Pathophysiology of the respiratory system II

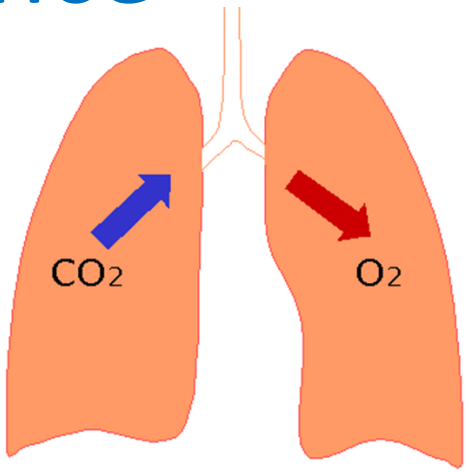
Reprační insuficience
Kontrola ventilace
Defense mechanisms of the respiratory system

Klasifikace poruch respirace

- (1) **Poruchy ventilace**: lokální nebo celk. hypoventilace
  - prostá hypoventilace (zpravidla mimoplicní příčina) (↓ V_A/Q poměru) $V'_A = (V_T - V_D) \times f$
    - CNS (intoxikace s útlumem resp. centra, úraz hlavy…)
    - obrna respir. svalů, myasthenia gravis
    - obstrukce horních dýchacích cest
  - obstrukční nemoci = zúžení dýchacích cest (↓ V_A/Q poměru, spirometrie **norm. FVC, ↓FEV1**)
    - lokalizovaná obstrukce
      - » bronchiální obstrukce (cizí těleso, nádor, zánět, uzliny..)
      - » atelektáza
    - generalizovaná obstrukce
      - » reverzibilní (astma bronchiale)
      - » ireverzibilní (CHOPN, cystická fibróza)
  - restrikční nemoci = redukce funkčního parenchymu plic nebo omezení dýchacích pohybů (spirometrie **↓ FVC, norm. FEV1**)
    - parenchymové (sarkoidóza, idip. plicní fibróza, pneumokoniózy, bronchopneumonie)
    - extraparenchymové (deformity hrudní stěny, páteře)
  - kombinované
- (2) **Poruchy difúze**: ztluštění alveolokapilární membrány
  - plicní fibróza
  - pneumokoniózy
    - silikóza, azbestóza,…
  - bronchopneumonie
- (3) **Poruchy perfuze** (Q): ↑ V_A/Q poměru (plicní zkrat)
  - plicní embolie
  - hypotenze

RESPIRAČNÍ INSUFICIENCE

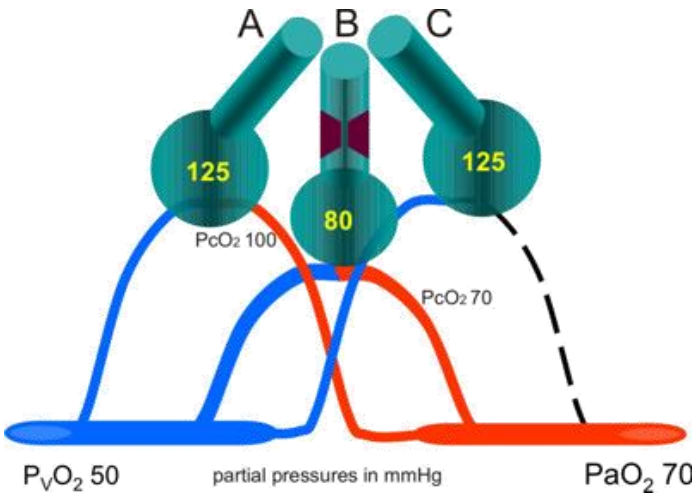
Respirační insuficience

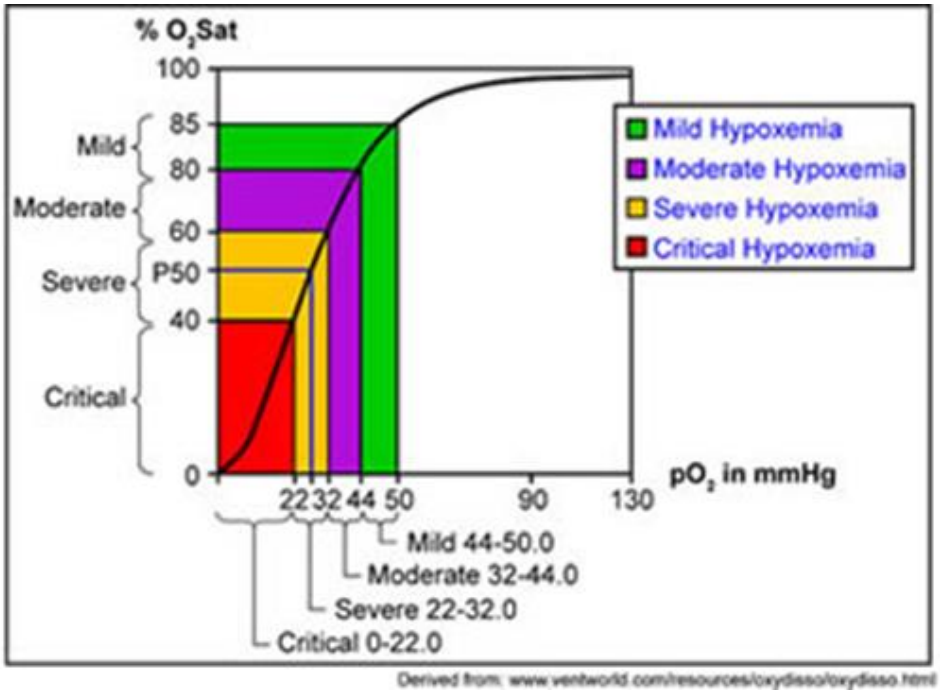


- prakticky všechny druhy respiračních poruch mohou vyústit do RI
  - tíže nemocí se hodnotí podle jejich efektu na výměnu plynů
- cílem respirace je dosažení optimálních hodnot krevních plynů jejich výměnou s okolím, proto jsou hl. kritérii resp. insuficience hodnoty kr. plynů
  - ↓paO_2 (hypoxémie) je konstantní součástí
    - a tím pádem rovněž pokles saturace hemoglobinu
      - pulzní oxymetrie!
  - ↑$paCO_2$ (hyperkapnie) jen někdy, často normo- či dokonce hypokapnie
- klasifikace resp. insuficience
  - I. typ neboli parciální neboli hypoxemická (↓paO_2 <10 kPa a normo či ↓$paCO_2$)
    - selhání oxygenace
  - II. typ neboli globální neboli ventilační (↓paO_2 <8kPa a ↑$paCO_2$ >6 kPa)
    - selhání mechanické ventilace
      - kompenzovaná – normální hodnota pH krve (vzestup bikarbonátů)
      - dekompenzovaná – pokles pH krve pod 7,36 (respirační acidóza)

Proč se O_2 a CO_2 chová odlišně

- naprostá většina plicních patologií s různým VA/Q (ne)poměrem způsobuje hypoxémii
- zda bude přítomna i hyperkapnie ovlivňuje
  - různá difuzibilita O_2 a CO_2
    - poruchy difuze zpravidla nevedou k hyperkapnii
  - rychlost ekvilibrace O_2 a CO_2 v plicní kapiláře
    - zrychlení průtoku ovlivní O_2 více
  - různá forma transportu O_2 a CO_2 krví
    - hyperventilace sníží PCO_2, ale vzhledem k tomu, že hemoglobin je 100%je saturován již při normální ventilaci, není další zvýšení účinné





