Pathophysiology of the respiratory system I

Structural properties of airways and lungs
Respiration and gas exchange
- ventilation & diffusion & perfusion

Pulmonary mechanics
Airflow resistance and dynamic collapse
Obstructive lung diseases(COPD and bronchial asthma)

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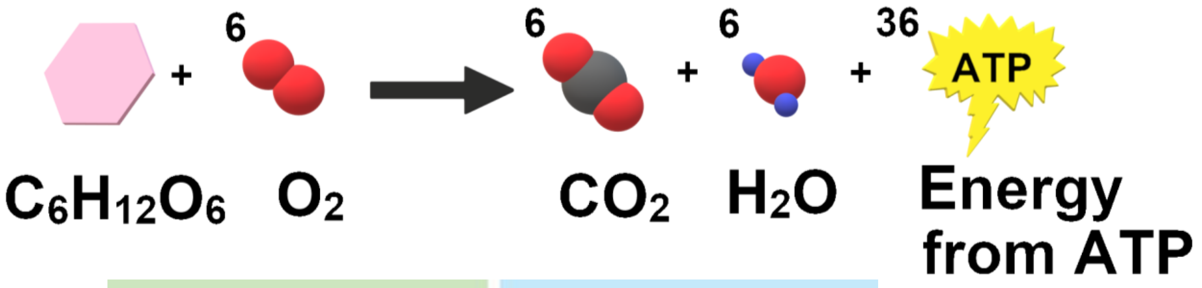
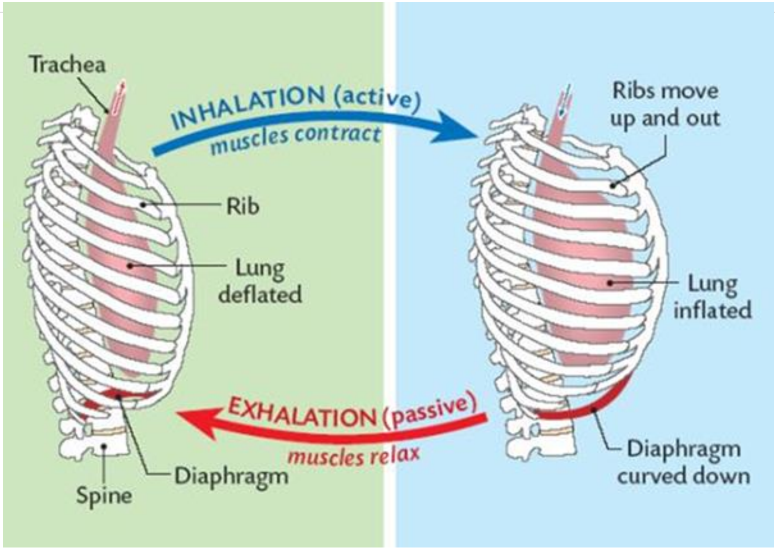
Warming up questions

- (1) **WHY** do we breathe???
  - gas exchange





- (2) **HOW** do we breathe???
  - principles of the quiet breathing
- (3) **WHEN** do we breathe???
  - all the time/non-stop, the death = „until the last breath“

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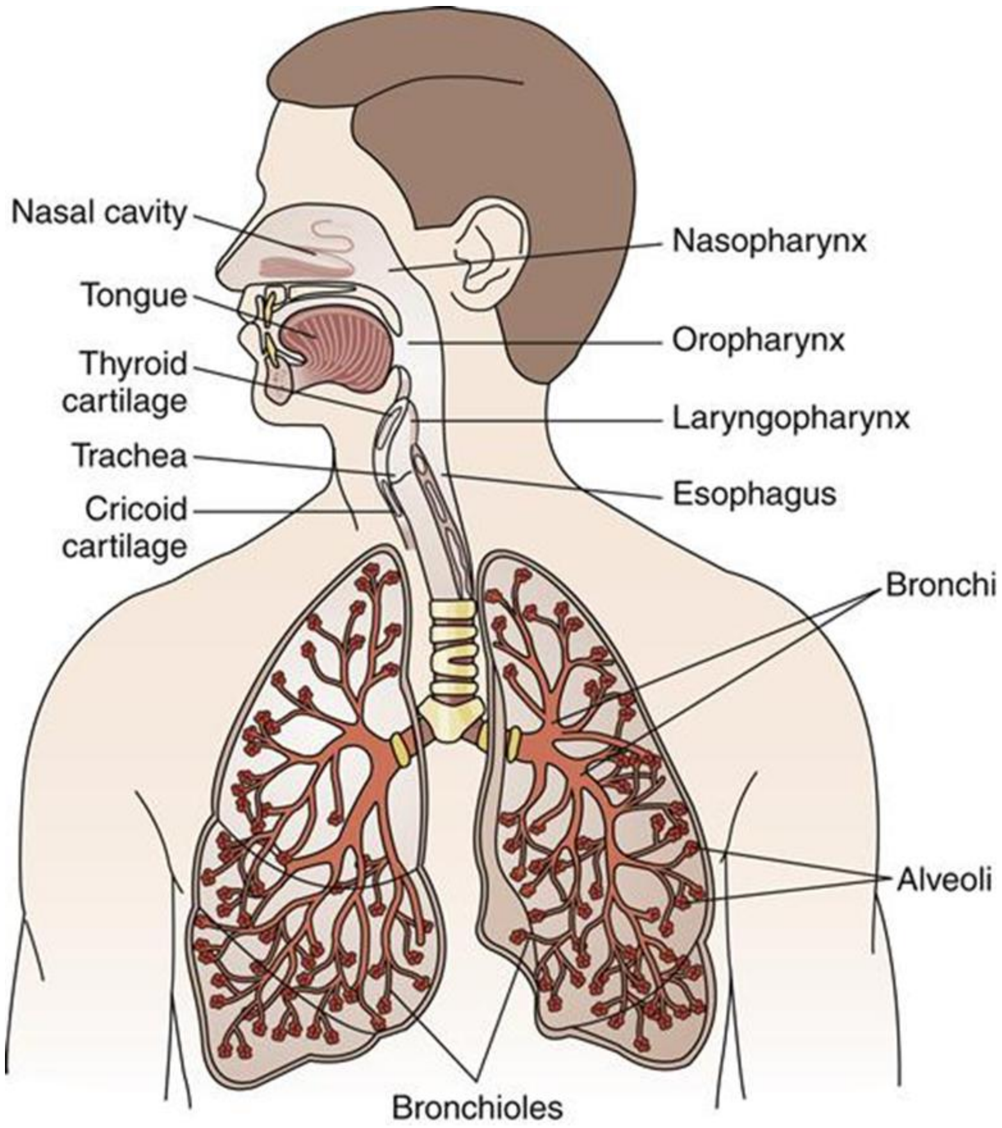
Nasal cavity
Tongue
Thyroid cartilage
Trachea
Cricoid cartilage
Nasopharynx
Oropharynx
Laryngopharynx
Esophagus
Bronchi
Alveoli
Bronchioles

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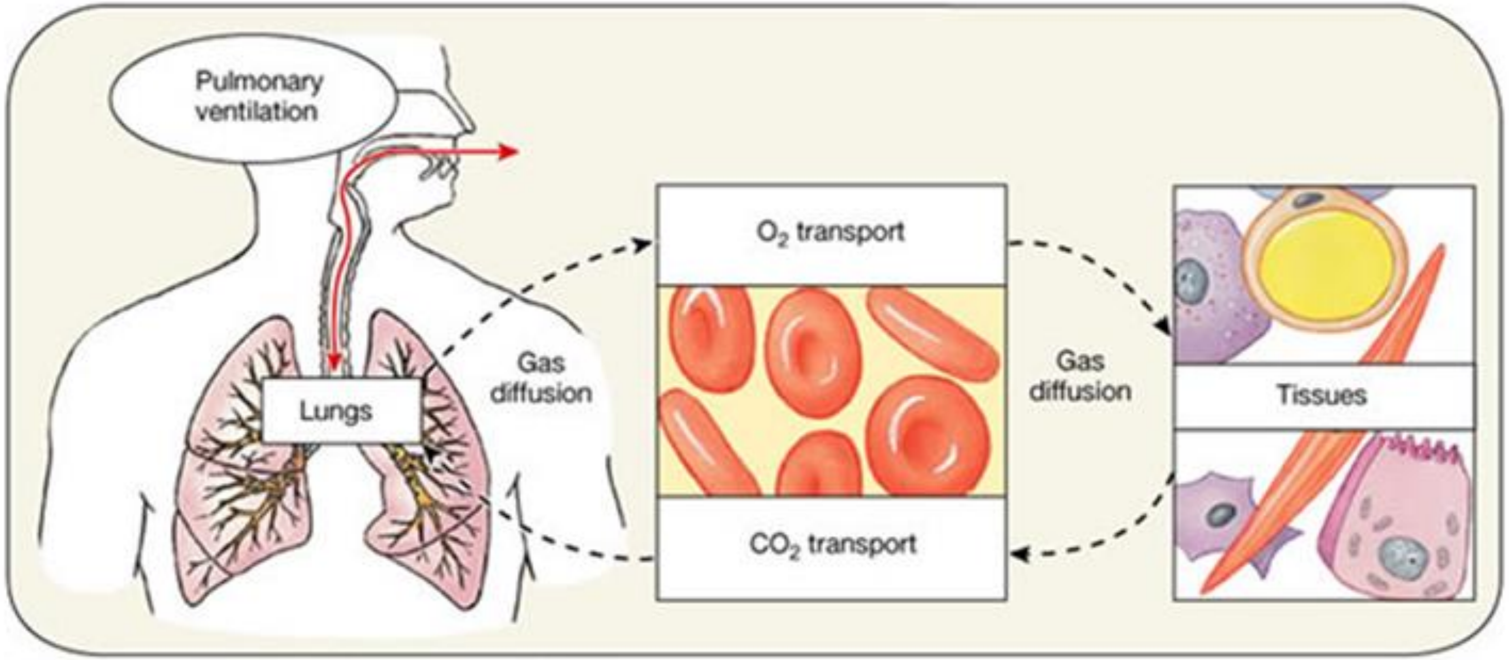
(1) STRUCTURAL-FUNCTIONAL CONSIDERATIONS IMPORTANT FOR PP OF RESPIRATION & PARTICULAR DISORDERS

Respiration and gas exchange in the lungs

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

death from lung disease is almost always due to an inability to overcome the altered mechanical properties of the lung or chest wall, or both



The delicate structure-function coupling of lungs

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

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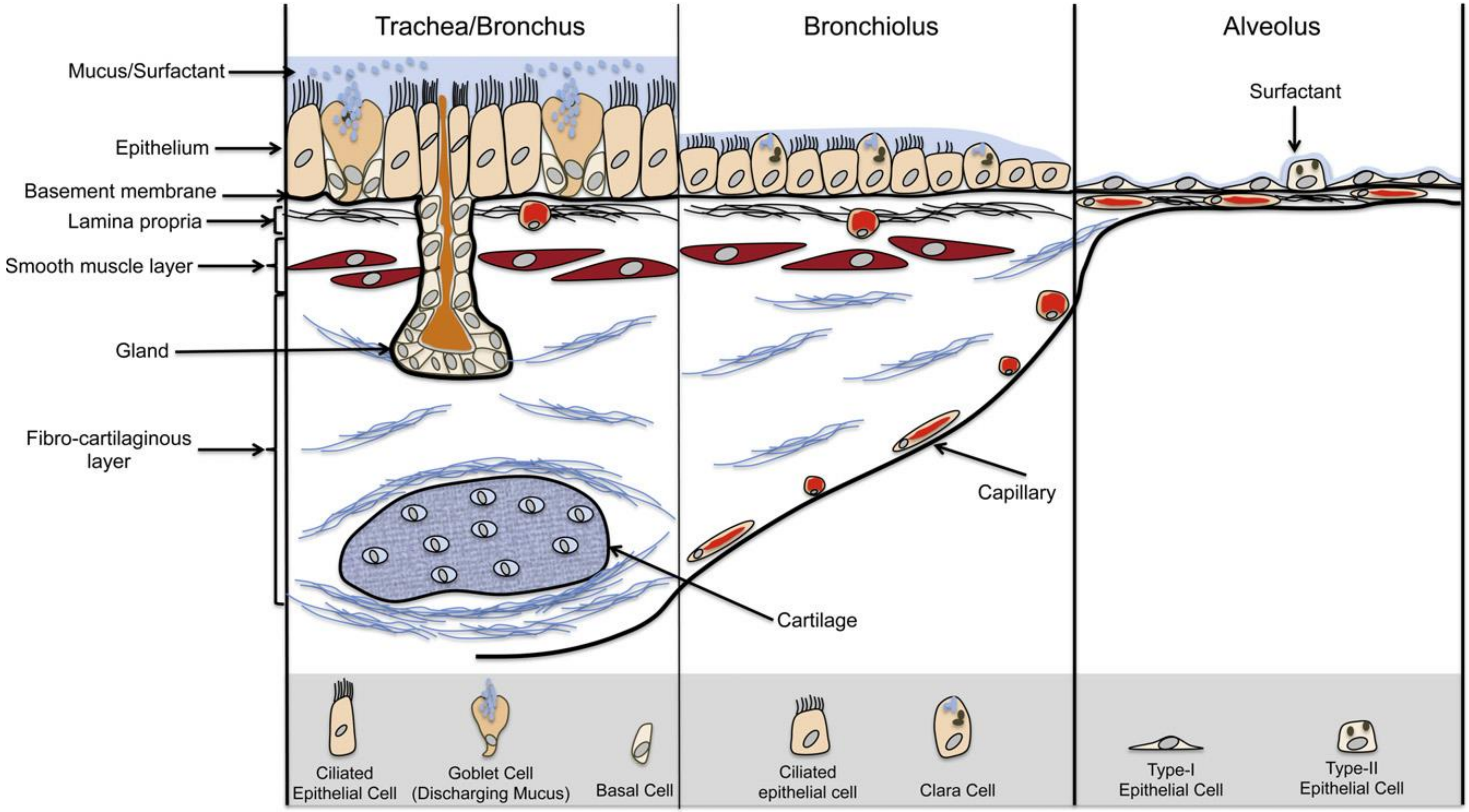
Wall structure of conducting airways and respiratory region



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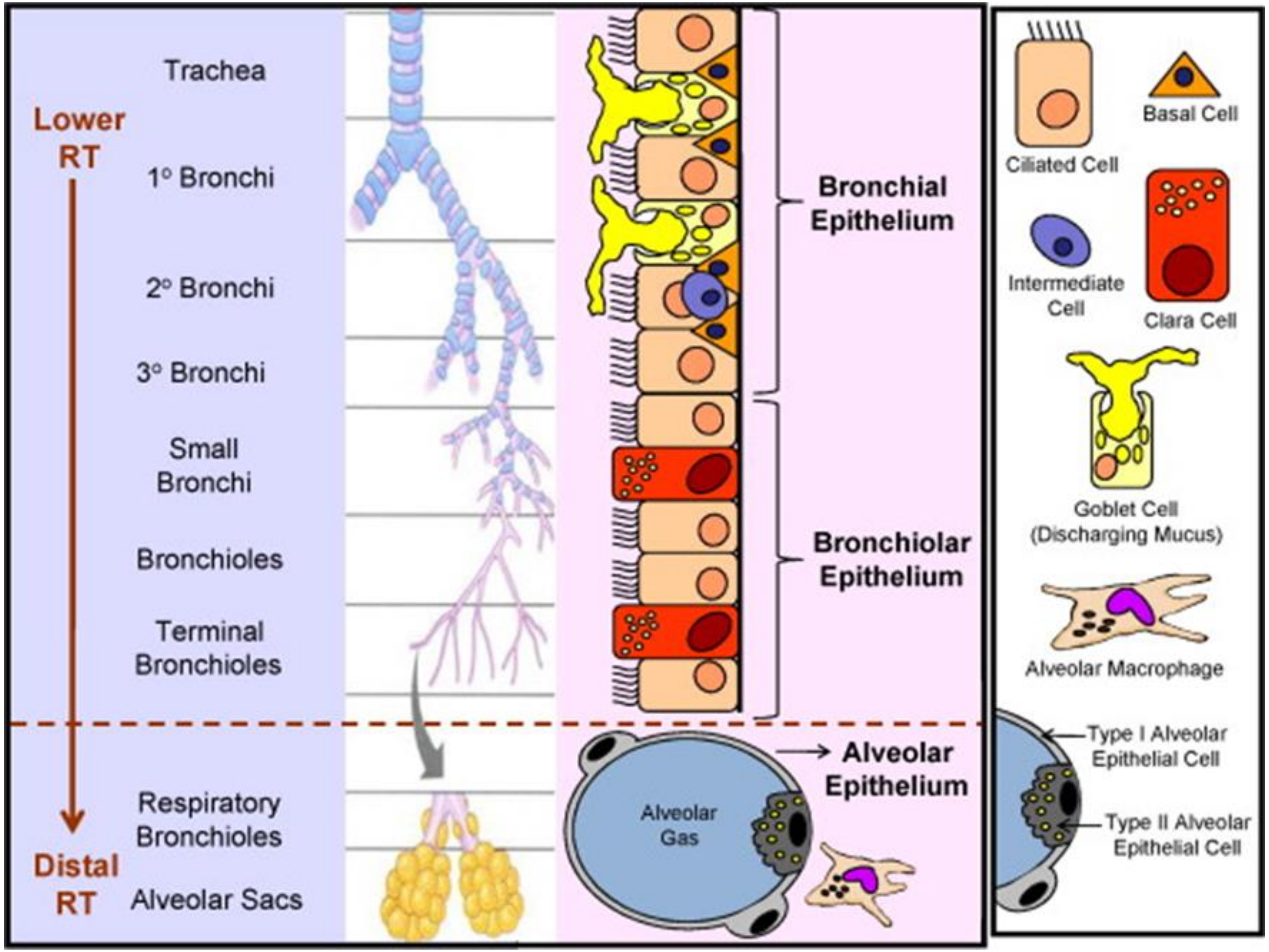
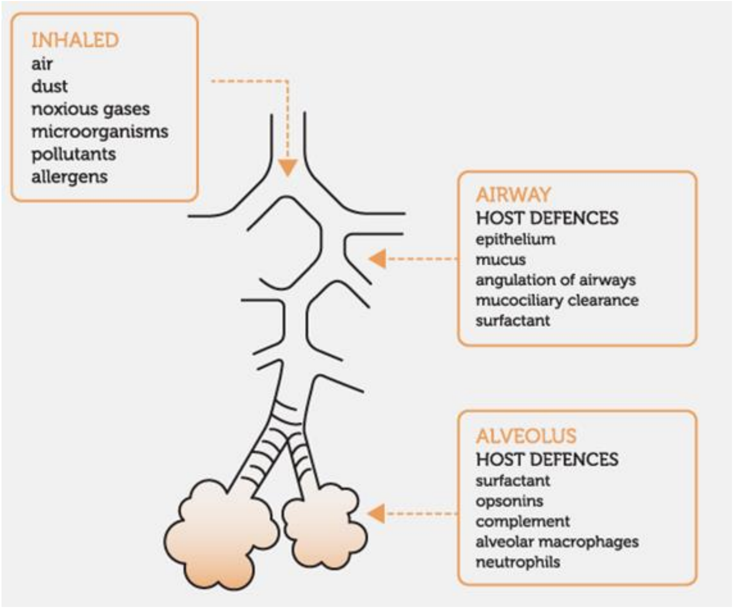
Lung defense – multiple mechanisms (details later)





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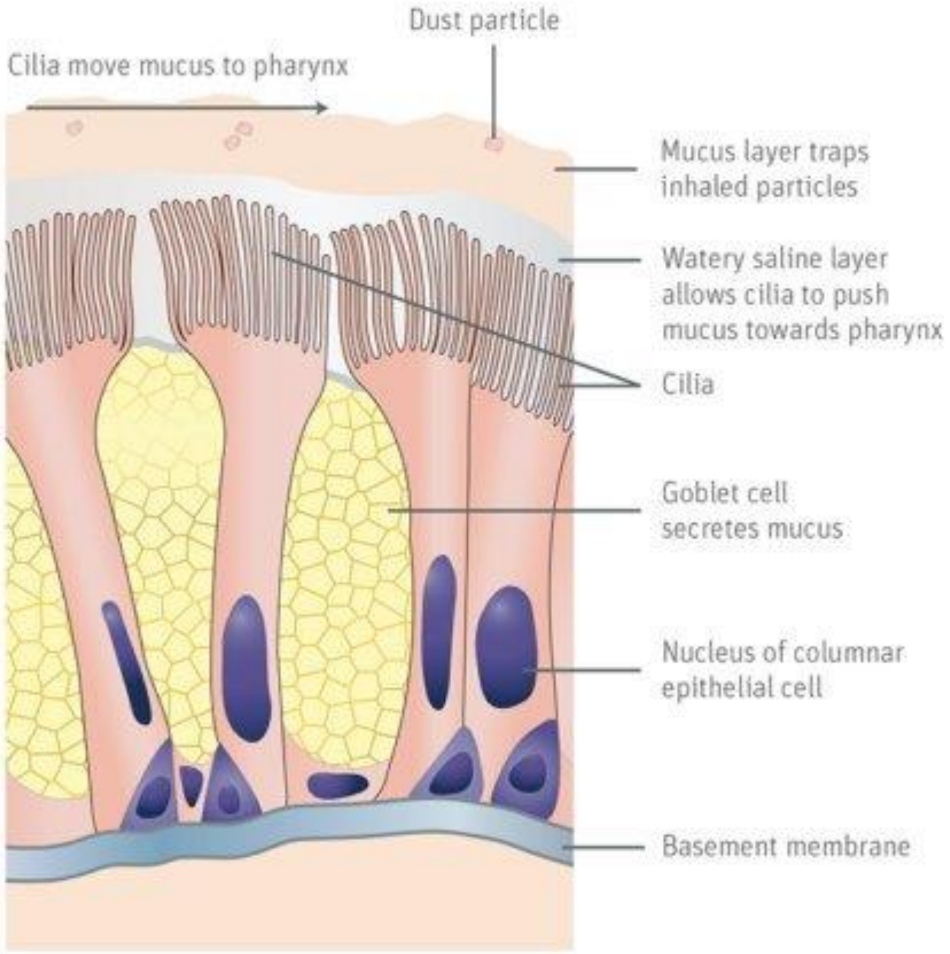
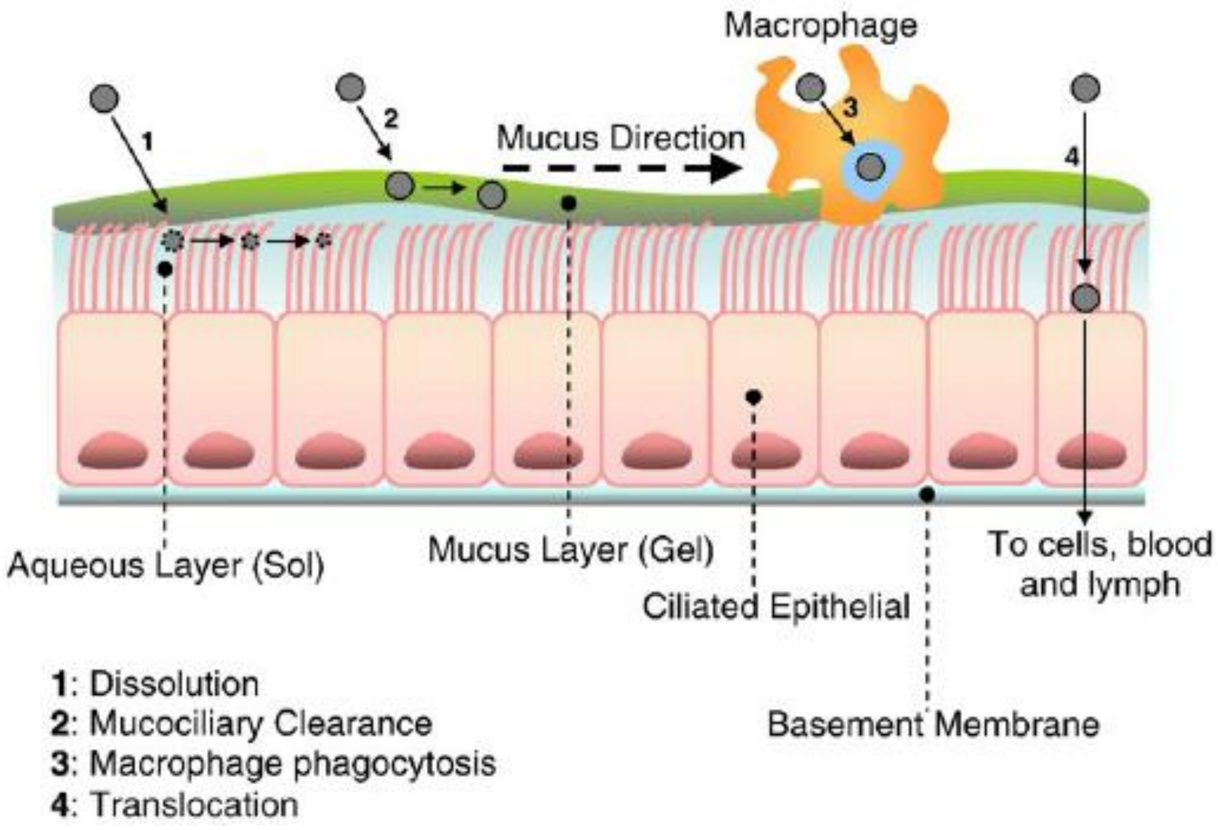
Mucocilliary escalator





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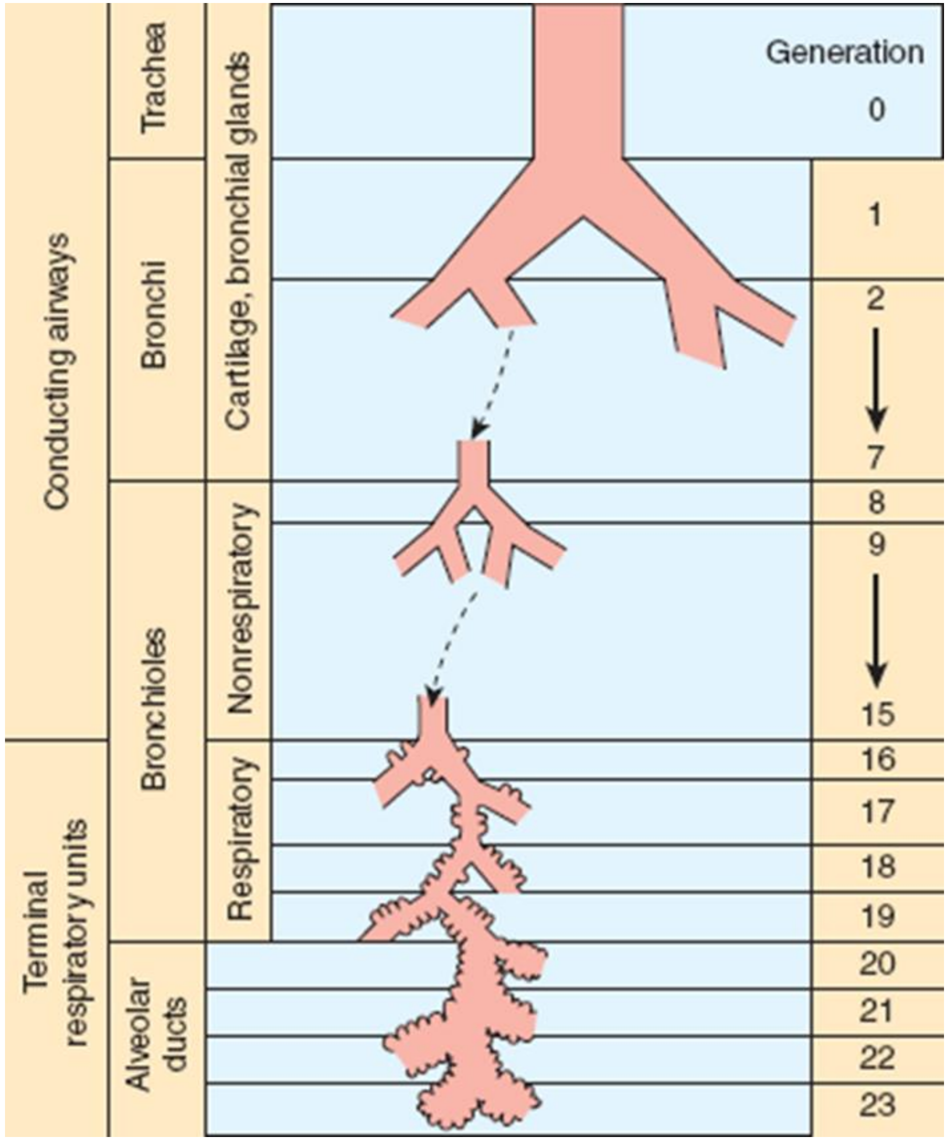
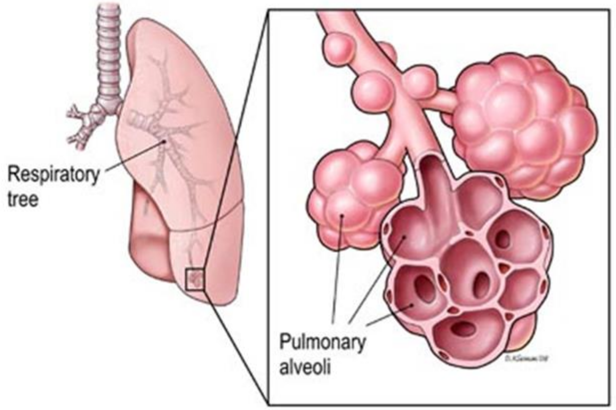
Structure of airways



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



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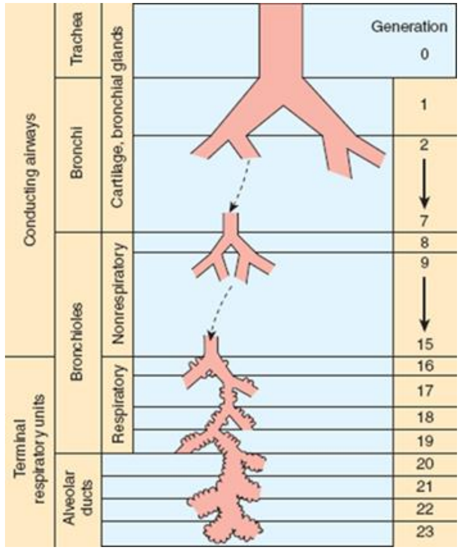
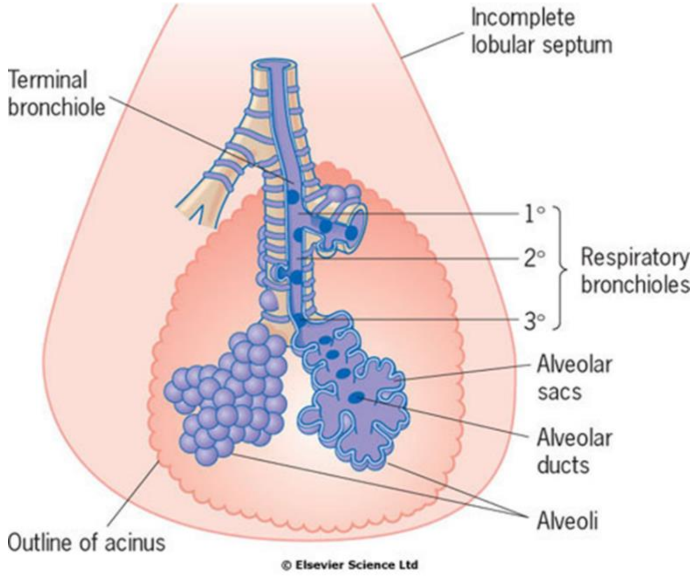
Functional classification of airways

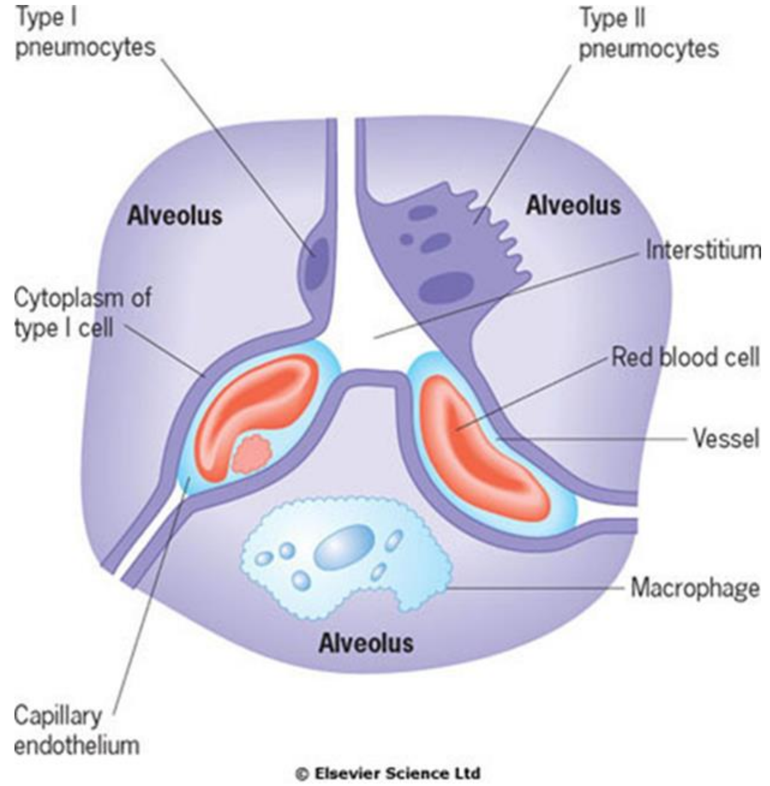
- Conducting airways (= **anatomical dead space**) – g1-15
    - nose (mouth)
    - larynx
    - trachea
    - main bronchi & non-respiratory bronchioles
  - gas conduction, humidification & warming, defense
- Acinar airways (= **respiratory space**) – g16-23
    - respiratory bronchioles
    - alveolar 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

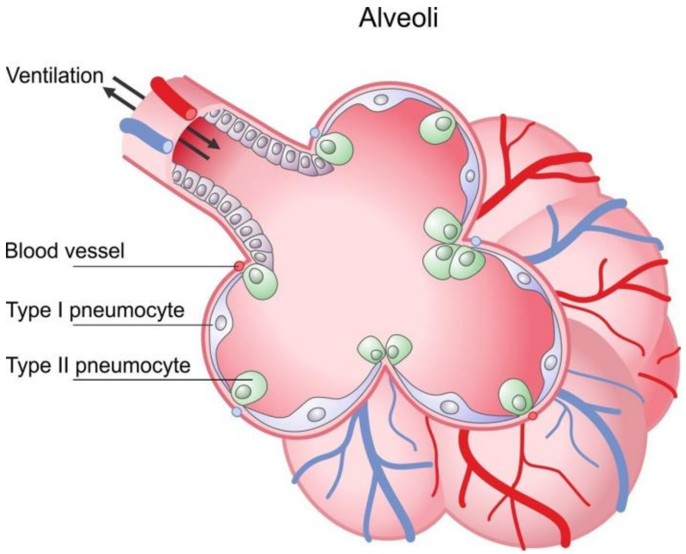




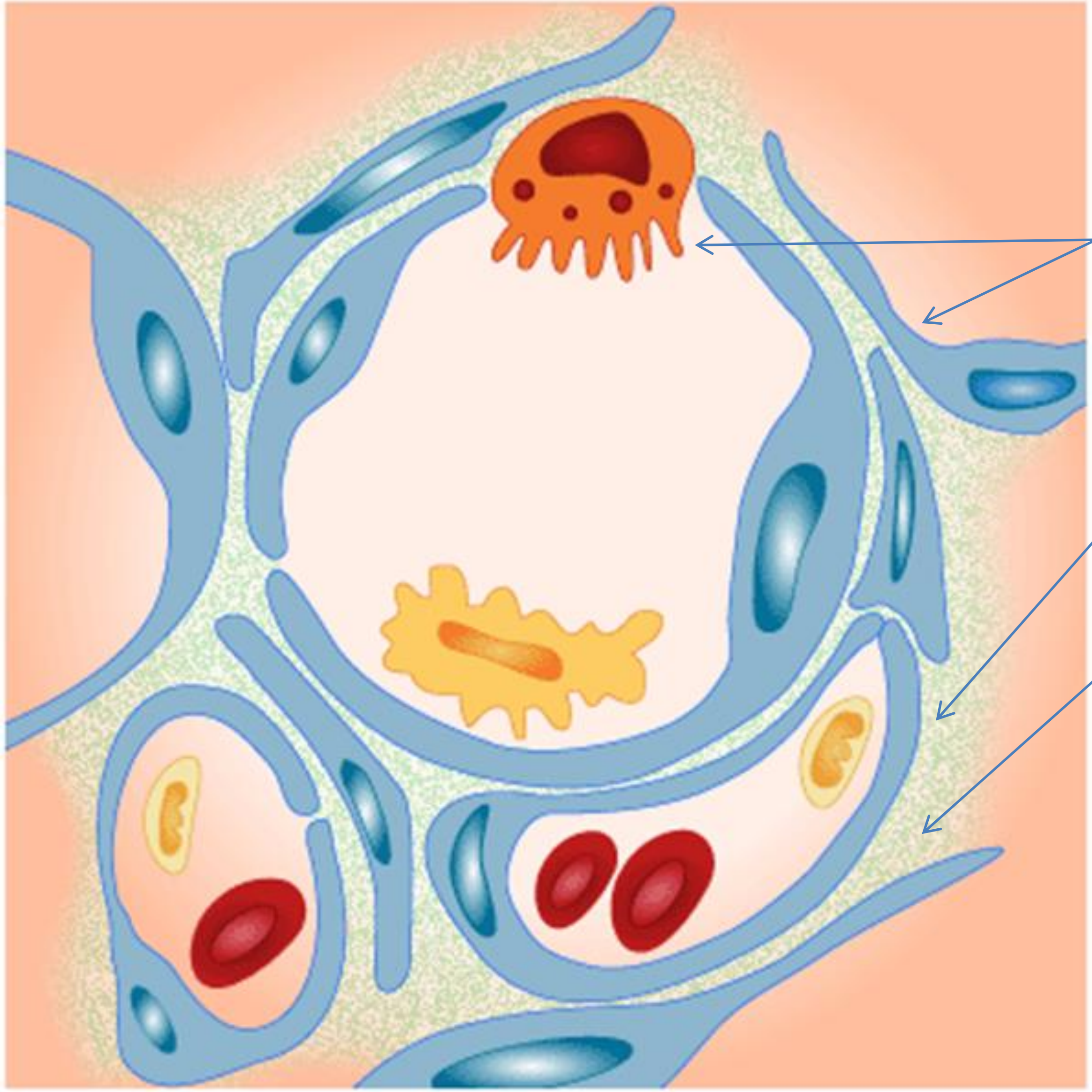
Alveoli

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





Alveolo - capillary barrier



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

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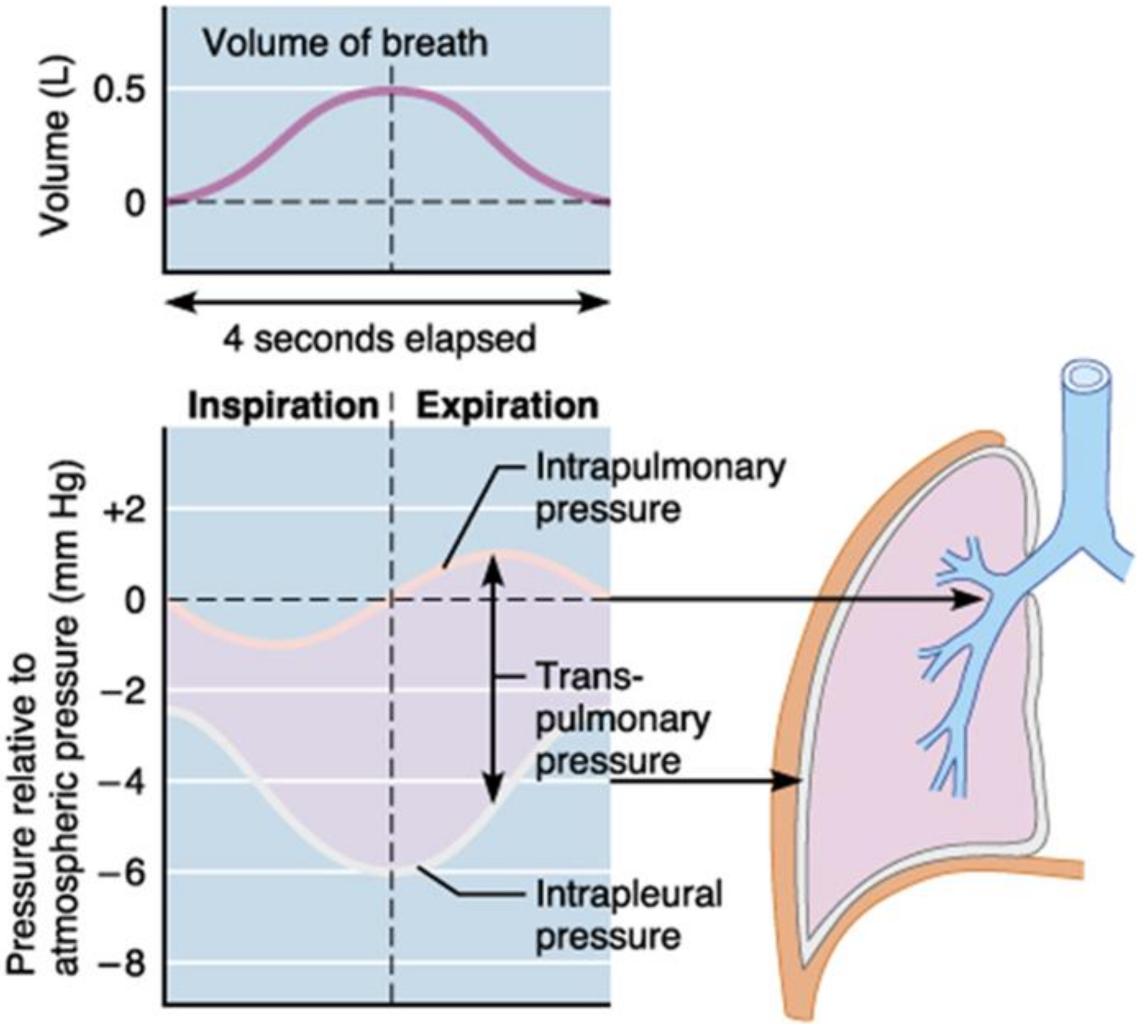
(2) PRINCIPLES OF VENTILATION AND ITS ABNORMALITIES

