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Pulmonary perfusion and diffusion disorders

Respiration process (pumonary gas exchange)

- Ventilation
- Diffusion
- Perfusion

Partial pressures

Parciální tlaky

	O_2 (%)	CO_2 (%)	PH_2O (kPa)	PN_2 (kPa)	PaO_2 (kPa)	PCO_2 (kPa)
Atmosfer. vzduch (suchý)	20,93	0,03	0,8	79,04	21,06	0,04
Exspir. vzduch	15,1	4,3	6,3	75,3	15,3	5,73
Alveolární vzduch	13,2	5,1	6,2	76,4	13,4	5,33
Arteriální krev	19,8	50	6,3	76,4	8 12,7	5,2 0,8
Venózní krev	14-15	55	6,3	76,4	5,2	6,13

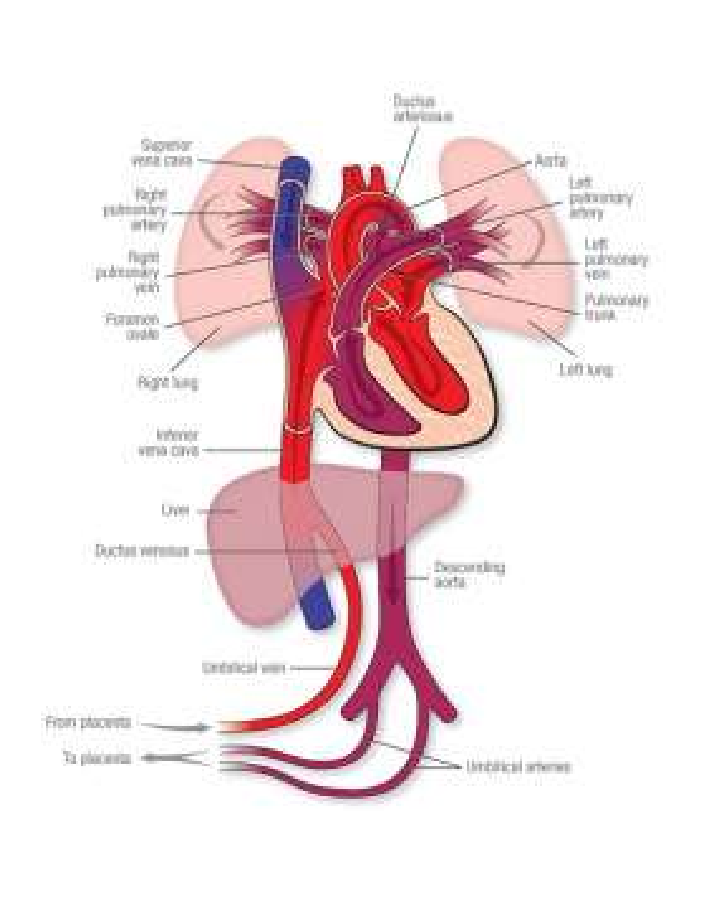
Differences between pulmonary and systemic circulation

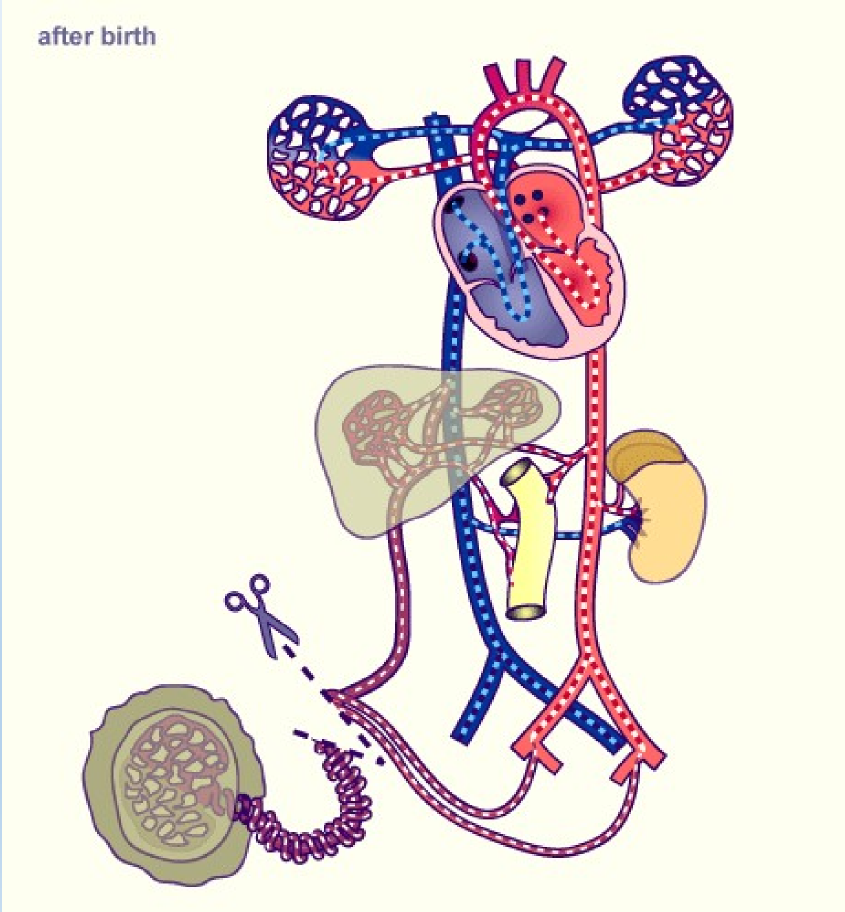
- Pulmonary circulation
- Low pressure
- Distribution into different segments is regulated uniquely by local metabolic factors (hypoxic vasoconstriction)
- Total CO is determined by the kidneys and left ventricle (which react primarily to systemic circulation parameters), only resistance is regulated in the lungs
- Low pressure gradient between pulmonary veins and arteries (sufficient ↑ BP in left atrium is mirrored in the pulmonary trunk)

- Systemic circulation
- High pressure
- Distribution into different segments is regulated metabolically (hypoxic vasodilation) as well as centrally (nervous system, hormones)
- Simultaneous regulation of resistance, mechanic function of the heart and circulating volume
- Difference between arterial and venous pressures is approx. 100 mmHg, ↑ BP in right atrium does not have a direct impact on MAP

- Most differences develop during the transition into postnatal circulation

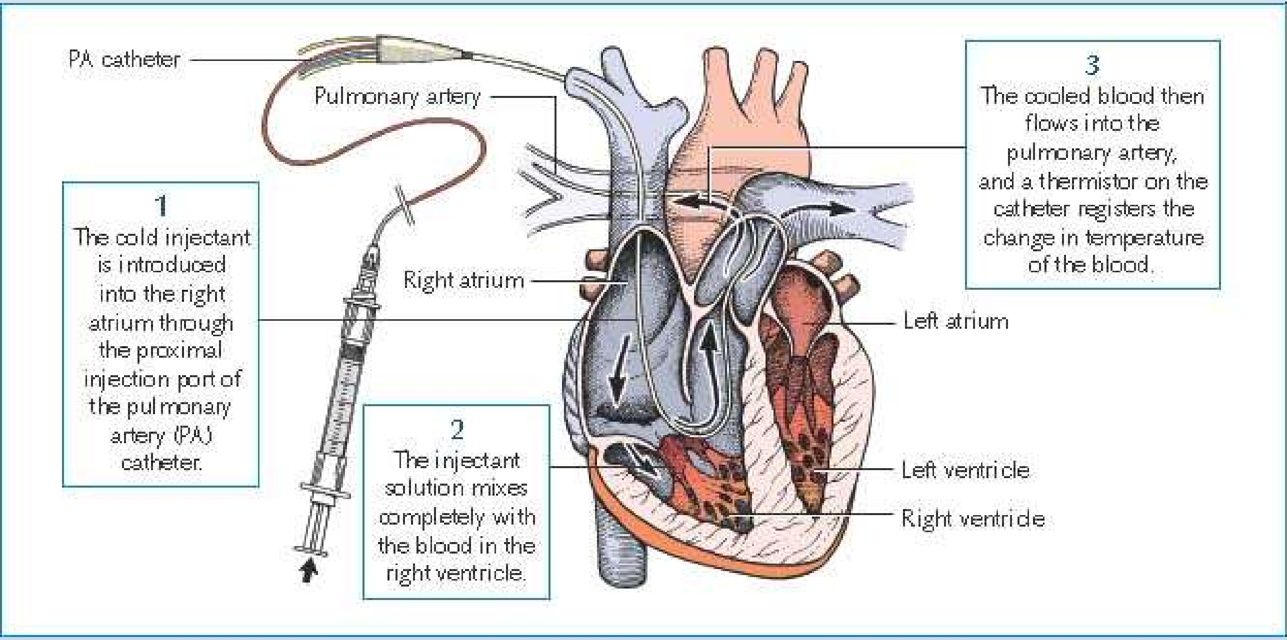
Fetal and postnatal circulatory system

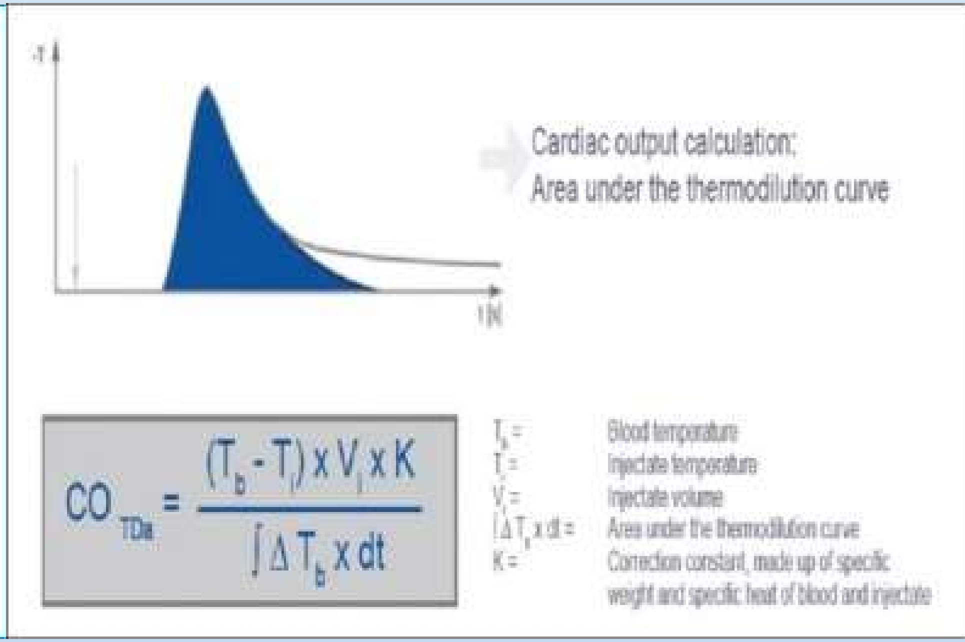




Perfusion assessment - total

- Right ventricular cardiac output:
  - (EDV-ESV) × HR (estimate – e.g. echocardiography)
  - termodilution (invasive) – rapid removal of cold marker in high flow (small area under curve)



