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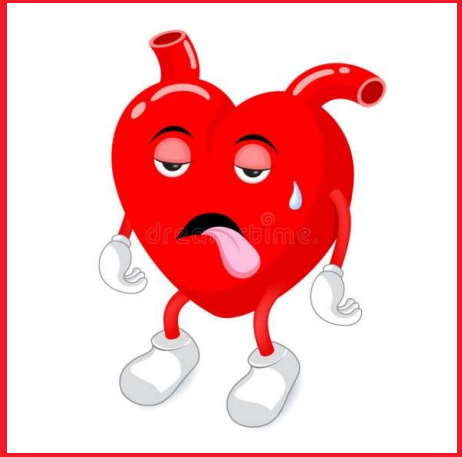
PATOPHYSIOLOGY OF HEART FAILURE



Lékařská fakulta Masarykovy univerzity

Heart as a pump

- Heart is a central organ of circulatory system
- Heart ejects blood into systemic and pulmonary arteries
- It removes blood from vena cava superior et inferior as well as from pulmonary arteries

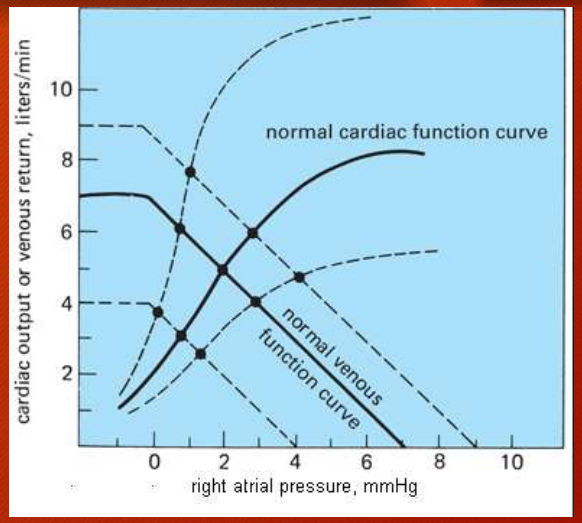
CO = SV (stroke volume) × f

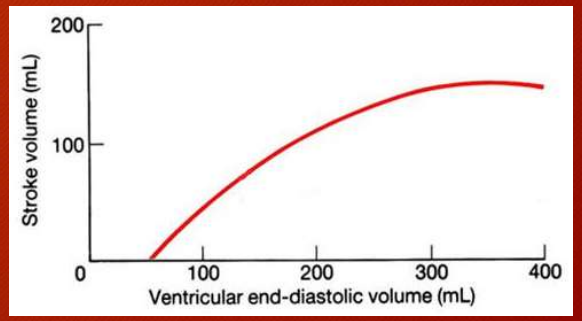
SV = EDV (enddiastolic volume) – ESV (endsystolic volume)

EF [%] = SV/EDV

Cardiac output has to match a venous return (↓CO in hypovolemic shock)

Frank-Starling mechanism: stretching of muscular fibres increases the force of muscular contraction (up to a peak – force decreases with further stretching – Starling curve SV/EDV)



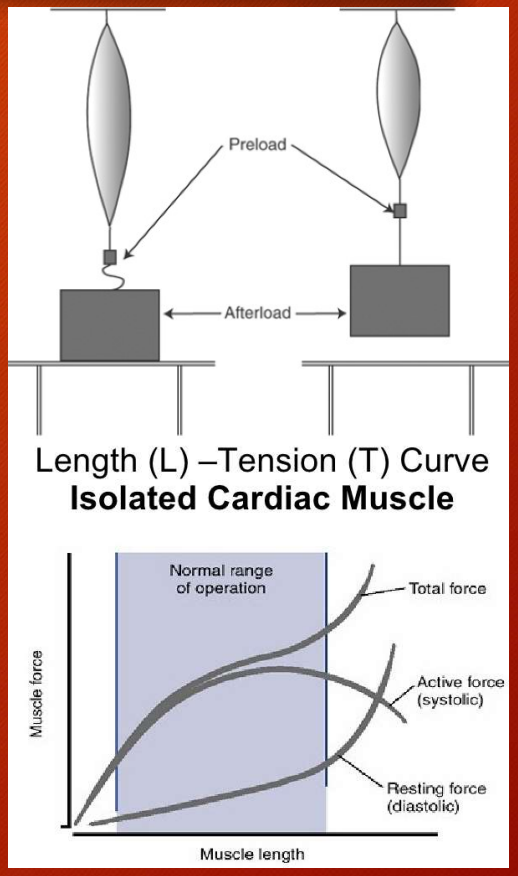


Mechanisms leading into heart failure

- Extracardiac causes
  - ↑ preload
  - ↑ afterload
- Primary – cardiac causes
  - systolic dysfunction(↓ inotropy)
  - diastolic dysfunction (↓ lusitropy, tachycardia)
  - bradycardia
  - ↑ preload and/or afterload (valvular disorders and shunts)

Preload and afterload in a muscular fibre

- Preload – force needed for keeping of muscle tension before the start of muscle shortening (isometric phase)
- Afterload – force needed for isotonic contraction
- Compared to skeletal muscle, cardiac muscle has much higher passive stretch force – during overstretching, the active force of contraction decreases, but the passive force increases – the resulting length-force curve is increasing
  - This also works in skeletal muscle, but the passive force is negligible in its working range, therefore, overstretching leads into the loss of total force



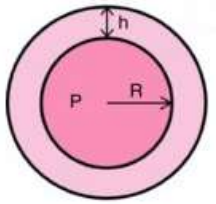
Preload and afterload in the heart

- Law of Laplace for wall tension in a hollow sphere: $\sigma = \frac{P \times r}{2h}$, where:

  P….pressure inside the sphere

  r….inner radius of the sphere

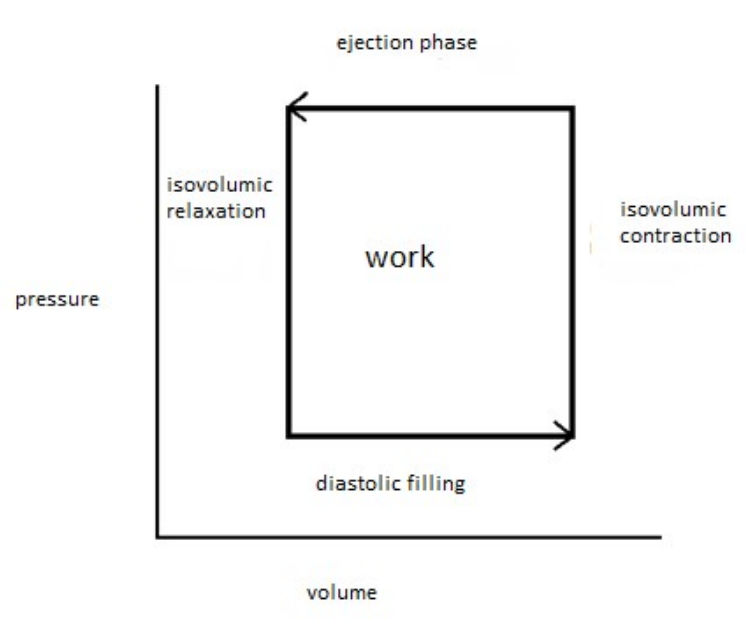
  h….sphere wall thickness

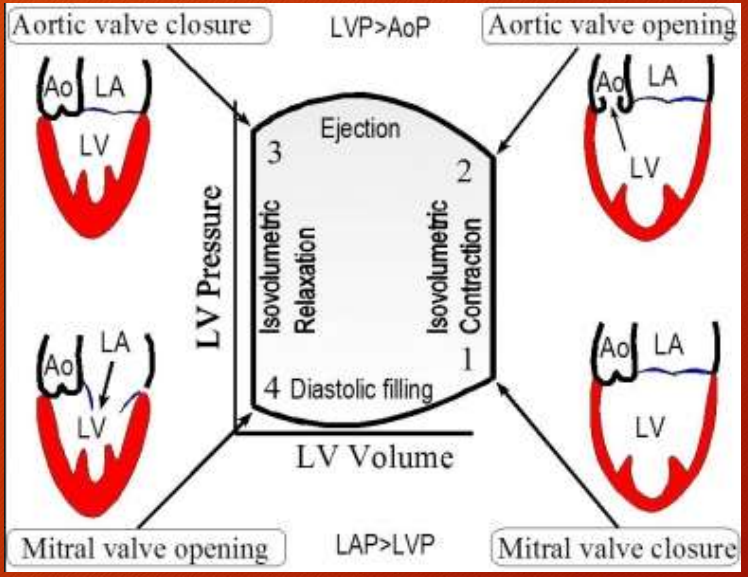


- Preload – wall tension ($N.m^{-2}$ = Pa – force per area) before the systole
  - The main factor is venous return → filling of cardiac ventricles
- Afterload – increase in wall tension during the systole
  - The main factor is a peripheral resistence, or pulmonary vascular resistence

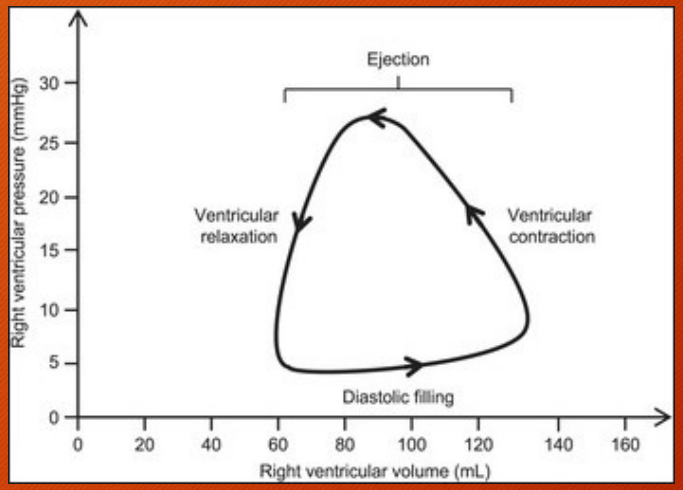
    in the case of the right ventricle
- Preload is higher in the right ventricle, afterload is higher in the left one

Muscular work of the heart – P-V diagram:

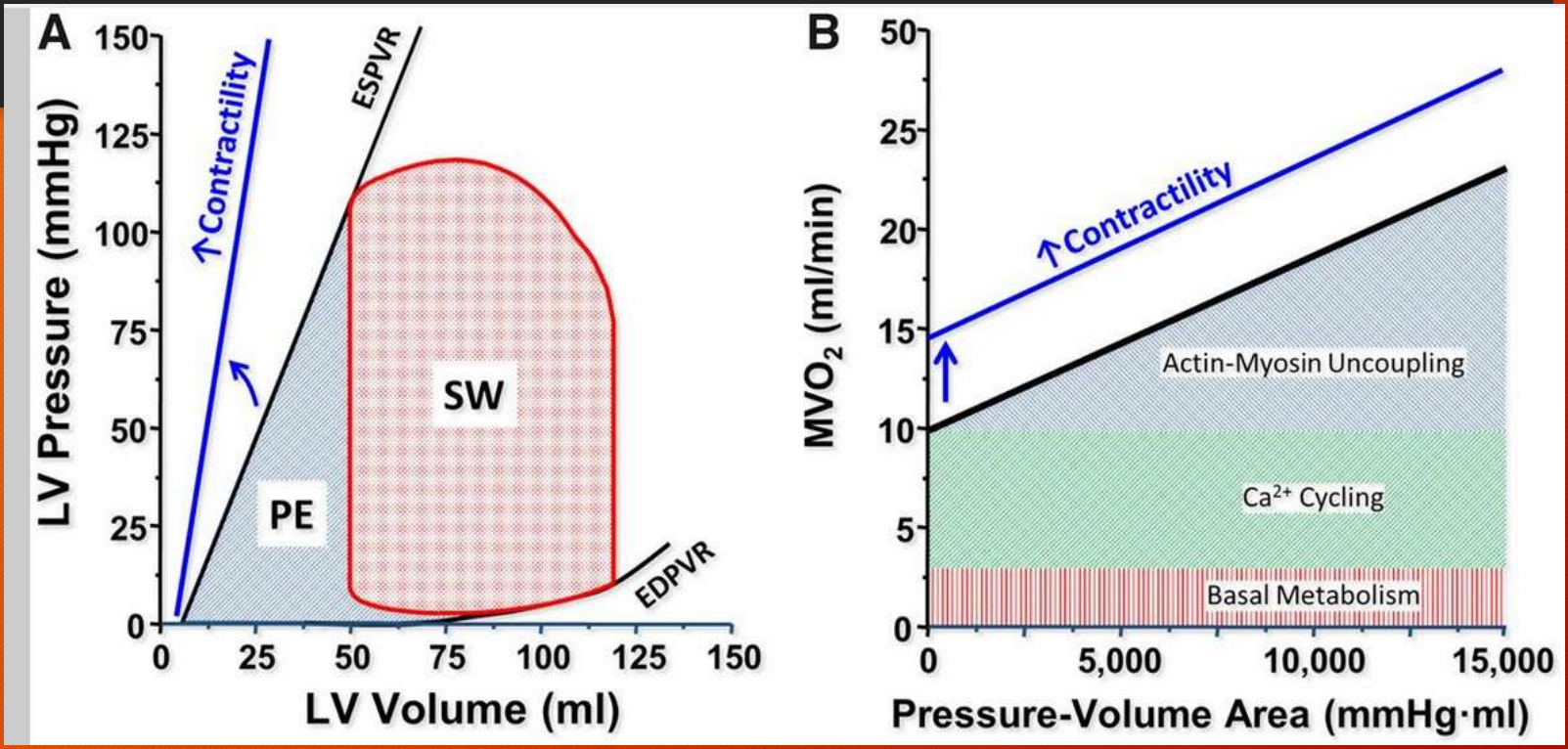




P-V diagram in the right ventricle



P-V diagram and energy consumption

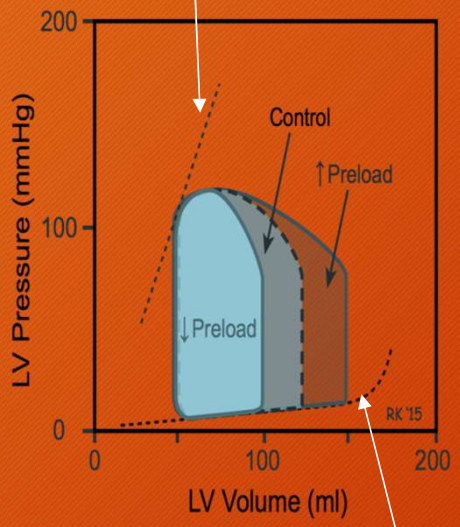


- PE: potential energy
- SW: stroke work
- MVO_2 ~ (PE + SW) × f

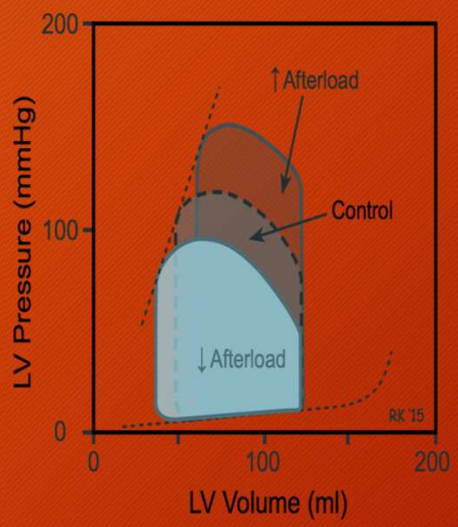
- Energy consumpton per a unit of myocardial volume corresponds to wall stress ($\sigma = \frac{P \times r}{2h}$; see hypertrophy)

P-V diagram during changes of preload or afterload

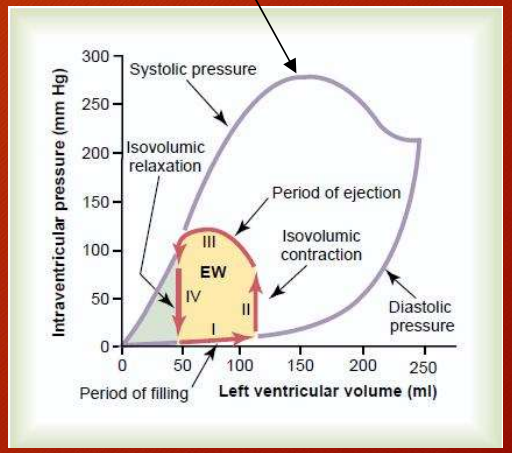
Endsystolic P-V curve



Enddiastolic P-V curve

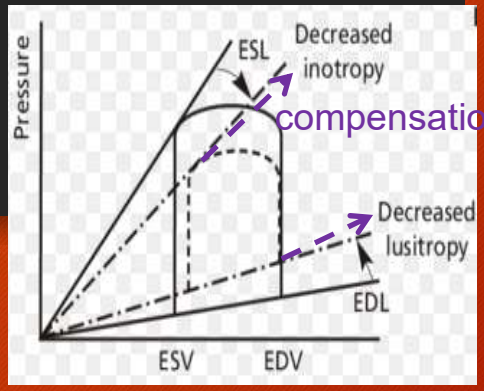


Limit of Frank-Starling mechanism (active muscular force decrease)