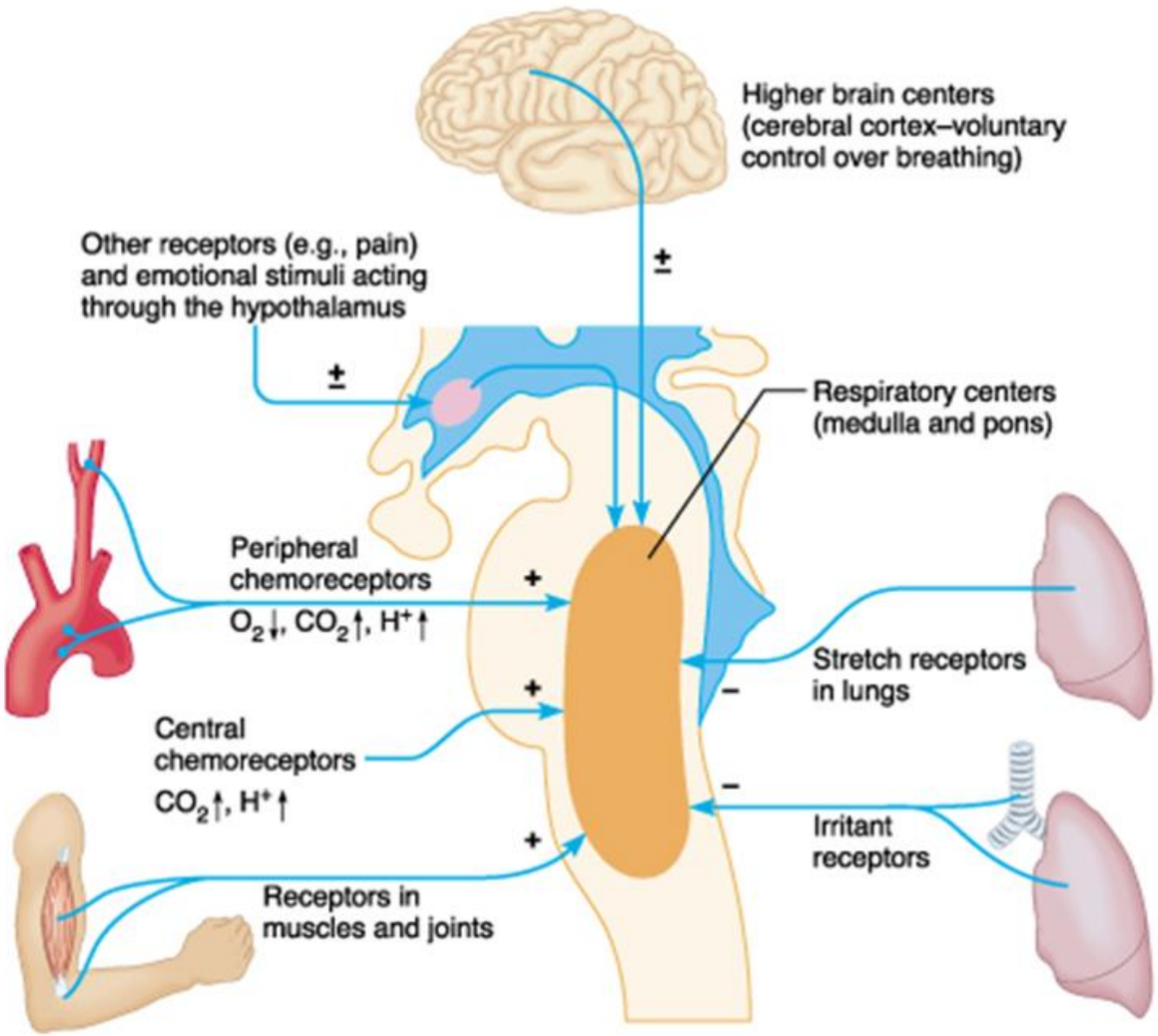
Respirační insuficience

- mimoplicní důvody změny paO_2 (hypoxemie) se zpravidla mezi RI neřadí
  - kardiovaskulární (zejm. srd. vady s pravolevým zkratem)
- klasifikace RI
  - latentní RI: hodnoty krevních plynů v klidu jsou normální, zhoršují se při zátěži
  - manifestní RI: hodnoty krevních plynů jsou patologické již v klidu
- průběh:
  - akutní: náhlý vznik
    - aspirace cizího tělesa, pneumotorax, astmatický záchvat, ARDS, plicní edém aj.
  - chronická: pomalu progredující, projevy kompenzace
    - CHOPN, plicní fibrózy, cystická fibróza
  - chronická s akutním zhoršením: exacerbace CHOPN

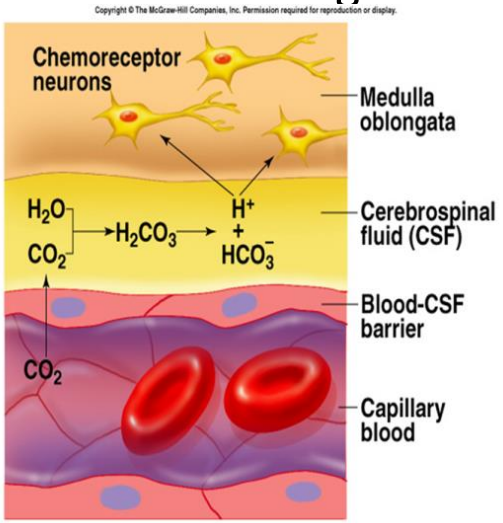
- diagnostika respirační insuficience
  - vyšetření krevních plynů a acidobazické rovnováhy (Astrup)
    - arteriální krev (a.radialis, a. cubitalis, a. femoralis)
    - arterializovaná krev (ušní lalůček)
    - kapilární krev (bříška prstů) – nepřesné
  - parametry:
    - pH krve – norma 7,36-7,44
    - paO_2 – parciální arteriální tlak kyslíku
    - $paCO_2$ – parciální arteriální tlak oxidu uhličitého
    - HCO_3 - bikarbonáty (norma 22,0-26,0 mmol/l)
    - BE – výchylka bazí (přebytek nebo nedostatek)
    - $SatO_2$ – nasycení hemoglobinu kyslíkem (norma > 90%)

CONTROL OF RESPIRATION & ITS DISORDERS

Control of respiration

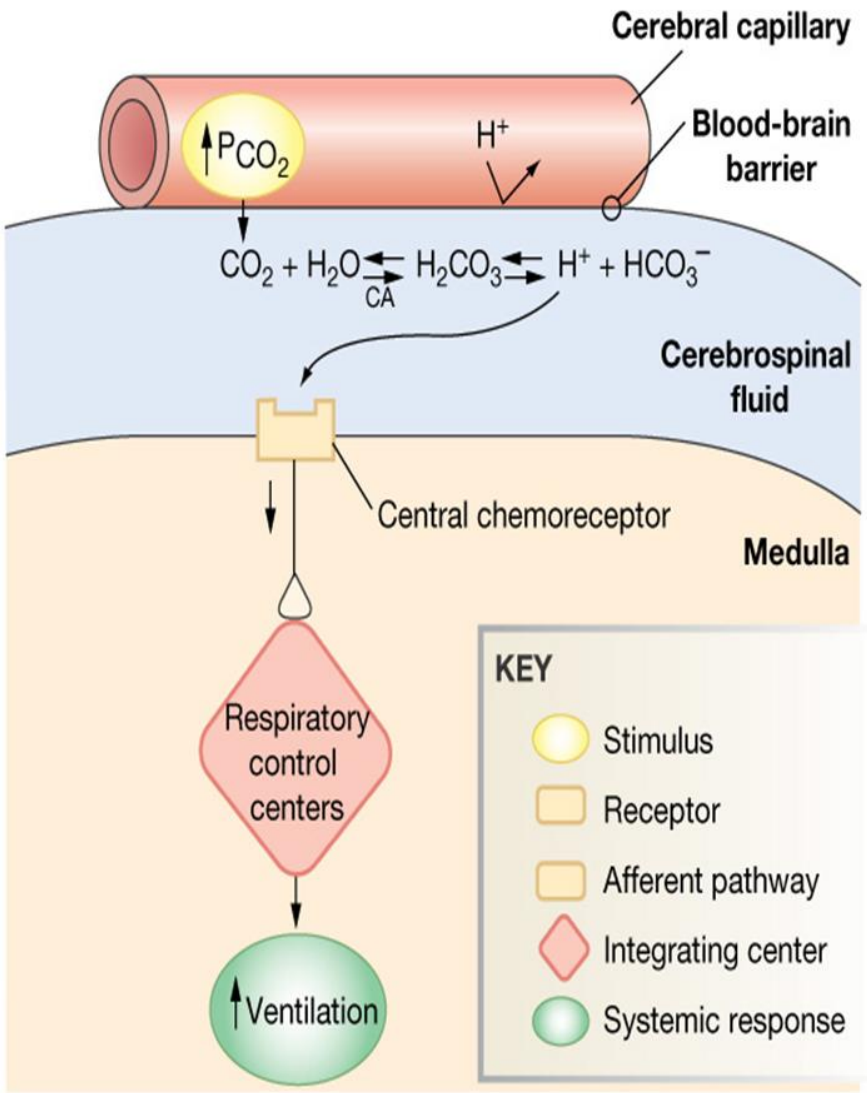


- central chemoreceptors in medulla oblongata



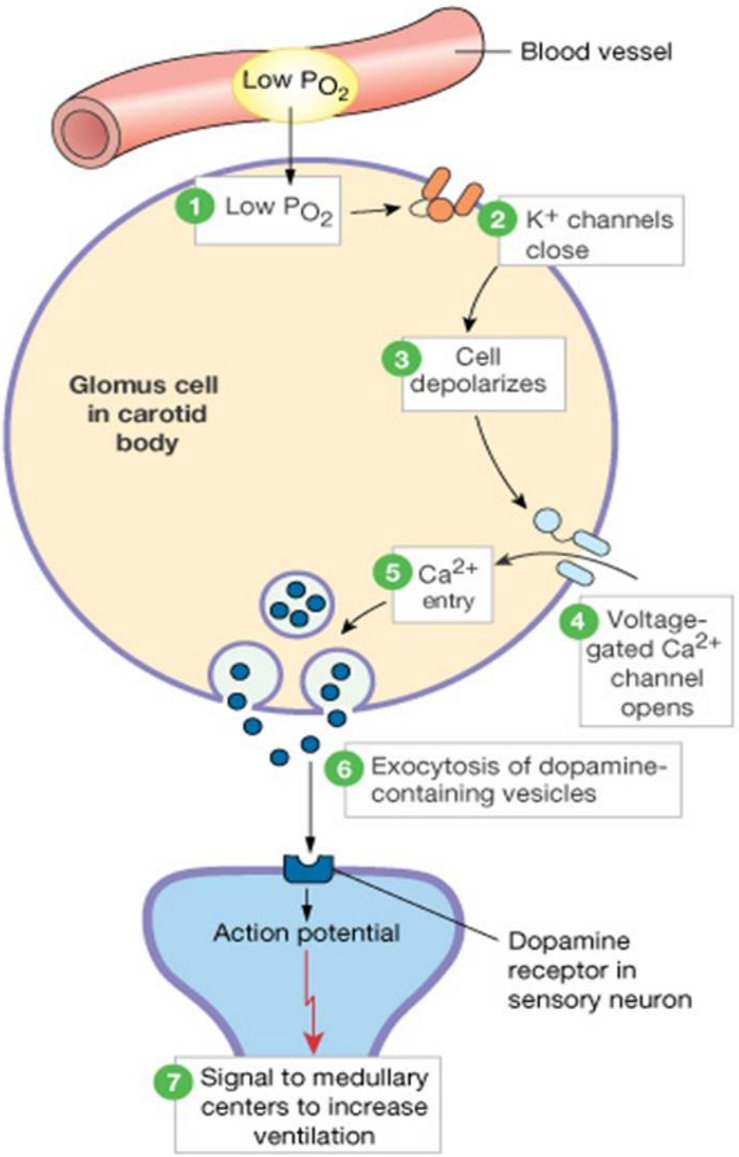
- peripheral chemoreceptors in aorta and glomus caroticum (via n. glossopharyngeus and vagus)
  - active when $\downarrow PaO_2$ below 10kPa
  - activation supported by hypercapnia
- pulmonary mechanoreceptors