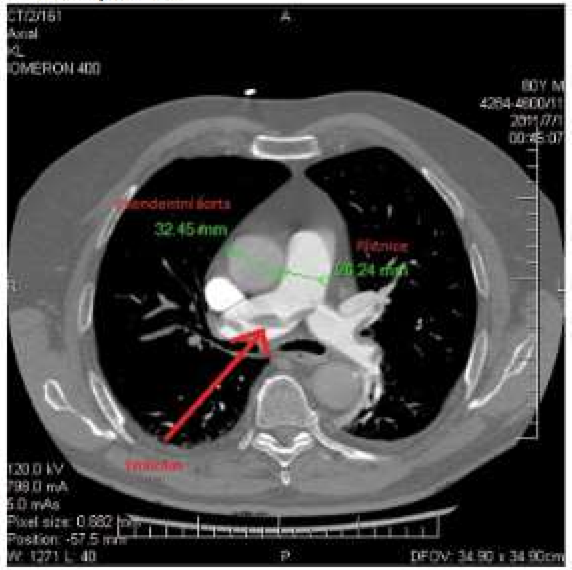


Perfusion assessment - local

- Scintigraphy
  - Perfusion scintigraphy (e.g. $^{99m}_{43}Tc$)
  - Ventilation-perfusion scan: combination of perfusion and inhalation scintigraphy
- Angiography
  - Digital subtraction angiography
  - CT angiography

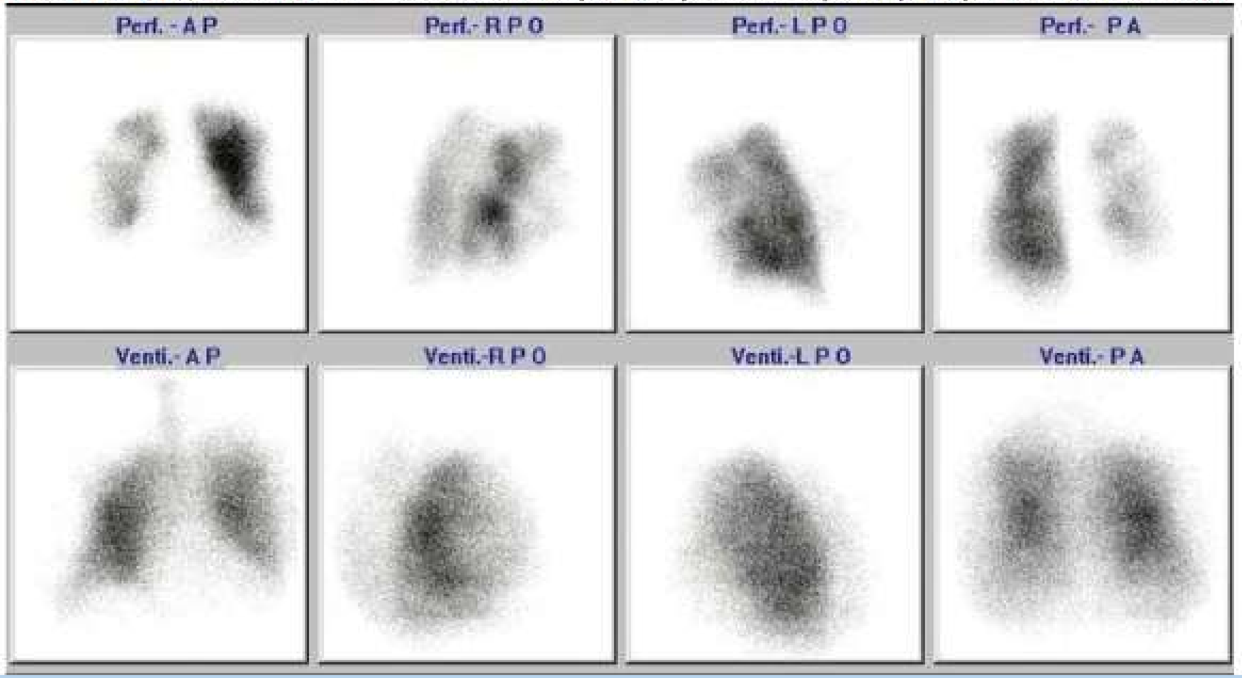
Pulmonary perfusion and V-P scan

Obrázek 2. Měření ascendentní aorty a plicnice, šipka ukazuje na embolus v bifurkaci a obou větvích plicnice



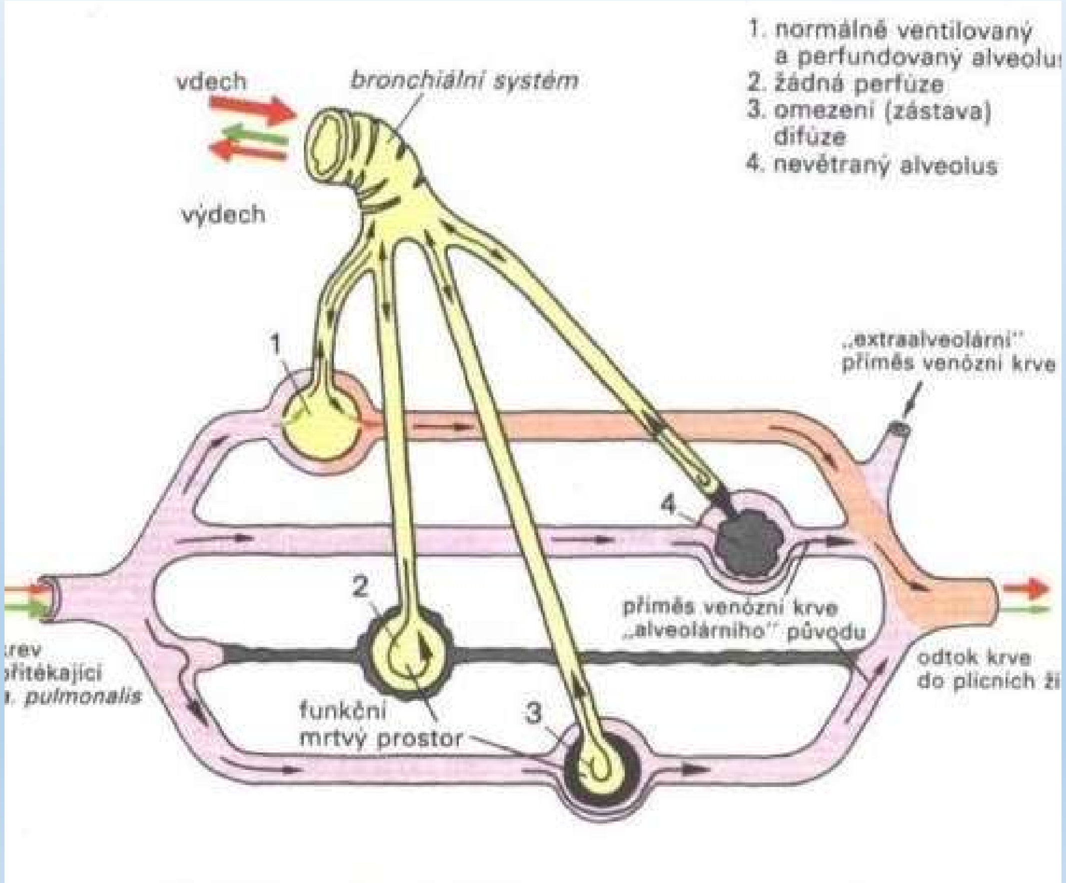
Bilateral pulmonary embolism

Obrázek 4. Pozitivní nález V-P scanu, defekty perfuze převážně v pravé plíci, při normální ventilaci



