Heart failure

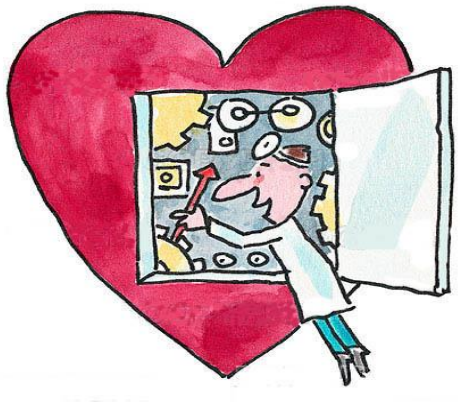
Compensatory mechanisms to maintain CO

Systolic and diastolic dysfunction

Heart remodeling patterns

Etiopathogenesis of HF

HF as a syndrome



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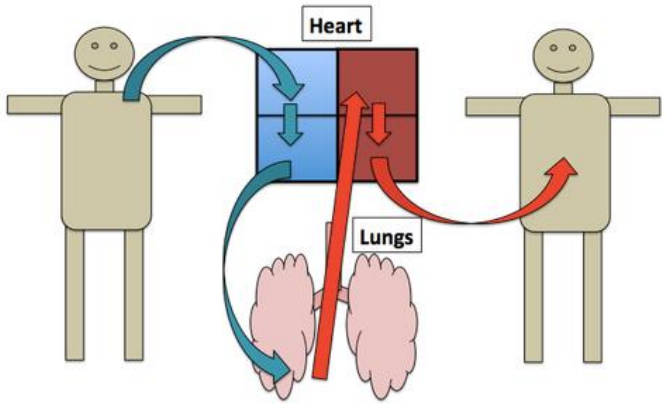
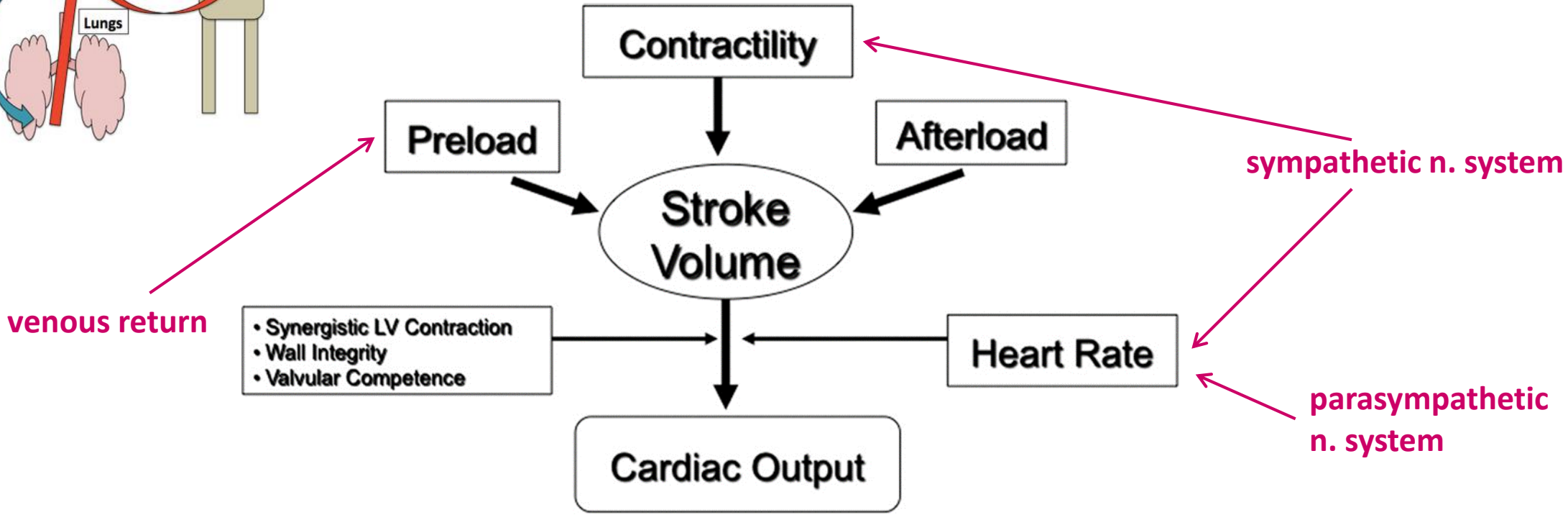
Heart failure syndrome (HFS)

- a **systemic illness** affecting several organs, creating high morbidity and mortality rates due to
  - the heart's **inability to deliver adequate oxygenated blood and metabolites** to the body **to meet end-organ** metabolic **needs** and oxygenation at rest or during exercise
  - and to **accommodate venous return**
    - typically due to the left ventricular pump dysfunction and related clinical symptoms (dyspnea, fatigue, exercise intolerance, metabolic dysturbances etc.) including signs of volume overload (pulmonary crackles, peripheral edema, etc.)
- HFS develops due to any structural and/or functional cardiac abnormalities
  - the pathophysiologic state perpetuates the progression of the failure, regardless of the precipitating event via several compensatory mechanisms (circulus vicious)
- classification of LHF is dependent on whether the left ventricular ejection fraction (LVEF) is reduced or preserved
- acute event or acute refractory form of chronic HF can be fatal, whereas chronic prognosis is characterized by terminal congestive heart failure symptoms

Heart needs a lot of energy to continually perform as a pump





CO (4–6 L/min) = SV (usually 1mL/kg, i.e. approx. 60–100mL) × f

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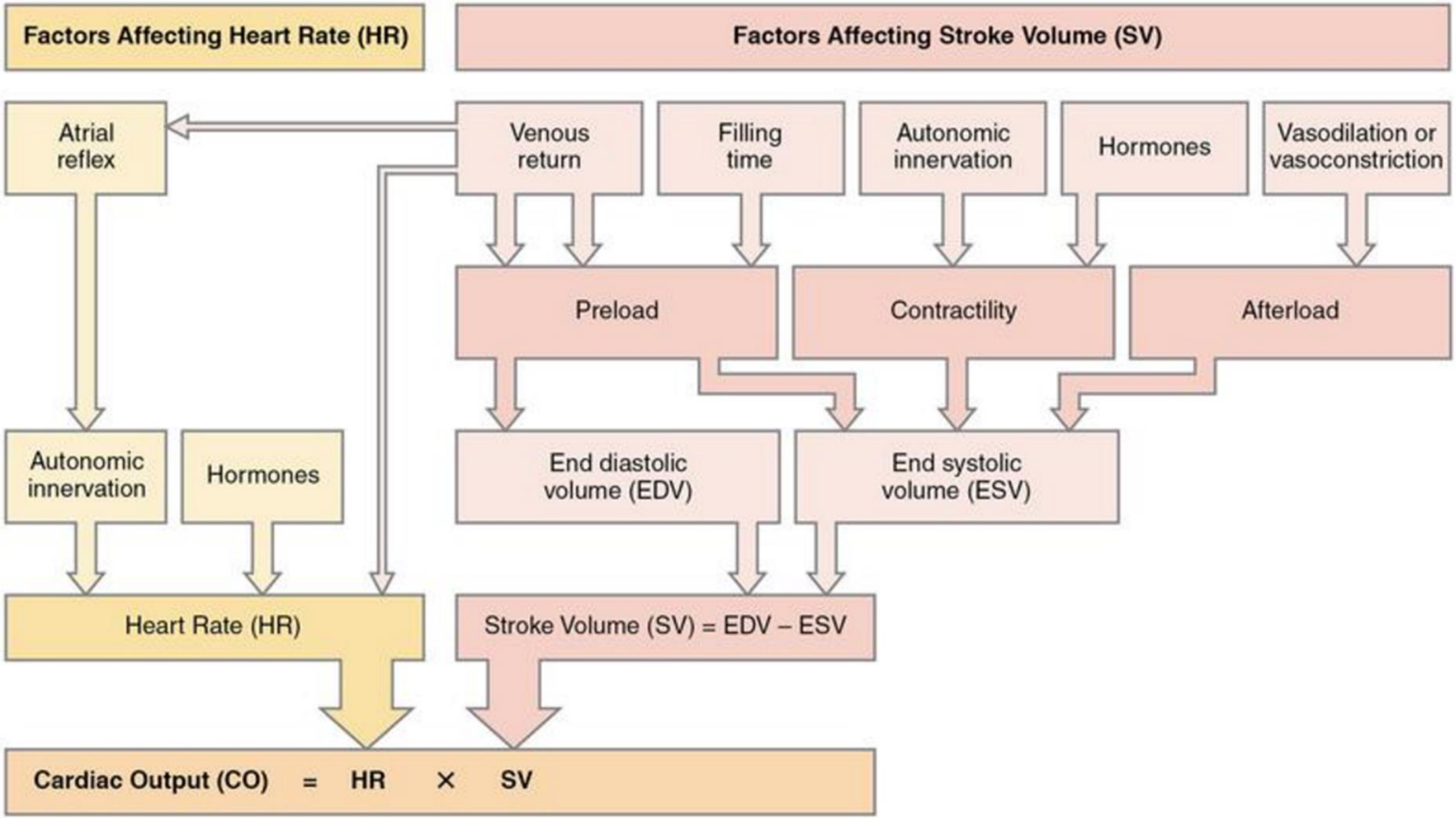
Factors Affecting Heart Rate (HR)
Factors Affecting Stroke Volume (SV)
Atrial reflex
Venous return
Filling time
Autonomic innervation
Hormones
Vasodilation or vasoconstriction
Preload
Contractility
Afterload
Autonomic innervation
Hormones
End diastolic volume (EDV)
End systolic volume (ESV)
Heart Rate (HR)
Stroke Volume (SV) = EDV – ESV
Cardiac Output (CO) = HR × SV

Functional classification of HF instead of CO

NYHA classification

Class	Symptoms
Class I	No symptoms with ordinary activity
Class II	Slight limitation of physical activity
	Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea or angina
Class III	Marked limitation of physical activity
	Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, dyspnea, or angina
Class IV	Unable to carry out any physical activity without discomfort
	Symptoms of cardiac insufficiency may be present even at rest

ACC/AHA classifications

Stage	Disease
Stage A	Patient at high risk for developing HF with no structural disorder of the heart
Stage B	Patient with structural disorder of the heart without symptoms of HF
Stage C	Patient with past or current symptoms of HF associated with underlying structural heart disease
Stage D	Patient with end-stage disease who requires specialized treatment strategies

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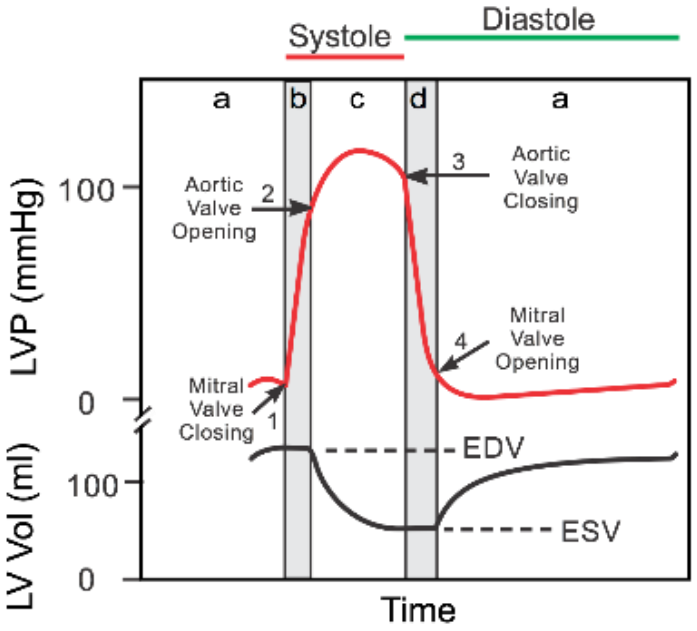
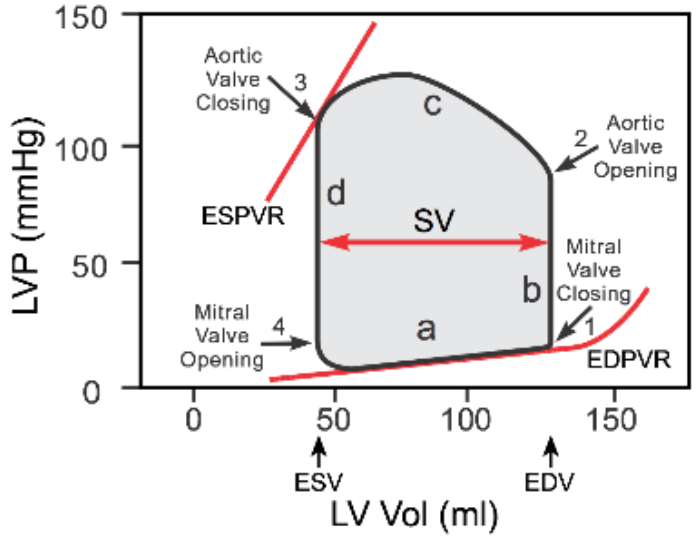
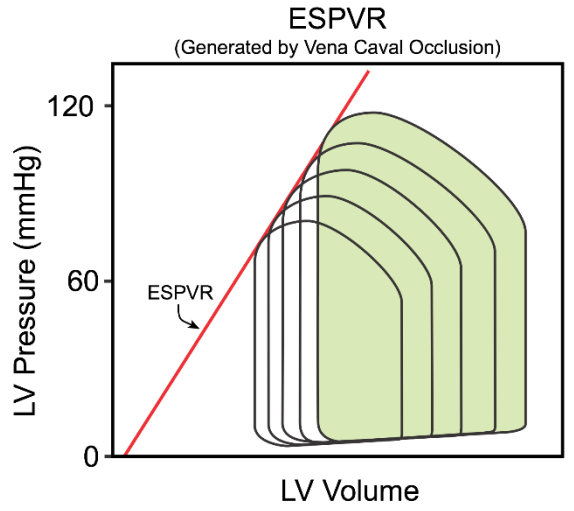
Mechanical work of the heart





- Ventricular filling occurs along the end-diastolic pressure-volume relationship (EDPVR), or passive filling curve for the ventricle. The slope of the EDPVR is the reciprocal of ventricular **compliance**
- The area within the loop is the ventricular stroke **work**
- The maximal pressure that can be developed by the ventricle at any given left ventricular volume is defined by the end-systolic pressure-volume relationship (ESPVR), which represents the **inotropic state** of the ventricle