Ventilation (breathing) as a mechanical process



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

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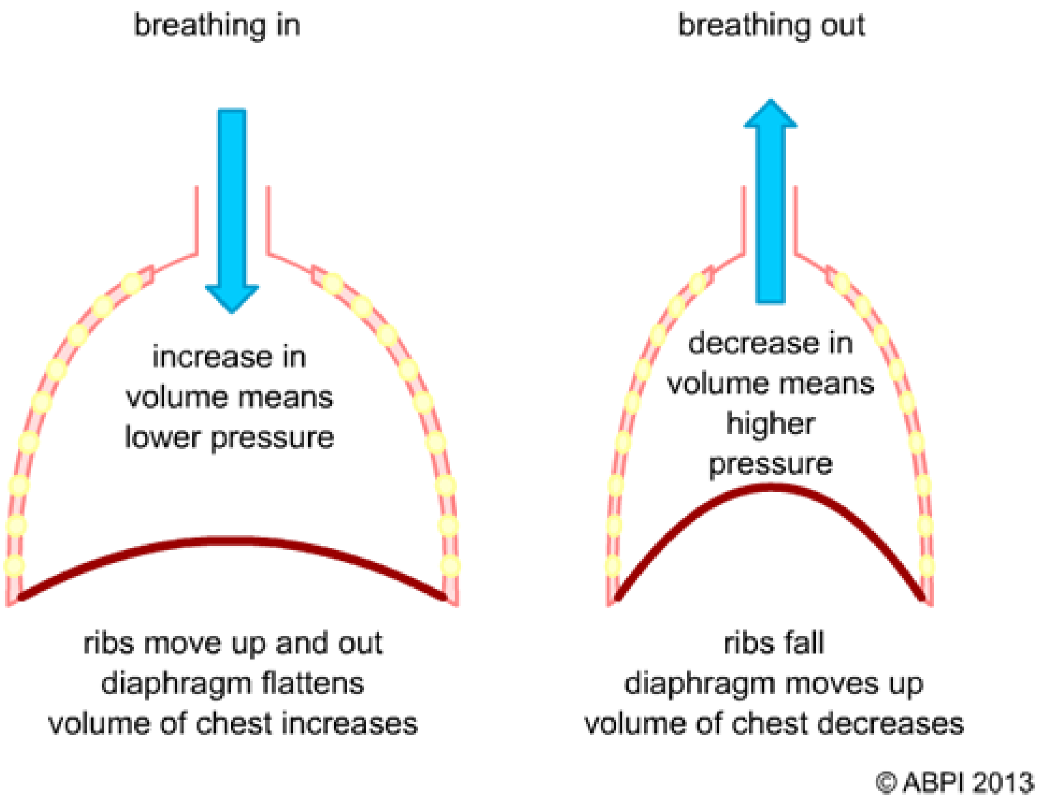
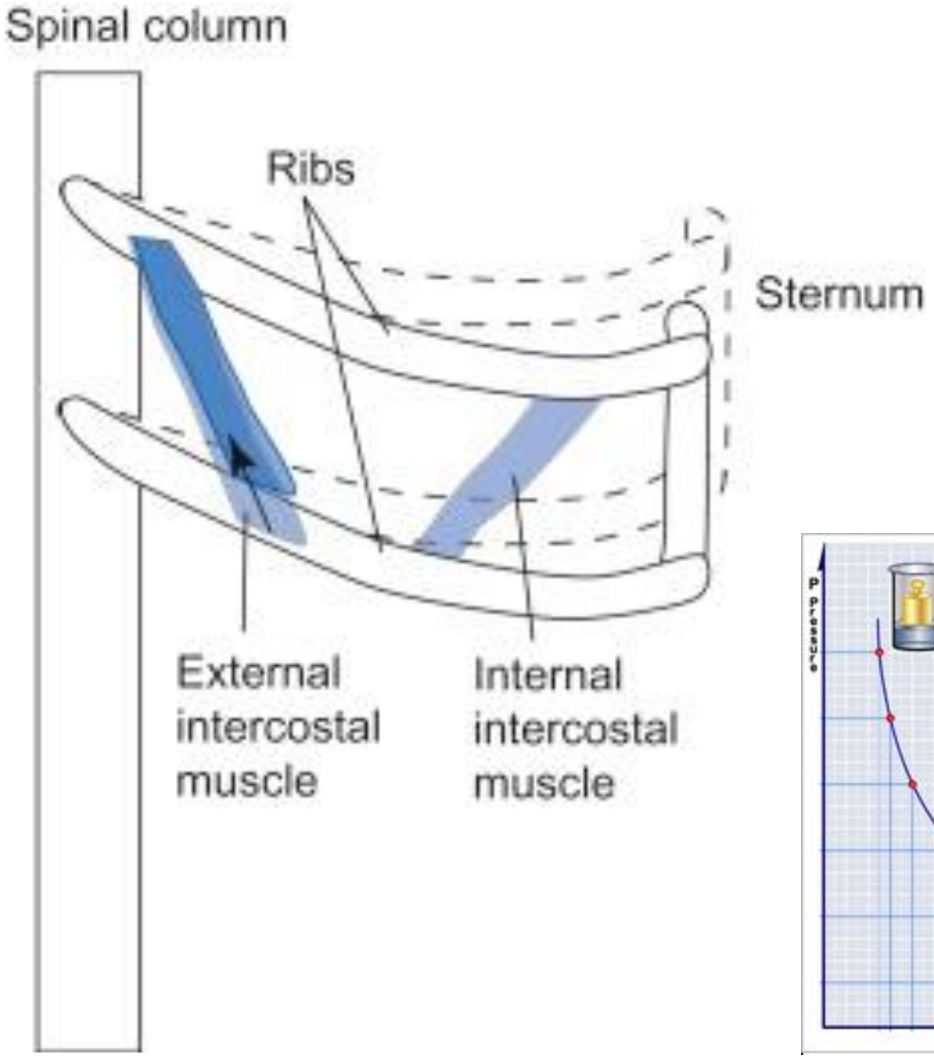
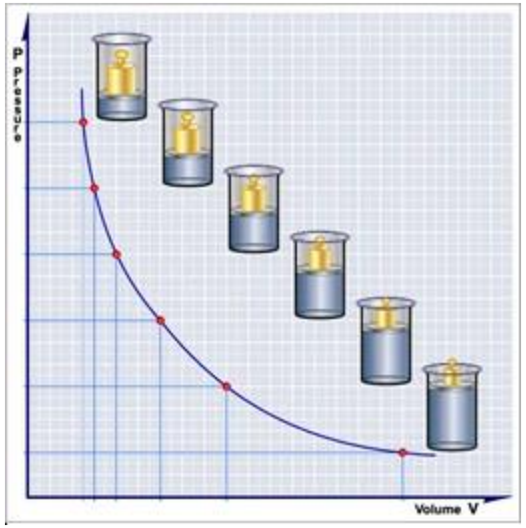
Muscles performing ventilation

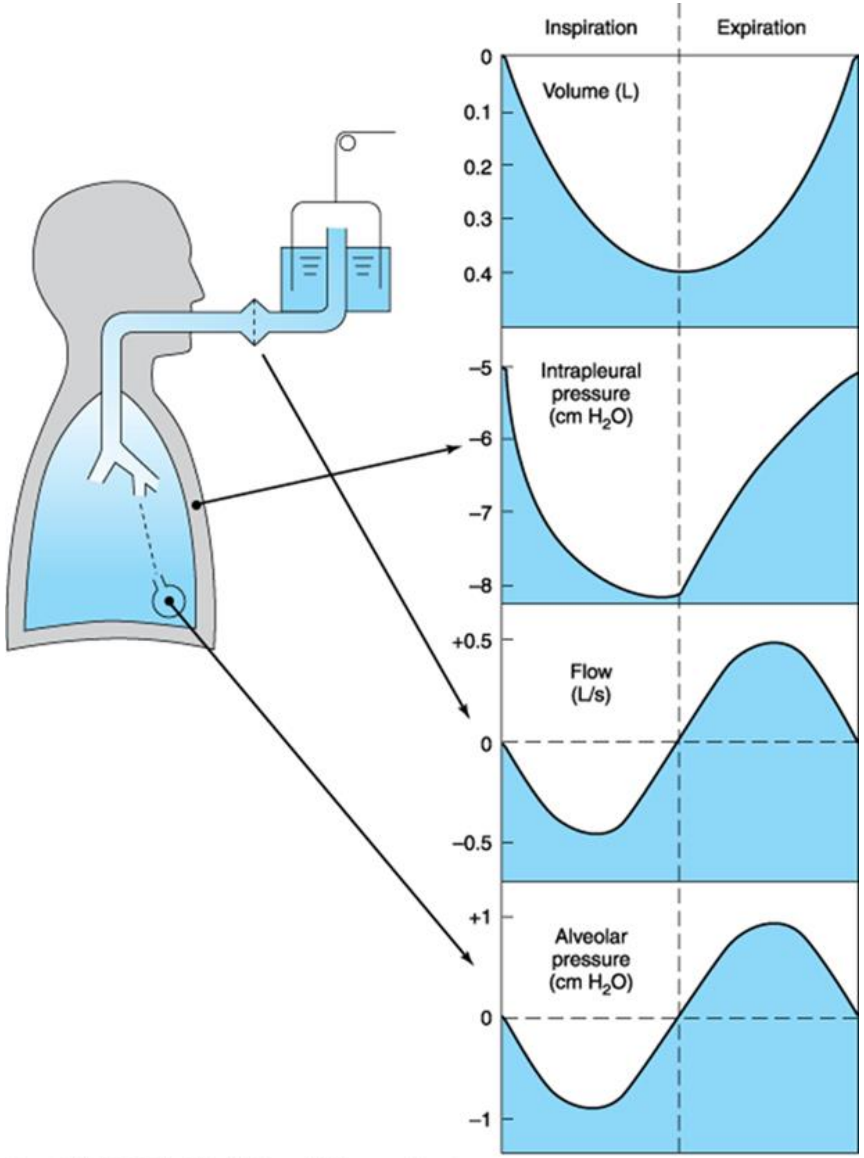






Boyle-Mariotte law (for ideal gas)

Mechanics of ventilation – breathing cycle



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

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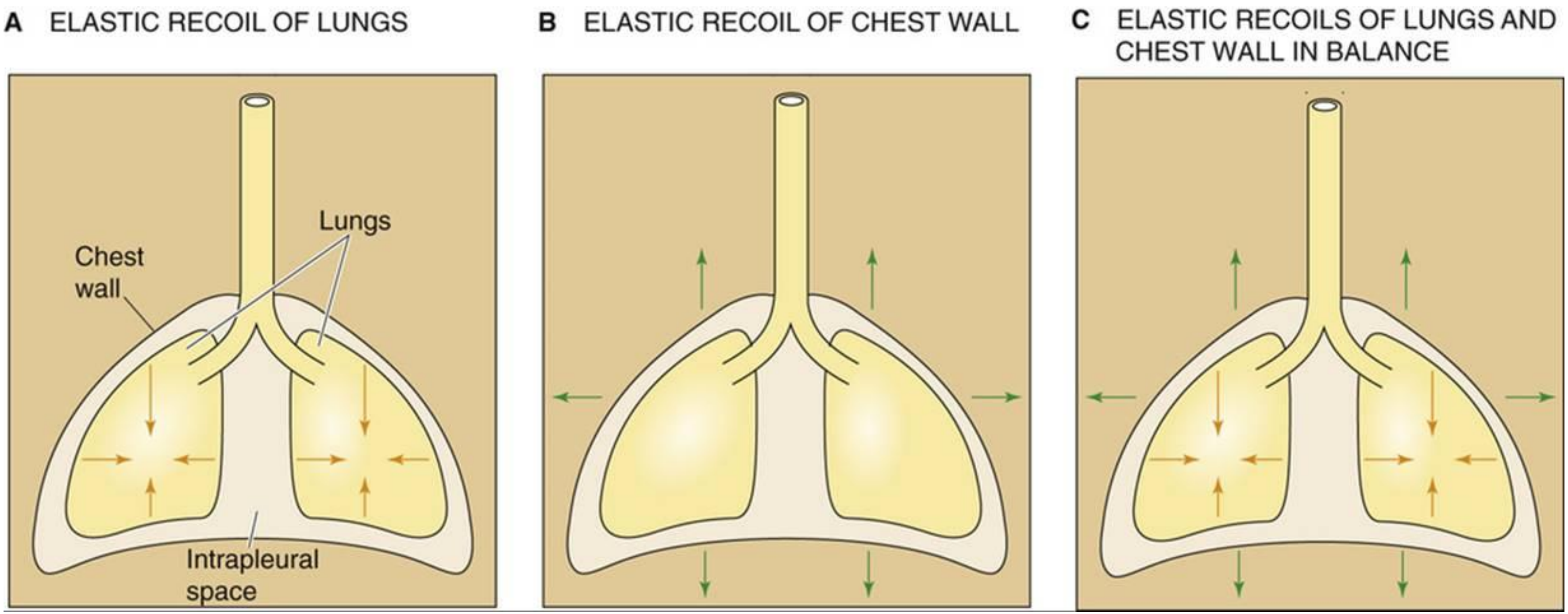
Mechanical properties of the chest wall vs. lungs

= opposing elastic recoil

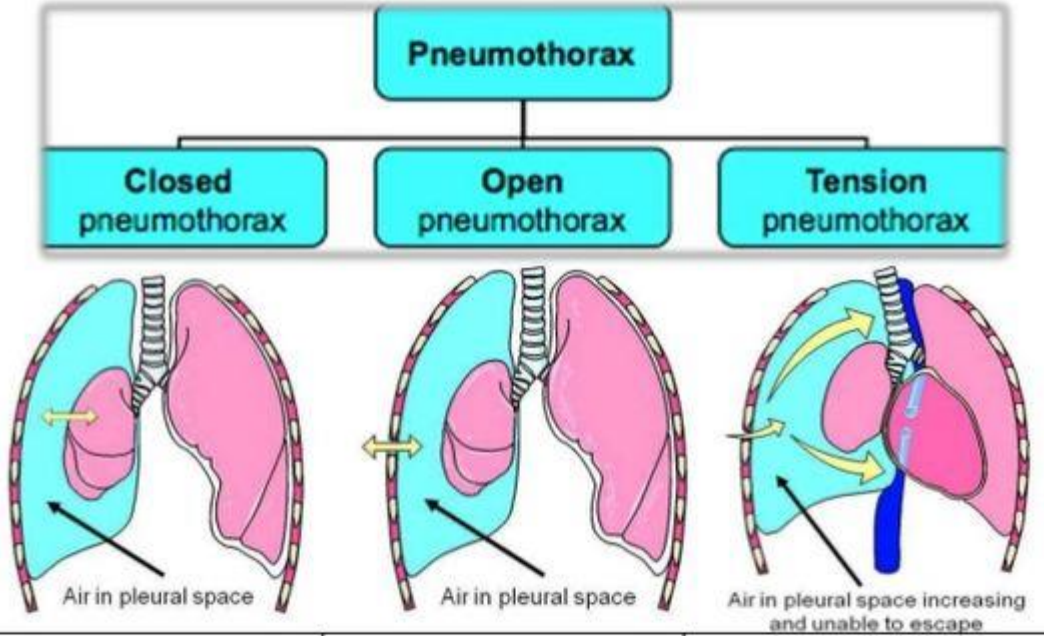


lung has a tendency to shrink
(surface tension + lung elasticity)

chest has a tendency to expand
(anatomy of thoracic cavity and muscles)

resulting balance

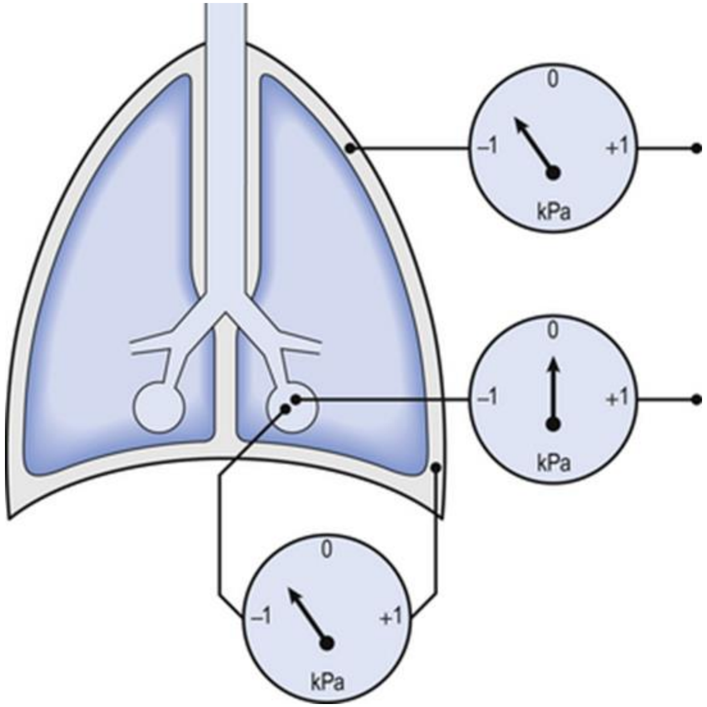
Pneumothorax = the absence of neg. i-pleural P



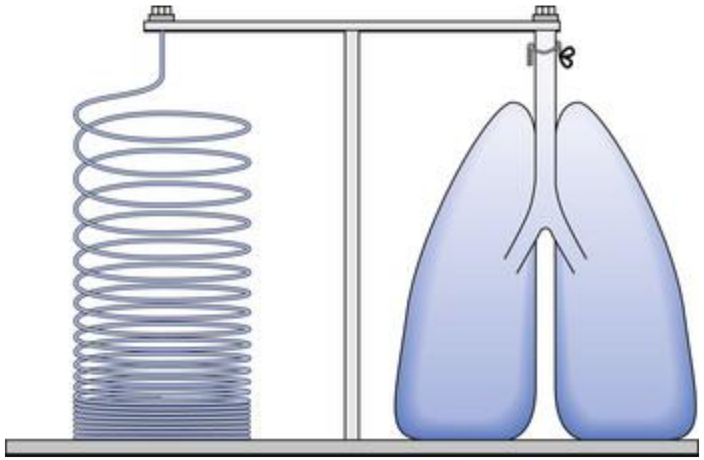
The pleural cavity pressure is < the atmospheric pressure	The pleural cavity pressure is = the atmospheric pressure	The pleural cavity pressure is > the atmospheric pressure

Is negative value of i-pleural P homogenous?

situation at the end of quiet expirium



gravitation and lung own weight decrease negativity at the bases (and vice versa on apexes)



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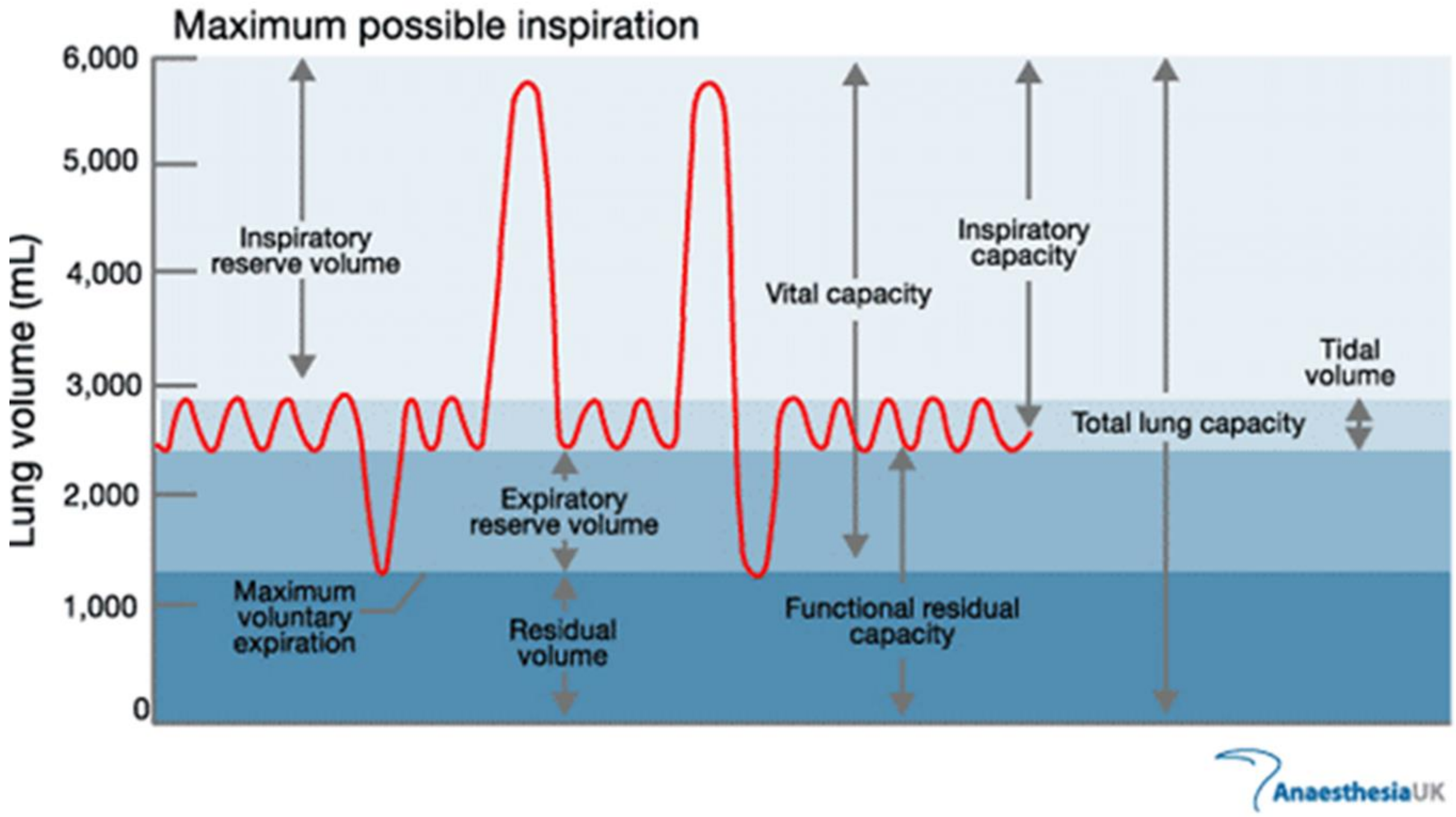
Lung volumes and capacities (tj. ≥ 2 volumes)



- The ratio of RV to TLC (**RV/TLC ratio**) in normal individuals is usually less than **0.25**
- abnormal = increased RV/TLC ratio in different types of pulmonary disease
  - obstructive diseases
    - ↑ RV
  - restrictive diseases
    - ↓ TLC

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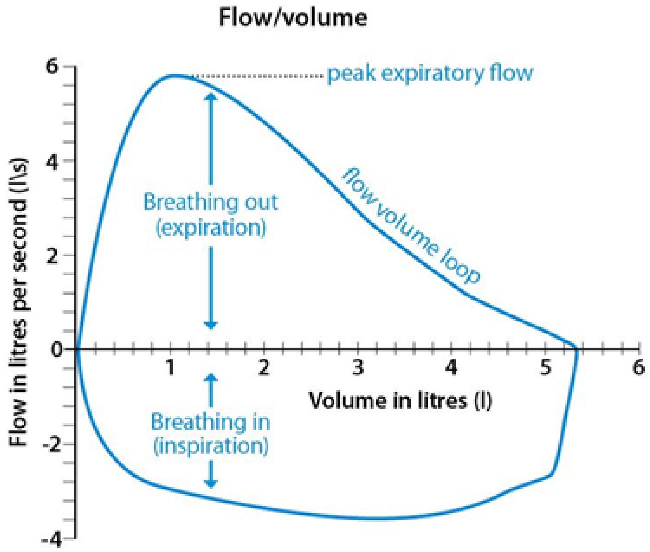
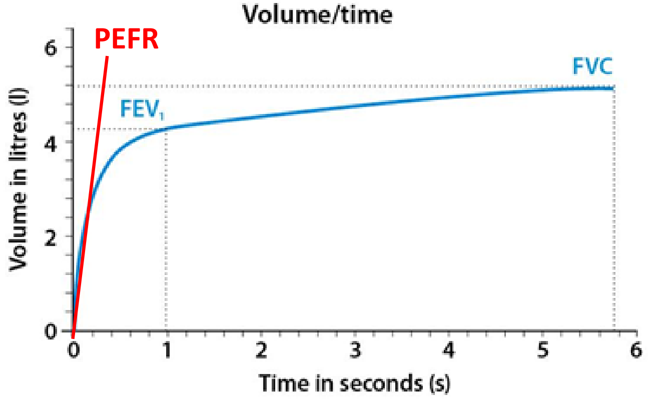
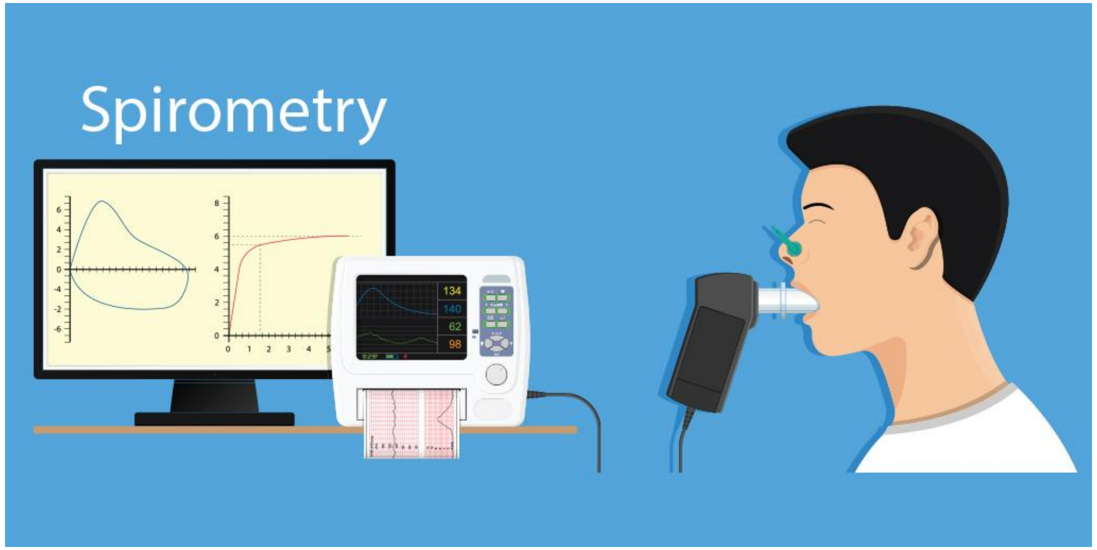
Spirometry





	Min	Ref	Max	Best	%Ref	SR
FEV1 [L]	3.76	4.31	4.99	4.31	100	0.0
FVC [L]	4.71	5.35	5.81	5.35	100	0.0
VC [L]	4.82	5.47	5.92	5.47	100	0.0
FEV1/VC [%]	68.1	78.8	-	78.8	100	0.0
		Normal range		Your best effort		



- absolutely most common pulmonary function test (PFT)
- allows to classify ventilation disorders
  - obstructive
  - restrictive
  - combined
- useful for provocation tests too
  - COPD vs. asthma → bronchodilator (s-B_2agonist)
  - bronchial hyperreactivity (metacholine)

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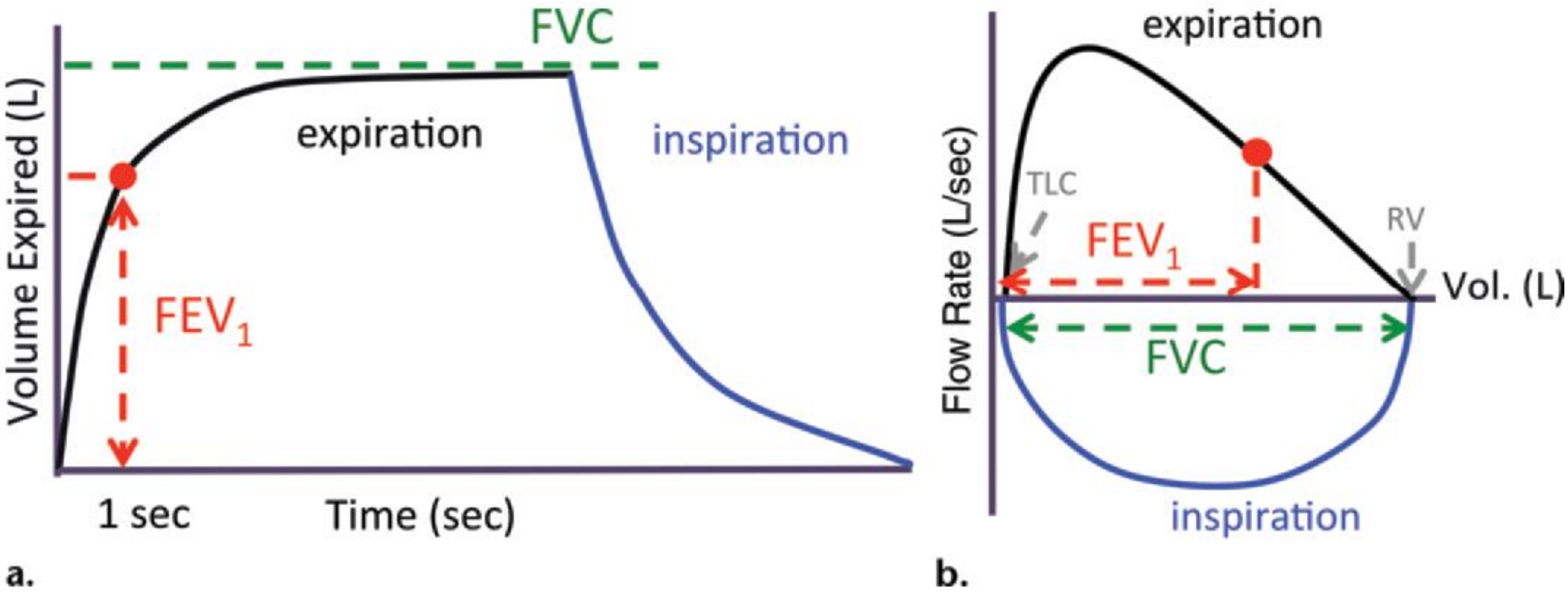
The most important parameters



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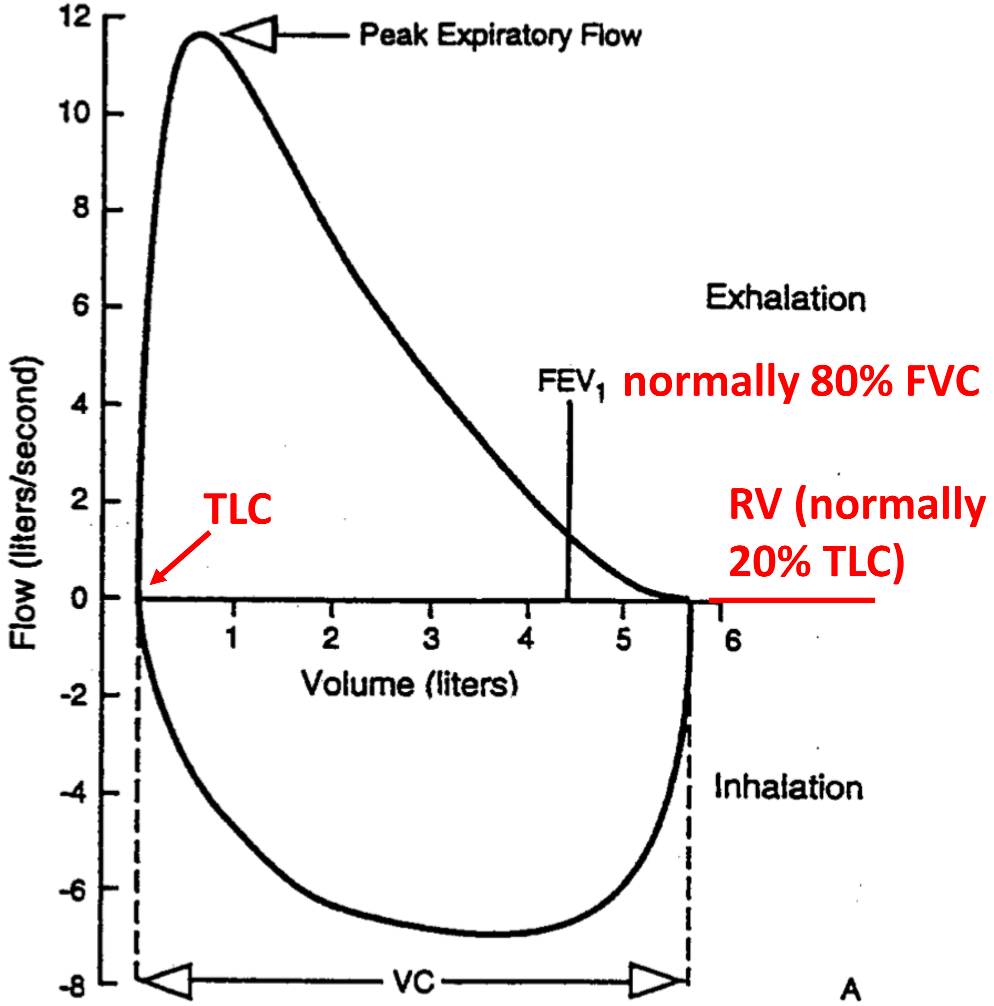
Spirometry limitation

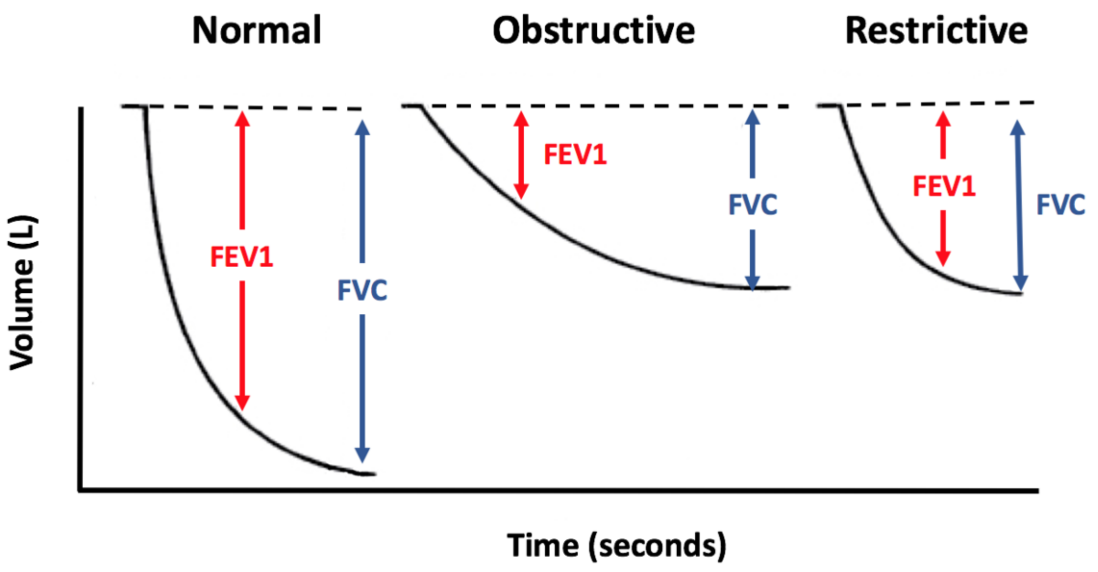


- spirometry can measure almost all volumes and capacities with exception of RV
  - RV, FRC and TLC

Spirometry in diagnosis of main types of ventilation disorders

cannot exhale normally

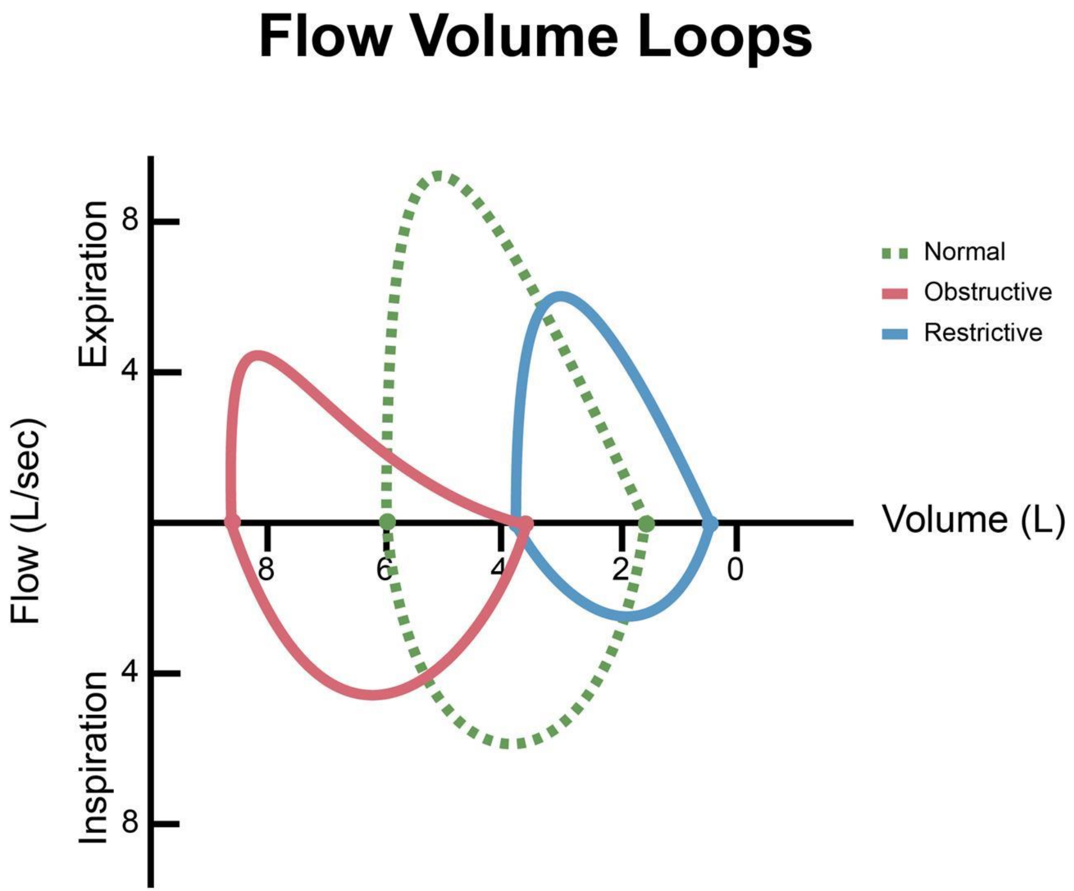
cannot inhale normally

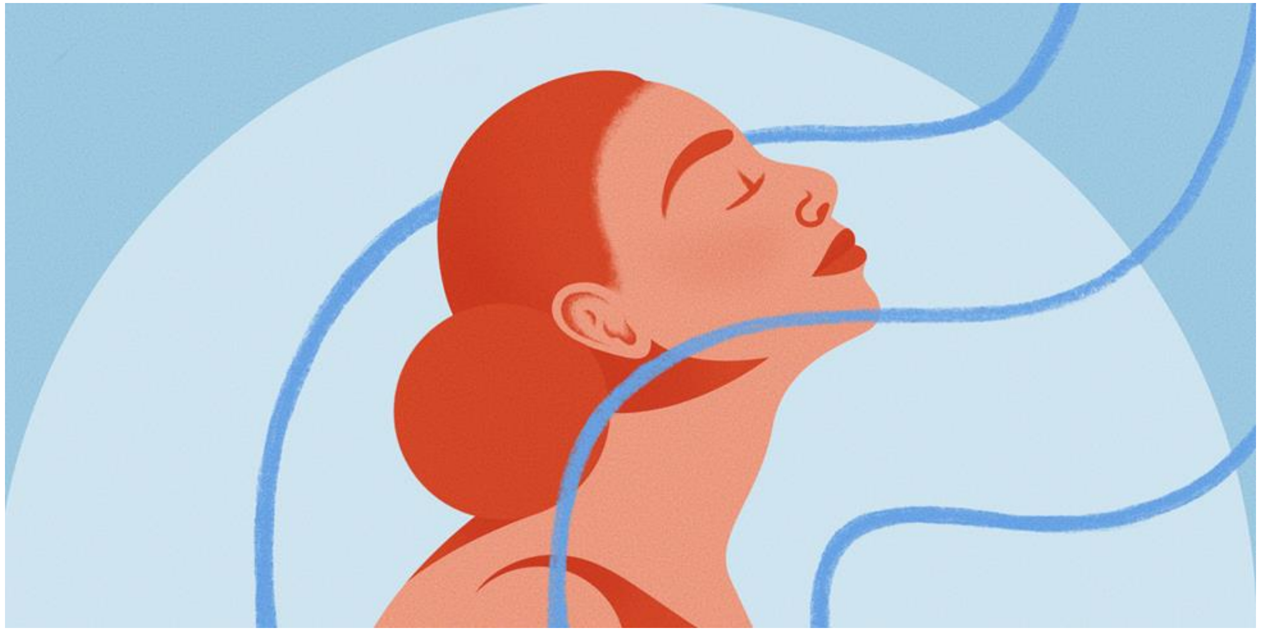


FEV1 = 3.3
FVC = 4.0
FEV1/FVC = 83%

FEV1 = 1.0
FVC = 2.0
FEV1/FVC = 50%

FEV1 = 1.8
FVC = 2.0
FEV1/FVC = 90%

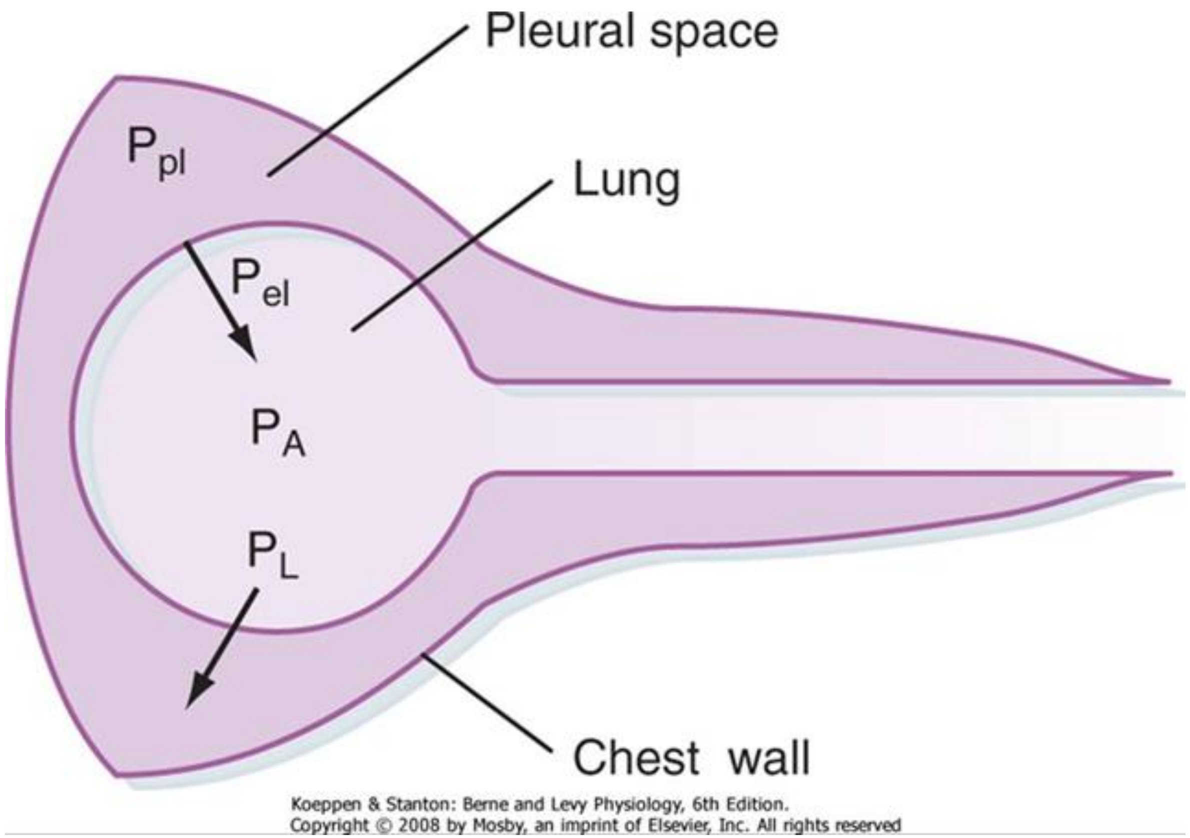




(3) DISTENTION OF LUNGS COSTS ENERGY – IN ORDER TO OVERCOME RESISTANCE

Lung mechanics has to deal with two types of resistance

- the pressure necessary to distend lungs has to overcome two kinds of resistance
  - **(1) STATIC = elastic recoil**
    - ~60-70% of the work of breathing
    - in the respiratory part of airways and lung parenchyma
  - **(2) DYNAMIC = airway resistance**
    - ~30% of the work of breathing
    - in the convection part of airways
- energy requirements for respiratory muscles to overcome these resistances are normally quite low
  - 2-5 % of a total O_2 consumption
- but increases dramatically when resistance increases (up to 30%)