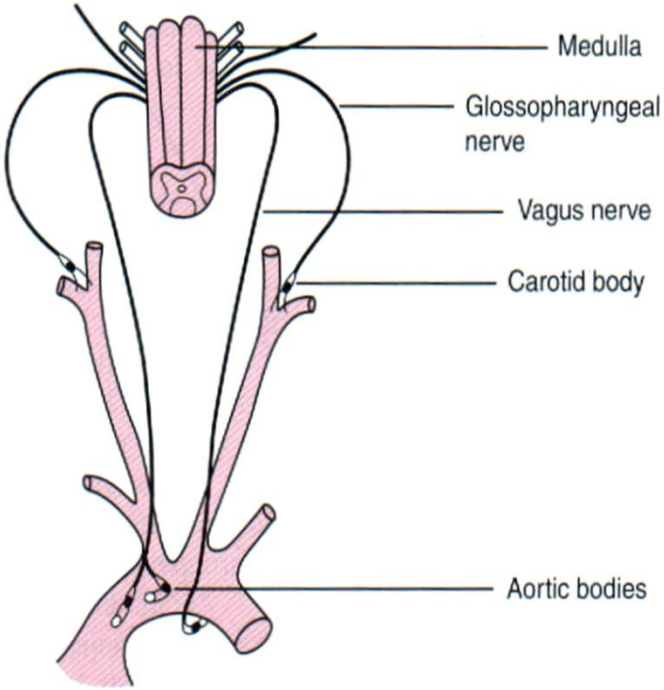
Central chemoreceptors



- 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) breathing
- very quick adaptation to acute or intermittent hypercapnia, however, gets adapted to chronic hypercapnia due to ↑HCO_3- in cerebrospinal fluid
  - problem in COPD - in these patients hypoxaemia is the chief stimulus to respiratory drive
  - oxygen treatment may therefore reduce respiratory drive and lead to a further rise in $PaCO_2$

Peripheral chemoreceptors - oxygen senzors

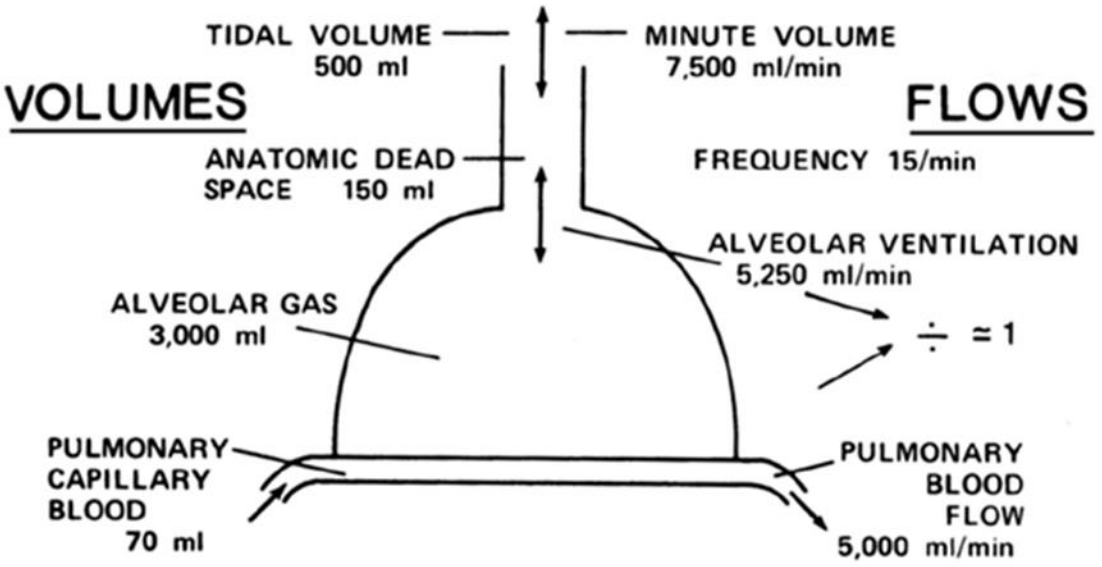




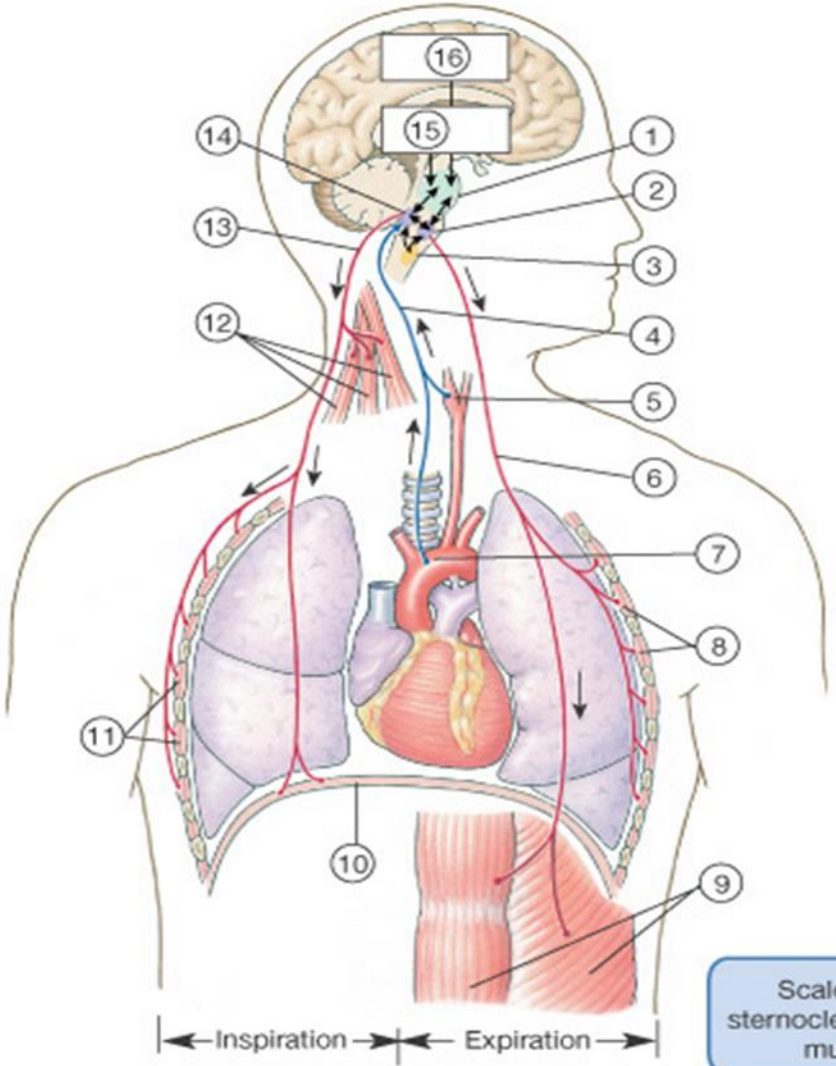
- Glomus caroticus and aortic bodies - sensitive to change of $Pa0_2$
  - decrease of 0_2 in these cells closes K^+ channels → depolarization → ↑ intracellular Ca^{2+} → excitation → activation of the respiratory centre
- When hypoxemia is not accompanied with hypercapnia, activation of this sensors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