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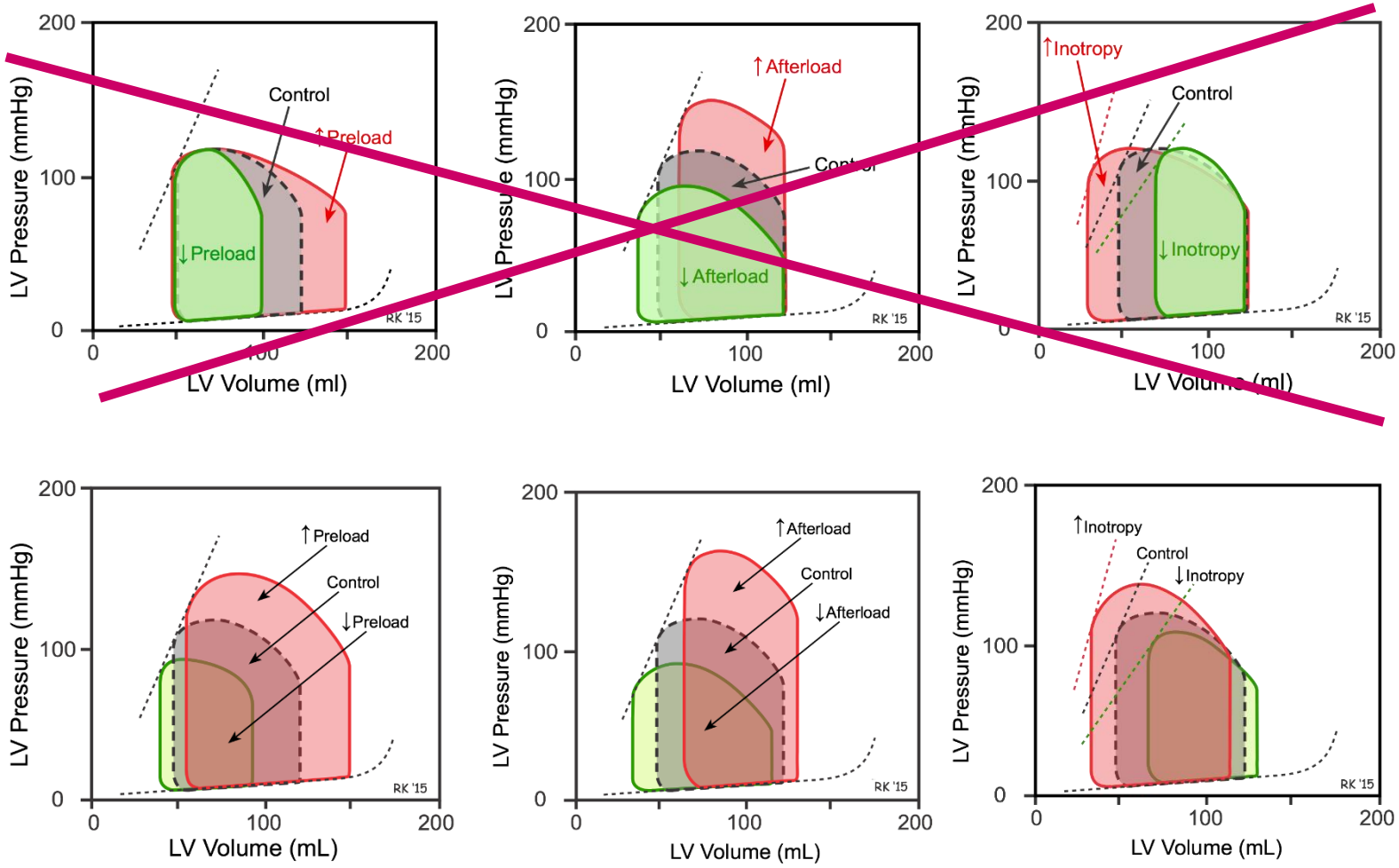
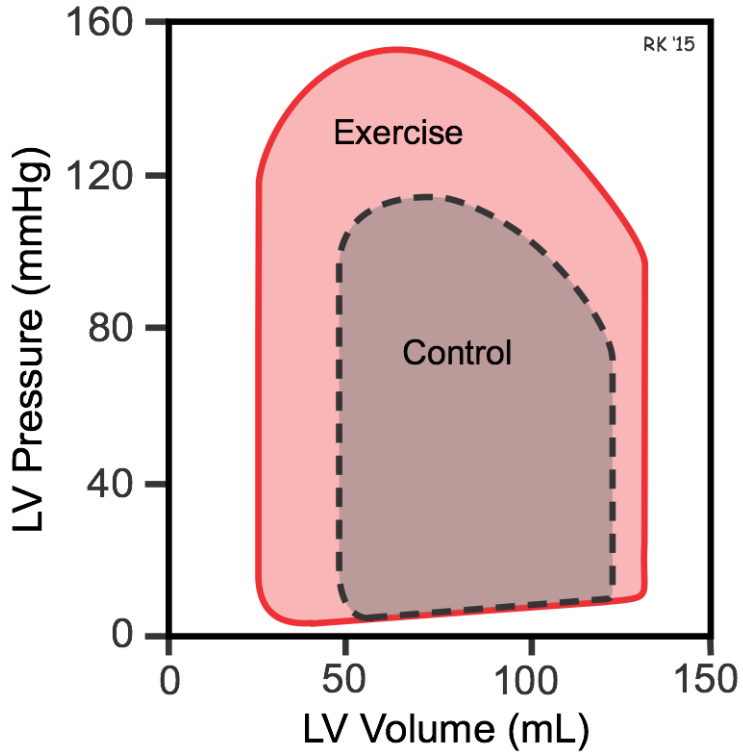
Changes in ventricular function in response to changes of preload, afterload and inotropy

- If effects considered separately
- These ventricular changes can be complex because preload, afterload and inotropy are **interdependent variables**
  - when one variable is changed (by disease), the other variables change in response
  - interactions between preload and afterload at constant inotropy
  - secondary changes of preload by changes in afterload
  - change in inotropy affects both preload and afterload



Interdependent Changes in Preload, Afterload and Inotropy during Exercise



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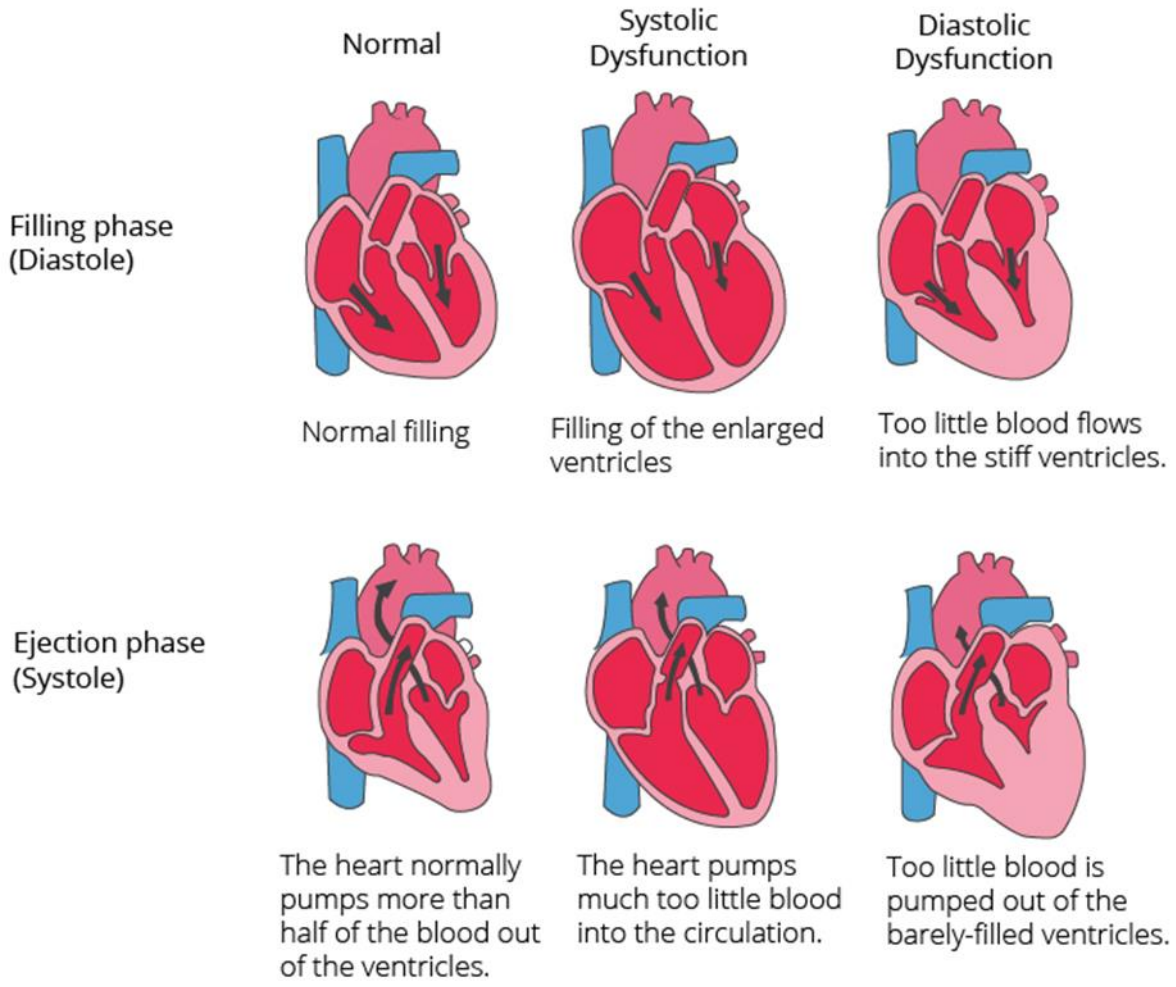
For heart to perform as a pump both systolic and diastolic function has to be preserved

- Pathophysiological spectrum heart failure (HF)
  - from asymptomatic cardiac dysfunction as a preceding stage in the progression to clinically overt HF
- **Myocardial dysfunction** is a state when CO is potentially affected
  - types of myocardial dysfunction
    - systolic and/or diastolic
    - acute or chronic
    - compensated or uncompensated
    - uni- or biventricular
- Systolic (dys)function
  - (impaired) ventricular contraction and ejection
- Diastolic (dys)function
  - (impaired) relaxation and ventricular filling
- Left ventricular dysfunction or heart failure (LHF) is the dominant picture of heart failure syndrome
  - approx. 70% HF patients has SdF
    - however often with component of DdF
  - approx. 30% HF patients has DdF
- But the right heart can develop isolated failure as well
- Biventricular failure is mostly an end-stage clinical situation of the heart failure syndrome



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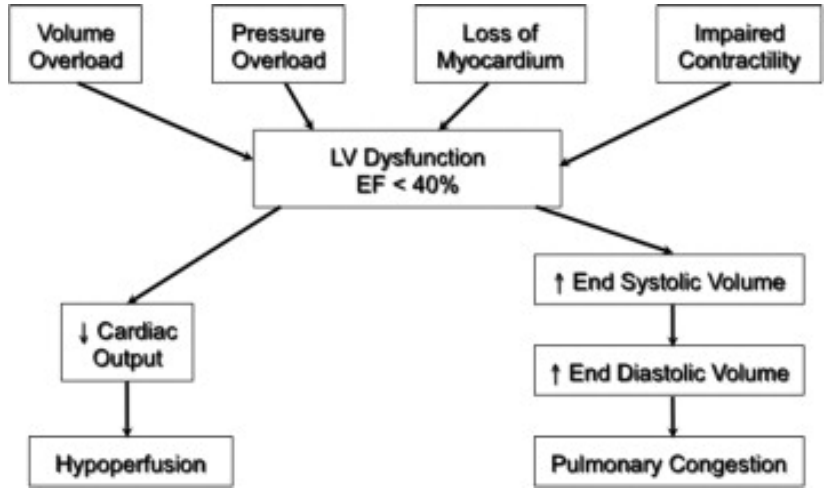
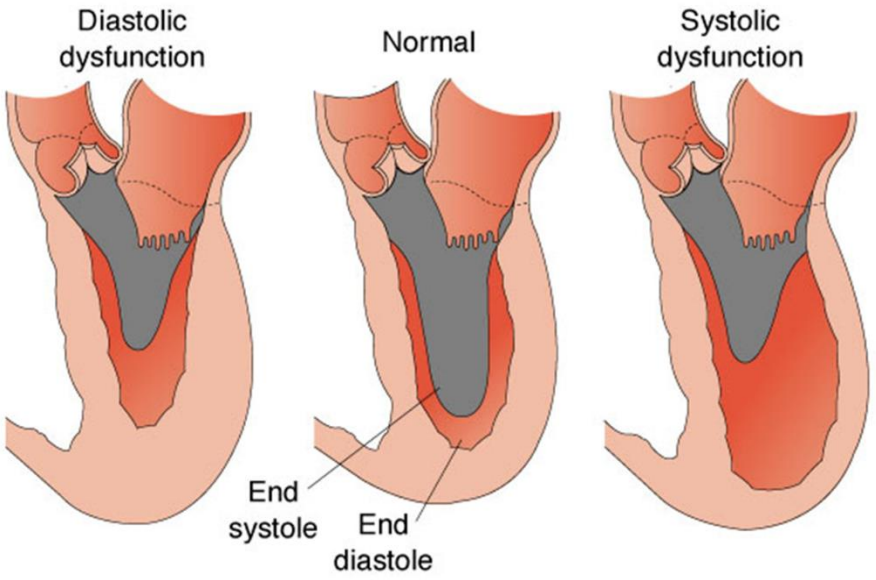
From cardiac dysfunction to heart failure

- Distinction between systolic or diastolic **LV dysfunction** depends on the **ejection fraction (EF)**
  - portion/percentage of blood volume (i.e. LVEDV) pumped from the ventricle in one heartbeat
  - EF <40% = systolic dysfunction
    - clinically HF with reduced EF (HFrEF)
  - EF >40% = diastolic dysfunction
    - clinically HF with preserved EF (HFpEF)
- Consequence of LV dysfunction
  - note! they are the same for systolic or diastolic dysfunction





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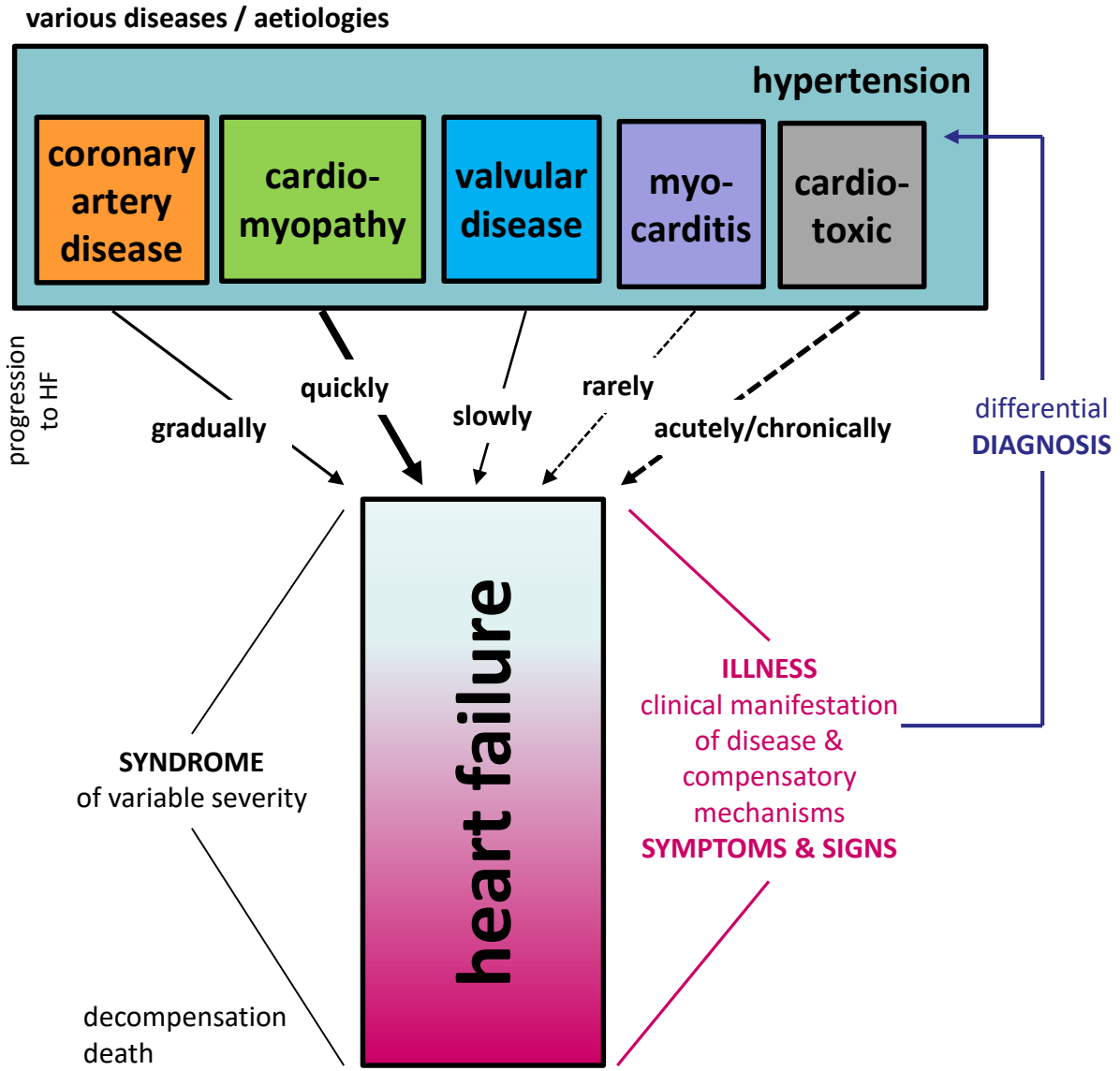
HF results from injury to the myocardium from a variety of causes



