# Pathophysiology of the respiratory system III – **Pulmonary blood flow**

Pulmonary circulation
Pulmonary hypertension definition & classification
– role of hypoxic pulmonary vasoconstriction and vascular remodelling
Pulmonary embolism
Pulmonary oedema
ARDS

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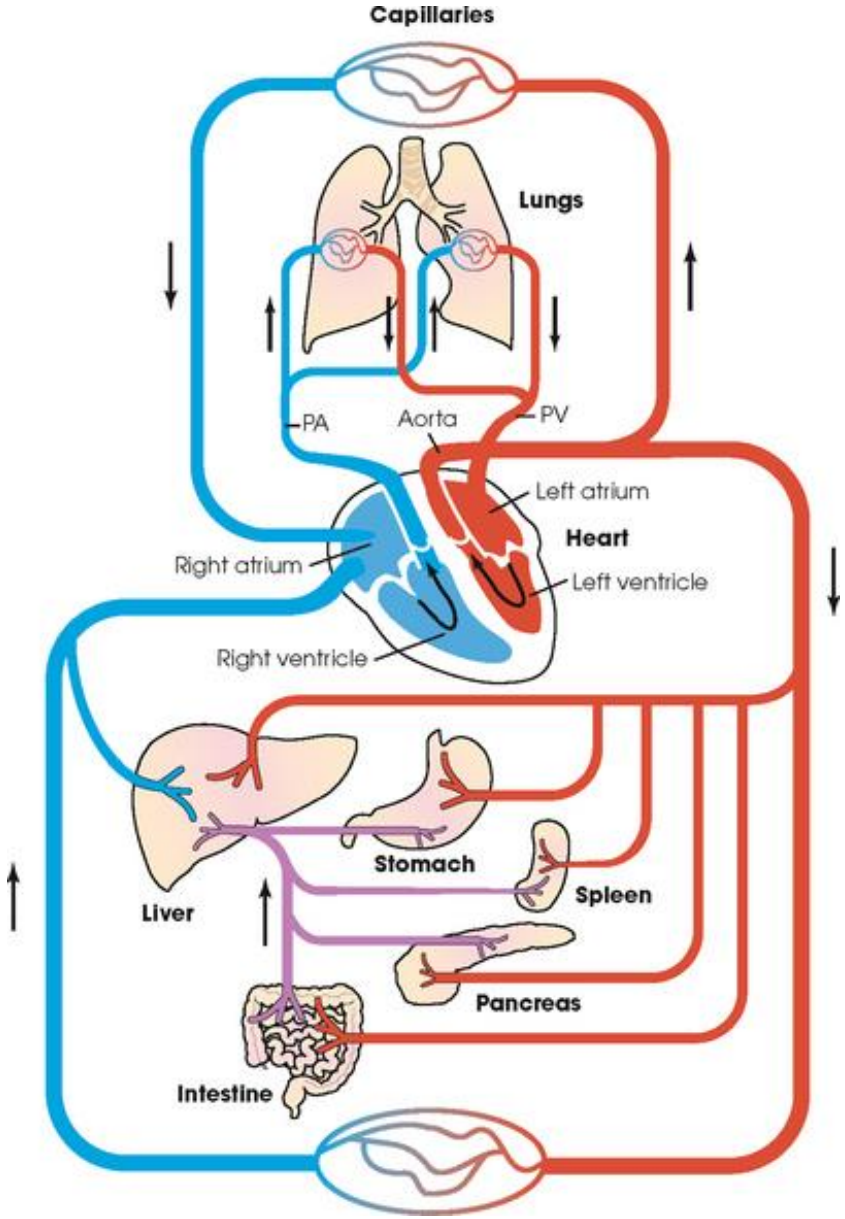
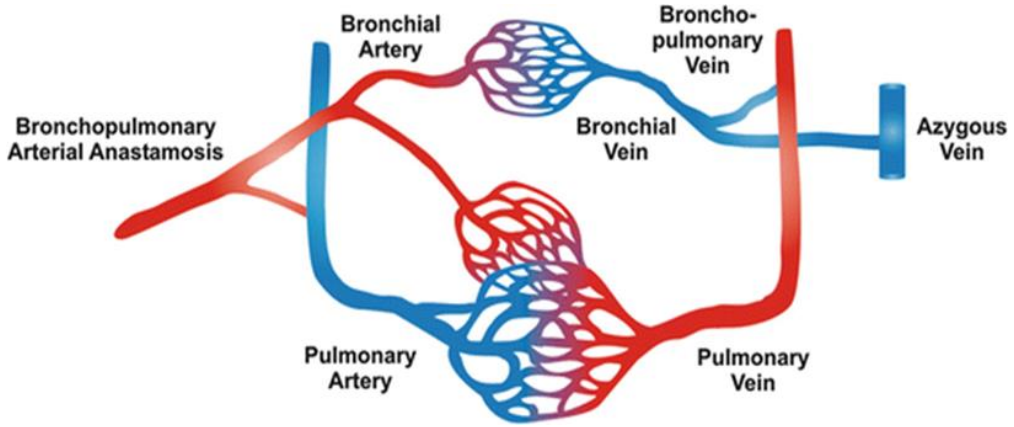
# Pulmonary vs. systemic circulation




- Lungs are the only organ through which **entire blood** passes!!!
  - the volume equals to the cardiac output (CO)
- The pressure is generated by the right ventricle (RV)
  - increased CO (e.g. physical activity) must by adopted by pulmonary circulation without a significant increase of the work of RV
    - see recruitment and distension of pulmonary vessels (capillaries)
  - therefore, given the differences in pressure and volume parameters in pulmonary bed, the **morphology of pulmonary vessels is different**
    - smaller amount of smooth muscle, larger distensibility by pressure and increased flow
    - however, smooth muscle of pulmonary arteries is very important – see hypoxic pulmonary vasoconstriction
- Pulmonary vascular resistance (PVR) varies between imperium and expirium, i.e. with changing lung volume (see further)
- Lungs have a **dual blood supply**
  - deoxygenated blood from RV via pulmonary artere (PA)
  - systemic (nutritional) supply of conductive zone airways via bronchial circulation
    - branching from descendent aorta
    - bronchial veins drain in small extent post capillary to pulmonary veins and are responsible for a physiological R-L shunt
- 4 main pulmonary veins drain into LA

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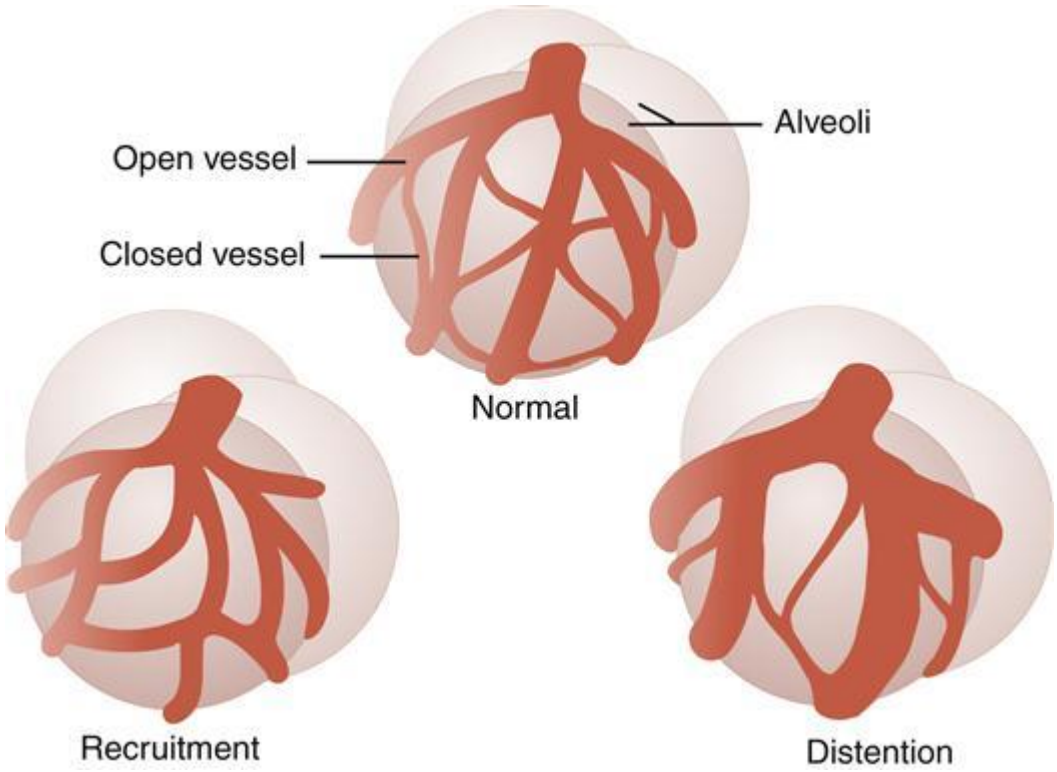
# The pulmonary capillary network




- The PA splits into left and right branches, further to smaller arteries an arterioles and finally to capillary network
  - this is a low-pressure system that **can expand two to three times the normal size before a significant increase in pulmonary capillary pressures is detectable**
    - normal PAP in a healthy adult ~22-25/8-10 mmHg (mPAP ~15 mmHg)
    - normal SAP in a healthy adult ~ 120/80 mmHg (mSAP ~96 mmHg)
  - under normal resting conditions, some pulmonary capillaries are closed and not perfused
- The pulmonary circulation has two mechanisms for lowering PVR when vascular pressures are increased because of increased blood flow
  - (1) recruitment = opening of previously closed capillary vessels
  - (2) distention = widening of capillary vessels

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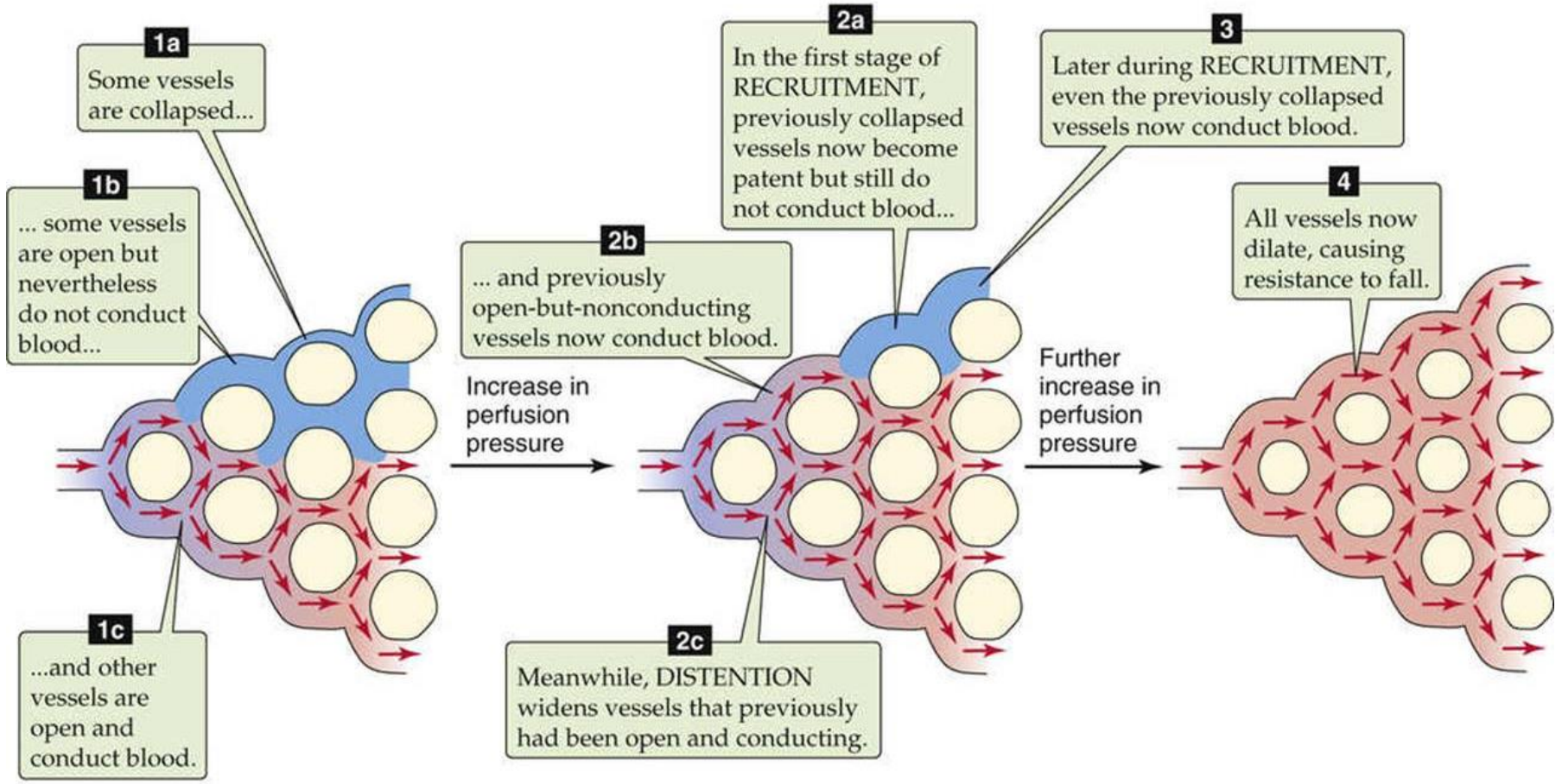
# Recruitment and distension of pulmonary capillaries

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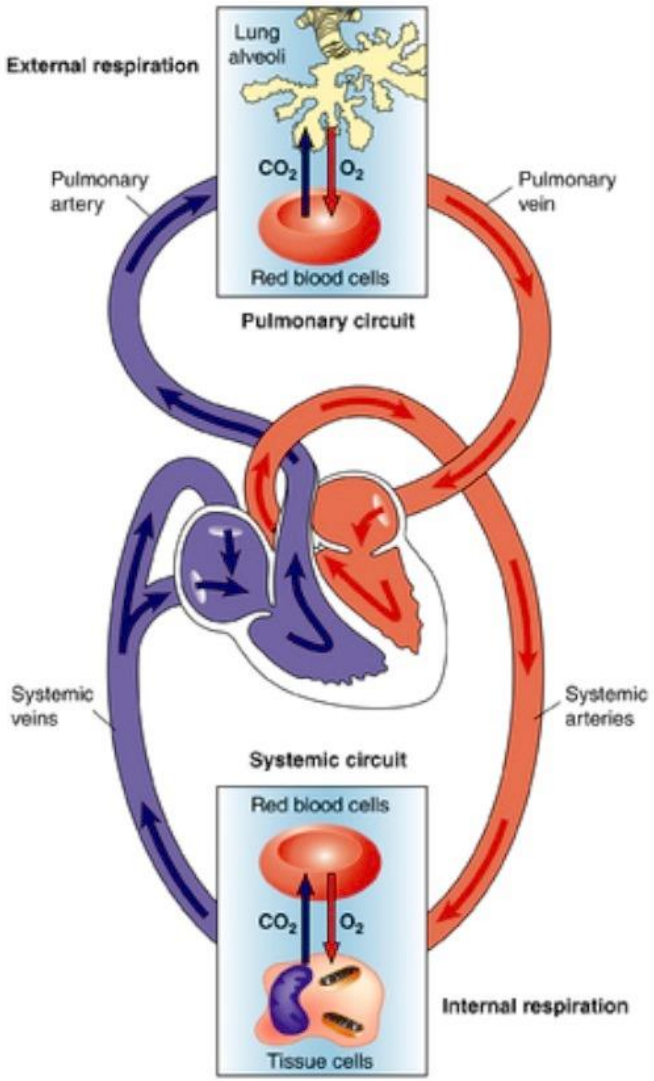
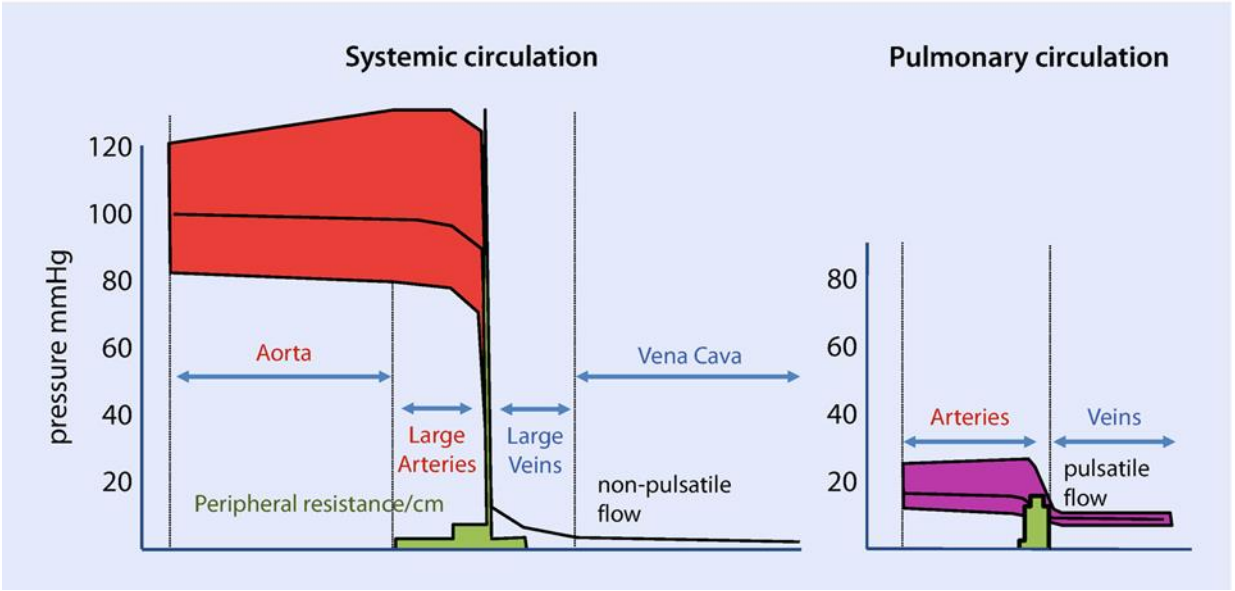
# Pulmonary vs. systemic circulation