Normal ventilation with perfusion defects in the right lung
www.iakardiologie.cz

Findings



Normal

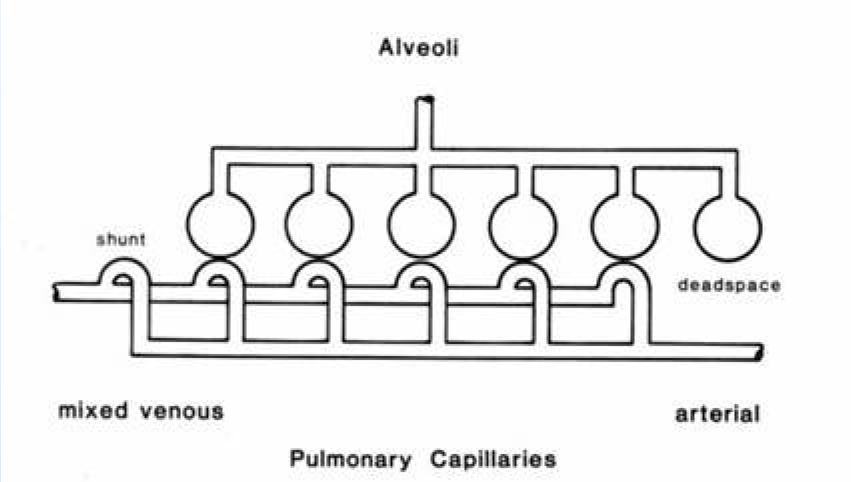
Right-to-left shunt

Dead space

Dead space AND Right-to-left shunt

Right-to-left shunt

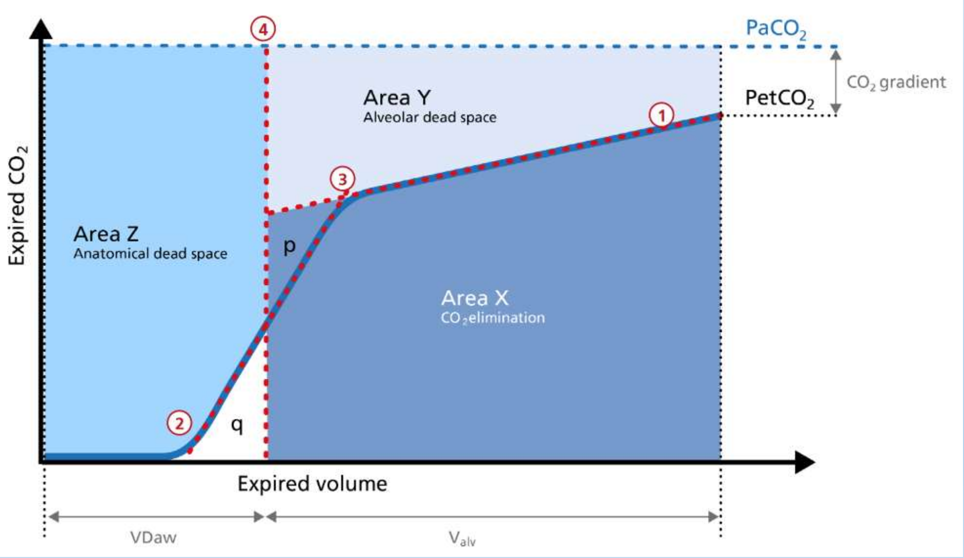
- Percentage of blood, which passed from right ventricle into left atrium without a change in blood gases (physiologically up to 0.10)
  - anatomical
  - functional (alveoli with low V_A/Q ratio)
  - Pathological



- Can be estimated using perfusion scintigraphy
  - Quantification of $^{99m}_{43}$Tc-labeled macroaggregated albumin uptake in pulmonary and systemic circulation
  - shunt[%] = (systemic aggregates – pulmonary aggregates)/systemic aggregates

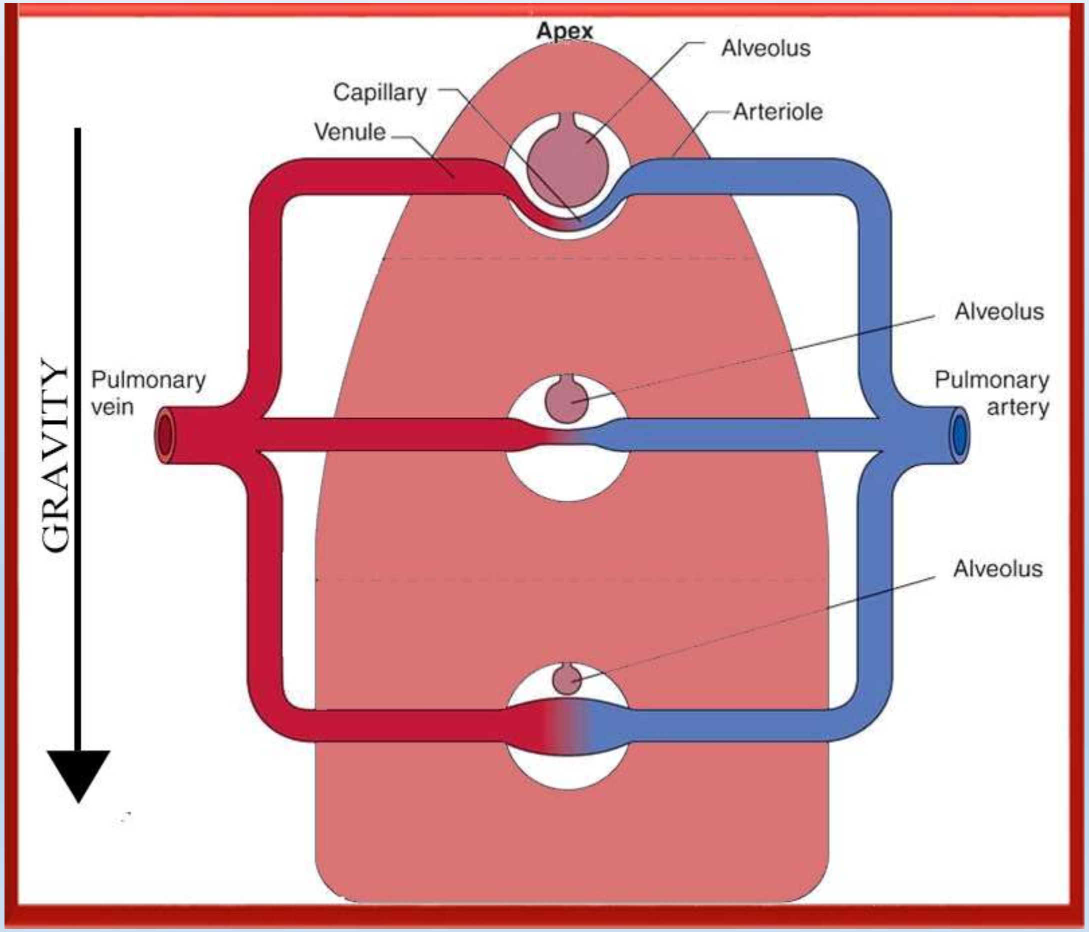
Dead space

- Volume with no gas exchange
  - can be estimated from the difference between $PaCO_2$ and pCO_2 in exhaled air at the end of expiration (end-tidal CO_2; $EtCO_2$) - capnometry
  - ↑ ($PaCO_2$ – $EtCO_2$) ↔ ↑ dead space
- Physiologically around 1/3 of tidal volume
  - anatomical
  - functional (alveoli with high V_A/Q ratio)
  - pathological

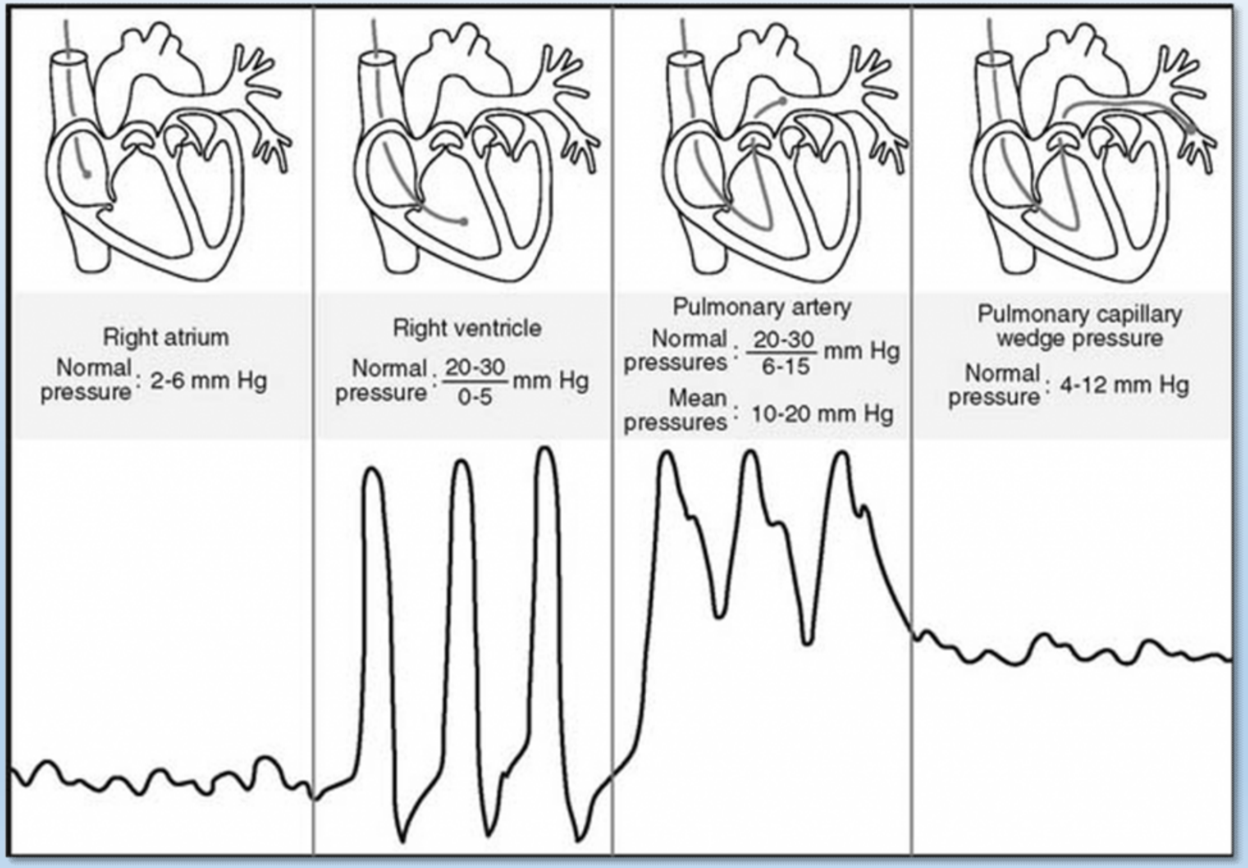


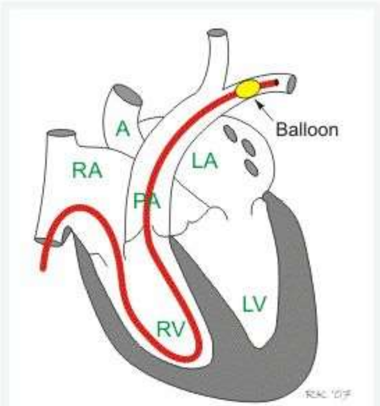
V_A / Q equilibrium

- ↑ V_A/Q – dead space
- ↓ V_A/Q – shunt
- V_A/Q ~ 1 – no shunt or dead space, or combined shunt and dead space (which is, to a degree, standard)



Pressures in pulmonary circulation





Balloon-tipped, Swan-Ganz catheter for measuring pulmonary capillary wedge pressure (PCWP).