- **multiple etiologies** can lead to final common clinical pathway
- aetiology = any disease causing a loss of a critical quantity of functional myocardial cells
  - some are common, some are rare
- ¾ of all HF patients have pre-existing **systemic arterial hypertension**
  - this risk factor alone doubles the risk of developing HF compared to normotensive patients – can lead to HF on its own
  - accelerates progression of any other aetiology

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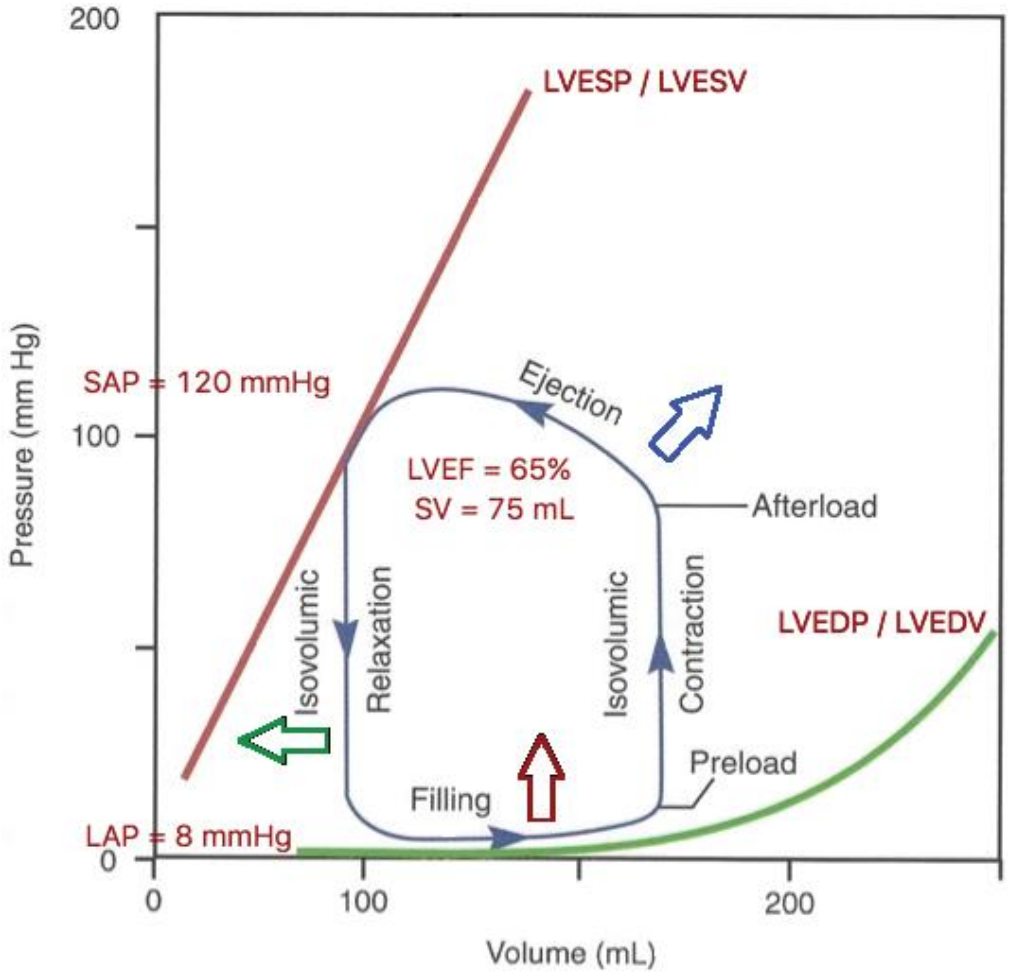
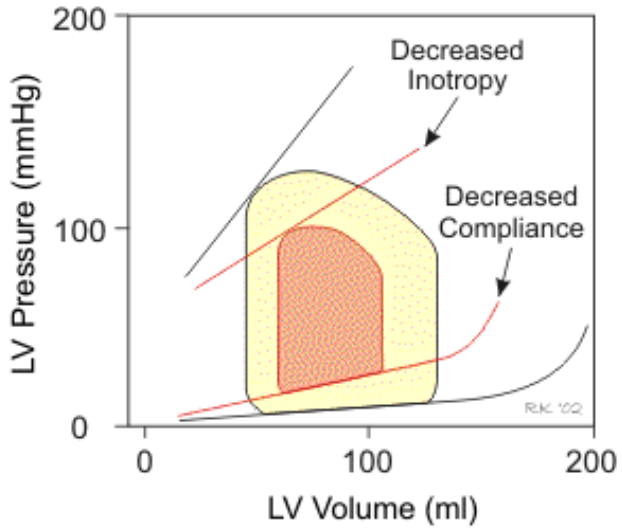
Left heart failure (LHF)

Left ventricular pressure-volume relationships:



- In systolic LHF, an adequate stroke volume cannot be sustained due to reduced ventricular systolic contractile function, which shifts the whole pressure-volume relationships to the right
- In diastolic LHF, an adequate filling cannot be realized due to diastolic stiffness (poor ventricular compliance, impaired relaxation, worsened end-diastolic pressure), which shifts the diastolic pressure-volume curve upward; however, the systolic pressure-volume curve does not change



Effects of a combination of systolic dysfunction (decreased inotropy) and diastolic dysfunction (decreased compliance) on left ventricular pressure-volume loop. Heart rate and systemic vascular resistance are unchanged.

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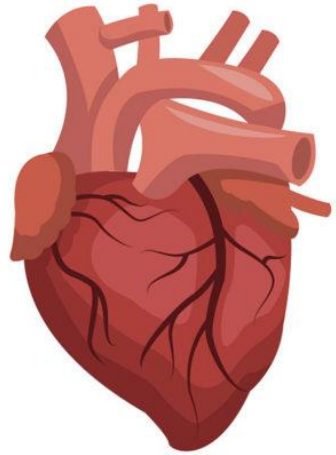

COMPENSATORY MECHANISMS TO MAINTAIN CARDIAC OUTPUT

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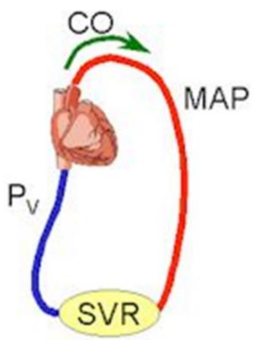
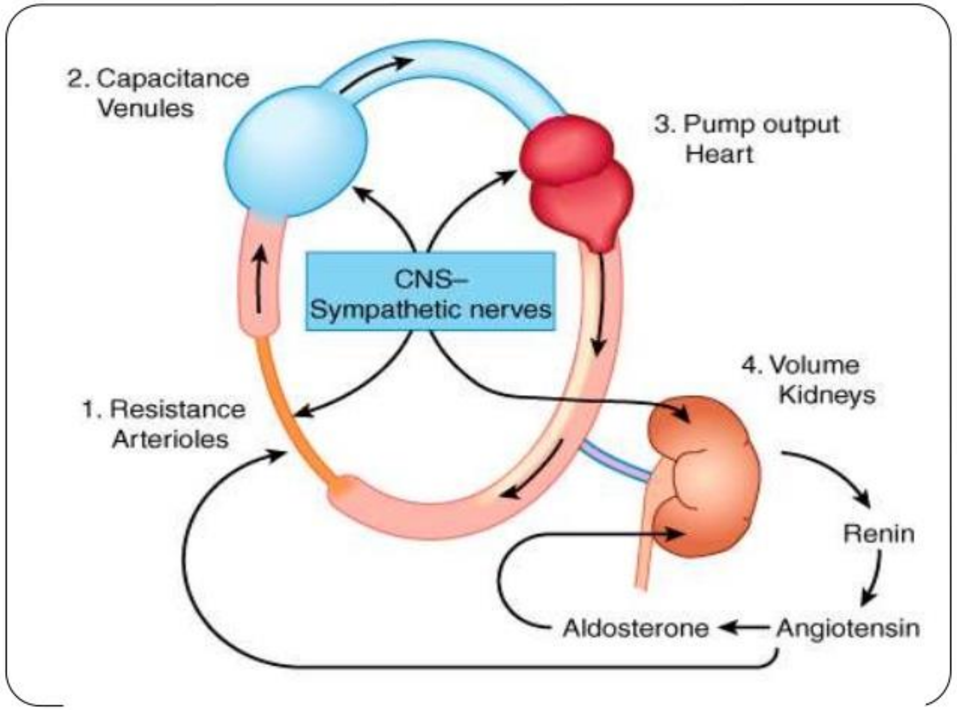
Compensatory mechanisms to maintain CO

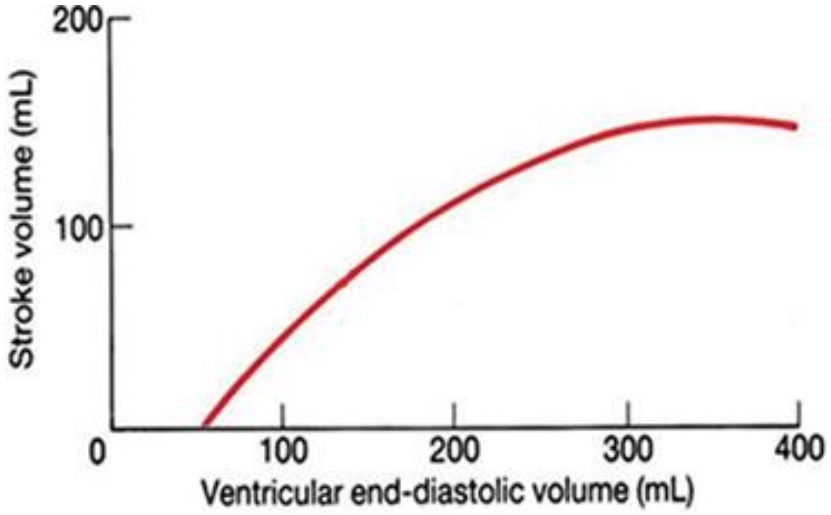
- Mean arterial pressure (MAP) is closely regulated and is defined as the product of CO and total peripheral resistance (TPR)
- The failing heart strives to balance “preload” and “afterload” for compensation of impaired contractility and to deter the development of congestion using a myriad of mechanisms
- CO sensing mechanisms
  - low-pressure volume receptors
    - present mainly in the cardiac atria
    - release of natriuretic peptides
  - high-pressure mechanoreceptors
    - located in the left ventricle, aortic arch, carotid sinus and renal juxtaglomerular apparatus
- From asymptomatic to symptomatic stages, several mechanisms are activated:
  - (1) the Frank–Starling mechanism
  - (2) neuro-hormonal activation
  - (3) ventricular remodelling

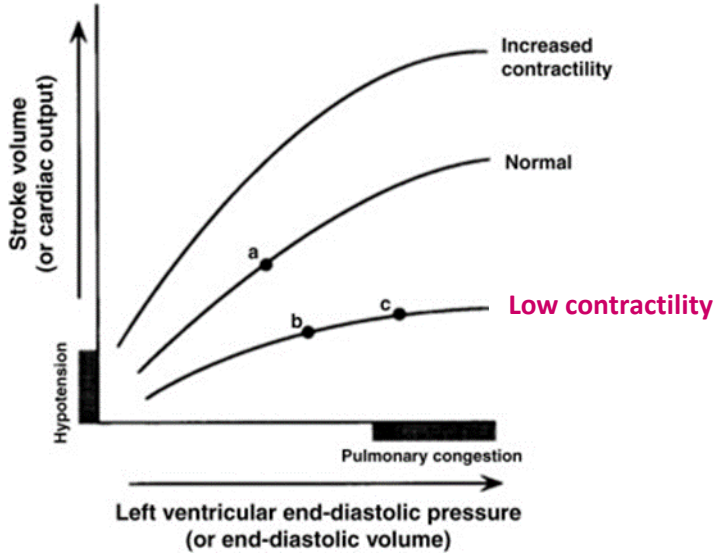




Compensatory mechanisms to maintain CO

- **(1) the Frank–Starling mechanism**
  - SV as a function of LVEDP
  - increases myocardial contraction power, but this positive effect reverses after the sarcomere length reaches the upper limit of 2.2 µm
  - efficient under various contractility





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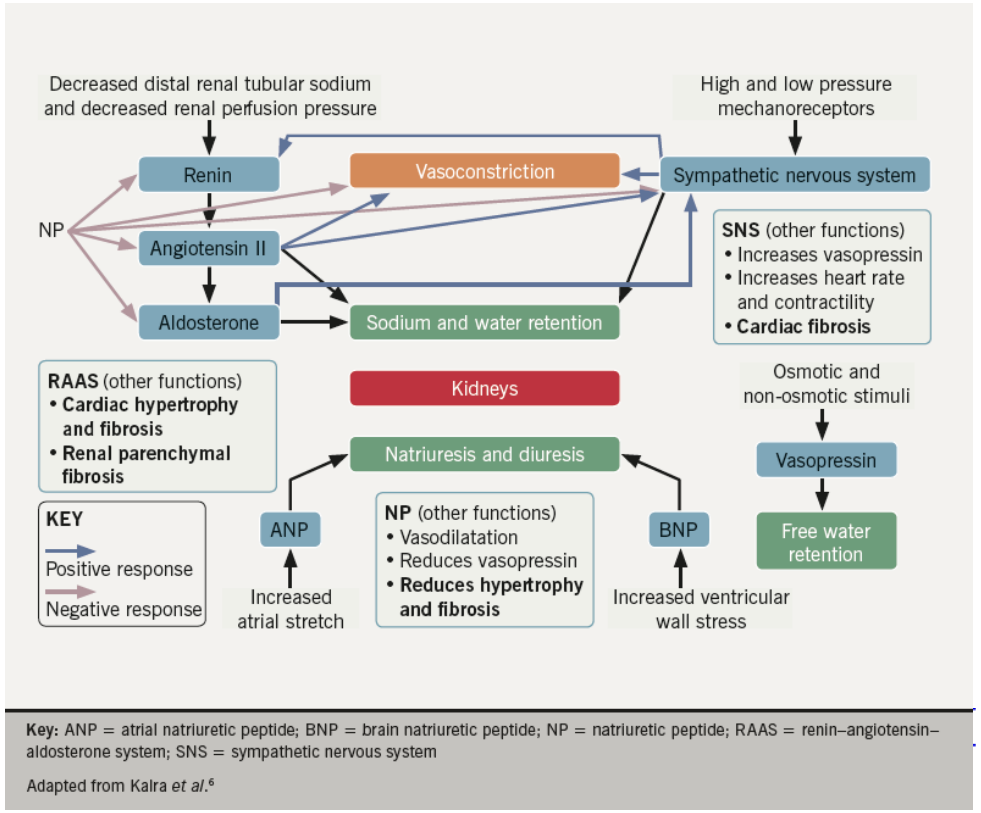
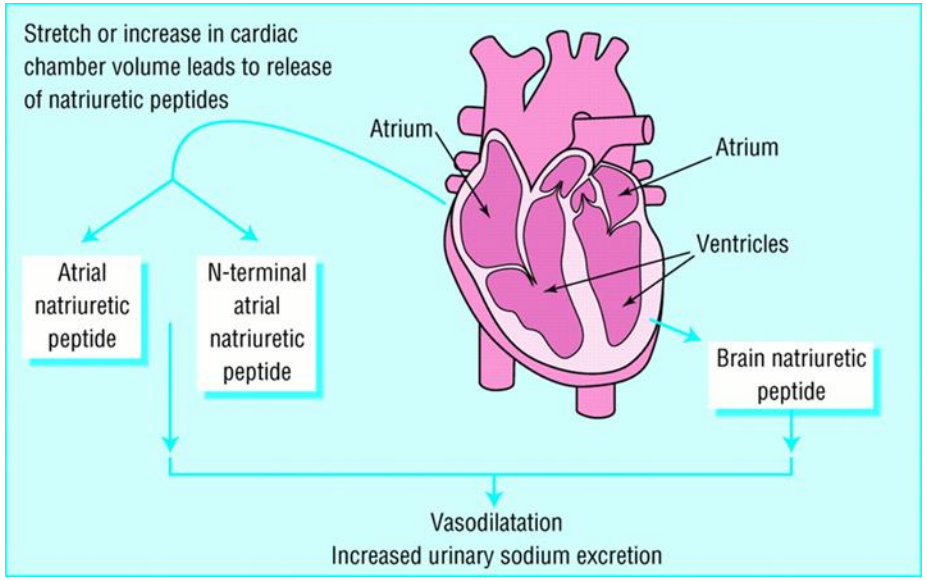
Compensatory mechanisms to maintain CO