- Pulmonary circulation
  - ↓ P / ↓ resistance / ↑ compliance
    - lower pressure gradient is sufficient to cover the distance between RV and LA
  - paradoxical response to ↓ $P_AO_2$ (i.e. alveolar hypoxia) – vasoconstriction
    - with the aim to optimise $V_A/Q$ mismatch by redistribution of blood to well ventilated parts of the lungs
- Systemic circulation
  - ↑ P / ↑ resistance / ↓ compliance
    - massive pressure gradient necessary to cover large distance between LV and RA
  - typical response to ↓ $P_aO_2$ (i.e. hypoxemia) – vasodilation
    - with the aim to increase perfusion and oxygen delivery

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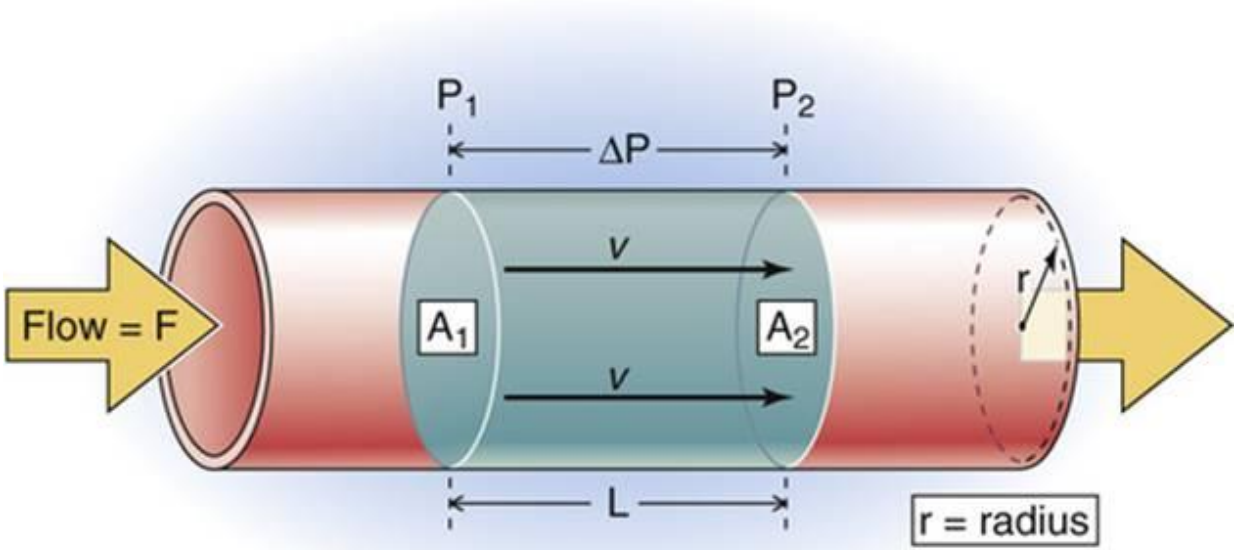
# Pulmonary vascular resistance




| | | |
|---|---|---|
| **Pulmonary vascular resistance** | $PVR = \frac{P_{pulm\ artery} - P_{L\ atrium}}{\text{cardiac output}}$ | R = resistance<br>$P_{pulm\ artery}$ = pressure in pulmonary artery<br>$P_{L\ atrium} \approx$ pulmonary capillary wedge pressure |
| | Remember: $\Delta P = Q \times R$, so $R = \Delta P / Q$<br>$R = 8\eta l / \pi r^4$ | $\eta$ = viscosity of blood; l = vessel length;<br>r = vessel radius |

$$SVR = \frac{\text{mean arterial pressure - mean right atrial pressure}}{\text{Qs (systemic blood flow)}}$$

$$PVR = \frac{\text{mean pulmonary artery pressure - mean left atrial pressure}}{\text{Qp (pulmonary blood flow)}}$$

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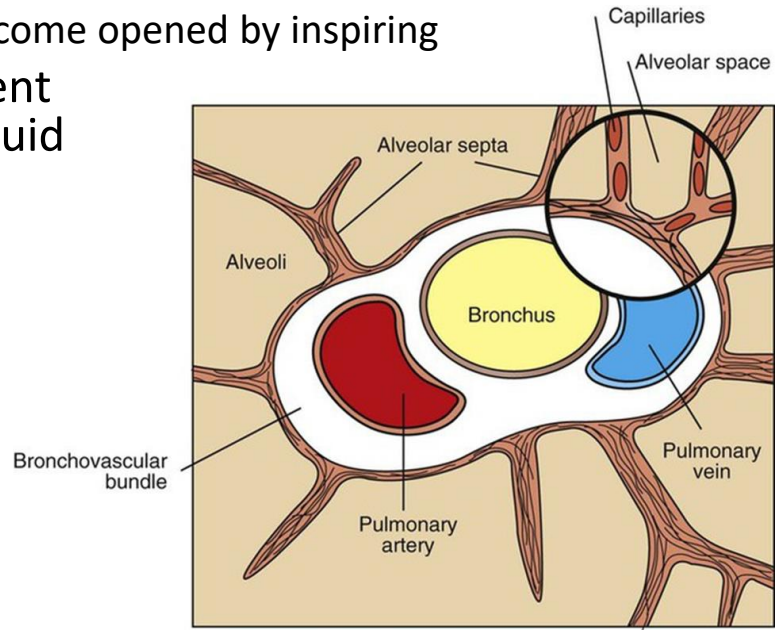
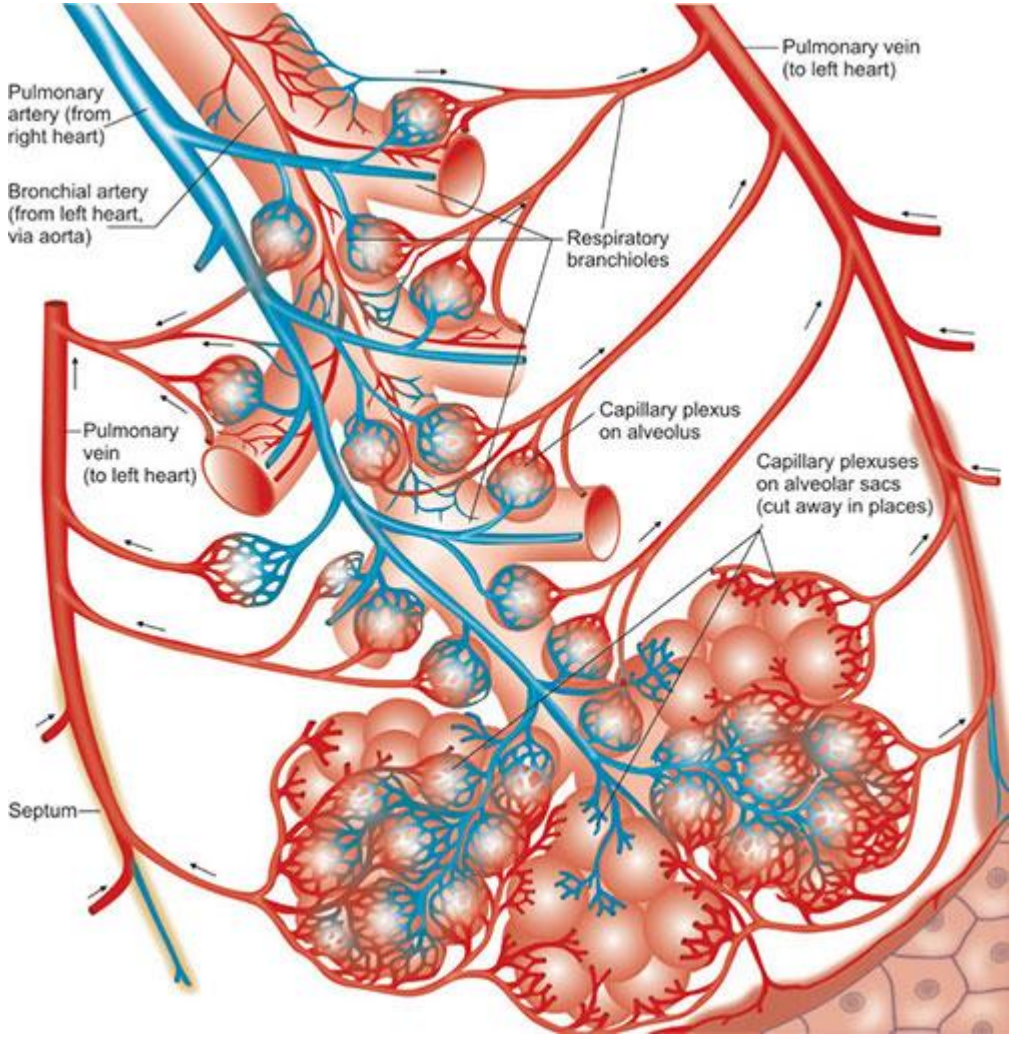
# Pulmonary alveolar and extra-alveolar vessels

- **alveolar vessels**
  - capillaries of alveolar septs exposed to alveolar pressure (changing during inspiration and expiration)
    - they become compressed by inspiring
- **extra-alveolar vessels**
  - arteries and veins in interstitium paralleling branching of airways
    - together they create a „**broncho-vascular bundle**“
  - they are distended by radial traction of elastic elements of interstitium
    - therefore they become opened by inspiring
  - this is a compartment initially collecting fluid in lung oedema

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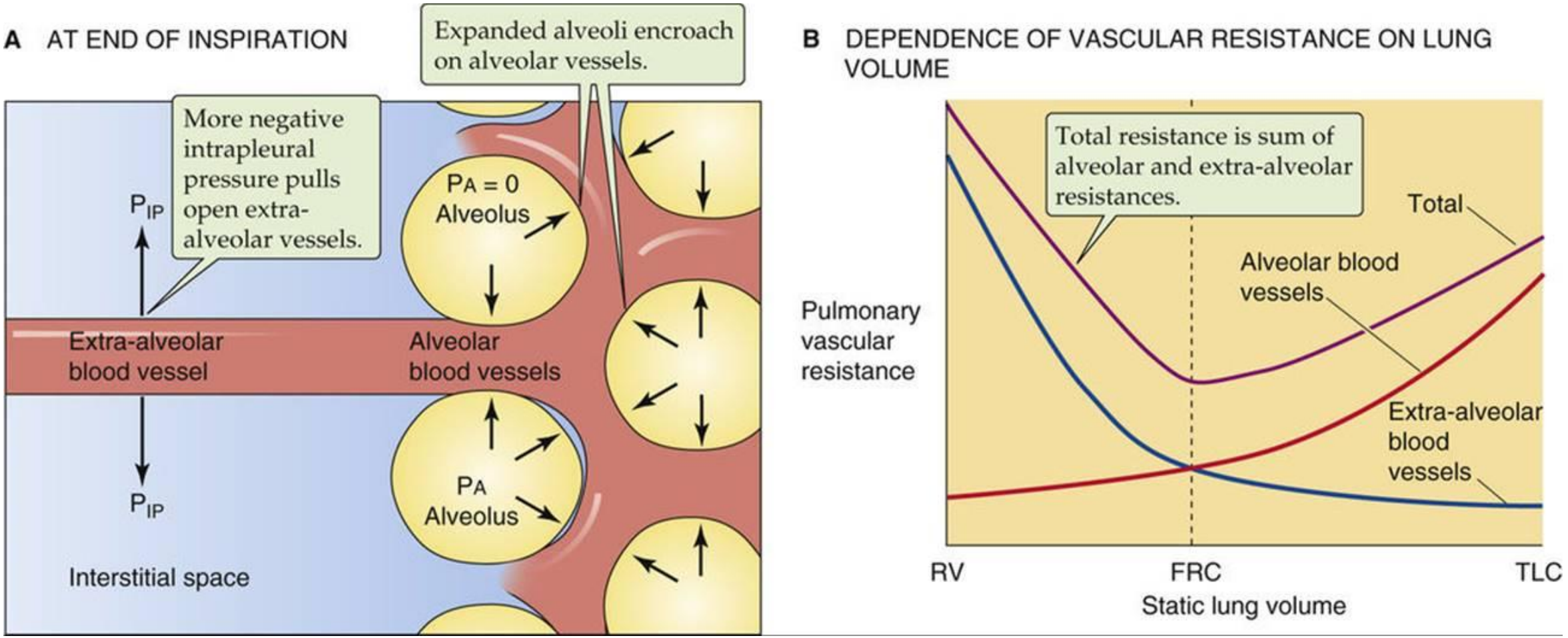
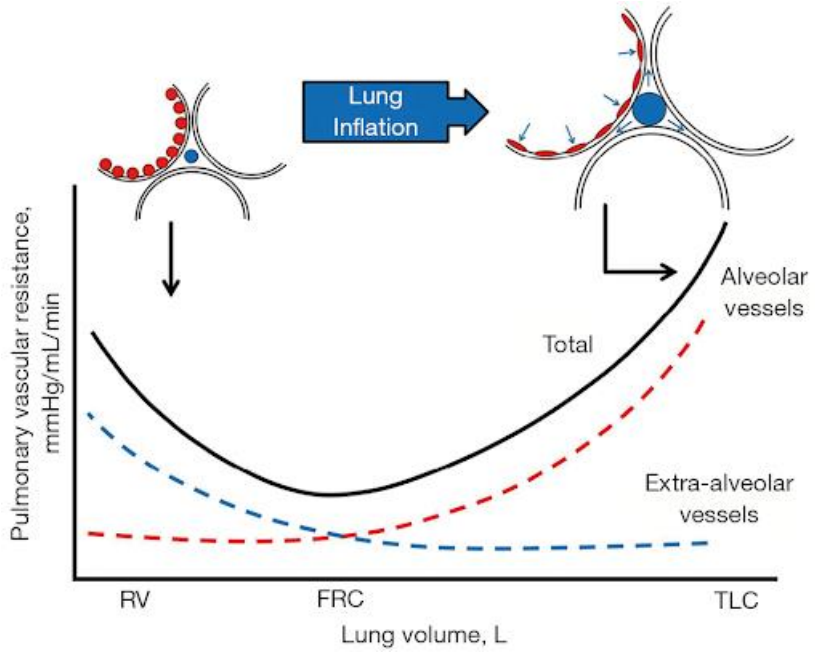
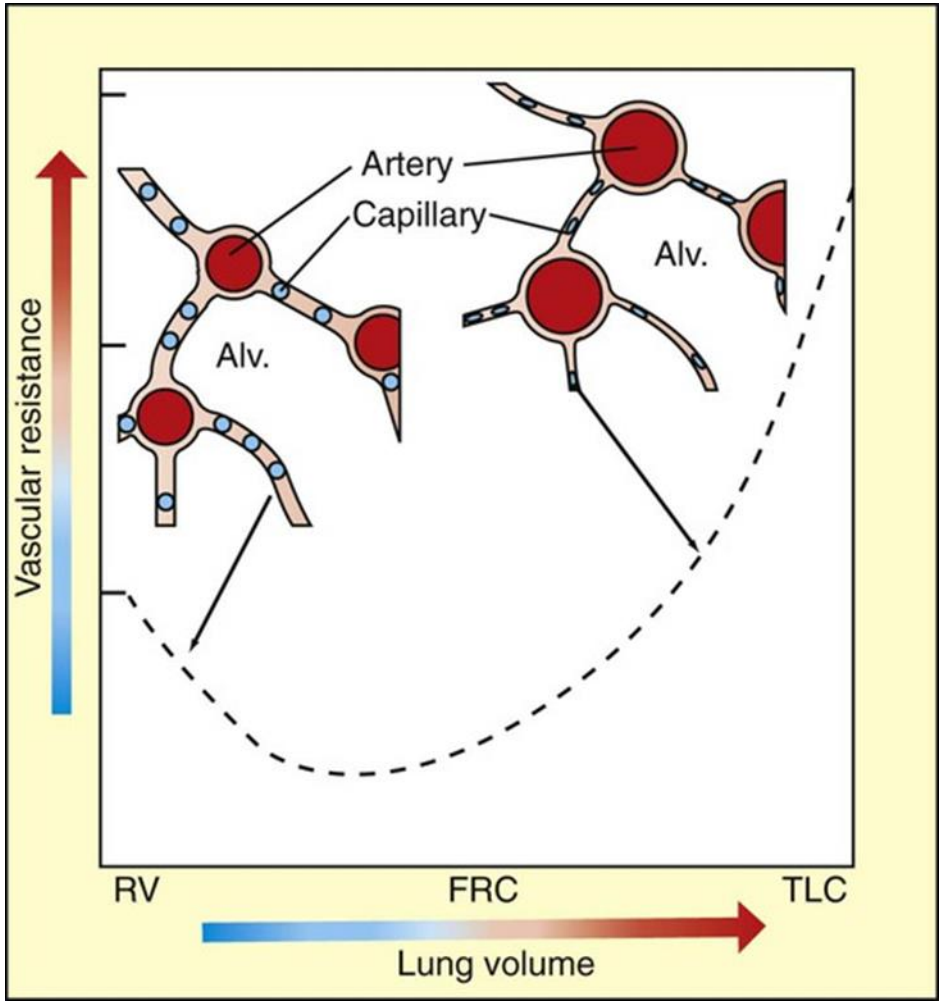
# Pulmonary vascular resistance - minimal at FRC



