Special Pathophysiology
Summer course
1997 - 2001
2002- 2023
General medicine, Dentistry

PATHOPHYSIOLOGY OF RESPIRATION 3

Respiratory Failure

R. Benacka, MD, PhD
Department of Pathophysiology,
Medical faculty, P.J. Safarik University Košice

Respiratory failure - Definition

- **Def:** pathophysiological unite = inability of the lung to meet the metabolic demands of the body. This can be from failure of tissue oxygenation and/or failure of CO_2 homeostasis
  - PaO_2 < 60 mmHg (7,9 kPa)
  - $PaCO_2$ >50 mmHg (6,5 kPa)

  At at normal air pressure 760 mmHg (101 kPA) at sea level)
- Ventilation failure: pathological reduction of alveolar ventilation
- **Forms:**
  - **Chronic RF:** end stage chronic lung disease
  - **Acute RF:** sudden onset of severe lung damage in adults (ARDS) or children and neonates (IRDS)

- **Type 1 : Hypoxemic RF - decrease in PaO_2; no / small increase in $PaCO_2$**
- **Type 2: Hypercapnic RF- significant decrease in PaO_2 + increase in $PaCO_2$**
- **Type 3: Perioperative RF – atelectasia;**
- **Type 4: Shock related RF** – **hypoperfusion of lungs** (shock lungs, MODS)

Respiratory failure

Type 1 (Hypoxemic respiratory failure)

PaO_2 is low (PaO_2 < 50 mmHg)

CO_2 is not elevated ($PaCO_2$ < 60 mmHg)

See Sect. 1.25

Type 2 (Hypercapnic respiratory failure)

PaO_2 is low (PaO_2 < 50 mmHg)

CO_2 is elevated ($PaCO_2$ > 60 mmHg)

See Sect. 1.26

Type 3 (Per-operative respiratory failure)

FRC falls below closing volume as a result of atelectasis.

Contributing factors:

Supine posture

General anesthesia

Depressed cough reflex

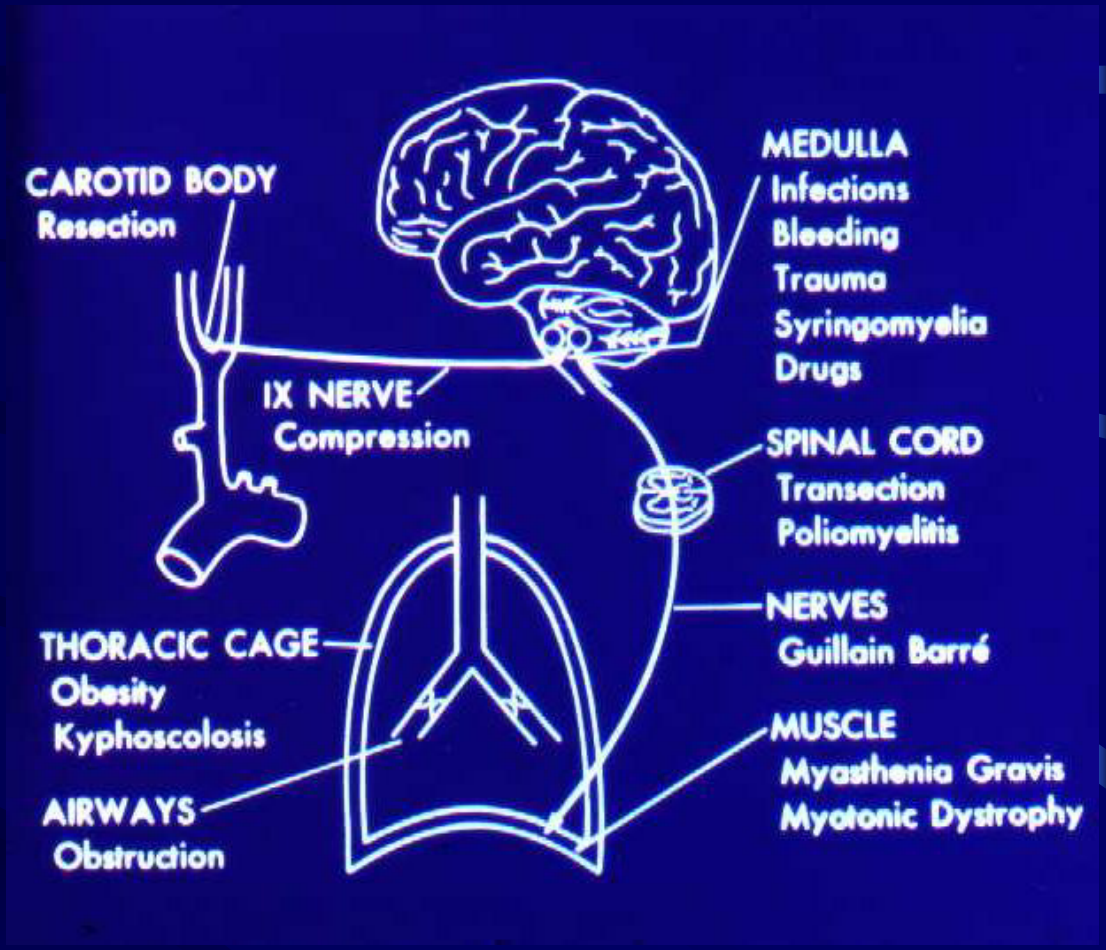
Splinting due to pain

Type 4 (Shock with hypo perfusion)

The proportion of the cardiac output to the respiratory muscles rises by as much as ten-fold when the work of breathing is high; this can seriously impair coronary perfusion during shock.

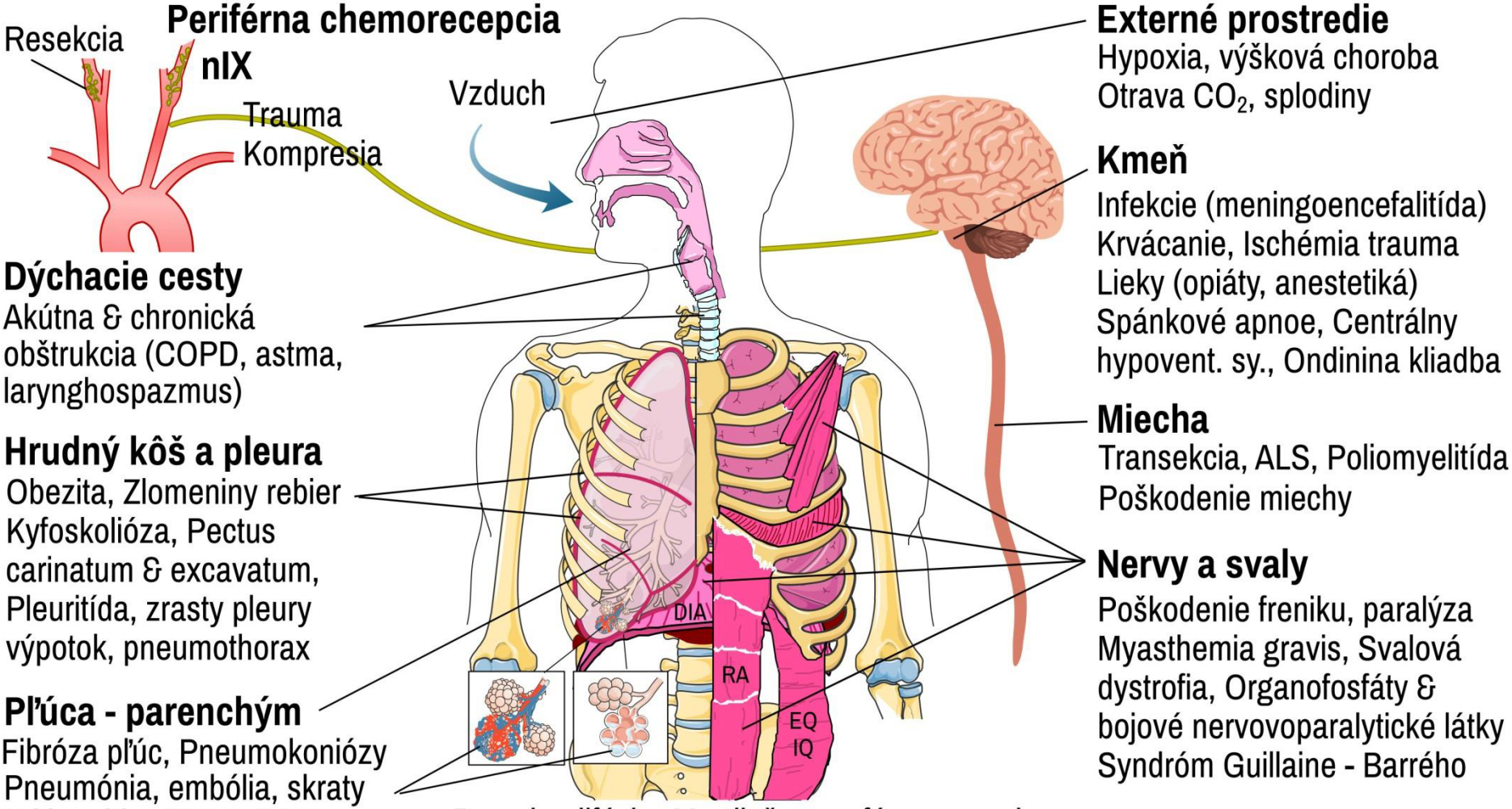
Respiratory failure - Etiology

- CNS (medulla)
- Peripheral nervous system (phrenic nerve)
- Respiratory muscles – diaphragm
- Chest wall - rib cage, spine
- Lung – interstitium
- Upper airways
- Bronchial tree
- Alveolar region – ducts, sacs, alveoli
- Pulmonary vasculature (primarily, secondarily)



Respiratory failure - Etiology

Picture in Slovak just for demonstration of previous slide (lecture)



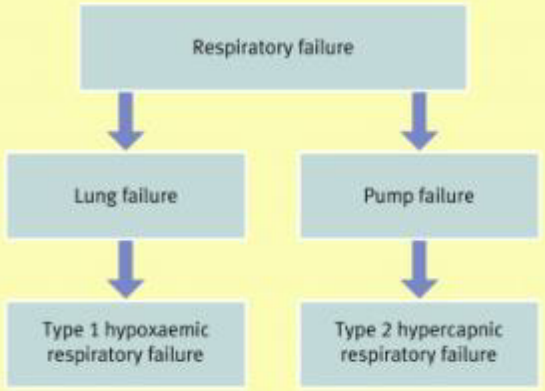
HYPOXEMIC FAILURE (TYPE 1)

- PaO_2 <60mmHg with normal or low $PaCO_2$ $\rightarrow$ normal or high pH
- Most common form of respiratory failure
- Lung disease is severe to interfere with pulmonary O_2 exchange, but overall ventilation is maintained
- Physiologic causes: V/Q mismatch and shunt
- Disorder of heart, lung or blood.
- Finding chest X-ray (CRX) abnormality:

- Normal or hyperinflation on CXR:
  - Cardiac shunt (right to left)
  - Asthma, COPD
  - Pulmonary embolism
- Focal infiltrates on CXR:
  - Atelectasis
  - Pneumonia

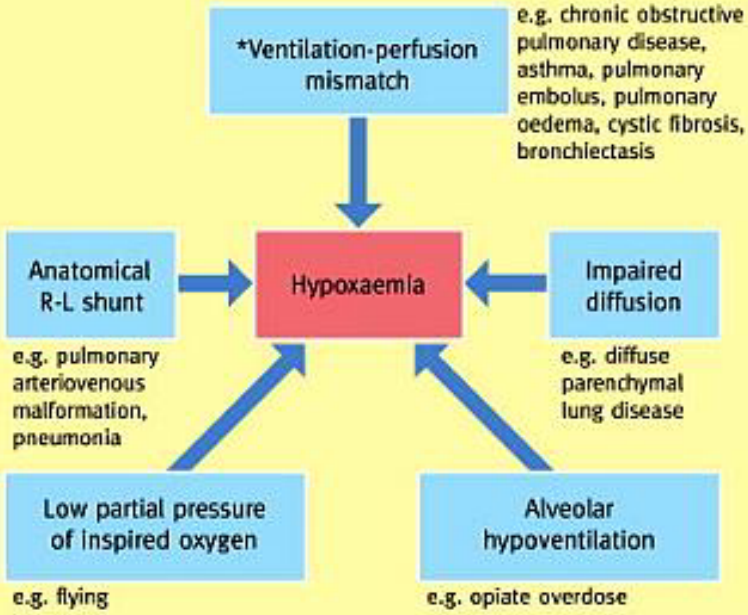
- Diffuse infiltrates on CXR:
  - Cardiogenic pulmonary Edema
  - Non cardiogenic pulmonary edema (ARDS)
  - Interstitial pneumonitis or fibrosis
  - Infections

Types of respiratory failure



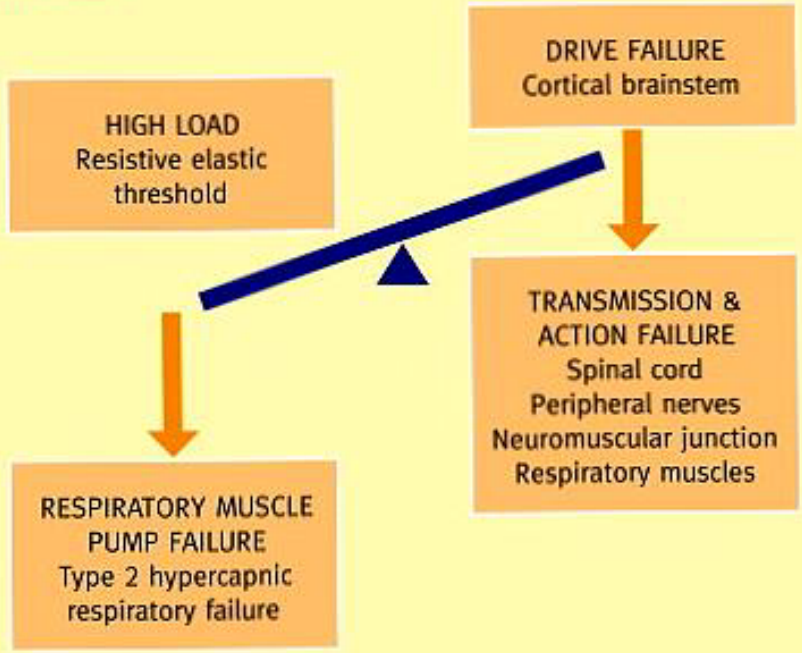
Type 1 hypoxaemic respiratory failure

Using the five pathophysiological mechanisms of hypoxaemia, a comprehensive list of conditions that cause hypoxaemia can be generated