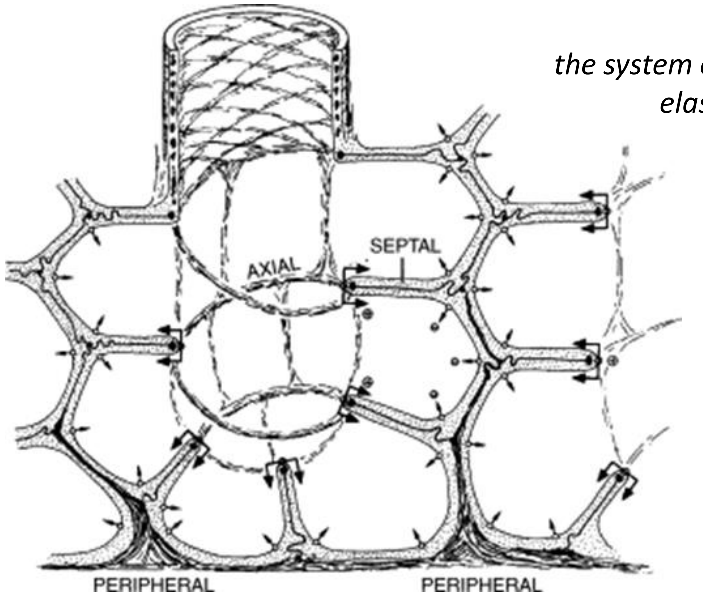


- Relationship between transpulmonary pressure (PL) and the pleural (Ppl), alveolar (PA), and elastic recoil (Pel) pressures of the lung
- Alveolar pressure is the sum of pleural pressure and elastic recoil pressure
- Transpulmonary pressure is the difference between pleural pressure and alveolar pressure

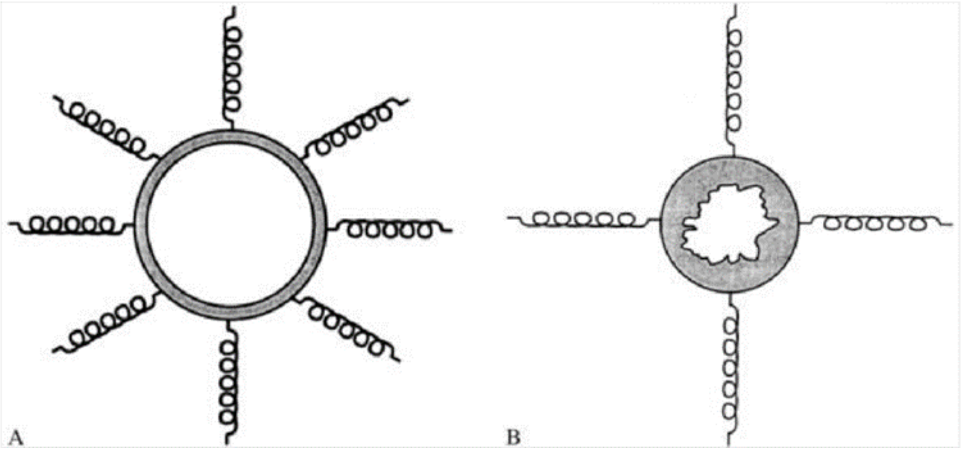
(ad 1) Elastic properties of the lung

(determining pressure – volume behavior of the lungs)

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



the system of airway elastic fibres



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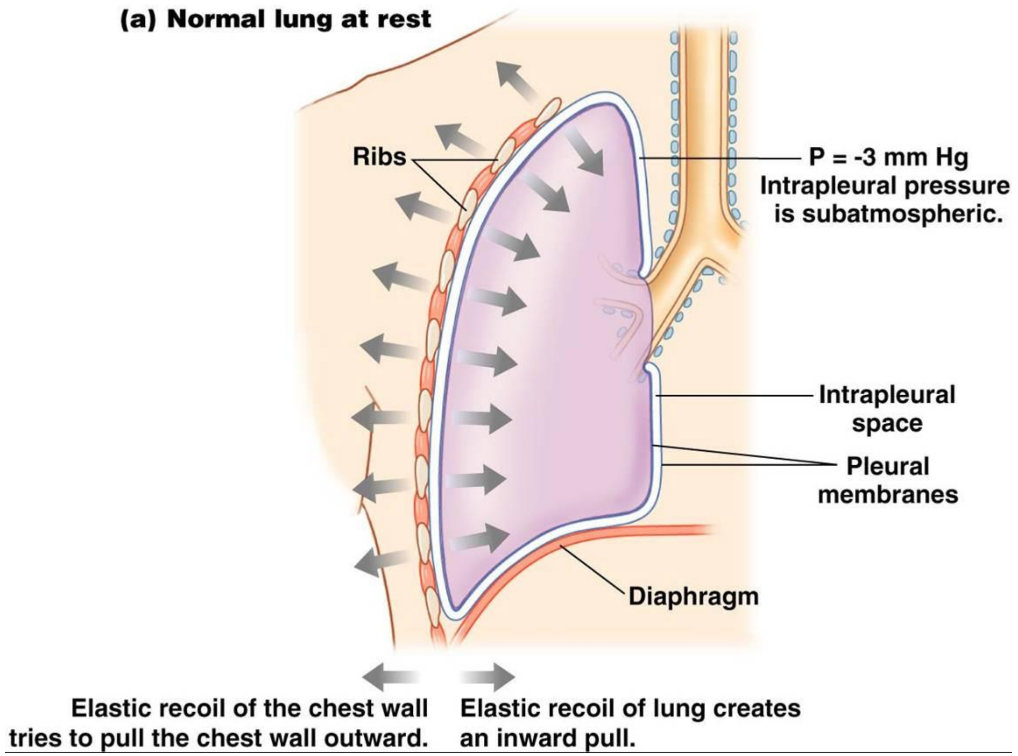
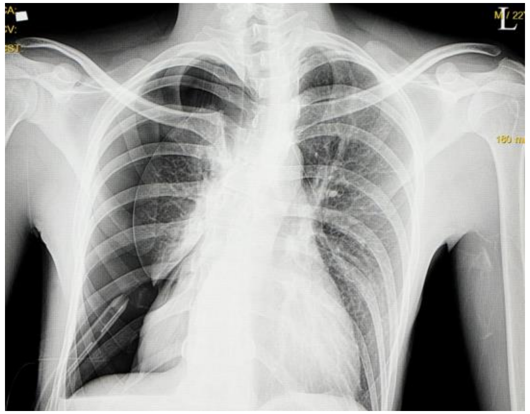
Situation in reaching FRV

- elastic recoil of lungs has a tendency to reduce lung volume (inwards), on the contrary, elastic recoil of chest wall has a tendency to expand the volume (outwards) = FRC represents the equilibrium and muscles are relaxed
- thorax surgery or trauma causes pneumothorax, lungs shrink to volume when transpulmonary pressure equals zero
  - chest expands
  - lung collapses, however, there is still air in – approx. 10% TLC





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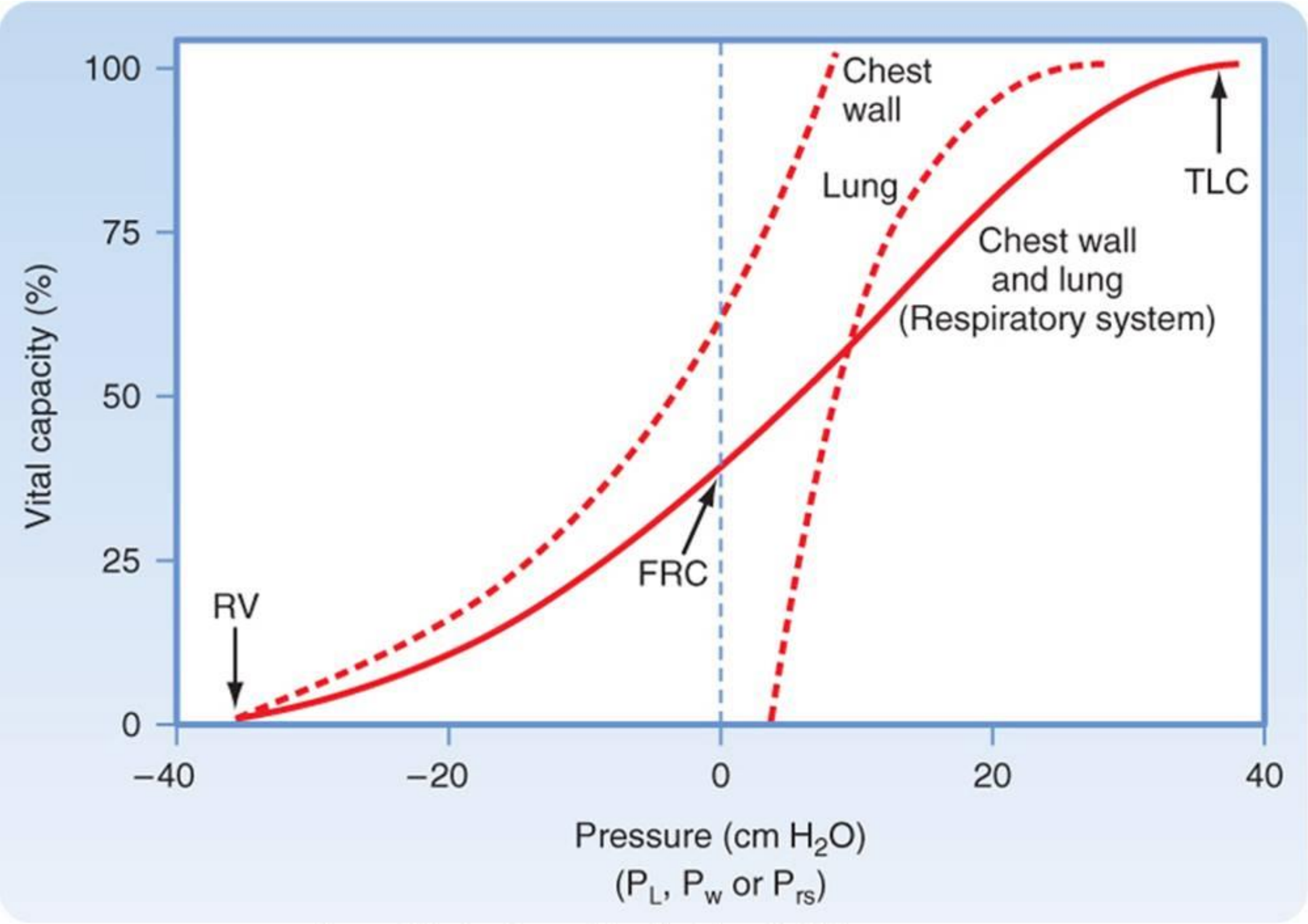
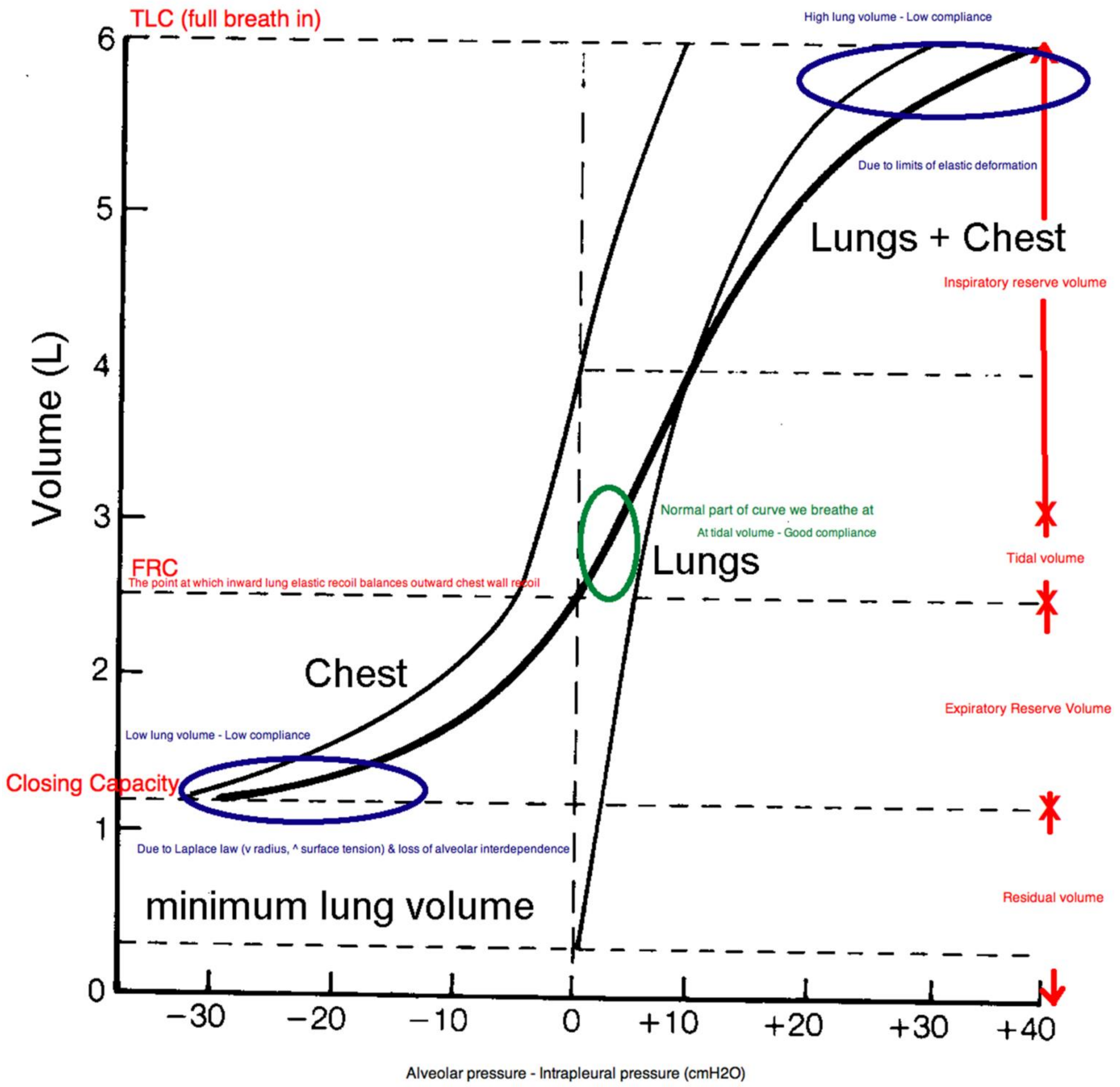


Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.

The transmural pressure across the respiratory system at FRC is zero. At TLC, both lung pressure and chest wall pressure are positive, and they both require positive transmural distending pressure. The resting volume of the chest wall is the volume at which the transmural pressure for the chest wall is zero, and it is approximately 60% of TLC. At volumes greater than 60% of TLC, the chest wall is recoiling inward and positive transmural pressure is needed, whereas at volumes below 60% of TLC, the chest wall tends to recoil outward


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

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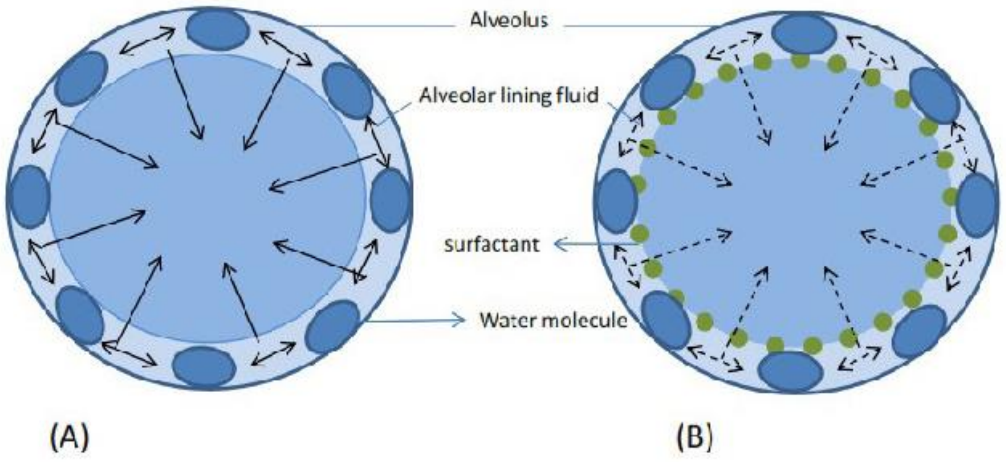
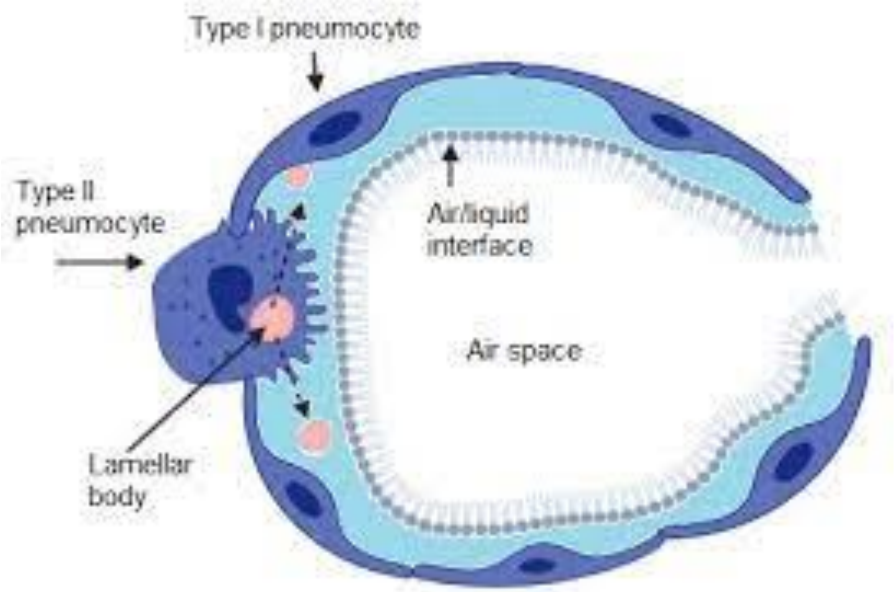
Elastic recoil is determined by two kinds of forces

- **lung compliance** (“distensibility”)
  – a measure of the relationship between this retractive force and lung volume (pressure-volume relationship)
  – defined as the change in lung volume brought about by unit change in transpulmonary (intrapleural) pressure (L/kPa)
- **surface tension** produced by the layer of fluid that lines the alveoli
  – determined by the cohesive (binding together) forces between molecules of the same type
    - on the inner surface of the alveoli there is a fluid that can resist lung expansion
    - there would be a lot of surface tension because there is an air-water interface in every alveolus
    - if surface tension remained constant, decreasing r during expiration would increase P and smaller alveolus would empty into large one
  – this collapsing tendency is offset by **pulmonary surfactant** which significantly lowers surface tension





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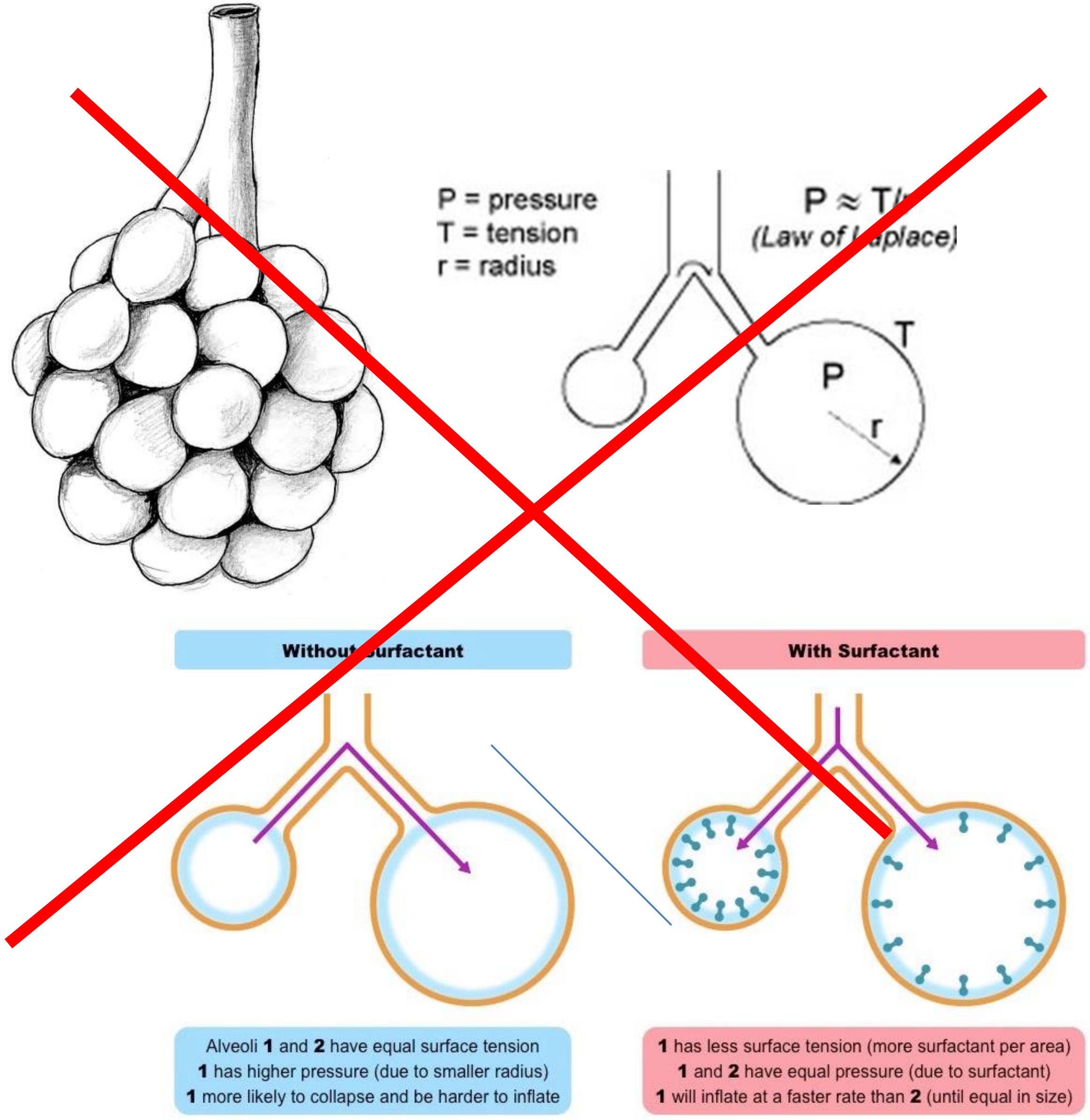
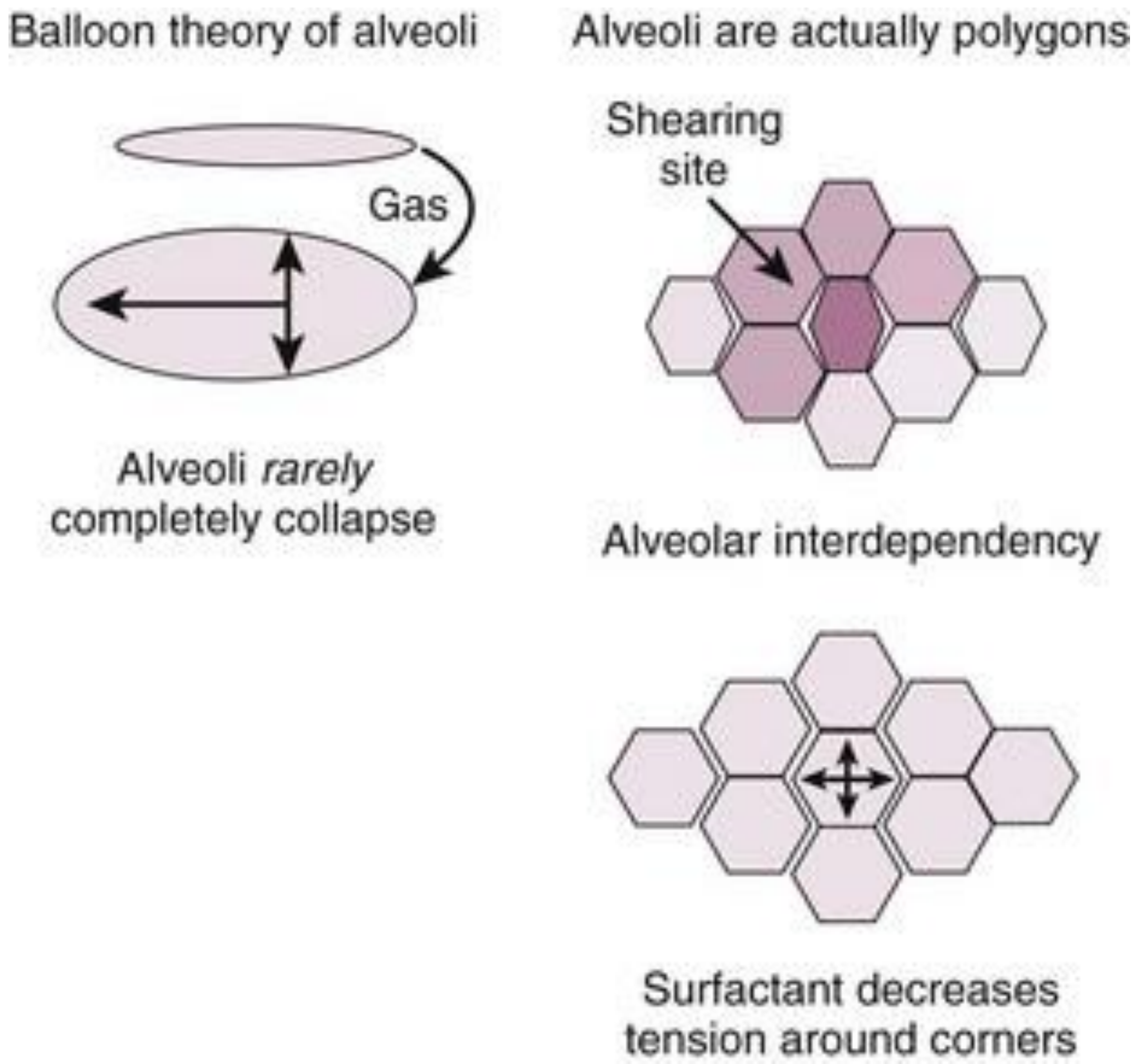
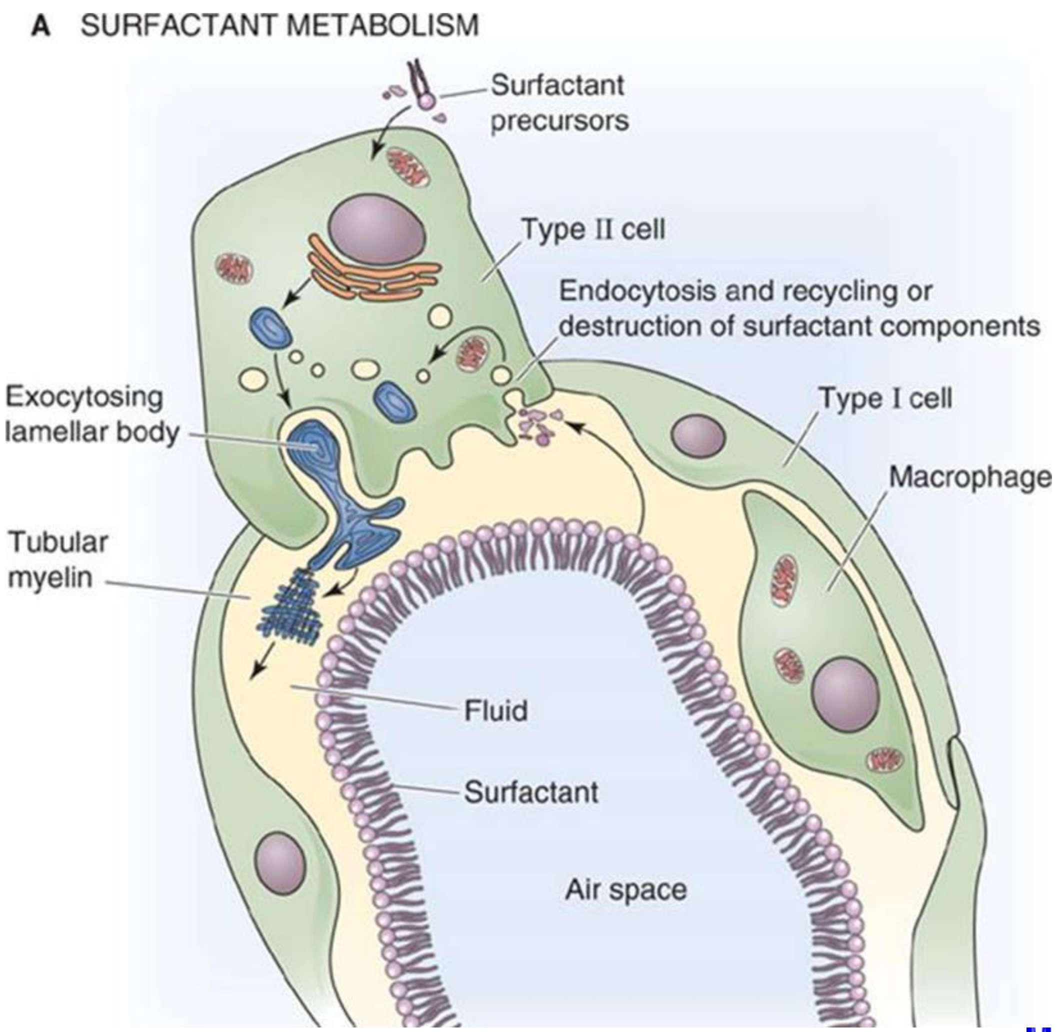
Historical misconception





Pulmonary surfactant

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



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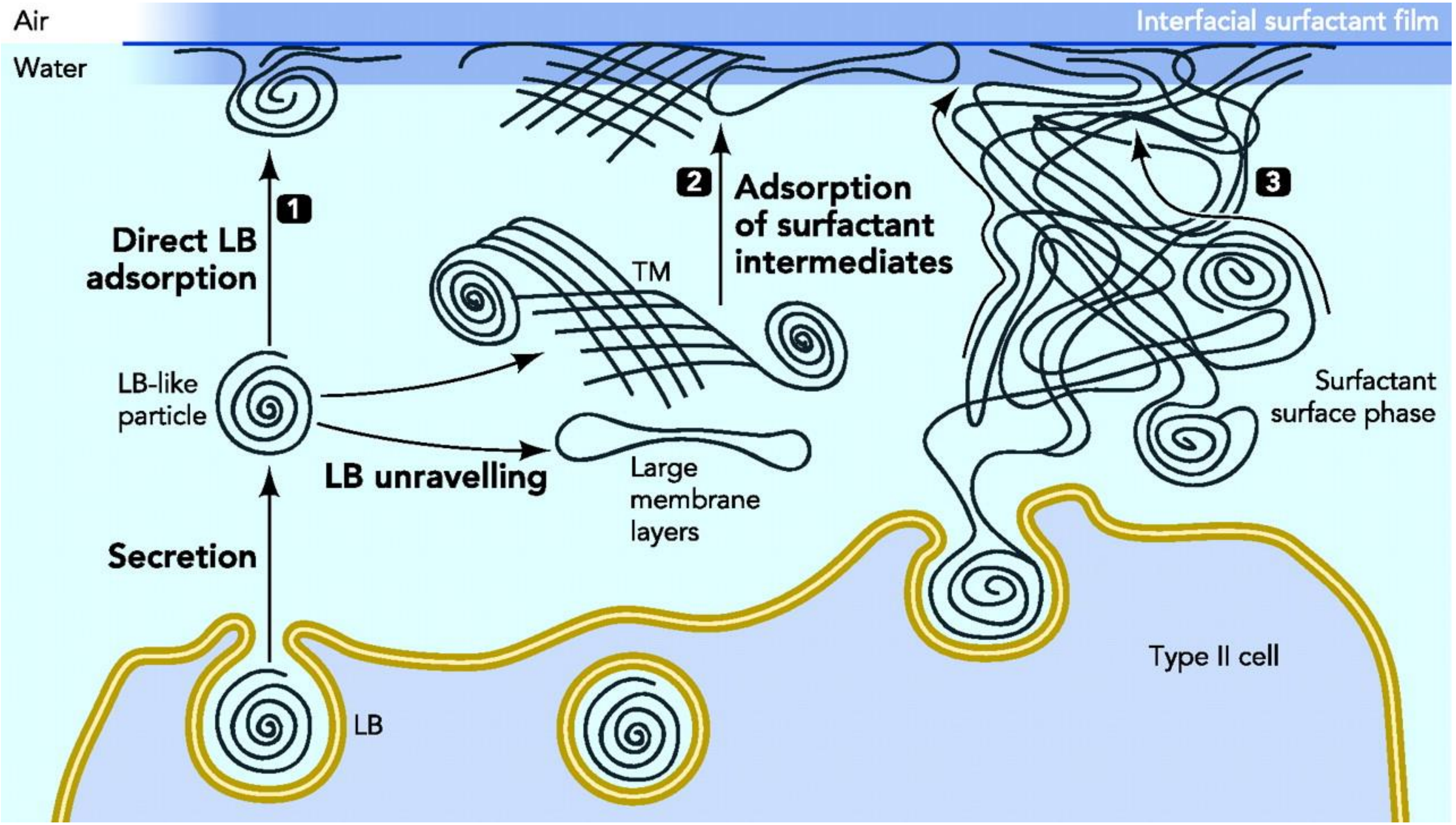
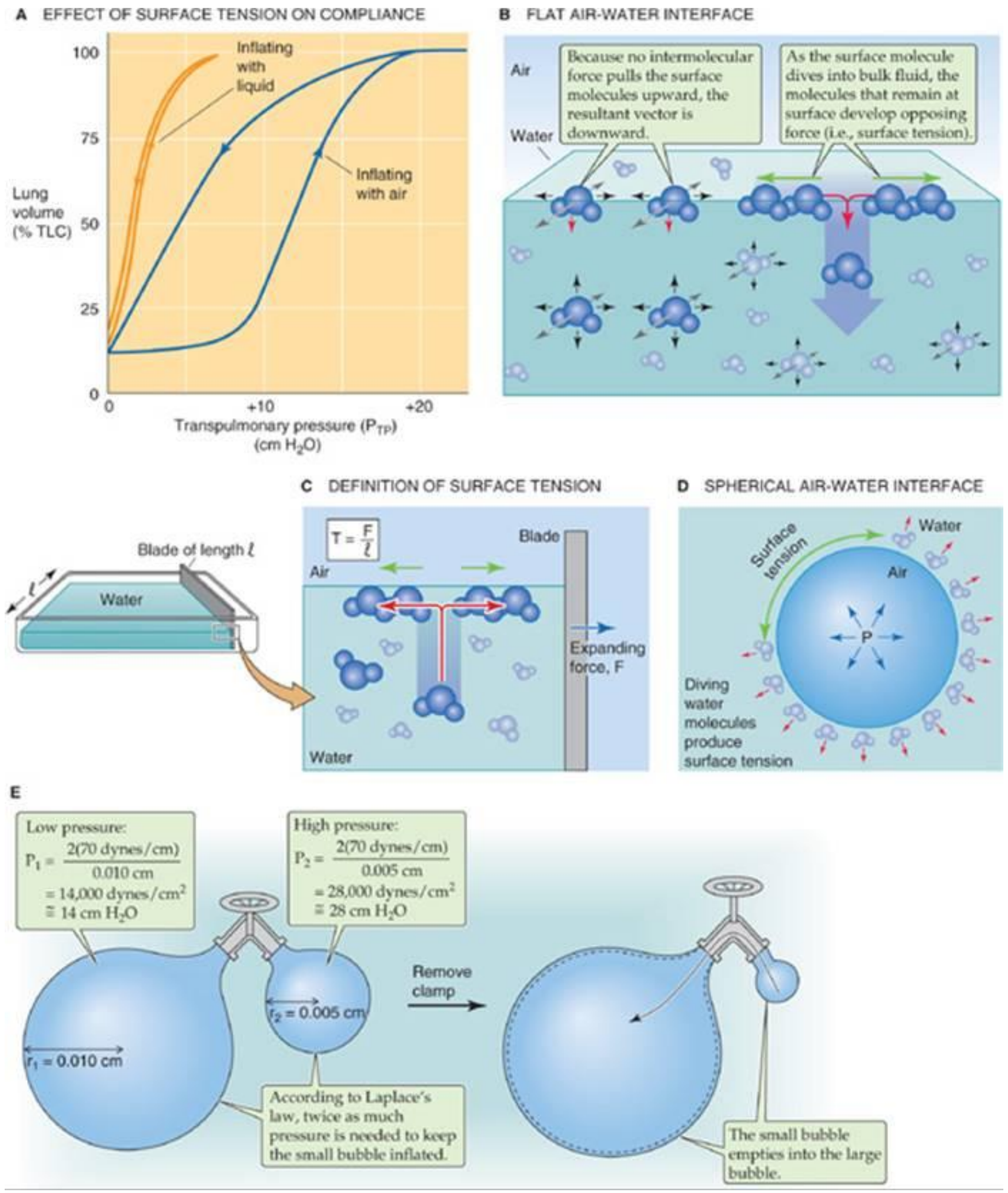
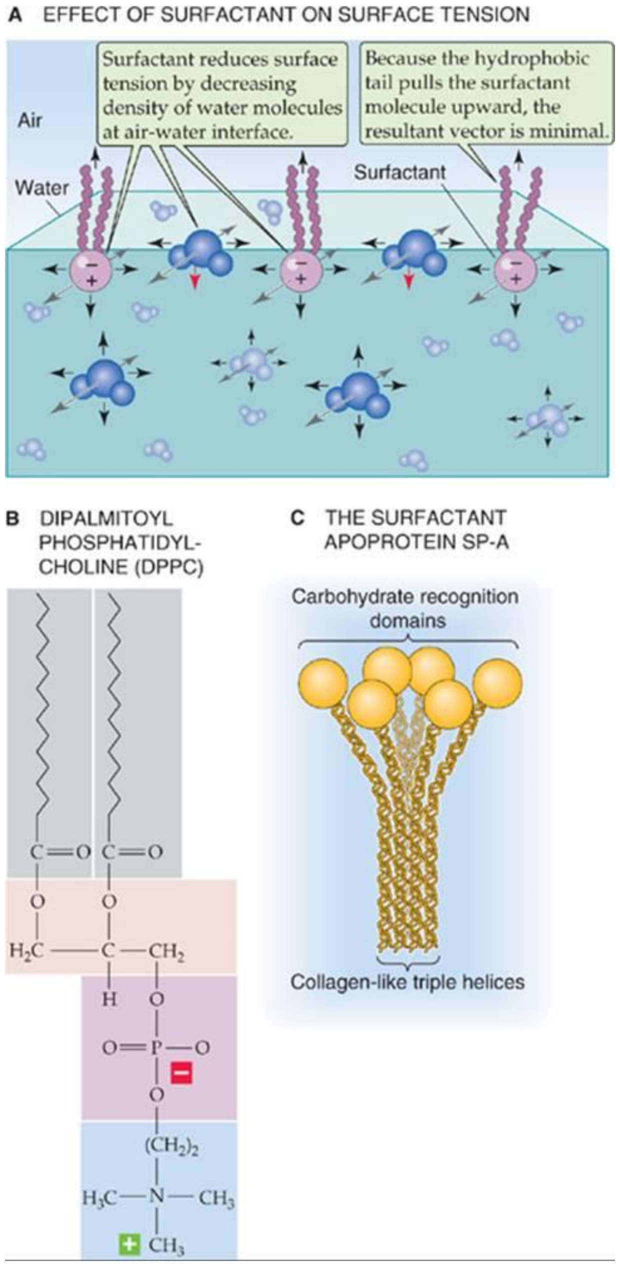
Pulmonary surfactant adsorption to the interface and surface film formation. Processes that may contribute to transport of surface active surfactant species to the interface include 1) direct cooperative transfer of surfactant from secreted lamellar body-like particles touching the interface, 2) unravelling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



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


A EFFECT OF SURFACE TENSION ON COMPLIANCE
Inflating with liquid
Inflating with air
Lung volume (% TLC)
100
75
50
25
0
0
+10
+20
Transpulmonary pressure (P_{TP}) (cm H_2O)
B FLAT AIR-WATER INTERFACE
Air
Water
Because no intermolecular force pulls the surface molecules upward, the resultant vector is downward.
As the surface molecule dives into bulk fluid, the molecules that remain at surface develop opposing force (i.e., surface tension).
C DEFINITION OF SURFACE TENSION
Blade of length ℓ
ℓ
Water
$T = \frac{F}{\ell}$
Blade
Air
Expanding force, F
Water
D SPHERICAL AIR-WATER INTERFACE
Surface tension
Water
Air
P
Diving water molecules produce surface tension
E
Low pressure:
$P_1 = \frac{2(70 \text{ dynes/cm})}{0.010 \text{ cm}}$
$= 14{,}000 \text{ dynes/cm}^2$
$\cong 14 \text{ cm } H_2O$
High pressure:
$P_2 = \frac{2(70 \text{ dynes/cm})}{0.005 \text{ cm}}$
$= 28{,}000 \text{ dynes/cm}^2$
$\cong 28 \text{ cm } H_2O$
$r_2 = 0.005$ cm
$r_1 = 0.010$ cm
Remove clamp
According to Laplace's law, twice as much pressure is needed to keep the small bubble inflated.
The small bubble empties into the large bubble.