Inotropy and lusitropy

- ↑ inotropy („ability to contract“) of the heart – shifts the endsystolic P-V curve up
- ↑ lusitropy („ability to relax“) of the heart – shifts the enddiastolic P-V curve down
  - In principle, the relaxation process is ATP-dependent as well – as it is enabled by pumping out the cytosolic Ca^{2+} – which is, however, stable and independent on cycle phase
- ↓ inotropy or lusitropy decrease an area of P-V diagram, i.e. the cardiac work decreases – compensation by RAAS and SNS increasing preload and afterload follows (similarly to the loss of peripheral resistence or circulating volume)
- Those compensatory processes contribute to heart failure development in the long term.



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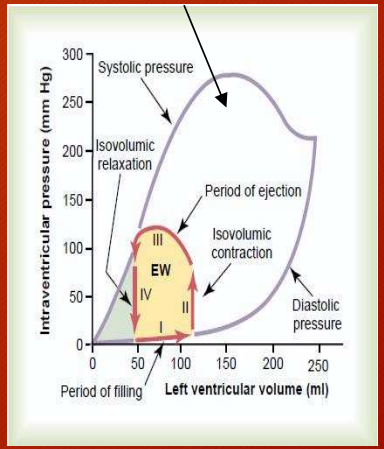


Passive contraction by elastic fibres (relaxation ability decreases)

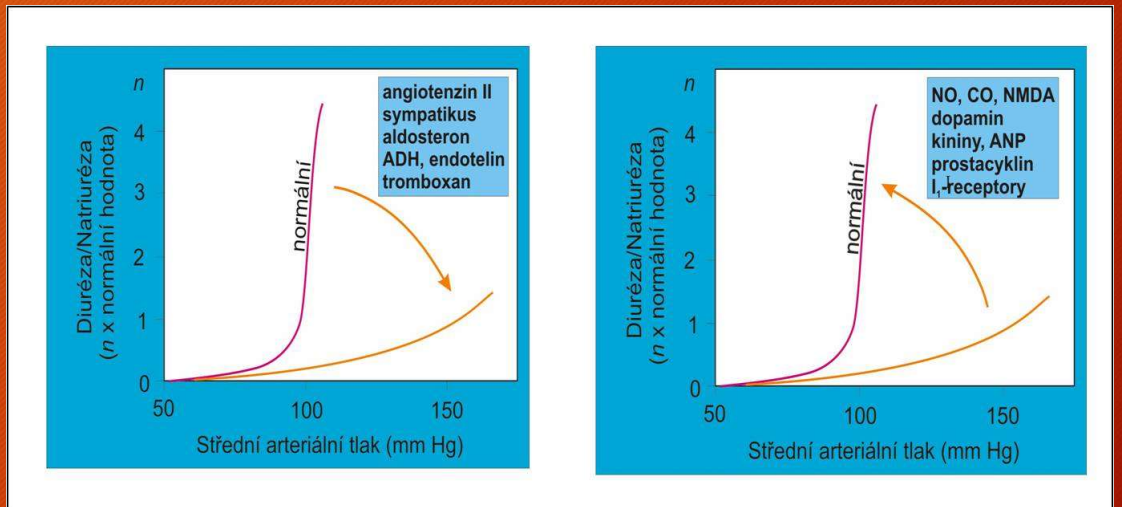
„Interests“ of the heart and perfused tissues

- Increasing of cardiac work means higher energy needs for the myocardium, however the increase of circulating volume/venous return an peripheral resistance is necessary to ensure the perfusion of key organs (heart, lungs, liver, kidneys…)
- On contrary, systemic hypotension is often associated with lower preload (e.g. severe hemorrhage, severe diarrhea) and/or afterload (e.g. anaphylaxis, sepsis)
- From the heart‘s viewpoint, ↓ preload and ↓ afterload are advantageous, regarding the blood supply to key organs they may be linked to circulatory failure caused by circulatory system inability to keep sufficient perfusion pressure (esp. in brain circulation – shock states)
  - But: heart must ensure its own perfusion

Regulation of circulating volume (preload)

- ↑ preload in ↑ systolic volume
  – renal function curve shift

- Most substances shifting the renal function curve to the right have also vasoconstriction effects, those promoting the shift to the left are often vasodilators



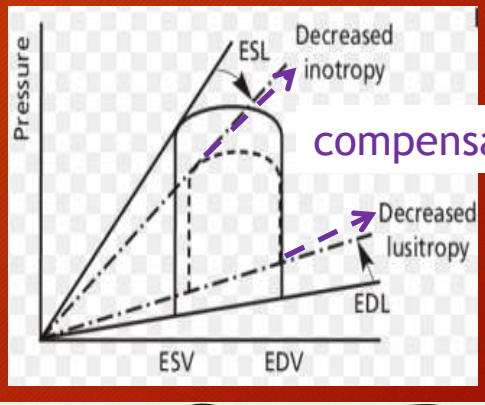
Regulation of systemic peripheral resistance (afterload)