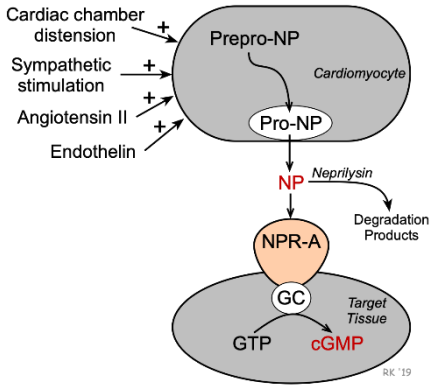
- **(3) neuro-hormonal activation** to augment MAP
  - **(3a) sympathetic nervous system activation**
    - mediated through β1, β2, and α1 receptors
    - chronotropic effect → increasing heart rate frequency
      - this positive effect is reversed after tachycardia reaches a threshold of 140–150 beats/min
    - inotropic effect → increasing contractility
    - increasing TPR
      - by peripheral vasculature (vasoconstriction)
    - activation of the renin–angiotensin–aldosterone system (RAAS) β1 and α1 receptors causing
      - peripheral vasoconstriction
      - sodium and water retention
  - **(3b) activation of RAAS** by kidney hypoperfusion
  - **(3c) activation of vasopressin**
    - release from hypothalamus and posterior pituitary facilitated by angiotensin II and central baroreceptors
  - **(3d) natriuretic peptide release**



Natriuretic peptides – potentially beneficial

- play a significant role in water and salt homeostasis
- counter-regulatory balance to the harmful neurohumoral pathways already discussed (3a – 3c)
- beneficial effects include
  - vasculature: direct vasodilatation = lowering of blood pressure
  - kidney: natriuresis and diuresis, lowering the release of renin from the kidneys, increasing renal blood flow
  - heart: decreasing cardiac hypertrophy and fibrosis
- natriuretic peptide system consists of three main peptides:
  - atrial natriuretic peptide (ANP)
  - B-type natriuretic peptide (BNP)
    - ANP and BNP released from myocytes in response to cardiac stretch
  - C-type natriuretic peptide (CNP)
    - released from endothelial cells
- biomarkers: elevated circulating levels of NP found in patients with chronic heart failure
  - assessment of BNP (or its inactive N-terminal fragment, NTproBNP) is now a key component of the diagnostic pathway for patients with suspected heart failure
- therapeutic potential: inhibition of the breakdown of natriuretic peptides (ANP, BNP, CNP and urodilatin) by a membrane bound endopeptidase neprilysin
  - caution since it breaks down also bradykinin and angiotensin II
    - has to be used together with ARBs





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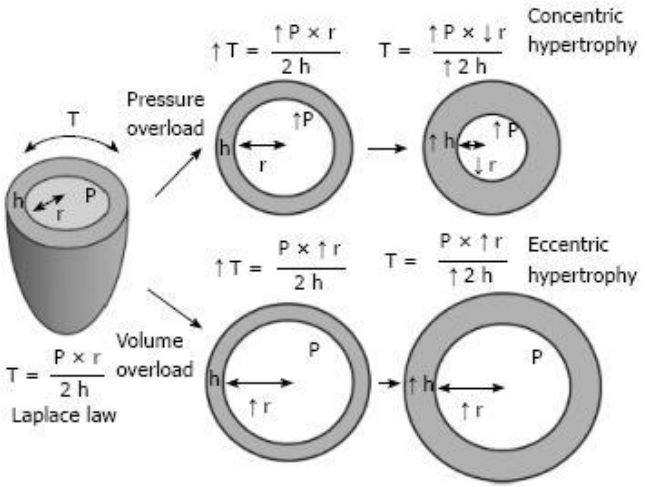
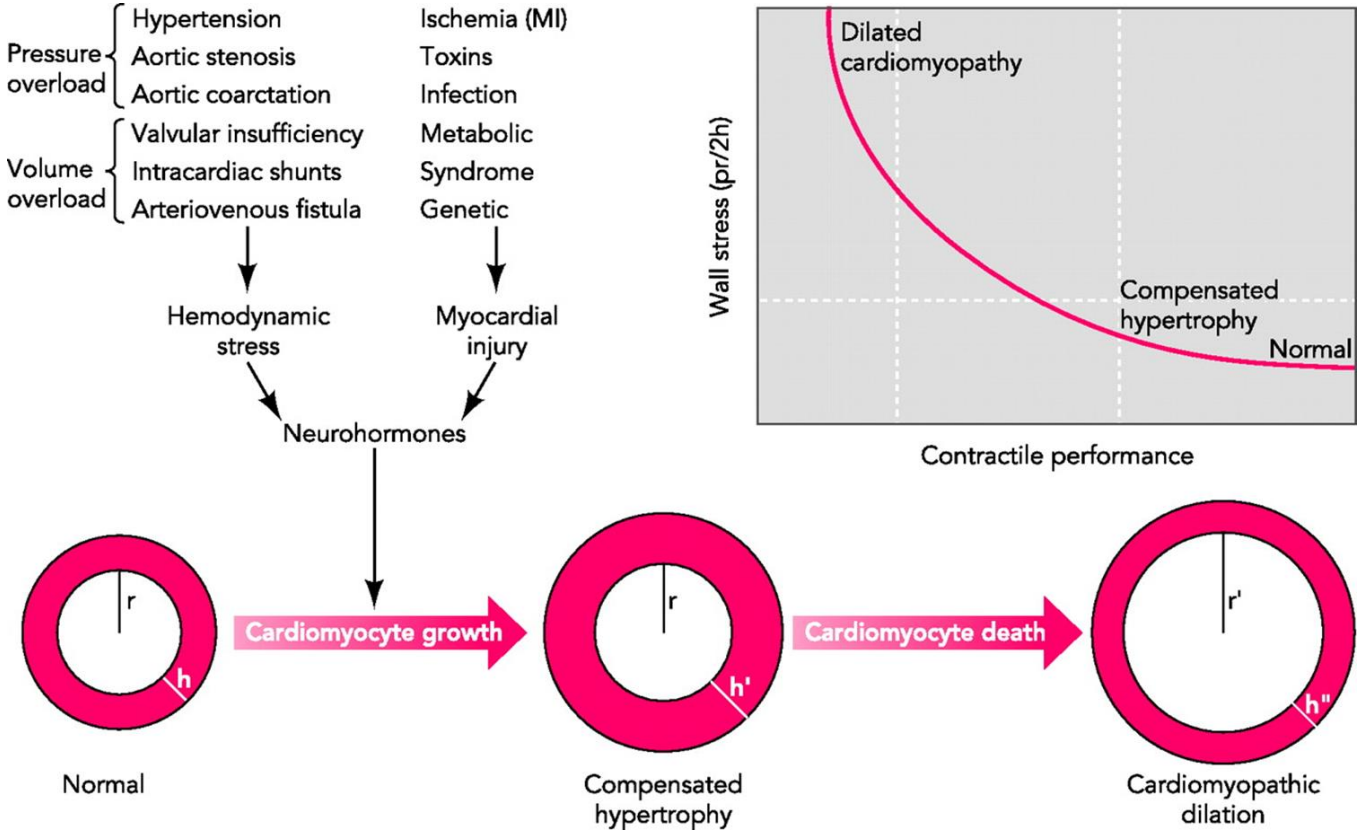
Compensatory mechanisms to maintain CO

- **(4) ventricular remodelling** as a response to
  - volume or pressure overload
    - increases in LV wall thickness decrease LV wall stress following Laplace's law, thereby maintaining cardiac efficiency

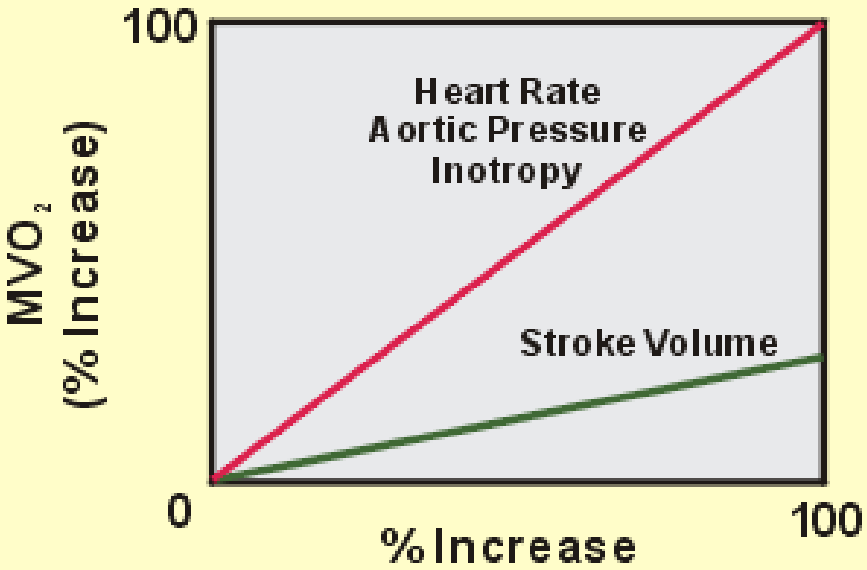


  - increased oxygen demand
    - wall tension + any degree of ischemia
  - background conditions



Factors influencing myocardial O_2 consumption (MVO_2)

- **(1) wall tension**
  - that's why O_2 demand is ↑ in pressure or volume overload
- (2) contractility
- (3) heart rate
  - that's why (i.e. 2 & 3) O_2 demand is ↑ during sympathetic activation
- (4) myocardial mass
  - that's why O_2 demand is ↑ in cardiac hypertrophy (esp. maladaptive)
- rough estimate of energetic demands of heart: **tension-time index** (TTI)
  - SBP x heart rate



Effects of changes in heart rate, aortic pressure, inotropic state, and stroke volume on myocardial oxygen consumption (MVO_2). Changes in stroke volume have a much smaller influence on MVO_2 than changes in heart rate, inotropy, or aortic pressure.

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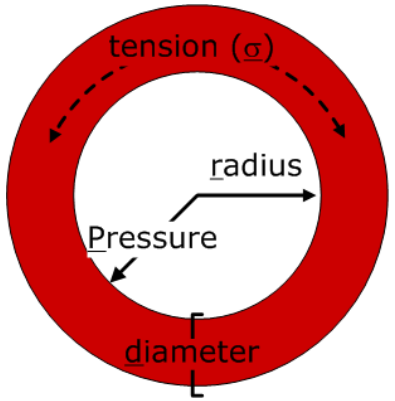
Wall tension x pressure or volume overload x MVO_2

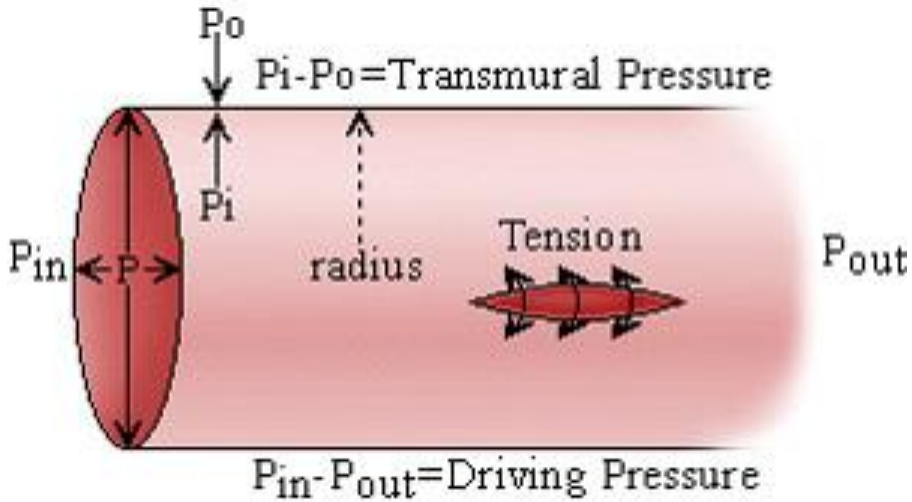
- wall tension (σ) = tension generated by myocytes that results in a given intraventricular pressure at a particular ventricular radius
- pressure and volume overload have very various effects on MVO_2
  - afterload = pressure
  - preload = volume (filling ~ end-diastolic pressure)
- $V = 4/3\pi \times r^3$
- $r = \sqrt[3]{V}$
- $\sigma = P \times \sqrt[3]{V} / d$

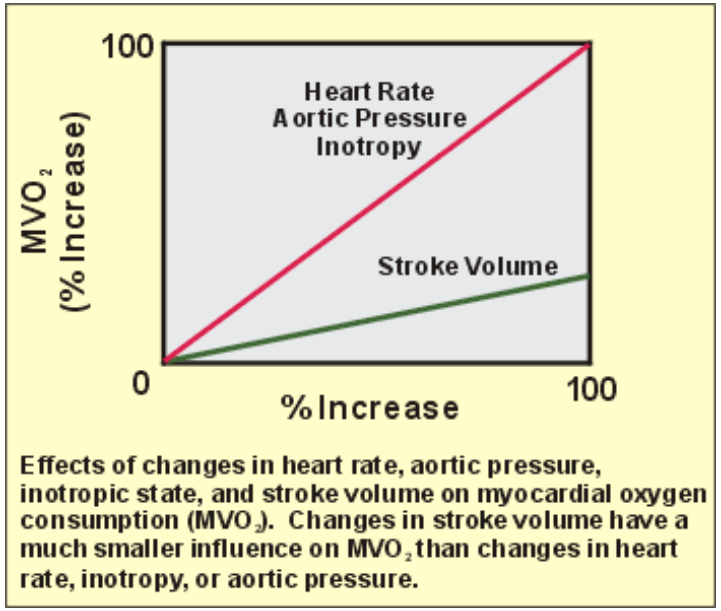


La Place law:

$\sigma = P \times r / d$

for detail see previous slide





Effects of changes in heart rate, aortic pressure, inotropic state, and stroke volume on myocardial oxygen consumption (MVO_2). Changes in stroke volume have a much smaller influence on MVO_2 than changes in heart rate, inotropy, or aortic pressure.

- 100% increase in ventricular volume (V) increases wall tension (σ) by only 26%
- in contrast, increasing intraventricular pressure (P) by 100% increases wall tension (σ) by 100%!