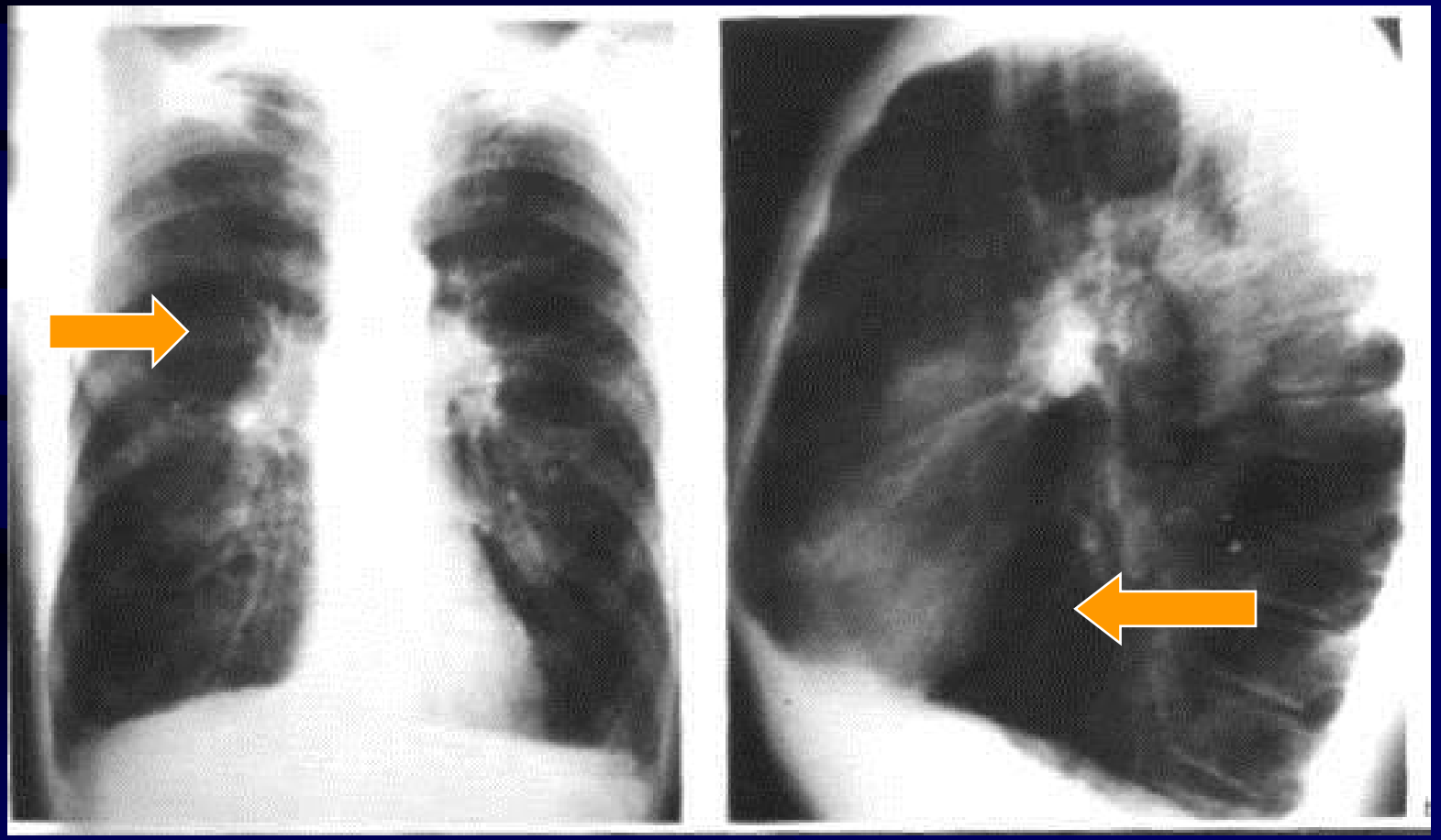


*V/Q mismatch is the most important cause of hypoxaemia

Type 2 hypercapnic respiratory failure is an imbalance between neural respiratory drive, the load on the respiratory muscles and capacity of the respiratory muscles



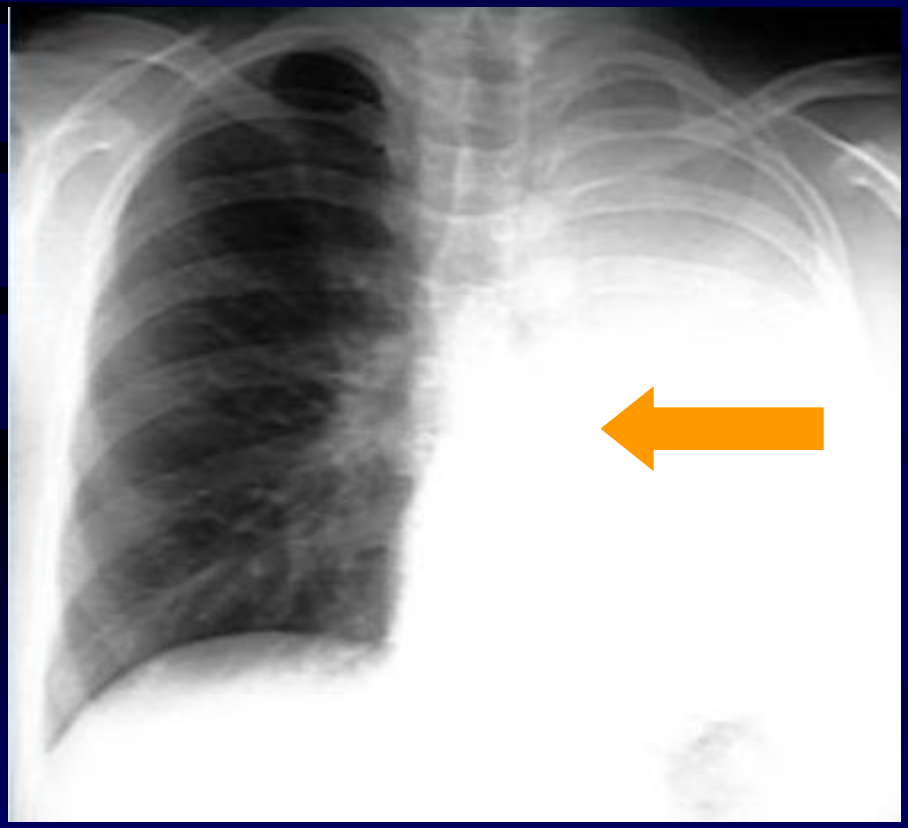
EXAMPLES



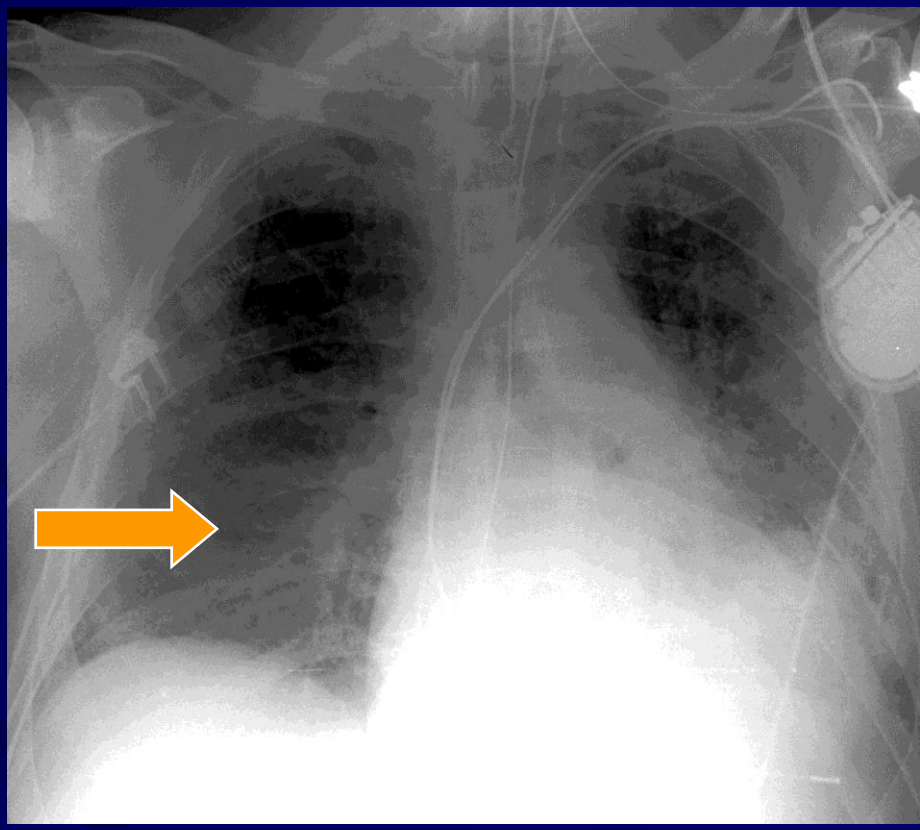
Hyperinflated Lungs COPD

EXAMPLES

Intrapulmonary shunt



Diffuse pulmonary infiltrates



Hypercapnic Failure (Type II, global)

- Hypercapnia ($PaCO_2$ >50 mmHg) Respiratory acidosis pH < 7.30
- Hypoxemia (PaO_2 < 60 O_2 mmHg Sat < 90%)
- Compensated by HCO_3^- : Renal response occurs over days to weeks

- **Acute**
  - Brain dysfunction: respiratory centre failure– sedative drug over dose, tumor, central hypoventilation
  - Hypothyroidism, Acute muscle weakness: myasthenia gravis, spinal injuries
  - Severe lung disease: asthma, pneumonia
  - Upper airways obstruction: foreign body, laryngeal edema

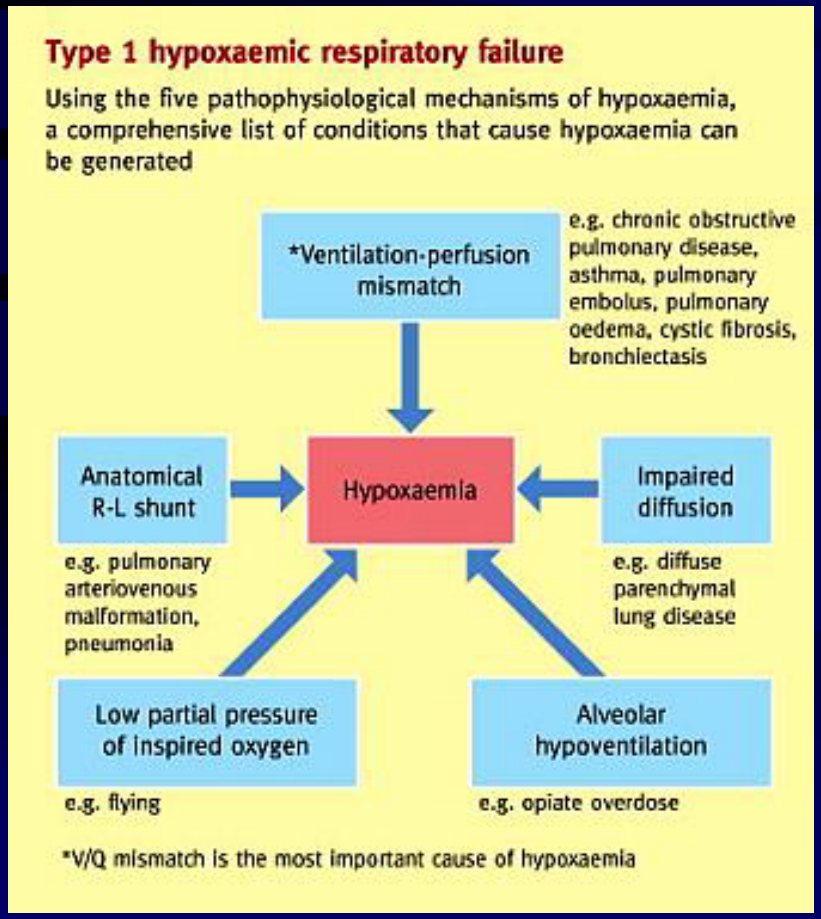
- **Chronic**
  - Muscle fatigue: Guillain-Barre, poliomyelitis
  - Chest wall/Pleural diseases: kyphoscoliosis, pneumothorax, massive pleural effusion
  - Airway obstruction: asthma, COPD, bronchiectasia, cystic fibrosis, tumor