A EFFECT OF SURFACTANT ON SURFACE TENSION
Surfactant reduces surface tension by decreasing density of water molecules at air-water interface.
Because the hydrophobic tail pulls the surfactant molecule upward, the resultant vector is minimal.
Air
Water
Surfactant
B DIPALMITOYL PHOSPHATIDYL-CHOLINE (DPPC)
C═O
C═O
O
O
H_2C
C
CH_2
H
O
O═P—O
O
$(CH_2)_2$
H_3C—N—CH_3
CH_3
C THE SURFACTANT APOPROTEIN SP-A
Carbohydrate recognition domains
Collagen-like triple helices

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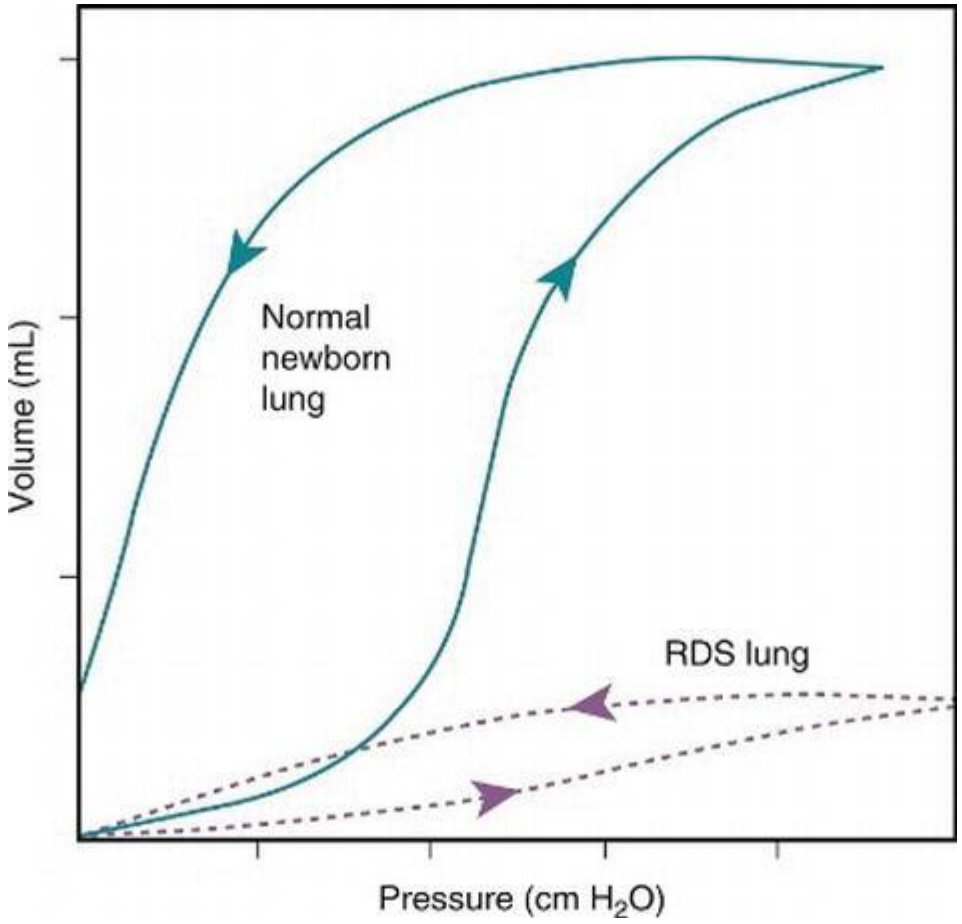
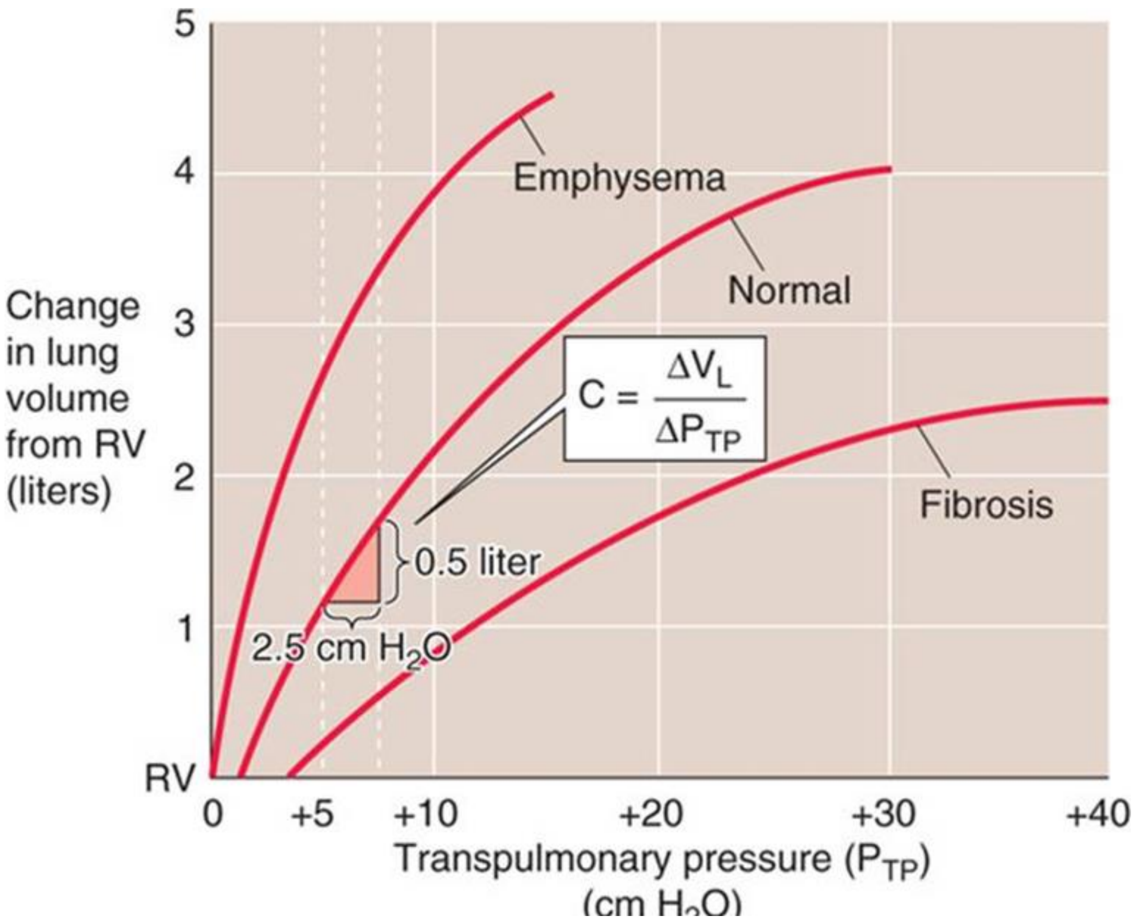
Newborn respiratory distress syndrome (nRDS)



- hyaline membrane syndrome
- surfactant substitution
  - porcine or modified bovine
    - sterilized
  - synthetic
  - next generation
    - recombinant SP proteins
- indication: nRDS
  - less convincing evidence for ARDS, aspiration, pneumonia, …

Abnormalities of elastic properties

- change of lung compliance (TLC, FRC, RV)
  - ↑ pulmonary **emphysema**, aging (↑TLC, ↑FRC, ↑RV)
  - ↓ **interstitial disease** (↓TLC, ↓FRC, ↓RV)
    - e.g. pulmonary fibrosis or bronchopneumonia
- lack of surfactant (↓TLC, ↓FRC, ↓RV)
  - infant or adult **respiratory distress syndromes** (IRDS or ARDS, resp.), i.e. tendency of lung to collapse
  - alveolar lung **edema** (damages/dilutes surfactant)
- diseases that affect the movement of the thoracic cage and diaphragm
  - marked obesity
  - diseases of the thoracic spine
    - ankylosing spondylitis and kyphoscoliosis
  - neuropathies
    - e.g. the Guillain-Barre syndrome)
  - injury to the phrenic nerves (spine C3-C5)
  - myasthenia gravis



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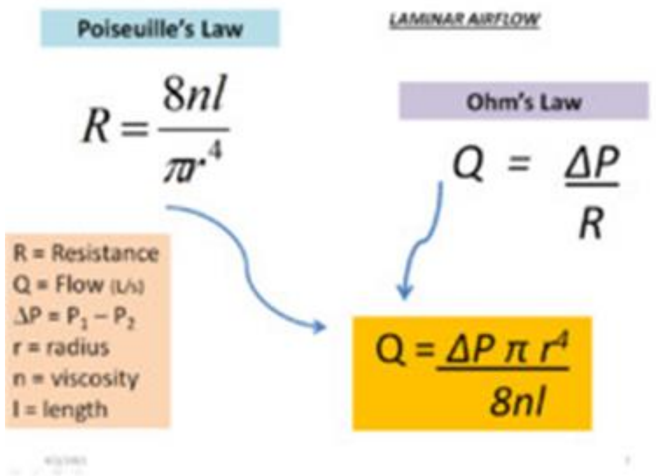
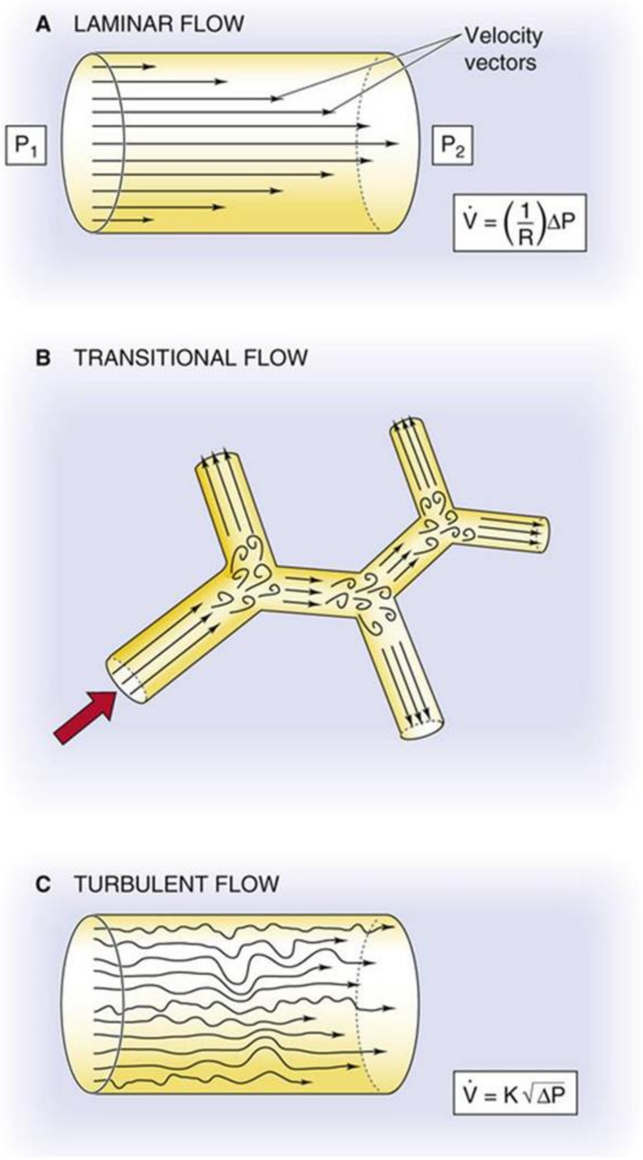
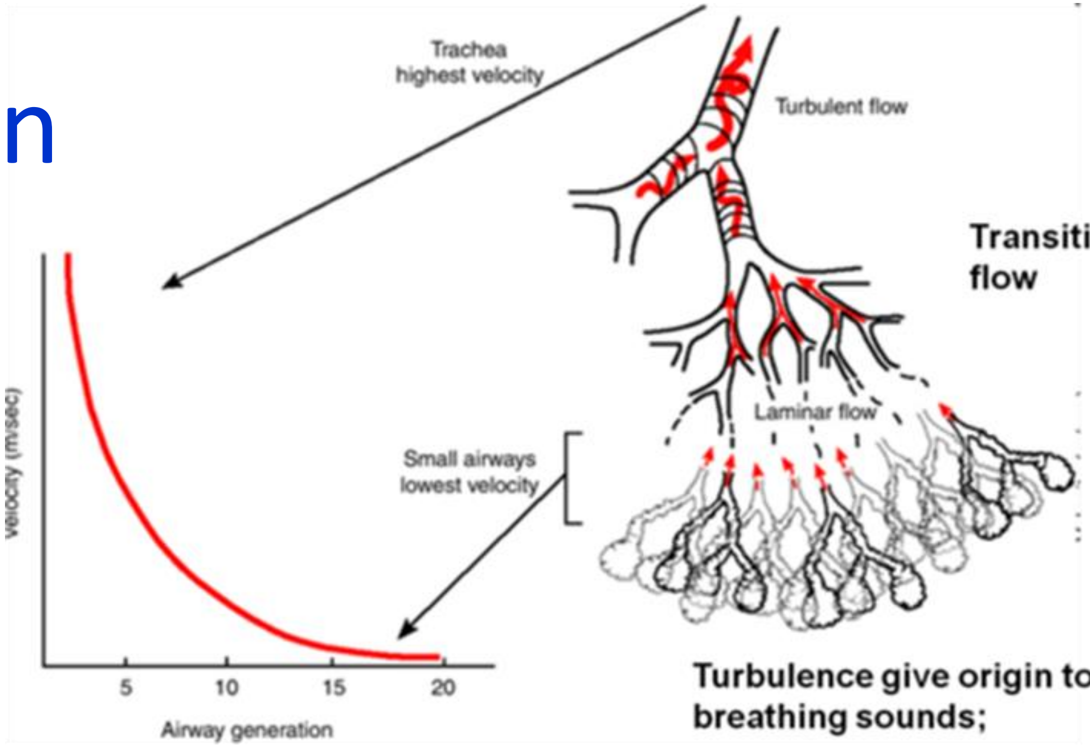
(ad 2) Airway (dynamic) resistance

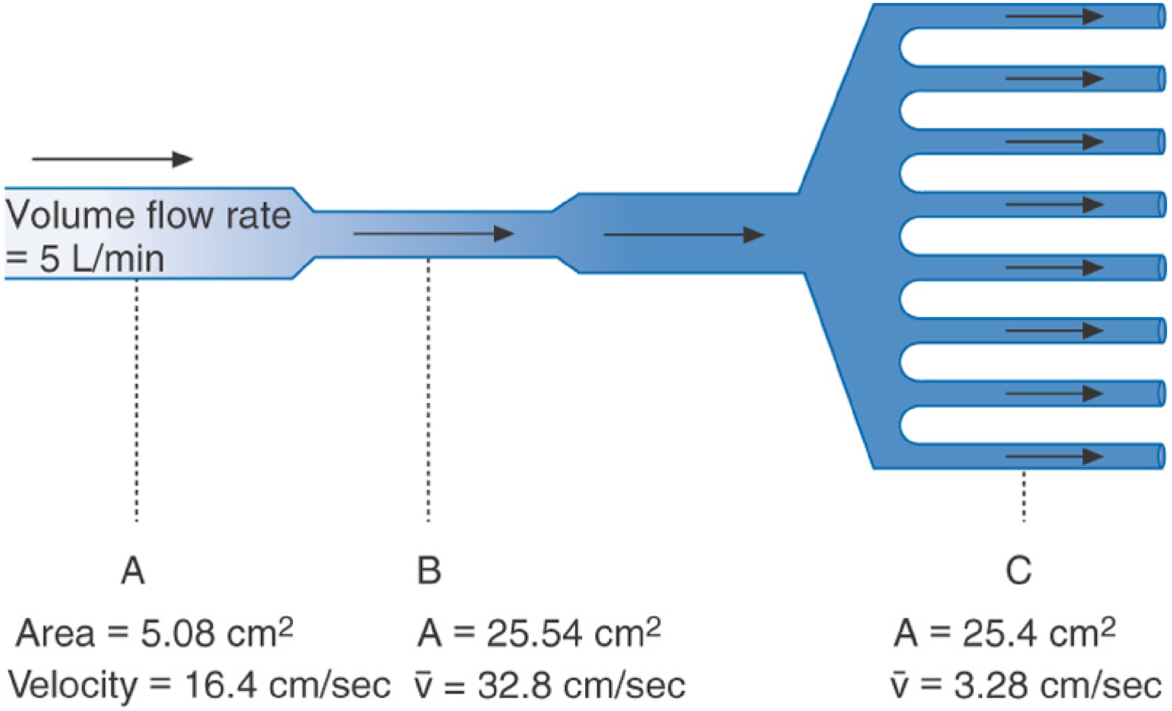
- Poiseuille's law for pressure states that pressure is
  - directly proportional to
    - flow
    - tube length
    - and viscosity
  - and it is inversely proportional to tube radius
- Overcoming increased resistance requires **forced expiration**





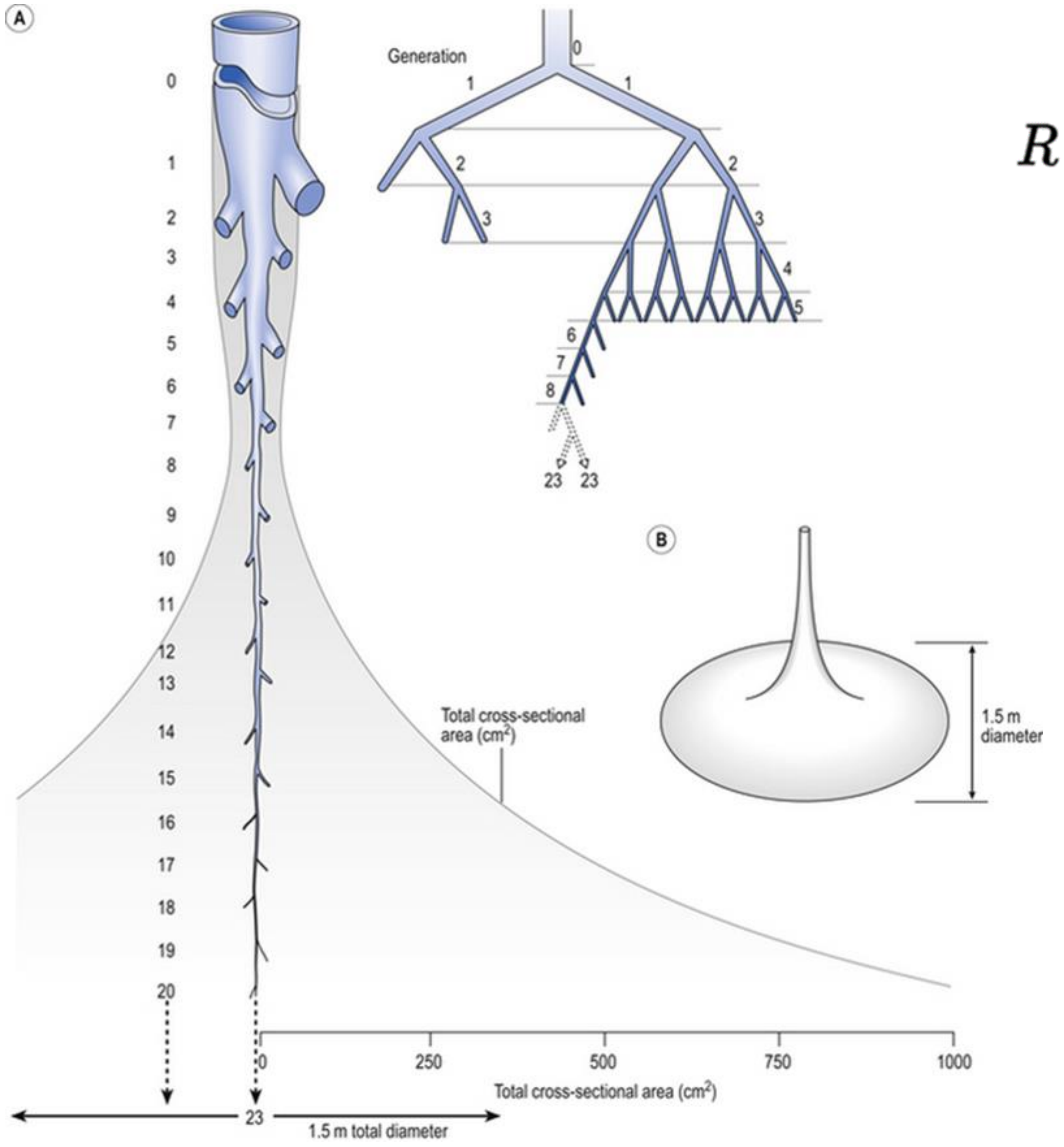
Airflow velocity and pattern



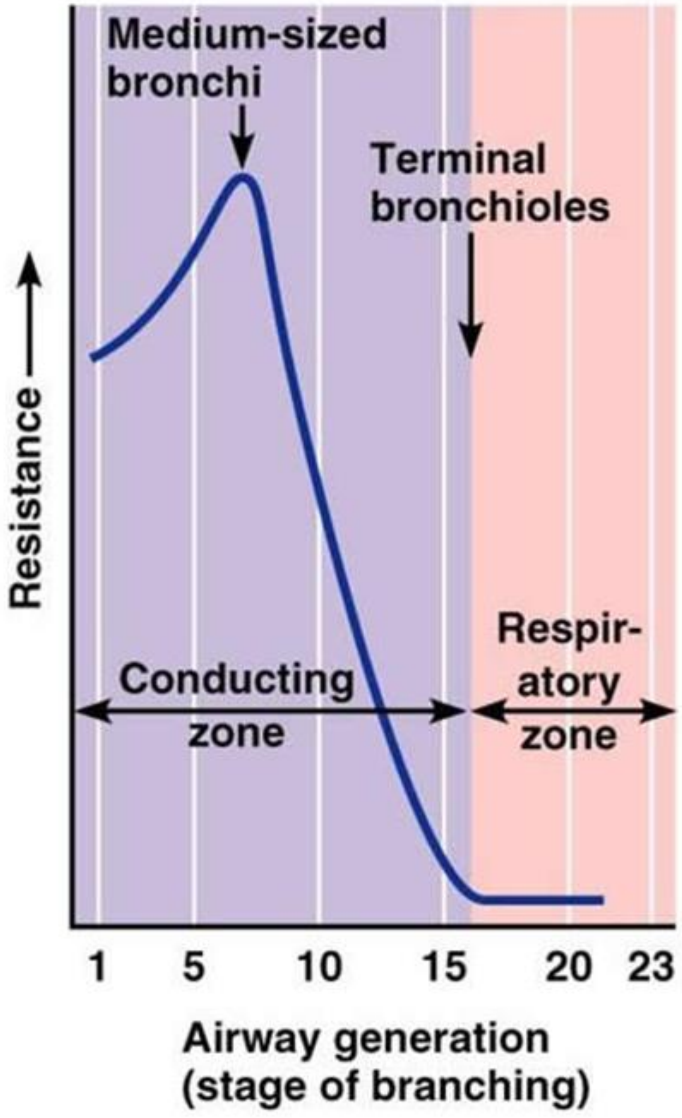


(Modified from Nave CR, Nave BC: Physics for the health sciences, ed 3, Philadelphia, 1985, WB Saunders.)

Airflow – where is the highest resistance?



$$R = \frac{8\eta l}{\pi r^4}$$



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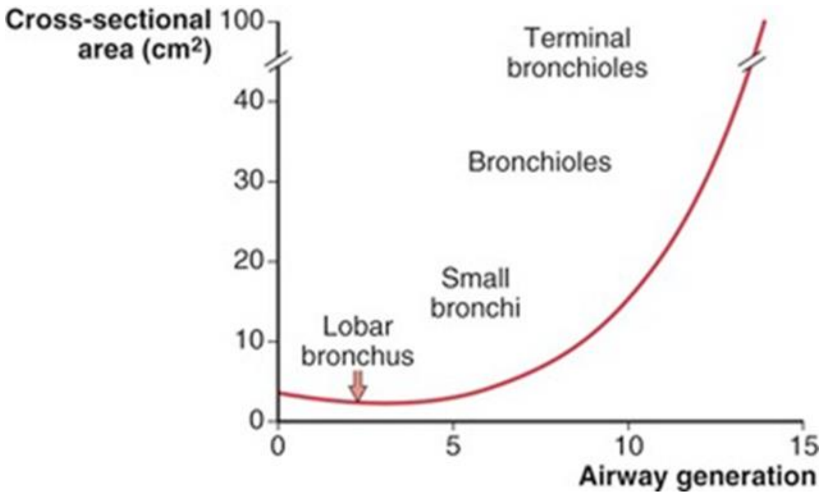
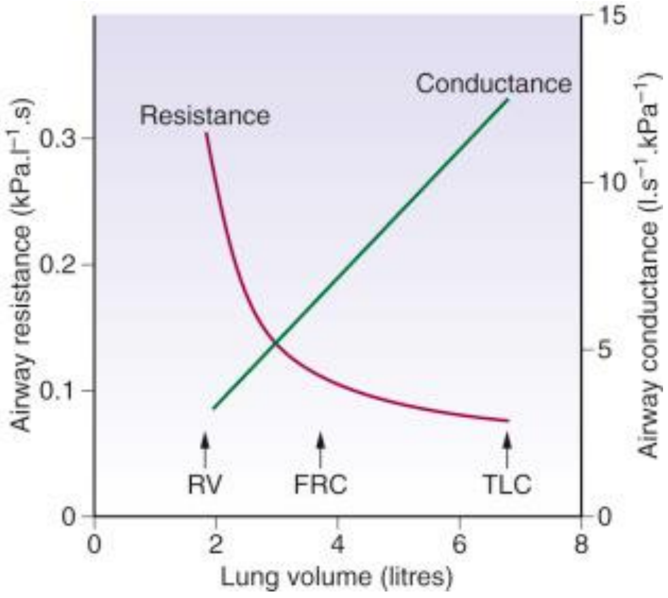
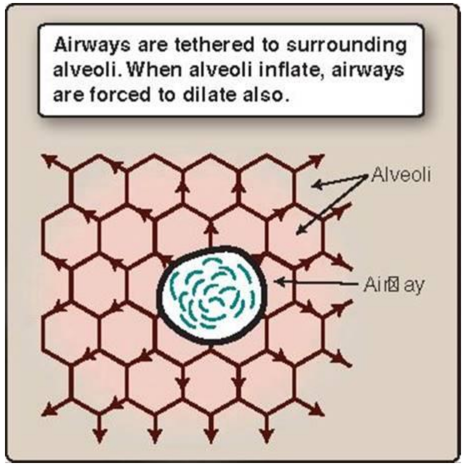
Airflow resistance





- From the trachea to the periphery, the airways become smaller in size, however, greater in number
  - **the cross-sectional area available for airflow increases as the total number of airways increases**
  - the flow of air is greatest in the trachea and slows progressively towards the periphery (as the velocity of airflow depends on the ratio of flow to cross-sectional area)
    - in the terminal airways, gas flow occurs solely by diffusion
- The **resistance to airflow** is very low (0.1-0.2 kPa/L in a normal tracheobronchial tree), **steadily increasing from the small to the large airways**
- Airway tone is under the control of the autonomic nervous system
  - bronchomotor tone is maintained by **vagal efferent nerves**
  - many **adrenoceptors** on the surface of bronchial muscles respond **to circulating catecholamines**
    - sympathetic nerves do not directly innervate them!
- Airway resistance is also **related to lung volumes**
  - because airways are 'tethered' by alveoli (i.e. pulled open by radial traction)
  - visible on bronchoscopy
  - patients with obstruction benefit from breathing in high lung volumes



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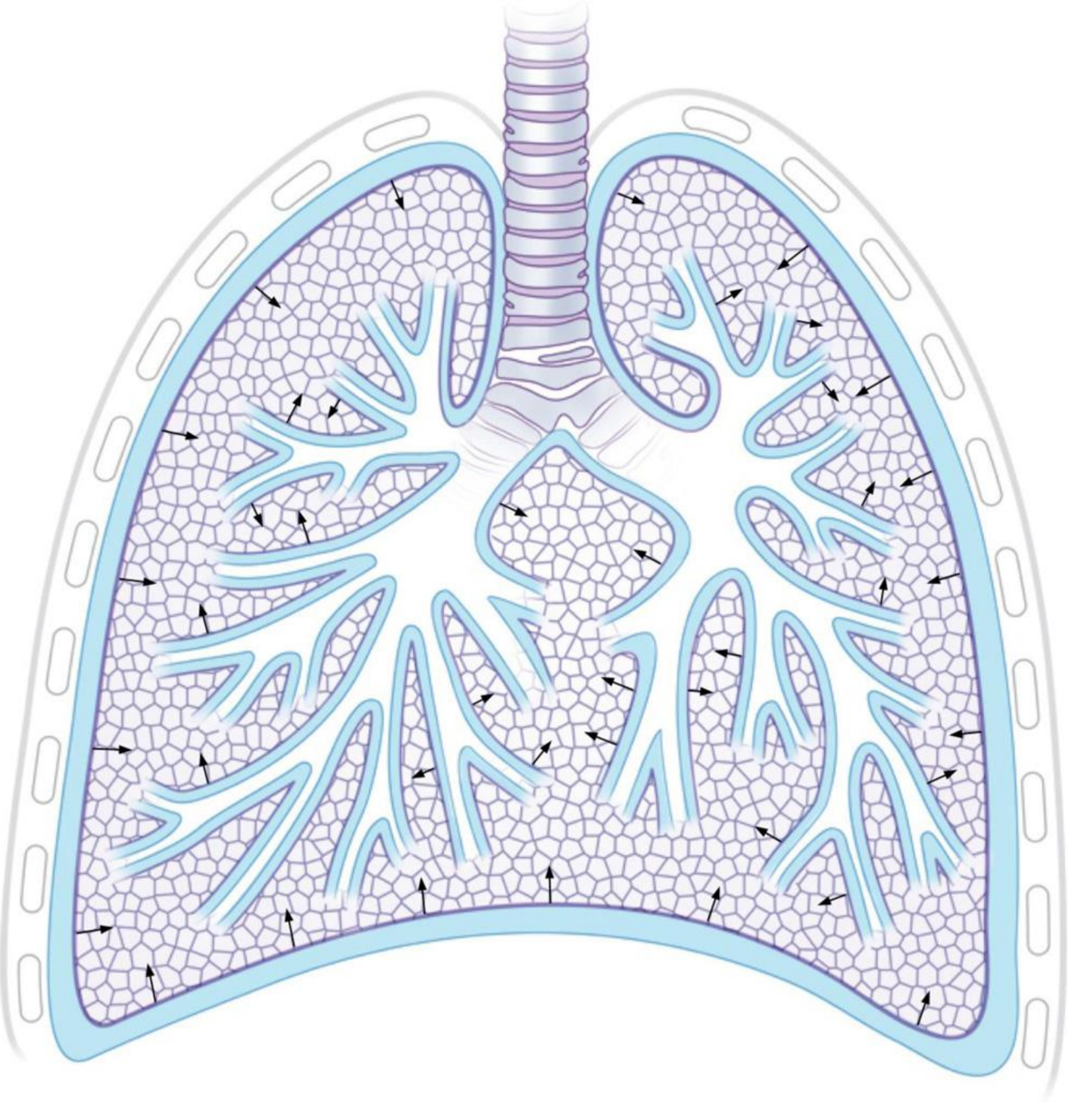
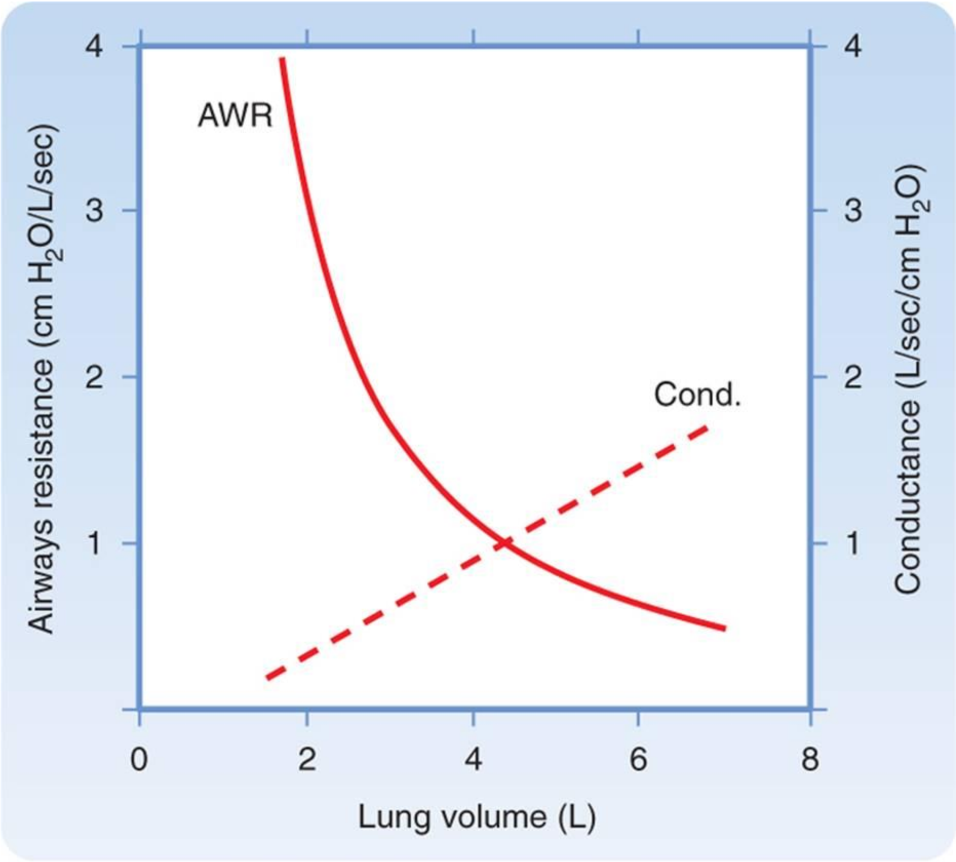
Airway-Parenchymal Interdependence