Respiratory stimuli

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



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


16
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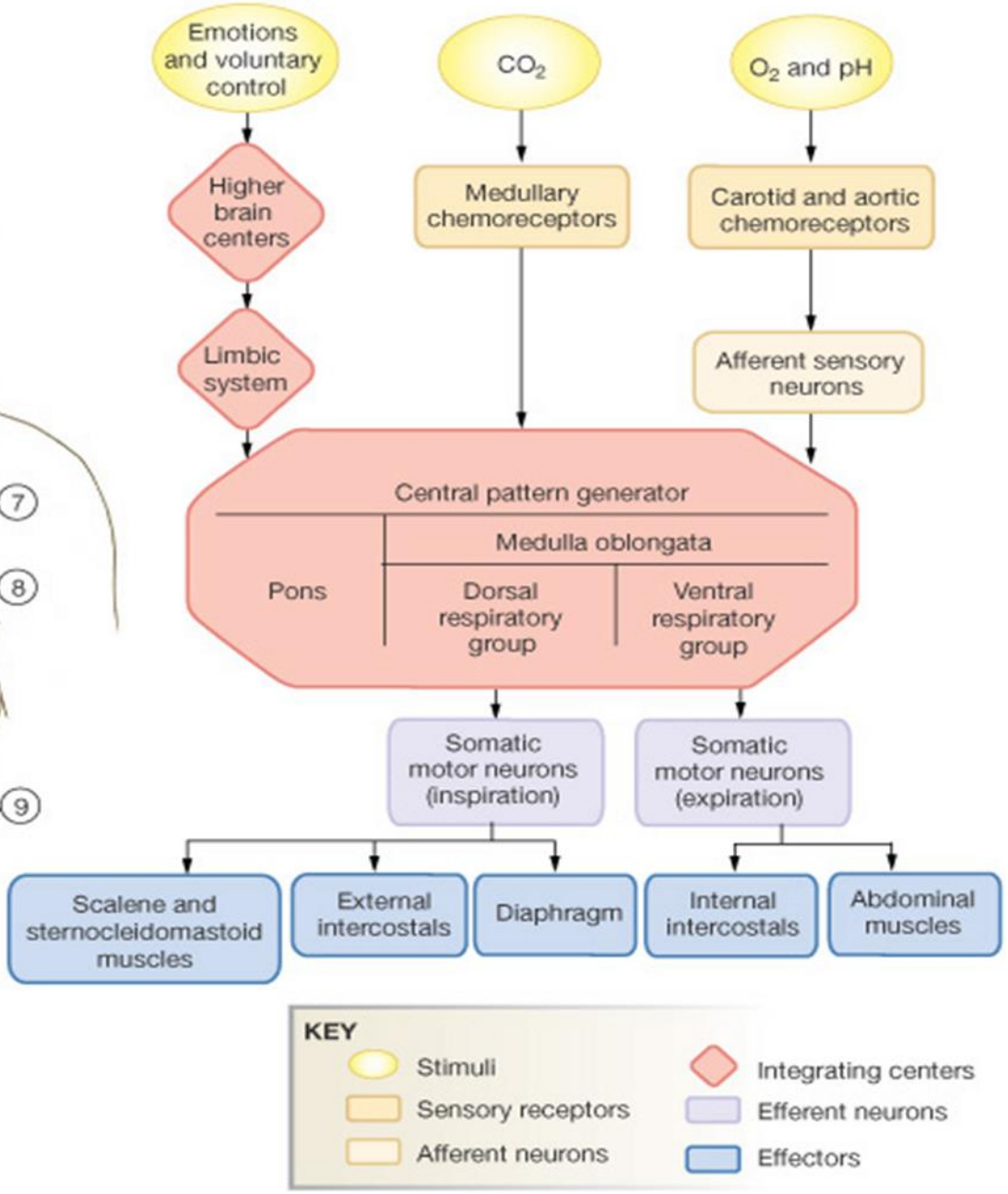
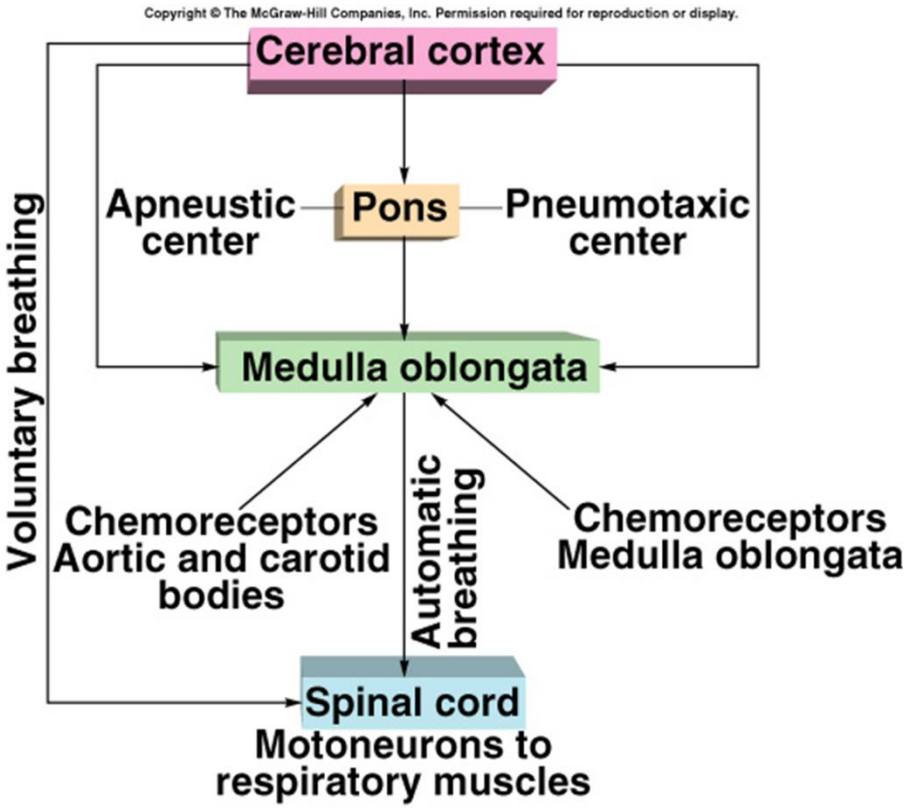
Inspiration
Expiration