- Vasodilatation
  - NO – produced in the endothelium by constitutive (eNOS) and inducible (iNOS) synthase
  - prostacyclins
  - histamine
  - bradykinin
  - pO_2, pCO_2 ,pH
  - adenosine
  - catecholamines
  - cGMP, cAMP
- Vasoconstriction
  - endothelin
  - ATII
  - ADH
  - catecholamines
  - thromboxane A2
  - Ca^{2+}

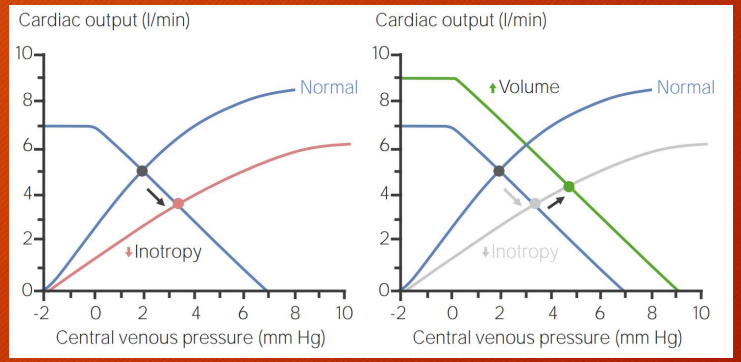
↑ afterload in↑ peipheral resistence – systemic vasodilation of resistence arterioles

Dilatation in acute cardiac insufficiency

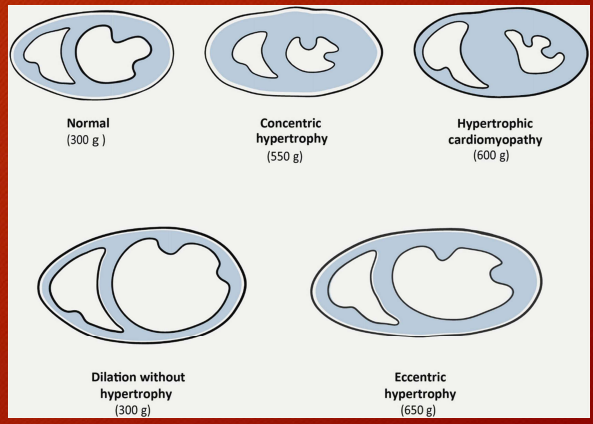
- acute reaction of the heart
- a consequence of increased enddiastolic volume
- enables the use of Frank-Starling mechanism in the acute cardiac insufficiency, but at the expense of higher metabolic requirement
- typically as a reaction to ↑ preload, heart failure decompensation
- renal compensation of hypotension increases preload!
  - failing heart produces natriuretic peptides to increase diuresis



compensation



www.lecturio.com/concepts/venous-function/

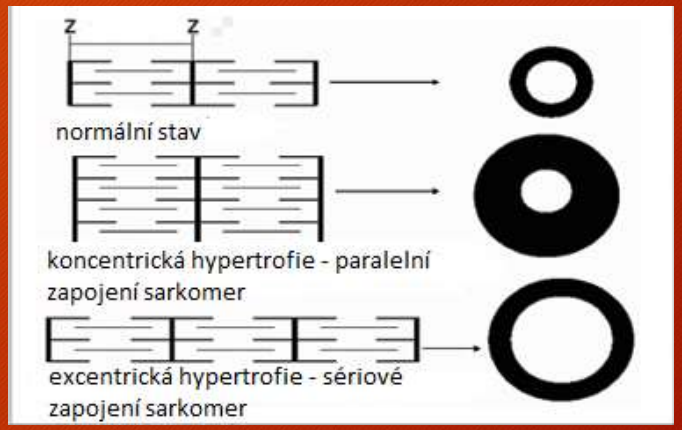


Cardiac remodelation (cellular level)

- Triggered by overload
- Proliferation factors reach the overloaded cardiomyocytes (catecholamines, angiotesin II, aldosterone, ADH, endothelin-1…)
- Expression of fetal genes (protooncogenes) → fetal phenotype
  - shorter action potentials
  - contraction depends on extracellular Ca^{2+} (slow removal → calcium overload)
- Cardiomyocyte hypertrophy
- Hypoxia in relative blood supply insufficiency (decrease of coronary blood reserve)
  - ↑ O_2 consumptions
  - microvascular compression
  - hypoxia changes the shape of some cells' action potentials → ↑ arrhythmia risk
  - apoptosis → myocardium replacement by fibrous tissue → impaired inotropy and lusitropy (vicious circle – see later)
  - autophagy – "rescue program" in hypoxic conditions (decrease of energetic needs by limiting metabolic conversion and contractile function))
- Smooth muscle cells hypertrophy → ↑ resistance (including coronary arteries)