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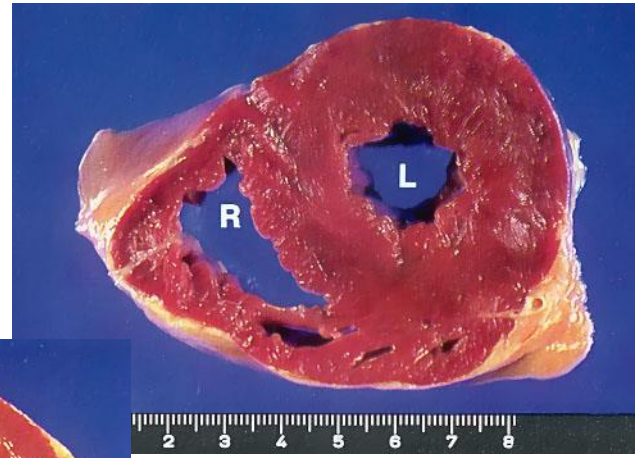
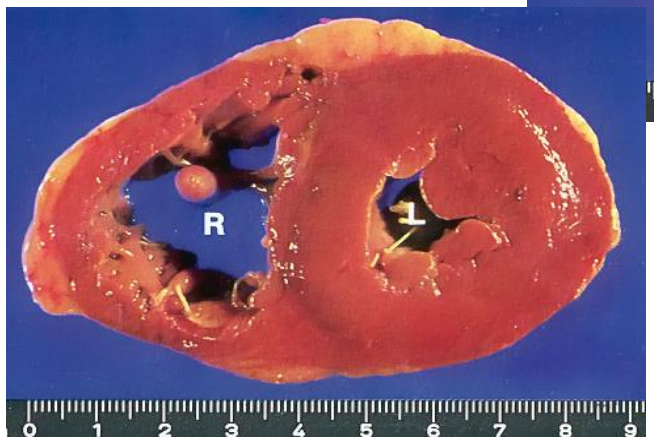
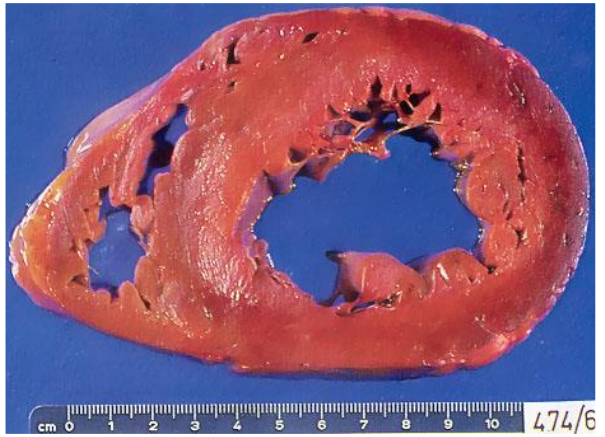
Why hypertrophy does not ↓ O_2 consumption at the end

- the heart develops hypertrophy to reduce ventricular wall stress and maintain function and efficiency in response to an increased workload
- hypertrophy (↑ **d**) normalizes wall tension (σ) per gram of myocardium in case of pressure or volume overload
  - $\sigma = P \times r / d$
  - initially, it does reduces MVO_2 when wall tension increases and heart has to generate higher pressure to overcome V or P overload
- however, as the total mass of myocardium increases, consumption of O_2 increases as well
  - myocardial hypertrophy is not paralleled by similar growth of coronary bed







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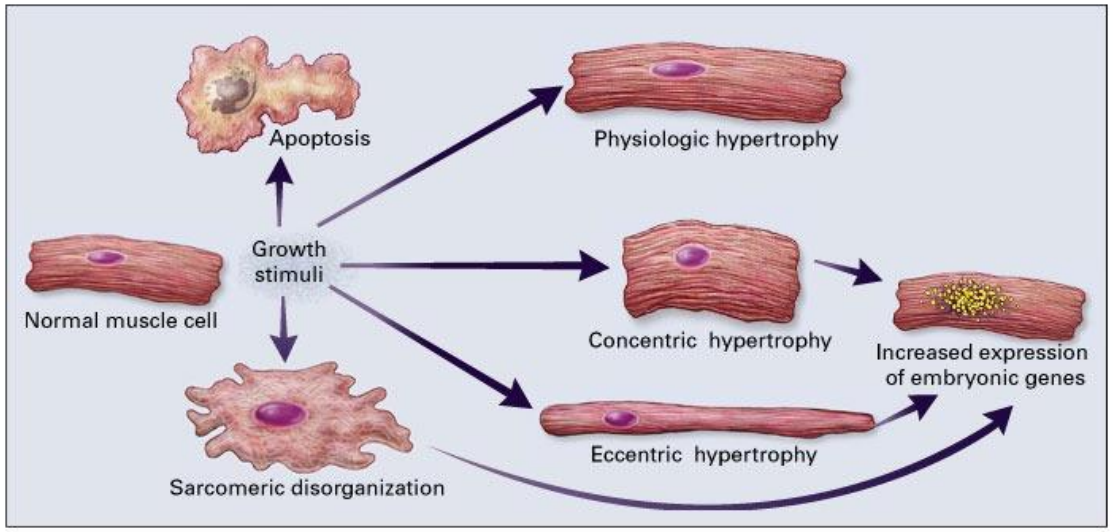
Cardiac hypertrophy - physiological

- individual cardiomyocytes often undergo enlargement
  - cardiac hypertrophy increases contractility, at least initially, through the addition of sarcomere units
- two types of hypertrophy (each form regulated by distinct cellular signalling pathways):
  - physiological
    - occur during normal postnatal growth, pregnancy and repetitive endurance training, and is mainly identified by a mild (10–20%) increase in ventricular volume with a coordinated increase in wall thickness (eccentric hypertrophy) and individual cardiomyocyte growth in both length and width
    - after relief of the stimulus, physiological hypertrophy is reversed and the heart returns to its original dimensions
    - no interstitial or replacement fibrosis or cell death
    - pathways: cell survival signalling, increased energy production and efficiency, angiogenesis proportional to the ventricular wall growth, antioxidant systems, mitochondrial quality control, and cardiomyocyte proliferation and regeneration
  - pathological
    - initially develops as an adaptive response, but pathological hypertrophy generally progresses to diastolic dysfunction and heart failure



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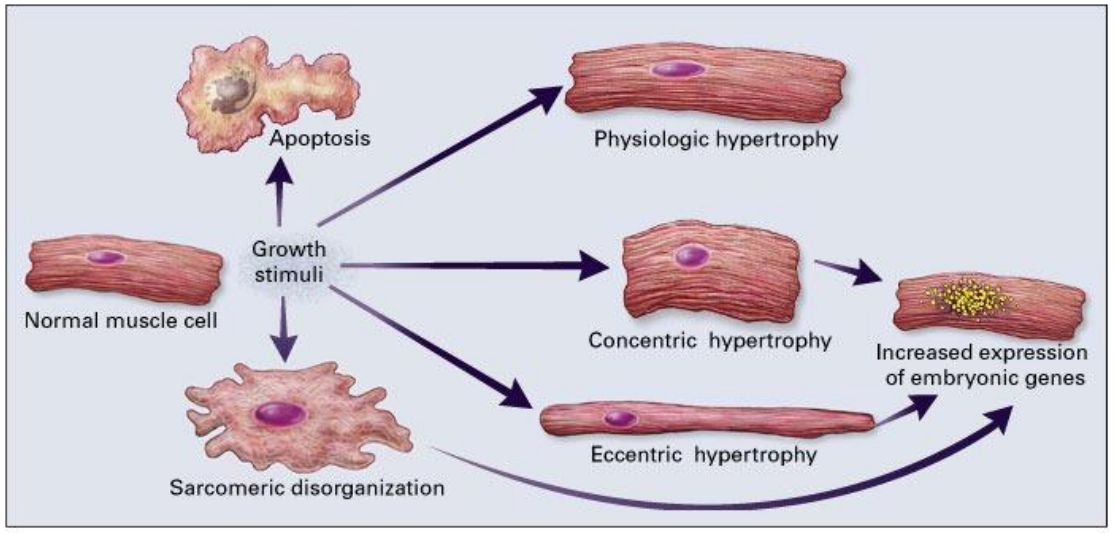

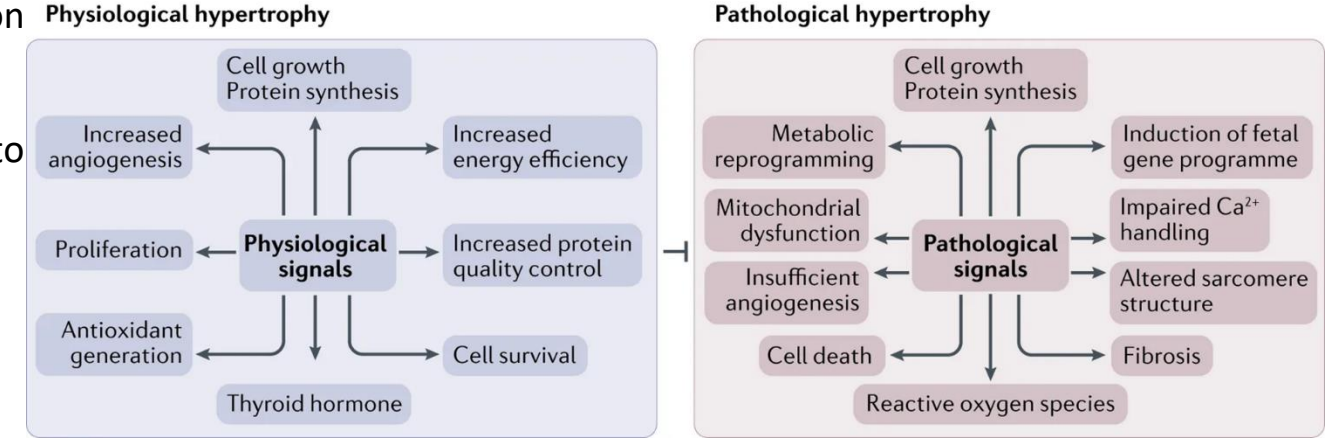

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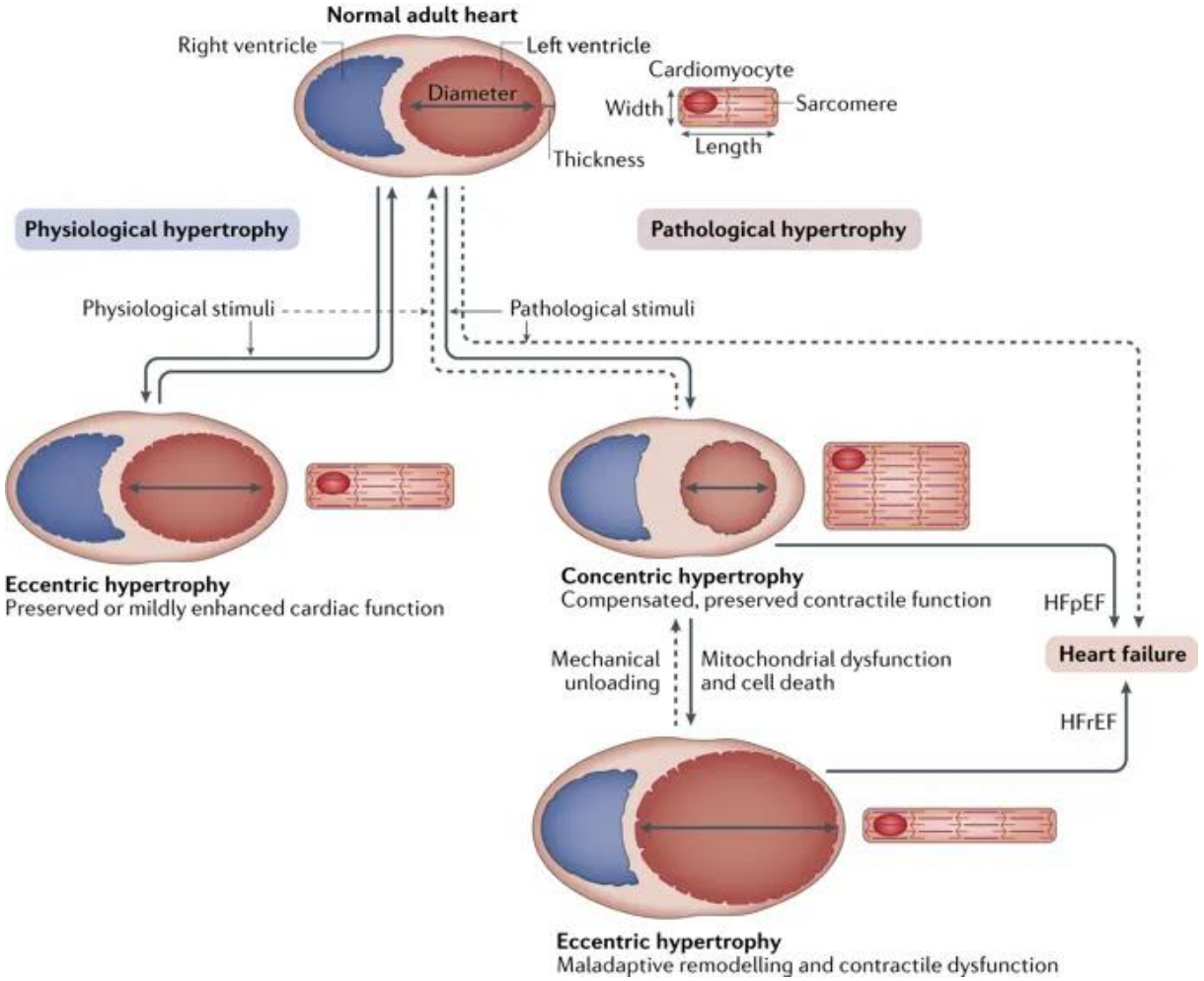
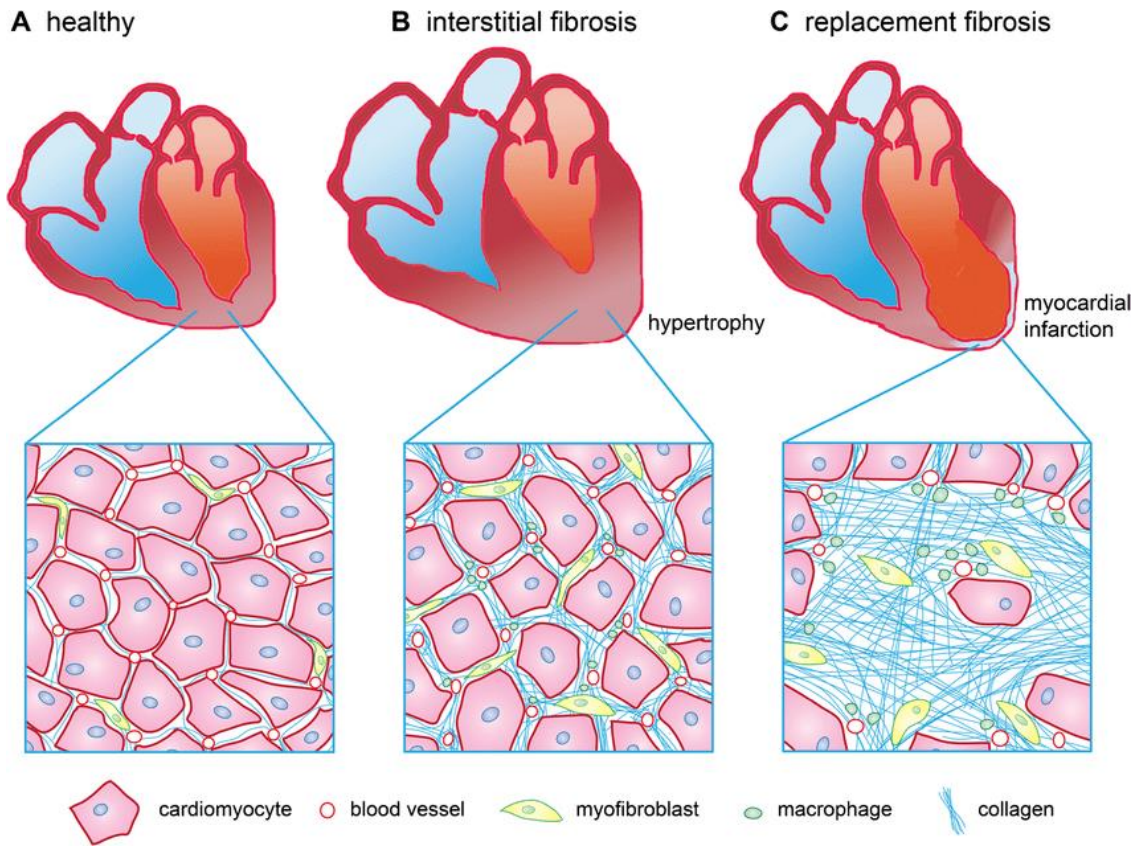
Pathological cardiac hypertrophy