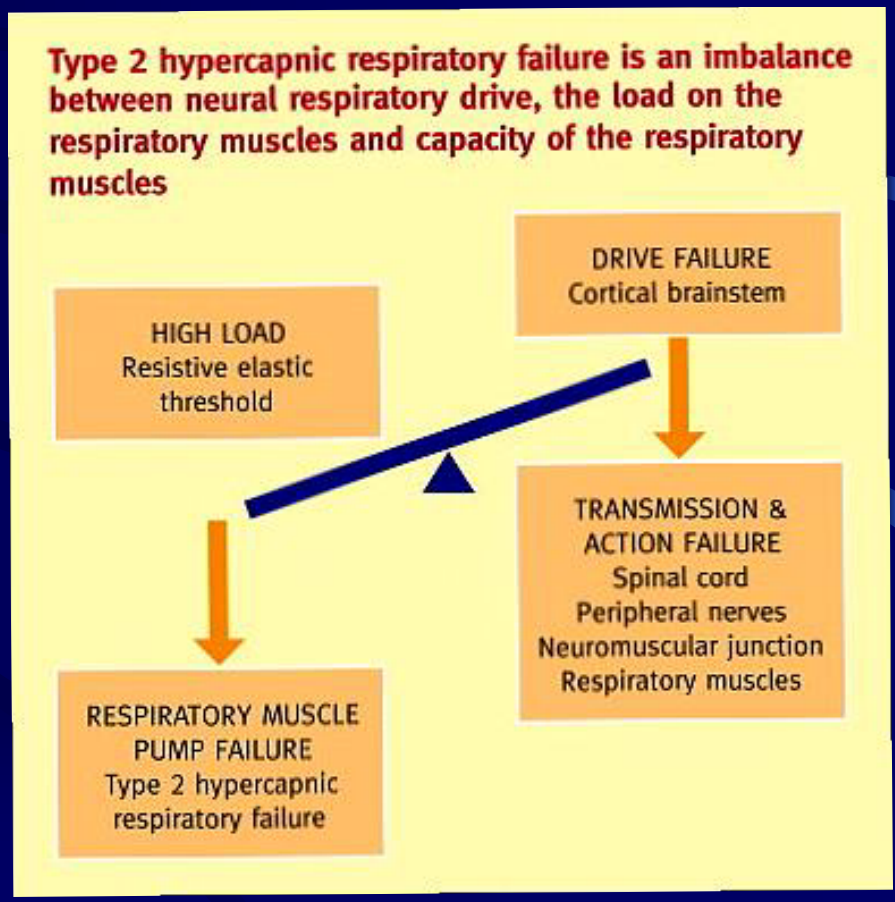
Type I

- Mild form - O_2 upload is lower-> diffusion problems, V/P problems
- Obstruction, distribustion, shunts

Type II, type III, type IV

- Severe forms
- Drive failure, high load, respiratory muscles, ribcage, neuromuscular failure





Type 3 RF (ATELECTATIC)

Characteristics:

- hypoxemia (↓ PaO_2 < 60mmHg); normal to ↑ PaCO2 >50 mmHg; ↓ pH (depends on HCO3-), ↑ ↑ FRC
- renal pH compensation with ↓ HCO3- production (days – weeks)
- Usually patients after surgery

- Causes:

A) Limitation, failure of pulmonary mechanics

- General anesthesia, supination, cough reflex attenuation, and ascites

B) Decreased airway patency

- Hypersecretion, mucus viscosity (cystic fibrosis)

- Mechanisms:

- Compression and subsequent airlessness of part of the lungs - atelectasis

Type 4 RZ (SHOCK)

- there is always hypoxemia (↓ PaO2 < 60mmHg)
- ↑PaCO2 >50 mmHg; ↓pH (depends on HCO_3-), ↓pH
- renal compensation of pH by ↑HCO3- production (days – weeks)
- Patients usually in shock, usually intubated, ventilated during resuscitation

Causes:

- A) High metabolic demands
  - Septic and hypovolemic shock
  - Severe physical muscle activity (lactic acidosis)
- B) Decreased cardiac output
- Cardiogenic shock, hypovolemic shock

Mechanisms

- Hypoperfusion of scans including respiratory muscles

Respiratory failure - Symptoms

Signs of Hypoxemia

- Dyspnea, tachypnea
- Cyanosis - unoxygenated Hb > 50 mg/l - not a sensitive indicator
- Restlessness, Apprehension
- Confusion, apathy
- Tachycardia, Dysrhythmias
- Metabolic acidosis (lactate)

Signs of Hypercapnia

- Dyspnea → resp. depression
- Headache
- Papilledema
- Tachycardia
- Drowsiness, coma
- Systemic vasodilation
- Heart failure
- Respiratory acidosis

- Circulatory changes- tachycardia, hypertension, hypotension
- Polycythemia - chronic hypoxemia - erythropoietin synthesis
- Pulmonary hypertension - Cor-pulmonale or right ventricular failure

Therapy

1. Oxygen Therapy

- Supplemental O_2 therapy essential to prevent tissue hypoxia
- titration based on SaO_2, PaO_2 levels and $PaCO_2$
- Tissue hypoxia occurs (normal Hb & C.O.) venous $PaO_2 < 20$ mmHg or $SaO_2 < 40\%$; arterial $PaO_2 < 38$ mmHg or $SaO_2 < 70\%$
- Increase arterial $PaO_2 > 60$ mmHg($SaO_2 > 90\%$) or venous $SaO_2 > 60\%$; O_2 dose either flow rate (L/min) or FiO_2 (%)

2. Artifitial ventilation

- Non invasive with a mask or Invasive with an endobronchial tube
- MV can be volume or pressure cycled
- For hypercapnia: - incr. alveolar ventilation and lowers $PaCO_2$, pH
  - rests fatigues respiratory muscles
- For hypoxemia: - O_2 therapy alone does not correct hypoxemia caused by shunt, Most common cause of shunt is fluid filled or collapsed alveoli (Pulmonary edema)

Risks of Oxygen Therapy

- **O_2 toxicity**:
  - FiO_2 35 to 40% can be safely tolerated indefinitely
  - very high levels (>1000 mmHg) CNS toxicity,seizures
  - lower levels (FiO_2 > 60%) and longer exposure: capillary damage, leak and pulmonary fibrosis
  - PaO_2 >150 can cause retrolental fibroplasia

- **CO_2 narcosis:**
  - $PaCO_2$ may increase severely to cause respiratory acidosis, somnolence and coma
  - $PaCO_2$ increase secondary to combination of a) abolition of hypoxic drive to breathe, b) increase in dead space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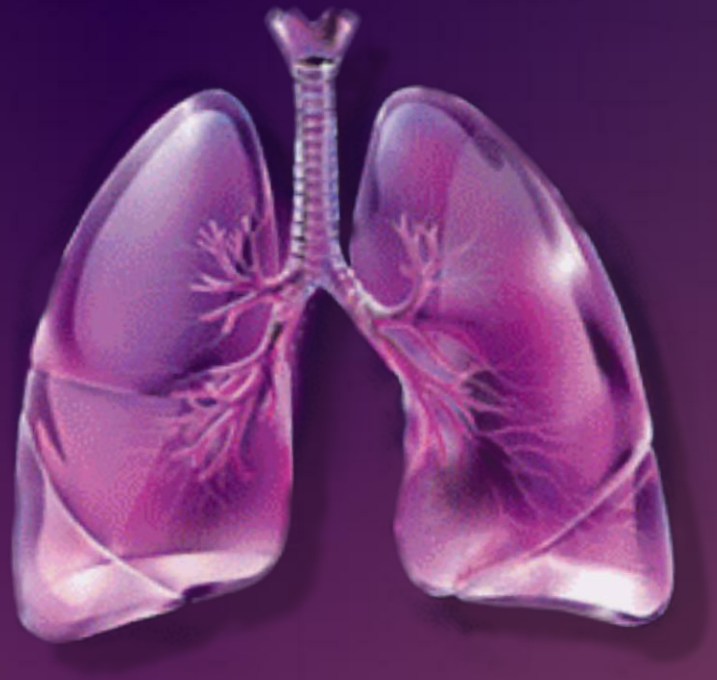

Serious lung dammage and apnoeic states

Adult Respiratory Distress Syndrome (ARDS)

- Def.: Acute respiratory failure due to variety of unrelated massive insults injuring lower airways and lungs? Known as: Acute respiratory failure, Da Nang Lung, Shock Lung, Capillary leak syndrome Traumatic wet Lung Adult hyaline membrane disease
- First described as clinical syndrome in 1967 by Ashbaugh & Petty
- Etio: various direct and indirect lung injury
- Pathg:
- Diffuse damage to gas-exchanging surface either alveolar or capillary side of membrane
- Increased vascular permeability causes pulmonary edema
- Pathology: fluid and RBC in interstitial space, hyaline membranes
- Loss of surfactant: alveolar collapse
- Aspiration (35.6%), Intravascular coagulopathy (12.5%)
- Severe pneumonia (12.0%) Fracture (5.3%) Sepsis (3.8%) Cardiopulmonary bypass (1.7%), Transfusion (5.0%) Buring (2.3%)
-

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ARDS - Causes

Direct lung injury	Indirect lung injury
Thoracic trauma lung contusion	Severe sepsis (common)
Aspiration of gastric contents	Severe shock
Toxic or hot gas inhalation	Drug overdose
Pulmonary infection (COVID)	Trauma, polytrauma
Embolia, fat – embolia	Blood transfusions !!!
Radiation	Pancreatitis
Drugs inhalation	Severe neurological injury
Reperfusion injury	Post-cardiopulmonary bypass
Near-drowning	Diabetic ketoacidosi
Coronary bypass	

Adult Respiratory Distress Syndrome (ARDS)

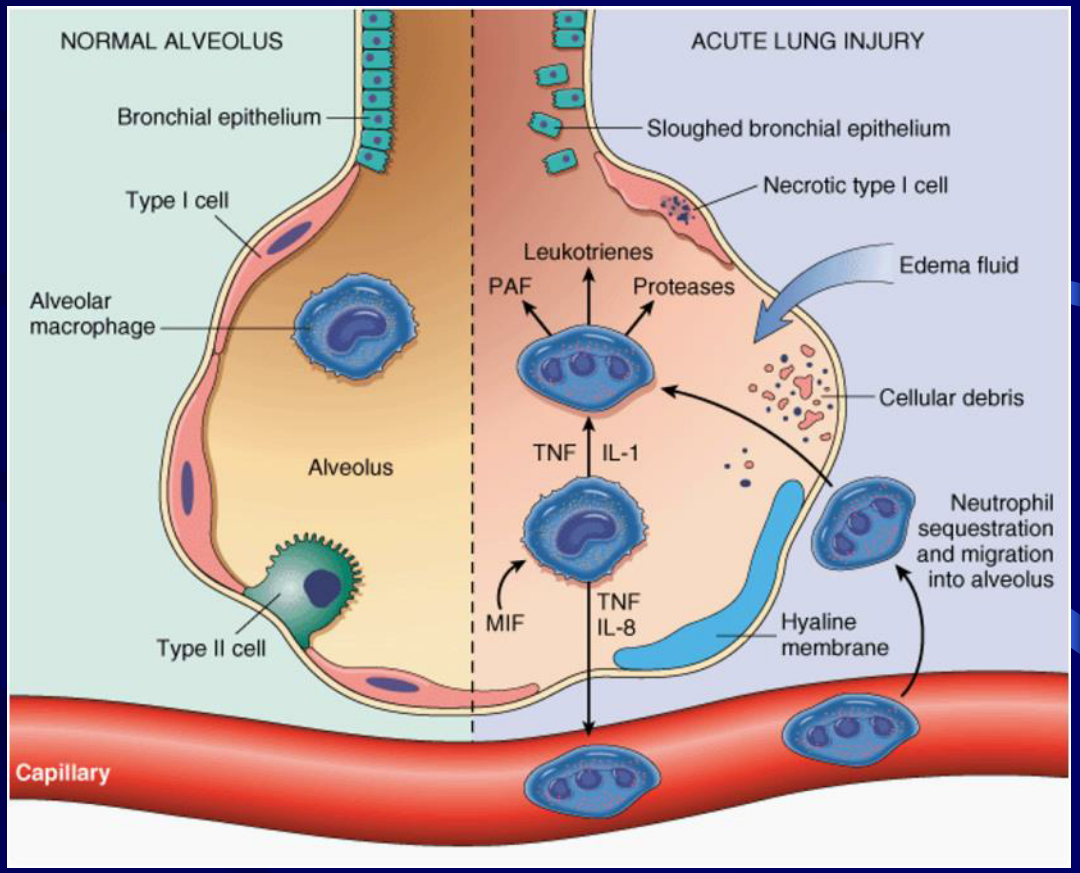
Damage to alveolar epithelium + vascular endothelium

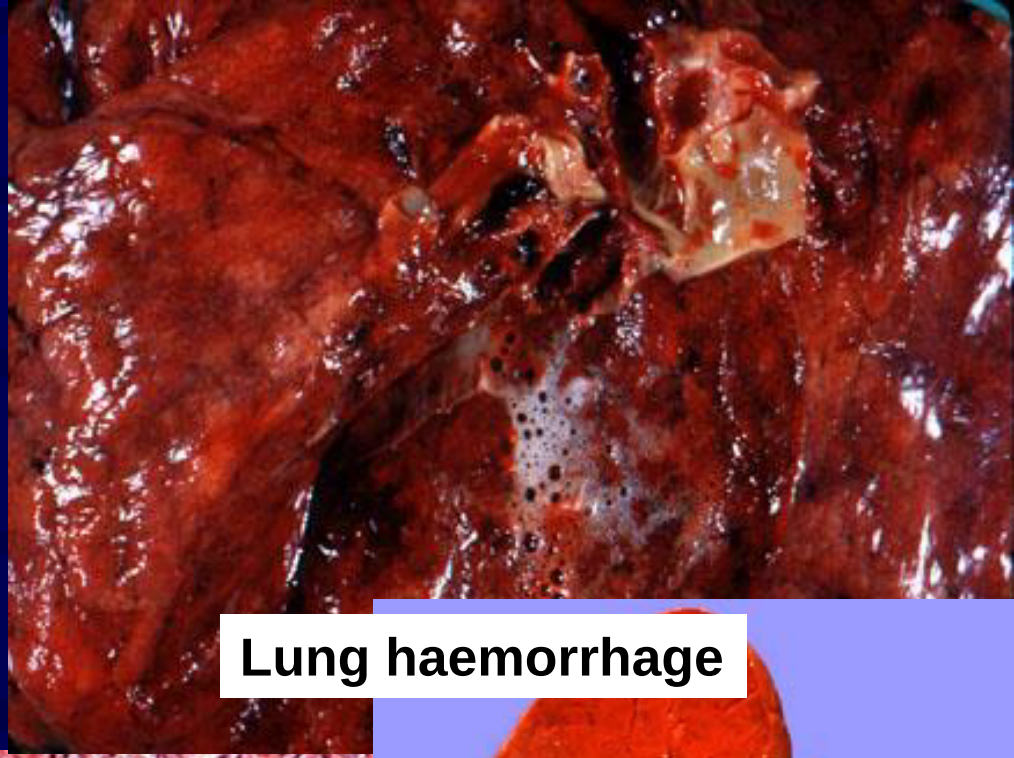
- Increased permeability of lung vessels → plasma and inflammatory cells leak into the interstitium → interstitial edema event.
- Interruption of surfactant production - damage to cells producing surfactant type II + exudate atelectasis,
- Dammage of alvoli epithel →alveolar pulmonary edema
- Disruption of perfusion and ventilation/perfusion ratios (V/Q) → shunt of blood through unventilated alveoli,
- Interstitial edema → increased alveolar-capillary gradient gas diffusion disorder
- Persistent inflammation → fibrous alveolitis (deposition of collagen in alveoli, vessels, interstitium decreased compliance (already within 5-7 days.