Cardiac remodelation in chronically ↑ preload and ↑ afterload

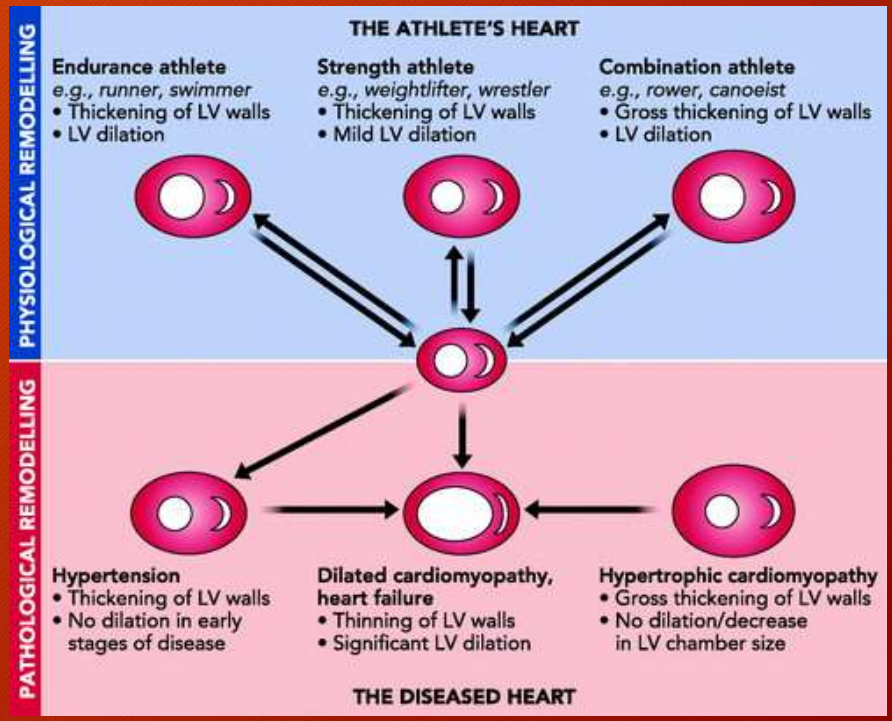
- Volume overload – eccentric hypertrophy (e.g. valvular regurgitation, left-to-right shunt)
  - wall tension is high (law of Laplace), but lusitropy increases
- Pressure overload – concentric hyperthrophy (e.g. valvular stenosis, hypertension)
  - all tension decreases - ↓ O_2 consumption, low lusitropy



- Physiological h/r ratio is 0,3 – 0,4, increases during physical effort
- Above 1,5 or below 0,2 decrease of CO

Other causes of cardiac hypertrophy

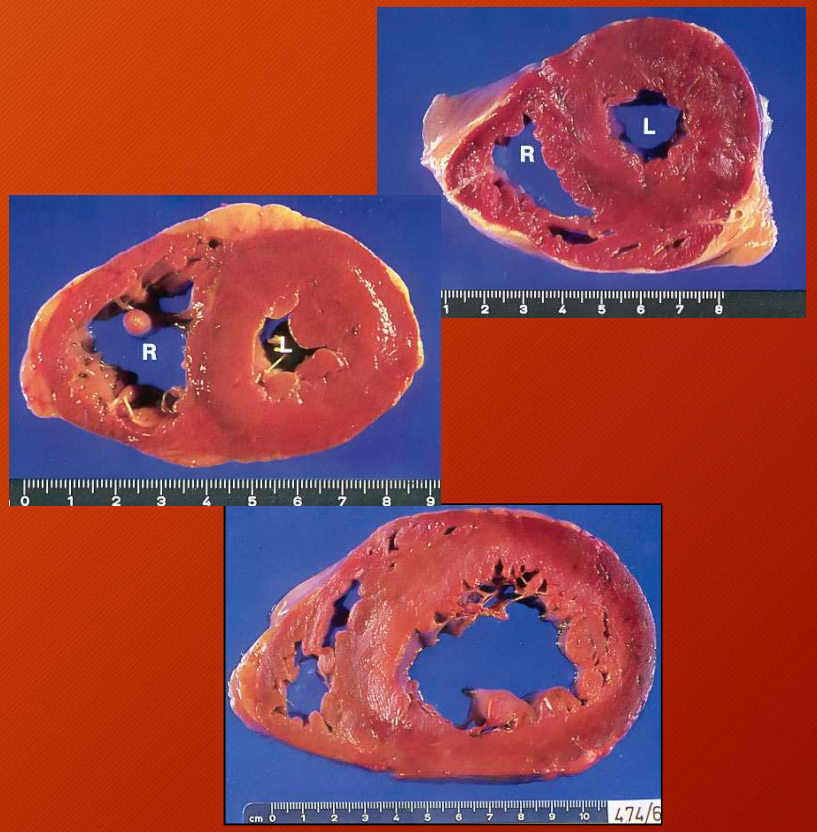
- eccentric: dilated or inflammatory cardiomyopathy
- concentric: hypertrophic cardiomyopathy
- mixed: IHD, reactive hypertrophy following myocardial infarction (eccentric in the ischemic area, concentric in unaffected part of the heart – i.e. combined systolic and diastolic dysfunction)
- Athletes: eccentric in endurance disciplines, concentric in strenght disciplines (CAVE anabolics) – usually reversible
  - high coronary reserve



Weeks et al., Physiology, 2011

Why (concentric) hypertrophy does not finally decrease myocardial O_2 consumption

- $\sigma = P \times r / 2h$
- When wall stress (i.e. neccessity to generate higher pressure during overload) increases (together with MVO_2), hypertrophy initially compensates wall stress and decreases MVO_2
- But as the myocardial mass increases, MVO_2 increases as well
  - pathological hypertrophy is not followed by adequate ”densing” of coronary vessels



Biochemic changes in heart failure

- Tissue hypoxia
- Impaired energetic metabolism (↓ATP and creatine phosphate)
- Decreased utilization of fatty acids, followed by glucose
- ↑ROS
- ↓pH
- ↑cytosolic Ca^{2+}
  - Increases the energy consumption – vicious circle