- Pressure in pulmonary trunk
- Pulmonary wedge pressure
  - A balloon-tipped catheter is carried by the blood flow into a branch of pulmonary artery, which is occluded this way („wedge“)
  - Pressure measured by the tip of a catheter thus reflects the left atrium pressure and not pulmonary arterial pressure

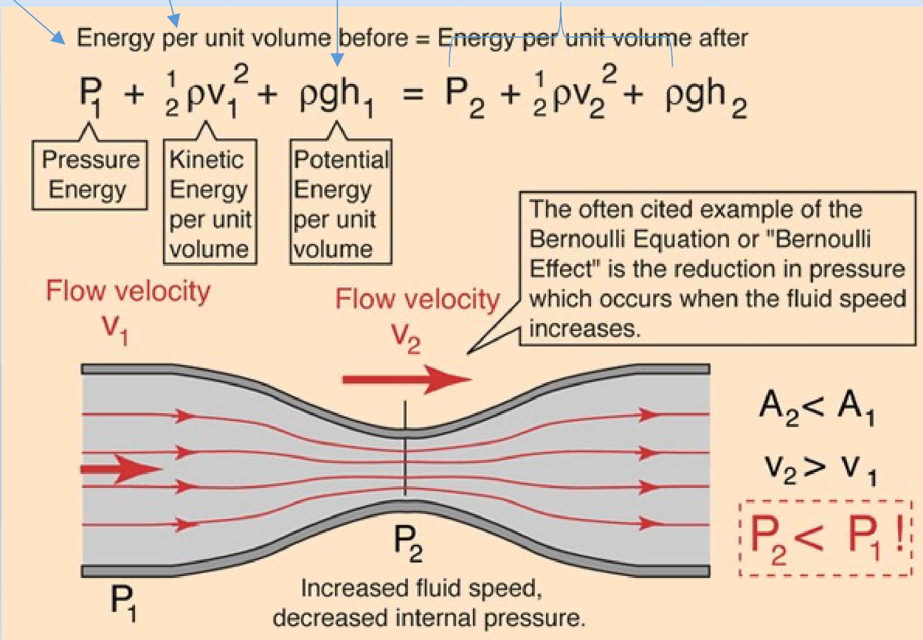
Noninvasive estimation of pulmonary pressures

Dynamic pressure (regurgitation jet)

static pressure (right atrium)

hydrostatic pressure (may be ignored)

Sum of pressures in pulmonary trunk

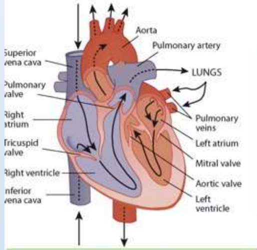


- Lower reliability than direct measurement, rather orientational (± 5 mmHg)
- 2D USG – estimation of right atrial pressure (P_{ra})
  - diameter of inferior vena cava (normal 1,5 – 2,5 cm)
  - change of inferior vena cava diameter during respiration (normal ≥ 50 %)
- Doppler USG – tricuspid and pulmonary regurgitation (see Bernoulli equation)
  - Systolic pressure in pulmonary trunk: $4(TRV_{end})^2 + P_{ra}$, where TRV_{end} is a flow velocity of tricuspid regurgitation at the end of the diastole
  - Diastolic pressure in pulmonary trunk: $4(PRV_{end})^2 + P_{ra}$, where PRV_{end} is a flow velocity of pulmonary regurgitation at the end of the diastole
  - Mean pressure in pulmonary trunk: $4(PRV_{bd})^2 + P_{ra}$, where PRV_{bd} is a flow velocity of pulmonary regurgitation at the beginning of the diastole
  - Result in torr; 1 kPa ~ 8 torr (this is why the velocities are multiplied by 4)

Pulmonary hypertension

- Mean pulmonary pressure> 25 mmHg at rest or > 30 mmHg during effort
- precapillary
  - hypoxic (e.g. COPD, esp. with chronic bronchitis predominance)
  - restrictive (e.g. ILD, pneumonectomy, severe emphysema)
  - vascular (e.g. pulmonary embolism, pulmonary arterial hypertension)
- postcapillary (e.g. left-sided heart failure)
- hyperkinetic (e.g. left-to-right shunts)

Pressures and CO in the right heart in pulmonary hypertension

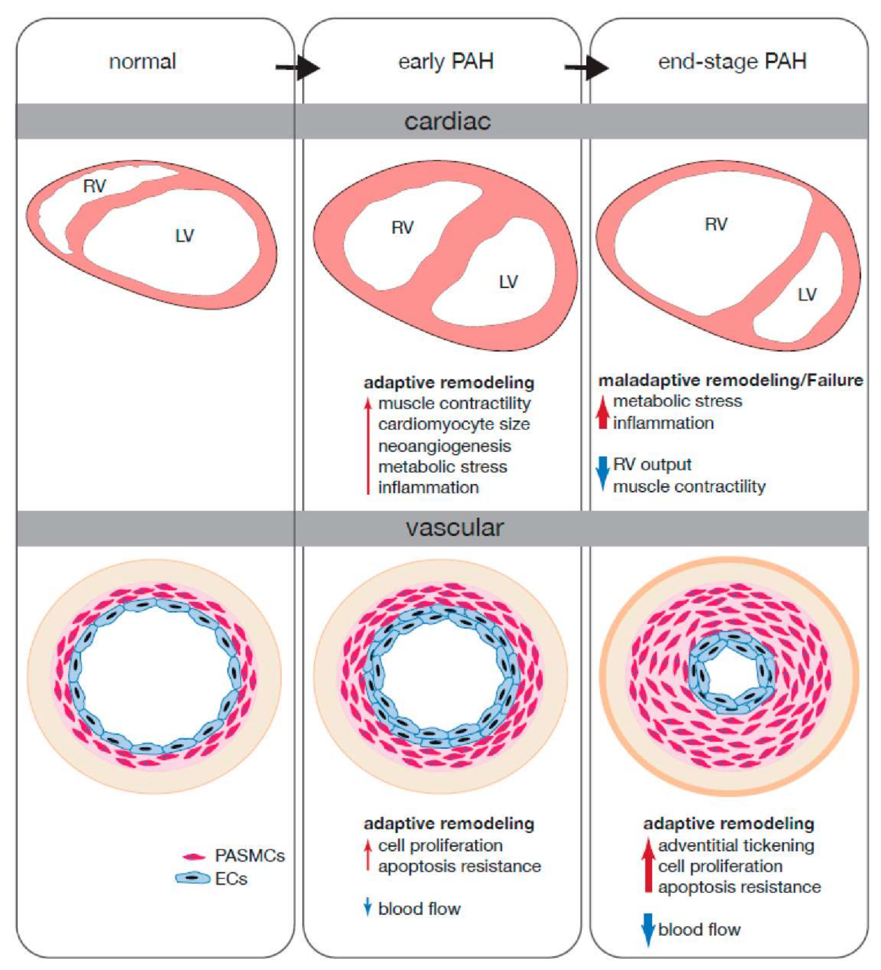


Hemodynamic Scenarios: Pulmonary Artery Catheter

	Right Atrial Pressure (mmHg)	Right Ventricular Pressure (mmHg)	Mean Pulmonary Artery Pressure (mmHg)	Pulmonary Capillary Wedge Pressure (mmHg)	Cardiac Index (L/min/m2)
Normal	0-8	15-25/0-8	<25	8-12	2.6-4.2
HFrEF, decompensated	↑	↑	↑	↑	↓
Pulmonary Arterial HTN	↑	↑	↑	↔	↔/↓
Pulmonic Stenosis	↑	↑	↔	↔	↔
Tricuspid Stenosis	↑	↔/↓	↔	↔	↔
Tricuspid Regurgitation	↑	↔	↔	↔	↔
Left-to-Right Shunt	↑	↑	↑	↔	↔
Right-to-Left Shunt	↔/↑	↔/↑	↑	↔/↑	↔
Tamponade/ Constrictive or Restrictive Cardiomyopathies	↑	↑	↔	↔/↑	↔/↓

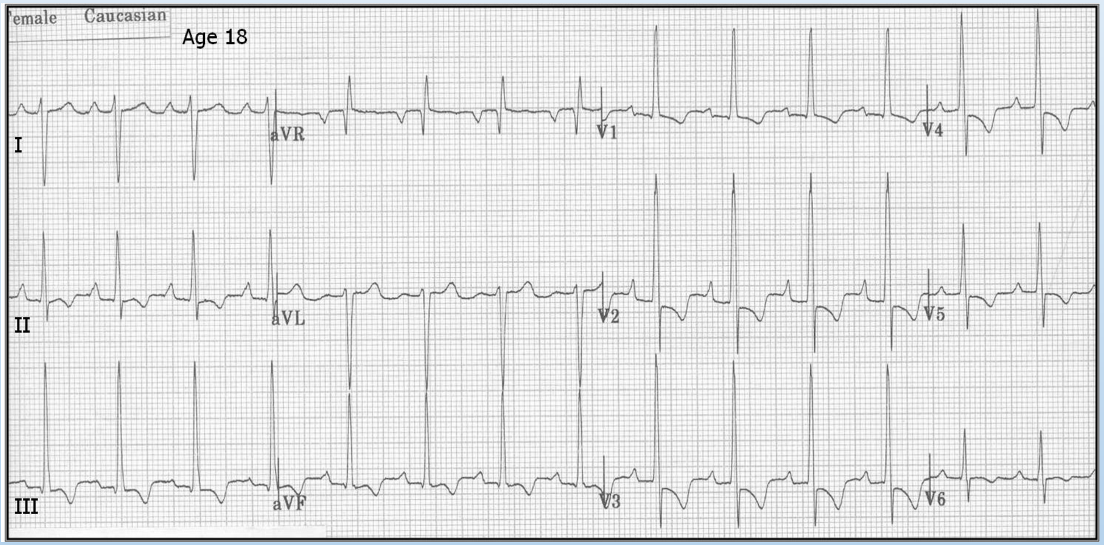
- HFrEF: heart failure with reduced EF
- Cardiac index: CO per body surface area
- In hyperkinetic PH ↑CO of the right ventricle