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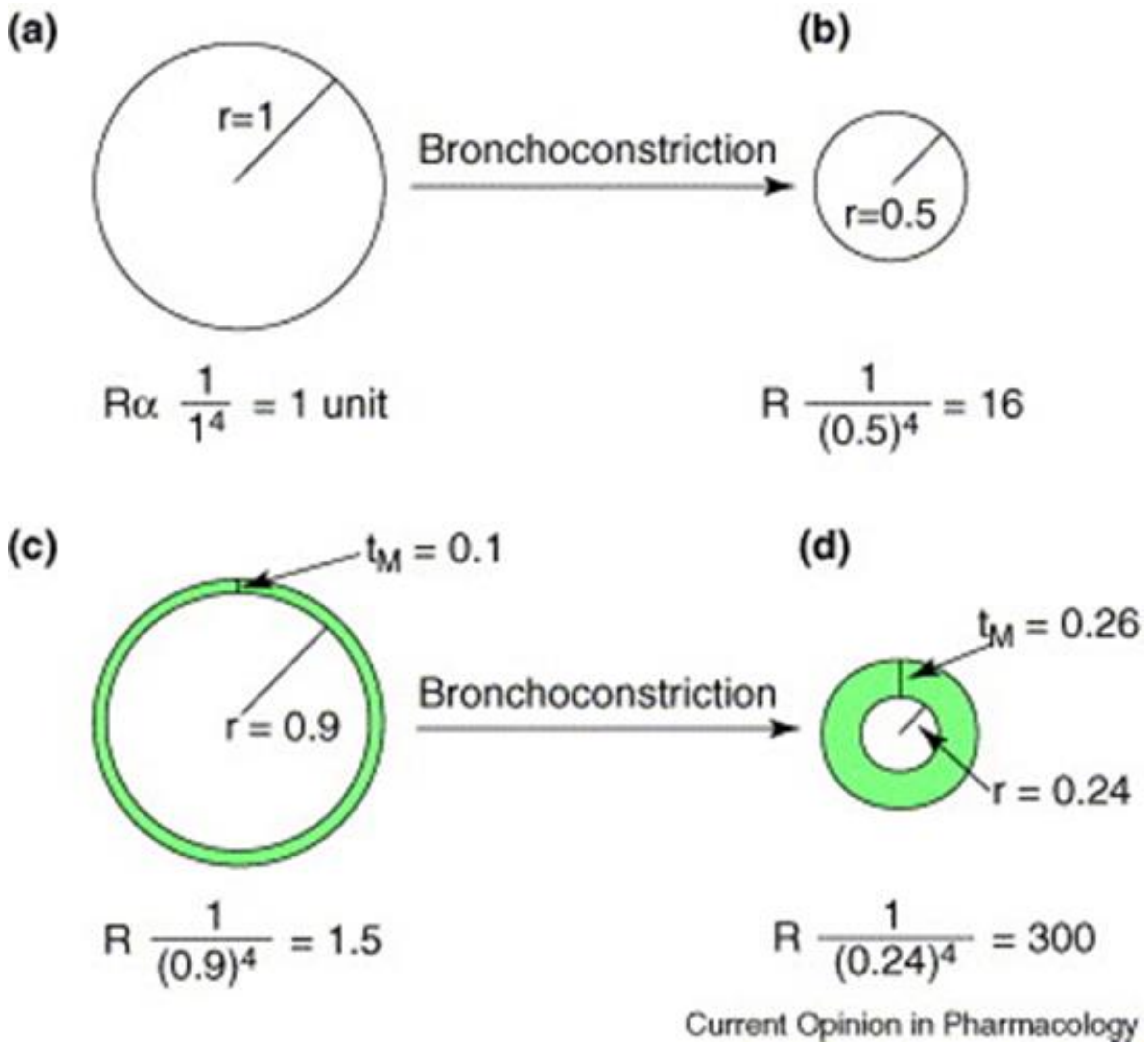
Airflow resistance – effect of changed airway diameter



$$R = \frac{8\eta l}{\pi r^4}$$

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

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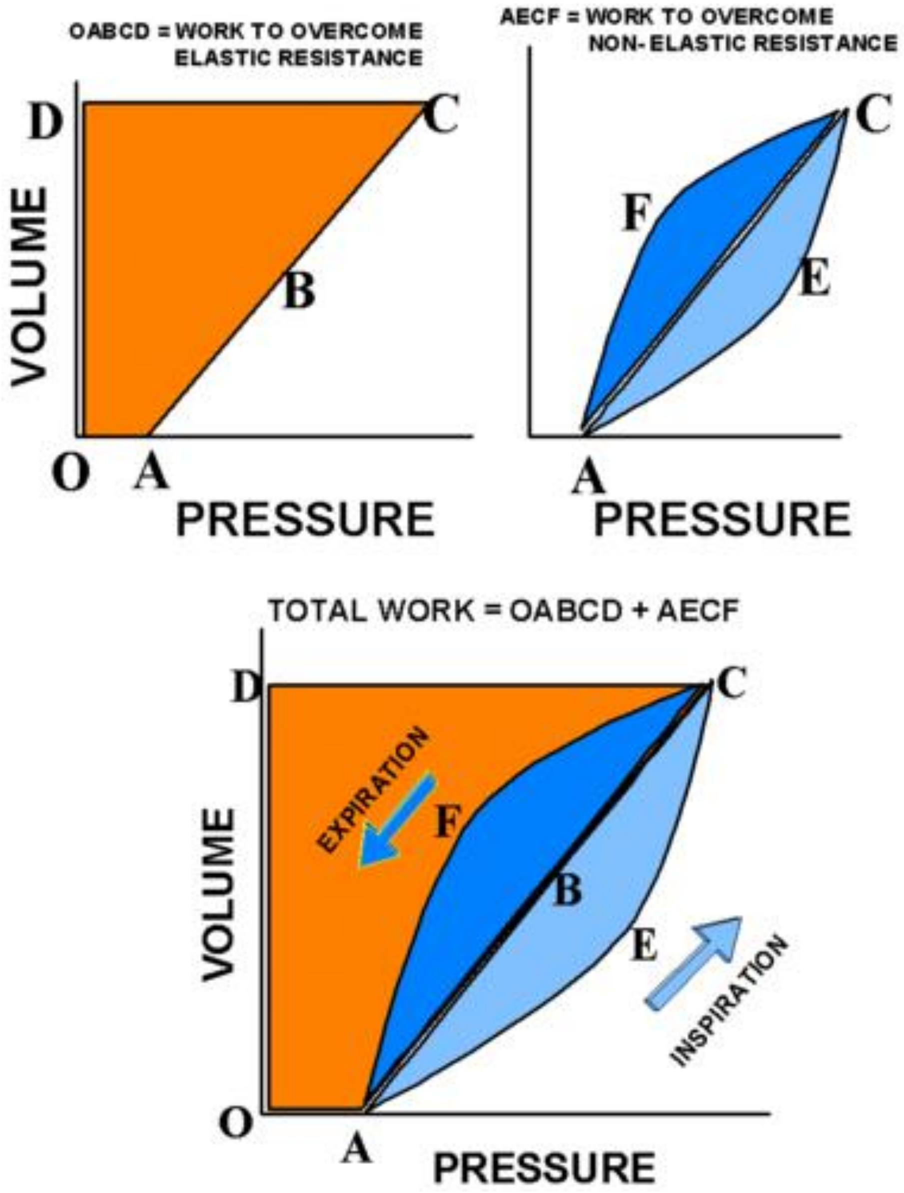
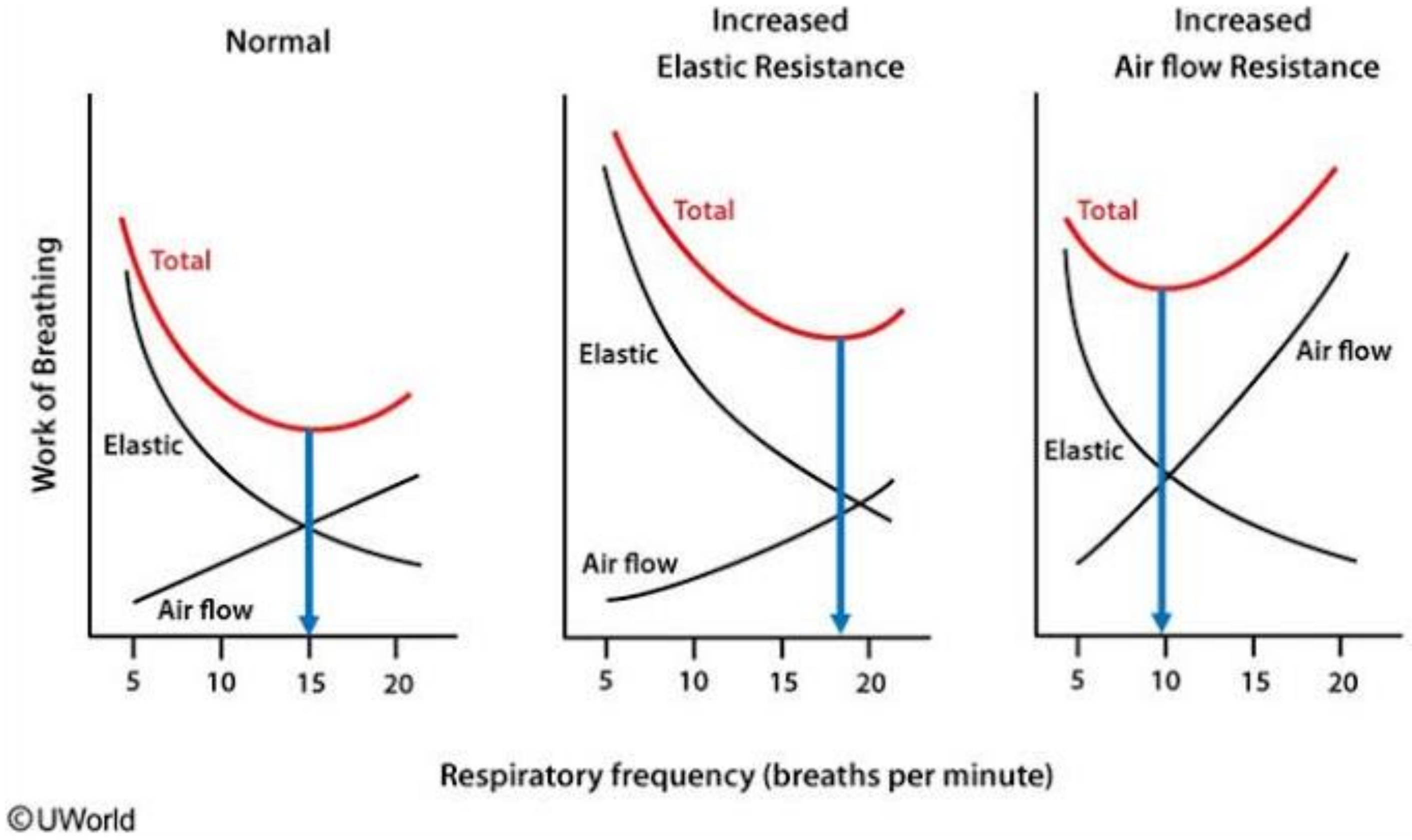
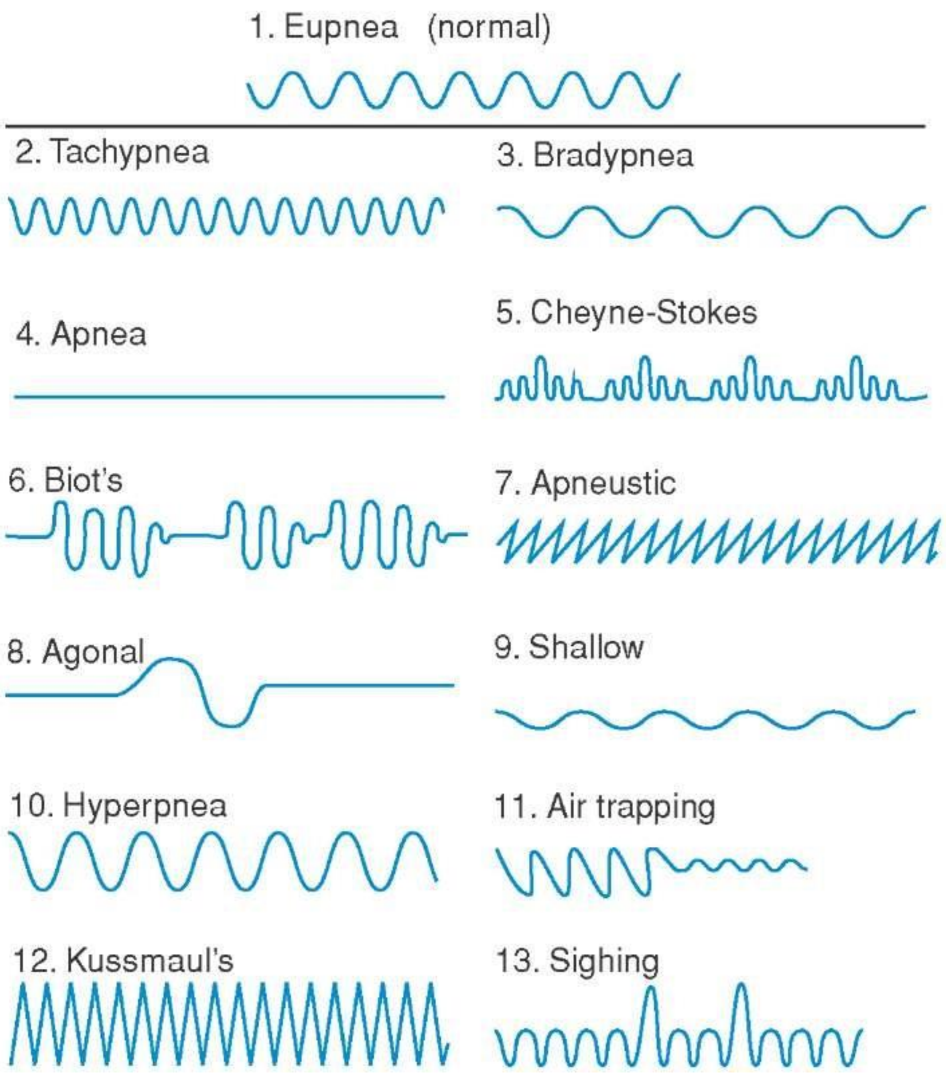
Work of breathing – to overcome resistance





Eupnoea vs. abnormal breathing pattern

- eupnoea
  - $f \times V_T$ = 12-18/min × 500 mL
- pathology according to fervency, volume and preferred position of the subjects
  - tachypnea × hypopnea
  - orthopnea × platypnea × trepopnea,
  - dyspnea
  - apnea



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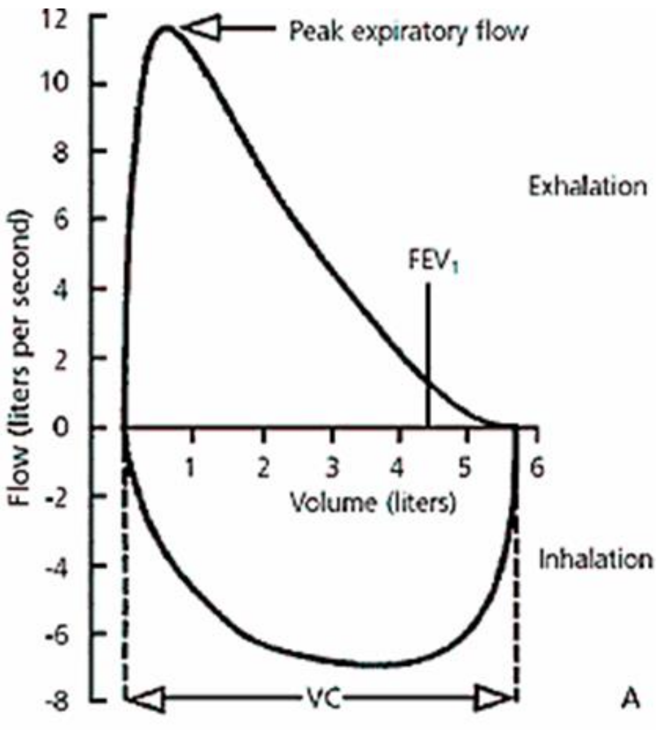
(4) DYNAMIC COMPRESSION OF THE AIRWAYS (DURING FORCED EXPIRATION SUCH AS IN MANY PULMONARY DISEASES)

Airflow pattern

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



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

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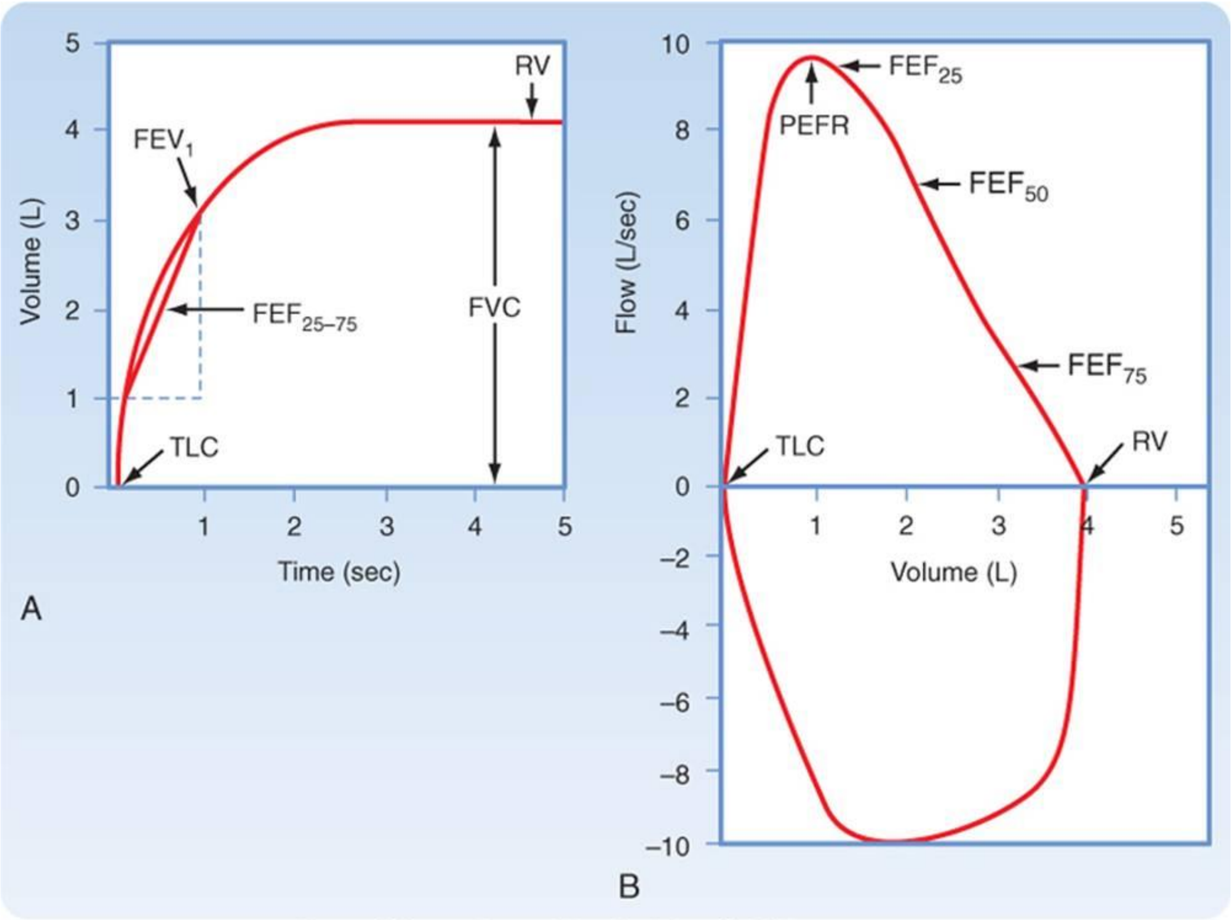
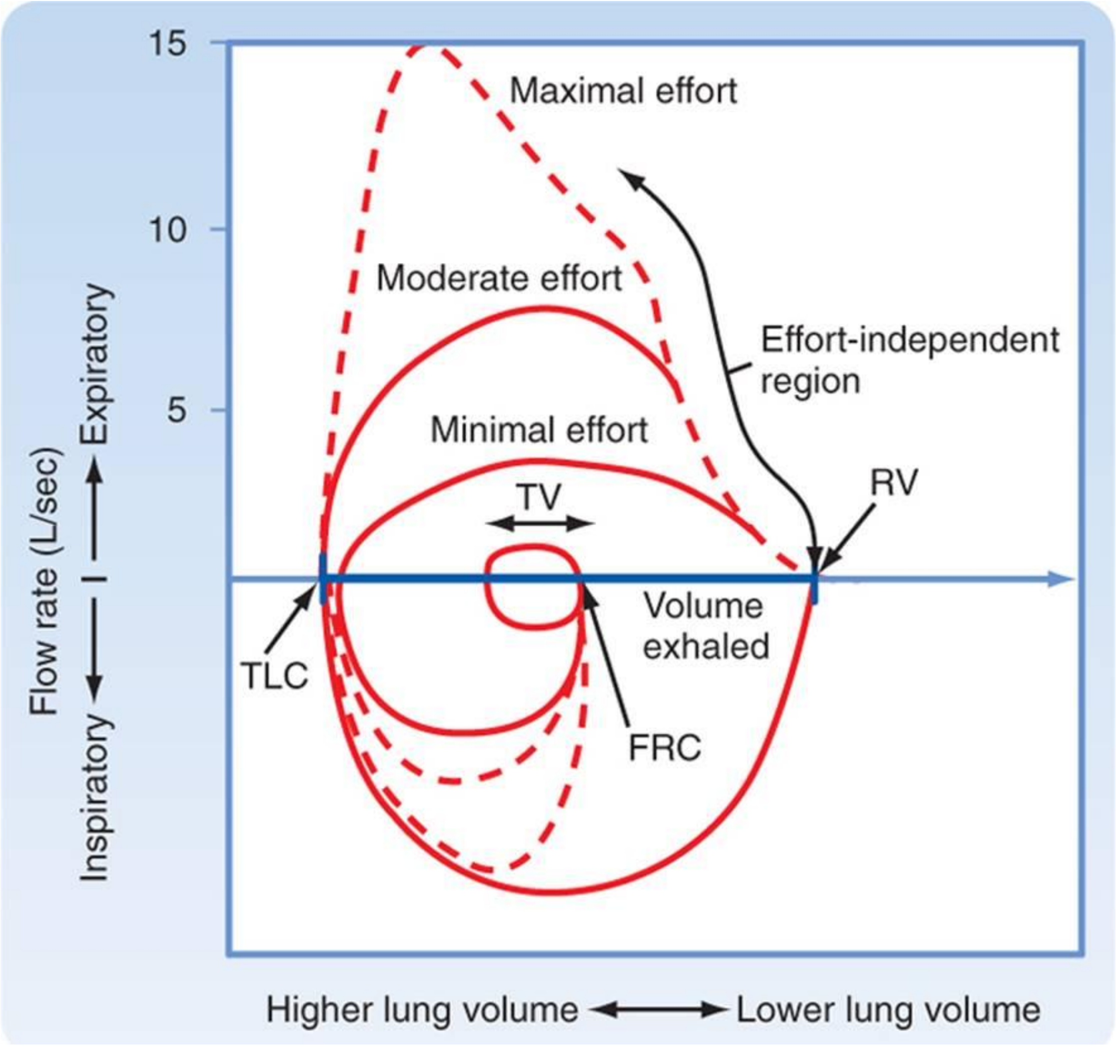
Flow-volume loop: peak inspiratory and expiratory flow rates are dependent on effort, whereas expiratory flow rates later in expiration are independent of effort.





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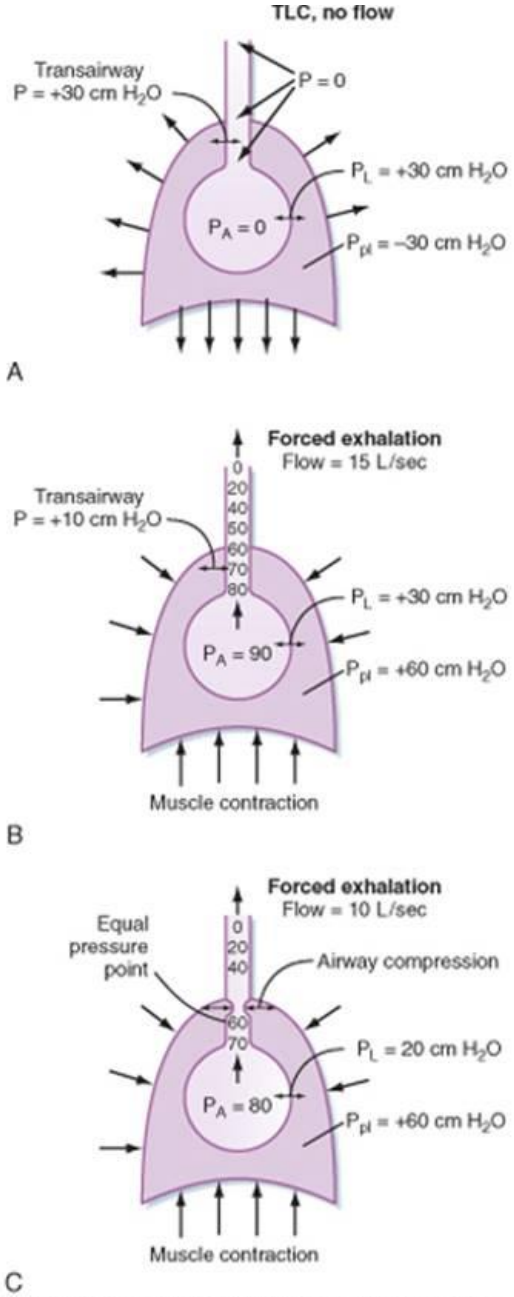

Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.

Why is expiratory flow limited?

- In forced expiration, the driving pressure raises both the P_{ALV} and the P_{PL}
  - between the alveolus and the mouth, a point will occur (C) where the airway pressure will equal the intrapleural pressure, and airway compression will occur
    - **equal pressure point**
  - however, this equal pressure point and event. compression of the airway is not fixed during the entire expiration (as the lung volume decreases)
  - initially, it does not exists in the absence of lung disease, since the equal pressure point occurs in airways that contain cartilage, and thus they resist collapse
  - later, the equal pressure point moves closer to the alveoli (due to airway obstruction or loss of radial traction in lung emphysema) causing transient occlusion of the airway
    - this, however, results in an increase in pressure behind it (i.e. upstream) and this raises the intra-airway pressure so that the airways open and flow is restored
  - the airways thus tend to vibrate at this point of **'dynamic airway compression/collapse'**

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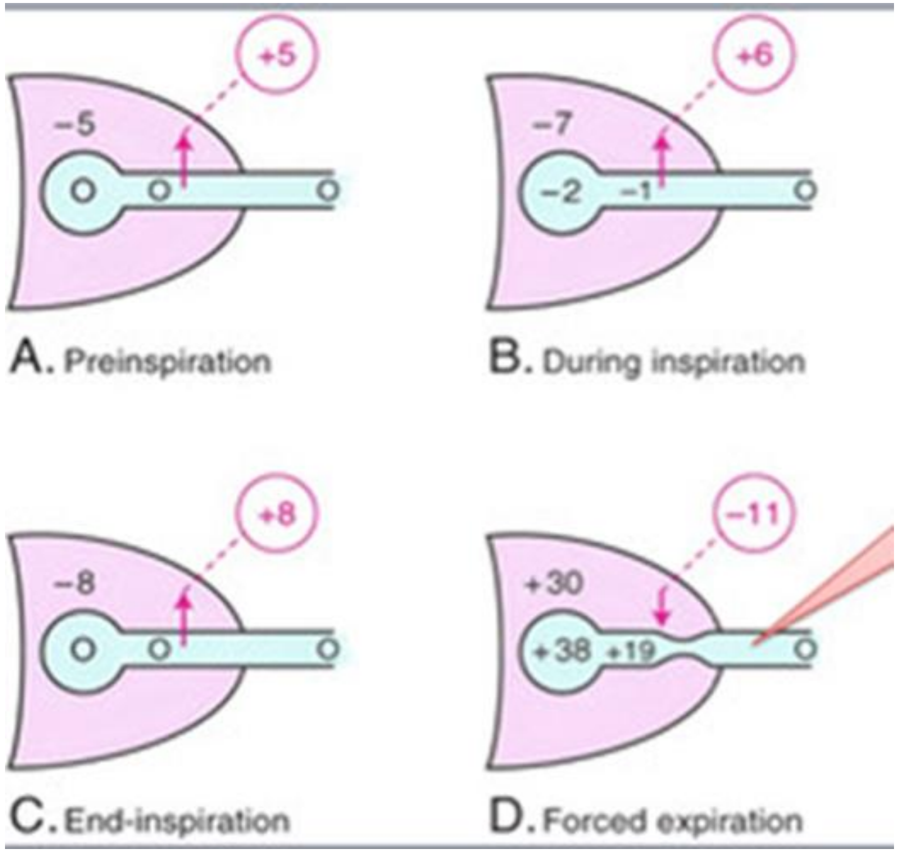
Dynamic airway compression/collapse



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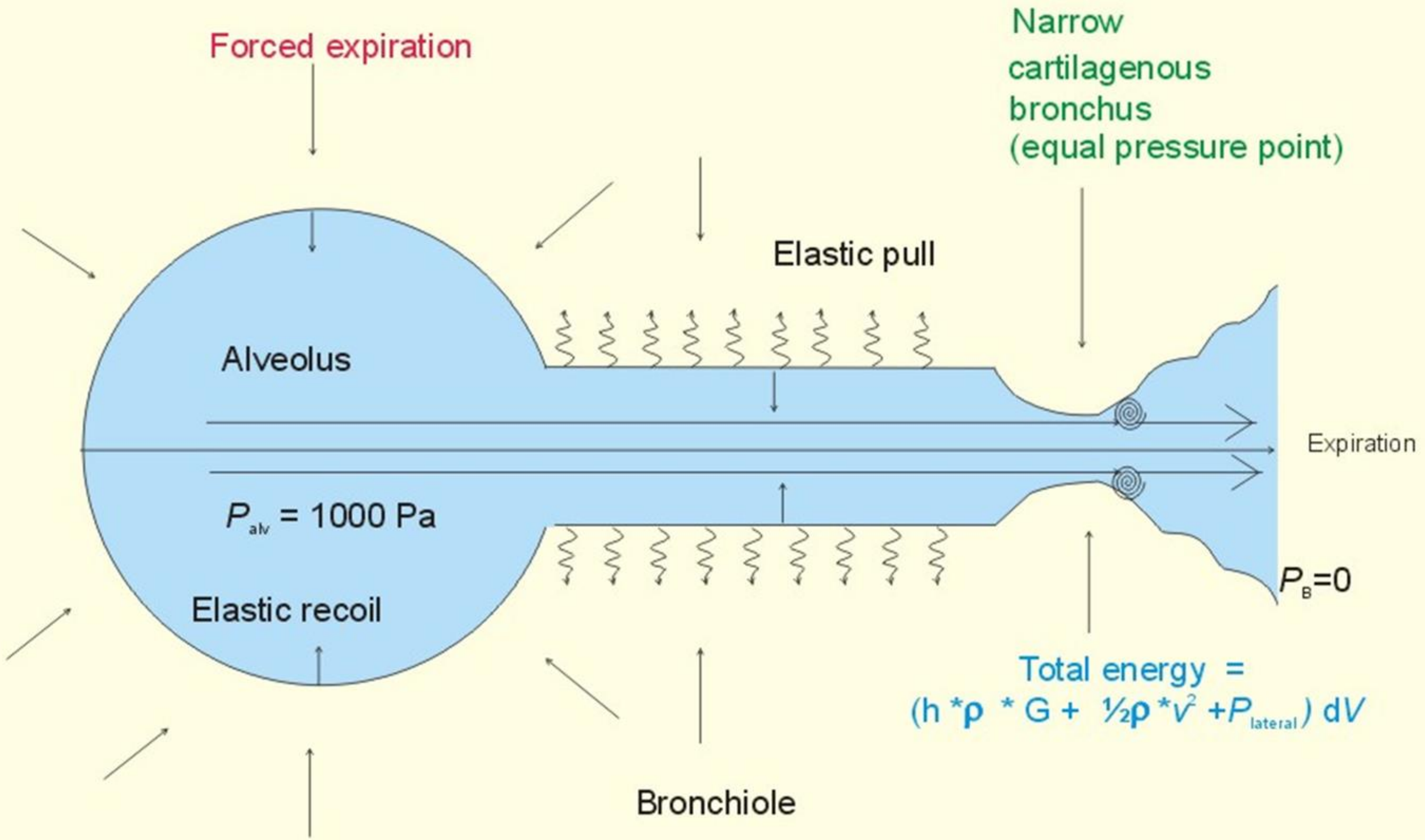
Dynamic Airway Collapse

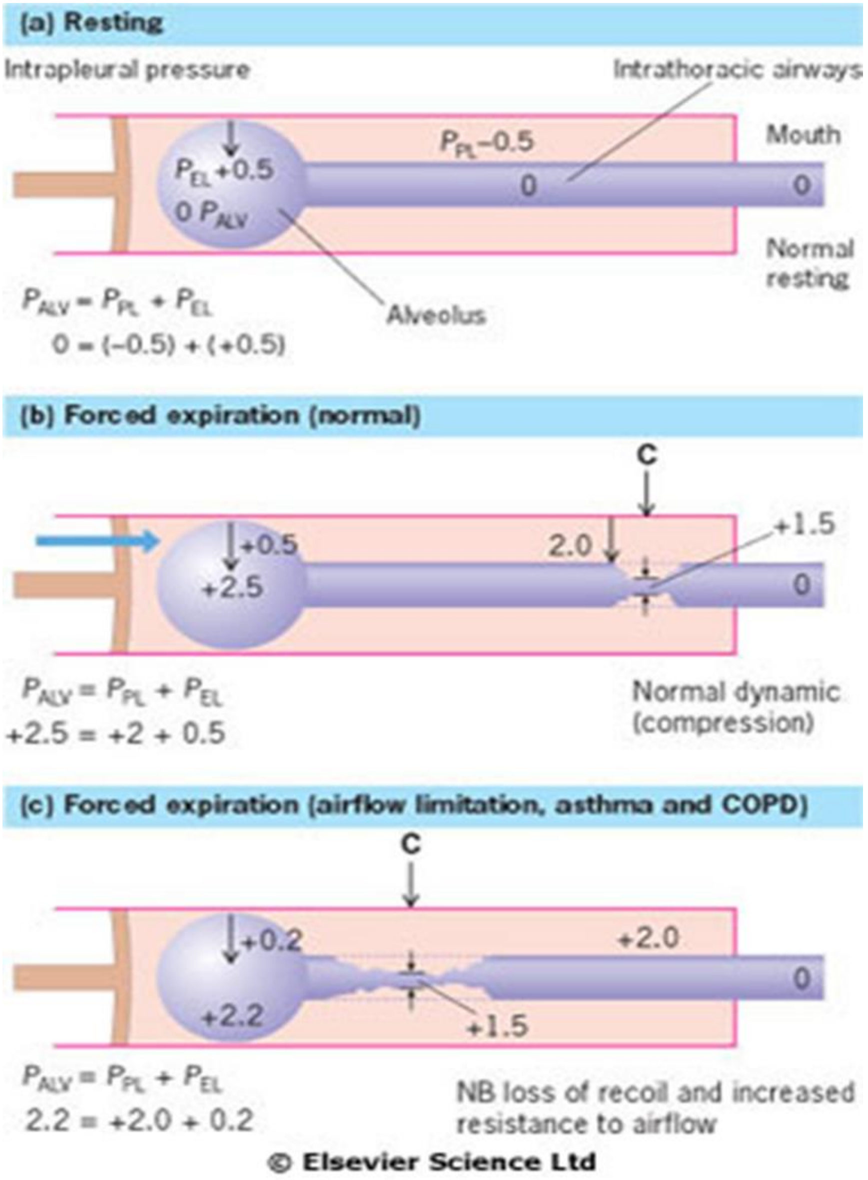


Expiratory effort --- Increased kinetic energy --- Reduced lateral pressure --- Dynamic Airway Collapse

Fig. 13-5

KMc

Dynamic compression in various situations



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

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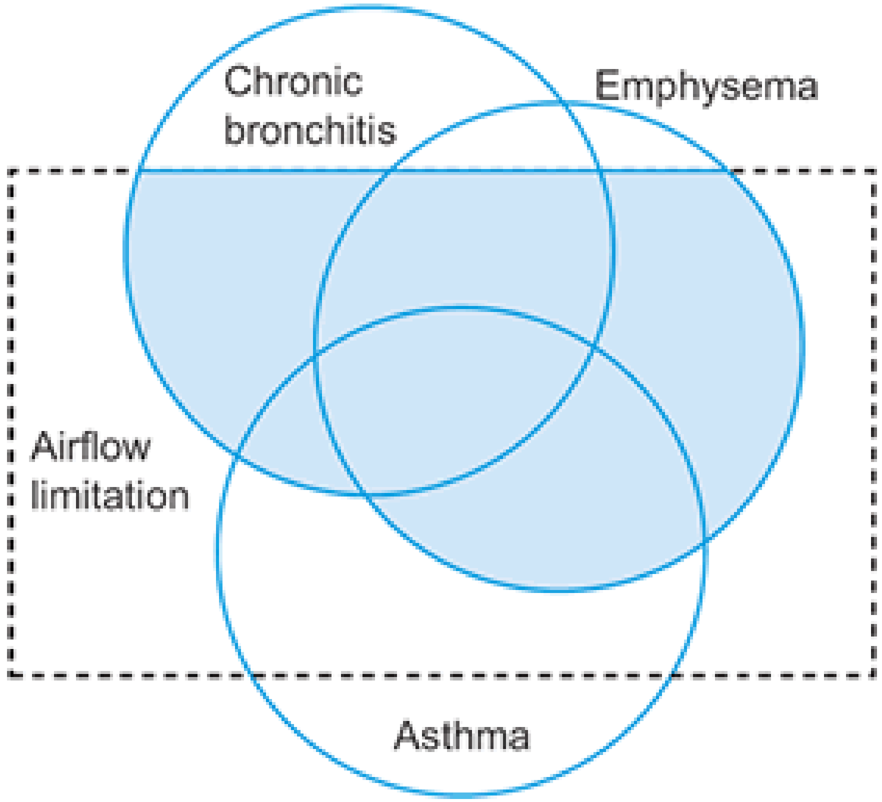
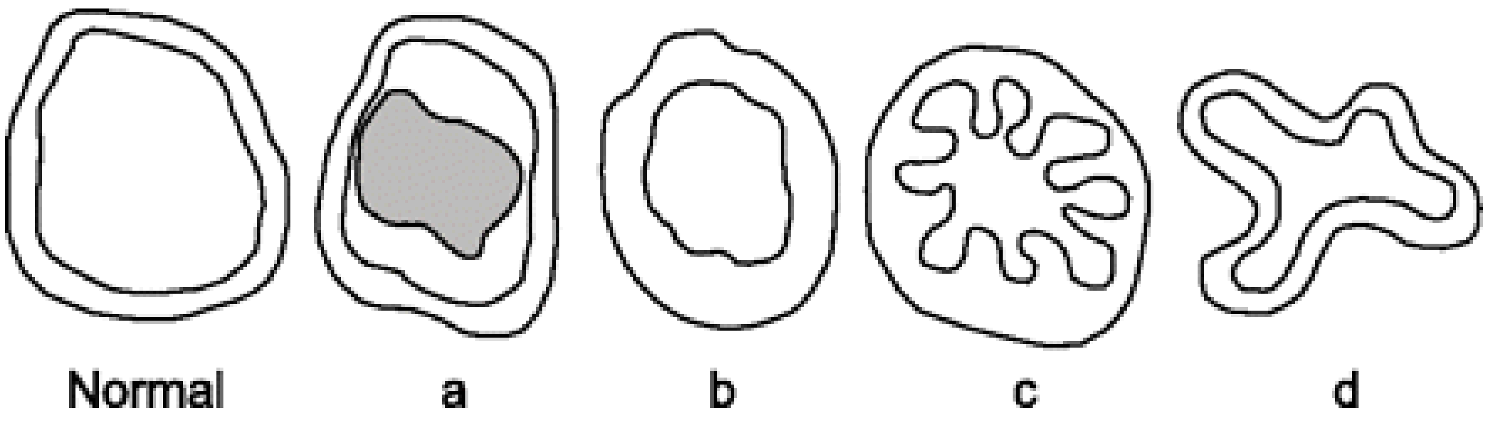


(5) MOST COMMON OBSTRUCTIVE DISEASES

Various mechanisms of airway obstruction

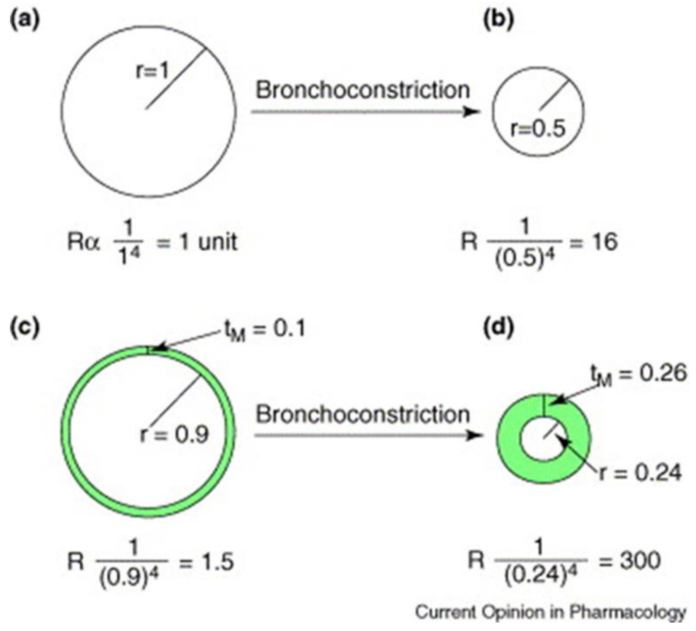


- Narrowing of the airway lumen may be due to:
  - a) **mucus**, cells or other material within the lumen
  - b) thickening of the airway wall that encroaches on the lumen (**hypertrophy**)
  - c) shortening of smooth muscle around the lumen (**bronchoconstriction**)
  - d) collapse of the airway wall into the lumen (**emphysema**)

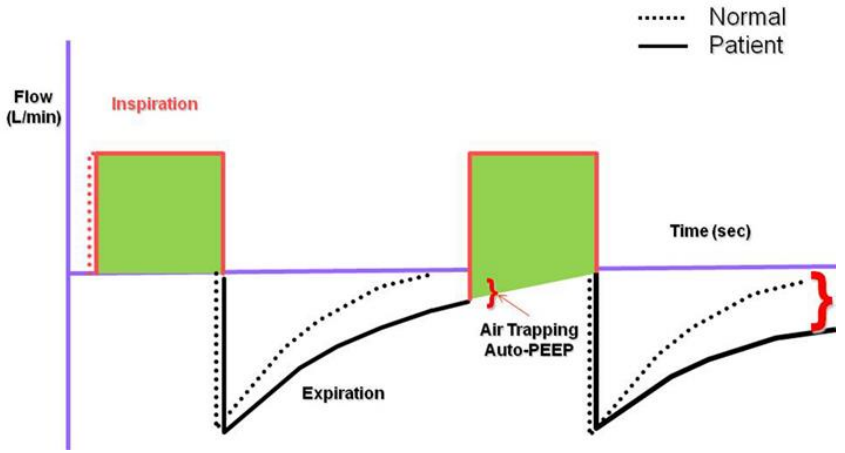
Ventilation disorders due to bronchial obstruction – basic pathophysiological characteristics

- obstruction in airways massively increases their **resistance** (dynamic resistance)
  - Hagen-Poiseuille law

$$R = \frac{8\eta l}{\pi r^4}$$



- since inspirium is an active process (muscles and negative alv. and transthoracic pressure overcome resistances) but expirium passive one, obstruction leads to an **impairment of expiration**
- participation of auxiliary respiratory muscles leads to
  - dynamic compression, air trapping and **hyperinflation of the lungs**
    - ↑ residual volume (FRC, RV, TLC)
  - ↑ breathing effort and thus **dyspnea**



- ↓dynamic ventilatory parameters (spirometry)
  - more time needed to exhale FVC (↓FEV1)

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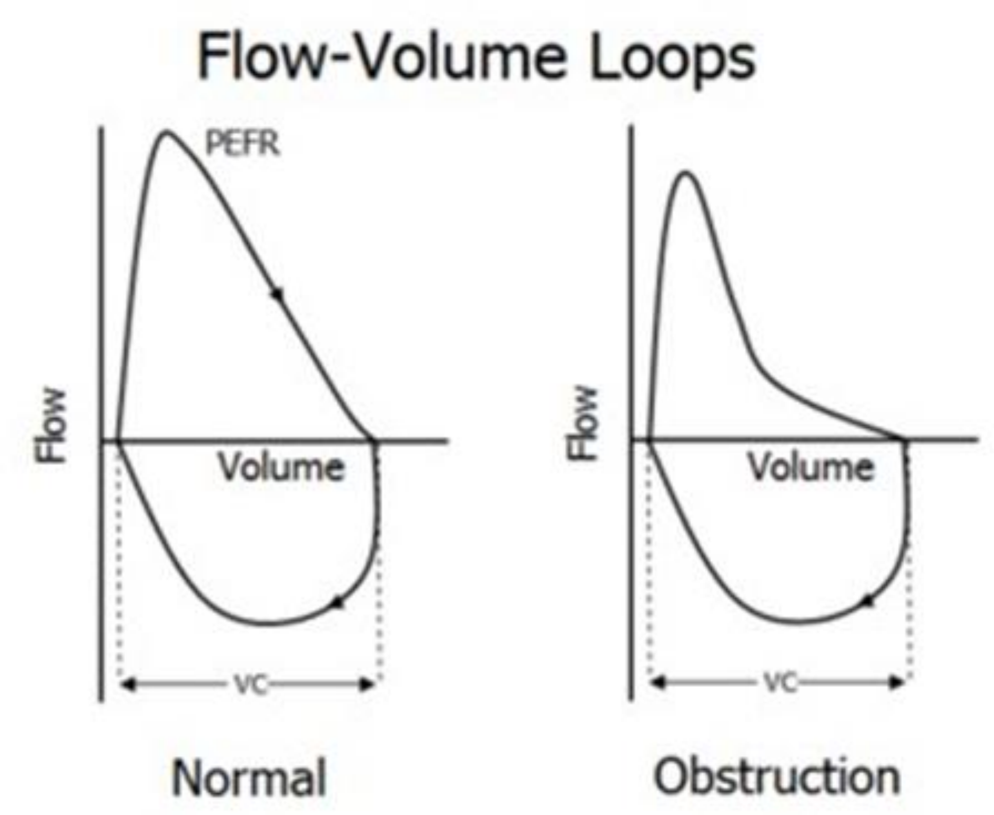
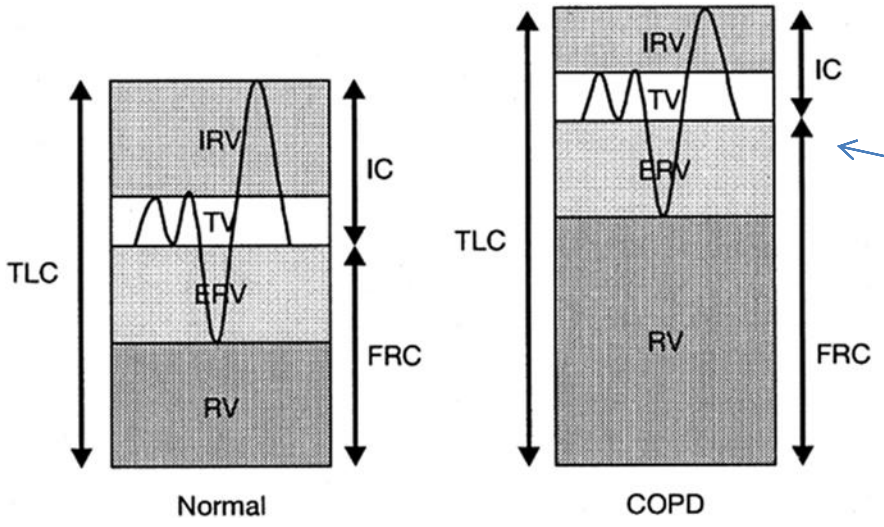
Airflow obstruction