Adult Respiratory Distress Syndrome (ARDS)

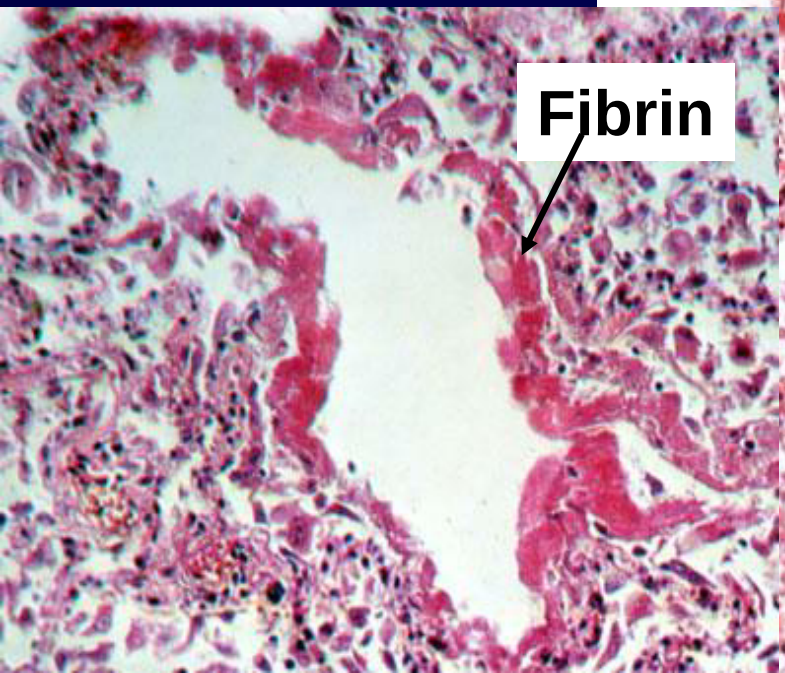
- Abnormally amplified and sustained inflammatory response - localized manifestations of SIRS (systemic inflammatory response syndrome)

- Activated Neu and Mf play a major role
- Uncontrolled release of inflammatory mediators
- Complement activation
- Cytokines TNF-a, IL-1b, IL-6, PAF
- Eicosanoids: PGE, LT, TXA
- Free O_2 radicals, NO
- Necrotic, apoptotic changes → debris formation, alveolar barrier disruption – epithelium, surfactant

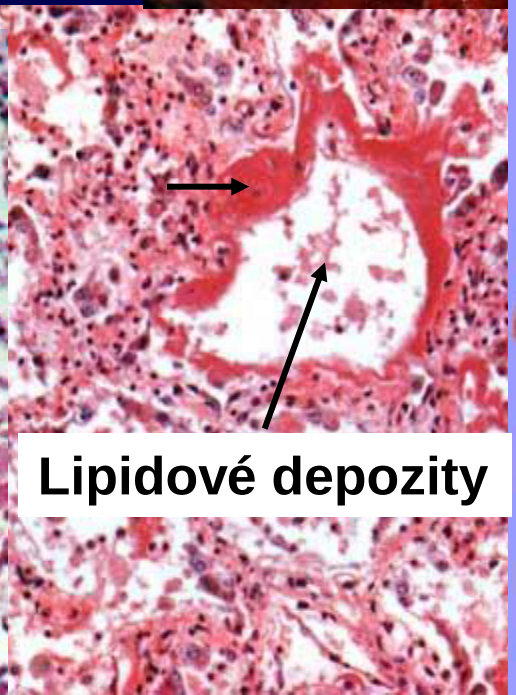




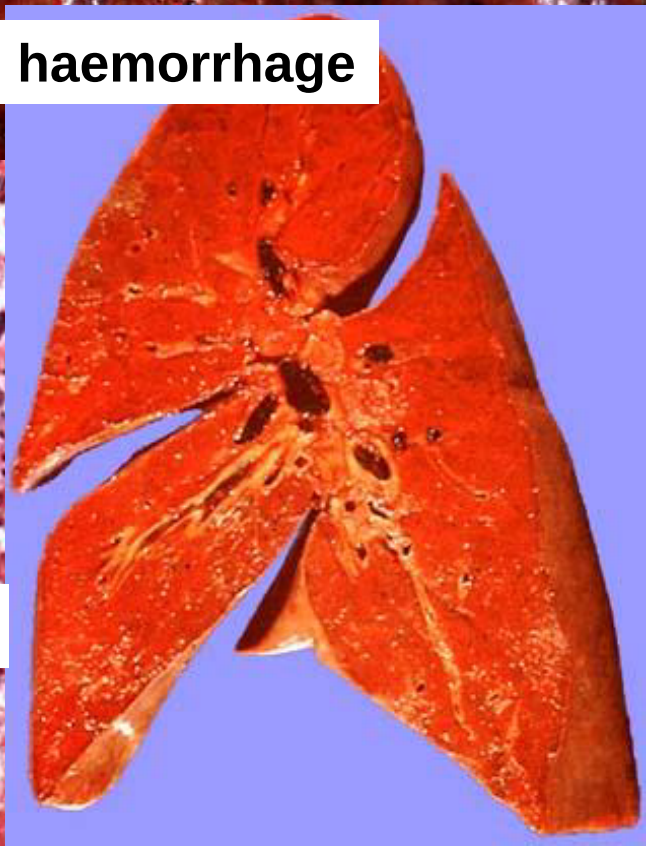
Lung haemorrhage



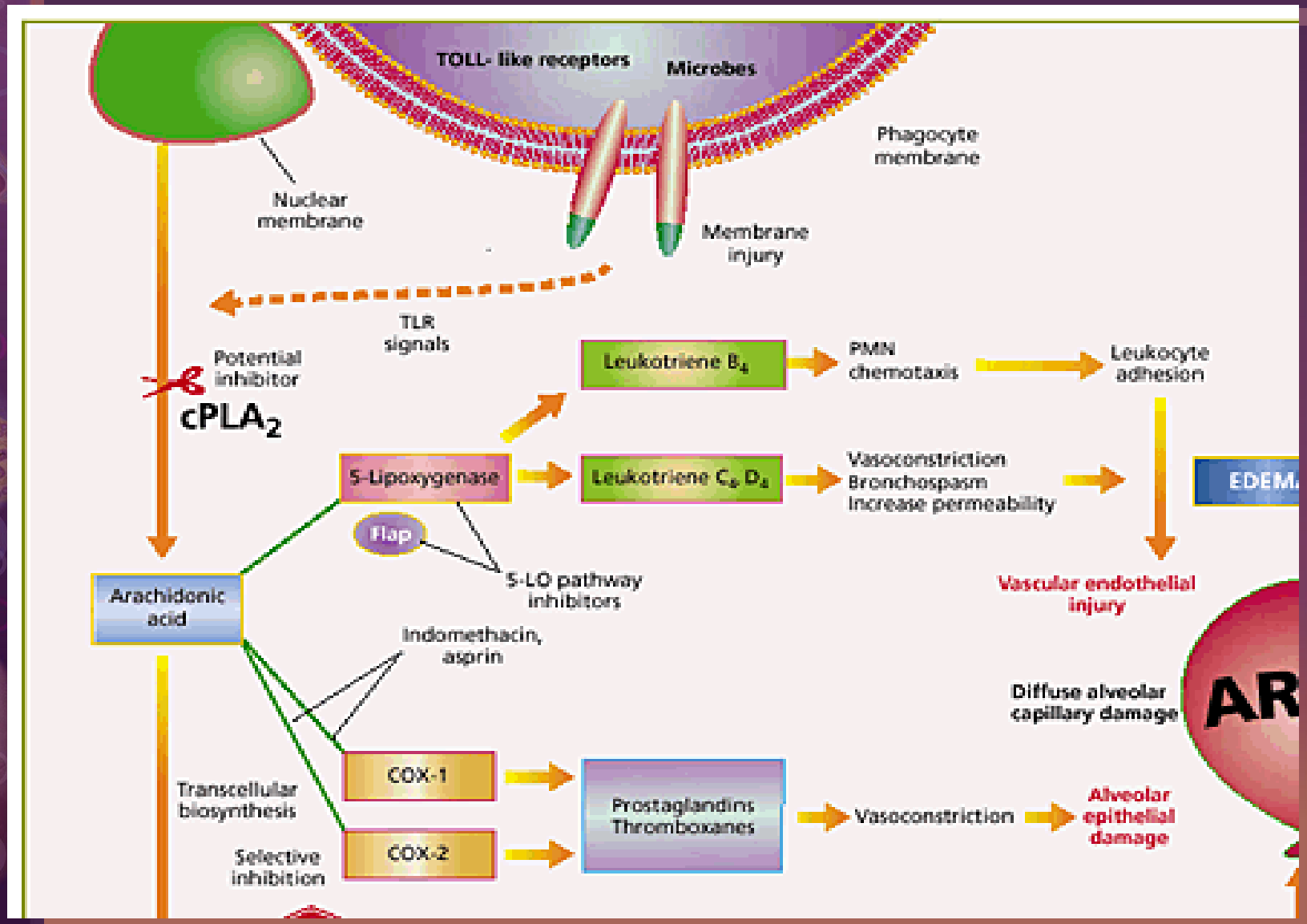
Fibrin



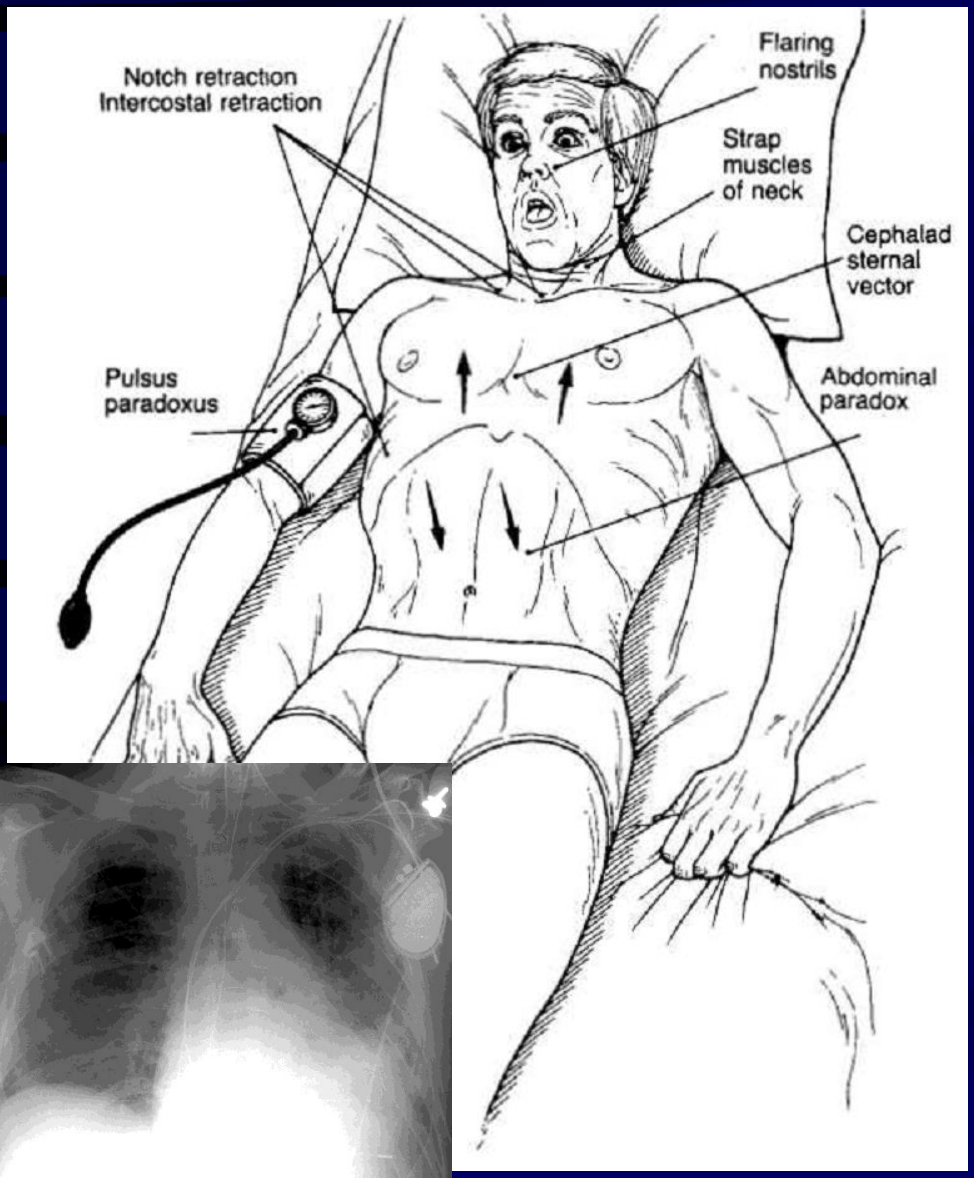
Lipidové depozity



Pathogenesis



ARDS - Manifestations



- labored breathing - severe inspiratory dyspnoea/ moving of nasal alae, muscles of the neck, intercostal retraction
- lungs are in an inspirational posi-tion, the abdominal wall is pulled down, sternum pulls upwards
- patient is excited, anxious
- tachypnea >20 b/min, hypertension sympaticotonia, pulse paradoxus
- central PaO_2 <50mmHg
- FiO_2 >0,6
- compliance <50 ml/cmH_2O
- increased shunt/dead space
- cyanosisCXR- diffuse infiltrates