Pulmonary hypertension – right ventricle



- Right ventricle – first concentric hypertrophy, then dilation and ↓ RV EF
  - In advanced stage decreased RV EF during effort instead of the increase
- Tricuspid and pulmonary regurgitation
- Pulmonary vessels – ↑ wall thickness (which prevents pulmonary edema, but on the other hand ↑ resistance – analogy to systemic hypertension)

ECG in right ventricular hypertrophy

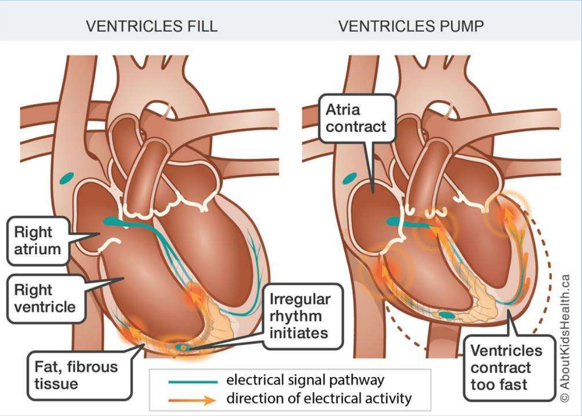


www.ecg.utah.edu

- Right-sided axis deviation (+110°)
- Deep S in left-sided chest leads (correspons with right-sided axis orientation in transversal plane)
- Dominant R in V1 (>0.7 mV)
- RBBB (incomplete or complete)
- P pulmonale (>0.25 mV)
- ST depressions, negative T in right-sided and inferior leads

Other causes of right ventricular hypertrophy

- Inborn defects with left-to-right shunt
- Valvular diseases
- Arrhythmogennic cardiomyopathy (ACM, syn. arrhythmogennic right ventricular dysplasia – ARVD)
    - ECG correlate: ε-wave – postexcitation of the right ventricle; VPC shaped as LBBB



Etiology of pulmonary hypertension

- Primary pumonary hypertension
- Inborn cardiac defects

pulmonary arterial hypertension

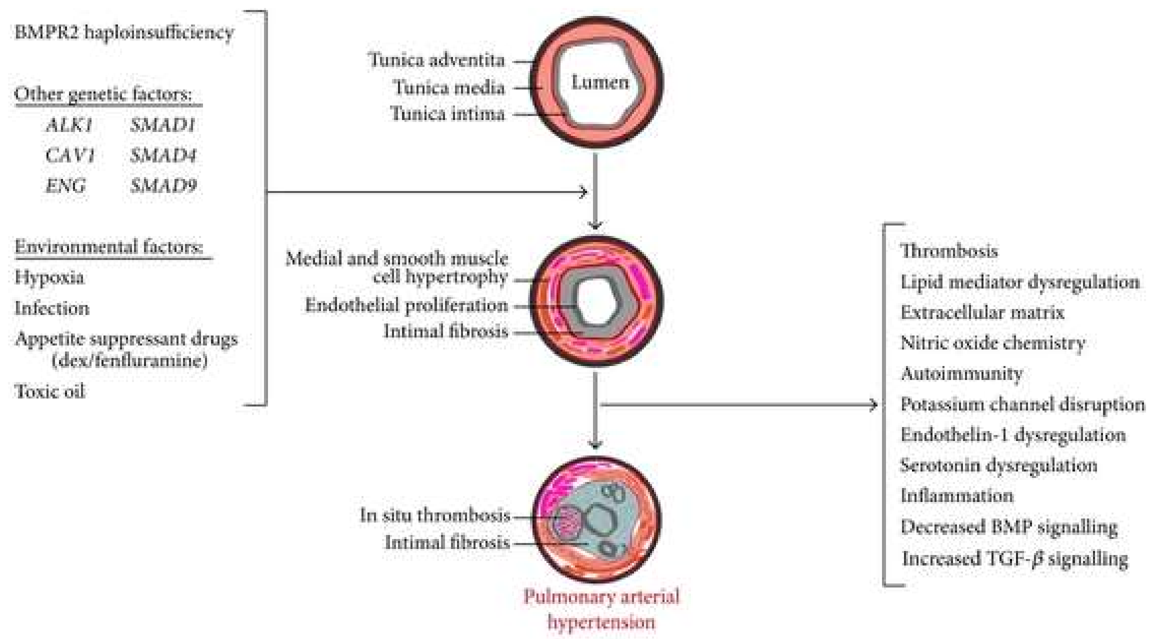
- Left-sided heart failure – pulmonary venous hypertension
- Pulmonary diseases
- Pulmonary embolism
- Other (e.g. sarcoidosis, disorders of hematopoiesis, lymphatic vessels)

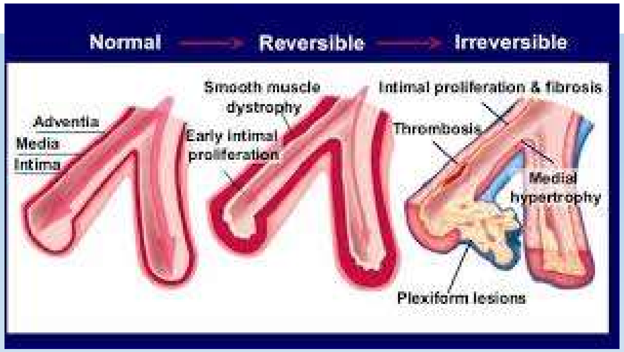
Pulmonary arterial hypertension

- Includes idiopathic hypertension, PAH in inborn cardiac defects, drug-induced PAH (anorectics), persisting PH of newborns or PAH related to connective tissue disorders
- Approx. 5 % of all the pulmonary hypertension cases (of which 50 % is idiopathic PAH)
- Heritable PAH – 6-10 % of cases – in 75 % mutation of BMPR2 (TGF-β receptor)
  - proapoptotic effect on vascular smooth muscle + antiapoptotic effect on endothelium
  - Low penetrance, BMPR2 mutations or ↓expression frequent also in other types of PAH

PAH pathogenesis

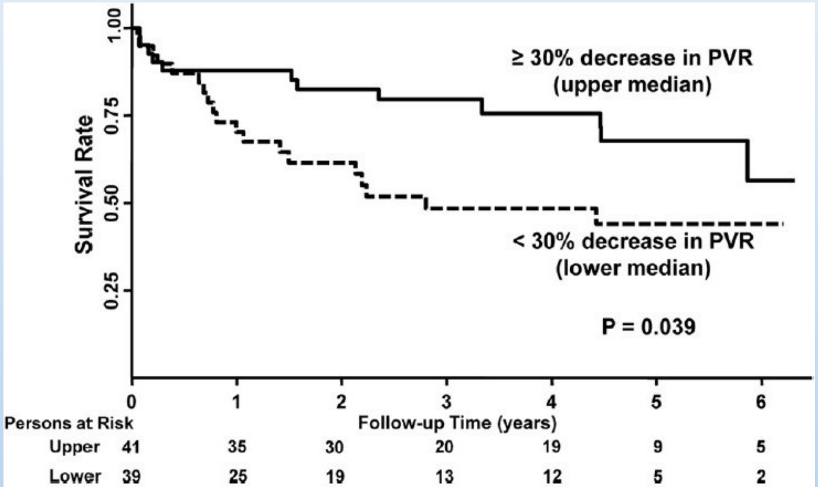
1) Vasoconstriction
   - Endothelial dysfunction
   - thromboxane A2 > prostacyclin (PGI2)
2) Vascular remodelation
3) microthrombi
4) plexiform lesions (irreversible)





Prognosis and treatment of PAH

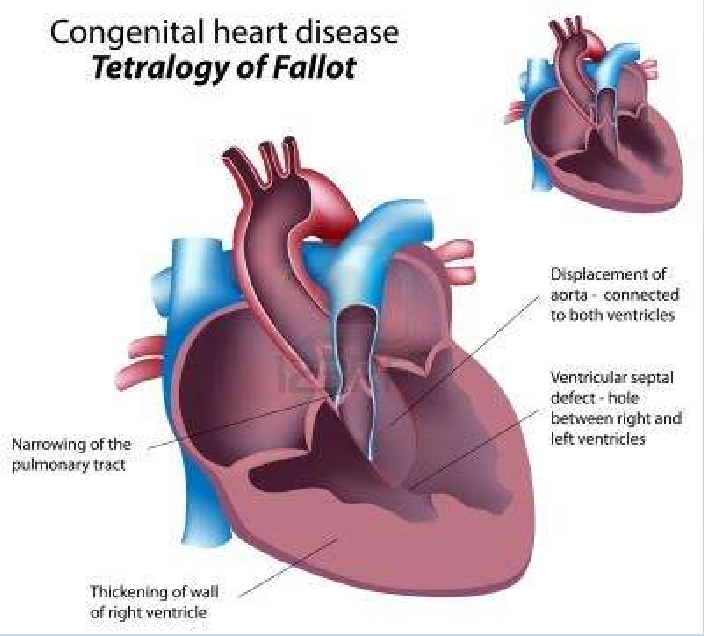
- Without treatment, the survival median is 3 years
- Anticoagulants
- Vasodilators (prostacyclin, sildenafil)
- In some patients (“responders“) PH decrease by >20 % during vasodilation test
    - Administration of NO in the inhaled air / i.v epoprostenol (synthetic prostacyclin) or adenosine
    - Good reaction to Ca^{2+} channel blockers, better prognosis
- Lung transplantation



Malhotra et al. 2011

Inborn cardiac defects

- Cyanotic
  - transposition of the great vessels
  - left ventricular hypoplasia
  - tetralogy of Fallot



