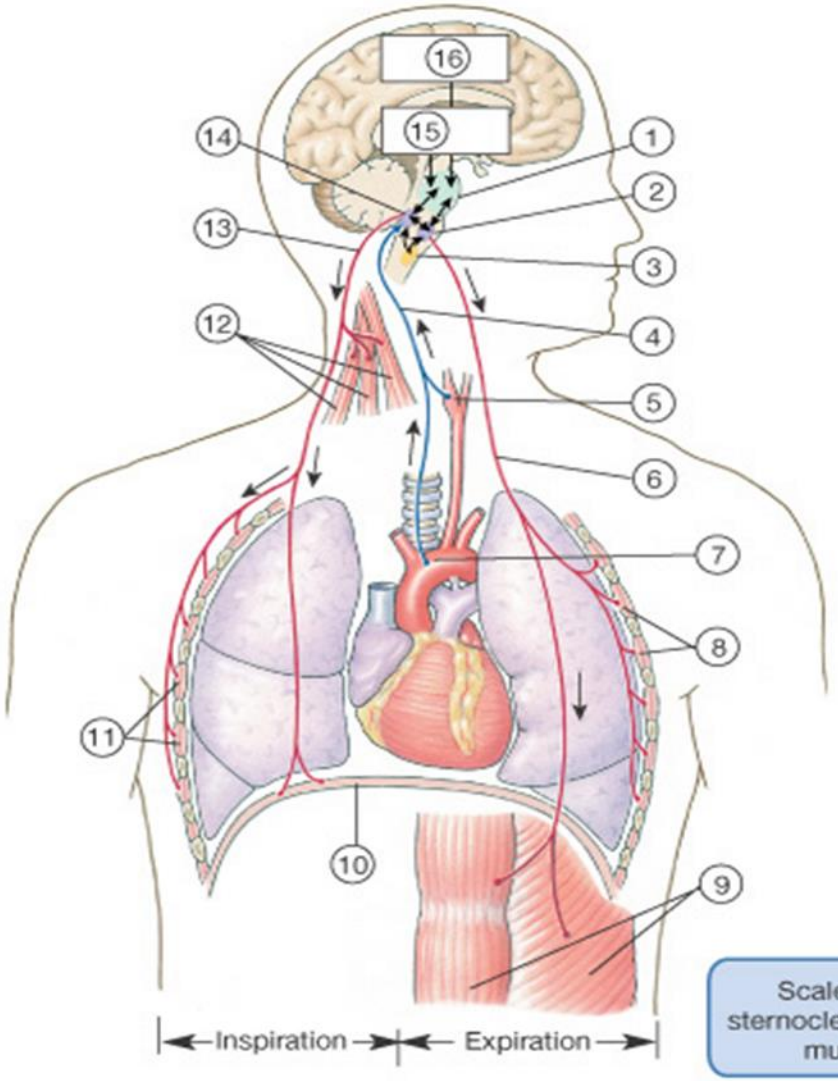
16
15
14
1
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7
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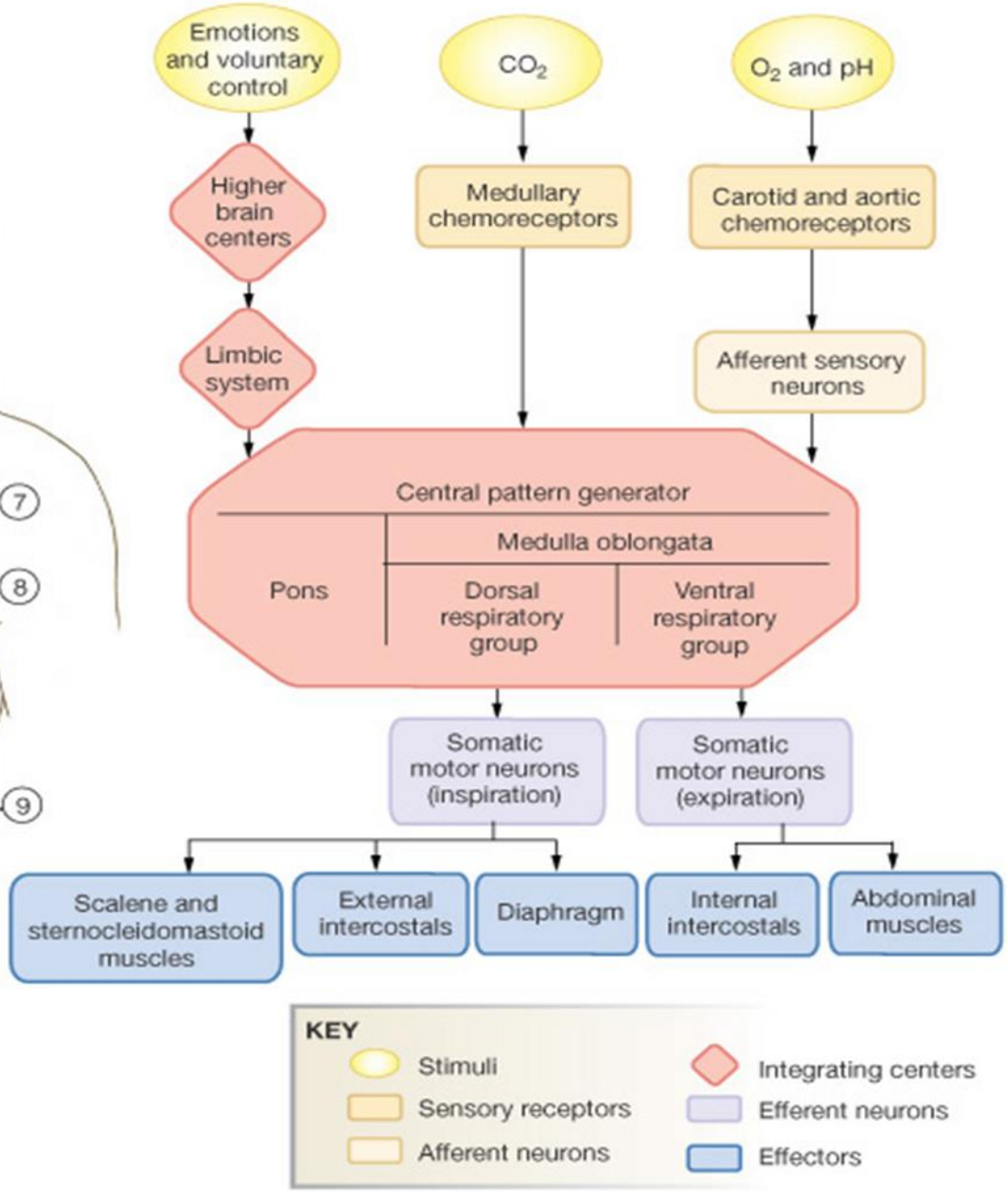
11
10
9
Inspiration
Expiration