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In fact, there are many LV remodelling patterns

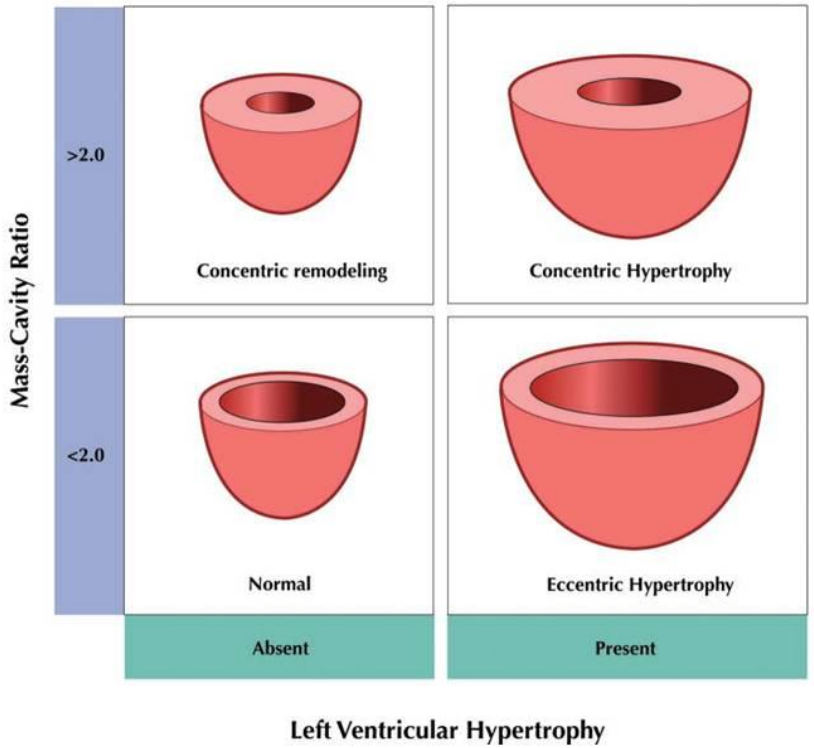

Figure 1. Diagram of LV Remodeling Patterns
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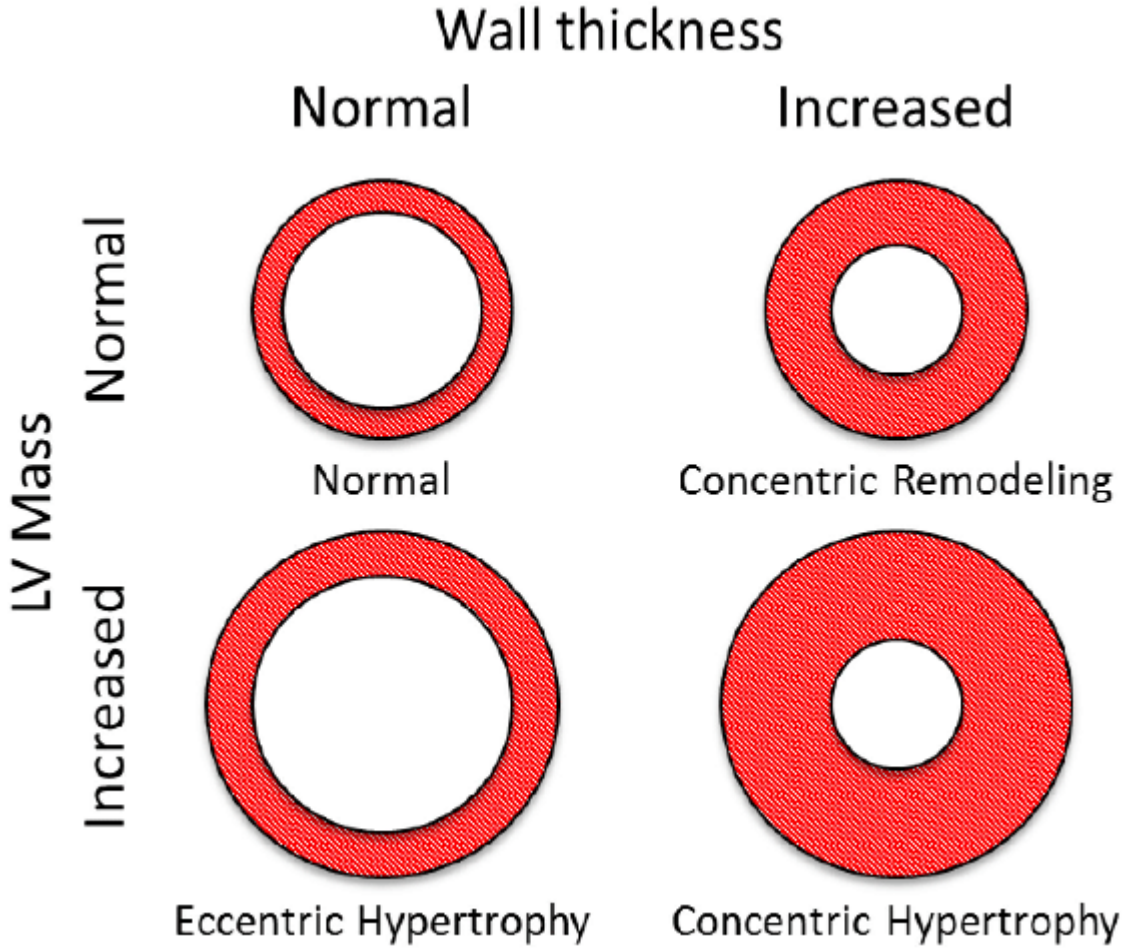

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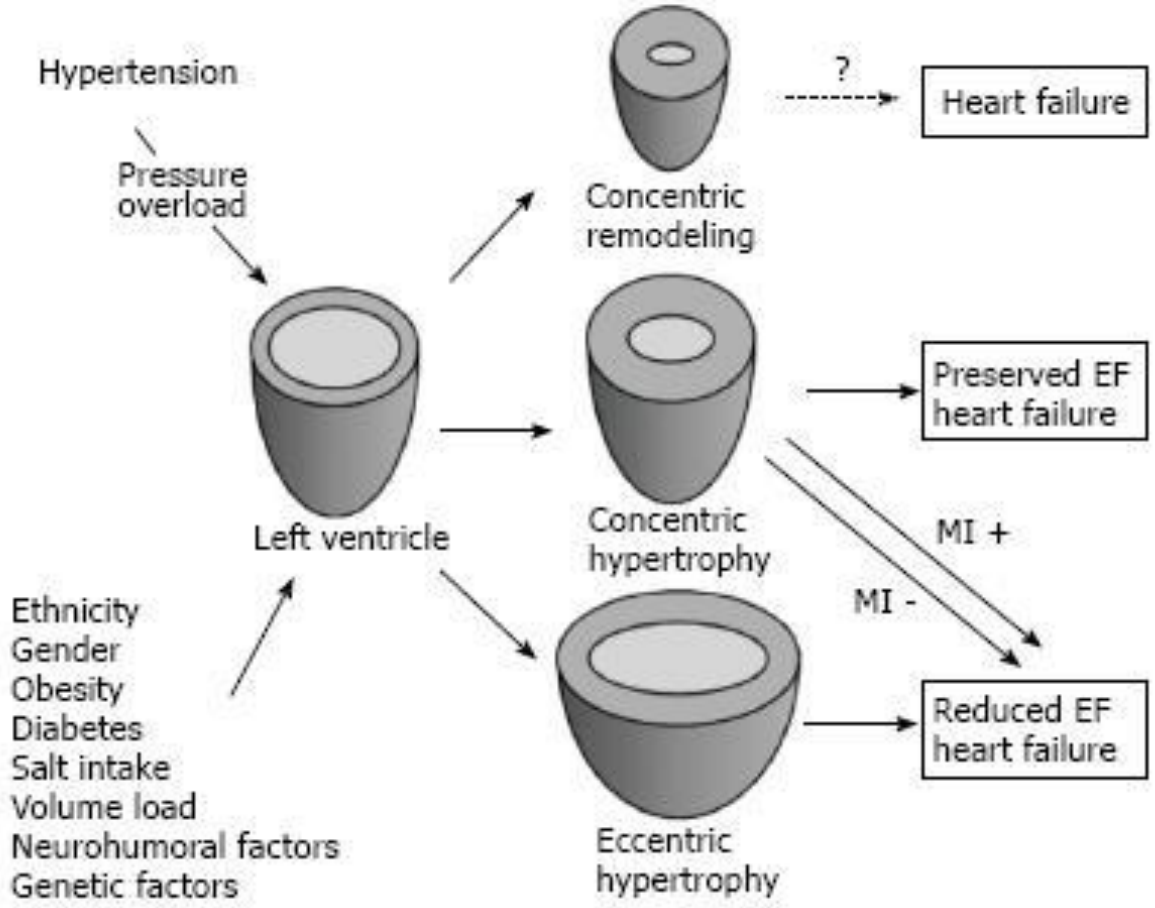
Various progression/prognosis of HF according to type od remodelling



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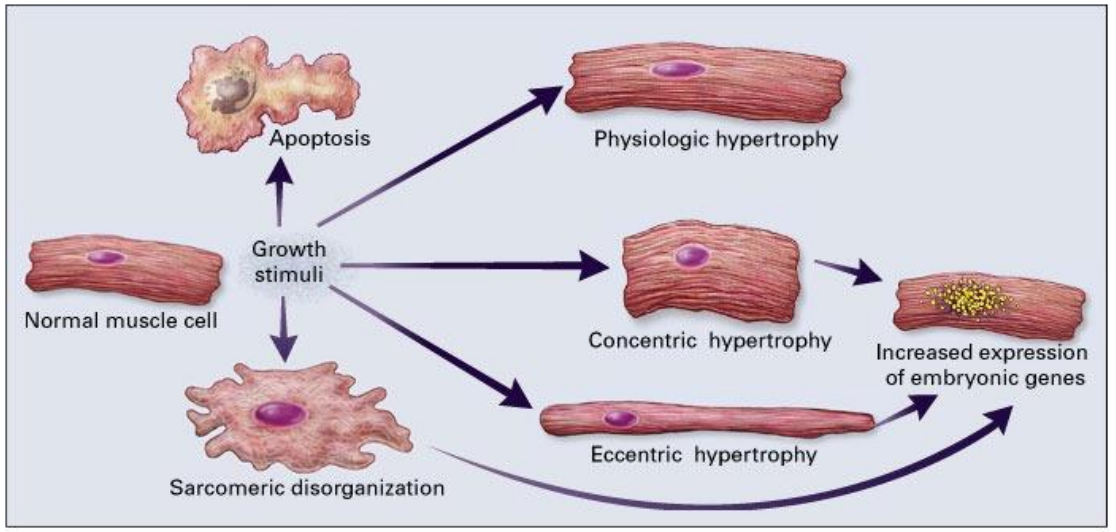
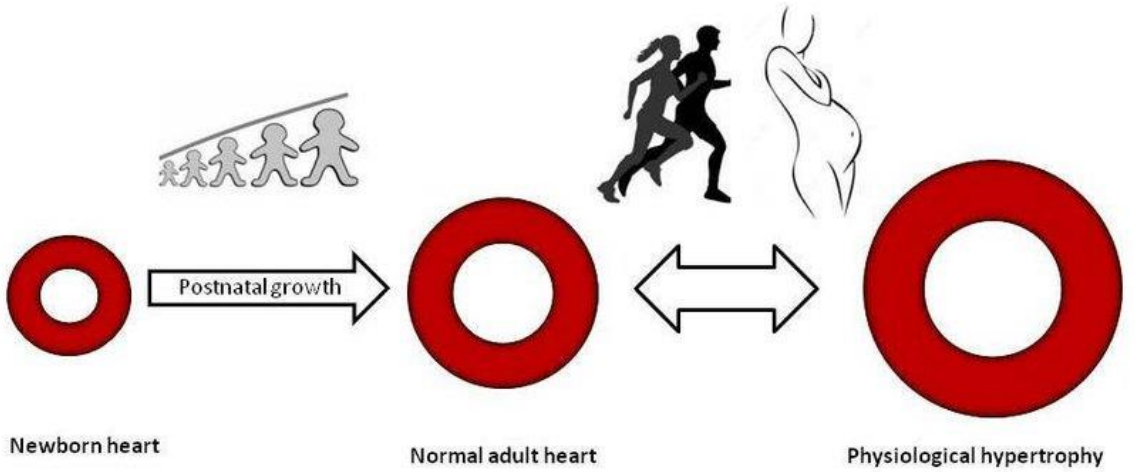
Cardiac hypertrophy - physiological

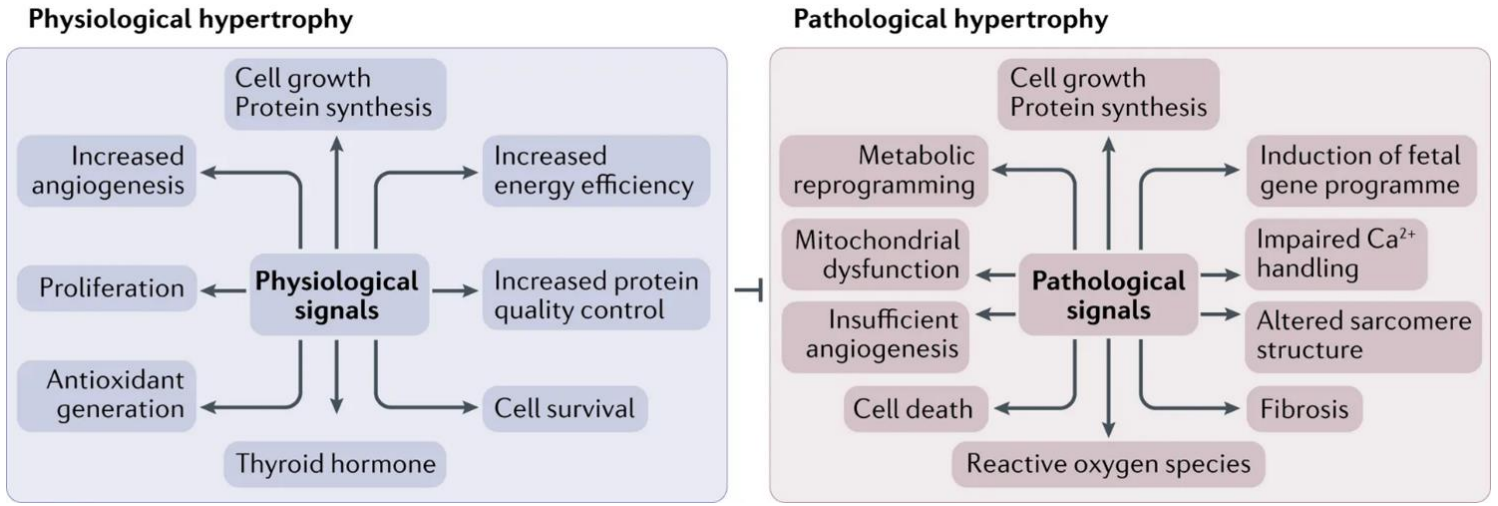
- individual cardiomyocytes often undergo enlargement
  - cardiac hypertrophy increases contractility, at least initially, through the **addition of sarcomere units**
- two types of hypertrophy (each form regulated by distinct cellular signalling pathways):
  - (1) physiological
    - occur during normal postnatal growth, pregnancy and repetitive endurance training, and is mainly identified by a mild (10–20%) increase in ventricular volume with a coordinated increase in wall thickness (eccentric hypertrophy) and individual cardiomyocyte growth in both length and width
    - after relief of the stimulus, physiological hypertrophy is reversed and the heart returns to its original dimensions
    - **no interstitial or replacement fibrosis** or cell death
    - pathways: cell survival signalling, increased energy production and efficiency, **angiogenesis** proportional to the ventricular wall growth, antioxidant systems, **mitochondrial biogenesis** quality control, and cardiomyocyte proliferation and regeneration