# Relation between lung volume and PVR




- PVR is the main determinant of RV afterload and can increase significantly at both extremes of lung inflation
  - as lung volume increases from residual volume (RV) to total lung capacity (TLC), the “alveolar” vessels (red) become increasingly compressed by the distending lung units, and so their resistance increases
  - whereas the resistance of the “extra-alveolar” vessels (blue) falls as they become less tortuous and dilate with lung inflation
- During healthy conditions, these opposing effects of inflation normally optimize at functional residual capacity (FRC), assuming patency of all lung units

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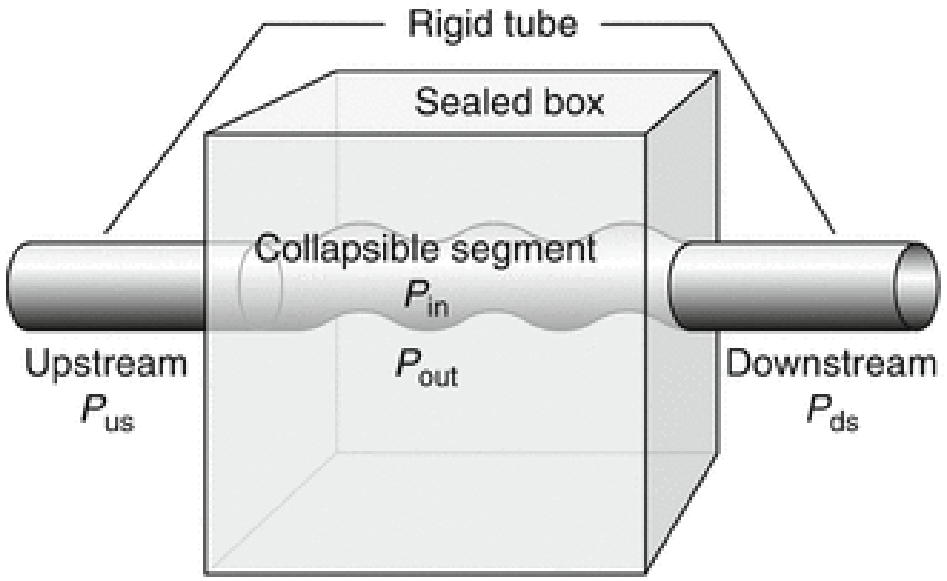
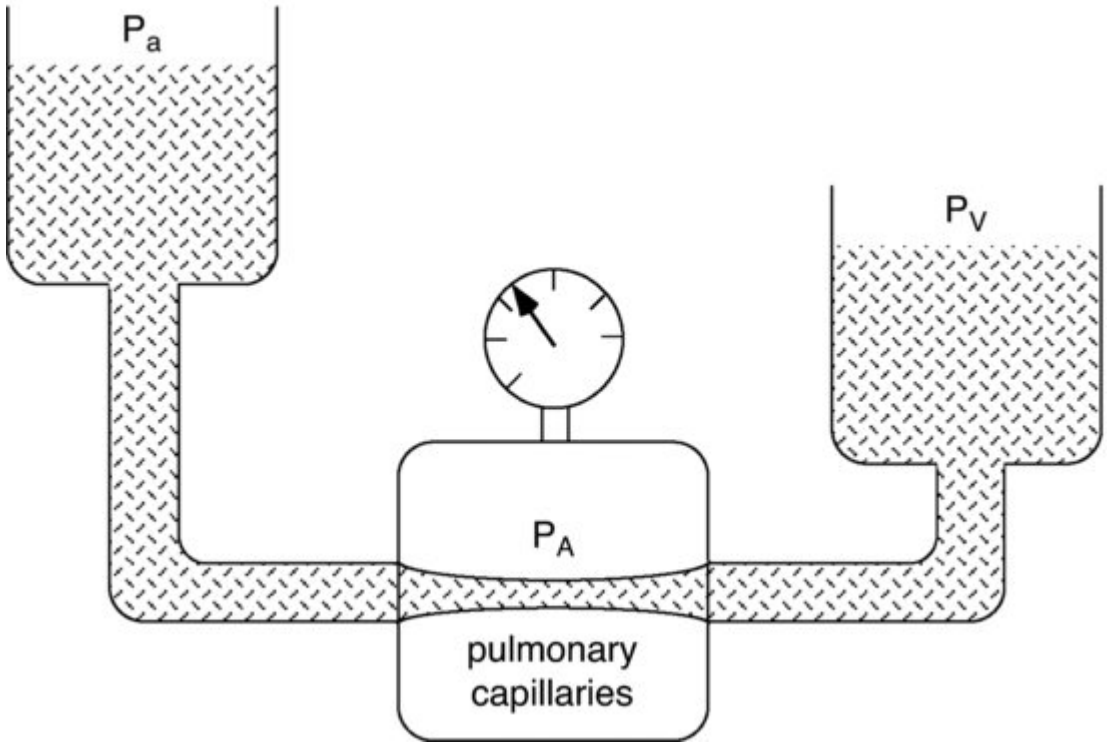
# „Starling resistor“ – effect of alveolar pressure on vessel diameter

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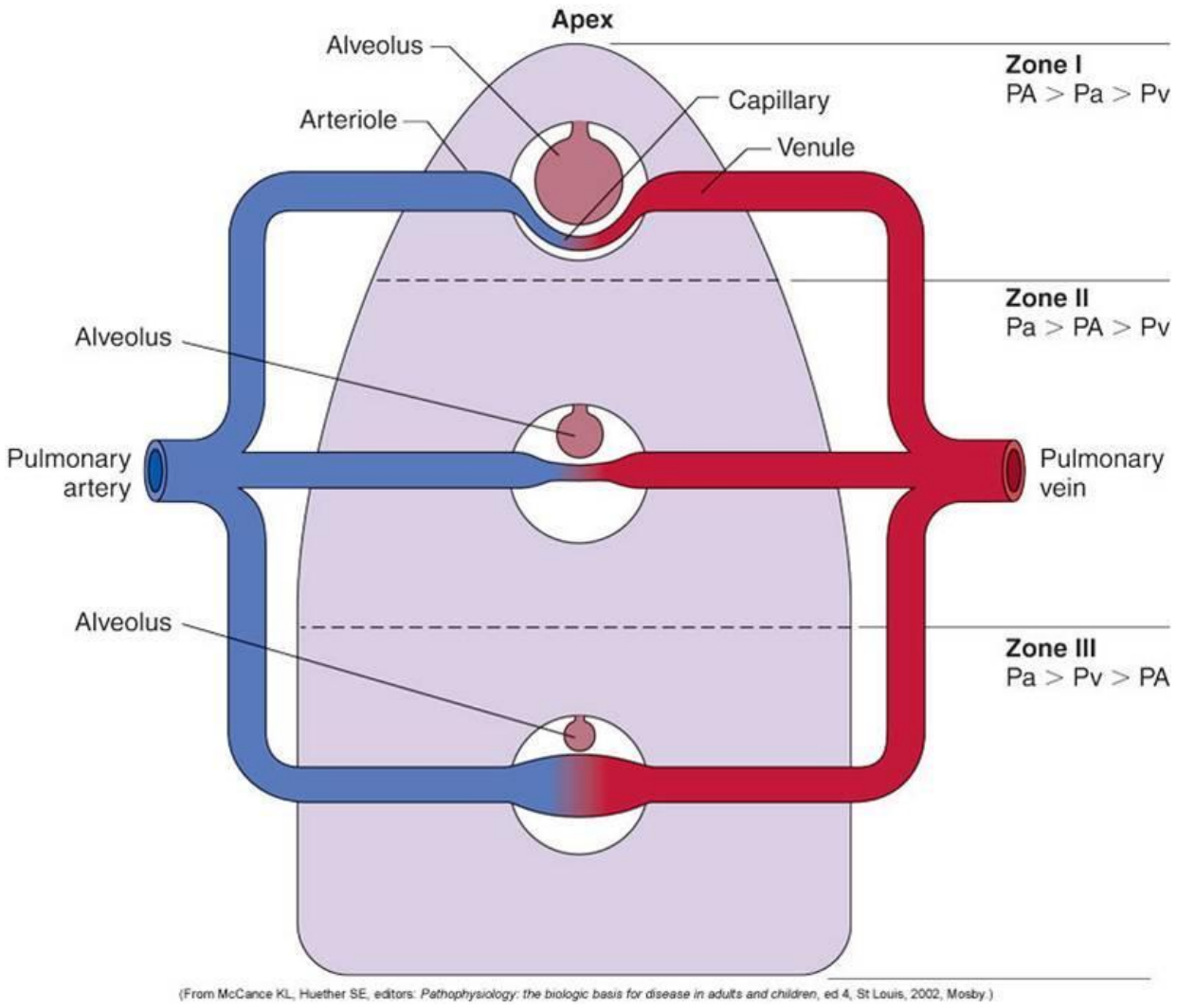
# Koncept plicních zón



(From McCance KL, Huether SE, editors: *Pathophysiology: the biologic basis for disease in adults and children*, ed 4, St Louis, 2002, Mosby.)

- zóna 1
  - u normální plíce (ve vzpřímeném postoji) prakticky neexistuje
  - patologicky se zvětšuje u
    - hypotenze/hypovolemie (např. krvácení)
    - mechanická ventilace plic s pozitivním přetlakem
- zóna 2
  - průtok je určen rozdílem Pa a PA a ne tlakovým gradientem Pa – Pv
  - patologicky se zvětšuje u
    - hypoventilace a dýchání s malým DO
- zóna 3
  - průtok je určen rozdílem Pa – Pv, protože oba jsou větší než alveolární tlak (PA)
  - patologicky se zvětšuje u
    - PH a atelektázy

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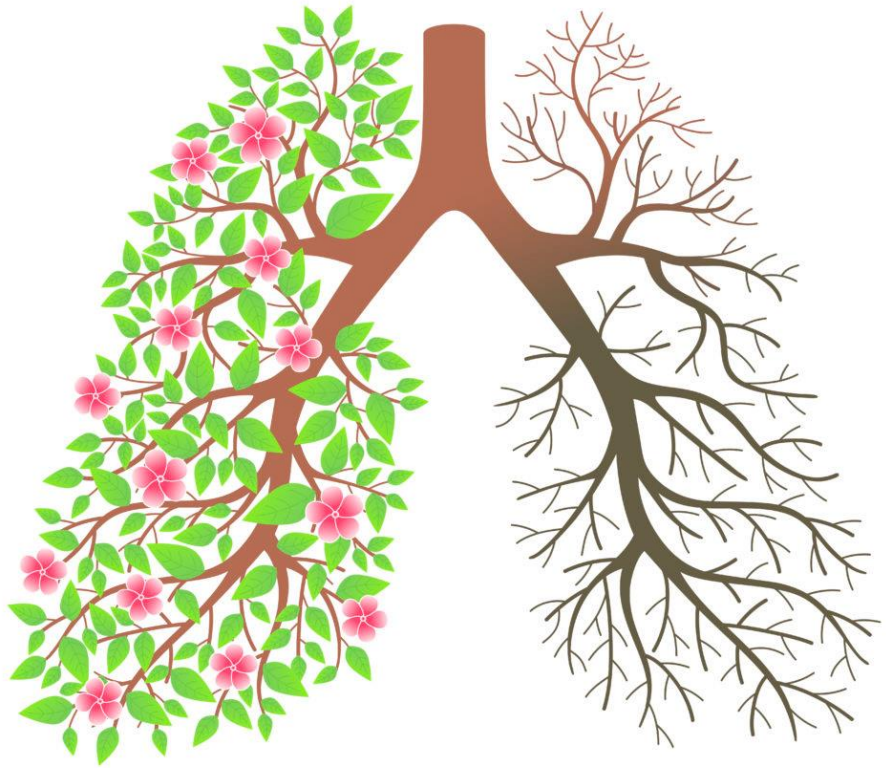