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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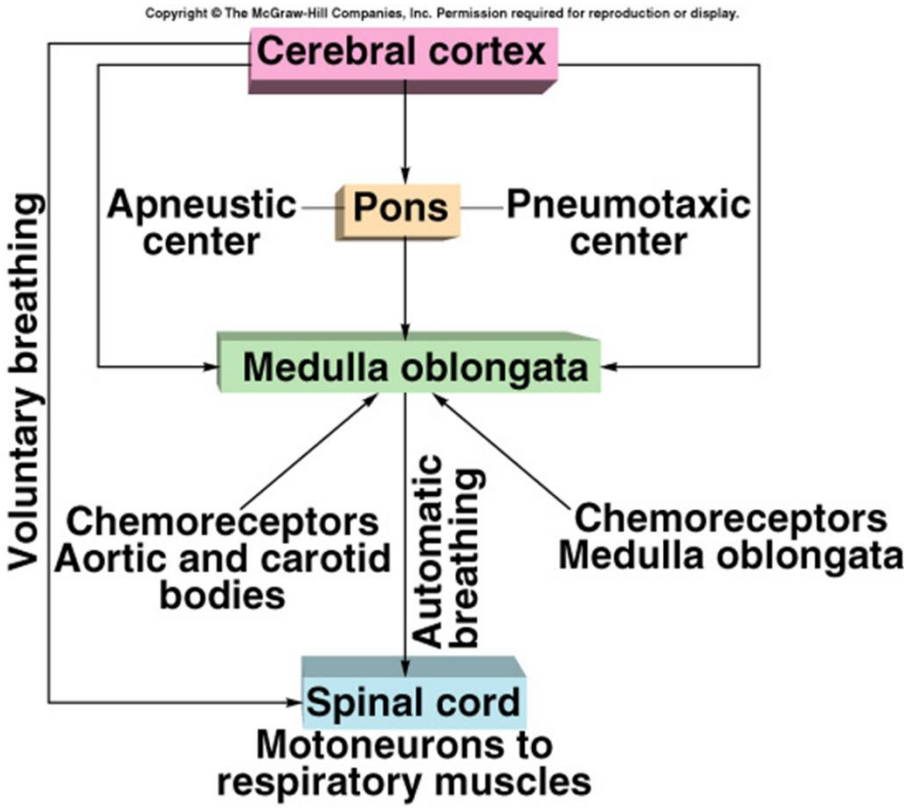
Respiratory centres