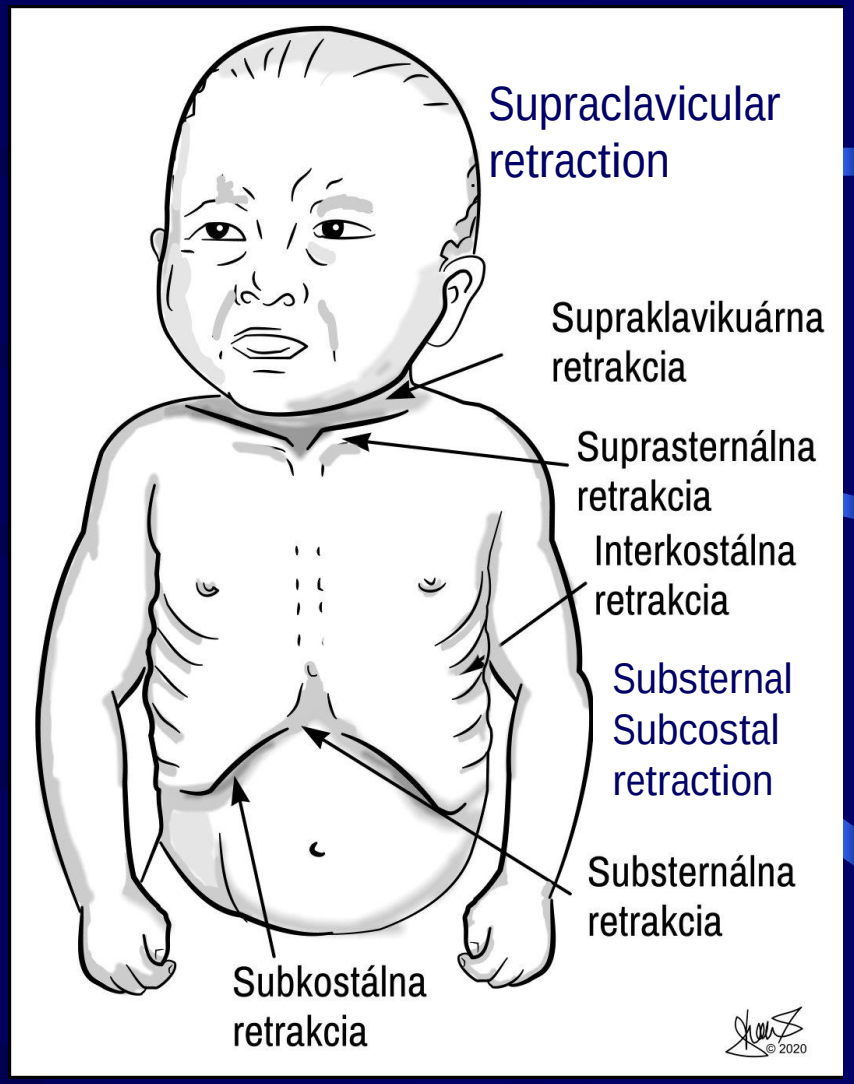
IRDS - Definintion

- Def: Infant respiratory distress syndrome (IRDS)(respiratory distress syndrome of newborn, surfactant deficiency disorder (SDD) hyaline membrane disease (HMD) = acute respiratory failuring
- Occ: 1% of newborns; males,caucasians; leading cause of death in preterm infants; the most common single cause of death in 1st month of life in developed world; infants of diabetic mothers
- Etio: - genetic defect of surfactant-associated proteins
  - structural immaturity in the lungs, neonatal infection

- Risk: preterm infants (50% in babies born at 26–28 weeks)
- - elective caesarean sections in term infants; dating back to
- - decreases with gestational age (25% at 30–31 weeks)
- Pat: waxlike layers of hyaline membrane line the collapsed alveoli of the lung; bleeding, overdistention of airways and damage`
- collapsed air spaces alternating with hyperexpanded areas, vascular congestio

IRDS - Manifestation

- shortly after birth tachypnoe (>60 b/min),tachycardia
- labored breathing: chest wall retractions,
- expir. grunting, nasal flaring
- hypoxia, cyanosis, hypercapnia
  - 1st day - critical, requires support.
  - 2nd day - stable on adequate support
  - 3rd day – resolution
  - Complications: metabolic disorders (acidosis, hypoglycaemia), hypotension (patent ductus arteriosus), low blood pressure, chronic lung changes, bleeding in the brain
- Hyaline membranes - eosinophilic, amorphous material (fibribrin, cellular debris, red blood cells, rare neutrophils and macrophages)



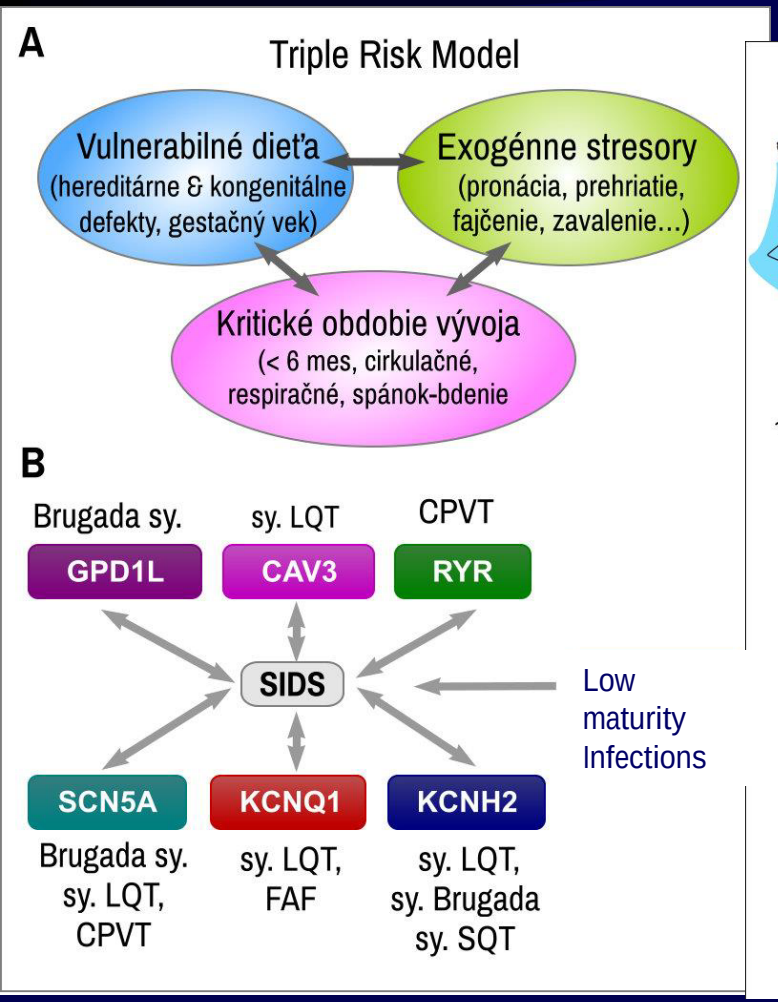
IRDS - Pathophysiology

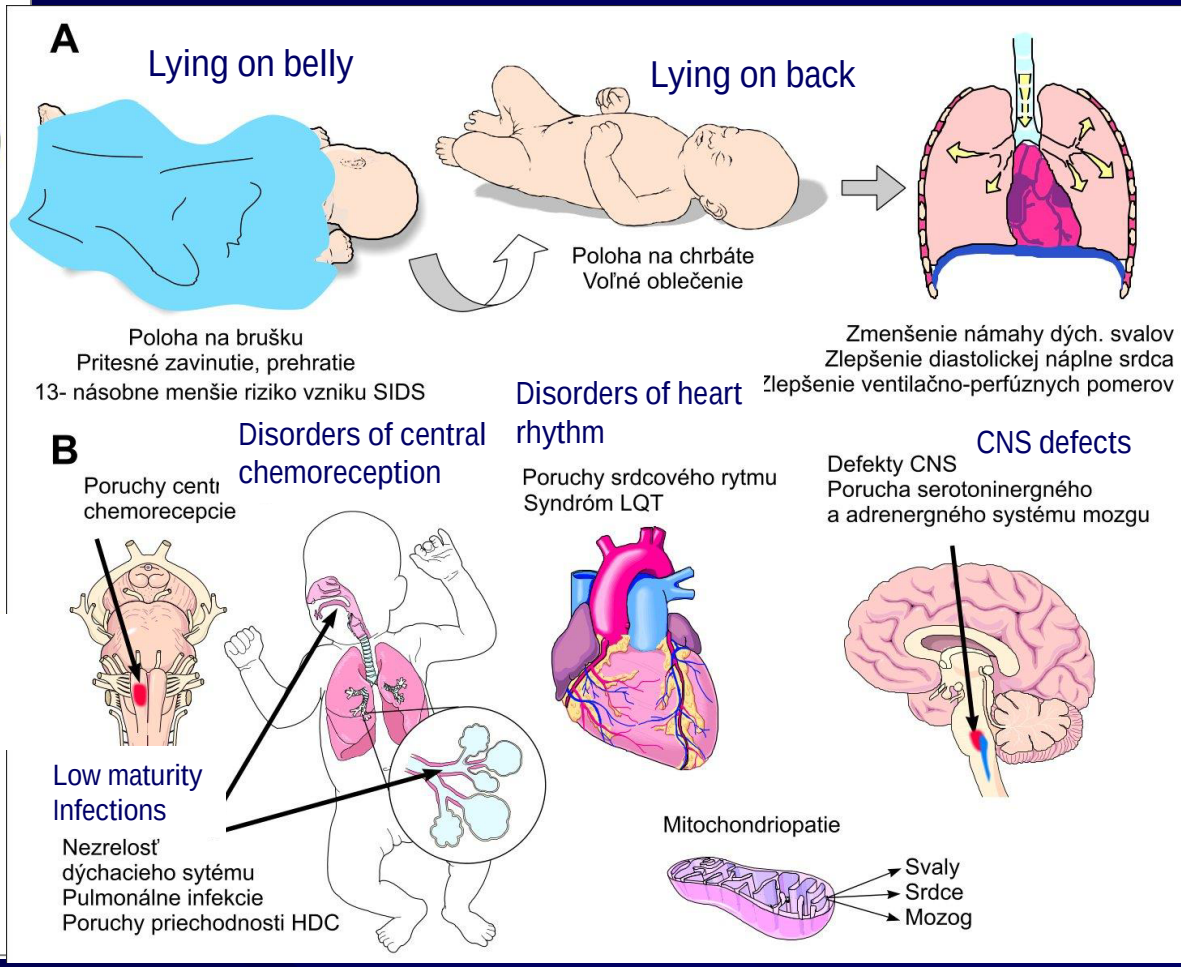
- **Ptg:** deficiency of surfactant → prevents collapse of the terminal air spaces ; deficiency of surfactant is related to an inhibition from the insulin that is produced in the newborn of diabetic mothers
- Pulmonary surfactant - complex system of lipids, proteins and glycoproteins that is produced in specialized lung cells type II cells pneumocytes.
- packaged in lamellar bodies, and extruded into the air spaces.
- layer reduces the surface tension of the fluid that lines the alveolar air space.
- Surface tension is responsible for approximately 2/3 of the inward elastic recoil forces.in air/water interface.
- Blood oxygen levels fall and carbon dioxide rises, resulting in rising blood acid levels and hypoxia.