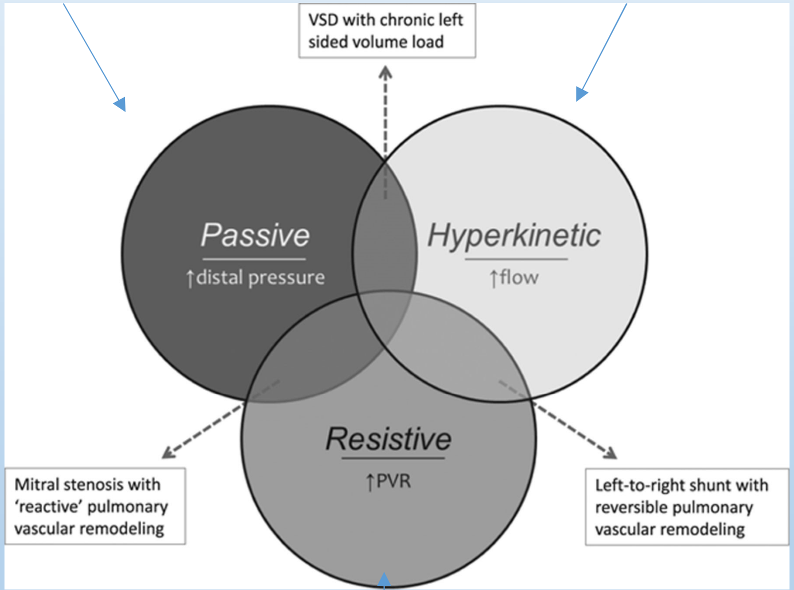
- Necyanotické
  - aortic stenosis
  - aortic coarctation
  - atrial septal defect
  - patent foramen ovale
  - ventricular septal defect
  - persistent ductus arteriosus
  - bicuspid aortic valve (rather a variant)

- Pumonary hypertension in:
  - persistent ductus Botalli (~100 %)
  - ventricular septal defect (~50 %)
  - atrial septal defect (~10 %)

Pulmonary hypertension in cardiac defects

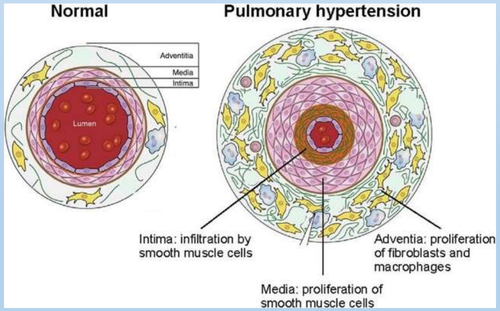
left heart defects

Uncomplicated left-to-right shunt



Eisenmenger syndrome

- Eisenmenger syndrome
  - severe form of pulmonary hypertension in left-to-right shunts
  - pulmonary pressures ~ MAP
  - irreversible remodelation of pulmonary vessels



  - Lefto-to-right shunt → right-to-left → systemic hypoxia

Pulmonary embolism

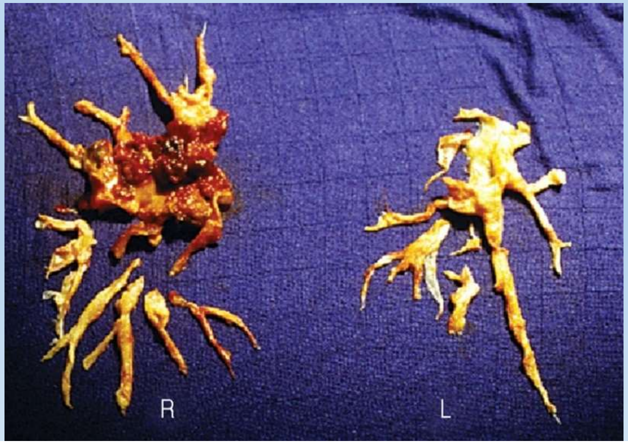
- ↑ V_A/Q
- Causes:
  - thromboembolism
  - fat embolism e.g. fractures) – emboli can bass through bronchopulmonary junctions
  - air embolism (e.g. venous catheterization)
  - tumour embolism
  - complications of pregnancy
    - amniotic fluid
    - mola hydatidosa
  - septic embolism (e.g. cardiac valves)

PE consequences

- ↑ dead space
- ↑ shunt (anatomic – blood flow through bronchopulmonary juctions, PFO)
- Hyperventilation (stimulation of juxtacapillary J-receptors – subj. dyspnea)
  - Partially compensates respiratory insufficiency
  - In milder forms of PE it leads into hyperkapnia and respiratory alkalosis
  - In severe form hypoxia and hyperkapnia – global resp. insufficiency
- Pulmonary hypertension in >50 % obstruction (the same as in pumonary resections)
- Cor pulmonale acutum RV dilation, right-sided regugitation, tachycardia, ↑troponin, ↑natriuretic peptides)
- “forward“ heart failure → obstructive shock
- Electromechanic disociation in severe embolism (circulatory arrest with normal electrical activity in ECG)
- Opening of PFO → shunt, paradoxical embolism
- Subacute massive (succesive) embolism – development during 1-2 weeks

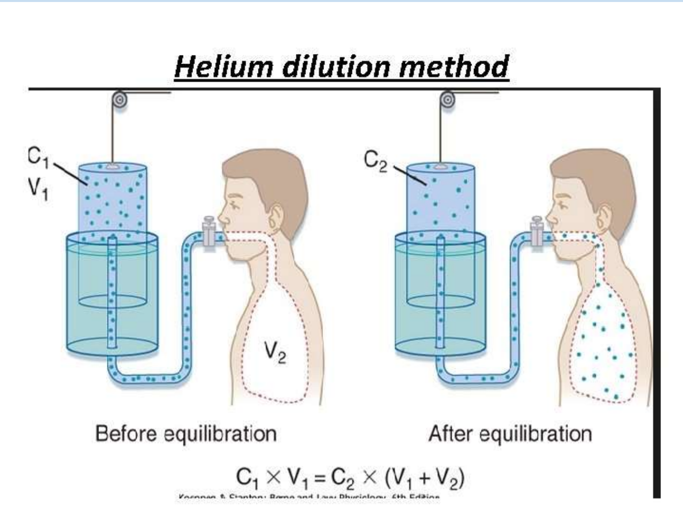
Pulmonary embolism and CTEPH

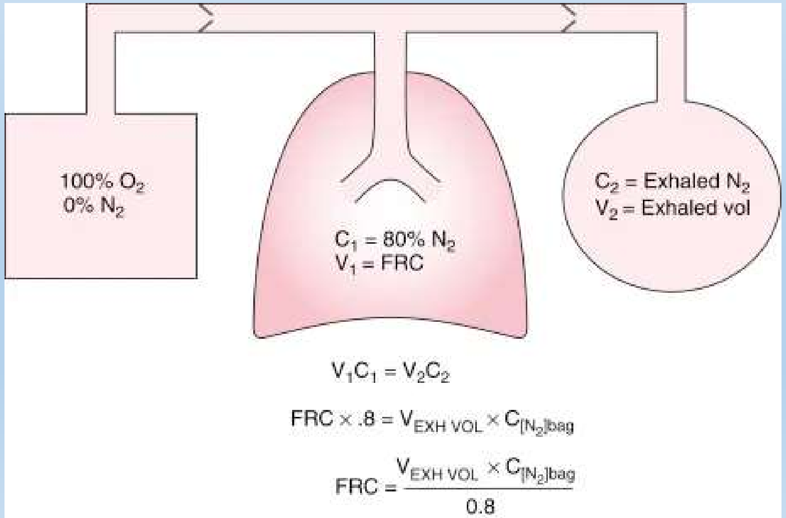
- Chronic thrombembolic pulmonary hypertension
- follows approx. 1-4 % of pulmonary embolisms, but 25 % CTEPH is without PE history
- Consequence of pulmonary embolism
  - bstruction of pulmonary circulation by unrecanalized thrombi
  - hyperperfusion in unaffected vessels → remodeltion with increased vascular resistence (as in PAH)
- Progression of dyspnea in a range of months



Diffusion – residual volume measurement

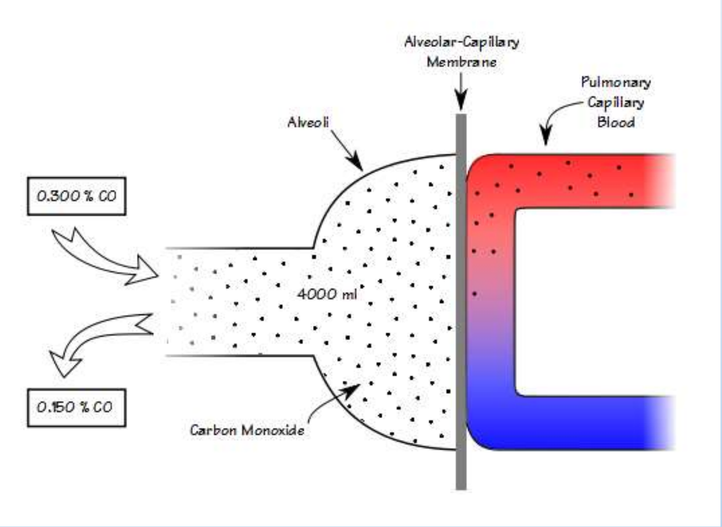
- Unlike other static parameters, residual volume and related parameters (functional residual capacity and total lung capacity) cannot be directly measured
- Options:
  - Dilution methods (e.g. helium dilution method)
  - Nitrogen washout test
  - Whole body plethysmography – RV estimate by the pressure change during expirium





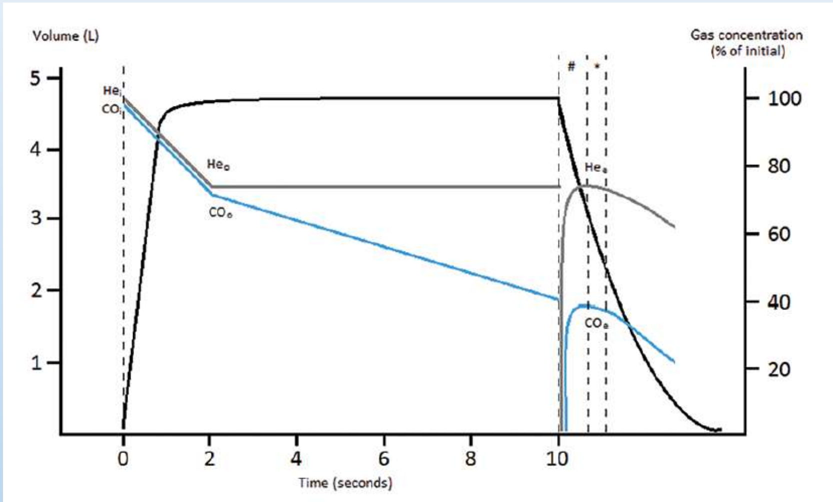
Diffusion assessment

- Transfer factor for CO (TLCO) or diffusing capacity (DLCO)
  - Can be calculated from decrease of CO concentration (high affinity to Hb) and inert gas concentration (e.g. He – see dilution methods), which accounts for residual volume
  - Usually single breath method – compares the concentrations of CO and He in the inhaled air and after holding breath, the time of breath holding is other factor in the calculus
  - Mixture: He 14 %; CO 0,3 %; O_2 21 %; N_2 rest
  - Attention for:
    - Valsalva or Müller manoeuvre
    - Slow inspiration
    - Gas leak