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

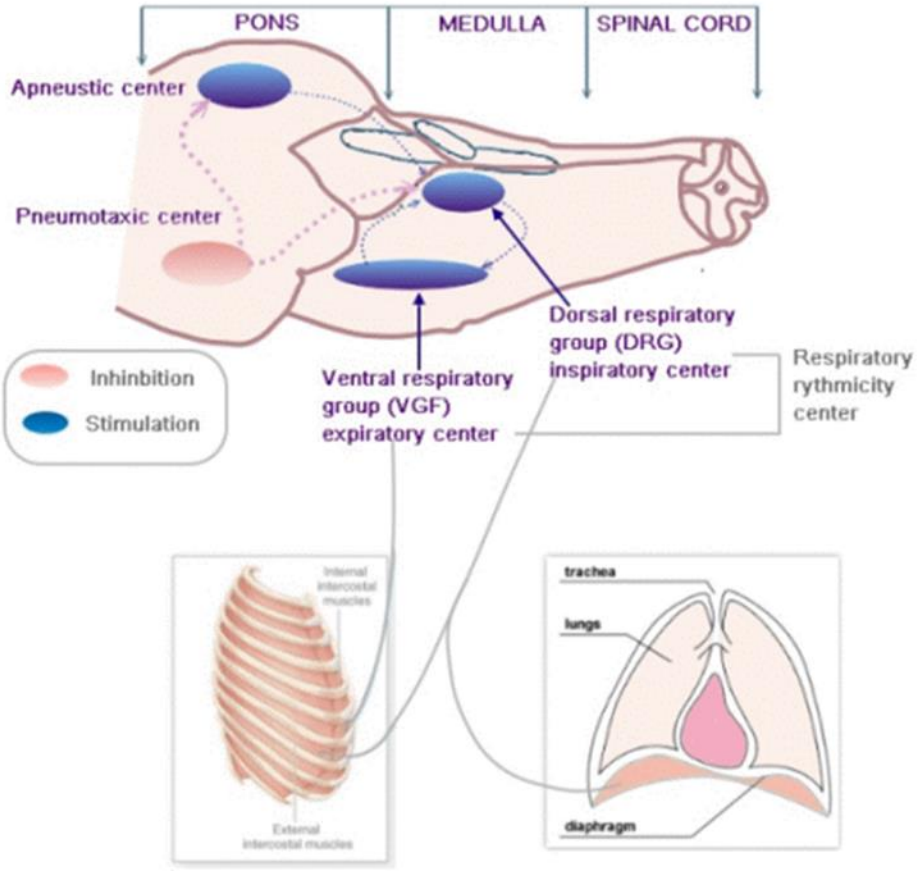
Respiratory centres



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

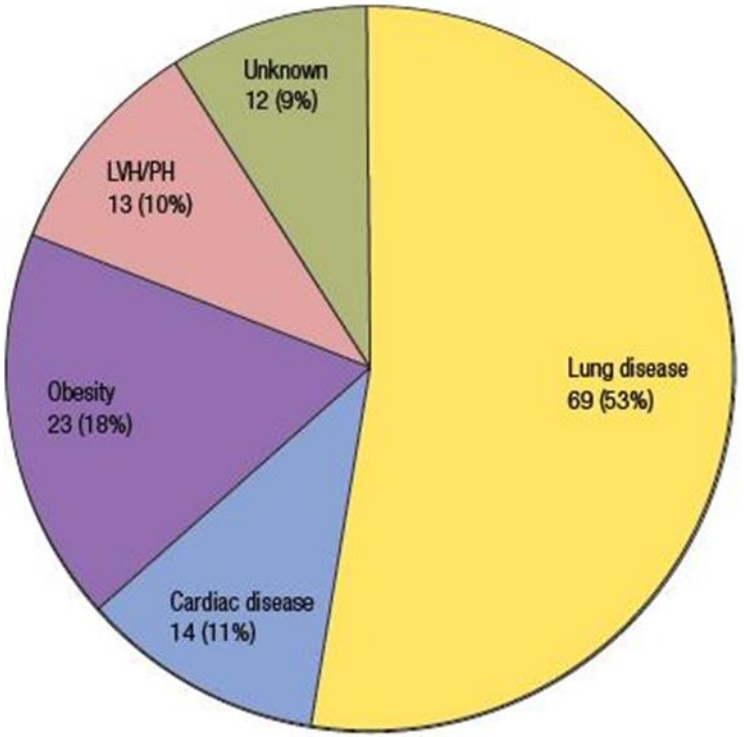
Higher respiratory centres

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

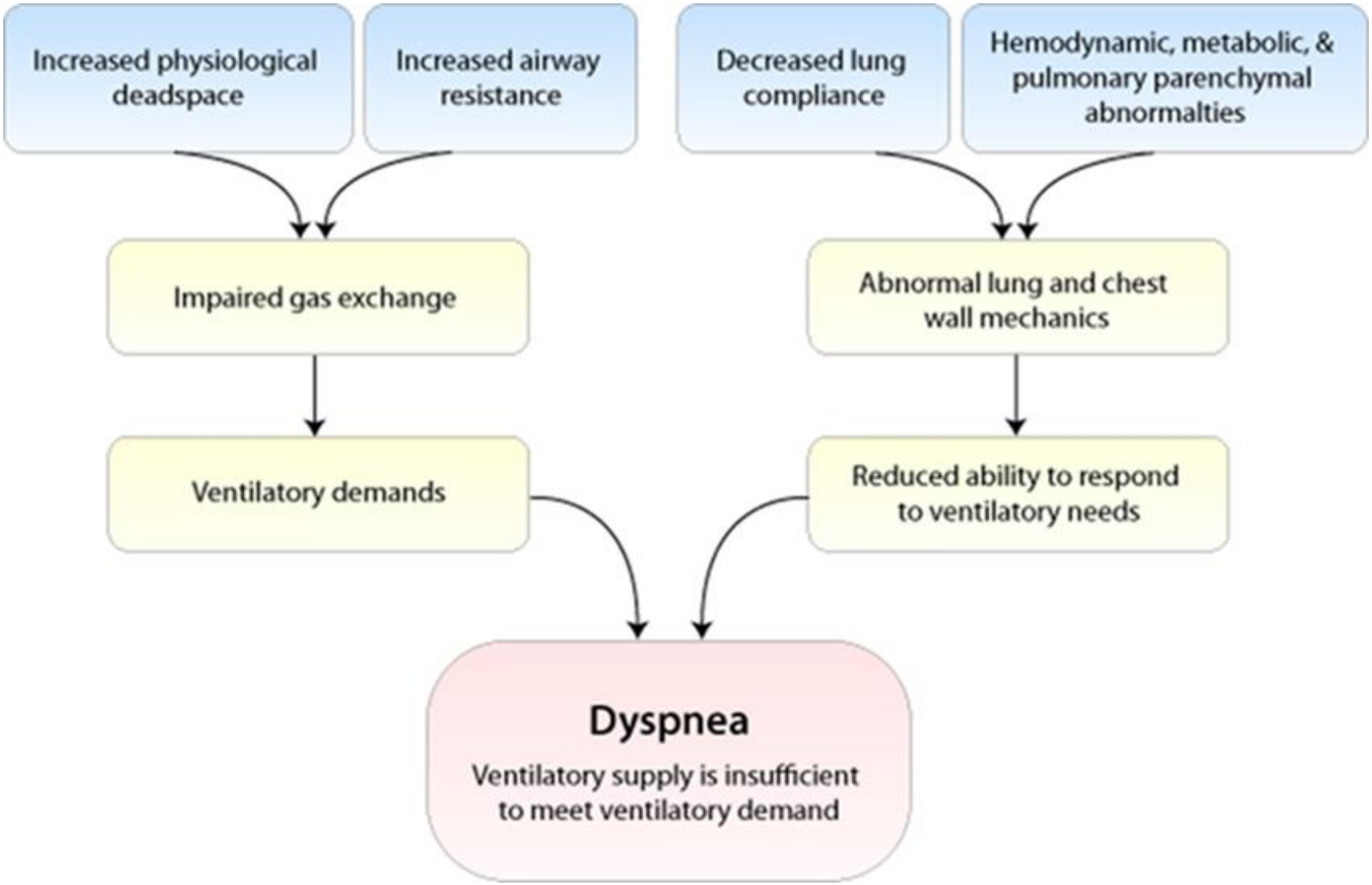


Dyspnea (breathlessness)

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

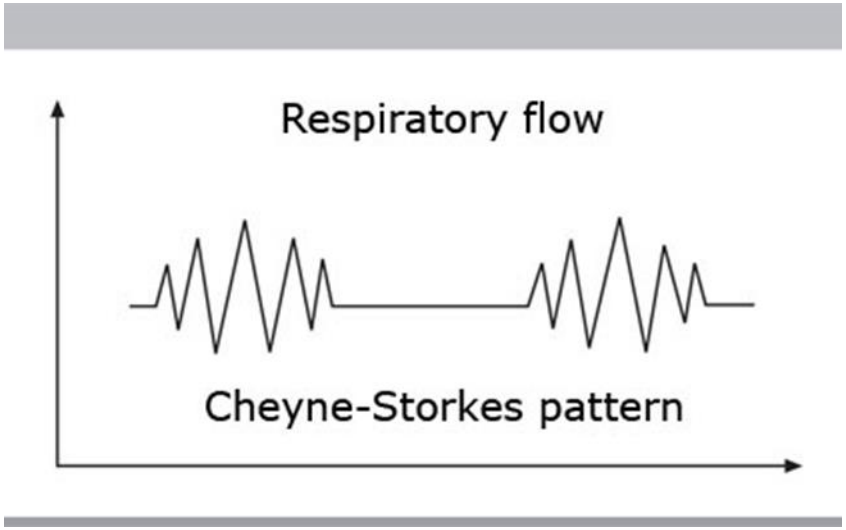


common causes of dyspnea


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

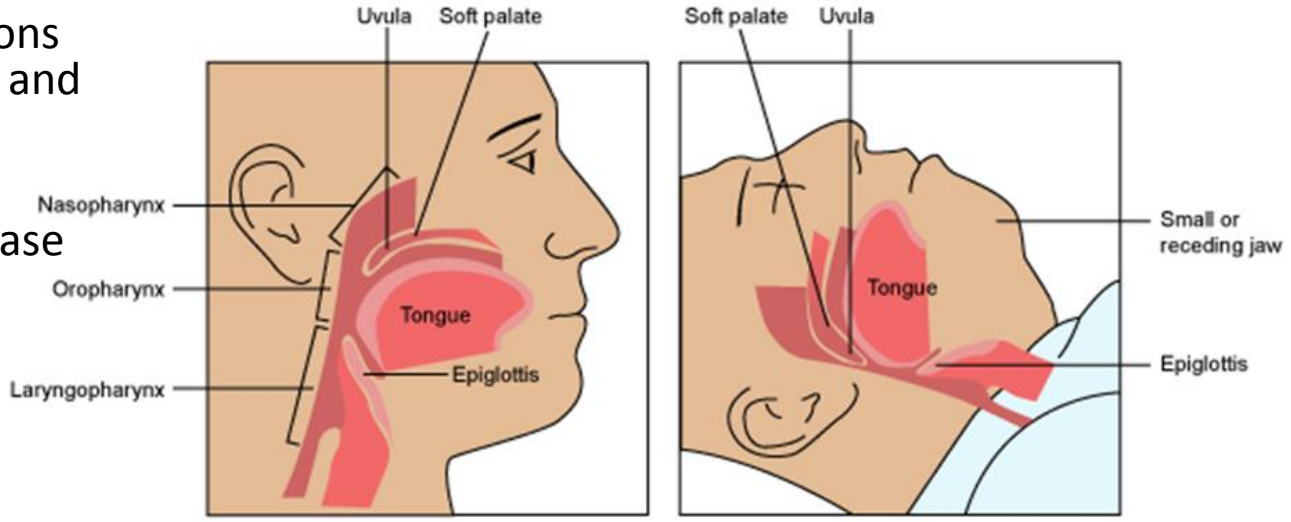
Apnea

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



Obstructive sleep apnea (OSA)

- Flow of air pauses or decreases during sleep because the airway has become narrowed, blocked, or floppy
  - breathing pauses can last from a few seconds to minutes
  - may occur 30 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 hypoxia
  - changes in the neurons of the hippocampus and frontal cortex
  - hypertension
  - coronary artery disease
  - type 2 diabetes
  - depression
  - sleepiness-related accidents



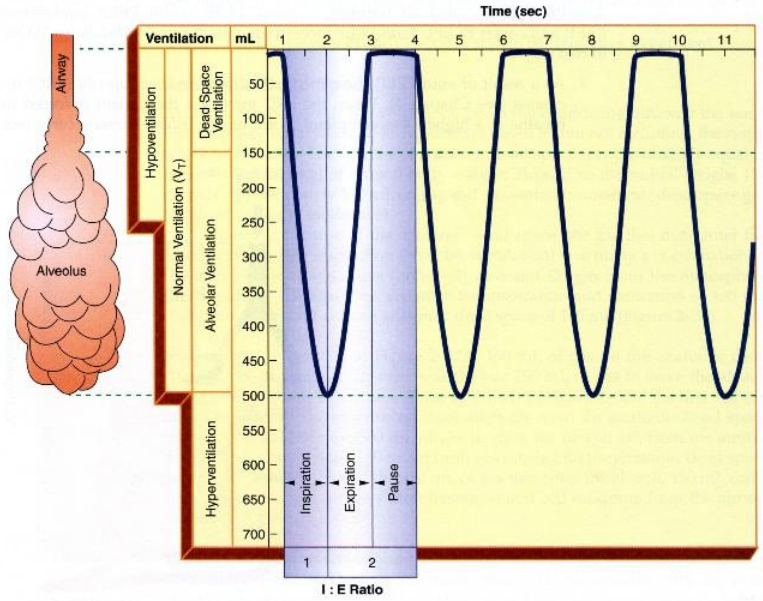


Figure 2–30. *Normal, spontaneous breathing (eupnea). The I:E ratio typically is 1:2.*

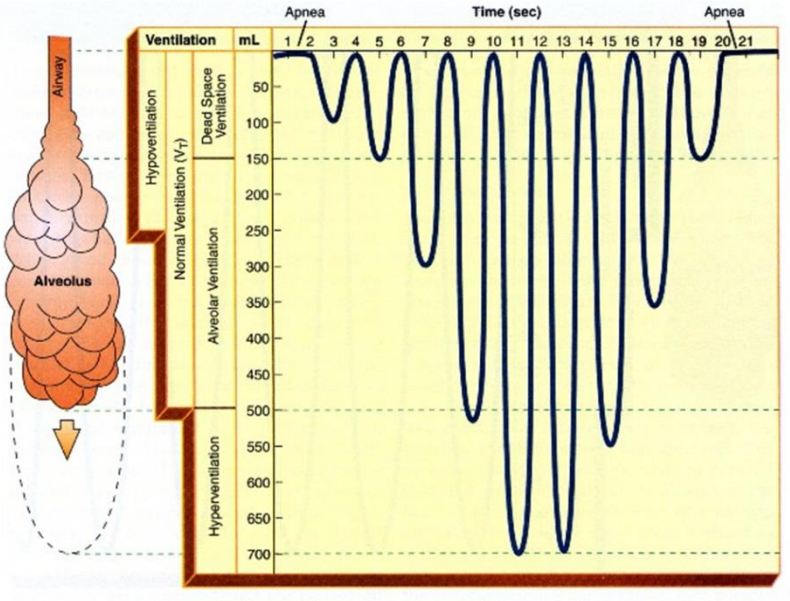


Figure 2–39. *Cheyne-Stokes respiration: A gradual increase and decrease in the volume and rate of breathing, followed by 10 to 30 seconds of apnea.*