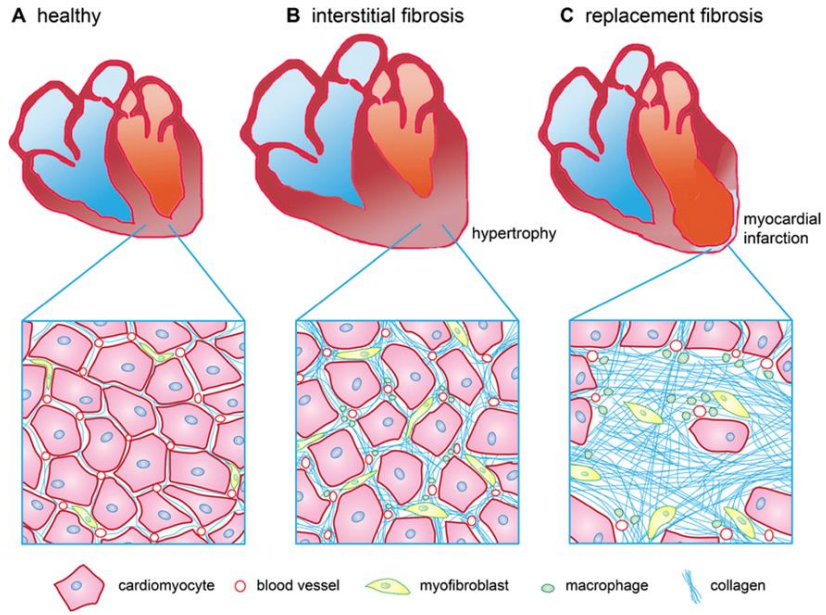




Cardiac hypertrophy - physiological

- (2) pathological
  - observed in patients with myocardial infarction, valvular diseases (aortic stenosis, mitral or aortic regurgitation), chronic hypertension, storage diseases (such as lipid, glycogen, and misfolded-protein storage diseases), and genetic cardiomyopathy resulting from mutations in genes encoding sarcomere proteins, such as hypertrophic cardiomyopathy (HCM).
  - metabolic syndrome (obesity and diabetes mellitus) are important comorbidities
  - initially identified by a reduction in ventricular chamber dimension with increased wall thickness (concentric hypertrophy), where cardiomyocytes typically increase in thickness more than in length
  - later, this might lead to ventricular chamber dilatation (eccentric hypertrophy) with impaired contractile function (maladaptive remodelling), with lengthening of individual cardiomyocytes
  - **initially** develops as an **adaptive response**, but pathological hypertrophy generally progresses to diastolic dysfunction and heart failure (with either preserved (HFpEF) or reduced ejection fraction (HFrEF))
  - pathways: cell death, **fibrosis**, dysregulation of Ca^{2+}-handling proteins, mitochondrial dysfunction, **metabolic reprogramming**, reactivation of fetal gene expression (such as those encoding atrial natriuretic peptide; natriuretic peptide B (BNP; also known as brain natriuretic peptide); myosin heavy chain, cardiac muscle β-isoform (MYHCβ; also known as myosin 7 or MYH7); and skeletal muscle α-actin), impaired protein and mitochondrial quality control, altered sarcomere structure, and **insufficient angiogenesis**





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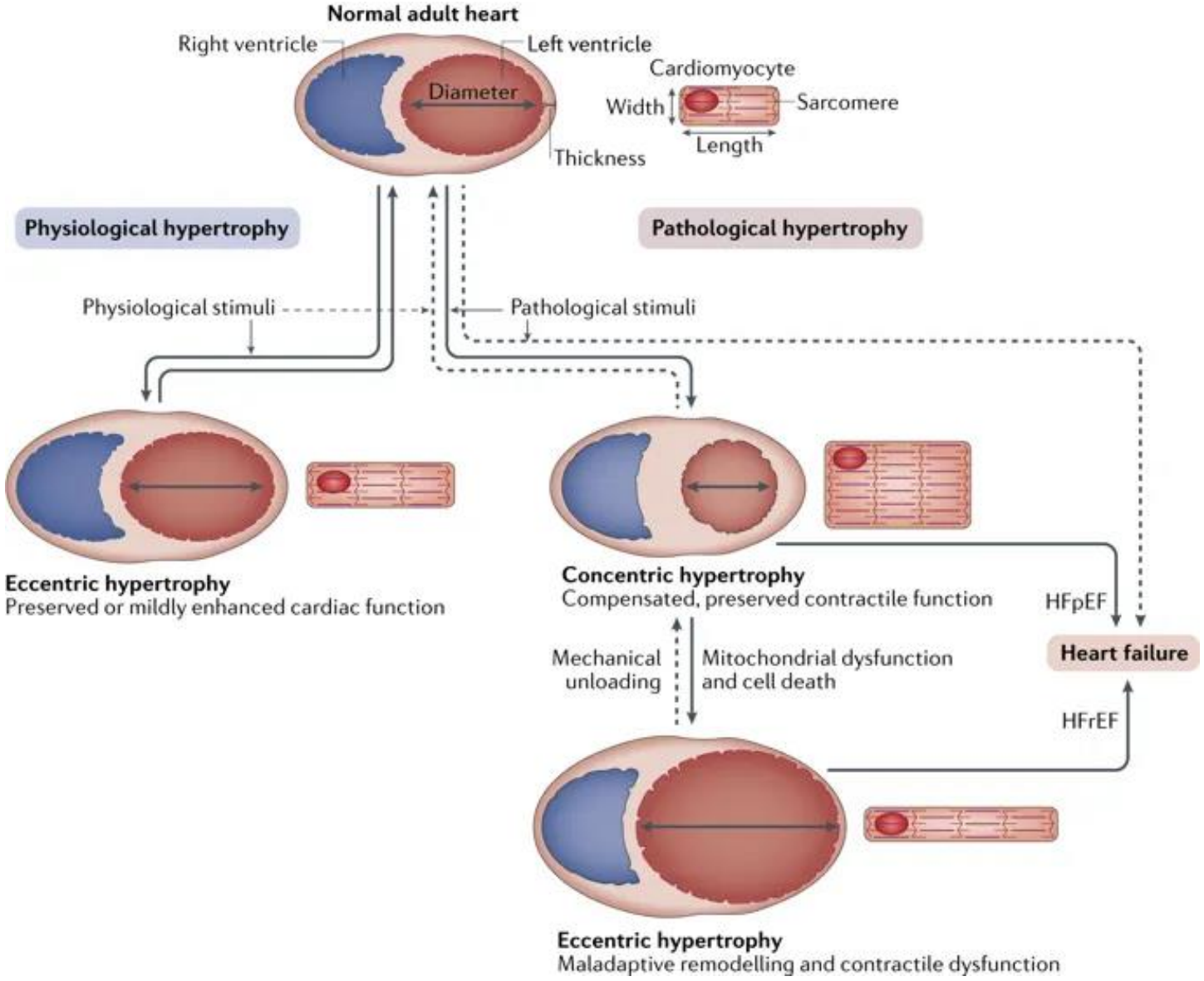

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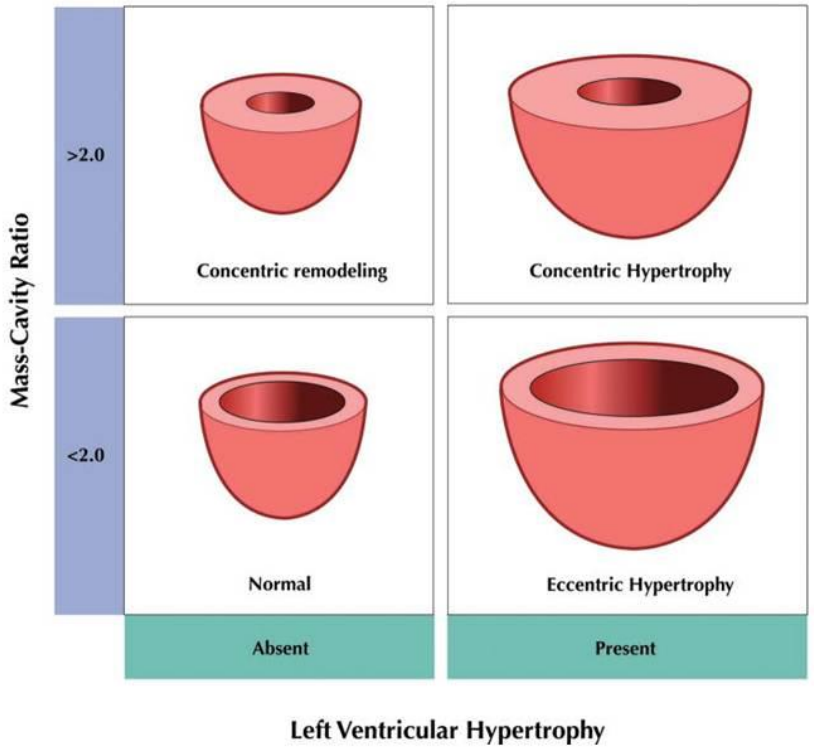

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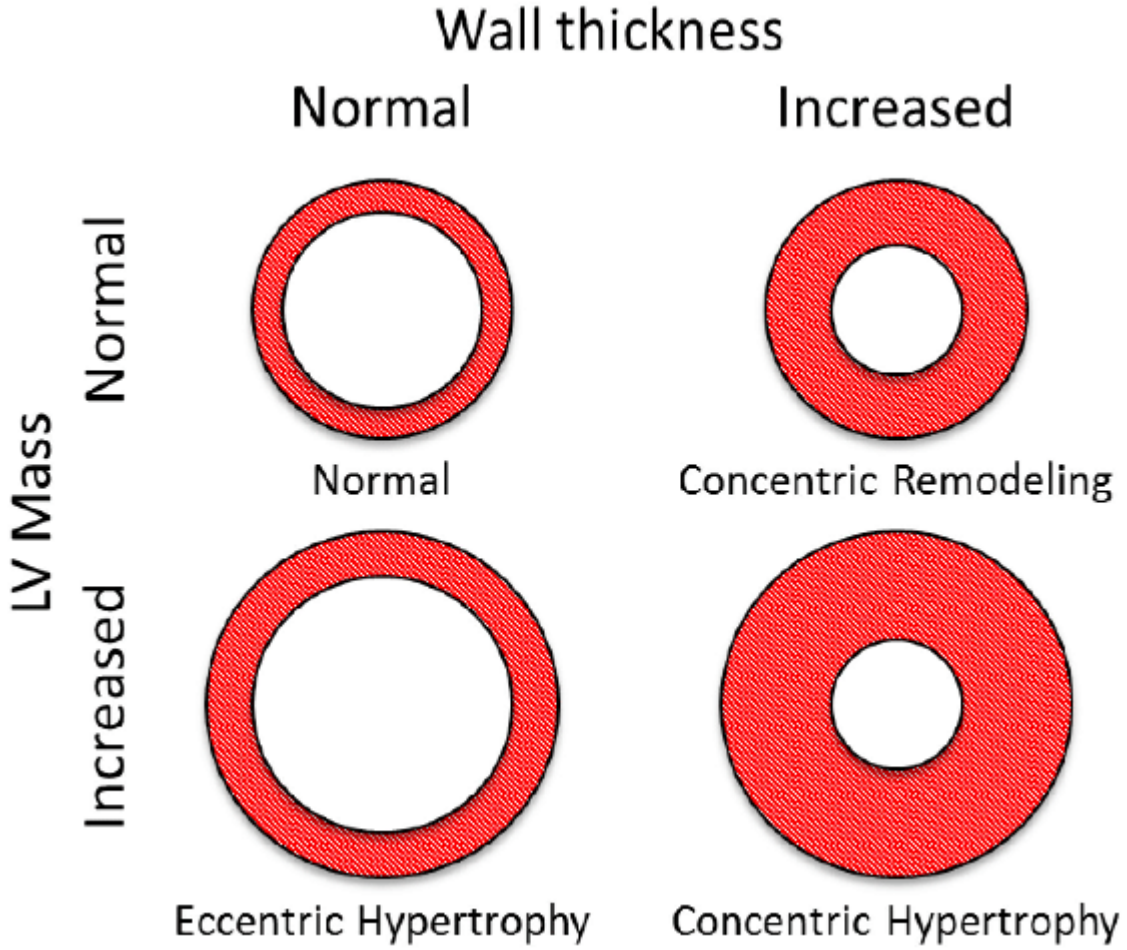

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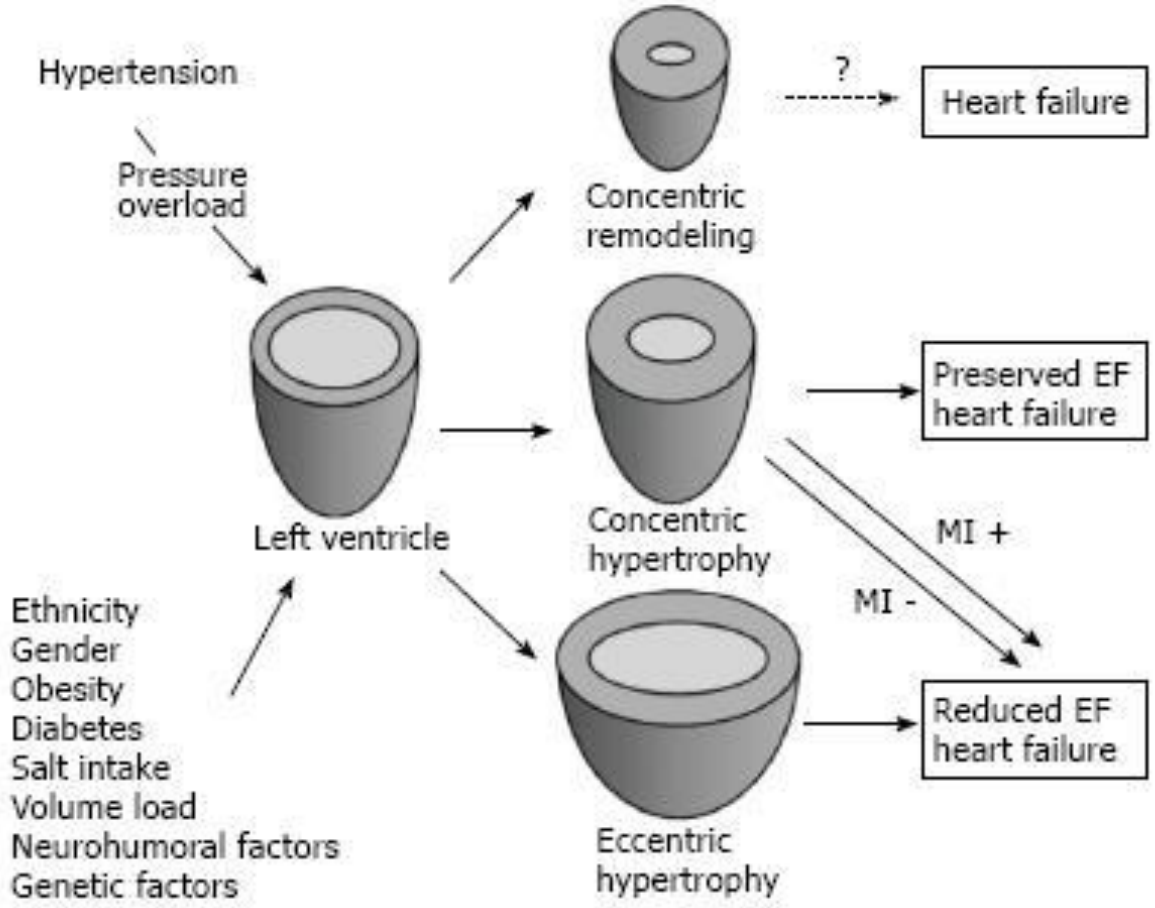