Systolic and diastolic heart failure

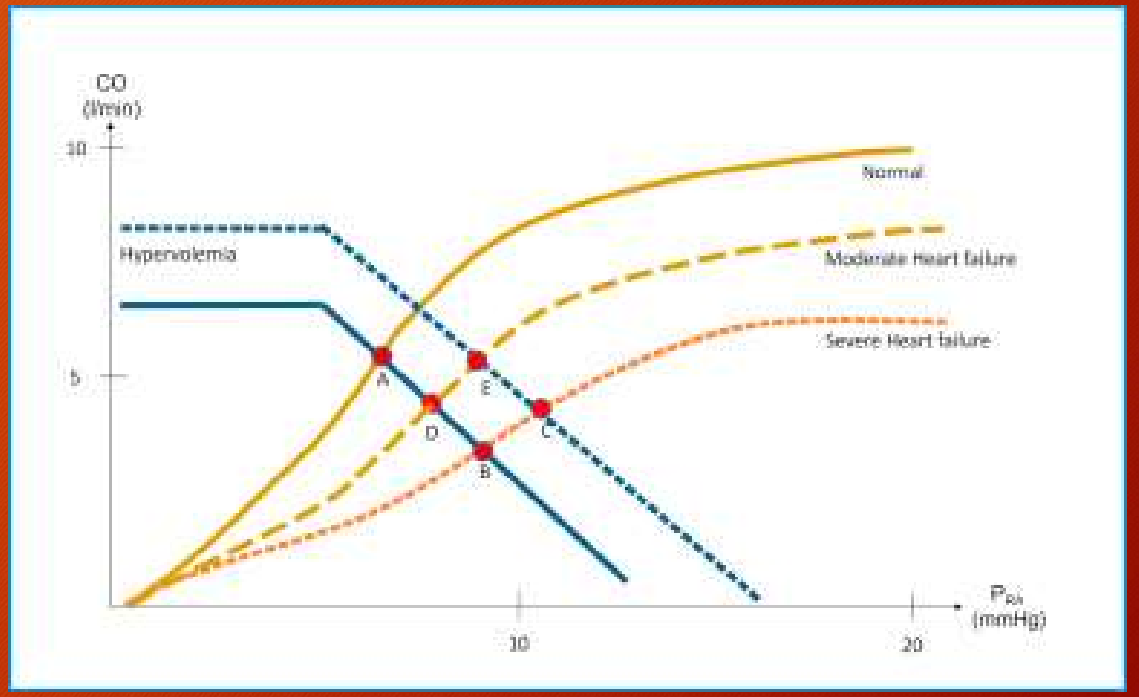
- Systolic (with reduced ejection fraction)
  - Impaired inotropy
  - ↓EF diagnosed as $\frac{EDV - ESV}{EDV}$, most commonly using USG
  - More common in men, younger patients, DCM
  - More often leads into the terminal heart failure
- Diastolic (with preseved ejection fraction – cave valvular disease)
  - Impaired lusitropy
  - Diagnosed using Doppler USG: ↑E/e‘ (flow through mitral valve/ mitral anulus movement at the beginning of the diastole) – blood is “pressed“ rather than “sucked“ into the ventricles
  - More common in women, older patients, hypertension, HCM, RCM, tachycardia
  - Prevalence of systolic and diastolic heart failure is approx. 60:40, mixed pattern is common – especially IHD

Heart failure – systemic effects

- Left-sided failure
  - backward
    - ↑hydrostatic pressure in pulmonary capillaries → pulmonary oedema
    - respiratory failure, pleural effusion (transudate)
    - pulmonary hypertension → secondary right-sided failure
  - forward
    - systemic hypotension→ shock
    - organ failure (liver, kidneys, GIT, brain)
    - muscular weakness, fatigue, cachexia
- Right-sided failure
  - backward
    - ↑hydrostatic pressure at the venous end of systemic
    - oedemas and effusions in systemic circulation (incl. pleural effusion)
    - anasarca (systemic oedema)
    - hepatomegaly, ascites
  - forward
    - isolated is a rarity
    - leads into ↓left ventricle preload → left-sided forward failure

Heart failure and renal function

- Low perfusion pressure in kidneys leads into lower diuresis and hypervolemia
- That softens the forward effects of heart failure, but worsens the backward effects
- This is more pronounced in pre-existing renal failure and hypervolemia



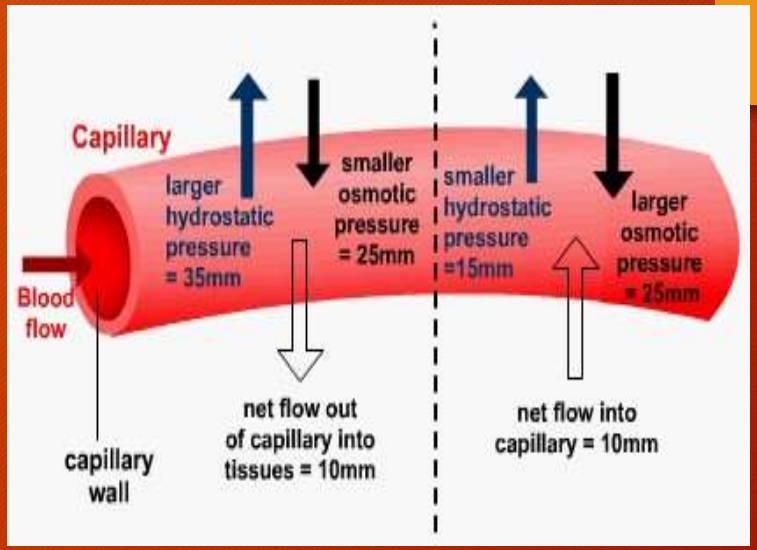
Etiology of left-sided and right-sided failure