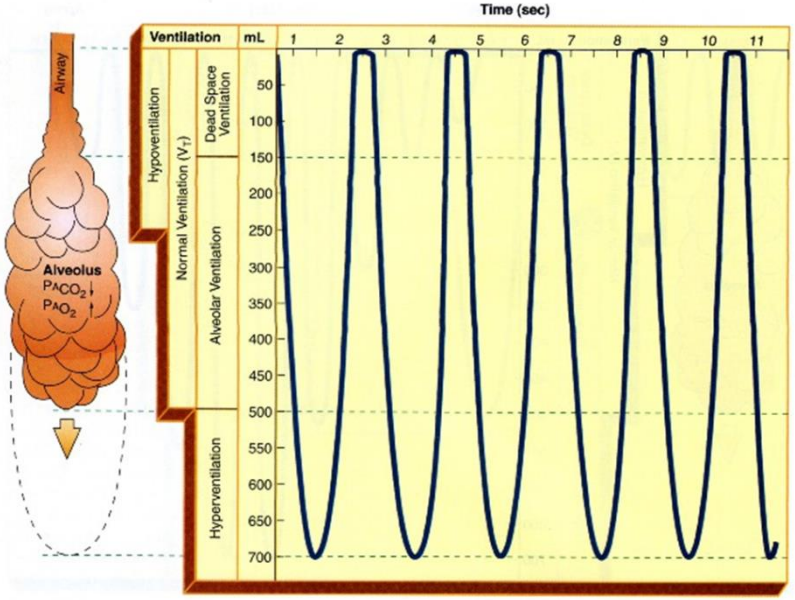


Figure 2–40. *Kussmaul's respiration: Increased rate and depth of breathing. This breathing pattern causes the $P_{A_{CO_2}}$ and Pa_{CO_2} to decrease and $P_{A_{O_2}}$ and Pa_{O_2} to increase.*

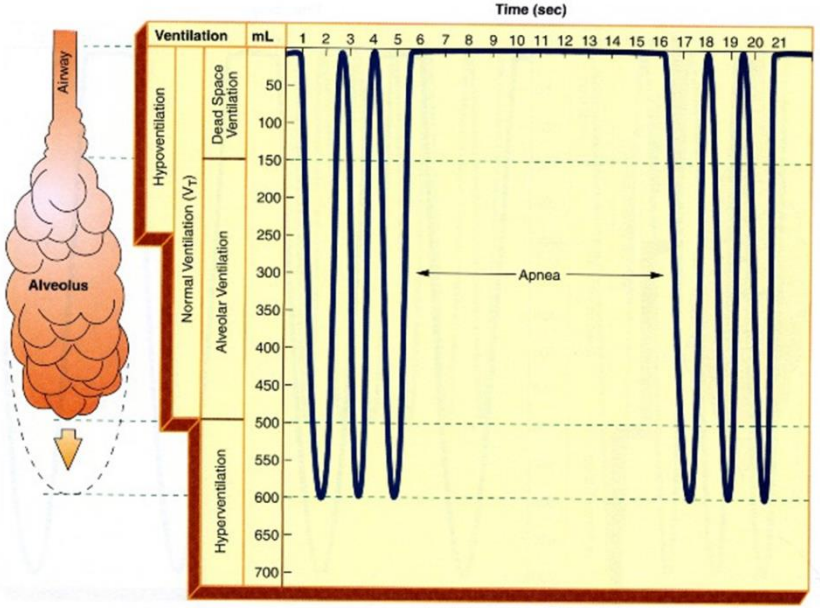
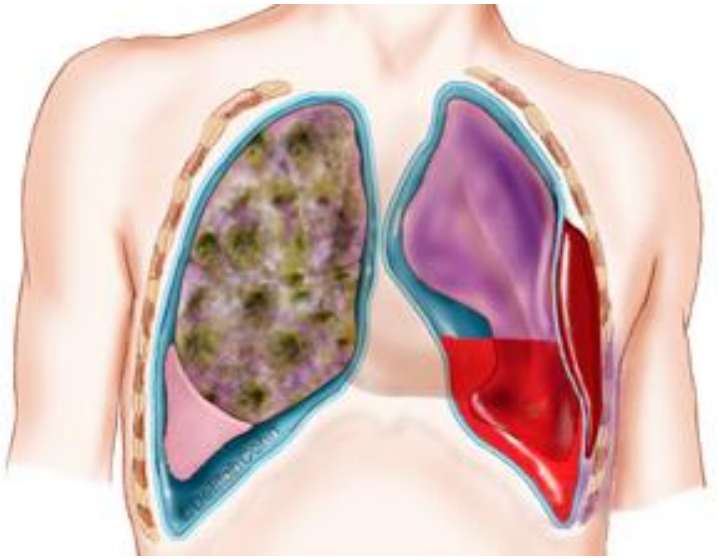


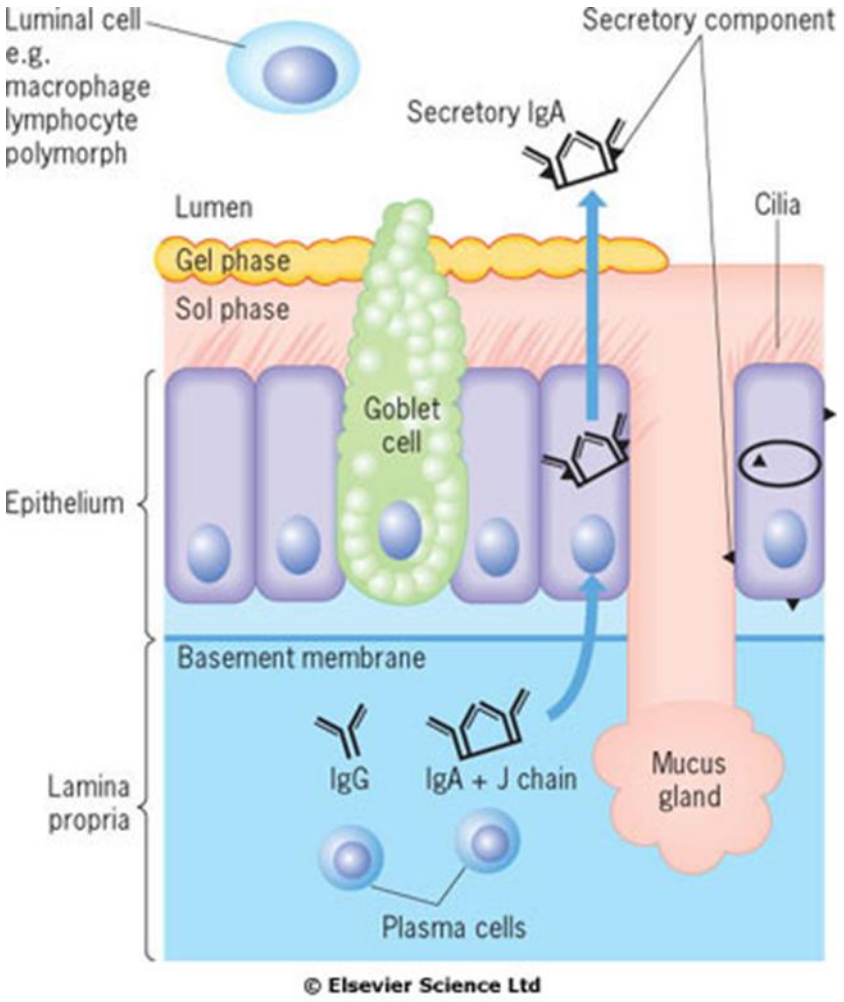
Figure 2–35. *Biot's respiration: Short episodes of rapid, uniformly deep inspirations, followed by 10 to 30 seconds of apnea.*