TLCO and DLCO assessment

- DLCO: ml . min^{-1} . mmHg^{-1}
- TLCO: mmol . min^{-1} . kPa^{-1}
- DLCO = TLCO × 2,987



$Va = Vi \times He_i/He_e$

$CO_o = CO_i(He_e/He_i)$

$kco = \ln(CO_o/CO_e)/t$

$Kco = kco / Pb$

$DLCO = Va \times Kco$

Va… volume exposed to helium (~TLC)
$He_{i,e}$, $CO_{i,e}$… concentrations of He and CO at the initial and ending point of breath
CO_o… initial alveolar concentration
kco… rate constant for CO removal (i.e. elimination constant)
Pb…dry air pressure (barometric – water vapor pressure at 37°C) ~713 mmHg = 95 kPa
Kco… CO transfer coefficient

Pulmonary capacity and diffusion in various diseases

Abnormal pattern of DLCO,KCO and VA in various disease states:

Conditions	VA	KCO	DLCO
Incomplete lung expansion (Diaphragm palsy, collapse)	↓↓↓	↑↑	↓
Loss of lung units (lobectomy, fibrosis)	↓↓↓	↑	↓↓
Diffuse alveolar damage(ILD)	↓↓	↓	↓↓↓
Emphysema	↓	↓↓	↓↓↓
Pulmonay vascular disease	Normal	↓↓	↓↓
High pulmonary blood volume (Shunt, cardiac failure)	Normal	↑	↑
Alveolar hemorrhage	↓	↑↑↑	↑↑

Dey et al., 2020

- Other causes of pulmonary diffusion changes (Nguyen et al., 2016)

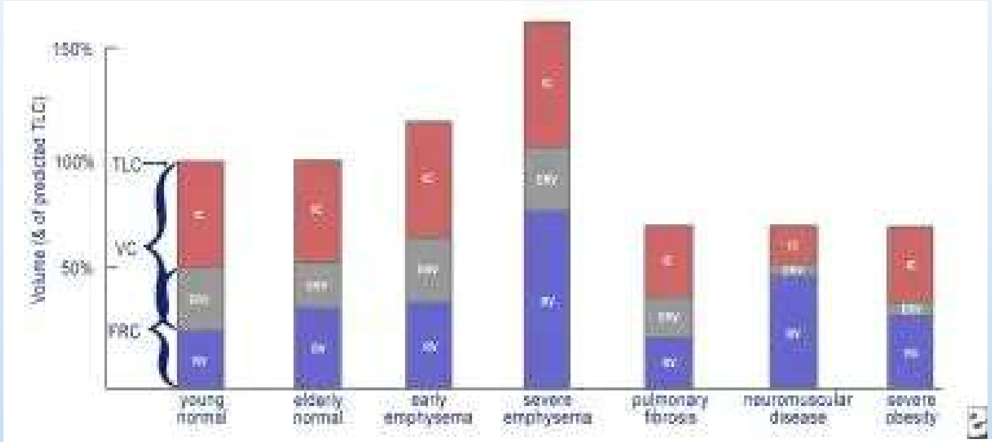
Table 1. Conditions and Other Variables Affecting DLCO Measurement

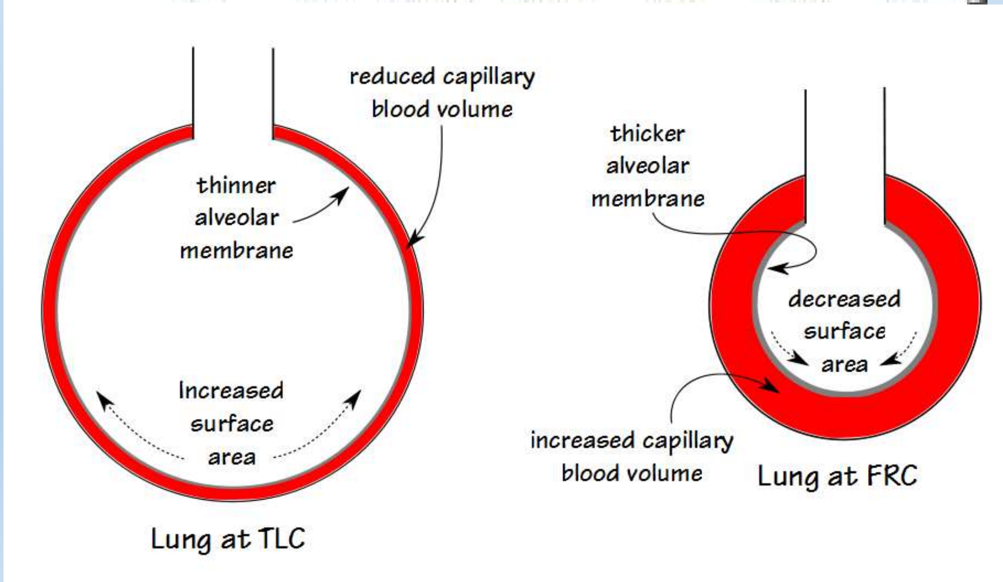
Increase DLCO	Decrease DLCO
Exercise (due to recruitment of capillaries)	Postexercise
Supine position (due to increased pulmonary capillary blood volume)	Standing
Müller maneuver (inspiration against closed mouth and nose after forced expiration)	Valsalva maneuver
Pulmonary hemorrhage	Lung resection
Polycythemia	Pulmonary emphysema (affecting capillary or alveolar bed)
Left-to-right shunt (eg, atrial septal defect)	Pulmonary vascular disease, including pulmonary arterial hypertension and chronic venous thromboembolism
Obesity	Interstitial lung diseases
Asthma	Anemia
Chronic bronchitis without major emphysema	Evening
Morning	Drugs (eg, amiodarone, bleomycin, methotrexate)
Pregnancy	Pulmonary lymphangitic carcinomatosis

- TLCO/DLCO generally assess the area and permeability of alveocapillary barrier
- Kco/kco also much depends on pulmonary perfusion

Lung volumes and diffusion parmeters in restrictive diseases

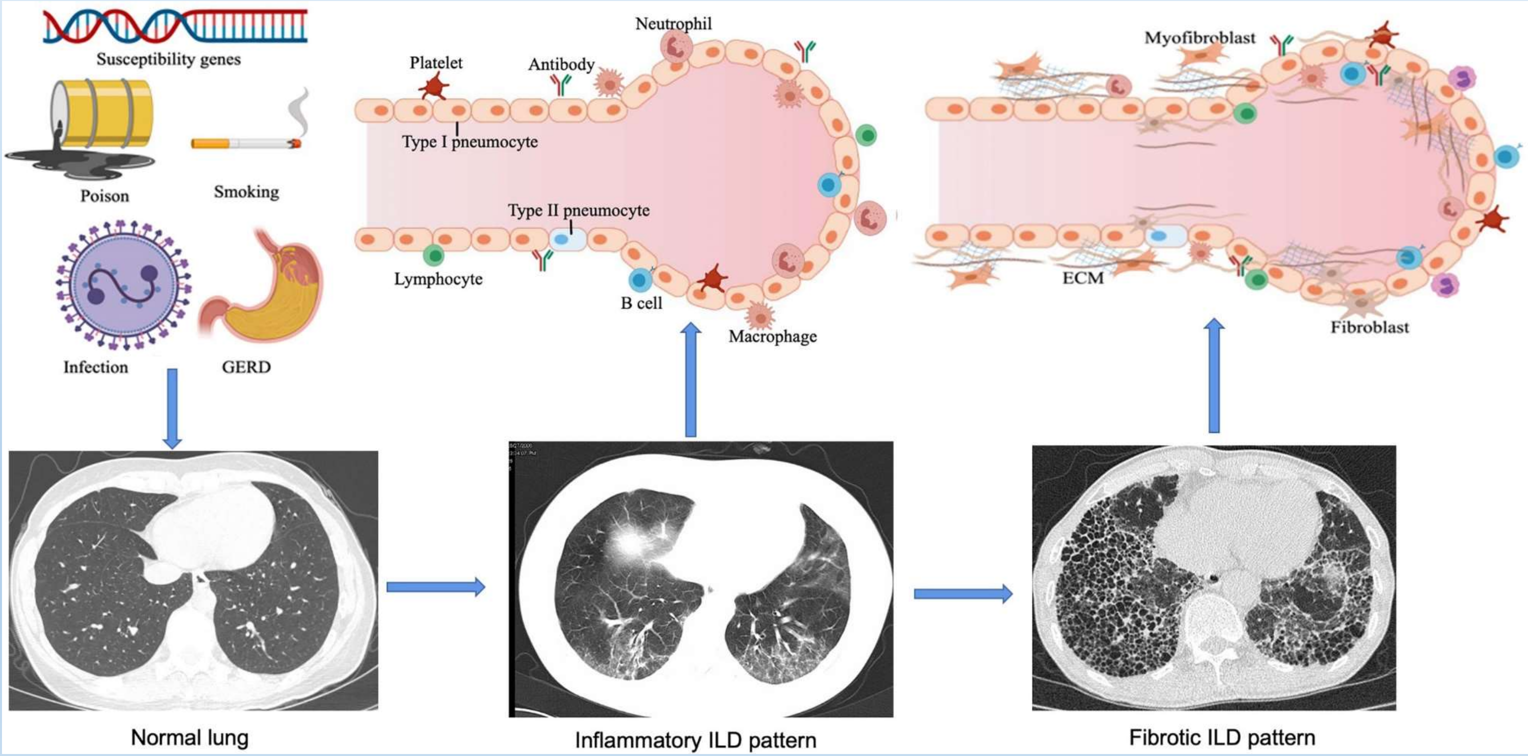
- In interstitial lung disease (ILD), there is parallel lowering of vital capacity and residual volume × high in extrapulmonary causes of restriction
- Generally, TLCO/DLCO is lower in pulmonary restriction or emphysema
    - It is high in high TLC value because of stretching and thinning of the alveolar membrane
- Kco (= DLCO/Va) decreases in high volumes (see emphysema)
- In low volumes, there is a compensation by ↑ perfusion and thus high Kco (e.g. extrapulmonary causes of restriction)
- In ILD, alveolocapillary barrier fibrotization follows – normal value of Kco is actually pathological in low lung volumes