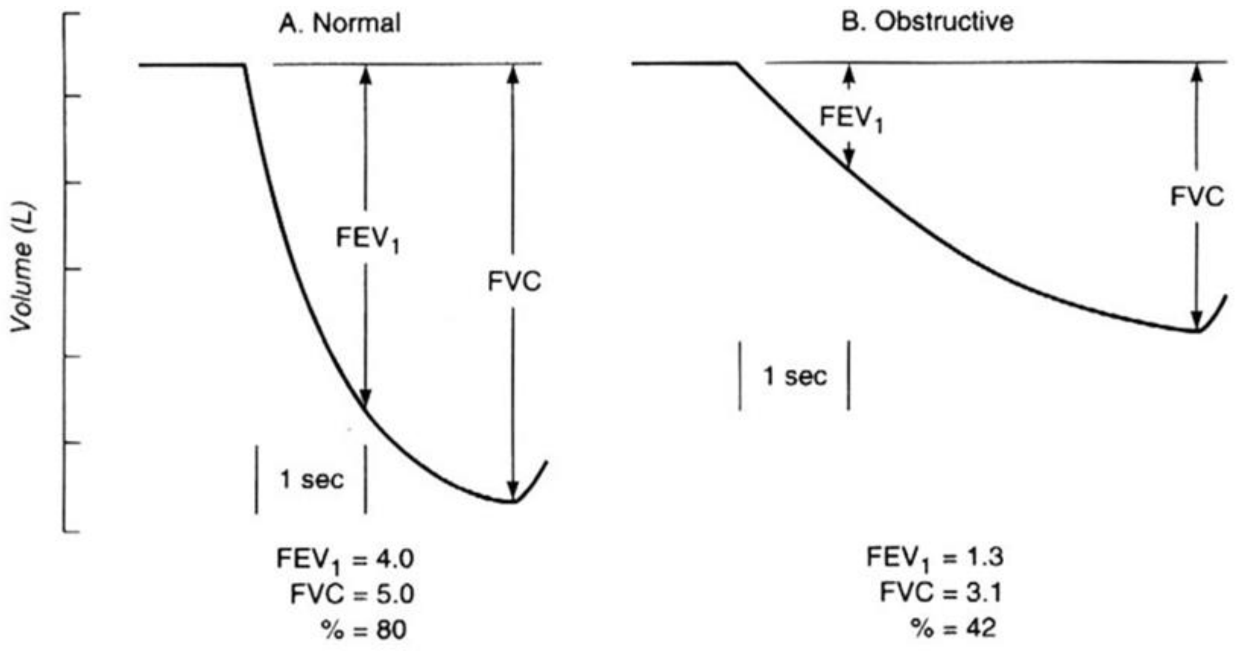
- In patients with severe COPD, limitation of expiratory flow occurs even during tidal breathing at rest
- To increase ventilation these patients have to breathe at higher lung volumes and also allow more time for expiration by increasing flow rates during inspiration, where there is relatively less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



Ventilation disorders due to bronchial obstruction – basic pathophysiological characteristics

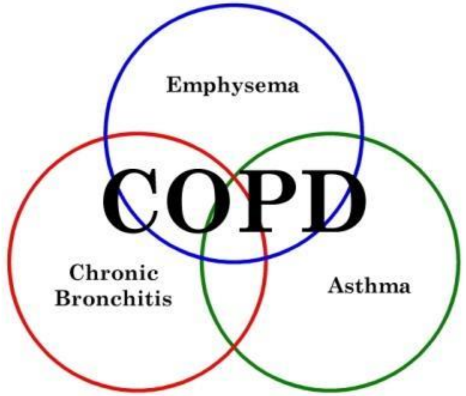


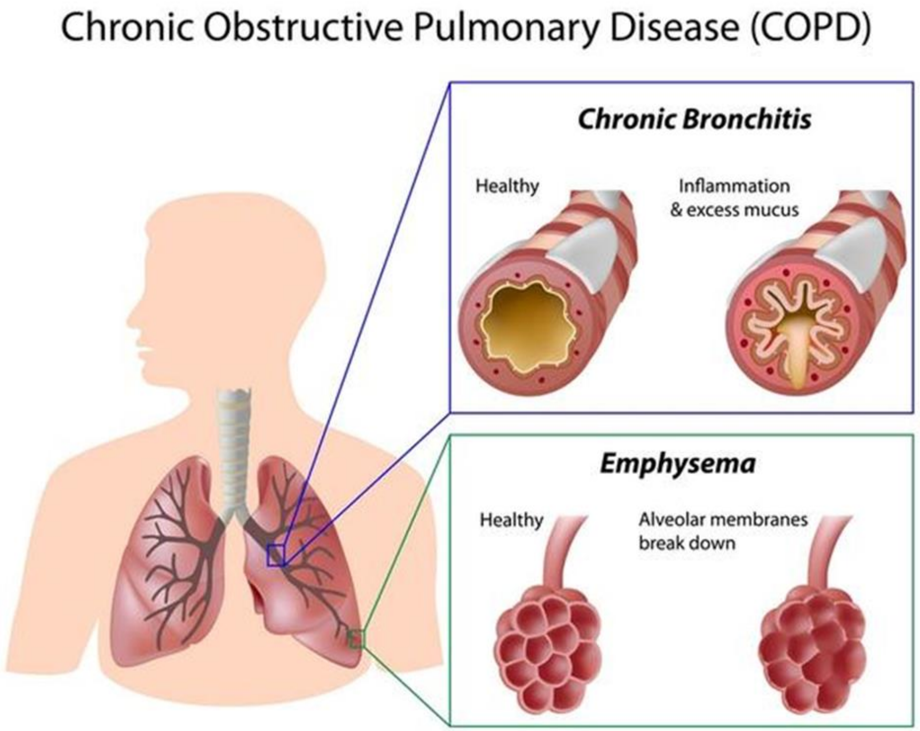
shift towards inspiration reserve volume with greater static resistances of airways (increased breathing effort)

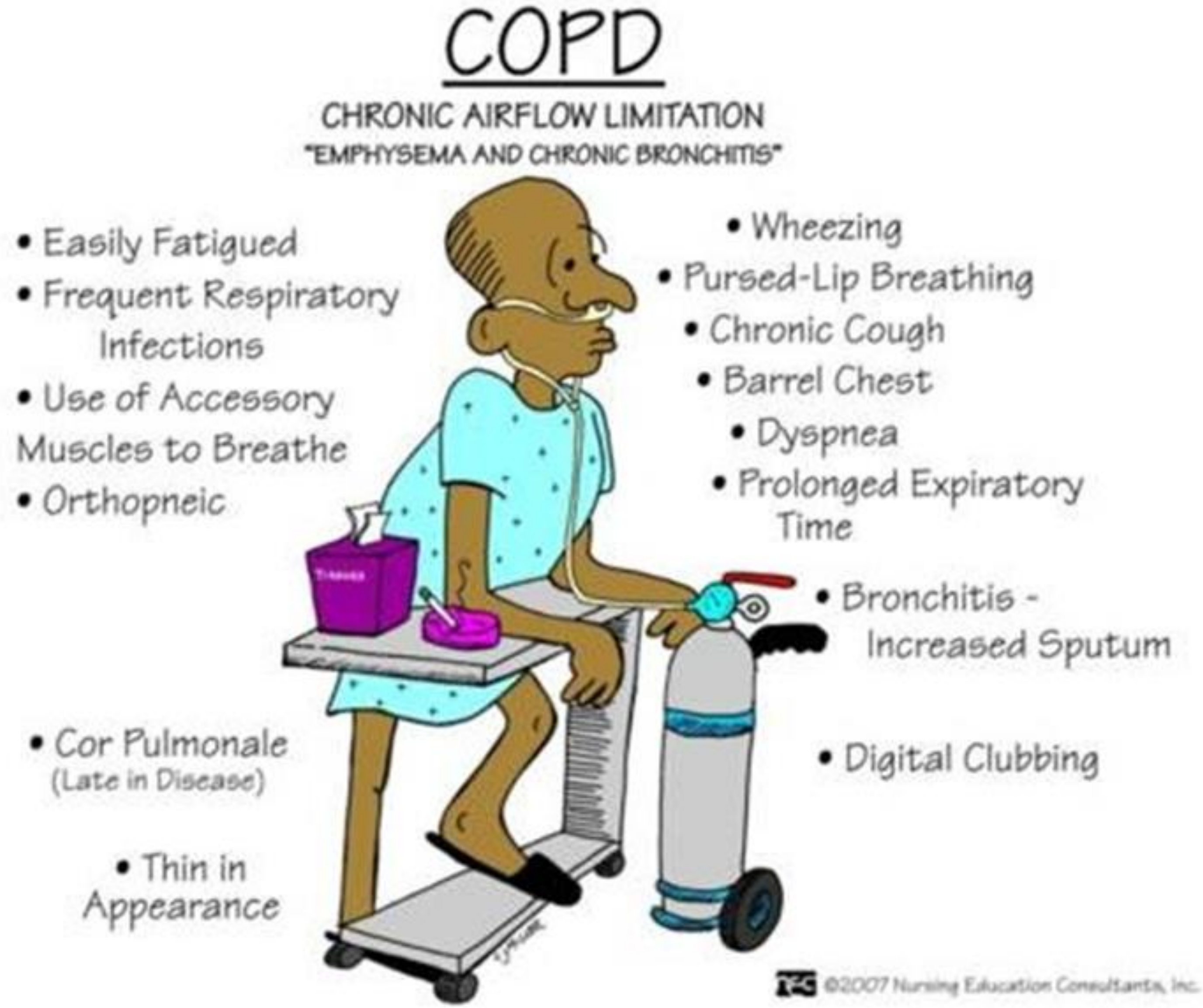


Chronic obstructive pulmonary disease (COPD)

- COPD is not solely **pulmonary** disease but **systemic** syndrome
- definition of pulmonary component of COPD:
  - permanent bronchial obstruction, not fully reversible, usually progressive, characterized by an abnormal inflammatory response to environmental harmful stimuli
  - bronchial obstruction in COPD is caused by an individually variable combination of:
    - **chronic bronchitis** (with excessive resp. secretion)
    - **pulmonary emphysema** (i.e. destruction of lung parenchyma)
    - **obstructive bronchiolitis** (with obstruction of small airways)
- systemic component comprises:
  - changes in pulmonary vasculature
  - hypoxic hypoxia







Stage I: Mild

Spirometry shows mild airflow limitation (FEV_1 ≥80% predicted; FEV_1/FVC <0.70). Primary symptoms are chronic cough and sputum production

Stage II: Moderate

Spirometry shows a worsening airflow limitation (FEV_1 ≥50% and <80% predicted; FEV_1/FVC <0.70). Patients often experience dyspnea, which may interfere with their daily activities.

Stage III: Severe

Spirometry shows severe airflow limitation (FEV_1 ≥30% and <50% predicted; FEV_1/FVC <0.70). Symptoms of cough and sputum production typically continue, dyspnea worsens, and repeated exacerbations occur.

Stage IV: Very Severe

Spirometry shows very severe airflow limitation (FEV_1 <30% predicted or FEV_1 <50% predicted; FEV_1/FVC <0.70 plus chronic respiratory failure). Complications such as respiratory failure or heart failure may develop.

1. Rodriguez-Roisin R, Anzueto A, Bourbeau J, et al; GOLD Executive Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2009). Global Initiative for Chronic Obstructive Lung Disease Web site: http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003. Accessed March 8, 2010.

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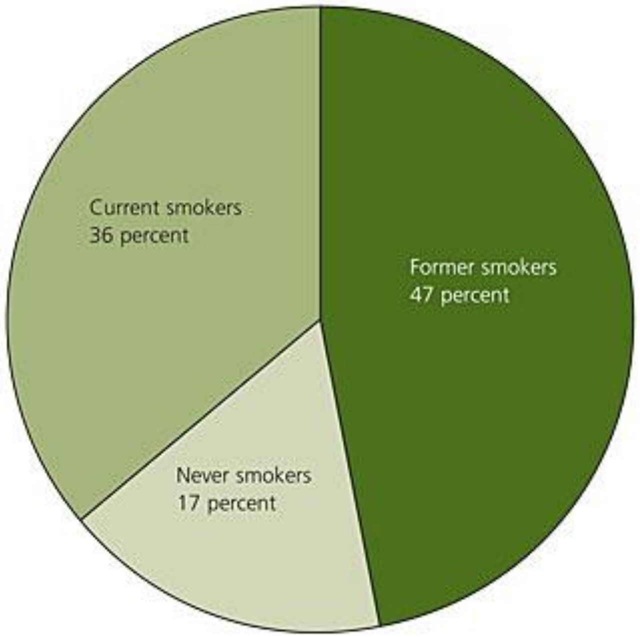
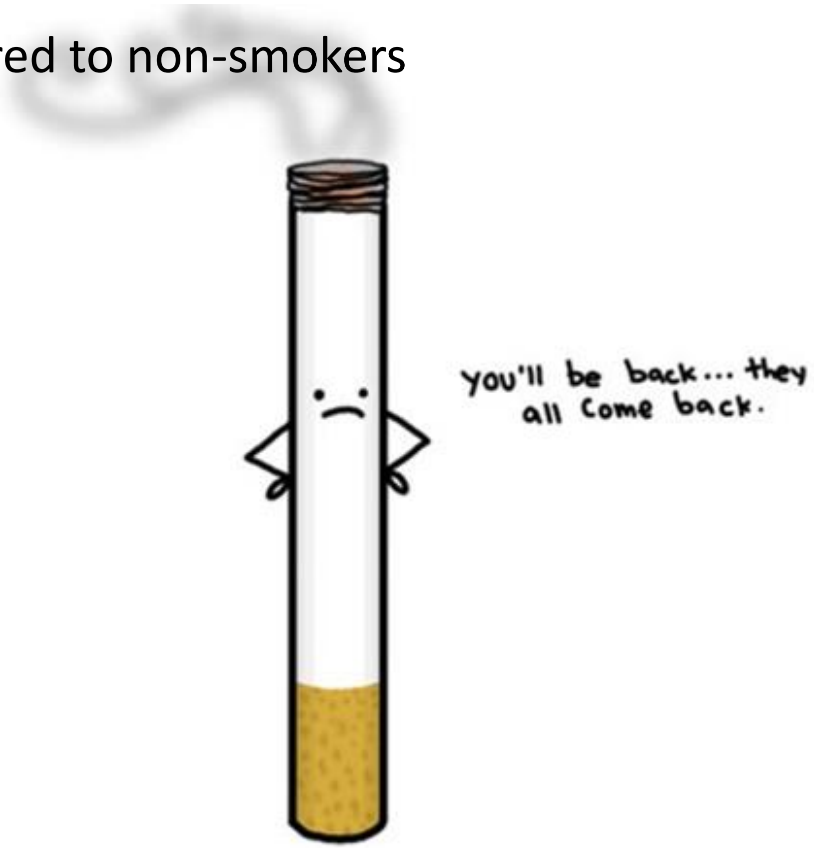
COPD

- COPD is one of the most frequent chronic illnesses and one of the commonest causes of mortality worldwide
  - 4^{th} place leading cause of death in countries with high prevalence of smoking
    - after MI, tumors and stroke
- **85-90% of COPD patients are smokers**
  - Incidence is increased up to twentyfold in smokers compared to non-smokers
  - even more so in workers exposed to air pollution





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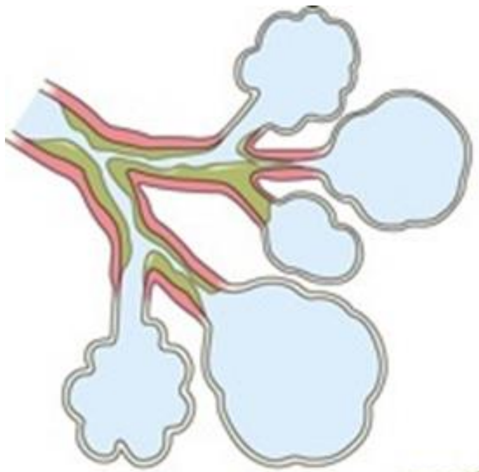
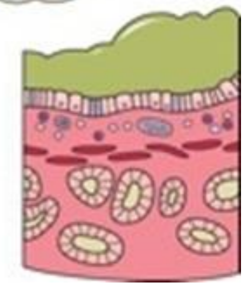
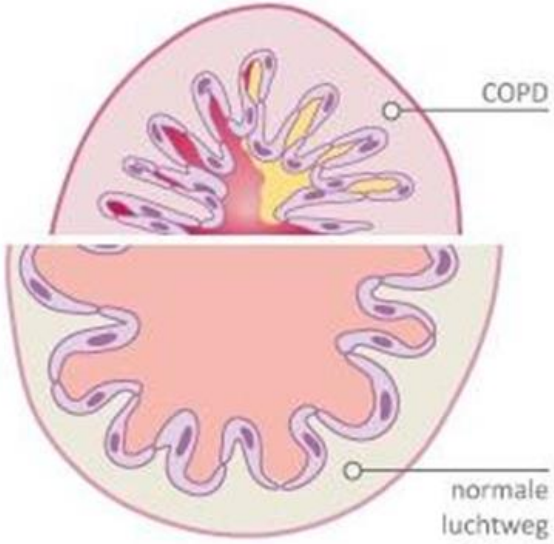
Chronic bronchitis (∅ >2mm) and bronchiolitis (∅ <2mm)

- symptomatic definition
  - hypersecretion of mucus and chronic productive cough that continues for at least 3 months of years for at least 2 consecutive years
- however patients typically suffer from chronic bronchitis without obstruction for a long time and only then develop bronchial obstruction (i.e. COPD)
  - there are of course patients with COPD without clinical signs of chronic bronchitis
  - some chronic bronchitis cases never progress to COPD
- in manifest COPD presence of chronic bronchiolitis is obligatory dominantly responsible (together with pulmonary emphysema) for obstruction
  - chronic persistent inflammation of small airways (∅ ≤ 2 mm)
  - the ratio between chronic bronchiolitis and pulmonary emphysema is entirely individual

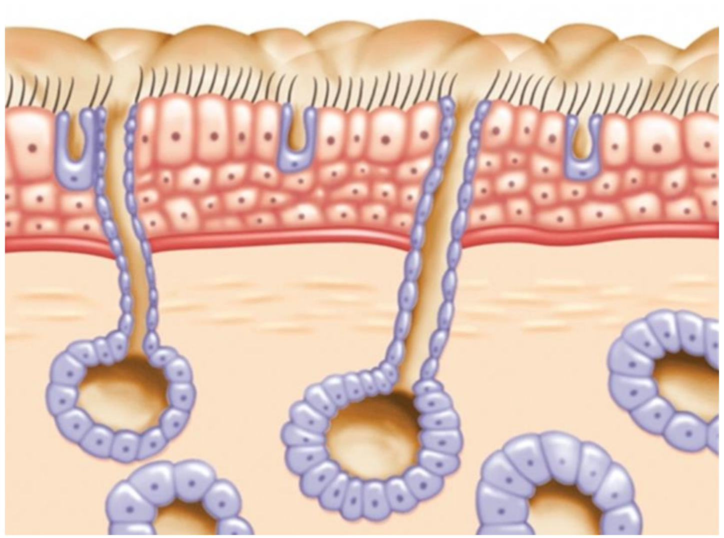


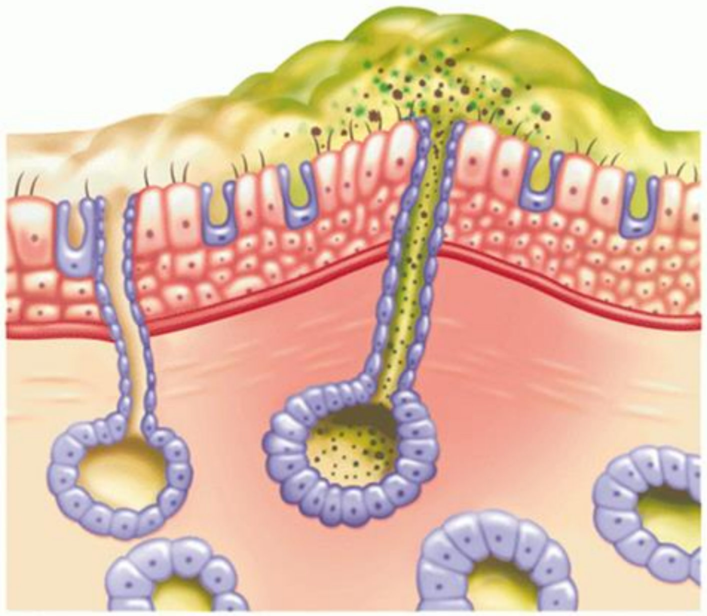




Chronic bronchitis – pathological anatomy

- inhaled irritants not only increase mucus production but also increase the size and number of **mucous glands** and **goblet cells** in airway epithelium
  - mucus produced is thicker and more tenacious than normal
  - sticky mucus coating makes it much more likely that bacteria, such as H. influenze and S. pneumoniae, will become embedded in the airway secretions, there they reproduce rapidly
- **cilia** function is impaired, reducing mucus clearance further
  - lung´s defense mechanisms are therefore compromised, increasing susceptibility to pulmonary infection and injury
- **bronchial wall** becomes inflamed and thickened from edema and accumulation of inflammatory cells
- initially chronic bronchitis affects only the larger bronchi, but eventually all airways are involved
- thick mucus and hypertrophied bronchial smooth muscle obstruct the airways and lead to closure, particularly during expiration, when the airways are narrowed
  - airways collapse early in expiration, trapping gas in the distal portions of the lung.
  - obstruction eventually leads to ventilation-perfusion mismatch, hypoventilation (increased $PaCO_2$) and hypoxemia





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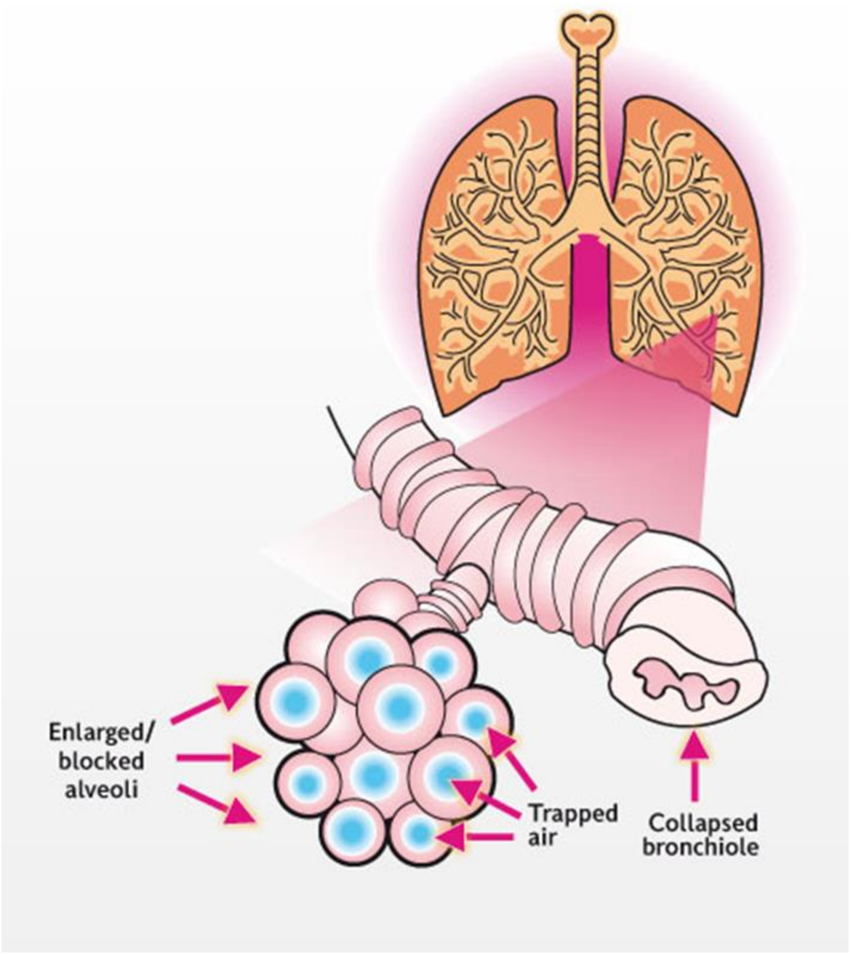
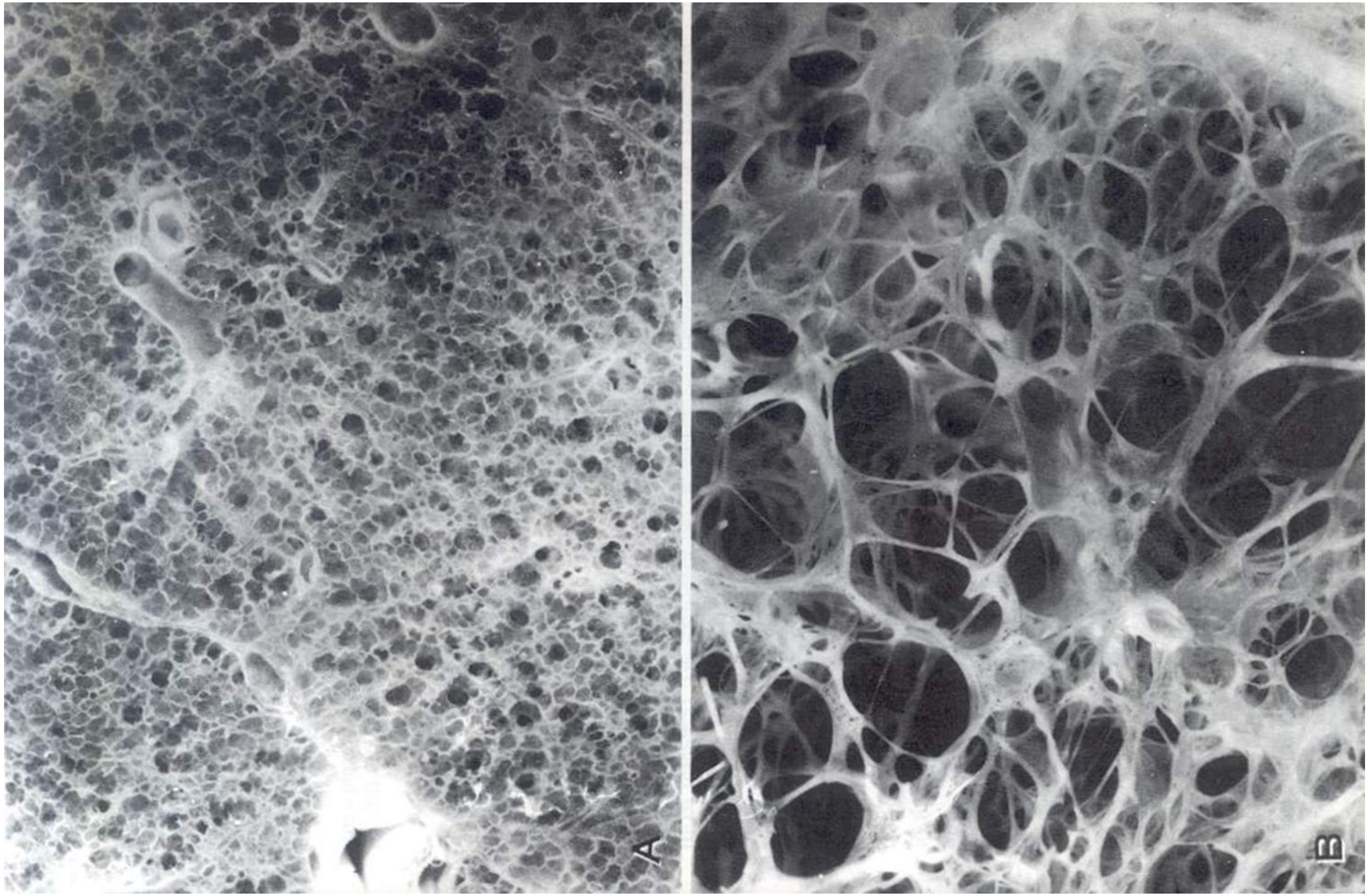
Lung emphysema

- abnormal permanent enlargement of gas-exchange airways = acini (i.e distally from terminal bronchioles) accompanied by **destruction of alveolar walls** and without obvious fibrosis
  - obstruction results from changes in lung tissues, rather than mucus production and inflammation, as in chronic bronchitis
- functional consequence:
  - major mechanism of airflow limitation is **loss of elastic recoil** leading to the **collapse of small airways** during expiration
  - expiration becomes difficult because loss of elastic recoil reduces the volume of air that can be expired passively,
  - combination of increased RV (and FRC) in the alveoli and diminished caliber of the bronchioles causes part of each inspiration to be trapped in the acinus
  - **hyperinflation** of alveoli causes large air spaces (bullae) and air spaces adjacent to pleura (blebs) to develop



Healthy (left) vs. emphysematous lung (right)



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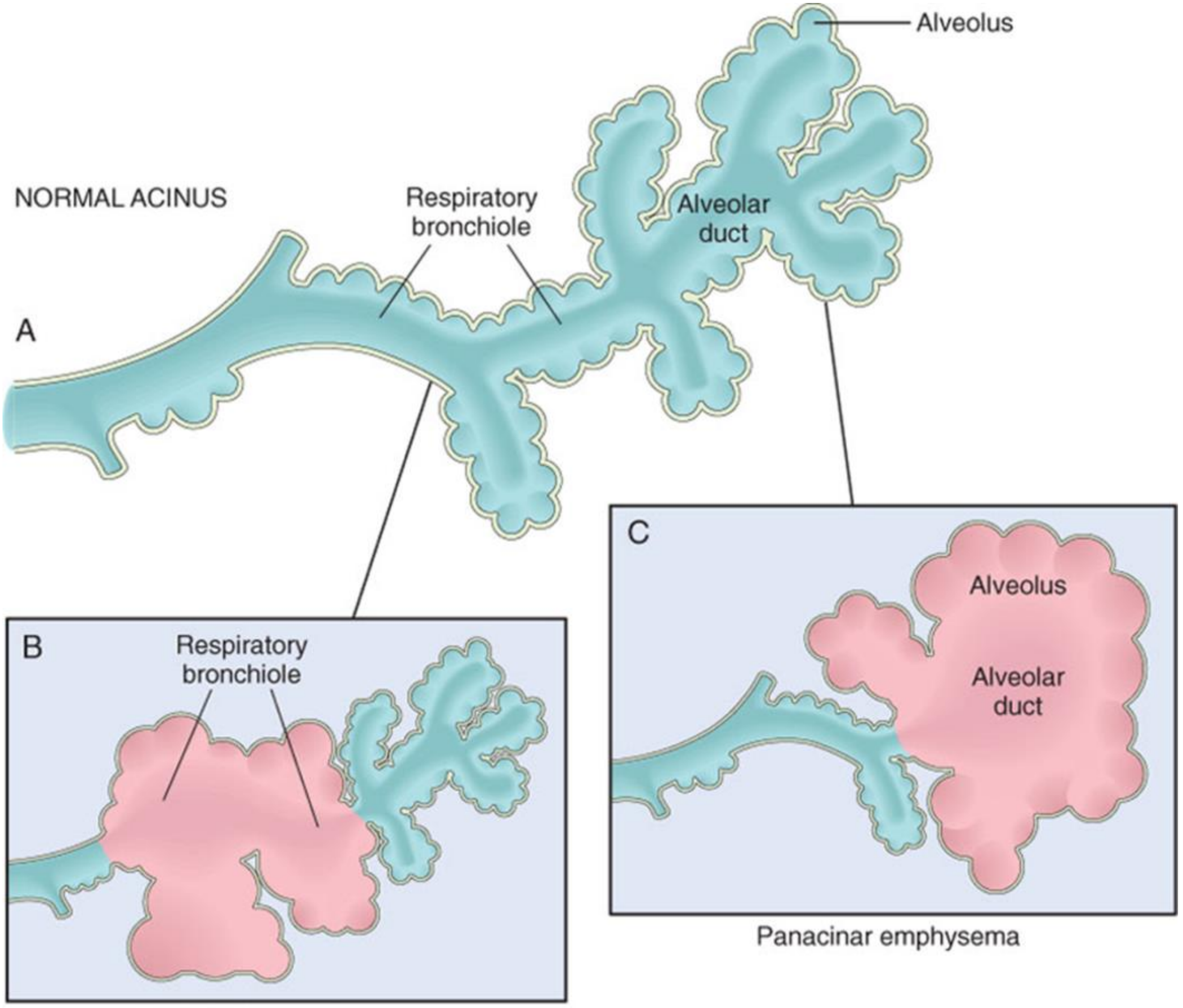
Emphysema types in COPD



Centriacinar emphysema

Panacinar emphysema

- Centrilobular (centriacinar):
  - septal destruction occurs in the respiratory bronchioles and alveolar ducts, usually in the upper lobes of the lung
  - alveolar sac (alveoli distal to the respiratory bronchiole) remains intact
  - tends to occur **in smokers**
- Panacinar (panlobular):
  - involves the entire acinus with damage more randomly distributed and involving the lower lobes of the lung
  - tends to occur in patients with **α1-antitrypsin deficiency**

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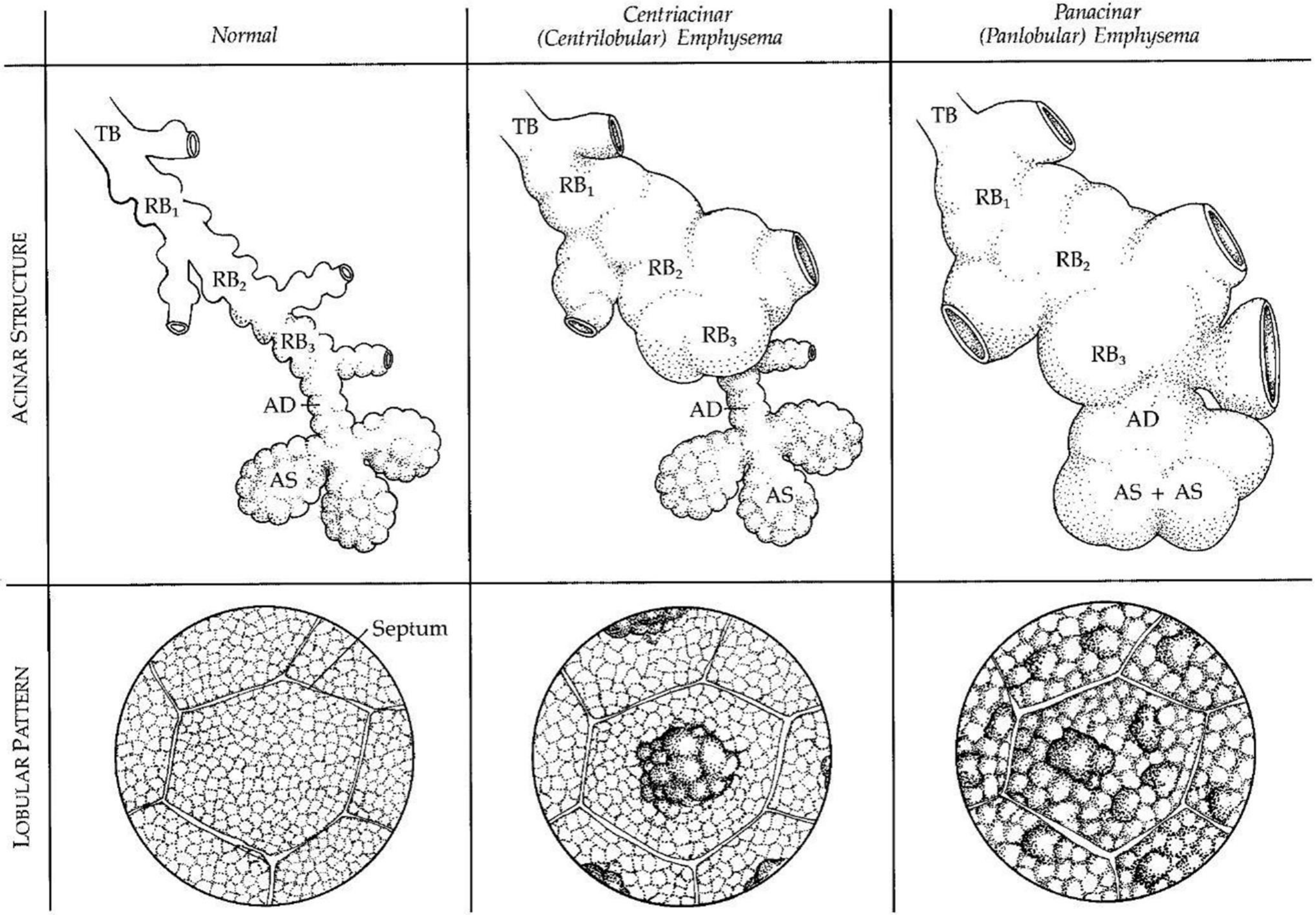
Normal
Centriacinar (Centrilobular) Emphysema
Panacinar (Panlobular) Emphysema
Acinar Structure
Lobular Pattern
TB
RB1
RB2
RB3
AD
AS
AS + AS
Septum

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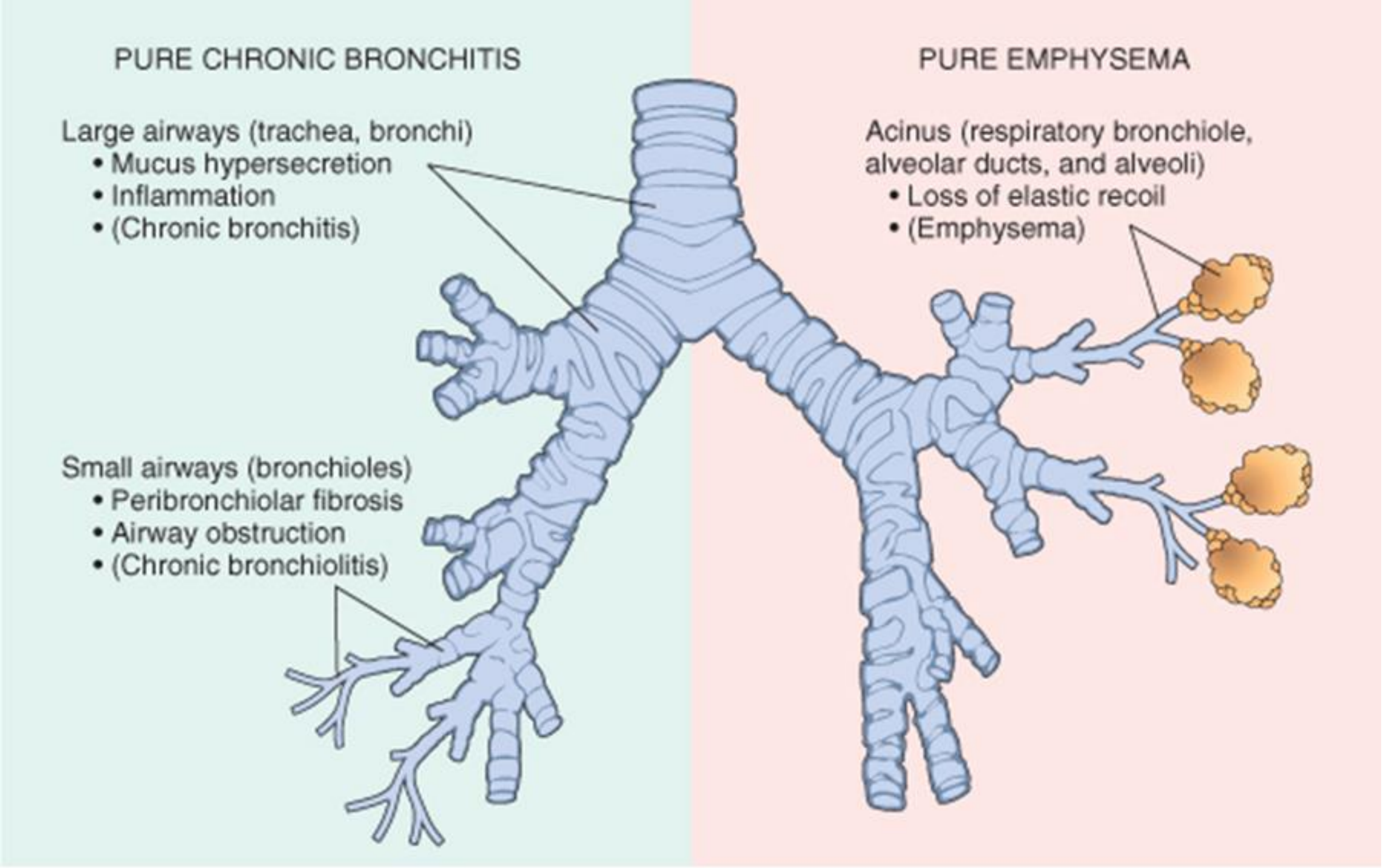
Variable overlap in COPD