# PULMONARY HYPERTENSION

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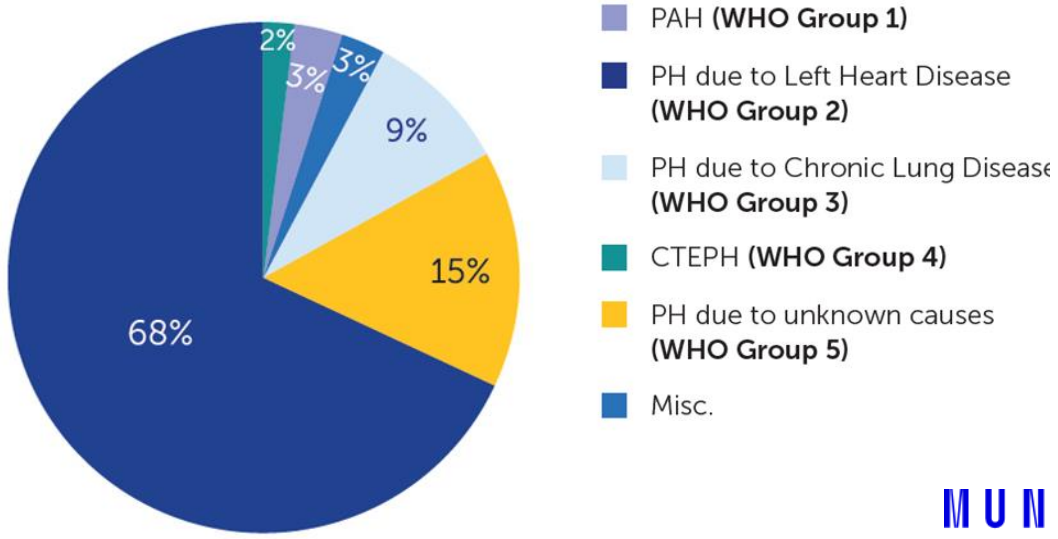
# Pulmonary hypertension (mPAP >25 mmHg) – diagnosis

- PH consists of a group of diseases with a resting mPAP ≥25 mmHg (≥25 mmHg during exercise)
  - initial diagnosis (or screening) by echocardiogram, however, Doppler estimates of PAP are inaccurate in many patients, and cannot be used to quantify RA, pulmonary venous, LA or LV pressures reliably
- PAP measured with right heart catheterization
- other parameters are necessary to classify and prognosticate patients appropriately
  - right ventricular end-diastolic pressure (RVEDP)
  - left ventricular end-diastolic pressure (LVEDP)
    - left heart catheterisation only in some patients (measurements of PV and LA pressure)
      - congenital heart defects or structural heart diseases
    - typically pulmonary blood flow and end-expiratory pulmonary artery wedge pressure (PAWP) commonly used as a surrogate of LVEDP

**Table 1: Classification Pulmonary Hypertension**

| | |
|---|---|
| Group 1 | Pulmonary Arterial Hypertension |
| Group 2 | PH from left-sided heart disease |
| Group 3 | PH from chronic hypoxic lung disease |
| Group 4 | PH from chronic blood clots |
| Group 5 | Unclear multifactorial mechanisms (sarcoidosis, hematological disorders, etc) |

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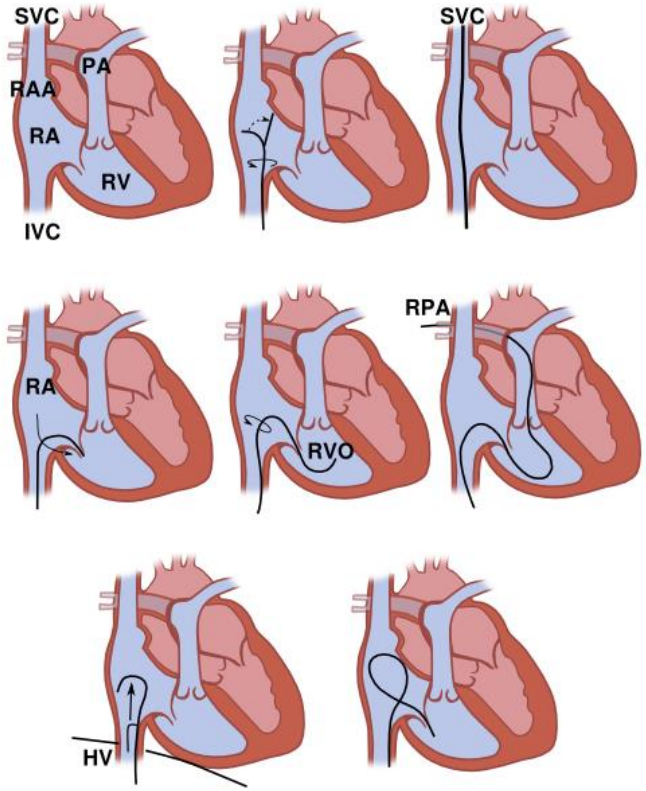
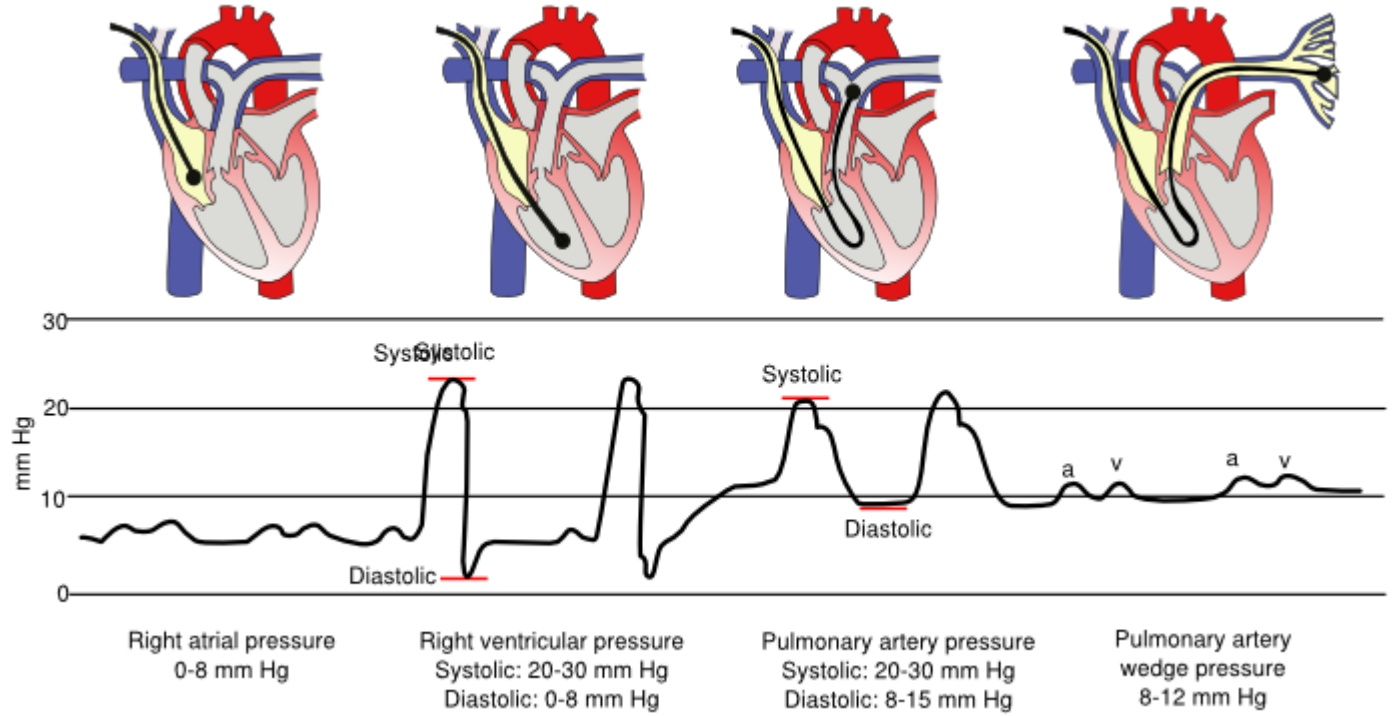
# Right heart (PA) catheterization

- precise assessment of pressure waves generated by the different cardiac chambers
- performed by pulmonary artery catheter (frequently referred to as a Swan-Ganz catheter) following local anaesthesia via the femoral, jugular, brachial or subclavian vein access

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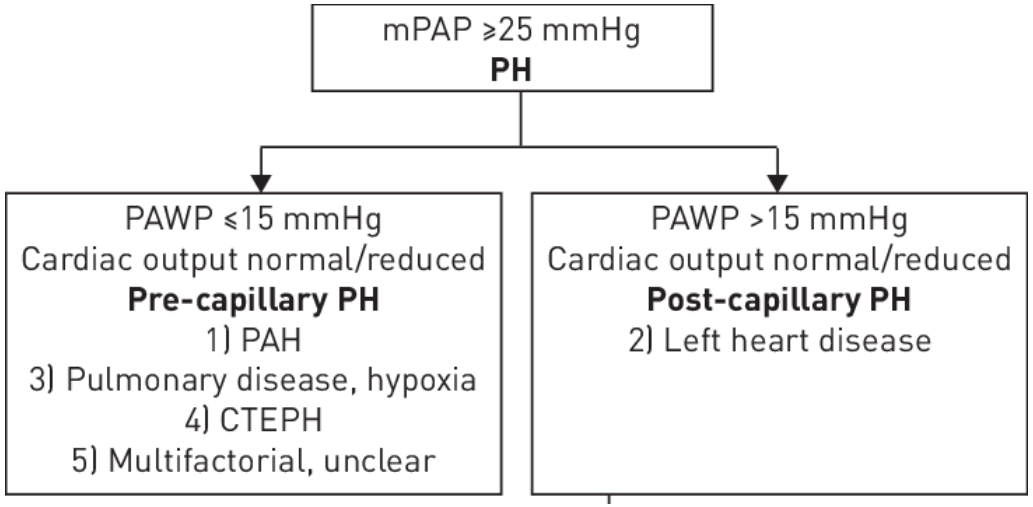
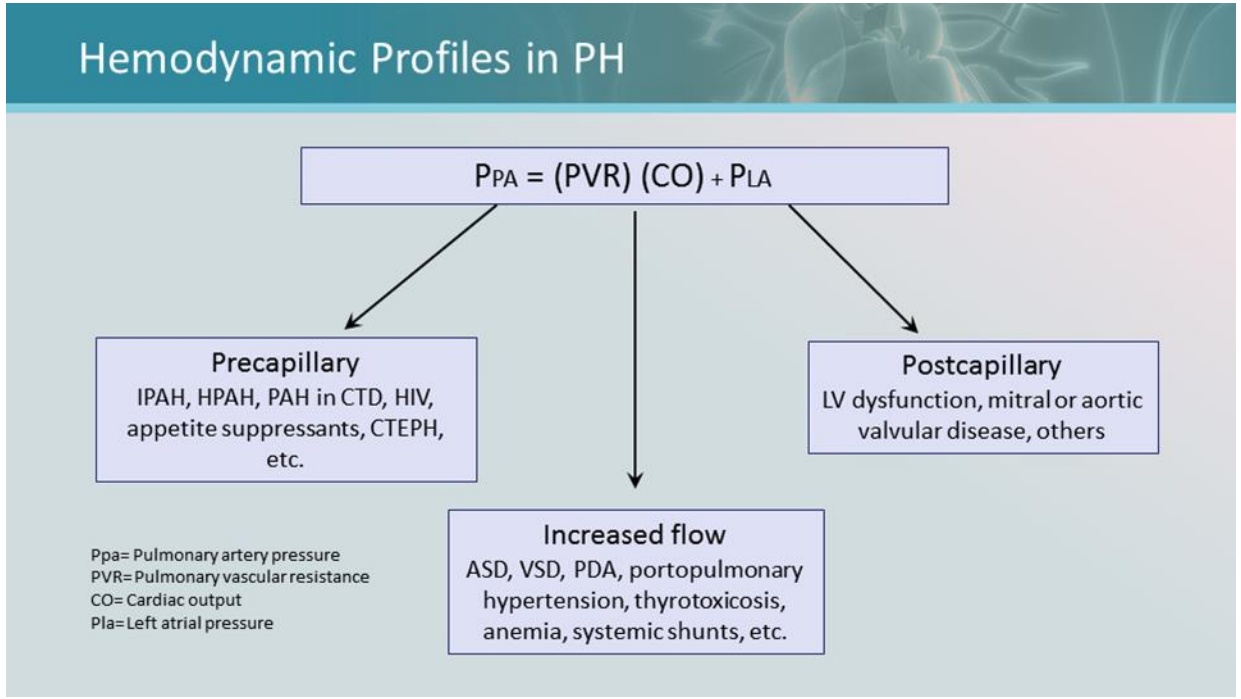
# Pulmonary hypertension (mPAP >25 mmHg) – pathogenesis

- pathogenesis is driven by **the triad of vasoconstriction, microthrombosis and remodelling of small pulmonary arteries**

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# Pulmonary hypertension (MPAP >25 mmHg) – classification

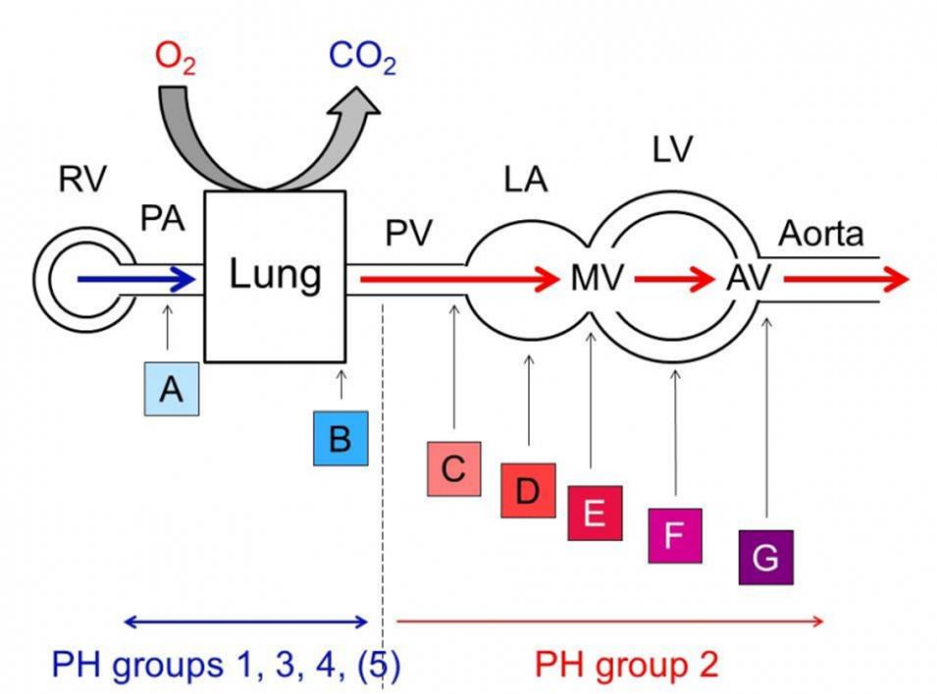
**Table 1. Clinical Classification of Pulmonary Hypertension**

| *Classification* | *Targeted treatment available?* |
|---|---|
| **Group 1*: Pulmonary arterial hypertension** | Yes |
| Including idiopathic, heritable, and HIV-associated; systemic sclerosis and other connective tissue disease; congenital heart disease; schistosomiasis; drug- and toxin-induced | |
| **Group 2: Pulmonary hypertension due to left heart disease** | No |
| Including systolic and diastolic dysfunction and valvular heart disease | |
| **Group 3: Pulmonary hypertension due to lung diseases and/or hypoxia** | No |
| Including chronic obstructive pulmonary disease, sleep-disordered breathing, and interstitial lung disease | |
| **Group 4: Chronic thromboembolic pulmonary hypertension** | Yes |
| **Group 5: Multifactorial pulmonary hypertension** | No |
| Including metabolic, systemic, and hematologic disorders (sickle cell disease), and others | |