- 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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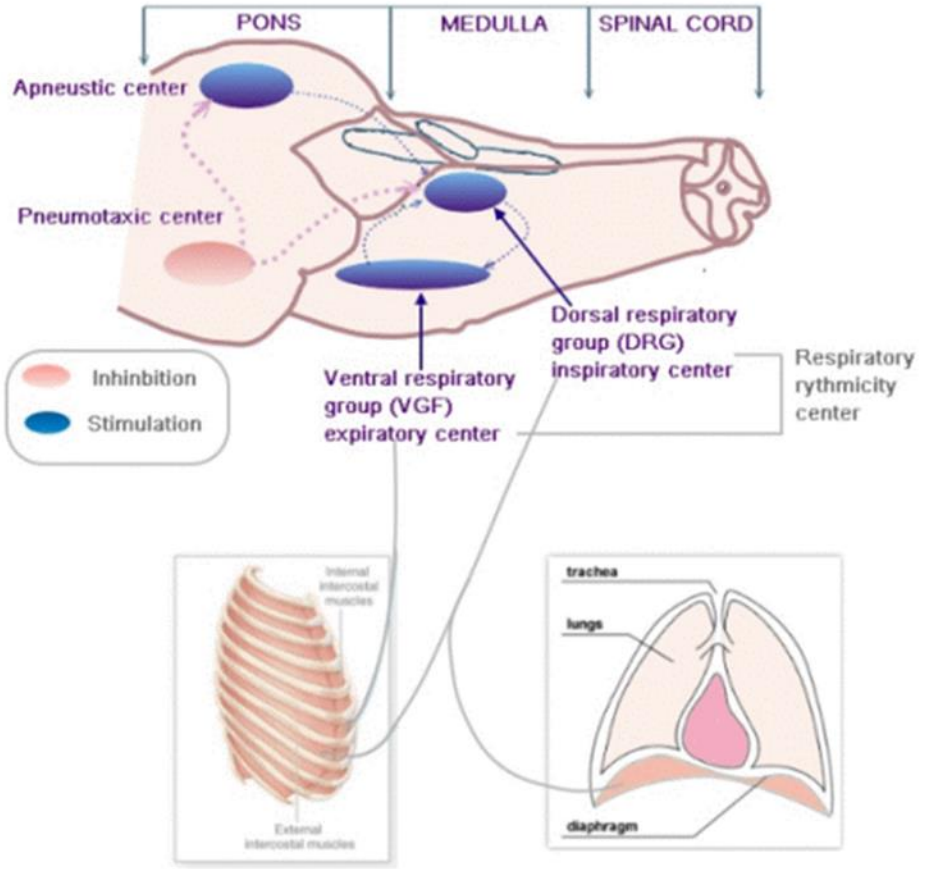
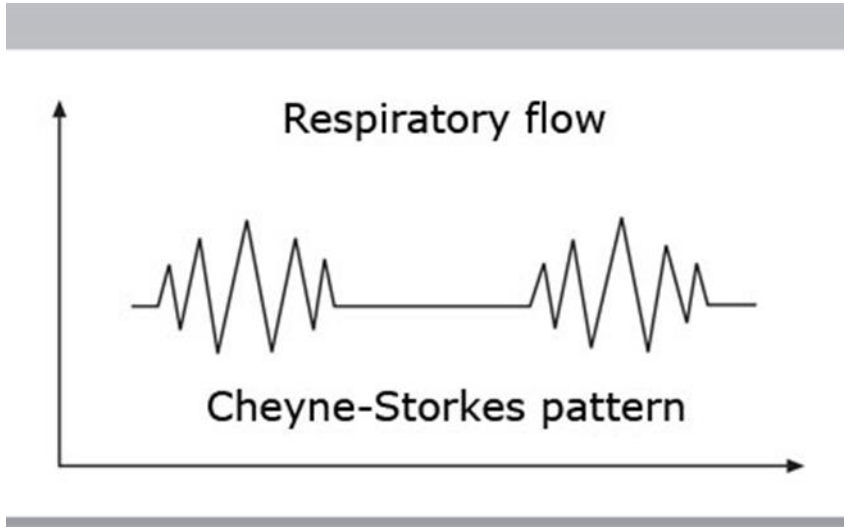
Higher respiratory centres