(acute) LUNG INJURY (incl. ARDS and INFECTION) AND REPAIR

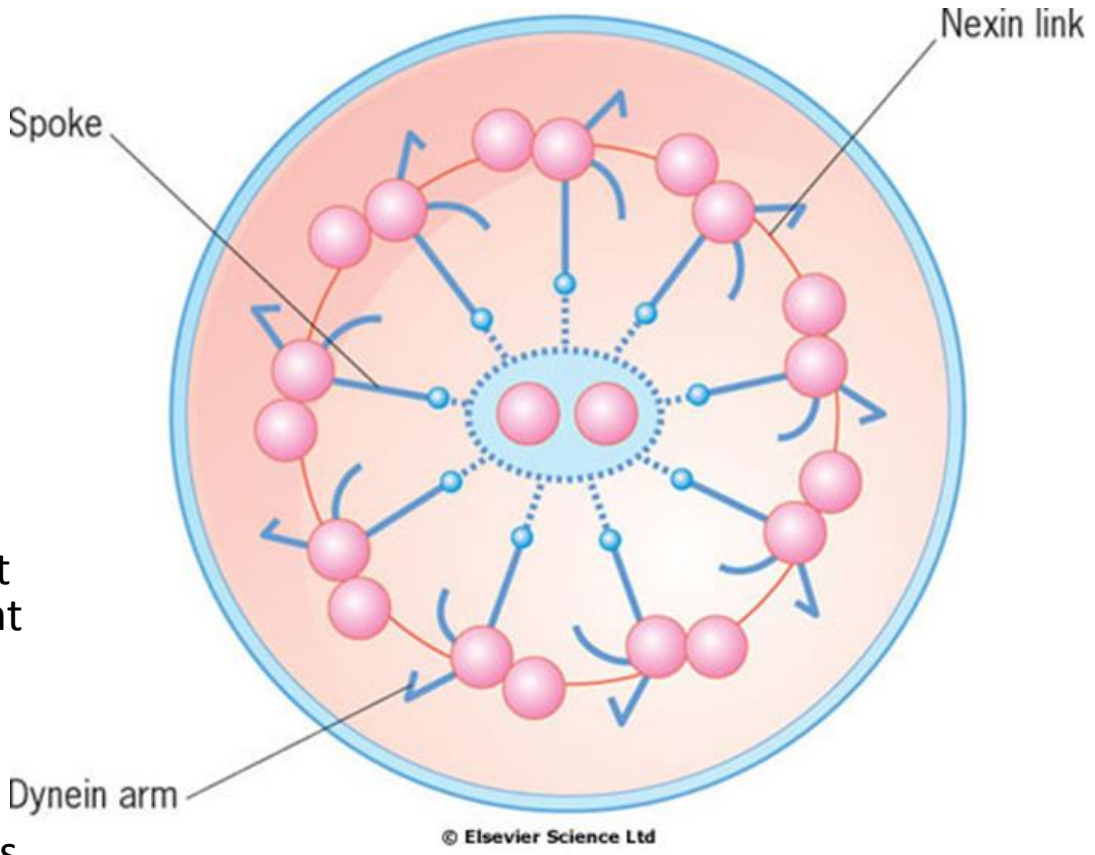
Defense mechanisms of the resp. tract

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



The ciliated epithelium

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



Respiratory tract secretions - mucus

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

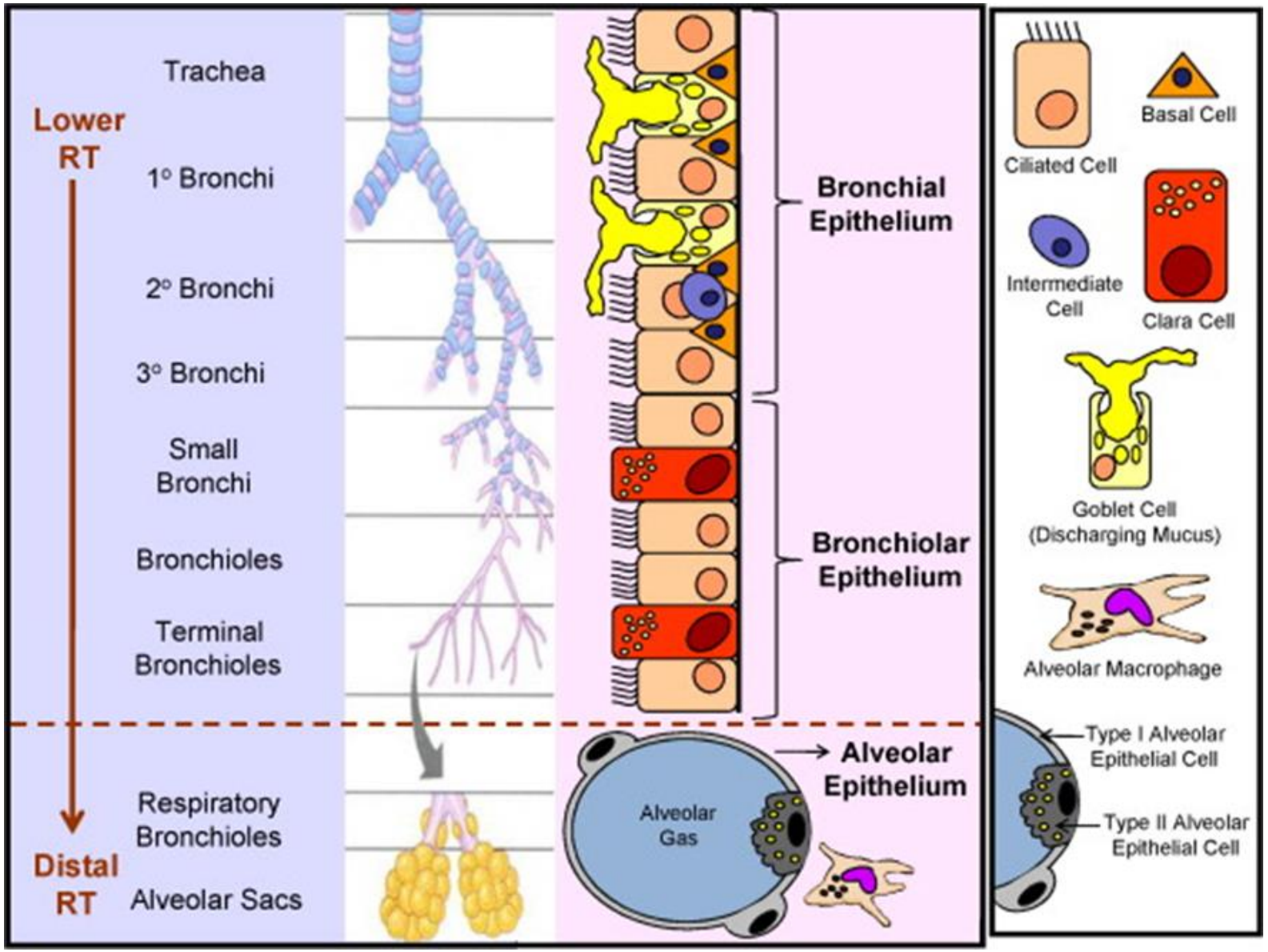
Humoral defense mechanisms

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

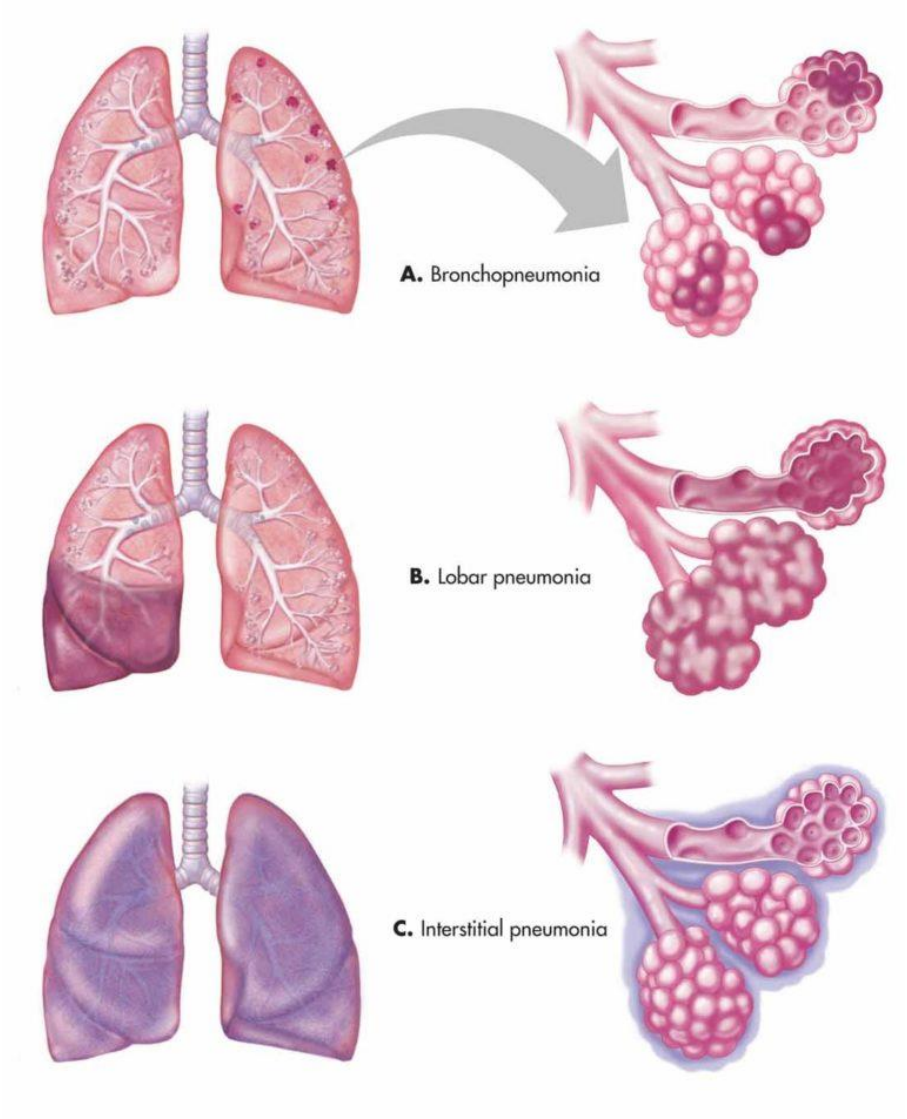
Cellular defense mechanisms

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

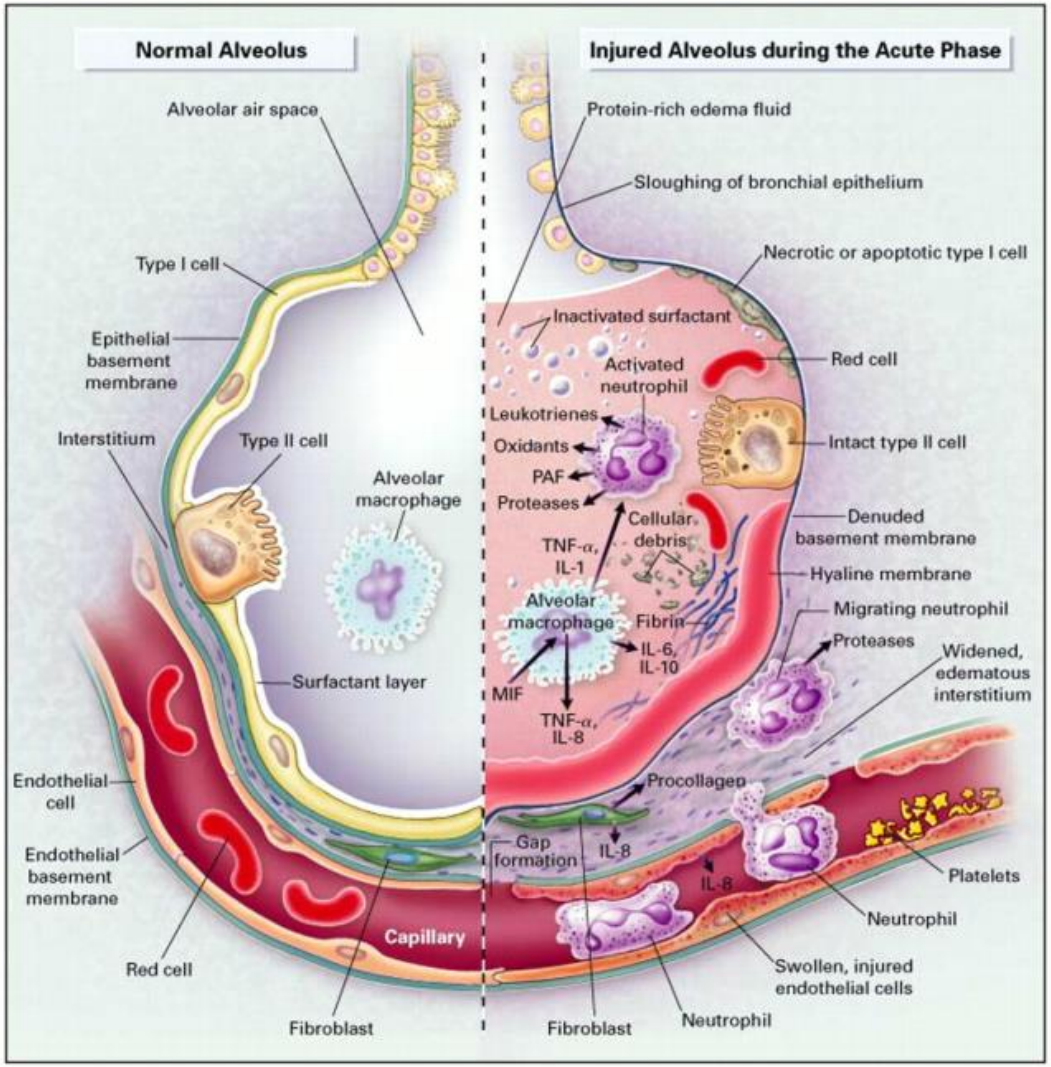
Summary – lung defense



Bronchopneumonie

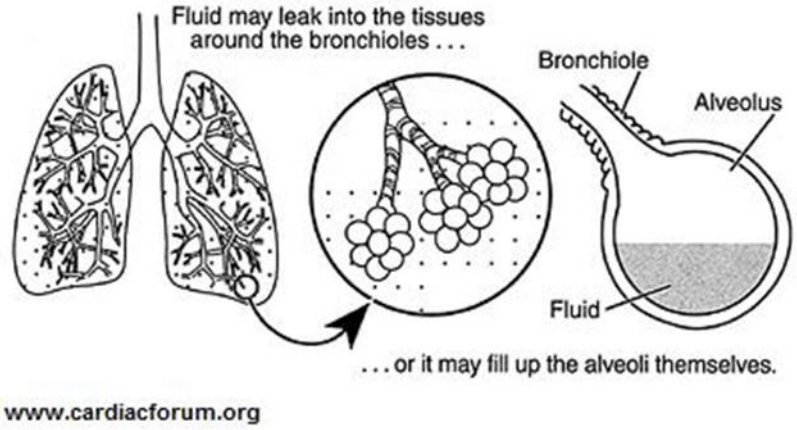


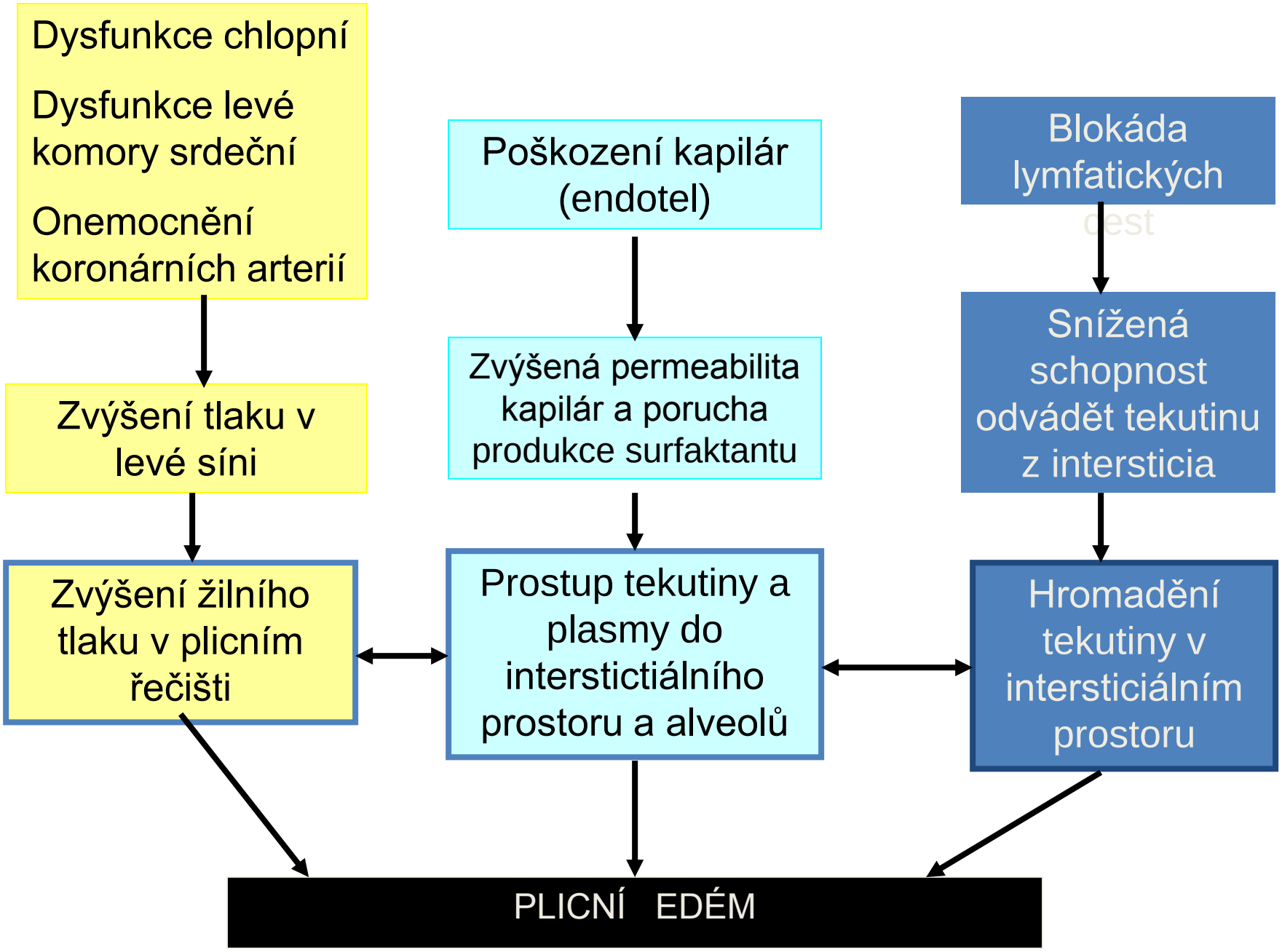
ARDS – nekardiogenní plicní edém



Plicní edém

- Nahromadění tekutiny v plicích
- Důvody
  - kardiogenní
    - zvýšení hydrostatického tlaku v kapilárách (kardiálně podmíněný plicní edém)
      - infarkt myokardu, stenóza dvojcípé chlopně
  - nekardiogenní
    - zvýšení propustnosti kapilár „syndrom vlhké plíce“ (ARDS)
      - u septických stavů - bílkoviny pronikají do intersticia => zvýšený onkotický tlak v intersticiu
    - snížený onkotický tlak v kapilárách