*HIV = human immunodeficiency virus.*

**—Also includes 1′ (pulmonary venoocclusive disease and/or pulmonary capillary hemangiomatosis) and 1″ (persistent pulmonary hypertension of the newborn).*

*Information from references 3, 4, and 6.*




- A–G level of the haemodynamic obstruction/problem:
  - A pulmonary arteries and arterioles
    - pulmonary arterial hypertension (group I)
    - pulmonary hypertension associated with lung diseases (group III)
  - B pulmonary venules: pulmonary veno-occlusive disease
  - C pulmonary veins: PV stenosis
  - D left atrium: stiff LA
  - E mitral valve: mitral stenosis, mitral regurgitation
  - F left ventricle: heart failure with reduced ejection fraction, heart failure with preserved ejection fraction
  - G left ventricular outflow tract: aortic stenosis

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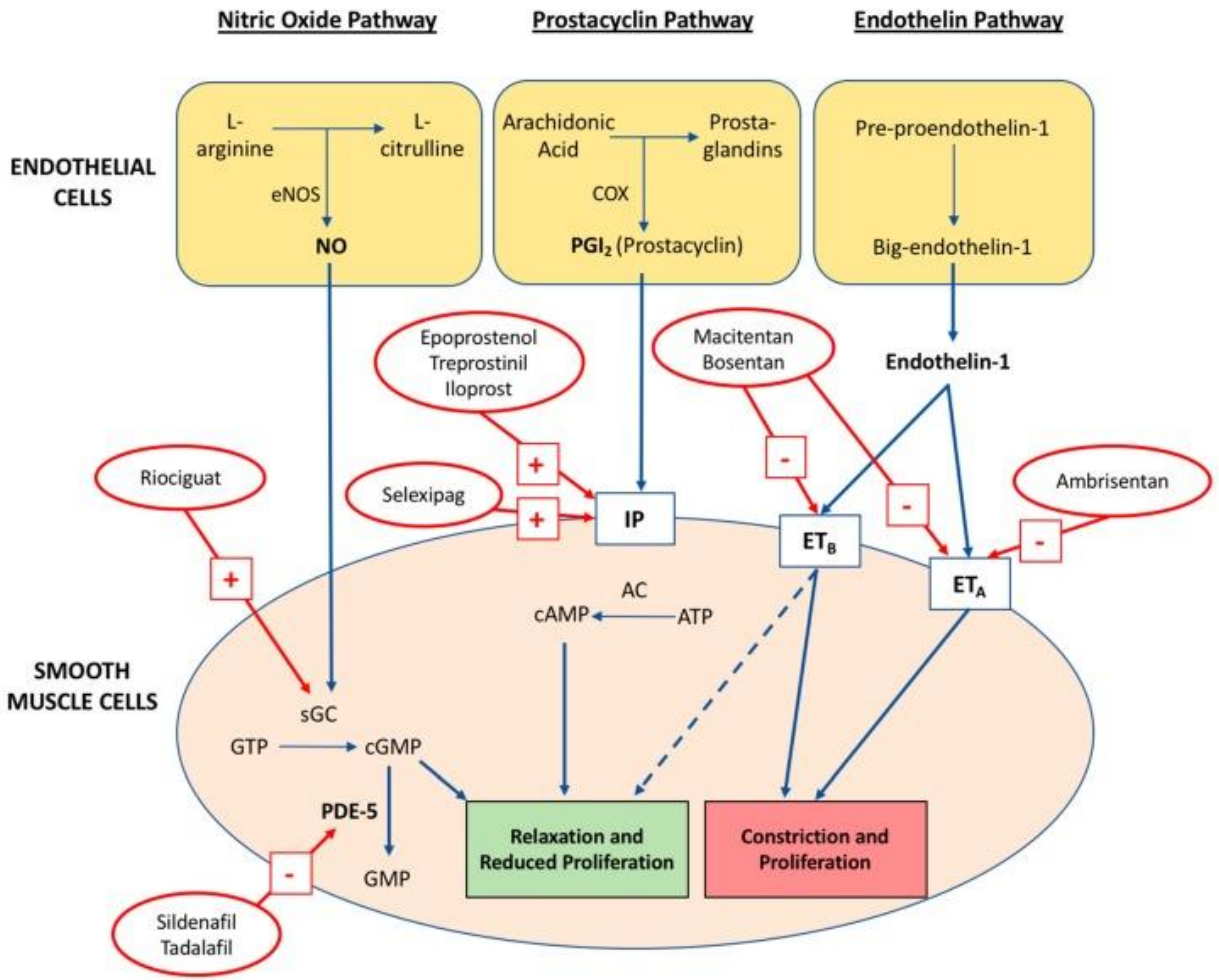
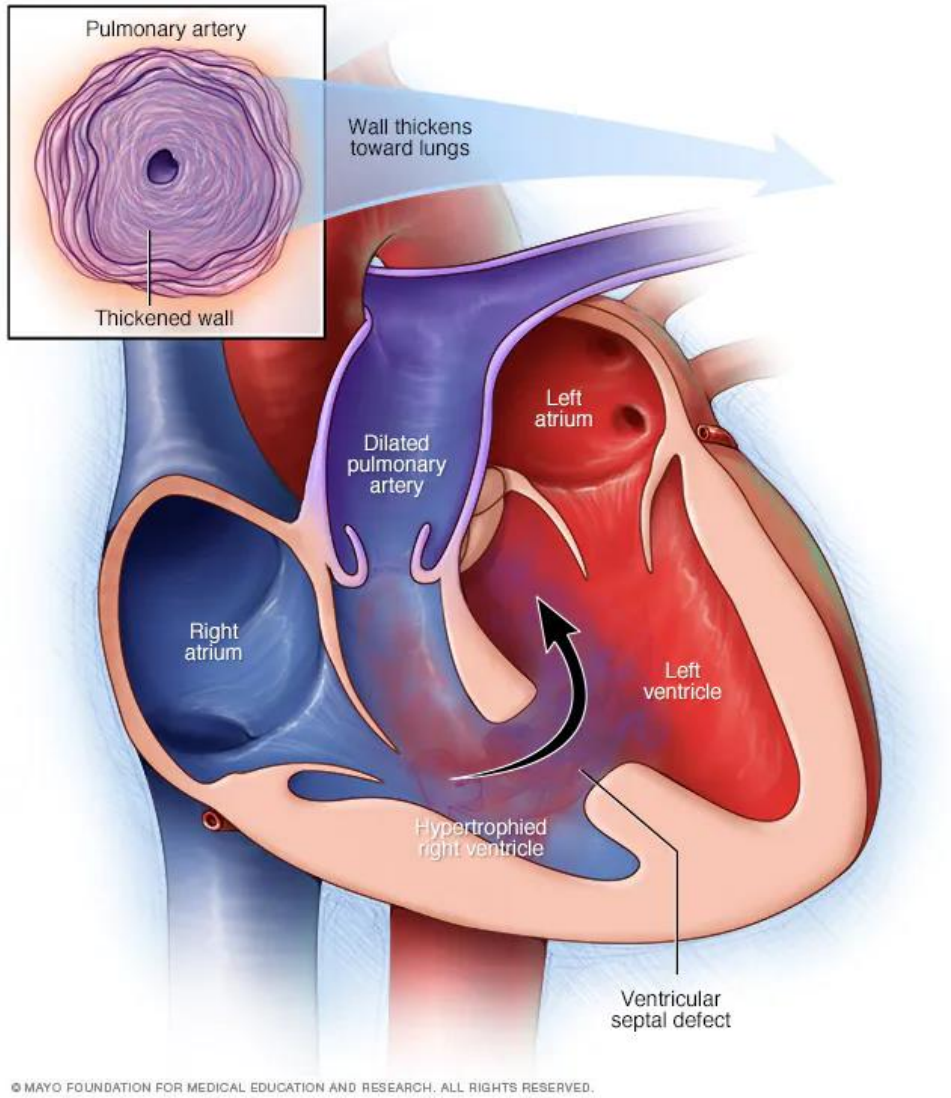
# Group 1: Pulmonary arterial hypertension (PAH)

- mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg (i.e. pre-capillary) and PVR > 3 Wood Units
- types of PAH
  - idiopathic (iPAH) comprising the majority of cases
    - iPAH has been found to be strongly associated with female gender, family history and genetic variants, especially bone morphogenetic protein receptor type 2 (*BMPRII*) mutations
  - secondary to
    - connective tissue diseases (CTD)
    - congenital heart disease - hyperkinetic
      - at the end might lead to Eisenmenger's syndrome
    - drugs, toxins, HIV, schistosomiasis, portal hypertension, …
- pre-capillary arterioles are affected by an angioproliferative vasculopathy that increases the PVR, thereby increasing the RV afterload with the resulting right heart failure being the ultimate cause of mortality
- management of PAH has advanced rapidly in recent years due to improved understanding of the pathophysiology revealing a disruption of three key signalling pathways
  - nitric oxide (NO)
    - phosphodiesterase 5 inhibitors (PDE-5i)
    - guanylate cyclase (GC) stimulators
  - prostacyclin ($PGI_2$) - thromboxane $A_2$ ($TXA_2$)
    - prostacyclin analogues and receptor agonists
  - endothelin-1 (ET-1)
    - endothelin receptor antagonists (ERAs) available as $ET_A$ selective or dual-action on $ET_A$ and $ET_B$ receptors



# PAH due to CHD – Eisenmenger's syndrome

- PAH develops in CHD patients as a result of increased pulmonary blood flow due to the presence of a left-to-right shunts
  - simple
    - atrial septal defect (ASD)
    - ventricular septal defects (VSD)
    - patent ductus arteriosus
  - complex
    - complete atrioventricular septal defect (AVSD)
    - truncus arteriosus
    - single ventricle
    - transposition of the great arteries with
- Eisenmenger's syndrome = reversal of the initial L-R shunt to the right-to-left (pulmonary-to-systemic) shunt due to remodelling of pulmonary vasculature





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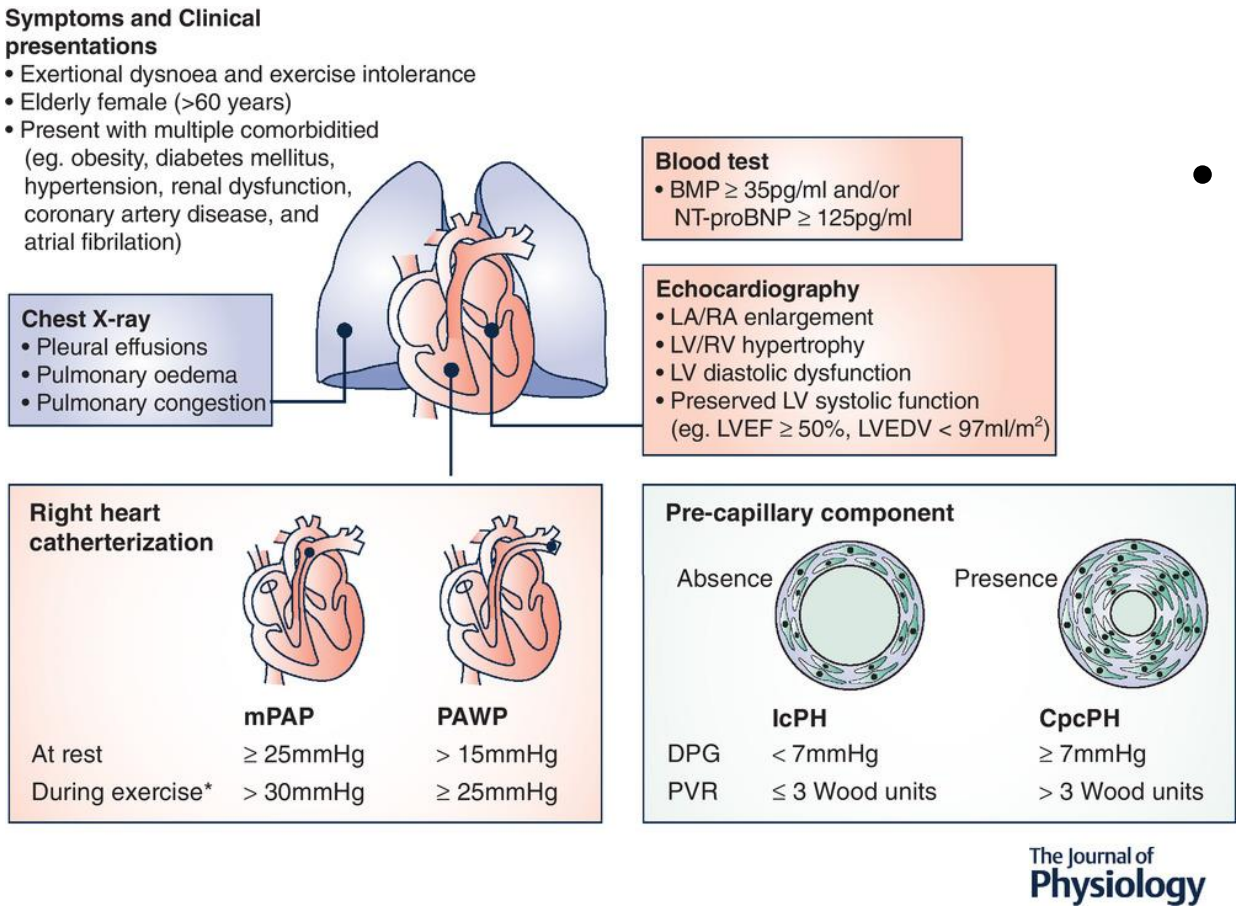
# Group 2: PH due to left heart disease (PH-LHD)




- mPAP ≥ 25 mmHg, PAWP > 15 mmHg (i.e. post-capillary) and PVR normal (< 3 Wood Units)
- causes
  - adult population
    - systolic or diastolic heart failure (HFpEF or HFrEF)
      - pulmonary vascular complications of heart failure with preserved ejection fraction
    - valvular disease
  - paediatric population
    - anatomical left-sided obstruction (e.g., valvar aortic stenosis, coarctation of the aorta, obstructive hypertrophic cardiomyopathy and others