SIDS & neonatal apnoeic states

- Def: Sudden infant death syndrome (SIDS) cot death, is the sudden unexplained death of a child < 1 year. death remain unexplained even after autopsy and detailed death scene investigation !!! diagnosis of exclusion --- infant's death is sudden and unexpected, remains unexplained after the performance of an adequate postmortem investigation SUDI 'undetermined' is now often used instead of SIDS
- Epi: 80% of sudden and unexpected infant deaths (SUID) sudden, without witnesses;19,200 deaths in 2015, down from 22,000 deaths in 1990. most common cause of death between one month and one year of age; 80% of cases < 6 months of age more common in boys than girls; 20 - 40% are, in reality, infanticides <10% are homicides
- Sy: occurs during sleep; 0.00 - 9:00 a.m. no noise, no struggle; leading cause of infant mortality < 0,5 y. in Western countries, 1/2 if neonatal deaths
- Etio: exact cause little known (it is primarily stop of heart) sudden cardiac death combination of risk factors susceptibility (genetics + ontogenesis), (specific risky time in development) + environmental stressors (sleeping on the stomach or side, overheating, cool sleeping environment, exposure to tobacco smoke, accidental suffocation (bed sharing), soft mattress, 39 weeks of gestation, child abuse intentional suffocation (<5% of SUID)

SIDS & neonatal apnoeic states





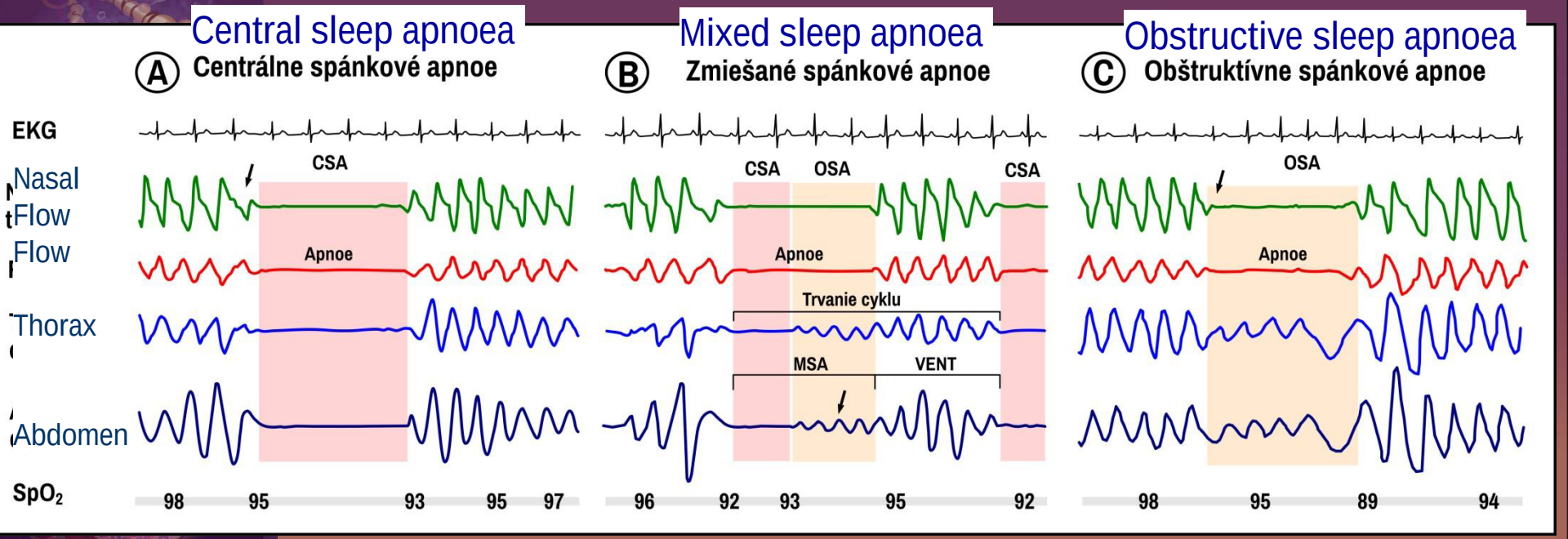
Sleep apnoea

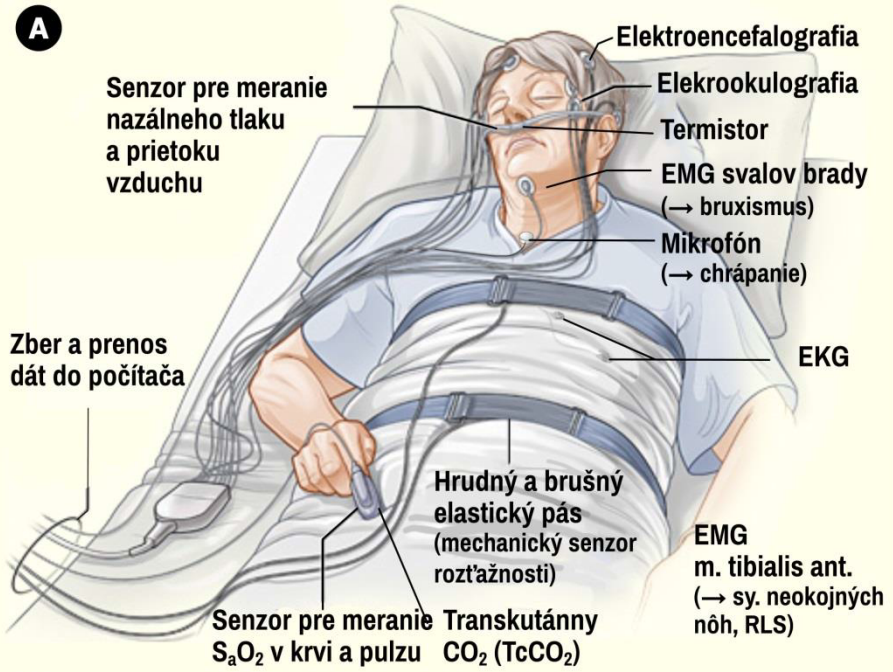
Def: Sleep related breathing disorders are any breathing disorders that occur during sleep. (International Classification of Sleep Disorders, ICSD) and also DSM-V (Diagnostic and Statistical Manual in Psychiatry) A special category within the so-called dyssomnic sleep disorders

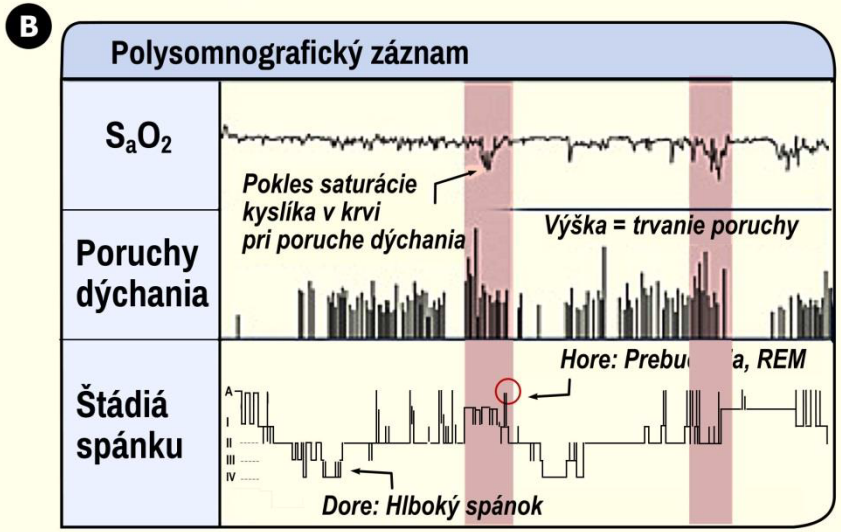
Formy: Night hypoventilation syndrome, etc. - Ondine's curse; congenital defects;

Sleep apnea syndromes (central SA, obstructive SA, mixed SA)

Ptg: Sleep is the time when the manifestations of respiratory instability occur; revealing even hidden manifestations

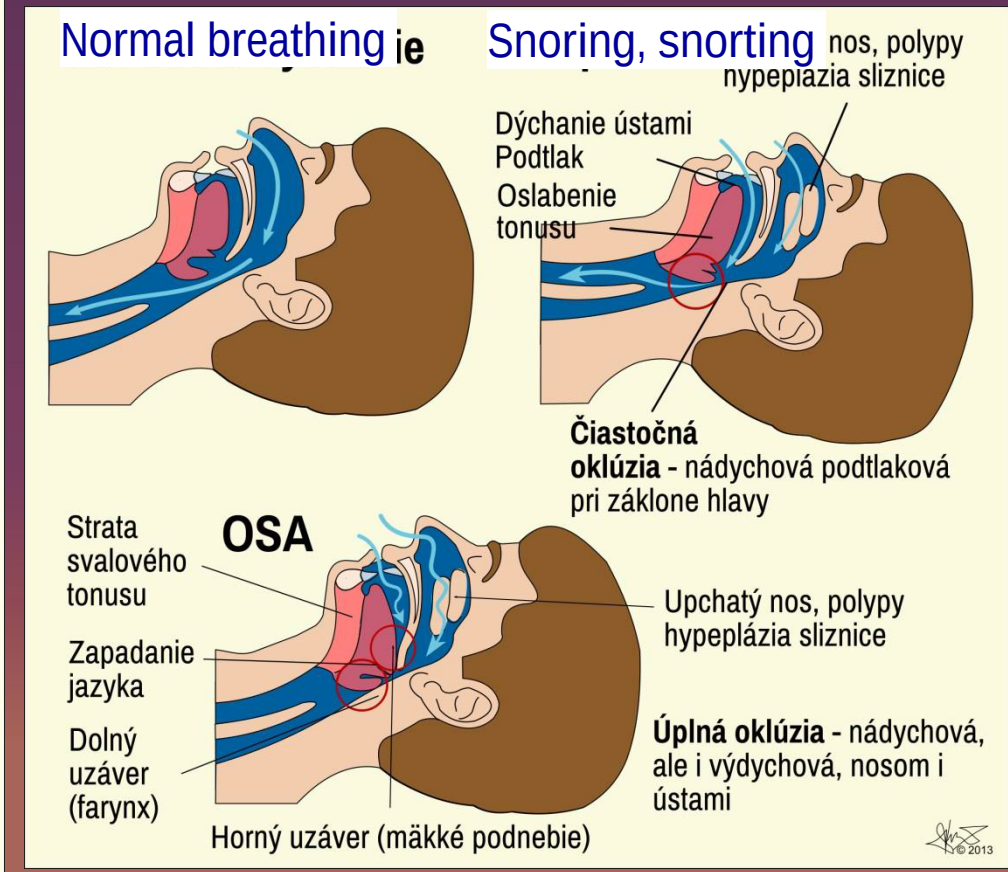






$$\text{Apnoicko - hypopnoický index (AHI)} = \frac{\text{(Apnoe + Hypopnoe). 60}}{\text{Celkové trvanie spánku (min)}}$$

$$\text{Respiratory distress Index (RDI)} = \frac{\text{(Apnoe + Hypopnoe +RERA). 60}}{\text{Celkové trvanie spánku (min)}}$$



Sleep apnoea

Central sleep apnoea (CSA) (10%) failure in creration of respiratory drive

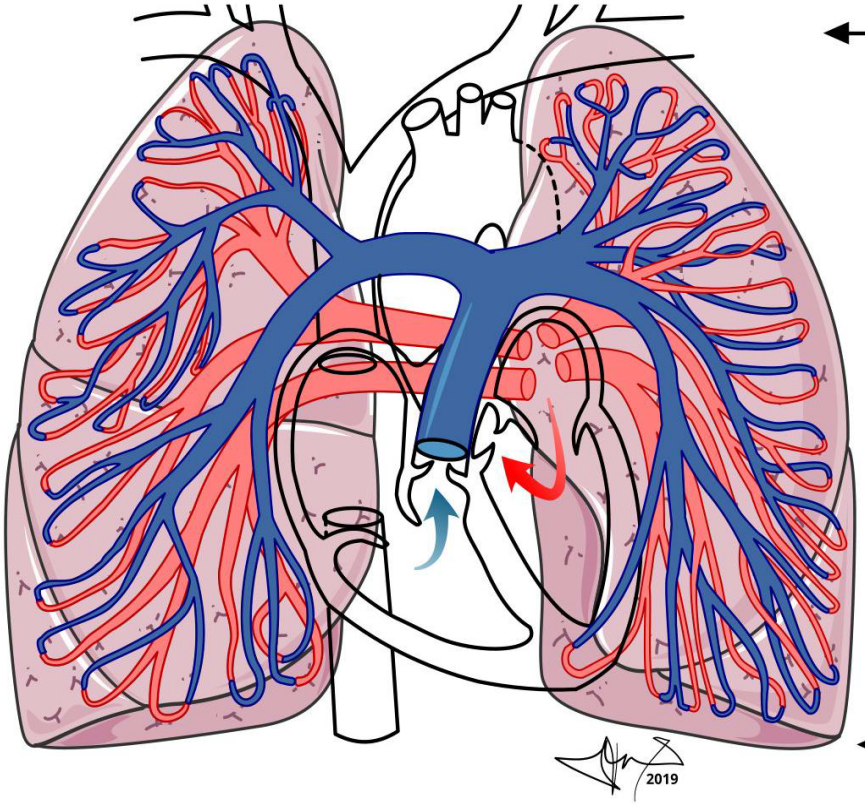
- hypercapnic type (does not work only during sleep) – hypoventilation hypercapnia, insufficient response to CO_2 (CMP)
- non-hypercapnic type (breathing is weak even when awake; hyperreaction to CO_2; heart failure, kidney failure, CNS lesion, at altitudes; at night they wake up to dyspnoea, Cheyne-Stokes breathing. → acute respiratory insufficiency (acute respiratory failure).