- 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



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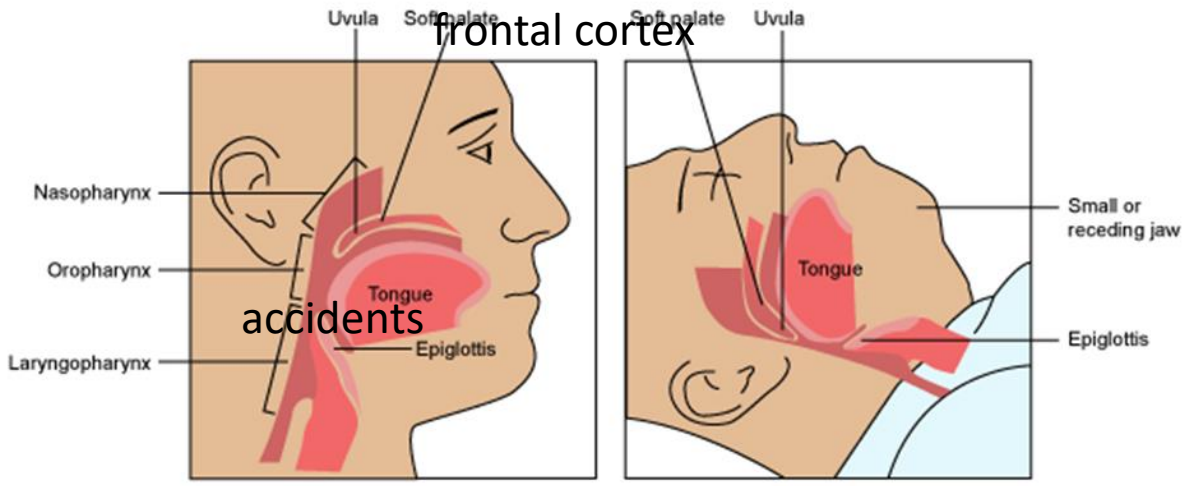
Obstructive sleep apnea (OSA)

- 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



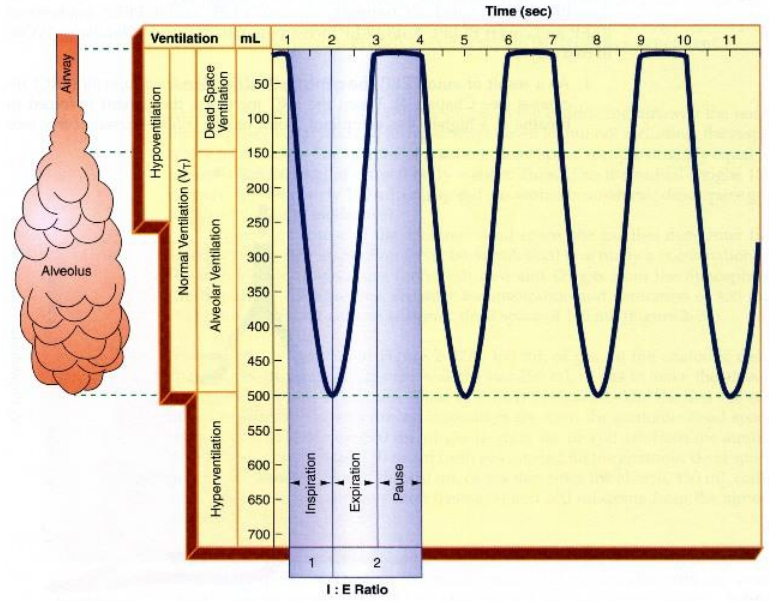


Figure 2–30. *Normal, spontaneous breathing (eupnea). The I:E ratio typically is 1:2.*