Interstitial lung disease

- Concommitant disorder of ventilation (restriction) and diffusion, later perfusion



Classification of ILD

1) From known causes
   - silicosis
   - asbestosis
   - coal miner lung
   - farmer‘s lung – allergy
   - drug-induced / postradiation ILD

   Anorganic dust

2) Idiopathic
   - Idiopathic pulmonary fibrosis (IPF)
   - Cryptogennic fibrotizing alveolitis
3) Granulomatous lesions
   - sarcoidosis
4) Other

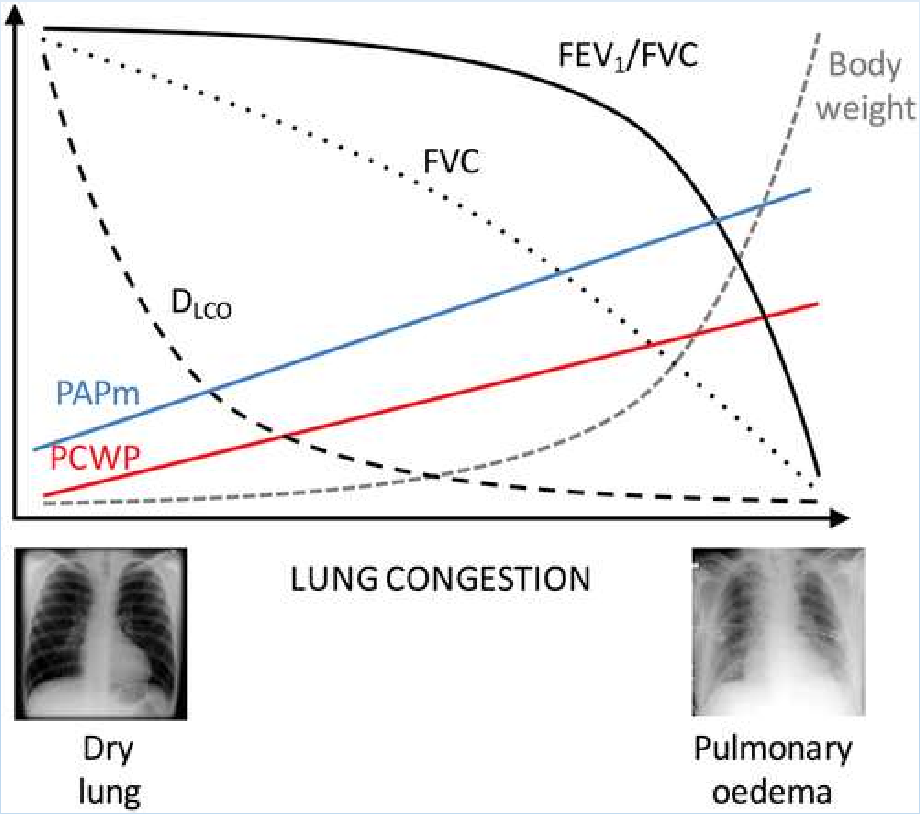
Consequences of interstitial lung disease

- Impaired diffusion – combination of shunt and dead space
- Pulmonary restriction
- Pulmonary hypertension
- Hypoxemia leading to respiratory alkalosis (hypoxia in right-to-left shunt and J-receptor stimulation), later hyperkapnia with ↑ dead space
- Prognosis is the worst in IPF (survival median 3-5 years), better in other causes

Pulmonary edema

- Disorder of diffusion, perfusion, later ventilation (restriction)
- $F = A \,.\, K \,.\, [(P_c - P_i) - \sigma(\pi_c - \pi_i)]$
- Most often a result of “backward“ left-sided heart failure or hypervolemia ($\uparrow P_c$)
- Pulmonary inflammation ($\uparrow K$ and $\downarrow \sigma$)
- Rarely in hypoproteinemia (π_c)
  - ↑ of interstitial fluid leads into ↑ lymph flow and ↓ interstitial protein concentration
  - This maintains the low oncotic pressure gradient

Pumonary edema and the main parameters of ventilation, diffusion + perfusion

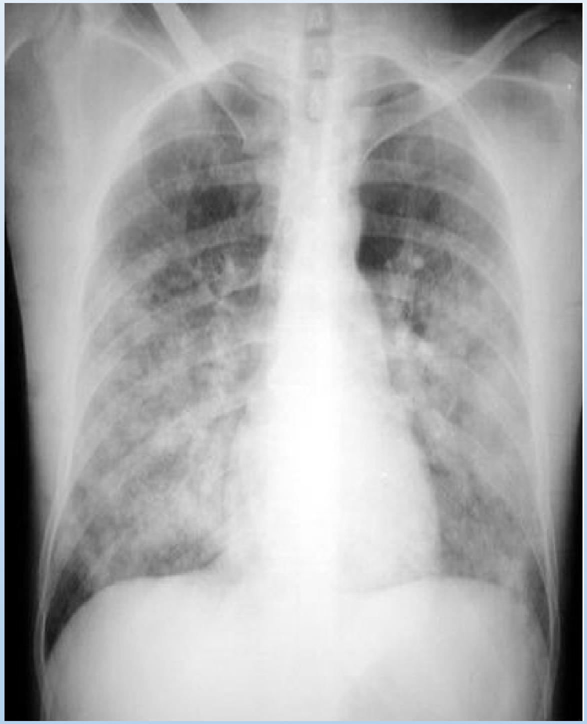


Types of pulmonary edema

- Interstitial
- Alveolar
- Pulmonary edema × pleural effusion

- Similarly as in pleural effusion or ascites, exudate and transudate can be distinguished
  - But the diagnostic proces is more difficult
  - Most pulmonary edemas are transsudates
  - Exception: ARDS

X-ray image

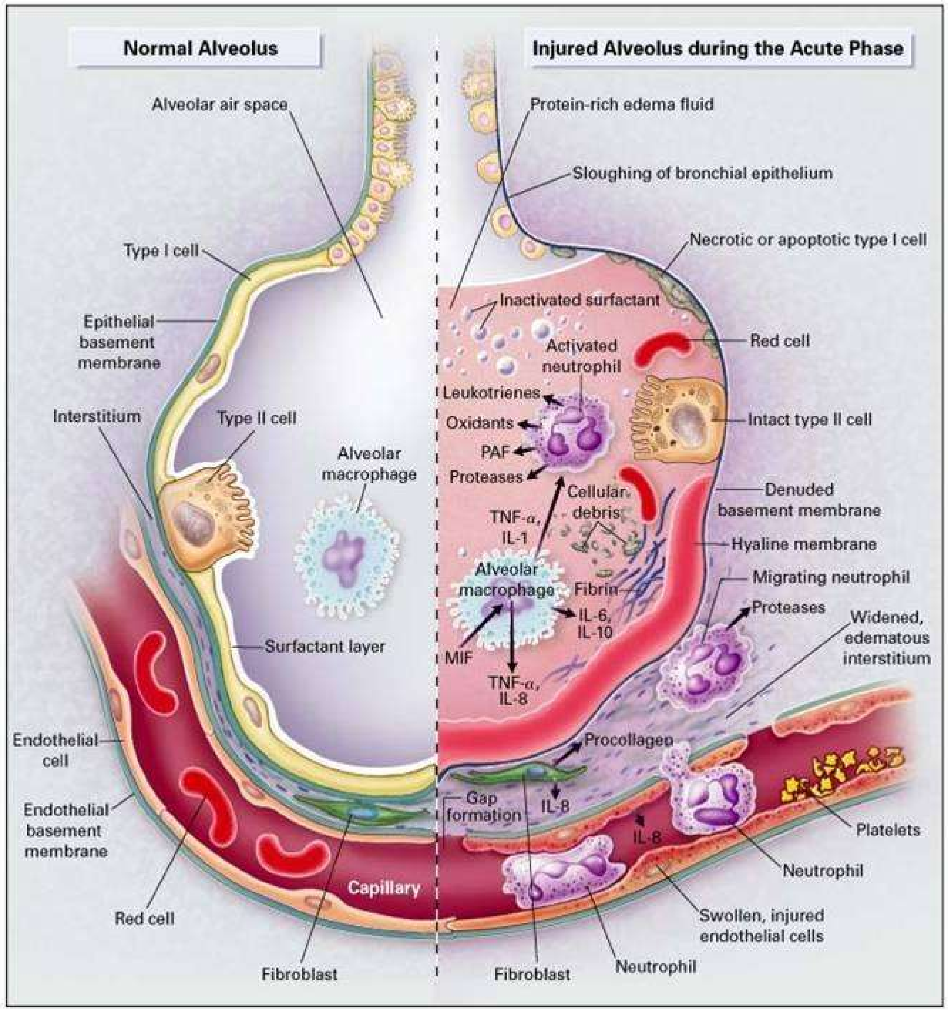


Pumonary edema

Bilateral pleural effusion

Adult Respiratory Distress Syndrome (ARDS – „shock lung“)

- Result of lung inflammation in SIRS, pulmonary infections, aspiration of gastric juice, drowning
- Exsudative phase (hours): cytokine release, leukocyte infiltration, pulmonary edema, destruction of type I pneumocytes
- Proliferative phase: fibrosis, ↑ dead space, proliferation of type II pneumocytes
- Reparative phase: ↓ inflammation, ↓ edema, continuing fibrosis, in most cases permanent restrictive diseases



Thank you for attention