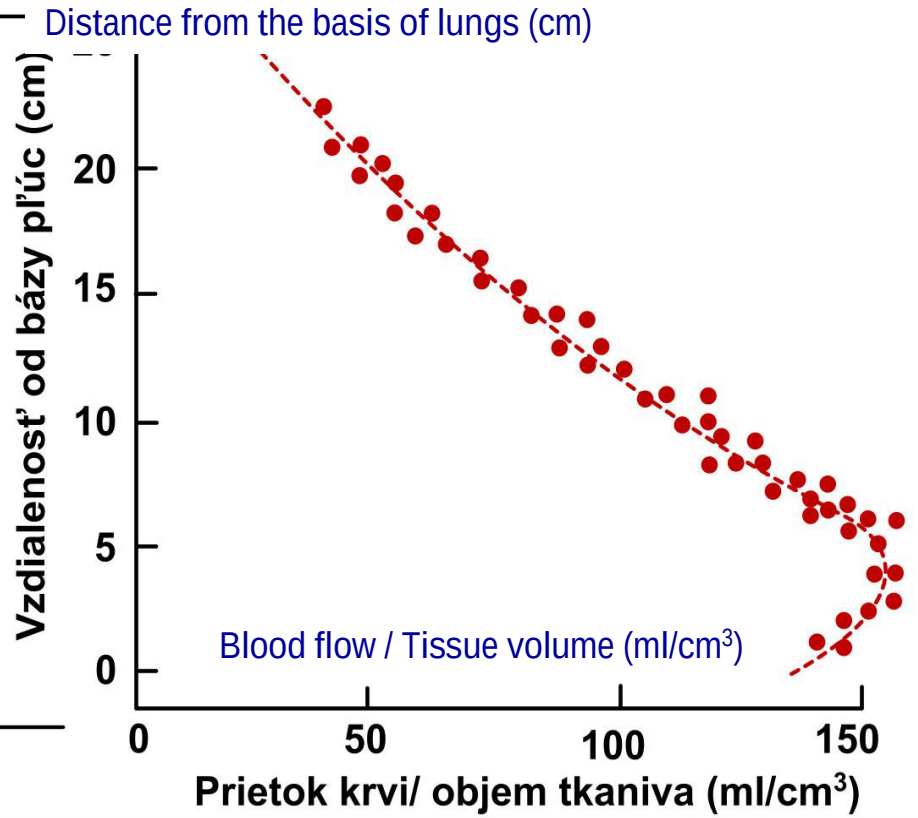
Obstructive sleep apnoea (OSA) (80%)

- Temporary, transient collapse (snoring) to complete HDC closure due to muscle weakness (this is also physiological) - root of the tongue, hypopharynx; obesity (70% of patients with OSA; men: women 2: 1; increase with age
- risk factor for cardiovascular disease (hypertension, coronary heart disease, stroke, congestive failure), worsens the course or protection (COPD) in 45% of card. Failures
- Mixed sleep apnea (10%)

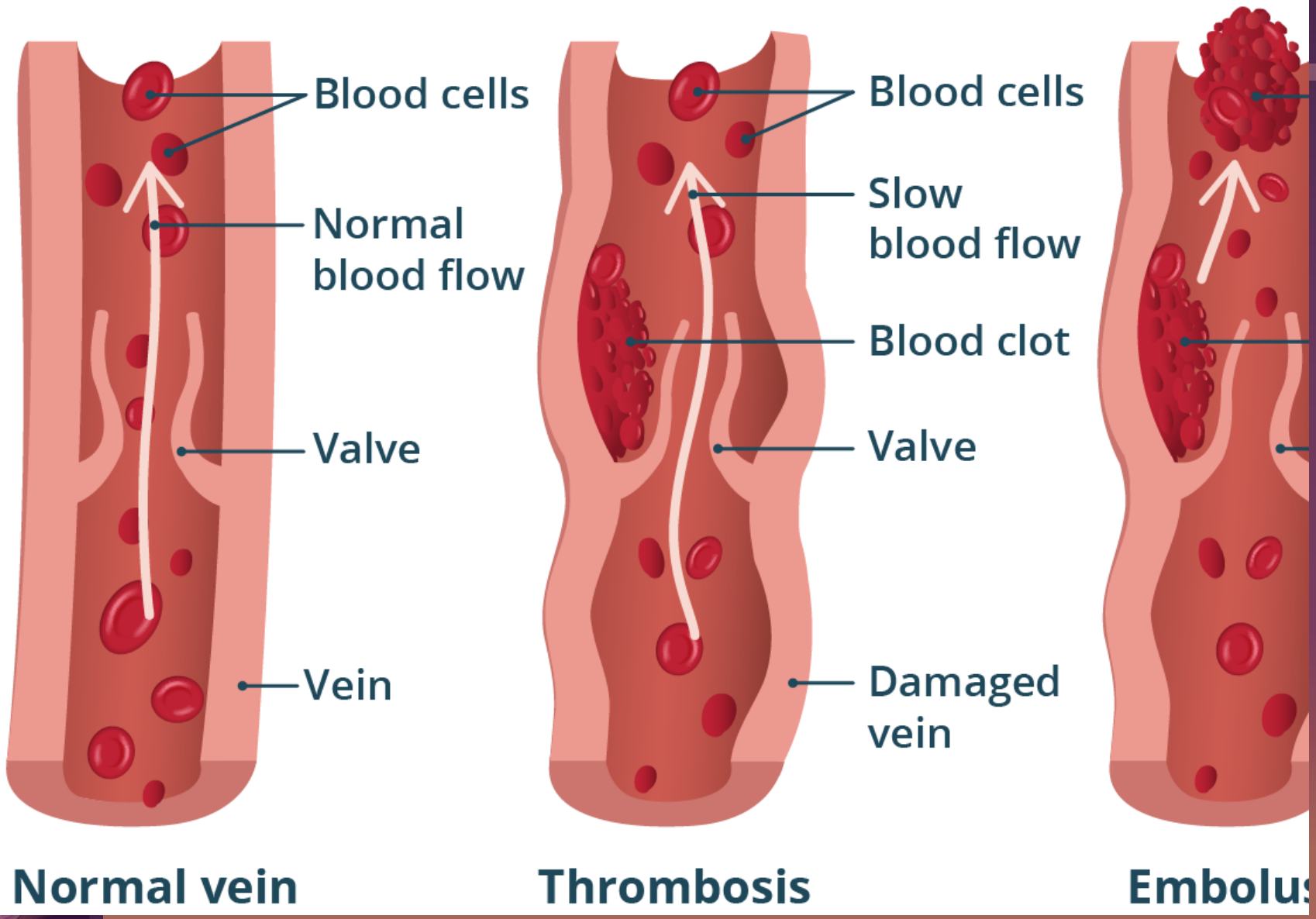
Pulmonary embolia

- Def: Pulmonary embolism (PE) is a serious and potentially life-threatening condition where a blood clot (or other material) blocks one or more arteries in the lungs, restricting blood flow and oxygen exchange.
- Etio: a) tromboembolia - blood clot from deep vein thrombosis (DVT), b) air - embolia; c) fat embolia





Embolism - caused by thrombosis (blood clot in a blood vessel)



Pumonary embolism

Risk factors include:

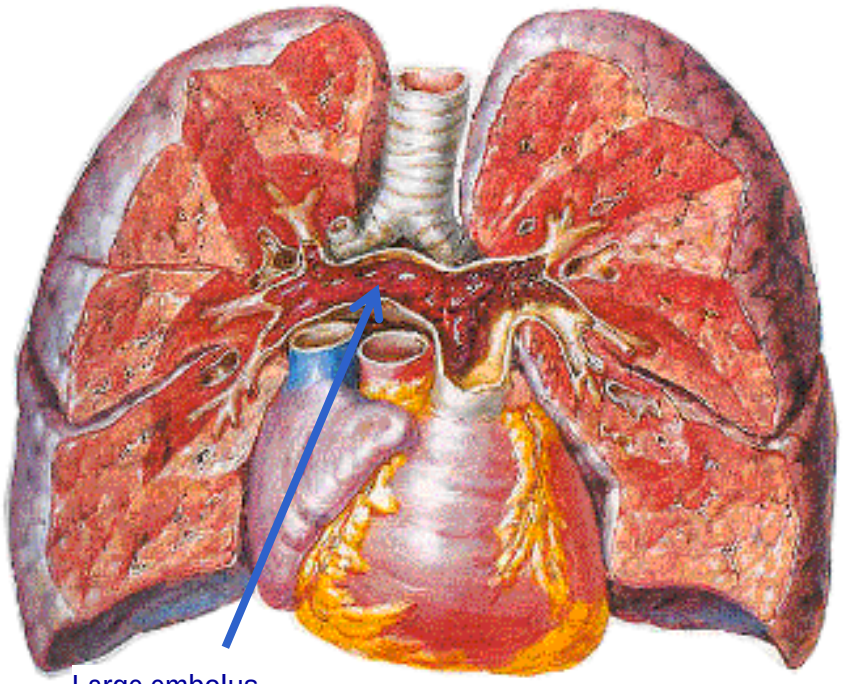
- Prolonged immobility (e.g., long flights, bed rest after surgery, or hospitalization)
- Recent surgery or injury (especially to legs, hips, or pelvis)
- Cancer
- Pregnancy or postpartum period
- Hormone therapy (e.g., birth control pills or estrogen replacement)
- Smoking, obesity, heart disease, or clotting disorders
- Family history of blood clots

Manifestations:

- Sudden shortness of breath (even at rest, worsening with activity)
- Sharp chest pain (often pleuritic — worse with deep breaths, coughing, or movement; may feel like a heart attack)
- Cough (sometimes with bloody or blood-streaked mucus)
- Rapid or irregular heartbeat (palpitations)
- Lightheadedness, dizziness, fainting (syncope), or anxiety
- Leg pain or swelling (from the originating DVT)
- Sweating, clammy skin, or low-grade fever

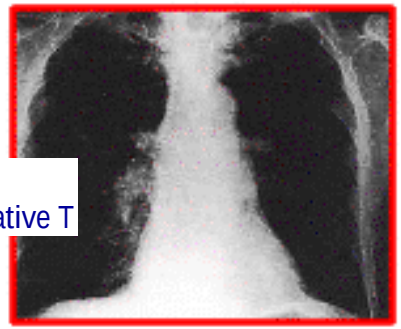
Pulmonary embolia

Pulmonárna embólia

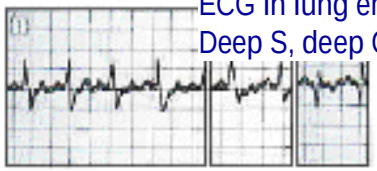


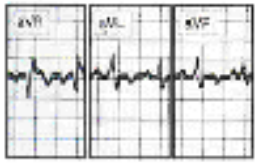
Large embolus

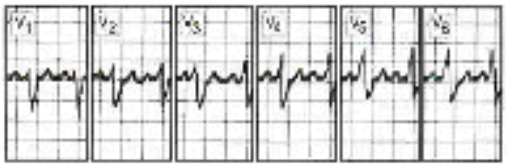
- Veľký embolus v centrálnej časti a. pulmonalis a jej vetvení
- Typické EKG pri pľúcnej embólii hlboké S, nápadné QII, negatívne TII

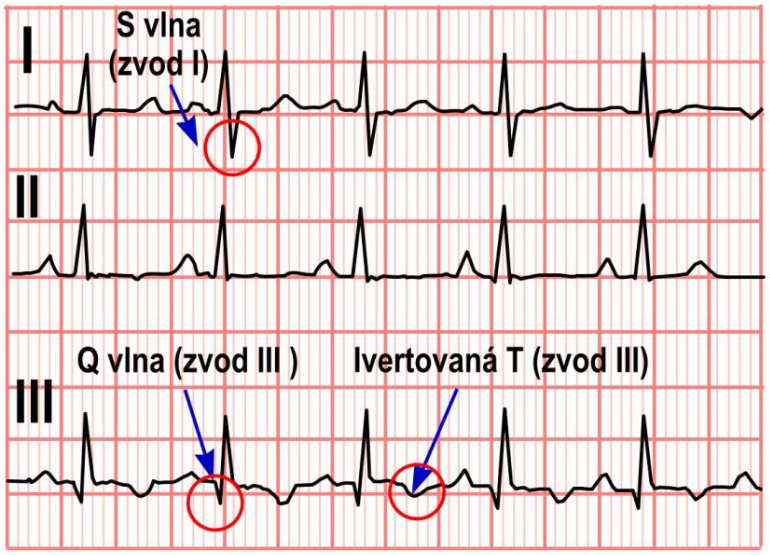


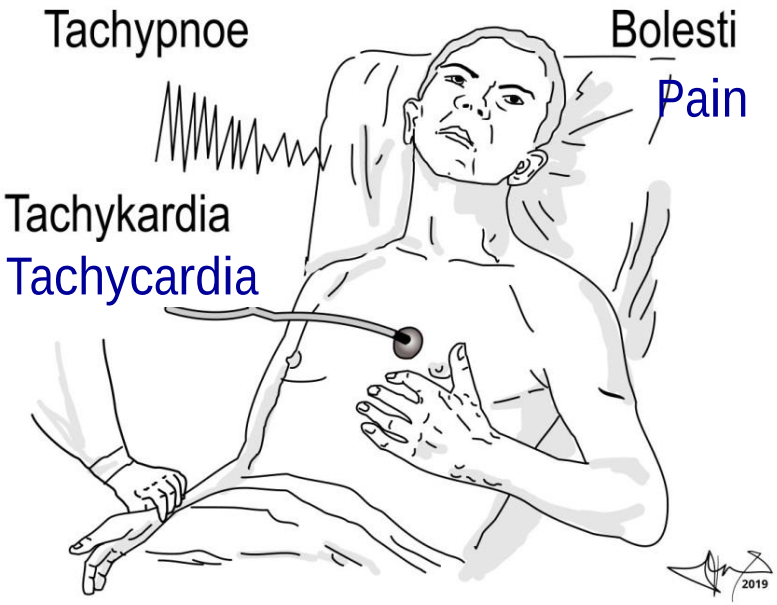
ECG in lung embolia
Deep S, deep Q, negative T











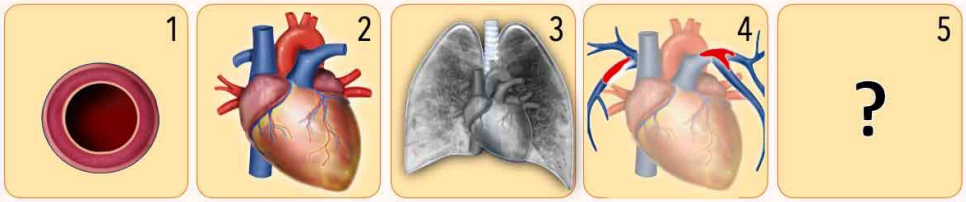
Pulmonary hypertension

- Definition: Pulmonary hypertension (PH) is an etiopathogenetically, symptomatically and prognostically heterogeneous group of diseases (or pathological findings, processes) with high pressure in the pulmonary circulation
- Mean pulmonary artery pressure (mPAP) at rest > 20.7 mmHg, measured by right heart catheterization Borderline form of PH (risk): 21 – 24 mmHg
- Final diagnosis only invasive: mean pressure in a. pulmonalis ≥ 25 mmHg at rest during right-sided cardiac catheterization
- Etiology: - Multifactorial
- (1) Genetic basis - in 60% of familial PAH, in 25% of idiopathic PAH, in 10% of other forms of PAH,
  - AD with incomplete penetrance (BMPR receptor 2 gene mutation (muscular hyperproliferation; progressive remodelling of the pulmonary arteries).
- (2) Exogenous factors
  - Other diseases - hyperkinetic circulation, vasculitis, HIV infection, anorexia, unlysed pulmonary embolism in CTEPH

Pulmonary hypertension

- Epidemiology: global prevalence 1%, ; pulmonary arterial hypertension (PAH) 6 /1mil.
- Forms:
- Group 1 (pulmonary arterial hypertension, including idiopathic, heritable, and drug- or toxin-induced forms);
- Group 2 (PH in left heart failure), the most common type, failure with preserved ejection fraction (PH-HFpEF), combined pre- and post-capillary PH
- Group 3 (PH due to lung diseases and/or hypoxia, COPD
- Group 4 (chronic thromboembolic PH);
- Group 5 (PH with unclear or multifactorial mechanisms).