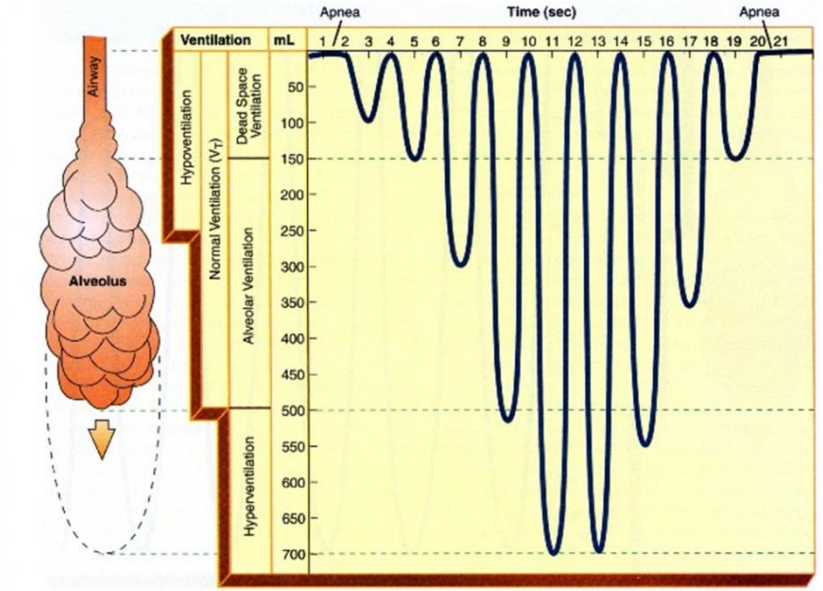


Figure 2–39. *Cheyne-Stokes respiration: A gradual increase and decrease in the volume and rate of breathing, followed by 10 to 30 seconds of apnea.*

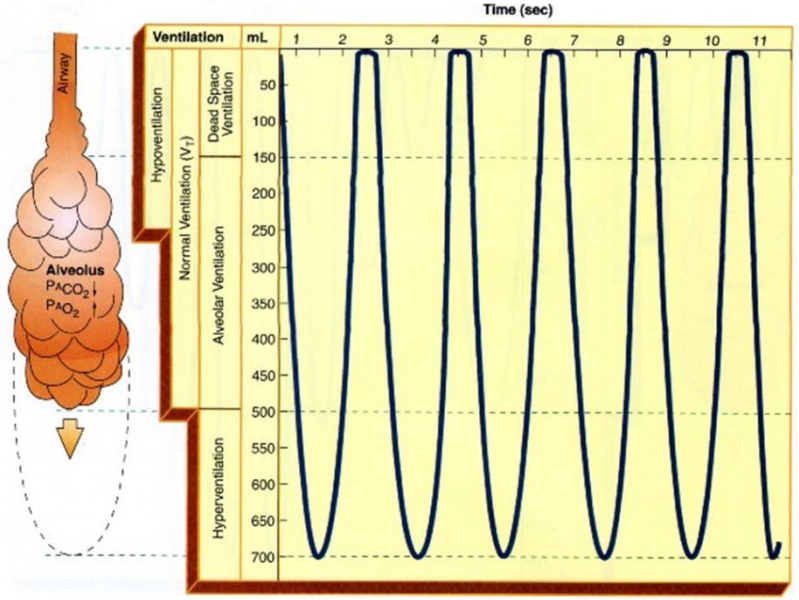


Figure 2–40. *Kussmaul's respiration: Increased rate and depth of breathing. This breathing pattern causes the $P_{A_{CO_2}}$ and Pa_{CO_2} to decrease and $P_{A_{O_2}}$ and Pa_{O_2} to increase.*