- Left-sided
  - Usually primary
  - IHD, MI
  - Cardiomyopathies
  - Left-sided valvular disease
  - Severe hypertension
  - Outflow tract obstruction
- Right-sided
  - Usually secondary
  - COPD, pulmonary arterial hypertension, pulmonary embolism→ cor pulmonale
  - Pulmonary hypertension in left-sided heart failure
  - MI in RCA area
  - Right-sided valvular disease
- Other causes
  - Left-to-right shunt
  - Pericardial effusion, constrictive pericarditis

} No pulmonary congestion

Starling forces and edema

- Actually pressures, or pressure gradients
- $F = A \cdot K \cdot [(P_v - P_t) - \sigma(\pi_v - \pi_t)]$, where:
  - F…filtration
  - A…filtration area
  - K…membrane permeability coefficient (for water)
  - σ…membrane reflection coefficient (for proteins)
- The pressure gradient is directed outside at the arterial end and inside at the venous end of a capillary
- Exception: glomerular capillaries (high hydrostatic pressure – cave shock)
- Pulmonary capillaries – filtration slightly prevails all along the capillary (low both hydrostatic and oncotic pressure gradient, low reflection coefficient)
- But the excessive water is either drained by lymphatic vessels or breathed out, the lungs stay „dry“

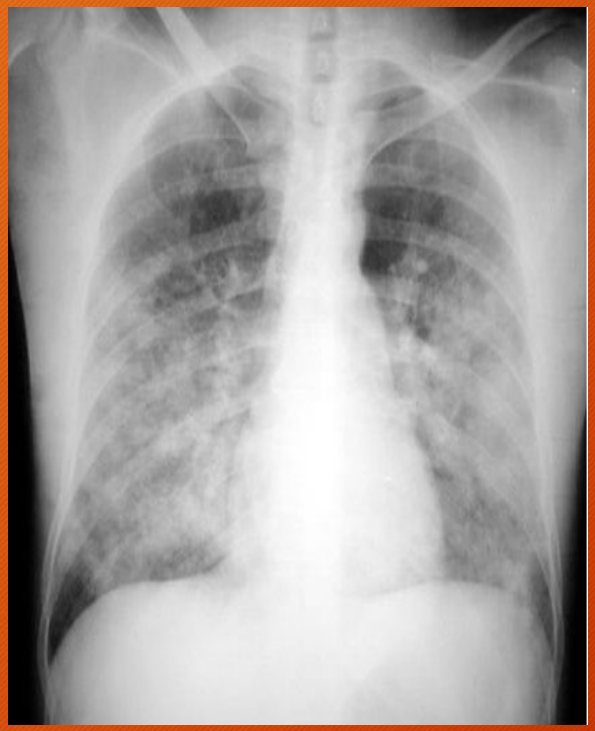


The flow from the capillary little exceeds the reabsorption – lymphatic drainage

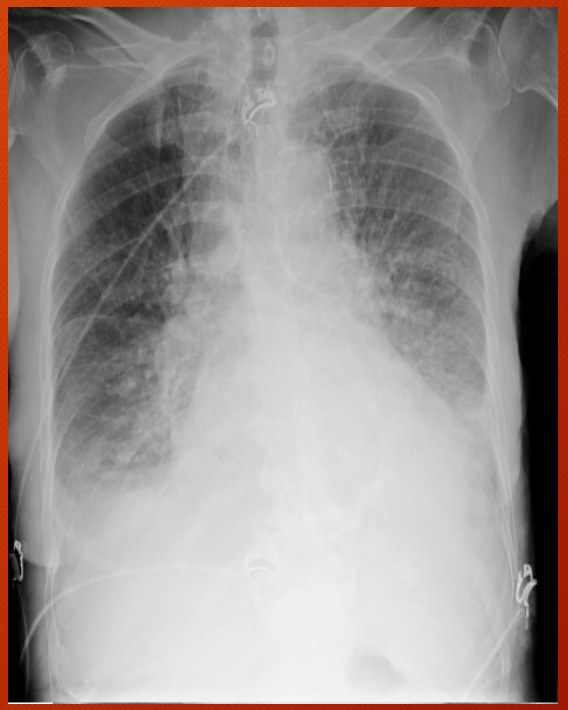
Pulmonary edema and pleural effusion

- Pulmonary oedema: fluid accumulation in the lung tissue („swamp“)
  - interstitial
  - alveolar
  - both fluid filtration and resorption from/to pulmonary circulation
  - treatment: medication
- Pleural effusion: fluid between the parietal and visceral pleura („lake“)
  - fluid is filtrated mainly from the systemic circulation and reabsorbed mainly into the pulmonary circulation
  - treatment: medication or surgery
  - In transudates, pulmonary oedema may be combined with pleural effusion

X-ray



Pulmonary edema



Bilateral pleural effusion

Heart failure according to rapidity of development

- Acute
  - De novo origin or through decompensation of chronic heart failure
  - Classification Killip I-IV
- Chronic
  - Slow development
  - Classification NYHA I-IV

Heart failure treatment

- Acute
  - Treatment of initiating cause
  - Rest in bed, hospitalization
  - O_2
  - Diuretics
  - Vasodilators (if not severe hypotension – i.e. „warm and wet“ failure)
  - Vasopressors (in cardiogenic shock – „cold and wet“)
  - Inotropics (e.g. catecholamines)
  - Opioids in dyspnea
  - Mechanical circulatory support
- Chronic
  - Treatment of initiating cause
  - Mild physical load
  - Conditioning training 3-5 times per a week 20-30 min
  - Diuretics
  - Heart rate reduction (ß-blockers, digoxin, ivabradine)
  - RAAS inhibition (prevents remodelling)
  - Implantation of ICD, BiV PM (arrhythmia)
  - Heart transplantation