WHO groups of Pulmonary Hypertension



1	2	3	4	5
Pulmonary Arterial Hypertension	PH associated with Left heart disease	PH associated with lung disease	PH associated with pulmonary arterial obstruction	PH with unclear or multifactorial causes
Rare	Very common	Common	Rare	Rare

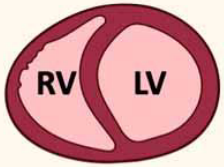
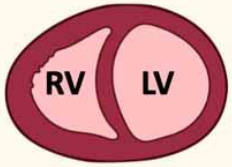
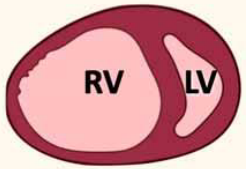
Pressure measurements in WHO groups

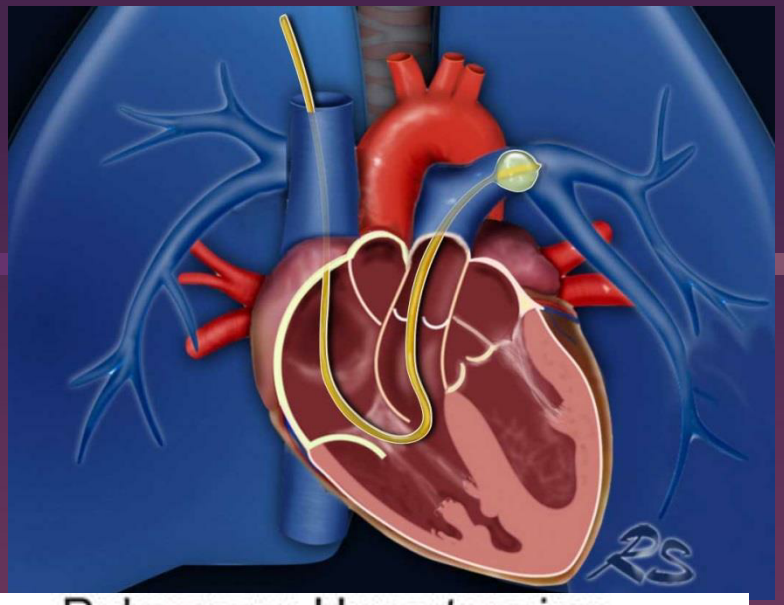
Pulmonary Hypertension	mPAP >20 mmHg	1-5
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2WU	1,3,4,5
Isolated post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR ≤2WU	2,5
Combined post- and pre-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVR >2WU	2,5

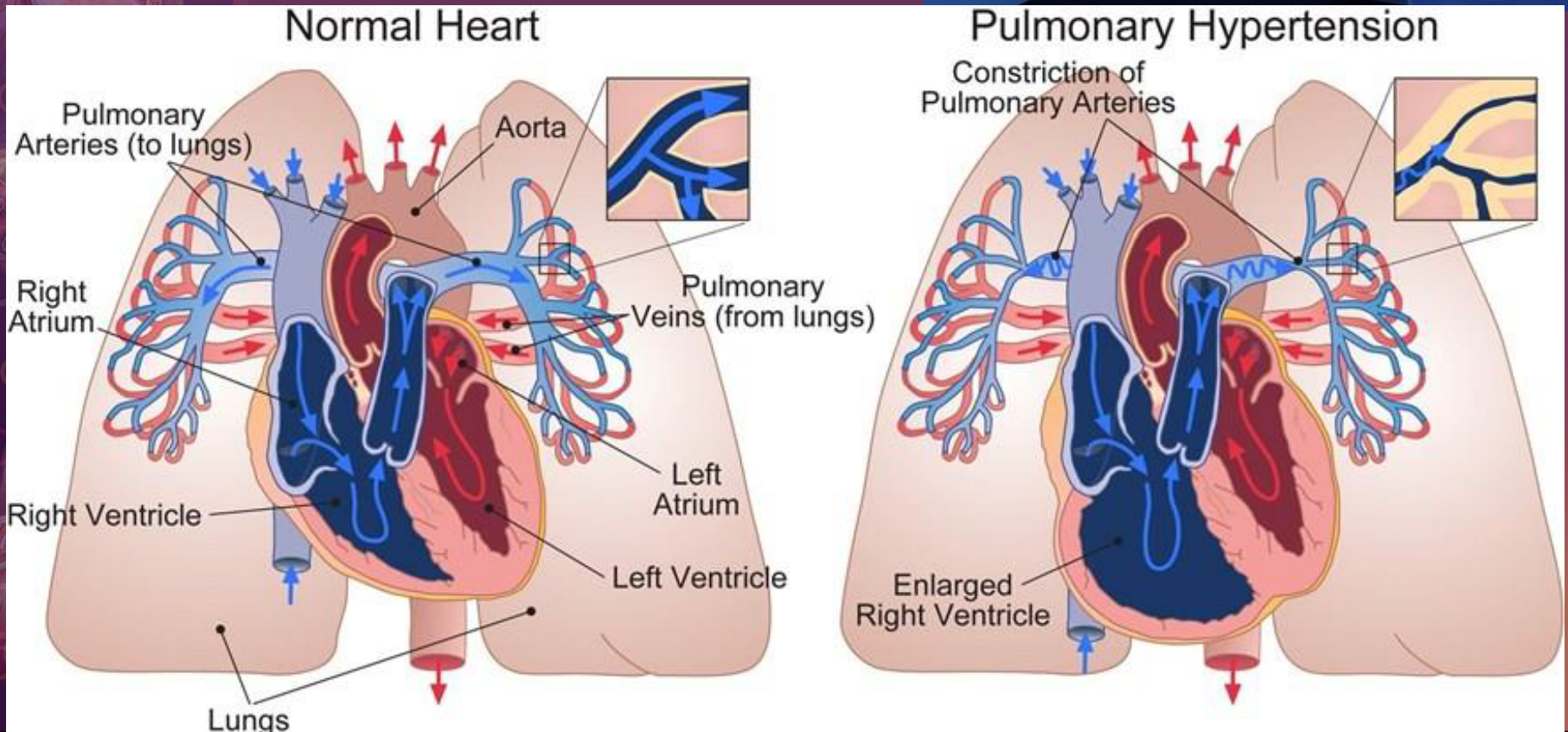
Pulmonary hypertension

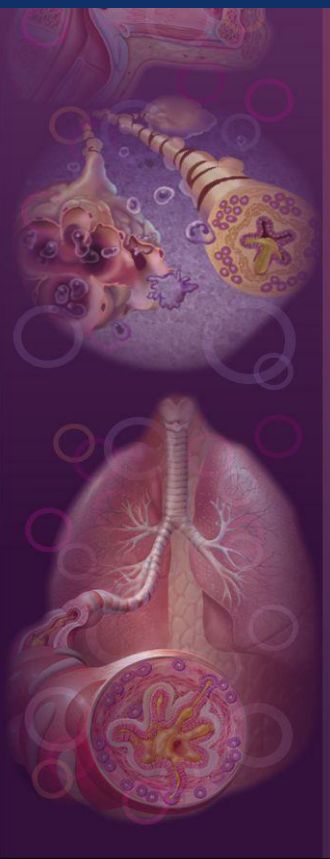
- Etiology: endothelial dysfunction, vascular remodeling, increased pulmonary vascular resistance;
- Risk factors genetic mutations (e.g., in the BMPR2 gene), connective tissue diseases (systemic sclerosis, congenital heart defects, HIV infection, chronic liver disease, and exposure to certain drugs or toxins
- Symptoms fatigue, dizziness or fainting spells,
- shortness of breath (initially with exertion and later at rest),
- chest pain or pressure, rapid or irregular heartbeat,
- swelling in the ankles or legs due to fluid retention.[
- ventilation-perfusion scans, right heart catheterization, while treatment is tailored to the underlying cause and PH group, incorporating lifestyle modifications (e.g., low-sodium diet, exercise), supportive therapies (e.g., diuretics, oxygen),
- pulmonary artery wedge pressure (PAWP) and pulmonary vascular resistance (PVR). Precapillary PH is defined by mPAP >20 mm Hg, PAWP ≤15 mm Hg,PVR >2,
- Postcapillary PH involves elevated PAWP >15 mm Hg

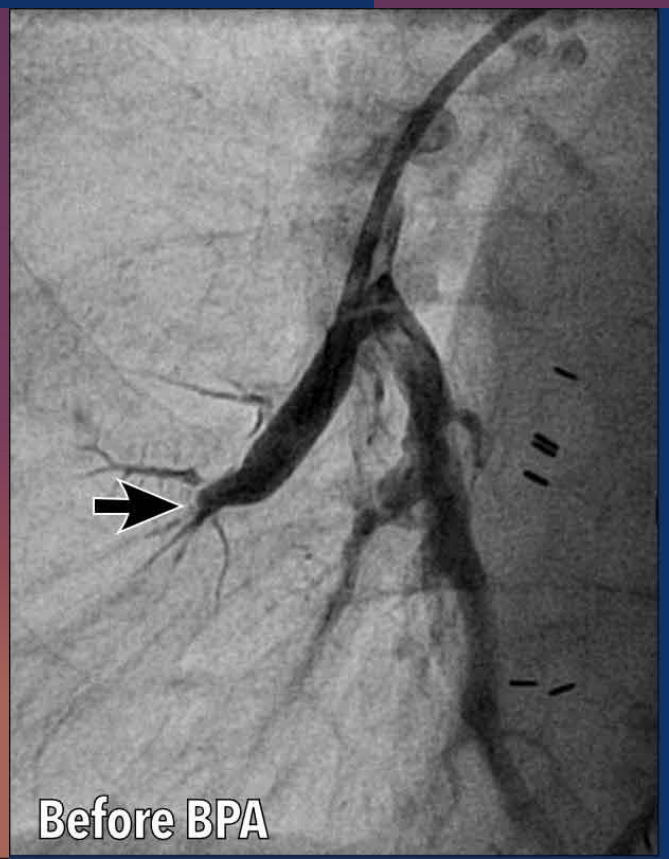
Cardiac remodelling in PH

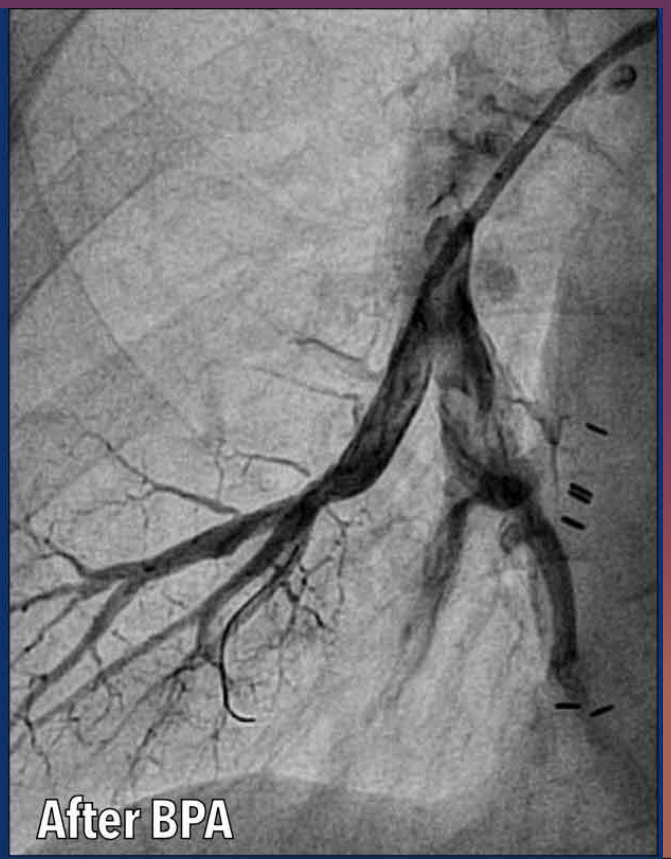
Asymptomatic Compensation	Mild Decompensation	Advanced Decompensation
		
Mild hypertrophy RV Normal Cardiac Output (CO)	Hypertrophied RV Mildly decreased CO	Dilated hypertrophied RV Severely decreased CO








Before BPA


After BPA