- stadia
  - intersticiální edém
    - tekutina pouze v intersticiu
    - zvýšený tok lymfy a rozšířená lymfat. cest
    - plicní funkce postiženy jen málo => rtg?
  - alveolární edém
    - tekutina prosakuje i do alveolů => postižení ventilace, dyspnoe (hypoxémie)
    - vykašlávání zpěněného sputa




Dysfunkce chlopní
Dysfunkce levé komory srdeční
Onemocnění koronárních arterií
Poškození kapilár (endotel)
Blokáda lymfatických
Zvýšení tlaku v levé síni
Zvýšená permeabilita kapilár a porucha produkce surfaktantu
Snížená schopnost odvádět tekutinu z intersticia
Zvýšení žilního tlaku v plicním řečišti
Prostup tekutiny a plasmy do interstictiálního prostoru a alveolů
Hromadění tekutiny v intersticiálním prostoru
PLICNÍ EDÉM

Plicní edém, důsledky

- důsledky pro mechaniku dýchání
  - sníží poddajnost plic
    - porucha surfaktantu $\Rightarrow$ kolaps alveolů
    - snížení ventilovaných objemů plic
  - zvýší odpor dýchacích cest - reflexní bronchospasmus
    - snížení objemů plic a edém v cestách
- důsledky pro dýchací plyny
  - snížení oxygenace (poruchy difuze)
    - snížení ventilačních objemů $\Rightarrow$ V/Q zkrat
    - porucha difuse pro snížení plochy, ztluštění membrány, snížení PAO2


I'M HAVING TROUBLE BREATHING
LYNCH