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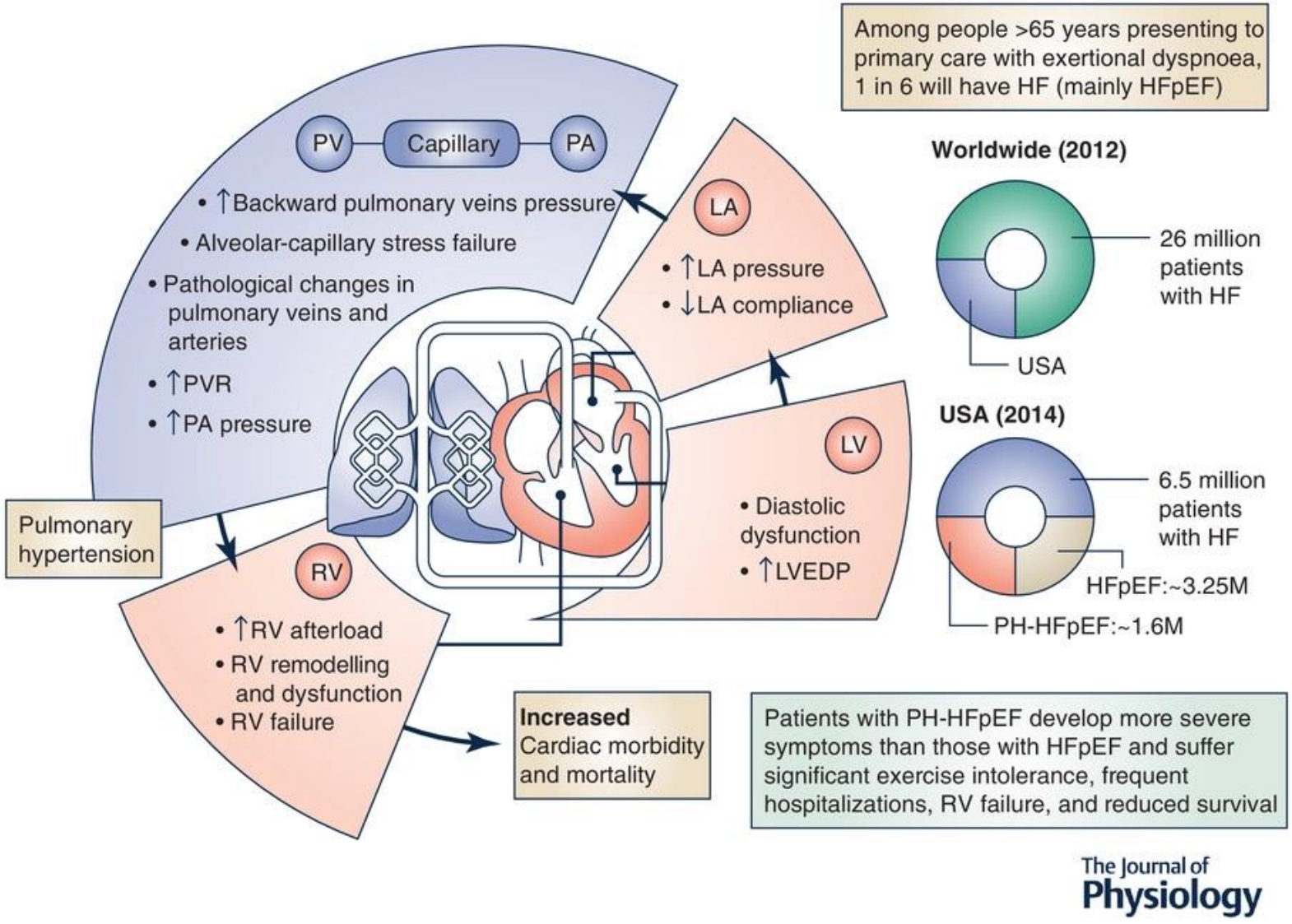
# Progression left heart disease to congestive heart failure

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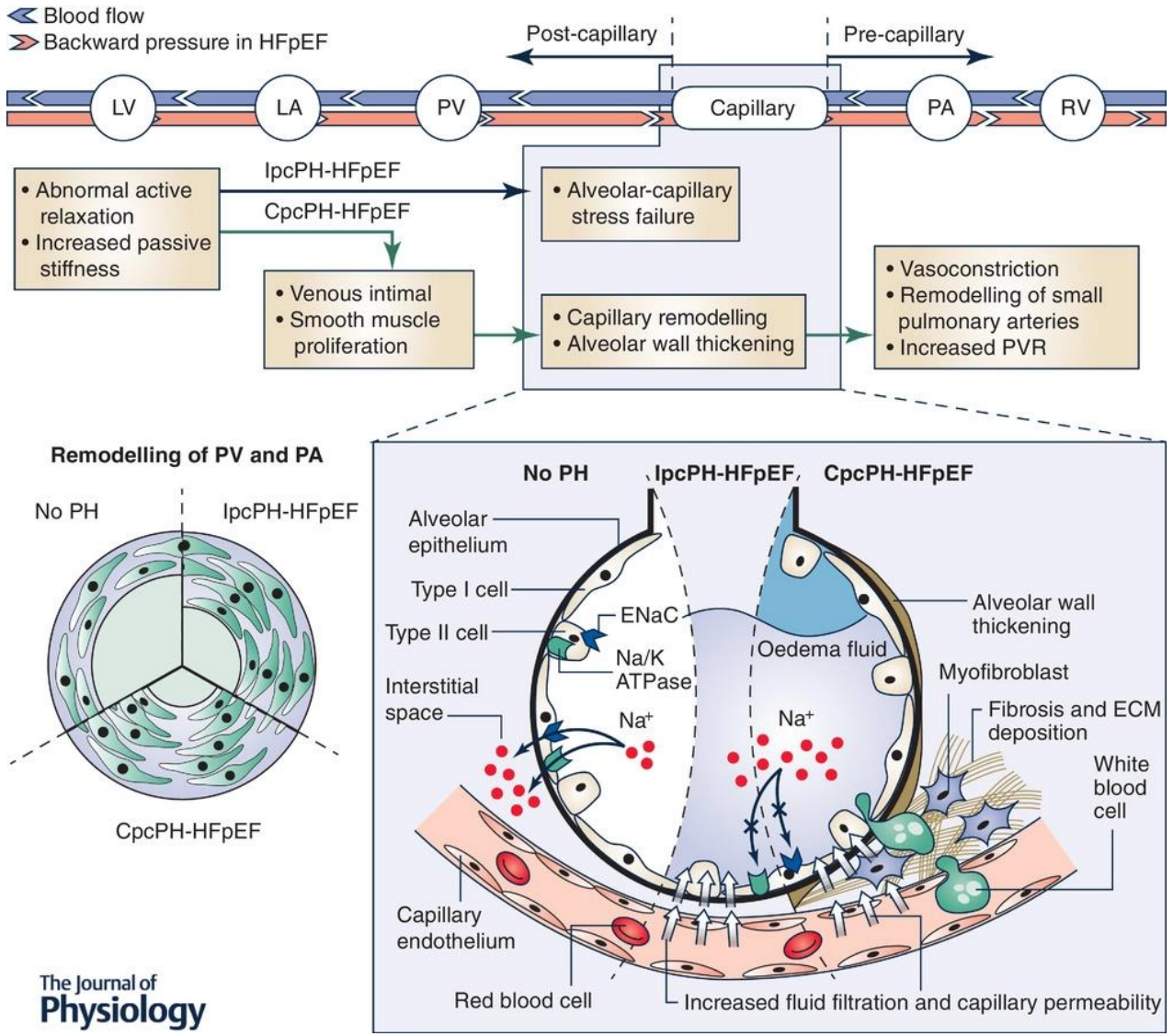
# Lung congestion can lead to oedema in LHD

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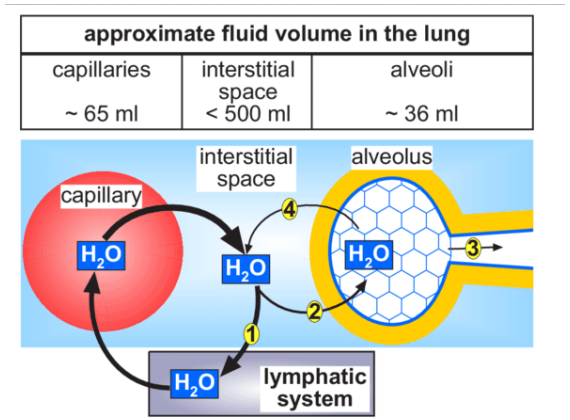
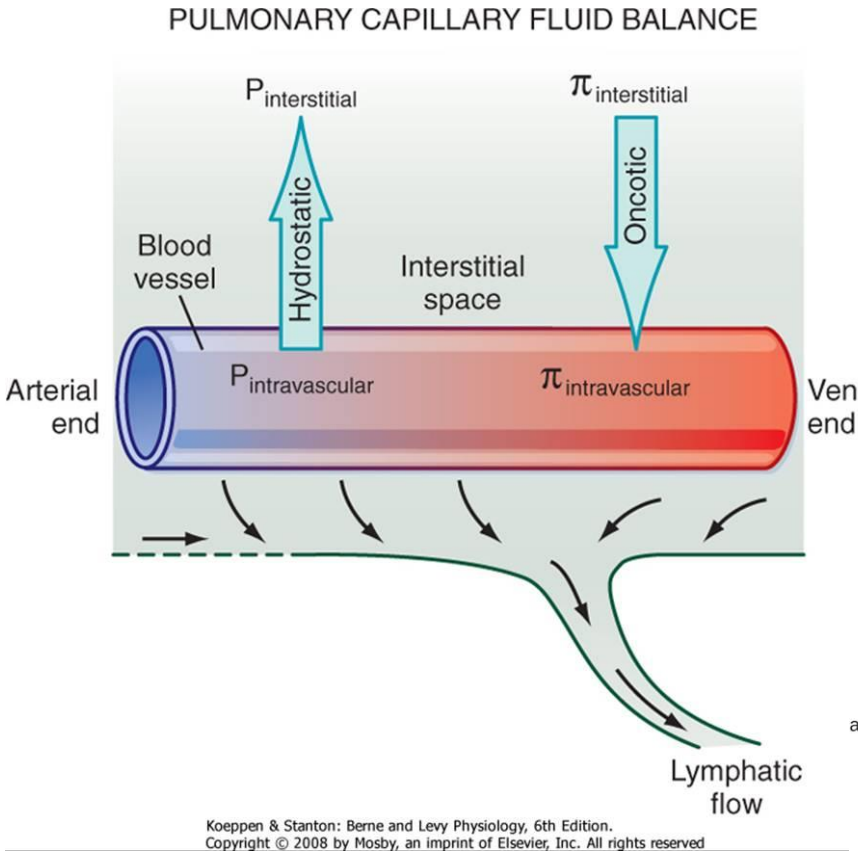
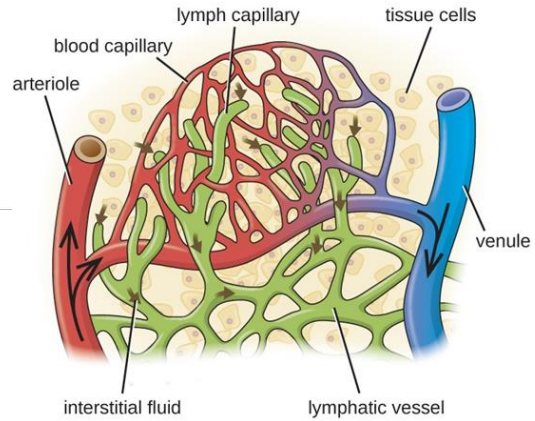
# Fluid balance in the lungs

- determined by
  - capillary hydrostatic pressure
    - low but still higher than pressure in the interstitium
  - colloid osmotic pressure
    - higher in capillaries than in interstitium, therefore opposes the hydrostatic pressure
  - capillary permeability (leakiness)
- in total, very small amount of fluid leaks into interstitial space and this amount is drained by lymphatics

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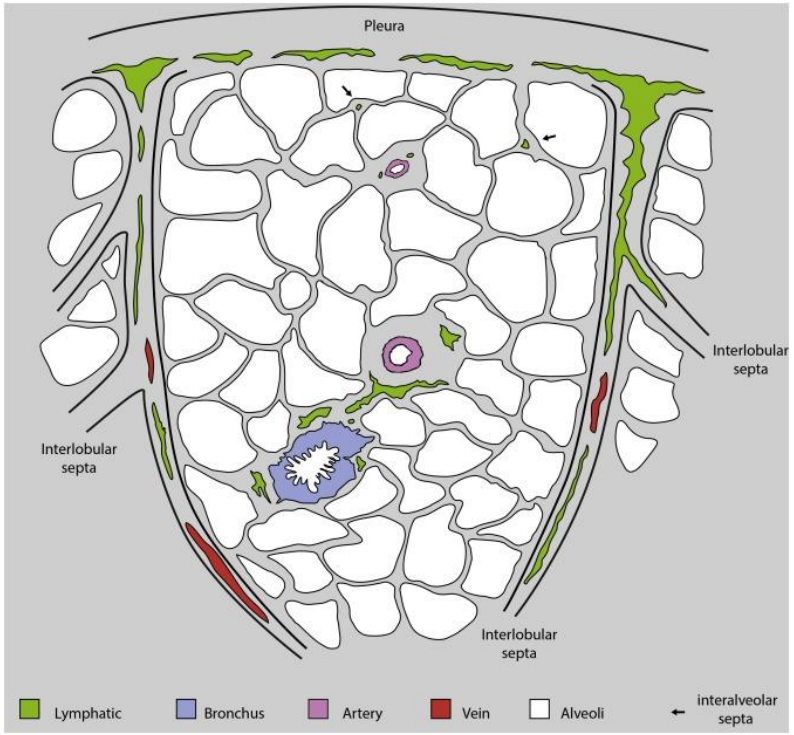
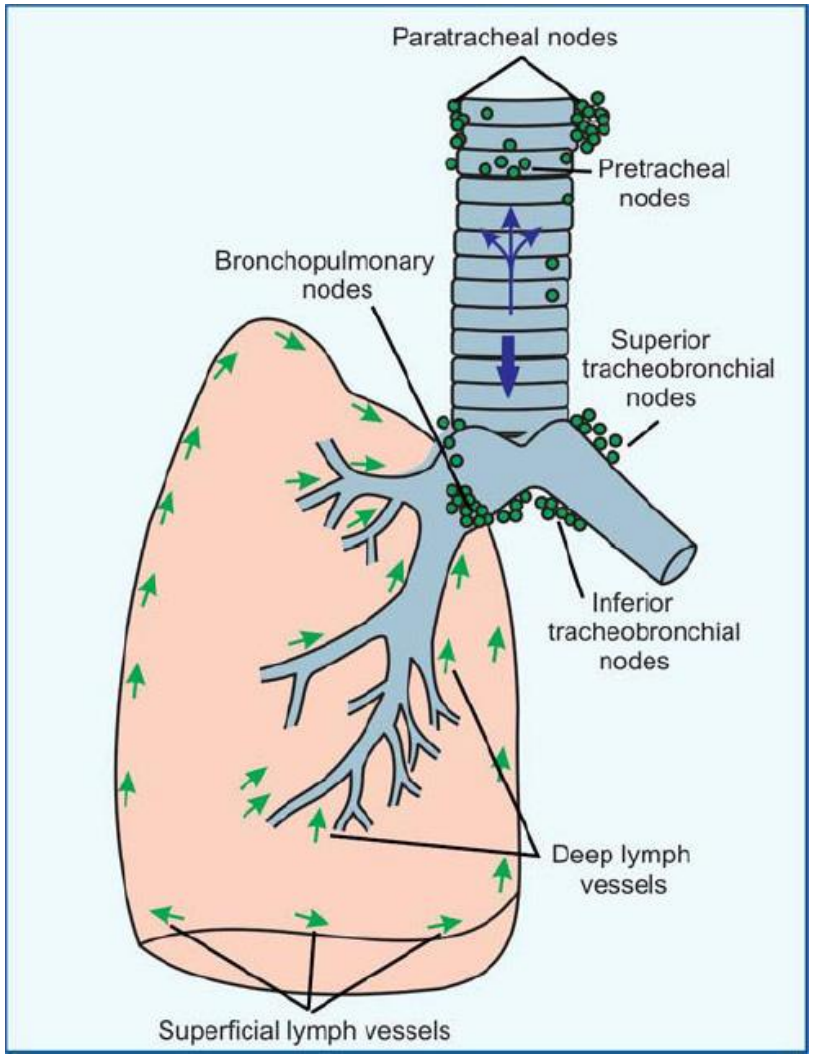
# Pulmonary lymphatics




- lymphatics start in the interstitial space between the alveolar cells and the capillary endothelium of the pulmonary arterioles
  - the tracheobronchial lymph nodes are arranged in five main groups:
    - paratracheal, superior tacheobronchial, subcarinal, bronchopulmonary and pulmonary