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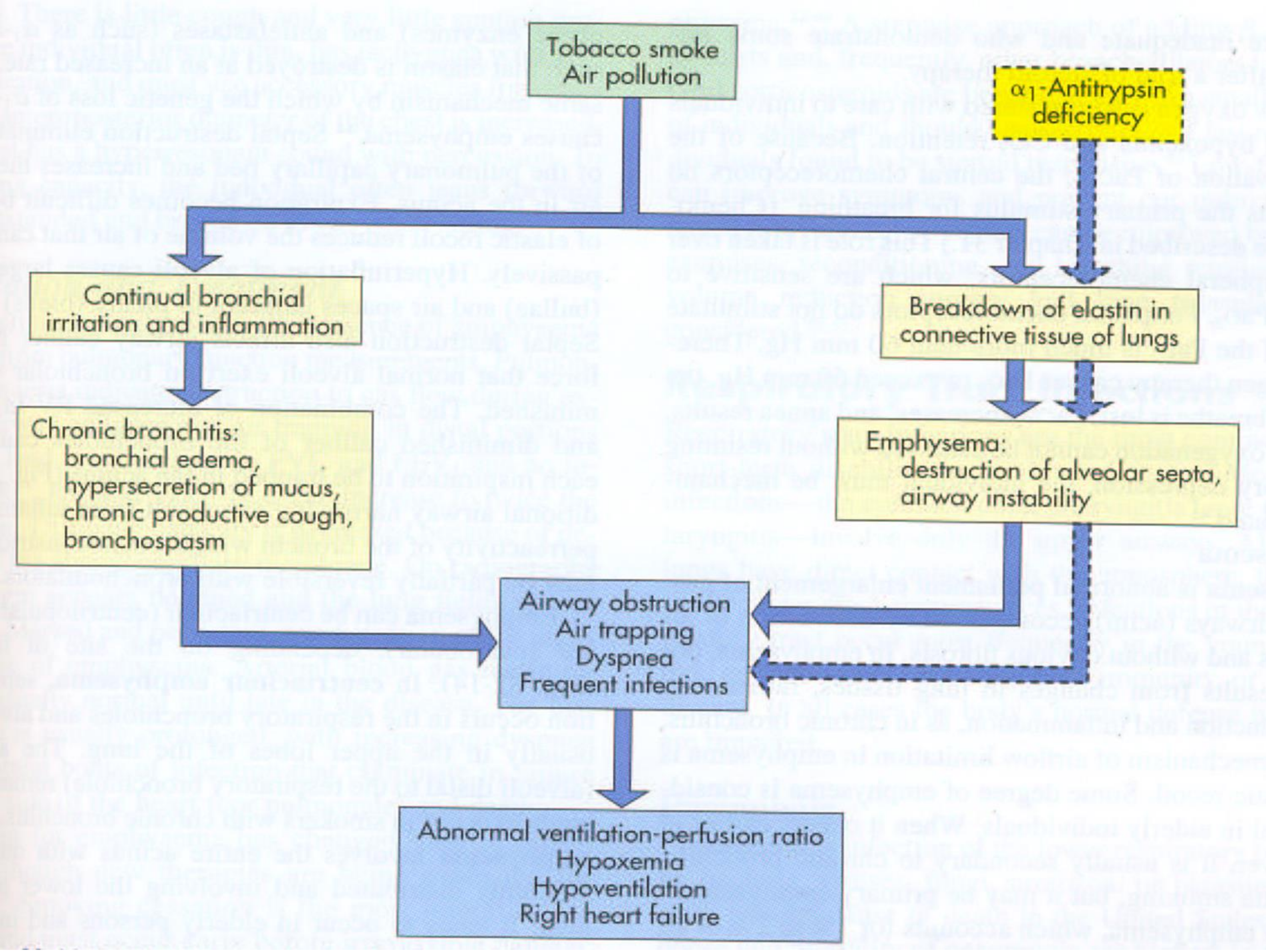
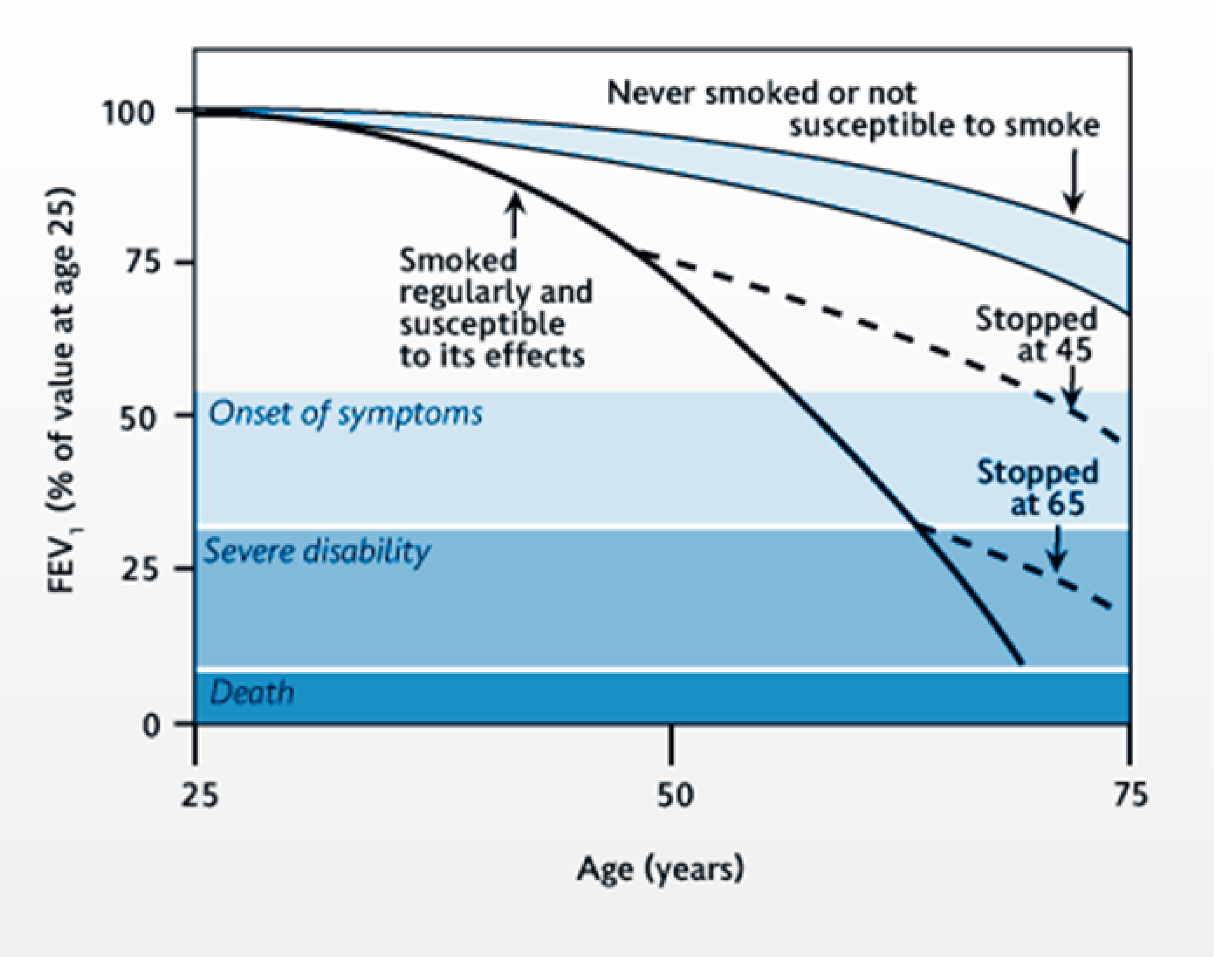
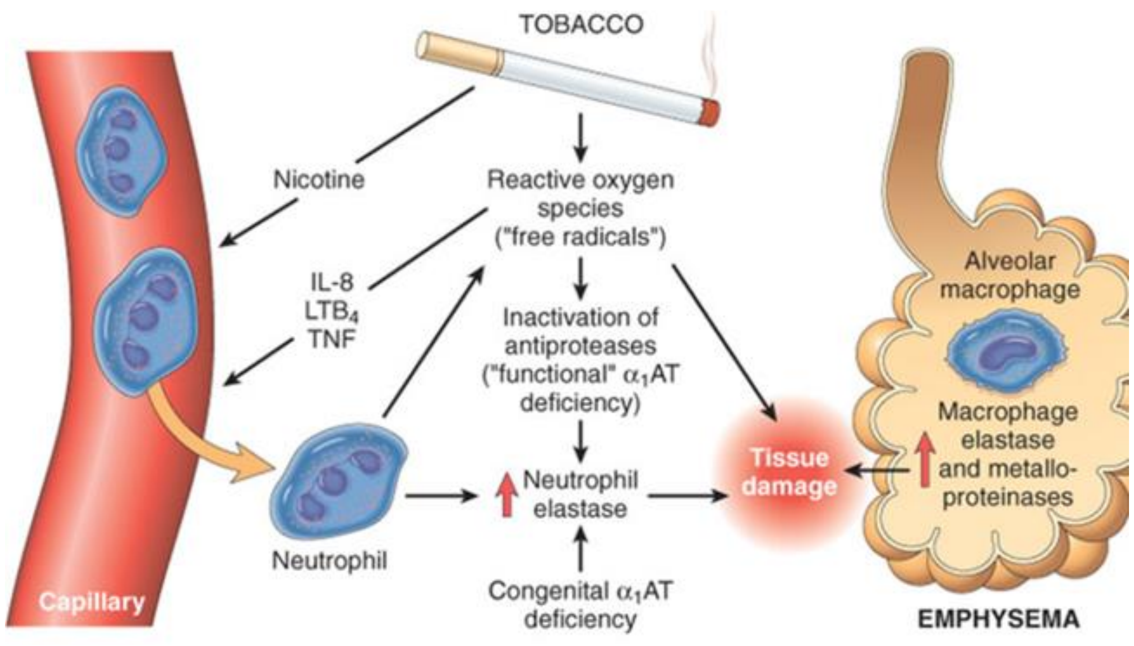

Tobacco smoke
Air pollution
α1-Antitrypsin deficiency
Continual bronchial irritation and inflammation
Breakdown of elastin in connective tissue of lungs
Chronic bronchitis:
bronchial edema,
hypersecretion of mucus,
chronic productive cough,
bronchospasm
Emphysema:
destruction of alveolar septa,
airway instability
Airway obstruction
Air trapping
Dyspnea
Frequent infections
Abnormal ventilation-perfusion ratio
Hypoxemia
Hypoventilation
Right heart failure

Etiology of COPD - multifactorial

- smoking
  - cigarette smoke and air pollution, tip the normal balance of elastases (proteolytic enzymes) and anti-elastases (such as α1-antitrypsin) so that elastin is destroyed at an increased rate
  - ↑ number of neutrophil granulocytes in inflamed airways
    - source of elastases and proteases favoring emphysema development
  - tissue injury due to reactive oxygen and nitrogen species
    - healing with the participation of macrophages (source of matrix metaloprotinases)
  - hypertrophy of mucus glands and thus CHB
  - impairment of surfactant
- airway hyper-reactivity
- genetics (= variable consequences in two persons with equal „smoking“ history)
  - α1-antitrypsin deficiency
    - α1-antitrypsin inhibits neutrophil elastase which has the ability to destroy lung tissue
    - identified more than 75 alleles in the gene for α1-antitrypsin
  - other genes
    - pro-inflammatory cytokines, growth factors, protease/anti-protease balance, antioxidants etc.
- exposure to other air pollutants (dust, smoke, professional exposure, car traffic fumes, biomass burning etc.)
  - the most risky are small particles ≤ 2.5 μm
- recurrent lower airways and lung infections

Effect of smoking





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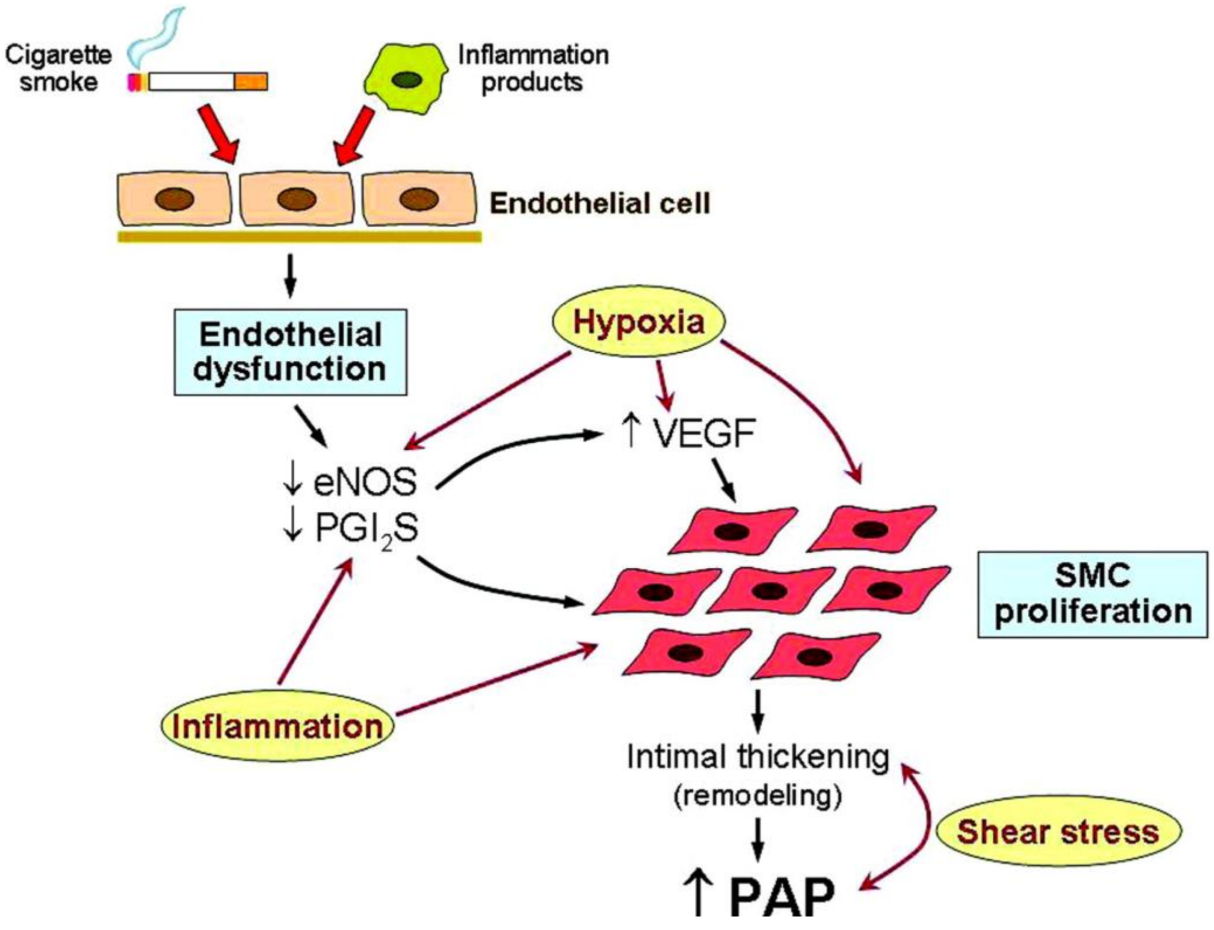
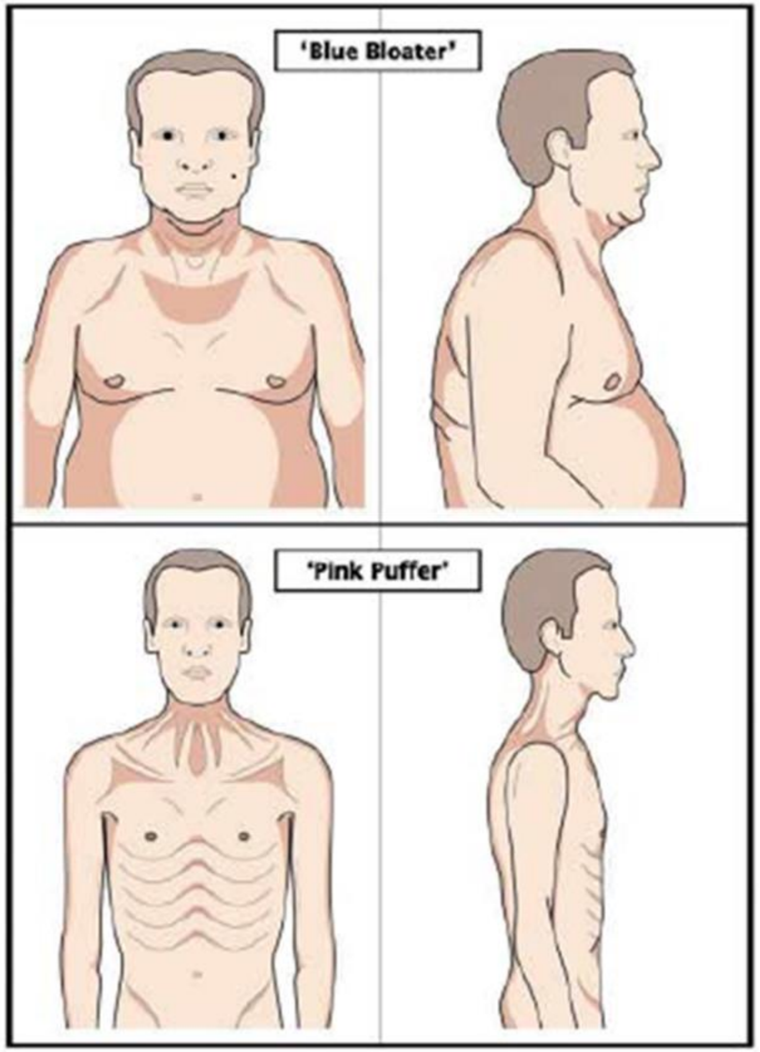
Pulmonary vessels in COPD



- remodelation (i.e. wall thickening, lumen narrowing and increased resistance) present very early in the time course of COPD
  - endothelial dysfunction
    - due to oxidative stress
  - hyperplasia of tunica intima
    - cells (inflammatory cells and SMCs) as well as ECM
  - hypertrophy of tunica media
- gradually hypoxia and loss of capillaries (emphysema) contributes to remodelation as well
  - vasoconstriction
  - later pre-capillary form of secondary pulmonary hypertension
- cor pulmonale

Hypoxic pulmonary vasoconstriction → pulmonary hypertension → cor pulmonale (hypertrophy) → congestive heart failure

Clinical heterogenity of COPD



- Type A – "pink puffer" - dominance of emphysema
  - patients with emphysema are able to maintain a higher alveolar minute ventilation ("puffers") than those with chronic bronchitis
    - therefore they tend to have a higher PaO_2 and lower $PaCO_2$ and are indeed „pink "
  - a thin, tachypneic patient using accessory muscles and pursed lips to facilitate respiration
    - thorax is barrel-shaped due to hyperinflation
  - there is little cough and very little sputum production (in „pure" emphysema)

- Type B – "blue bloater"– dominance of bronchitis
  - bronchitis patients are often „blue" due to hypoxemia (and central cyanosis)/hypercapnia
  - they regularly exhibit right heart failure due to an increase in pulmonary artery pressure impairing right ventricular function
    - this leads to peripheral edema ("bloaters")

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TABLE 22-2	Characteristics of Emphysema and Chronic Bronchitis	
Characteristic	**Type A Pulmonary Emphysema ("Pink Puffers")**	**Type B Chronic Bronchitis ("Blue Bloaters")**
Smoking history	Usual	Usual
Clinical features		
Barrel chest (hyperinflation of the lungs)	Often dramatic	May be present
Weight loss	May be severe in advanced disease	Infrequent
Shortness of breath	May be absent early in disease	Predominant early symptom, insidious in onset, exertional
Decreased breath sounds	Characteristic	Variable
Wheezing	Usually absent	Variable
Rhonchi	Usually absent or minimal	Often prominent
Sputum	May be absent or may develop late in the course	Frequent early manifestation, frequent infections, abundant purulent sputum
Cyanosis	Often absent, even late in the disease when there is low PO_2	Often dramatic
Blood gases	Relatively normal until late in the disease process	Hypercapnia may be present Hypoxemia may be present
Cor pulmonale	Only in advanced cases	Frequent Peripheral edema
Polycythemia	Only in advanced cases	Frequent
Prognosis	Slowly debilitating disease	Numerous life-threatening episodes due to acute exacerbations

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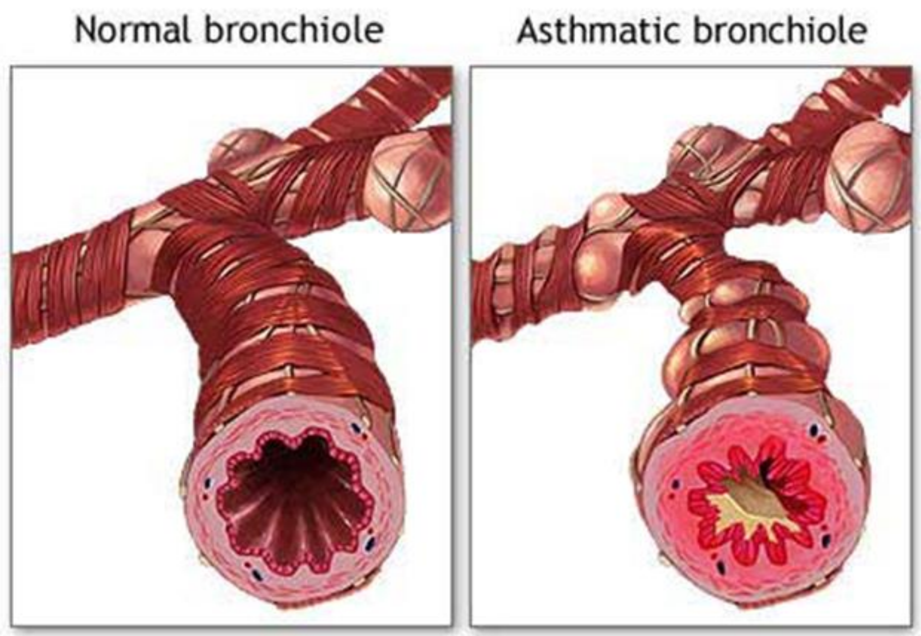
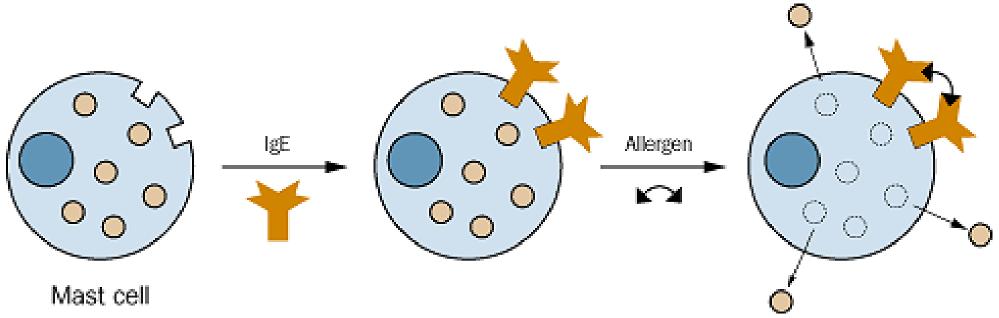
Bronchial asthma

- prevalence
  - 5-10% children
  - ~ 5% adults
- definition (GINA 2006)
  - a **chronic inflammatory disorder** of the airways in which many **cells** play a role
  - chronic inflammation causes an associated increase in **airway hyper-responsiveness** that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning
  - these episodes are usually associated with widespread but variable **airway obstruction** that is often reversible either spontaneously or with treatment
- types
  - allergic (extrinsic)
    - IgE-mediated bronchoconstriction
  - non-allergic (intrinsic)
    - IgE-independent = bronchial hyperreactivity
      - damage of epithelium
      - increased sensitivity to bronchoconstrictive agents





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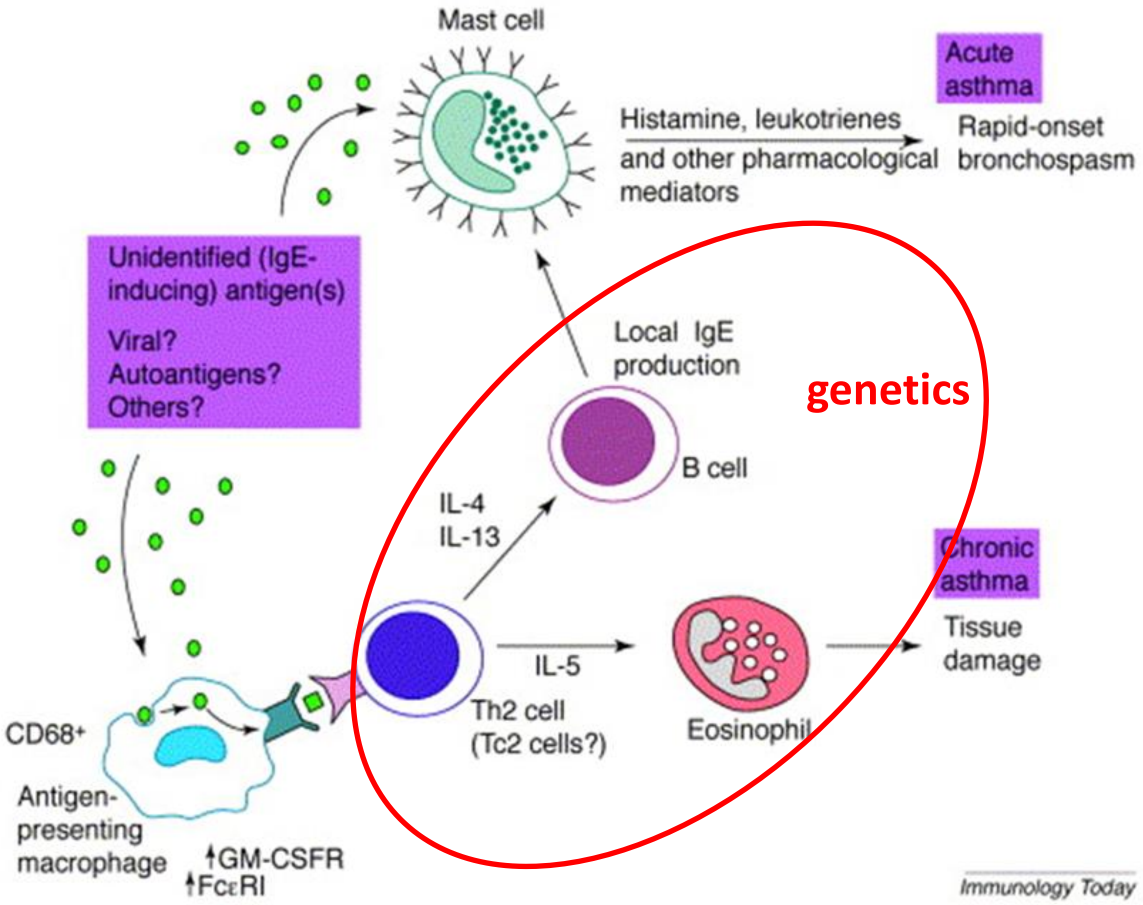
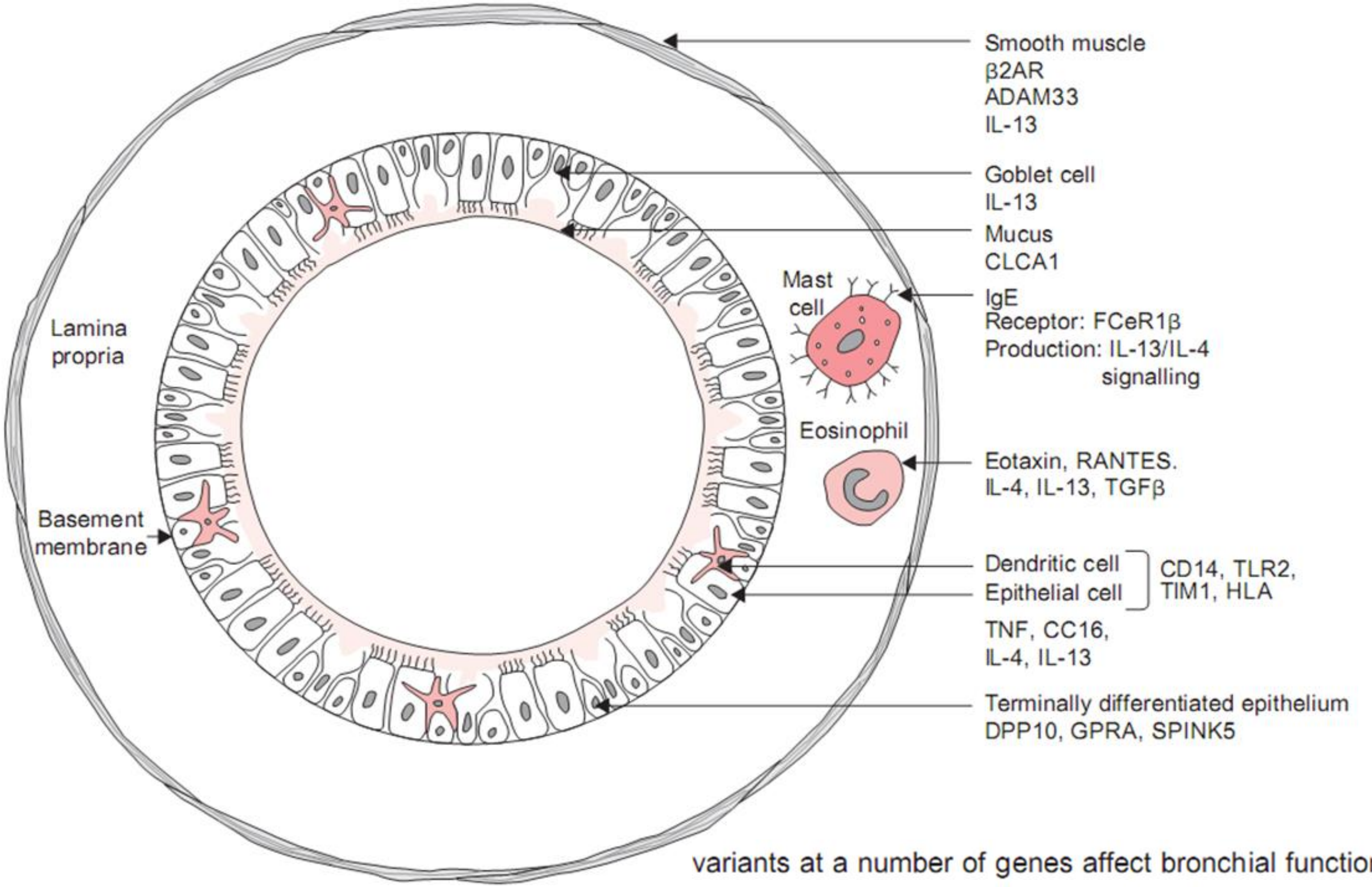
IgE-mediated asthma



- due to the **atopy**
  - genetic predisposition to the alteration of immune response towards immunopathological reaction of type 1
    - ↑ formation of IgE
    - ↑ activity of CD4+Th2 cells (cytokines IL-4, 5, 6, 13)
    - altered Ag presentation by APC
    - different reactivity of target cells to mediators (histamine)
    - ↓ suppressor activity of T cells
    - ↑ number of mast cells
    - ↑ concentration of FcεR1 on their surface
  - IgE antibodies directed often against (aero)allergens
    - domestic (dust mites)
    - pollen
    - infection agents (bacteria, viruses)
    - others

Polygenic nature of asthma



variants at a number of genes affect bronchial function.

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Sensibilisation phase in atopic subjects

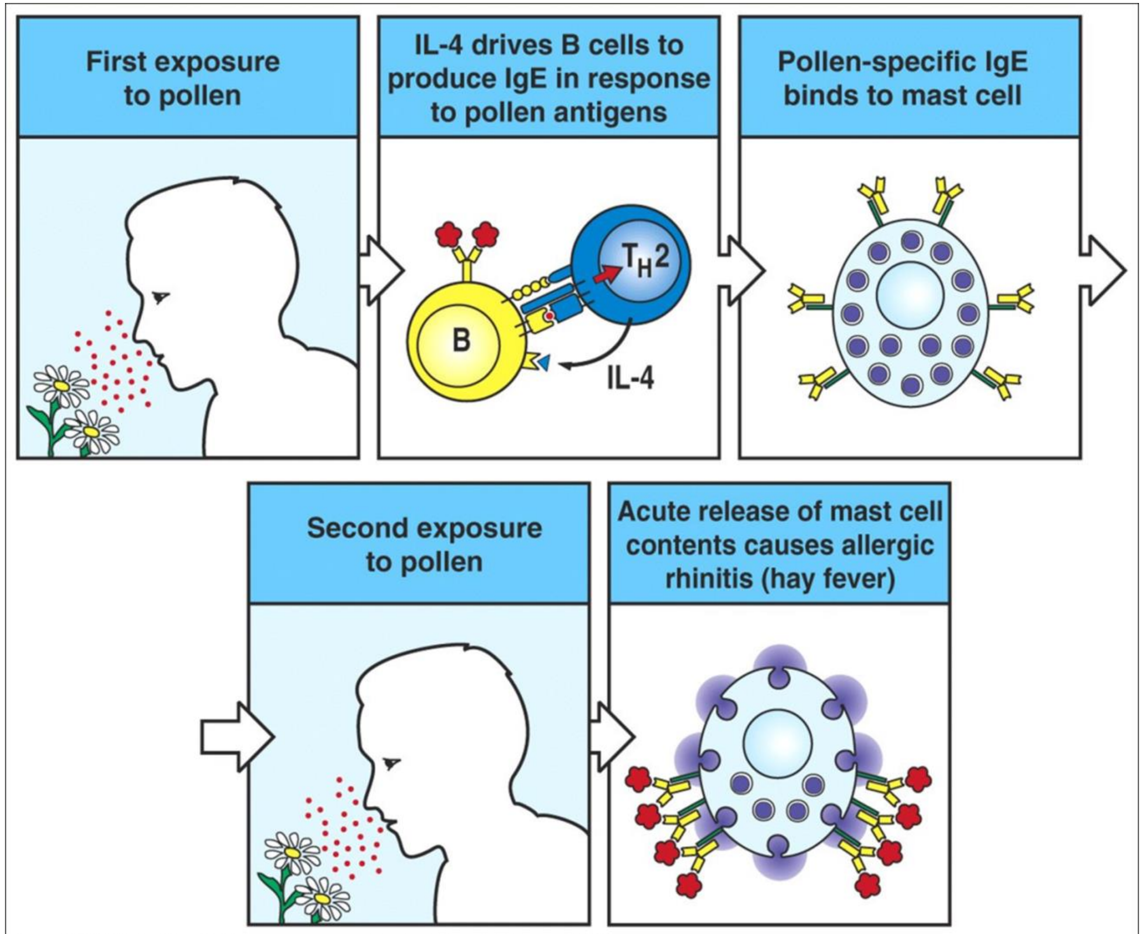
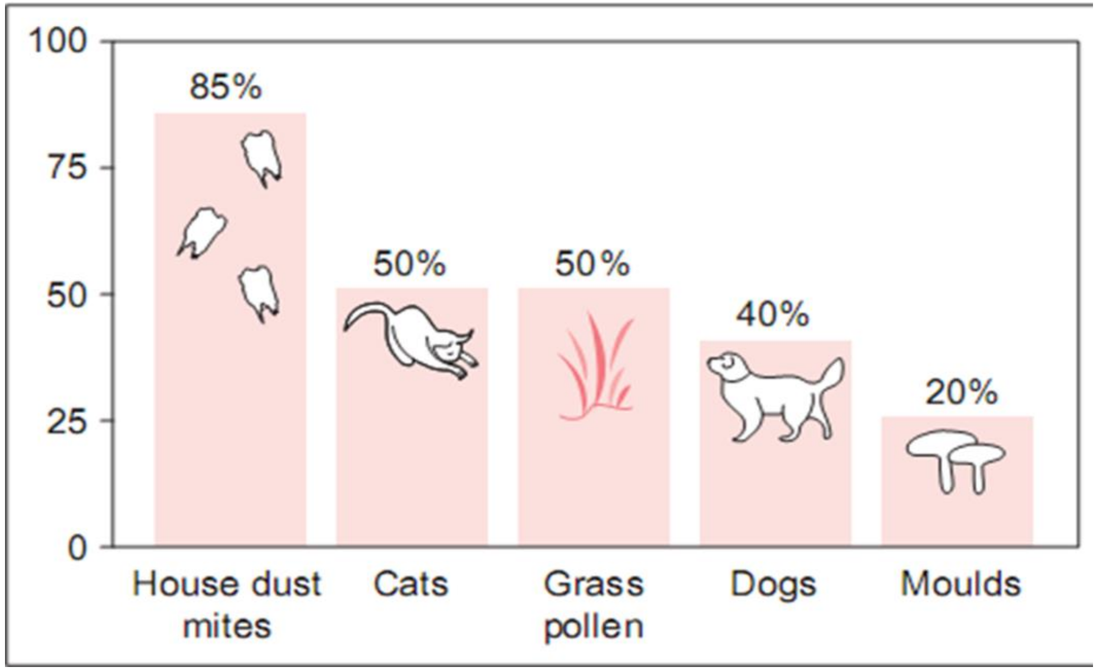


Figure 23-1 Case Studies in Immunology, 4/e (© Garland Science 2004)

Proportions of asthmatic children sensitized to common allergens



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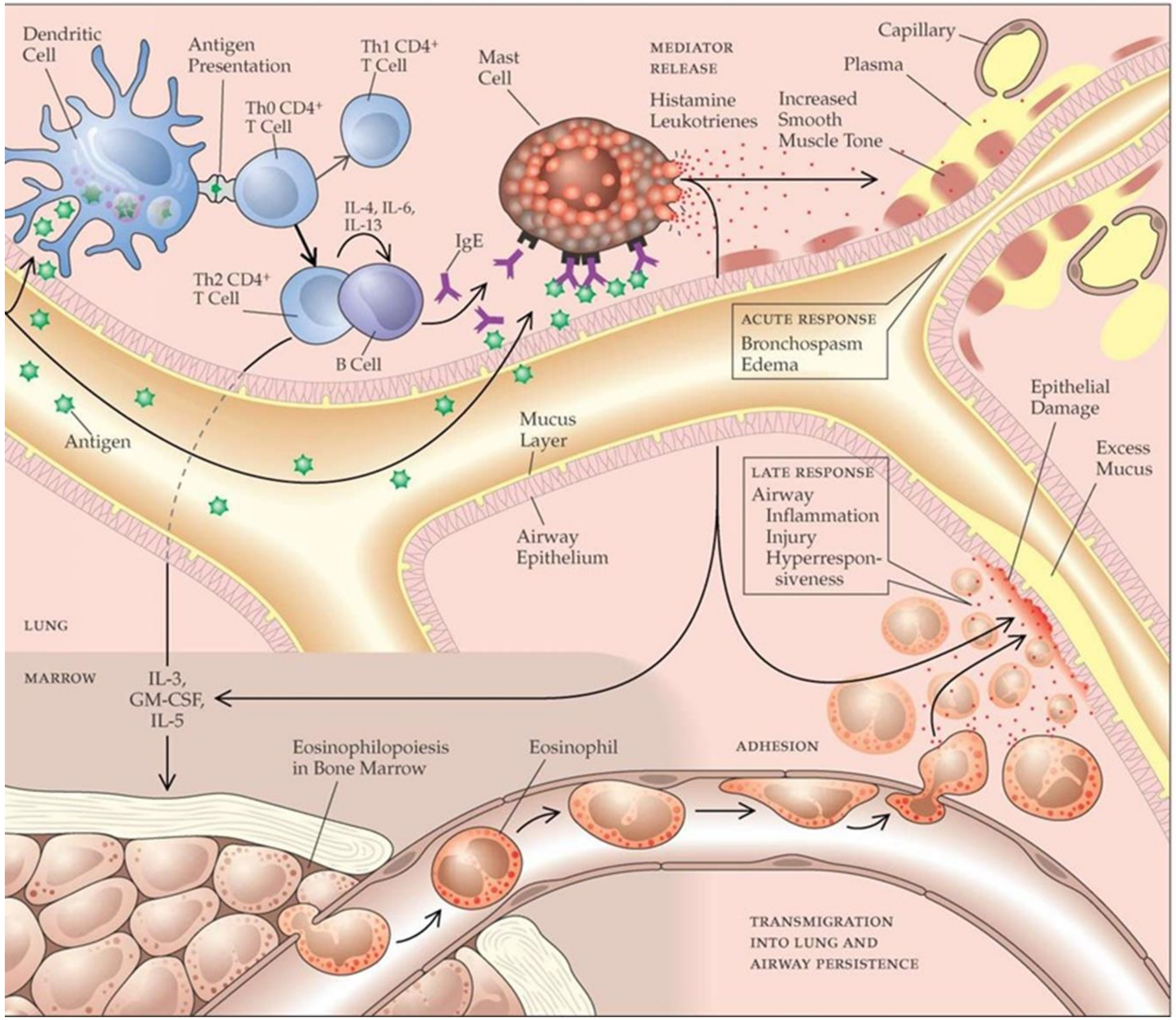
Pathogenesis of allergic asthma



Inhaled antigen is processed by dendritic cells and presented to Th2 CD4+ T cells. B cells are stimulated to produce IgE, which binds to mast cells. Inhaled antigen binds to IgE, stimulating the mast cell to degranulate, which in turn leads to the release of mediators of the immediate response and the late response. Histamine and the leukotrienes produce bronchospasm and airway edema. Released chemotactic factors, along with factors from the Th2 CD4+ T cells, facilitate eosinophil traffic from the bone marrow to the airway walls. These late responses are proposed to lead to excessive mucus production, airway wall inflammation, injury, and hyperresponsiveness. (GM-CSF—granulocyte-macrophage colony-stimulating factor; IFN-y—interferon gamma; IL—interleukin)

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Table 7.1 Characteristics of Th1 and Th2 cells

	Th1	Th2
Cytokines	• IL-2, IFN-γ • IL-3, GMCSF	• IL-4, IL-5, IL-10, IL-13 • IL-3, GMCSF
Main receptors	• IL-12Rβ, IL-18R • CXCR3, CCR5	• CCR4
Effector functions	• Macrophage activation • Complement-binding • Opsonization • Neutrophil activation	• Production of IgE • Production of neutralizing antibodies • Suppression of macrophage activation • Eosinophil activation, proliferation, maturation, recruitment

GMCSF, granulocyte macrophage colony stimulating factor; IL, interleukin; IFN, interferon; IgE, immunoglobulin E.