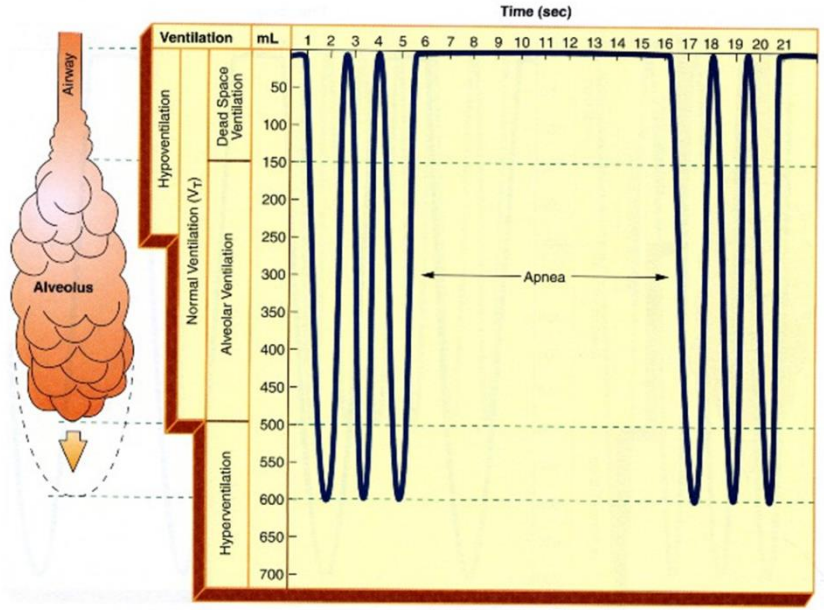


Figure 2–35. *Biot's respiration: Short episodes of rapid, uniformly deep inspirations, followed by 10 to 30 seconds of apnea.*

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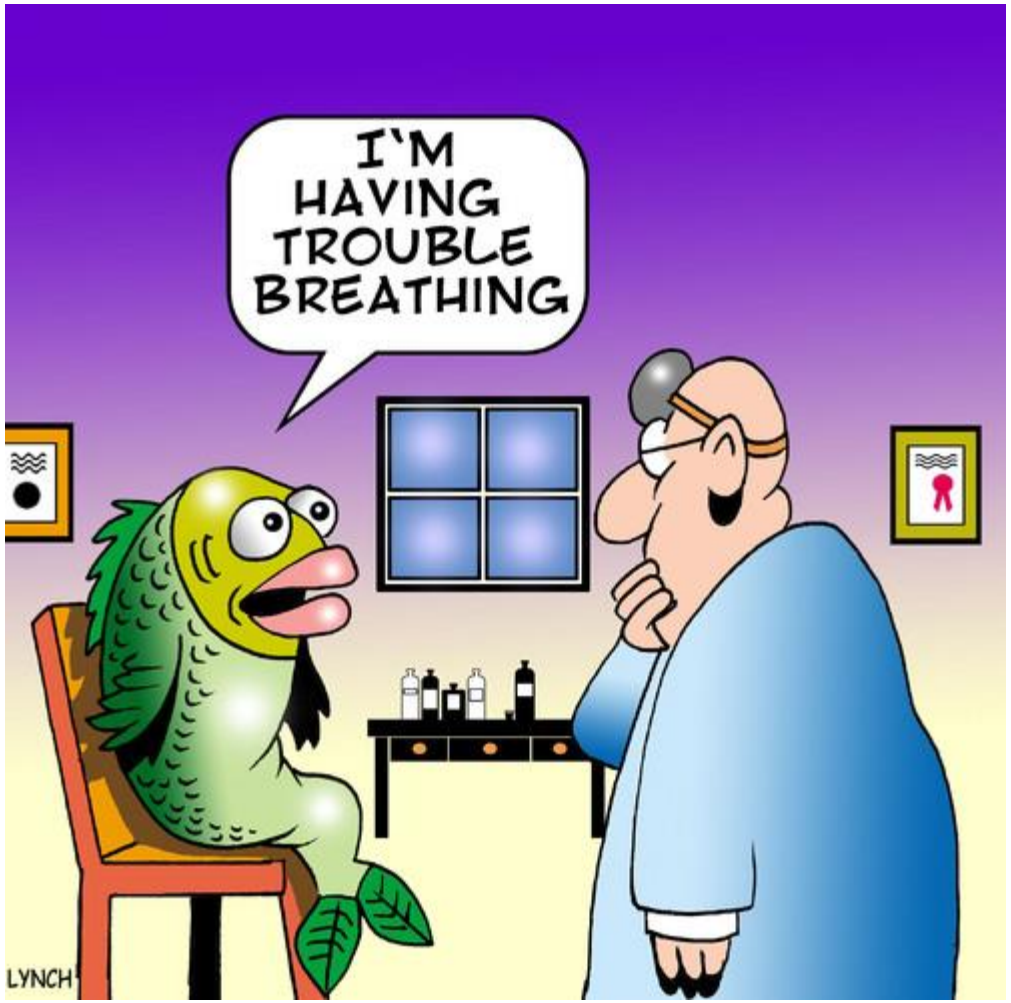

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