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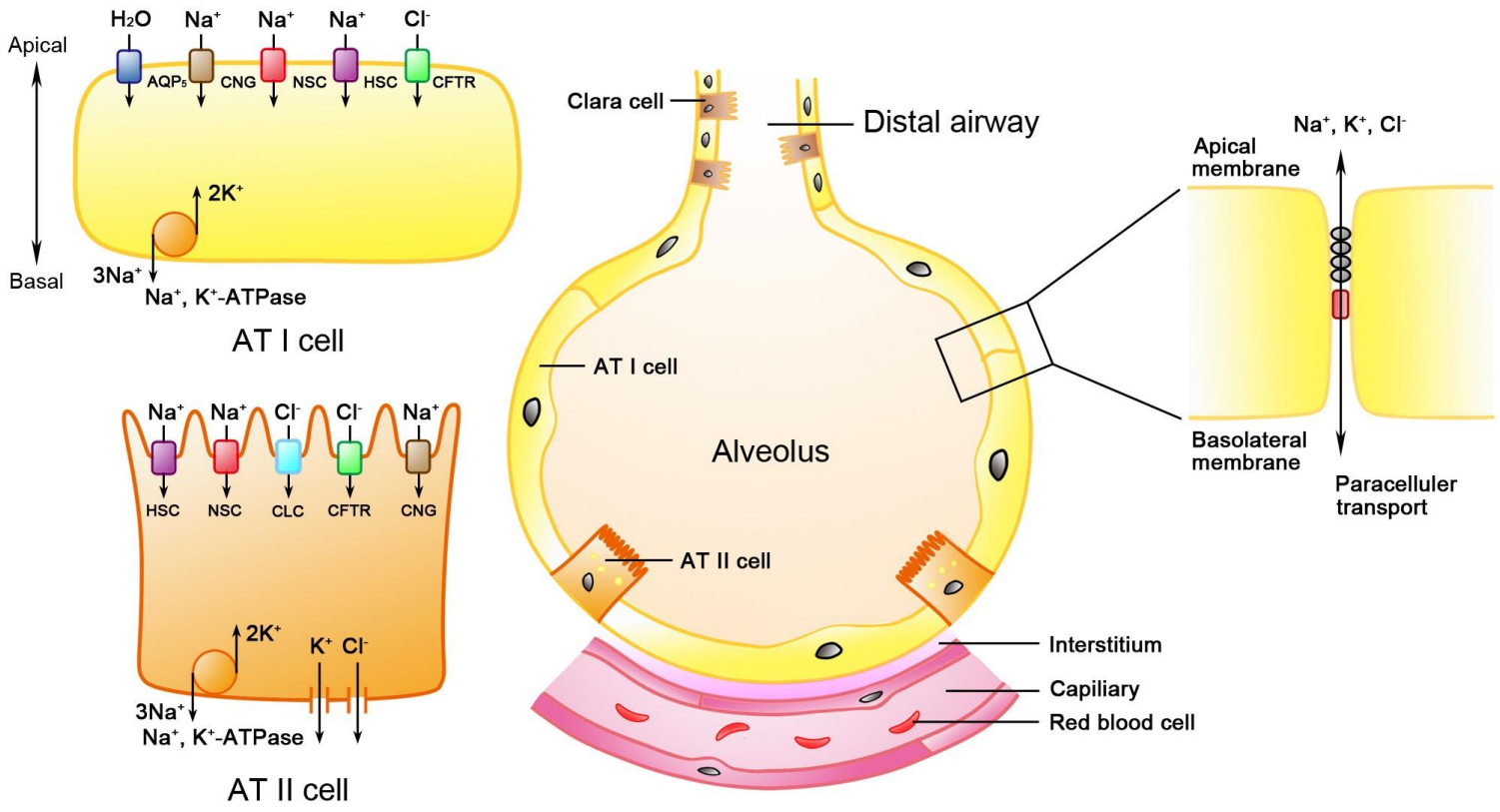
# Alveolar fluid clearance




- The alveolar epithelium is composed of squamous Alveolar Type I (AT I) and cuboidal Alveolar Type II (AT II) cells
- Both AT I and AT II cells contain amiloride-sensitive epithelial Na channels as well as Na+/K+-ATPase which are involved in alveolar transepithelial sodium transport
- In addition, AT I cells have aquaporin 5, which contributes to either water or gas exchange
- AT II cells have the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) and Chlorine (Cl-) channels, which mediate apical Cl- transport
- The tight junctions (a chain in grey between Alveolar Epithelial Cells (AECs)) and adherens junctions (in red between AECs) between adjacent alveolar epithelial cells provide a physical barrier from paracellular solute transport

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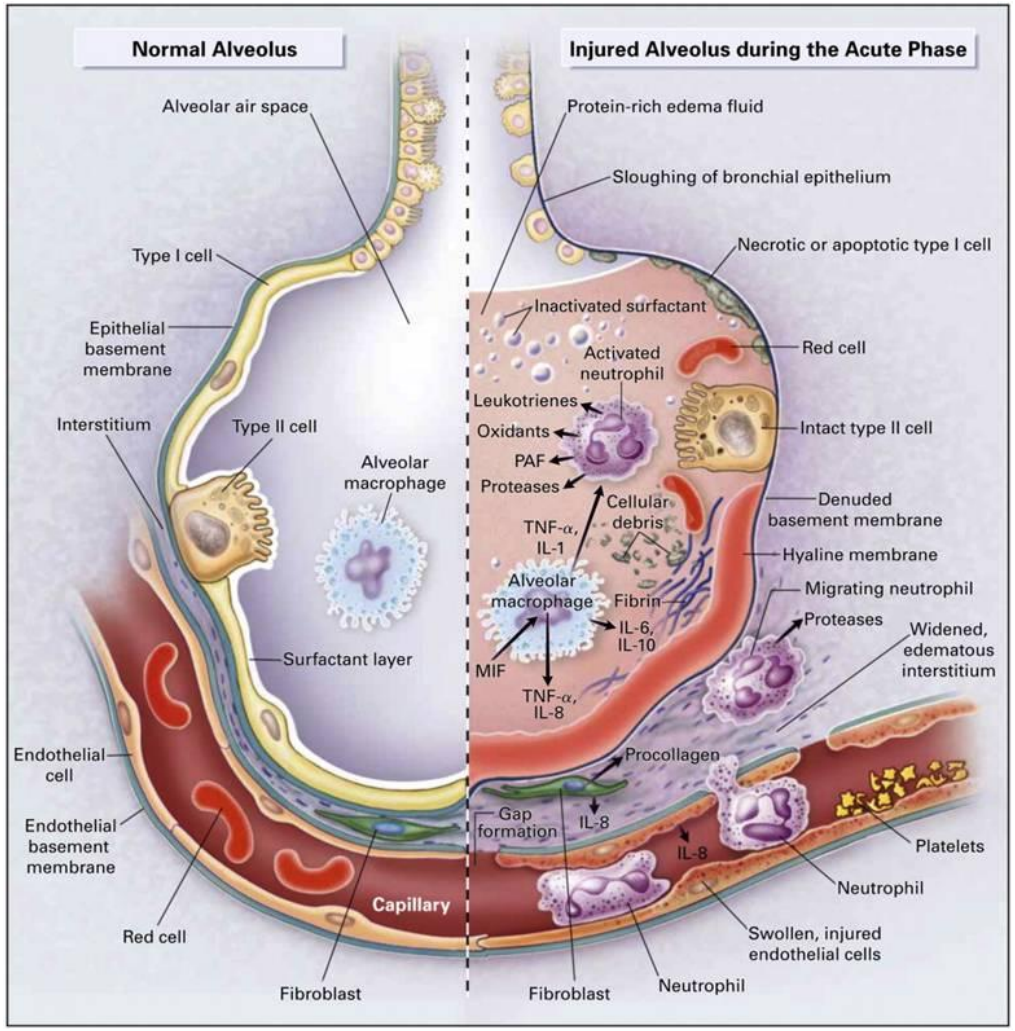
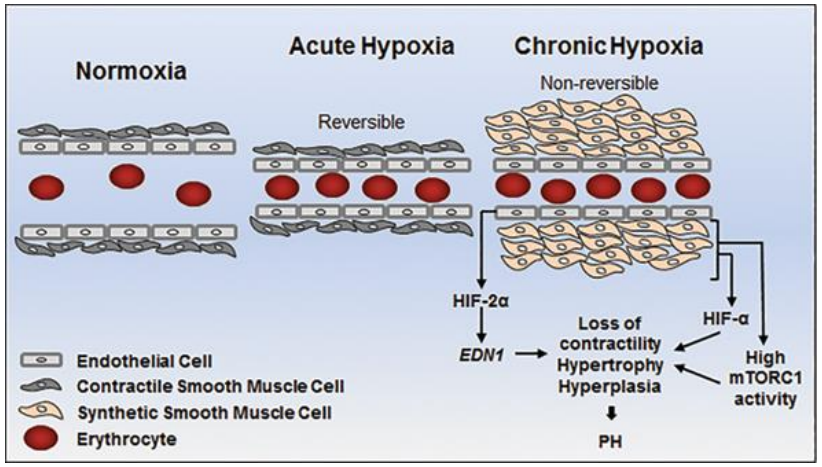
# Lung oedema

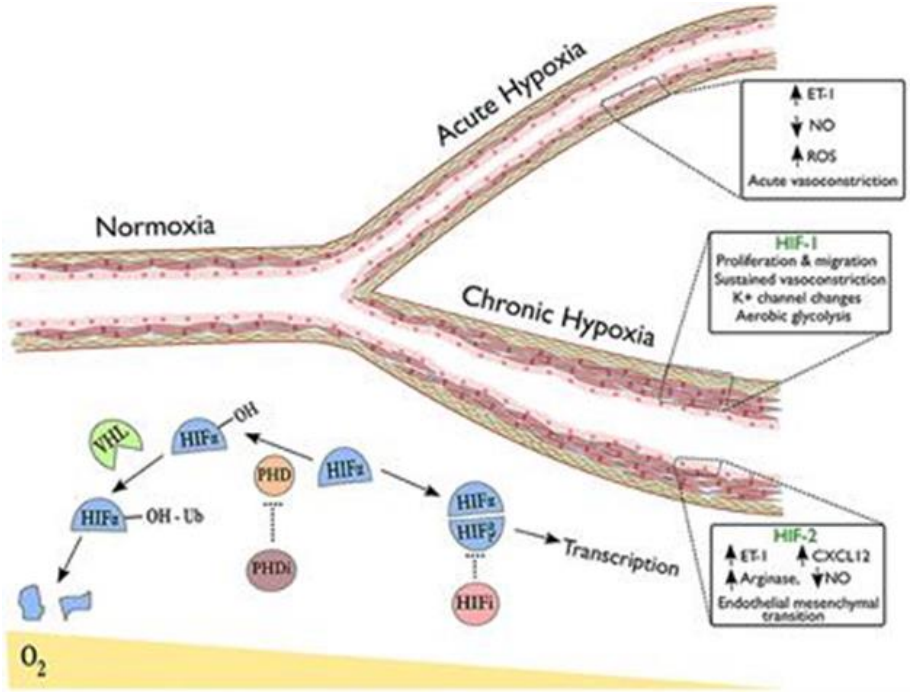
- interstitial or alveolar oedema
- cardiogenic
  - result of acute decompensation of left sided heart failure
    - commonly precipitated by fluid overload, rise in BP (hypertensive emergency), myocardial infarction, acute valvular disease, tachyarrhythmia, acute renal injury
- non-cardiogenic = direct injury to alveoli (inflammation) increasing capillary permeability
  - serious clinical form is denoted as acute respiratory distress syndrome (ARDS)
  - causes
    - external
      - pulmonary infection
      - inhalation of toxic substances or aspiration
      - chest trauma
    - internal
      - sepsis
      - low oncotic pressure
- consequences – an impaired gas exchange
  - diffusion impairment
  - change of lung compliance – intrinsic restrictive ventilation disease



# Group 3: PH due to lung disease and/or chronic hypoxia

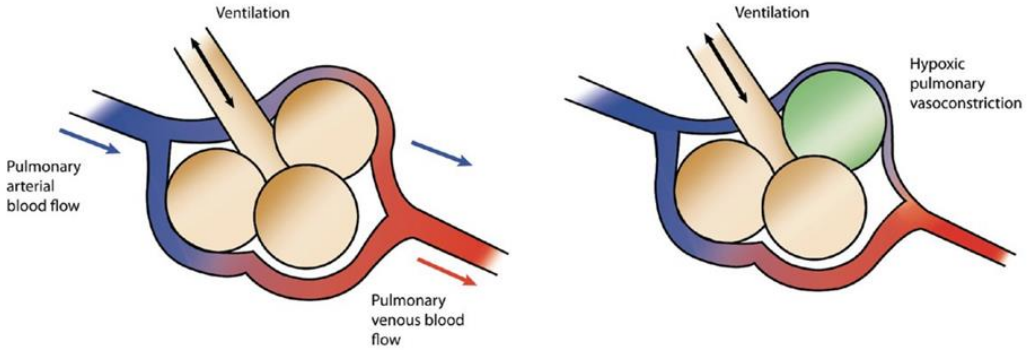
- causes - chronic
  - COPD
  - interstitial lung disease
    - scarring and inflammation in the lungs
  - overlap syndromes
  - conditions that cause hypoxemia
    - obstructive sleep apnea
    - alveolar hypoventilation disorders
  - chronic exposure to hypoxia – high altitude
- mechanisms (thin air = thick vessels)
  - acute hypoxia leads to vasoconstriction occurring due to alterations in redox and NO signaling and release of vasoactive mediators
  - vessel remodeling in the context of sustained hypoxic exposure due to HIF-dependent processes

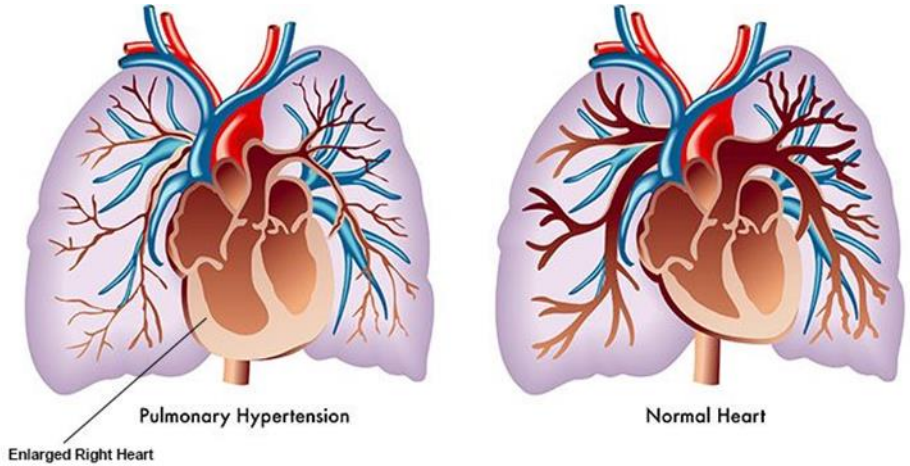


# Hypoxic pulmonary vasoconstriction (HPV)

- a physiological phenomenon in which small pulmonary arteries constrict in the presence of **alveolar hypoxia** (low oxygen levels)
  - as in **hypoventilation** and **low $V_A$/Q ratio**
    - typically in obstructive diseases (since these are chronic) resistant to compensatory hyperventilation such as chronic bronchitis
- a homeostatic mechanism that is intrinsic to the pulmonary vasculature
  - intrapulmonary arteries constrict in response to alveolar hypoxia, diverting blood to better-oxygenated lung segments, thereby **optimizing ventilation/perfusion matching and systemic oxygen delivery**
    - chronically happens with low V/Q ratio (and event. in long-lasting hypoventilation)
- mechanisms involve (in brief)
  - in response to alveolar hypoxia, a mitochondrial sensor dynamically changes reactive oxygen species and redox couples in pulmonary artery smooth muscle cells (PASMC)
  - this inhibits potassium channels, depolarizes PASMC, activates voltage-gated calcium channels, and increases cytosolic calcium, causing vasoconstriction
  - sustained hypoxia activates rho kinase, reinforcing vasoconstriction, and hypoxia-inducible factor (HIF)-1α, leading to adverse pulmonary vascular remodelling and **pulmonary hypertension** (PH)
  - this pre-capillary PH leads to right heart remodelling – **cor pulmonale**