Table 7.2 Characteristics of regulatory T (Treg) cells

nTreg	aTreg: Th3	aTreg: Tr1
• T cell: T cell/APC contact • Generated in thymus • CD4+, CD25hi, CD45RO+, GITR+, CTLA4+, CD103+, Foxp3+ • Protect against autoimmunity • 5–10% of CD4+ T cells	• Soluble/membrane TGF-β • Generated in periphery (post-thymic) • Variable CD25 expression • Inhibit Th1 and Th2 responses	• Soluble IL-10 • Generated in periphery • (post-thymic) • Variable CD25 expression • Inhibit Th1 and Th2 responses

Major characteristics of subsets of CD4+ Treg cell bases on cell-surface markers, immunosuppressive cytokine secretion and suppressive action. nTreg, natural Treg; aTreg, adaptive Treg; Th, T helper cell; Tr1, T-regulatory cell type 1; APC, antigen-presenting cell, TGF, transforming growth factor; IL, interleukin. (From Van Oosterhout AJ, Bloksma N (2005). Regulatory T-lymphocytes in asthma. *Eur Resp J*, **26**:918–932.)

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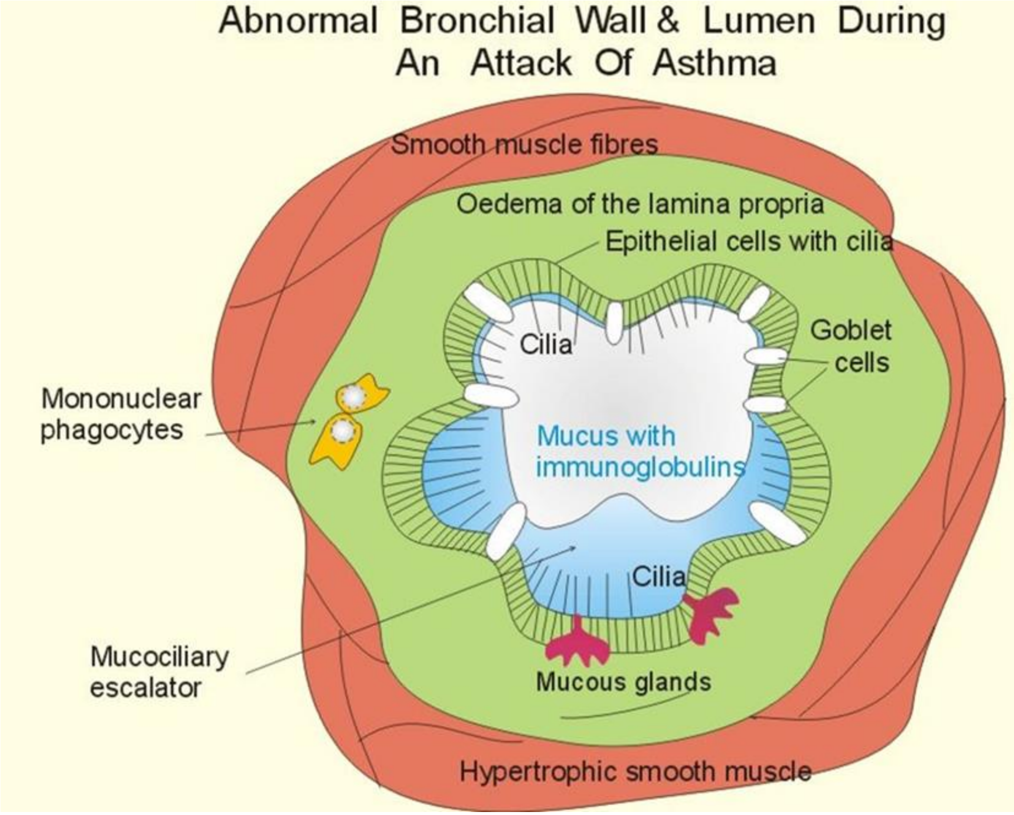
Asthma – acute, late and chron. phase



- early phase (acute attack)
  - 15-30 min, mediators of mast cells (**histamine**)
    - immediate biological response but as wells as chemotaxis of other cell types
  - ↑ secretion of mucus, edema of the bronchial wall
  - contraction of SMCs (bronchospasms)

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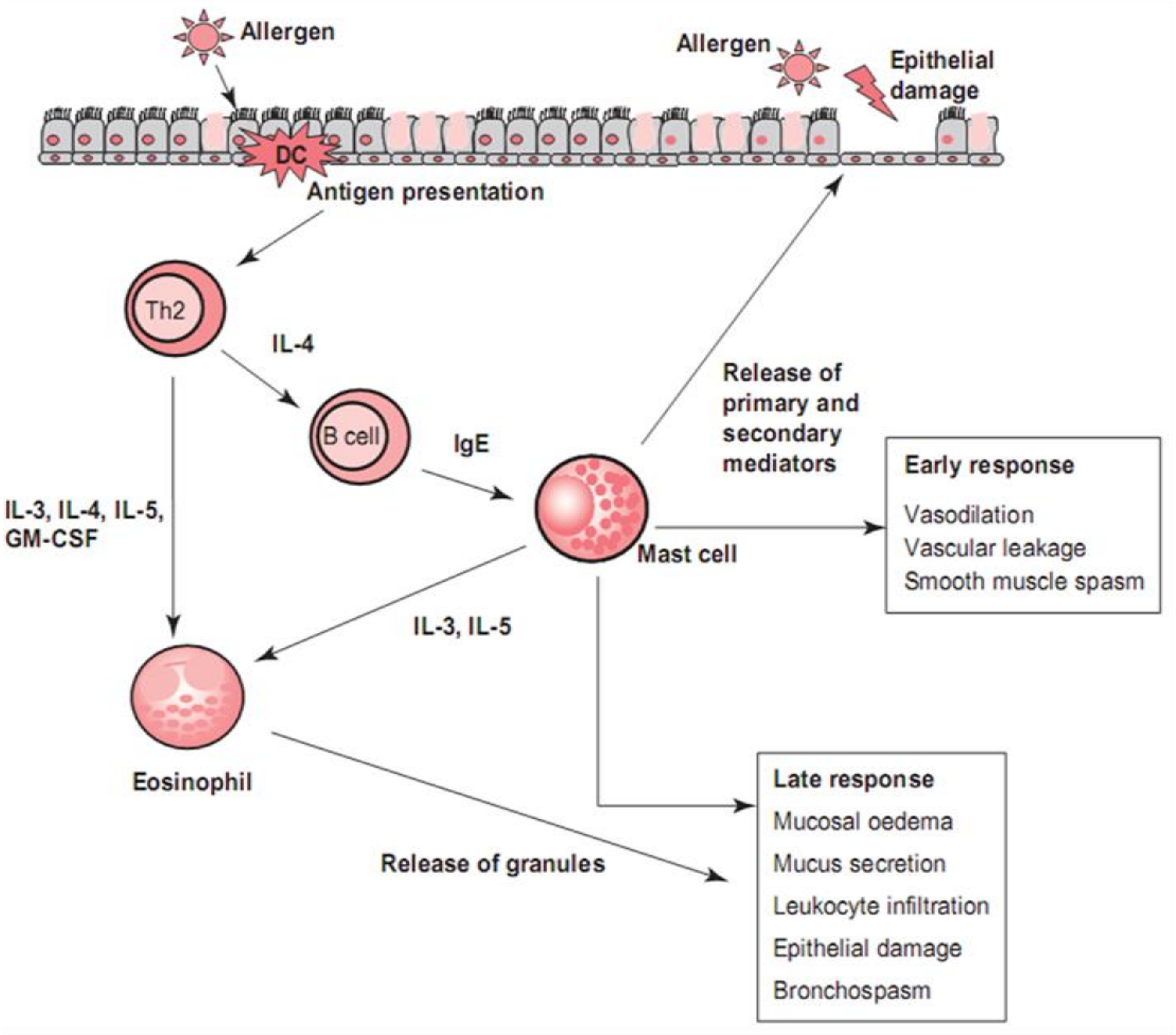
Asthma – acute, late and chron. phase



- late phase
  - after 4-8 hrs
  - mediators of neutrophils, **eosinophils**
    - **leukotrienes** C, D and E, basic and cationic protein etc.
  - inflammation (hyperemia, edema), hypersecretion of mucus, event. destruction of epithelium

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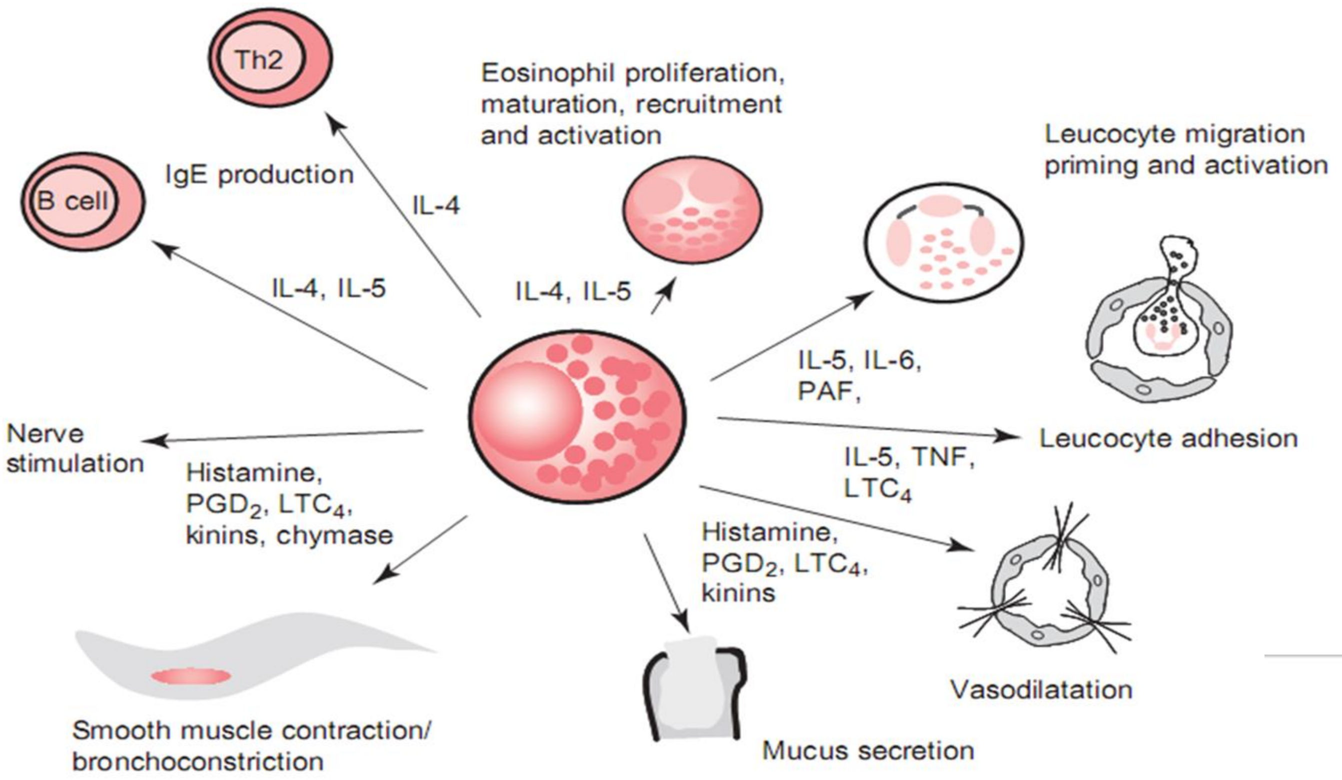
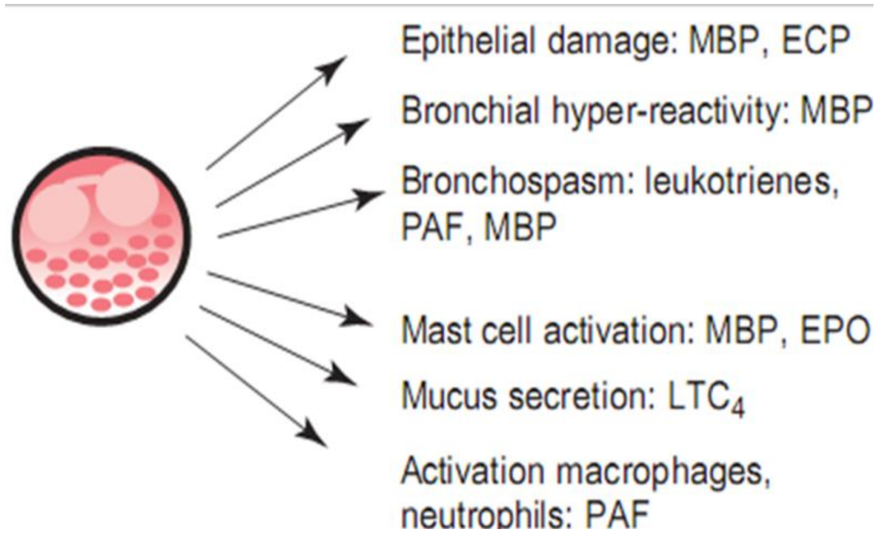
Mediators of mast cells and eosinophils





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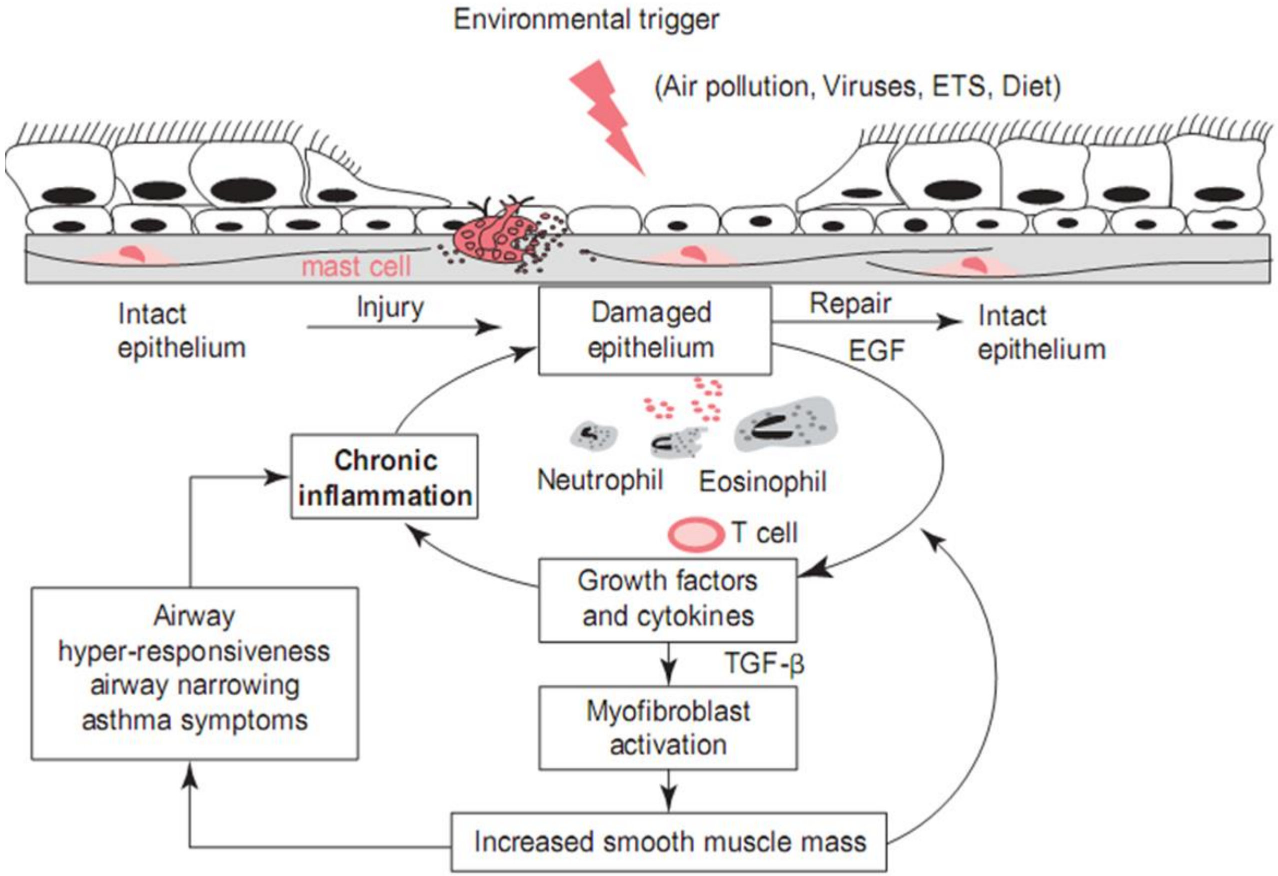
Asthma – acute, late and chron. phase



- chronic phase
  - chronic inflammation + repair processes lead to irreversible structural (**remodelation**) and functional (**hyper-reactivity**) changes of airways constituting a vicious cycle
  - epithelium
    - ↓ cilia, desquamation
    - hypertrophy of mucus glands and hyperplasia of goblet cells
  - basal membrane
    - fibrotisation in subepithelialspace (collagen)
  - muscle layer
    - hypertrophy and hyperplasia of SMCs

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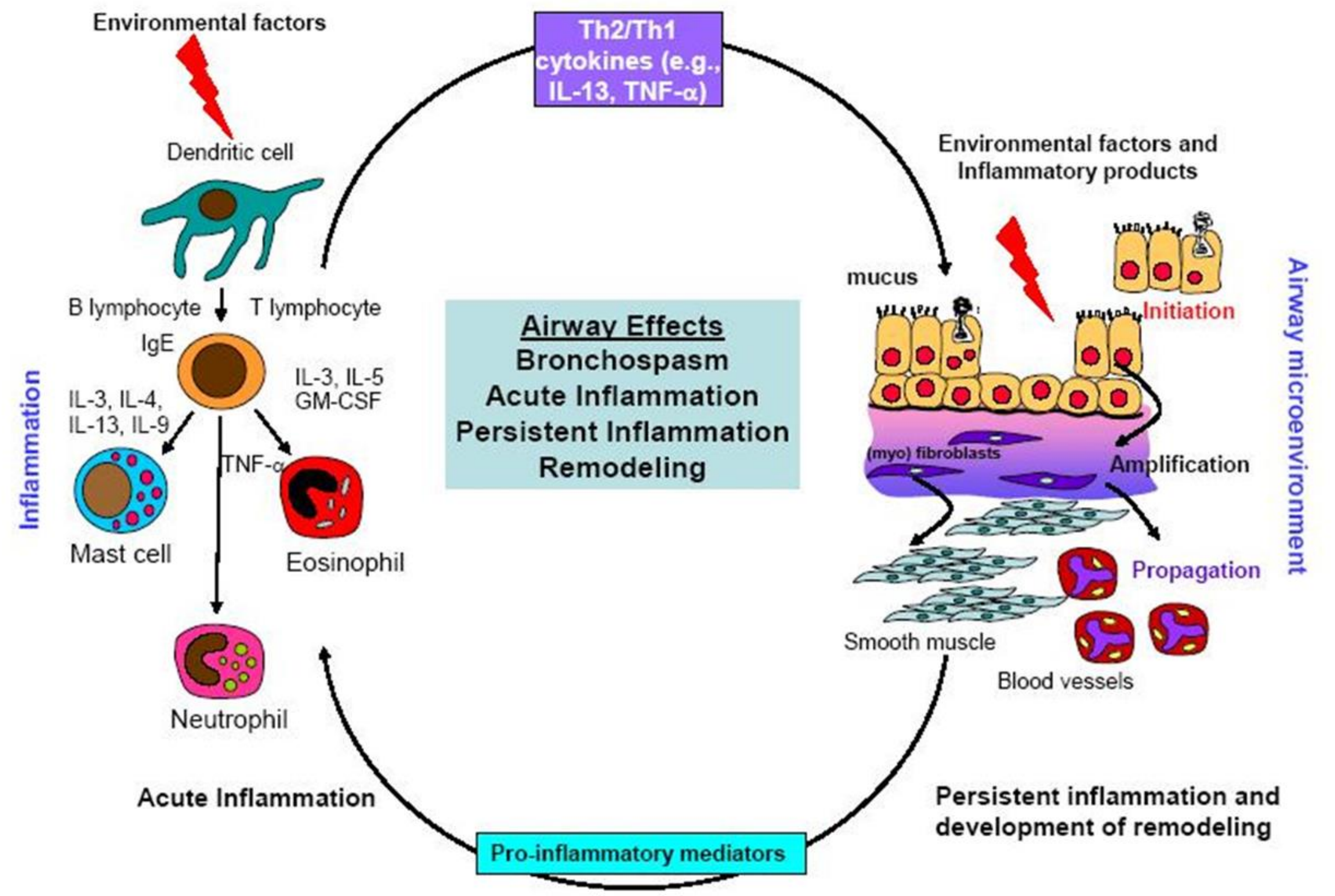
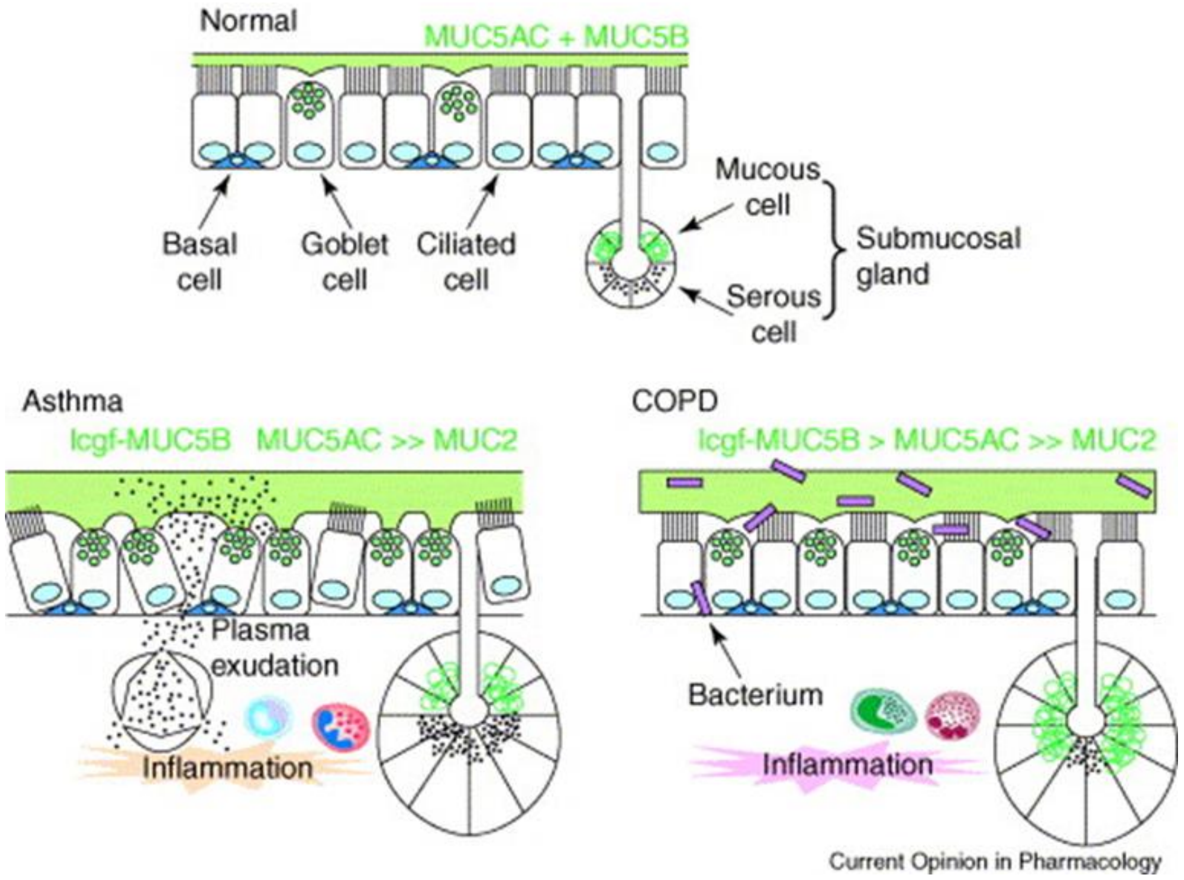
FIGURE 2–2. FACTORS LIMITING AIRFLOW IN ACUTE AND PERSISTENT ASTHMA



Key: GM-CSF, granulocyte-macrophage colony-stimulating factor; IgE, immunoglobulin E; IL-3, interleukin 3 (and similar); TNF-α, tumor necrosis factor-alpha

Source: Adapted and reprinted from The Lancet, 368, Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults, 780–93. Copyright (2006), with permission from Elsevier.

Mucus pathophysiology in asthma and COPD: similarities and differences



- In asthmatics, there is increased luminal mucus, a similar or increased ratio of mucin (MUC) 5B (low charge glycoform [lcgf]) to MUC5AC, small amounts of MUC2, epithelial 'fragility', marked goblet cell hyperplasia, submucosal gland hypertrophy (with normal mucous to serous cell ratio), 'tethering' of mucus to goblet cells, and plasma exudation. Airway inflammation involves T lymphocytes and eosinophils. In COPD, there is increased luminal mucus, an increased ratio of lcgf MUC5B to MUC5AC, small amounts of MUC2, goblet cell hyperplasia, submucosal gland hypertrophy (with an increased proportion of mucous to serous cells), and respiratory infection (possibly owing to reduced bacterial enzymatic 'shield' from reduced serous cell number). Pulmonary inflammation involves macrophages and neutrophils.

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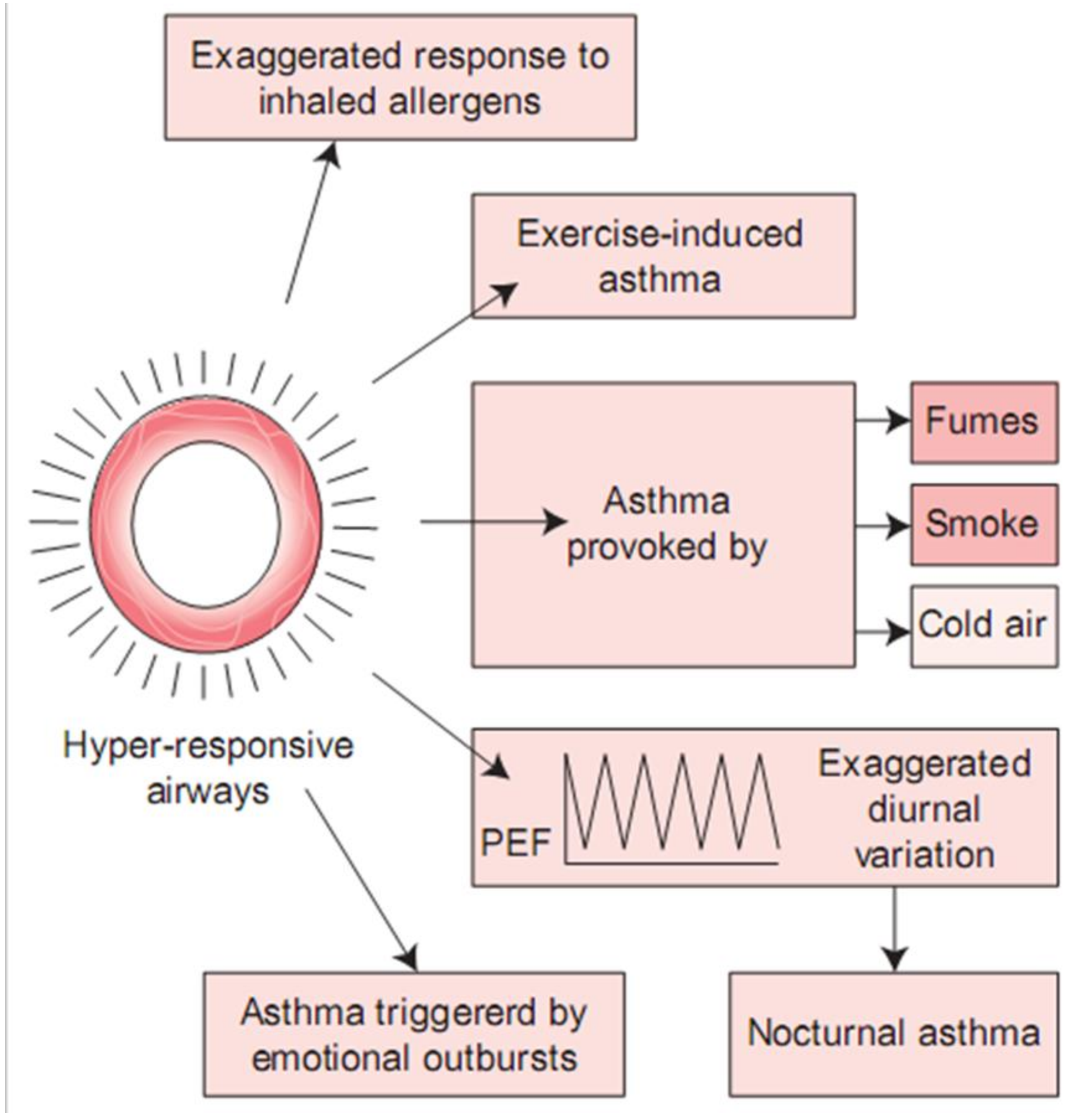
The hyper-responsive airways in asthma respond to a wide-range of provoking factors



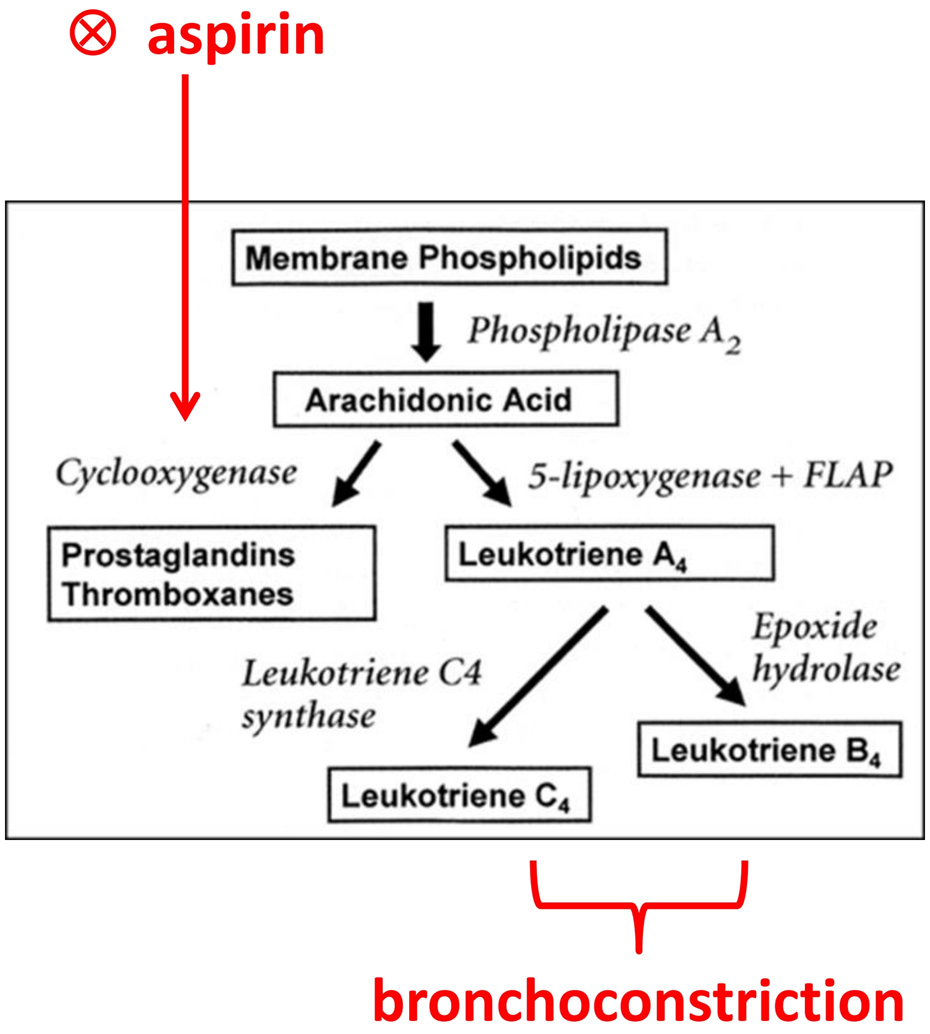
- parasympathetic nerve endings are close to the surface
  - damage leads to their exposure and increase of bronchoconstriction potential
- bronchomotoric tests
  - bronchodilations tests - reversibility of bronchial obstruction
    - salbutamol 200-400 ug
    - ipratropium 80 ug
  - bronchoconstriction test – bronchial hyperreactivity
    - histamine 1g in 100 ml of physiol. soution
    - metacholin

Table 1.4 Stimuli that can provoke asthma symptoms

- Cold air
- Exercise
- Climate, including changes in temperature and humidity, e.g. fog
- Air pollution, both indoor and outdoor
- Fumes, including smoke, perfume, sprays
- Allergens, including house dust mite, cat, dog, moulds
- Medications, including
  - β-blockers used for heart disease and high blood pressure
  - non-steroidal anti-inflammatory drugs such as aspirin used for pain relief or arthritis
- Emotion, including stress and loss (bereavement)
- Hormonal, such as premenstrual and during pregnancy
- Night-time and early morning
- Foods, including preservatives, such as tartrazine (orange colouring), monosodium glutamate (used in Chinese food), sulphites (included in some wines) and allergens such as peanuts, shellfish
- Workplace exposure to agents to which individuals become sensitized
- Alcohol
- Viral respiratory tract infections such as the common cold and influenza

Aspirin-induced asthma (AIA)

- typical features:
  - first manifestation in 3rd-4th decade, more often women
  - whole year persisting cold
  - nasal polyps and blockade
- frequency:
  - ~10% of adult cases of asthma is in fact AIA
    - in general population 0.3-0.9%
- „aspirin trias“
  - sensitivity to ASA
  - asthma
  - persisting rhinosinusitis with nasal polyposis and eosinophilia



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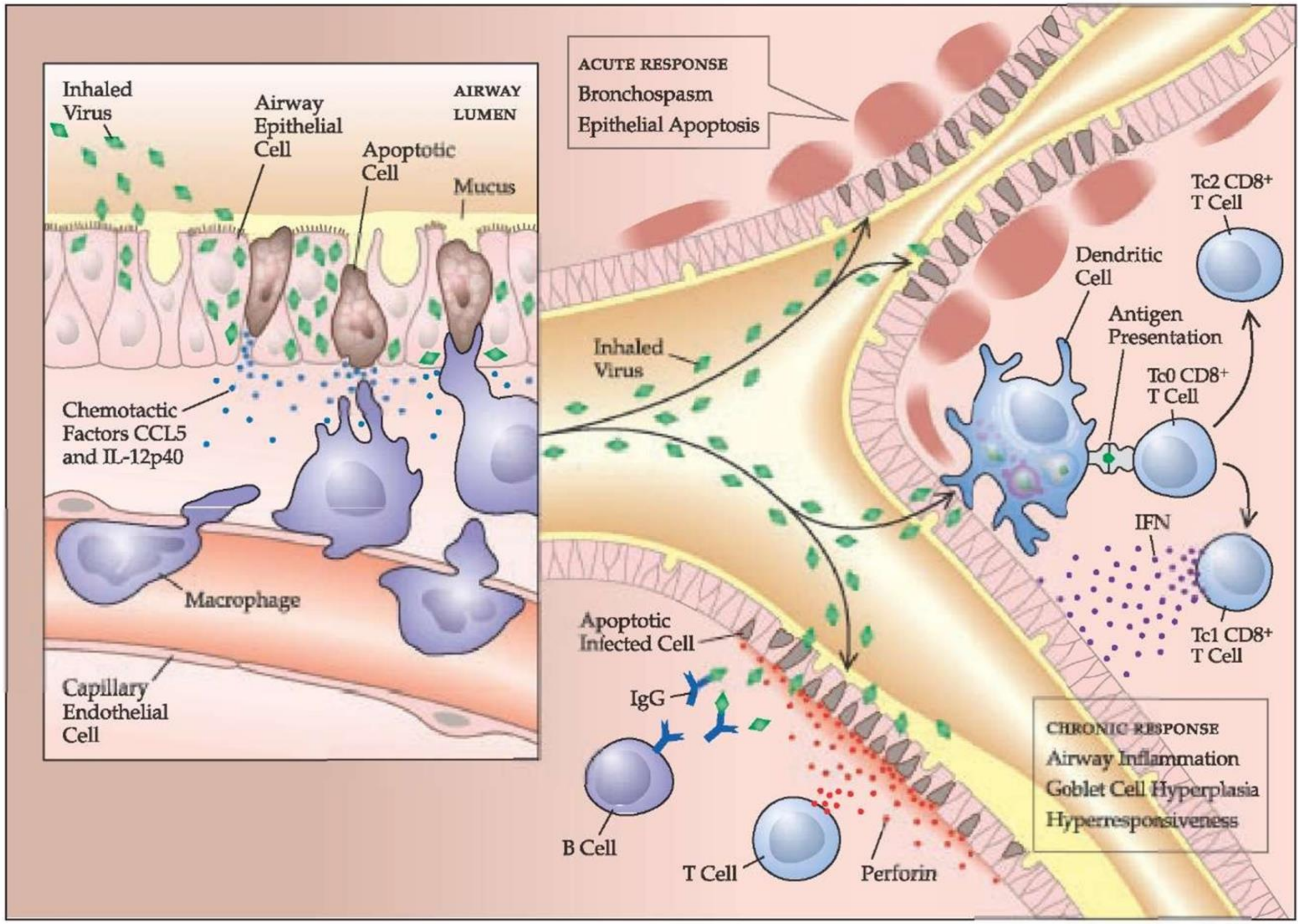
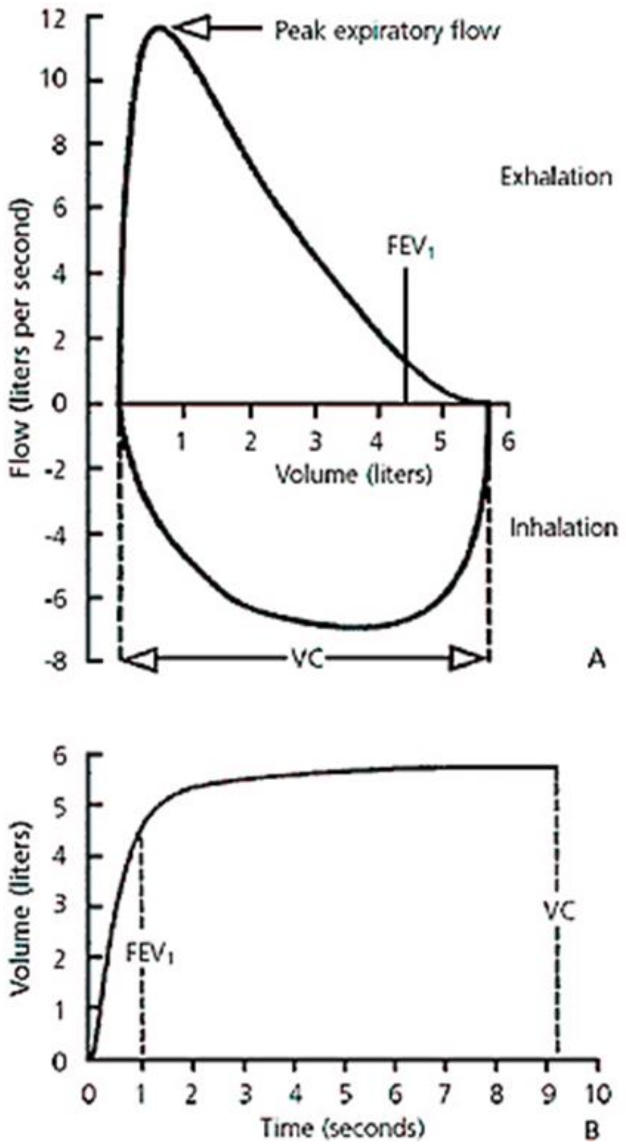
Pathogenesis of virus-induced asthma



Inhaled virus infects epithelial cells and leads to apoptosis of some of them. The release of chemotactic factors promotes the recruitment of macrophages into the lung parenchyma, where they ingest the dead epithelium. An acute response consisting of bronchospasm occurs at this time. Similar to allergic asthma, the inhaled virus is processed by dendritic cells and presented to Th2 CD8+ T cells. These cells produce copious amounts of IFN-y. Perforin released from the T cells leads to apoptosis of infected cells. B cells produce IgG, which is capable of neutralizing the virus. These events are thought to be related to the chronic response, which consists of airway inflammation, goblet cell hyperplasia, and airway hyperresponsiveness. (IFN-Y—interferon gamma; IL—interleukin; CCL—chemokine ligand)

Asthma – clinical manifestation

- During full remission
  - individuals are asymptomatic and pulmonary function tests are normal
- During partial remission
  - no clinical symptoms but pulmonary function tests are abnormal
- During attacks
  - dyspnea and ↑respiratory effort, wheezing, non-productive coughing, tachycardia and tachypnea
- Diagnosis
  - spirometry
    - ↓ expiratory flow rate, forced expiratory volume (FEV1), and forced vital capacity (FVC)
    - ↑ FRC and total lung capacity (TLC)
  - blood gas analysis shows respiratory insufficiency
    - initially partial (i.e. hypoxemia with respiratory alkalosis)
    - later global (i.e. hypercapnia and respiratory acidosis)



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