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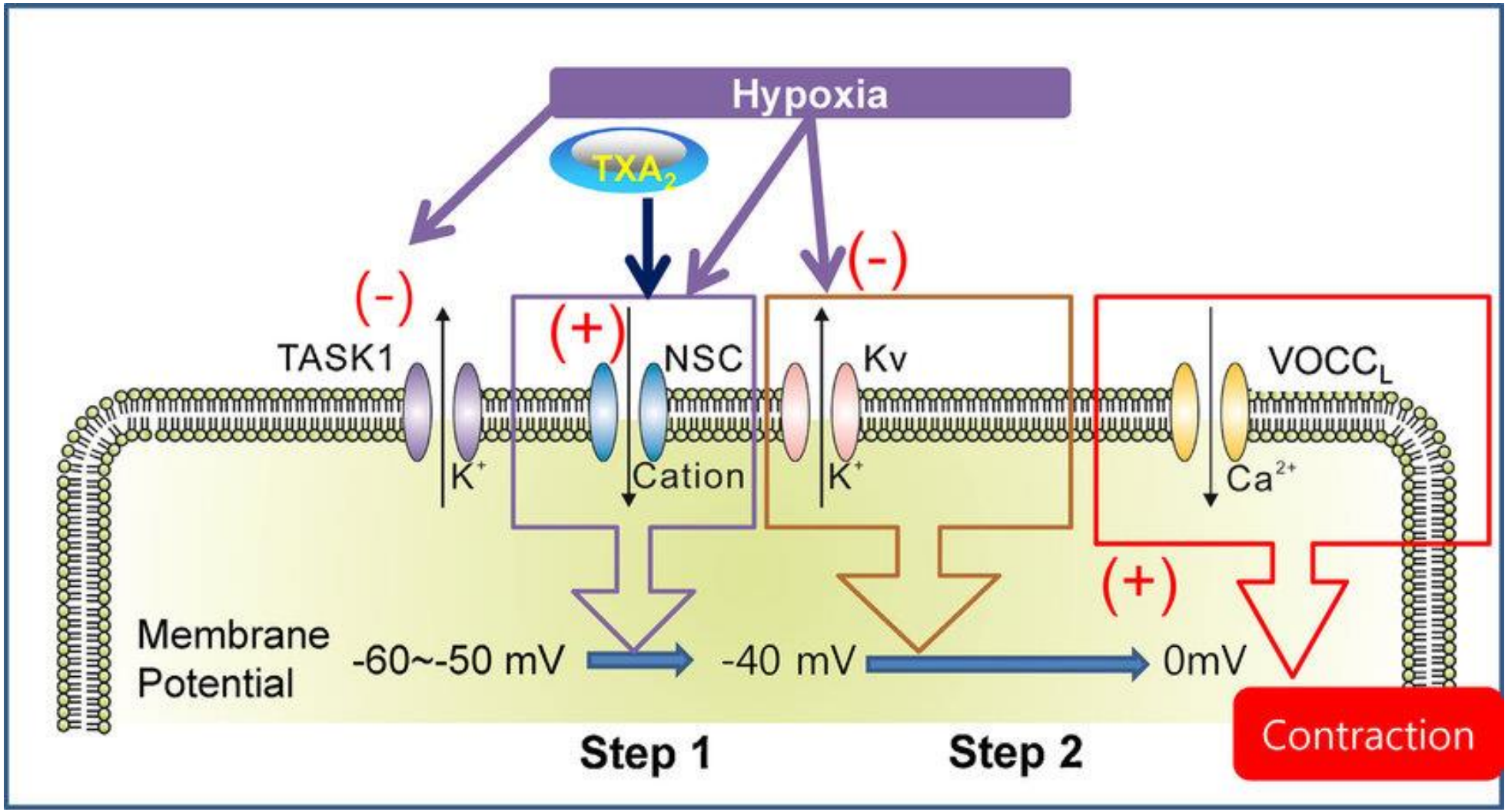
# Mechanism of HPV




The current model of the cellular mechanism of hypoxic pulmonary vasoconstriction in a rat pulmonary artery (PA). Relevant ion channels are displayed. Under normoxia, the membrane potential of the smooth muscle of the PA is held at approximately −50 mV because of the TASK-like background current of a K + channel. Hypoxic conditions initially decrease TASK activity. When combined with TXA 2 , activation of NSC induces membrane depolarization up to the threshold voltage for activation of K v channels (Step 1). In addition to the NSC activation, hypoxic inhibition of the K v current further depolarizes the membrane potential (Step 2). As the membrane potential depolarizes above −40 mV, the activation of VOCC L eventually allows for Ca 2+ influx for contraction of smooth muscles. K v , voltage-gated K + channel; NSC, nonselective cation channel; TASK-1, background-type K + channel with a two-pore domain (K2P); TXA 2 , thromboxane A 2 ; VOCC L , voltage-gated L-type Ca 2+ channels.

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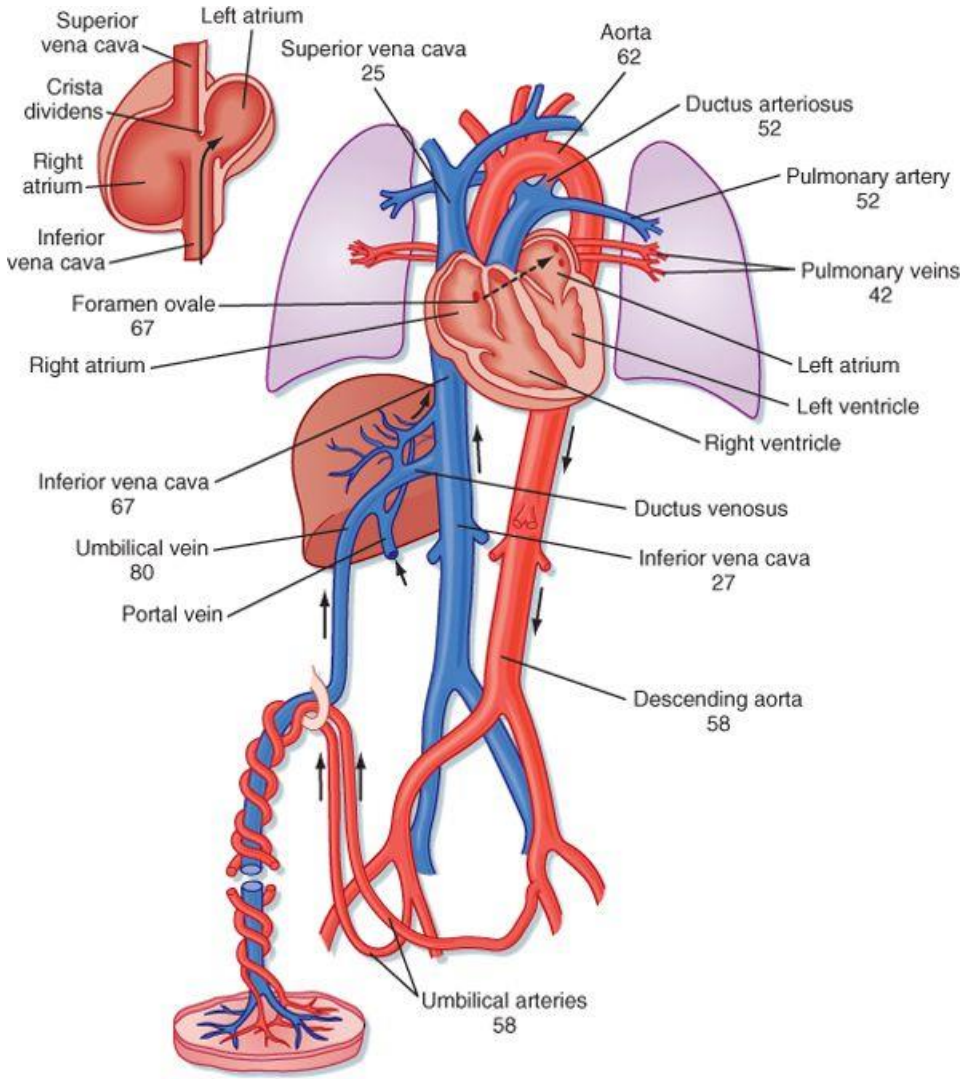
# Primary role in non-ventilated foetal lung where HPV diverts blood to the systemic vasculature






- at birth
  - lung inflation and reaching stable volumes
    - surfactant
  - pulmonary blood flow
    - increase of alveolar $P_AO_2$ relieves HPV and leads to vasodilation
      - subsequent circulatory changes (closure of foetal shunts)
  - resorption of fluid from alveoli
    - role of pneumycytes

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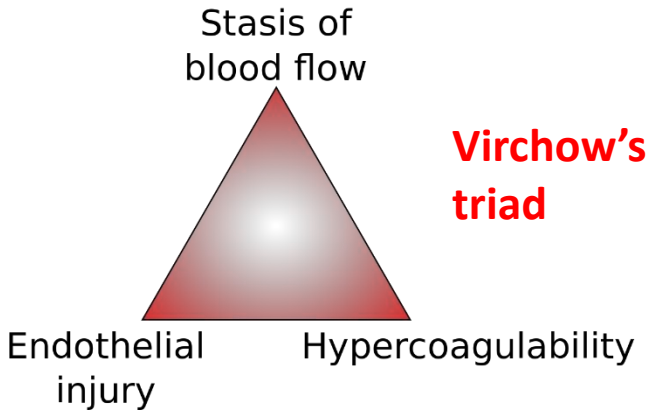
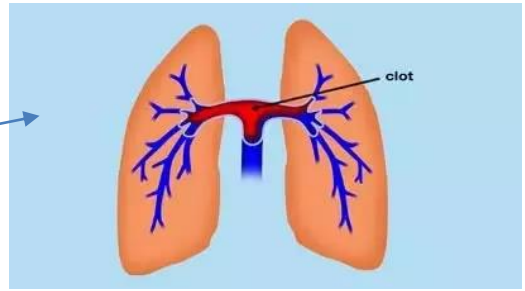
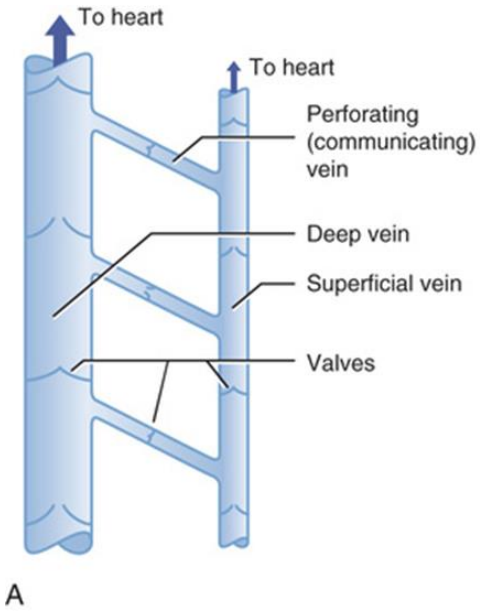
# Group 4: Chronic thromboembolic PH (CTEPH)

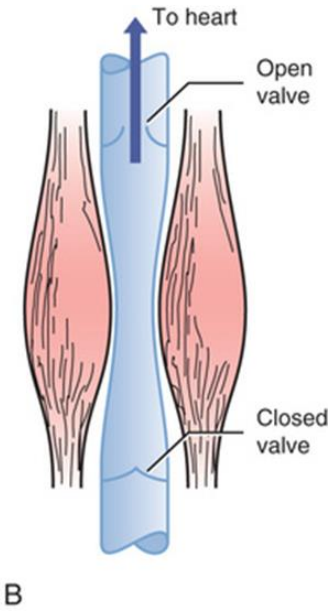
- ~50% of CTEPH patients never have had a specific episode of thrombosis that they recall
  - meaning typically deep vein thrombosis (DVT) event. followed by pulmonary embolism
    - DVT frequency: calf, popliteal, femoral, pelvic, portal, hepatic (Budd-Chiari sy), renal vein in nephrotic sy
    - PE frequency: femoral (and other above knee)
  - dg. venous duplex US + d-dimers (active fibrinolysis)
  - superficial thrombophlebitis might co-exist with DVT!
  - PE severity
    - acute – small, sub-massive and massive (haemodynamic instability)
      - saddle PE
    - chronic
- it is therefore important to rule out CTEPH on every PH patient as it is a potentially curable disease
  - pulmonary angiogram
  - perfusion (V/Q) scan




**Virchow's triad**

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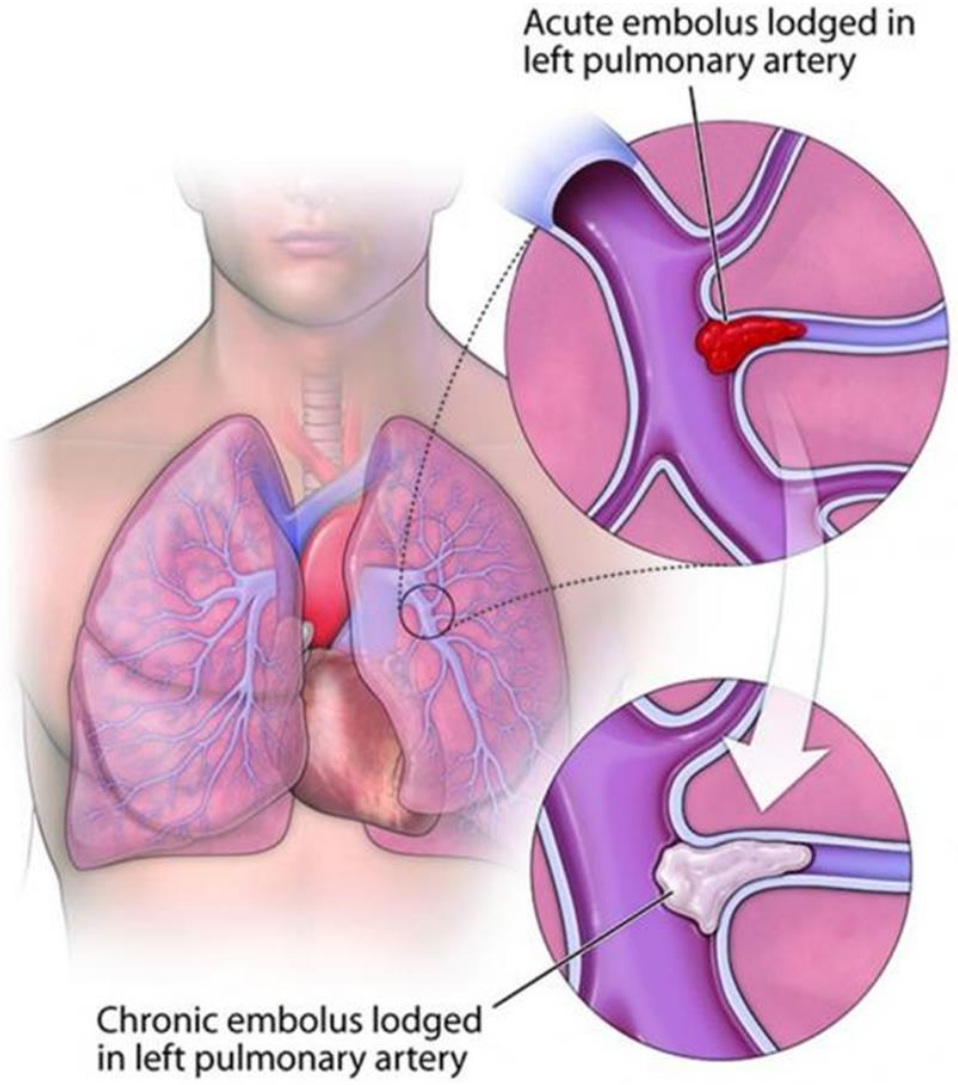
# CETPH




- 3%-5% of all PE cases due to organised blood clot following
  - acute PE
  - recurrent PE (successive)
- treated invasively by
  - pulmonary thromboendarterectomy (PTE)
  - percutaneous balloon angioplasty
  - lifelong anticoagulation

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