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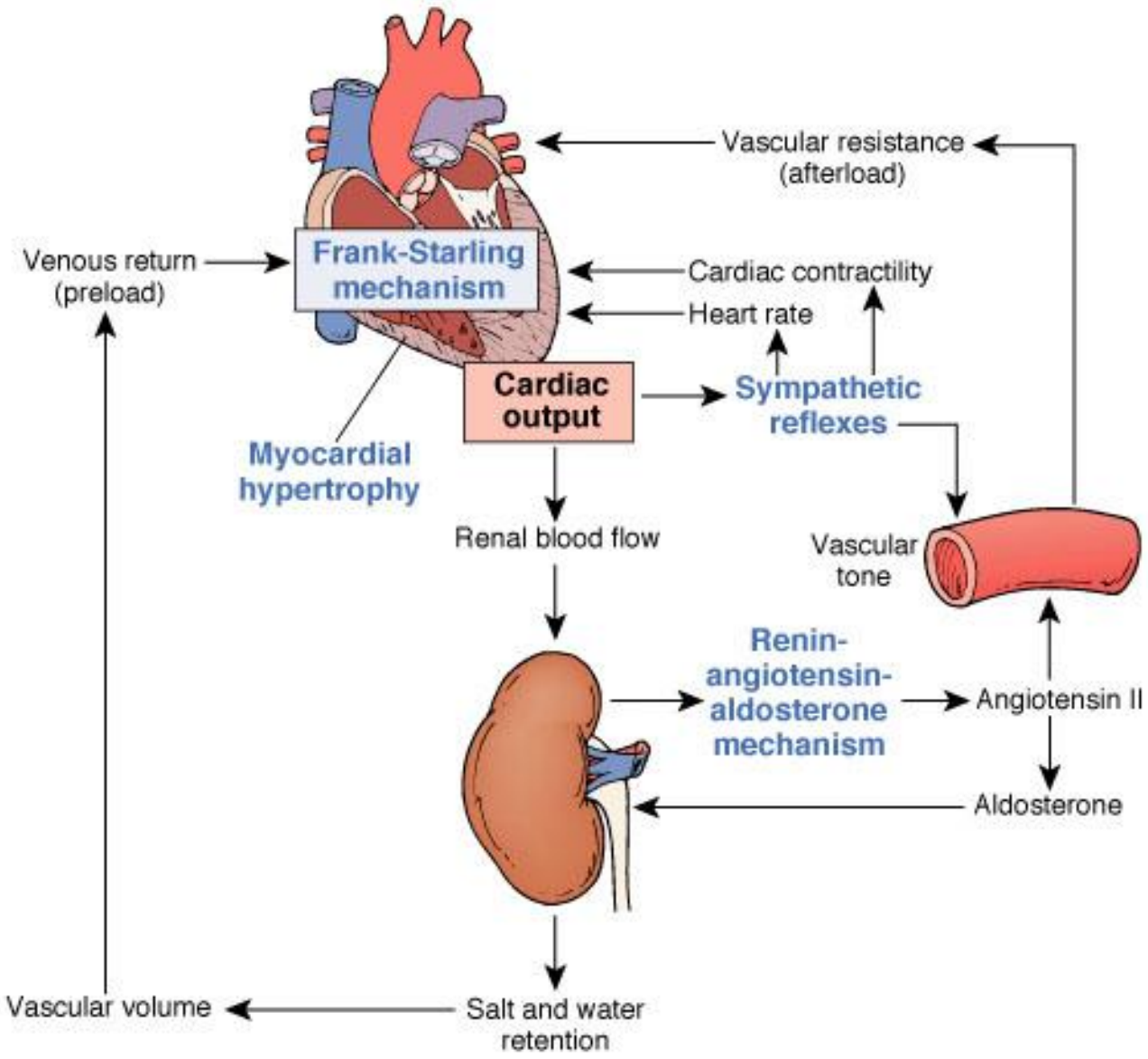
Summary – compensatory mechanisms operating in HF



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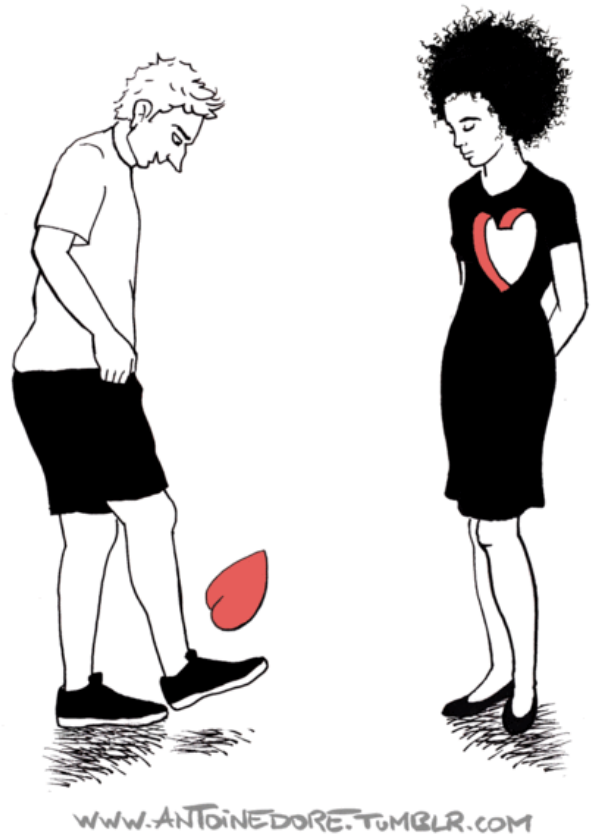

HEART FAILURE AS A CLINICAL SYNDROME

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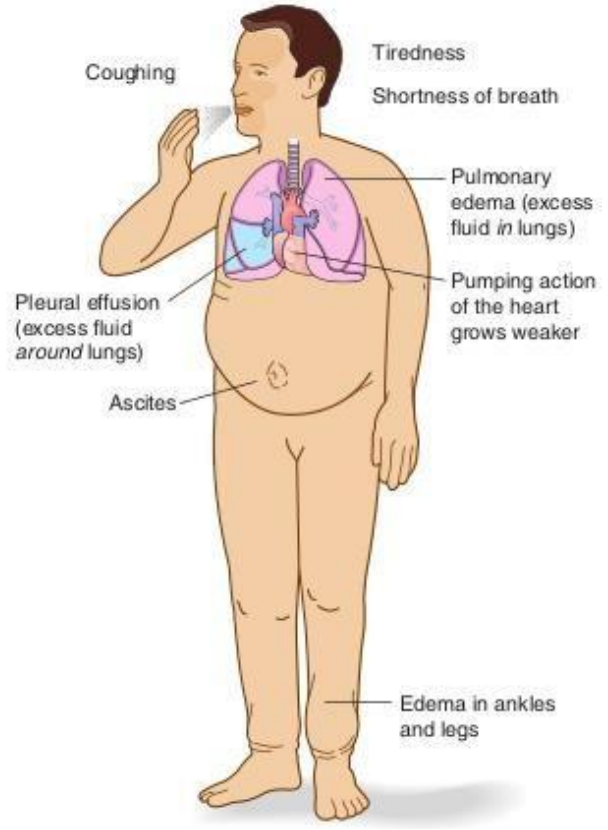
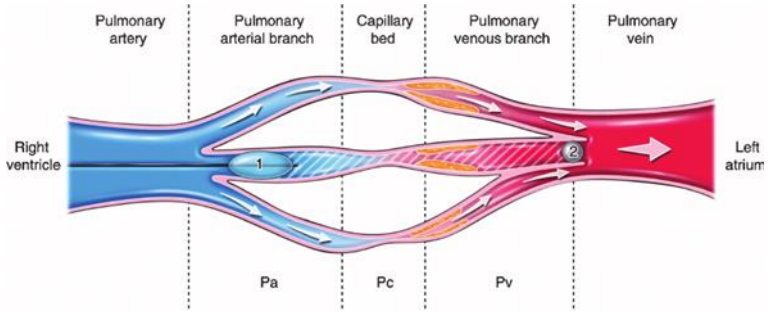
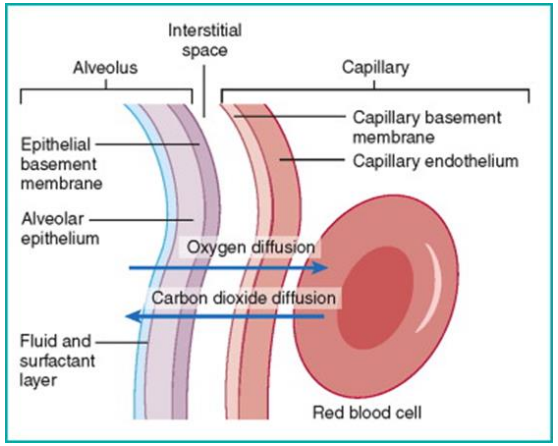
Signs and symptoms of HF

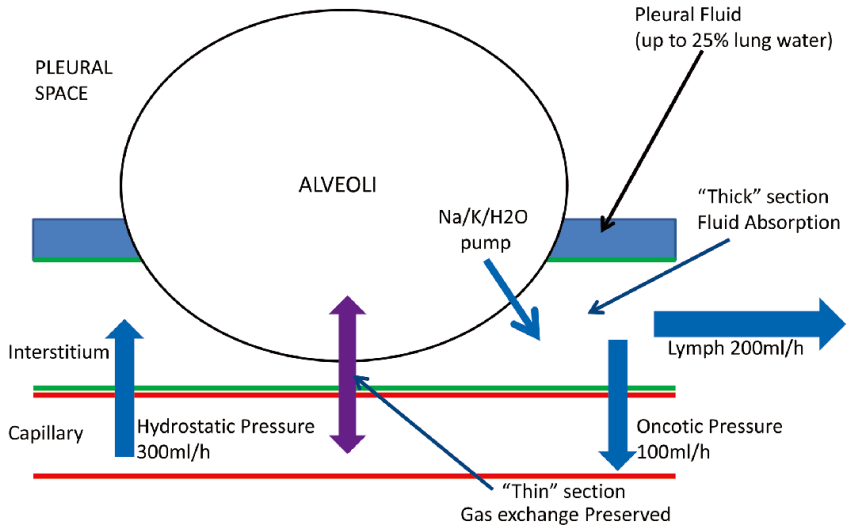
- result of the clinical sequelae of inadequate CO
  - fatigue is common as the failing heart cannot sustain enough CO to meet the body's metabolic needs and conserves blood flow to the heart and brain
  - nausea and lack of appetite may also occur as blood is shifted from the gastrointestinal tract to the more vital organs.
  - palpitations can occur as the failing heart tries to accommodate for the lack of CO with a faster heart rate (HR)
- and lack of efficient venous return
  - dyspnea, cough, and wheezing result from increased pressure in the pulmonary capillary bed due to ineffective forward flow from the left ventricle
  - lower extremity edema, as well as ascites, occurs when the right ventricle is unable to accommodate systemic venous return = **congestive heart failure**



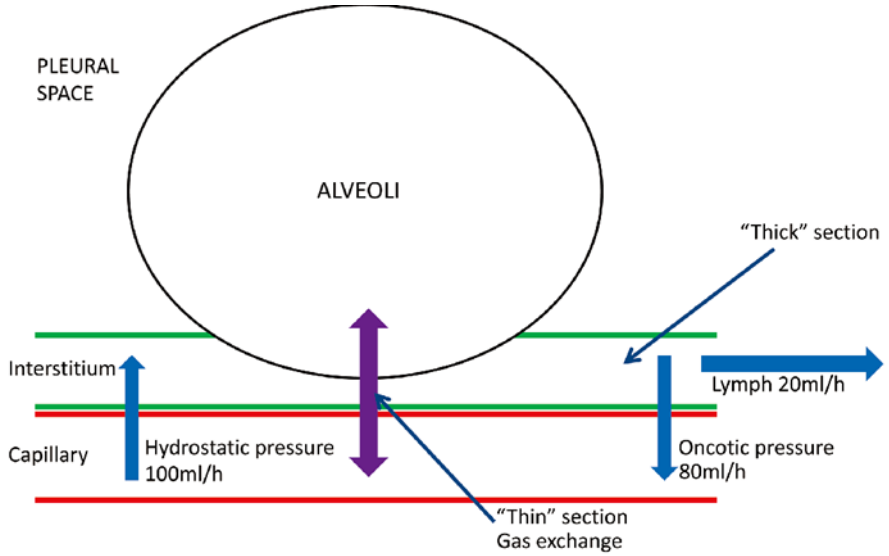


Alveolar-capillary barrier → pulmonary edema

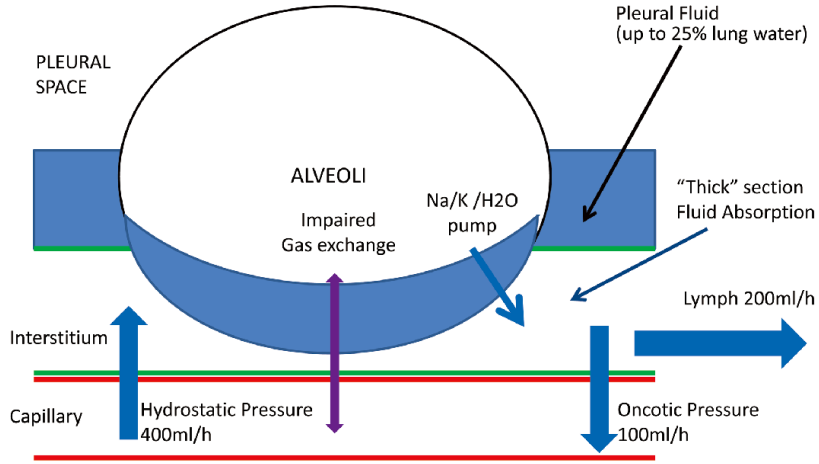




(1) interstitial edema



(2) alveolar edema



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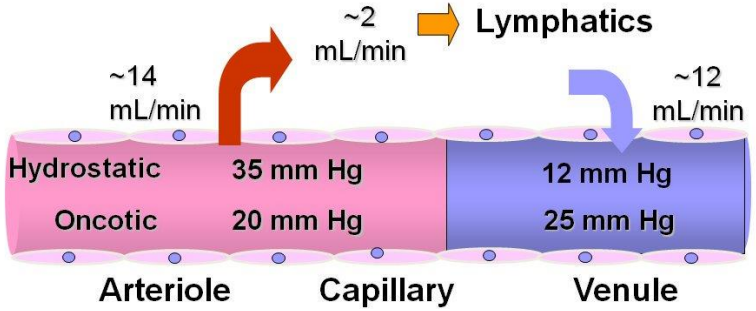
Pathophysiology of pulmonary congestion/edema

- accumulation of fluid in the lungs, resulting in impaired gas exchange and arterial hypoxemia
- occurs sequentially
  - first developing in the hilar region of the lungs,
  - followed by filling of the interstitial space (= interstitial edema)
  - and finally, in its most severe form, by alveolar flooding (= alveolar edema)
- pulmonary edema is the result of an imbalance between the forces that drive fluid into the alveoli and the mechanisms for its removal
  - Starling equation
- simplistic model, pulmonary edema has been traditionally classified into 2 categories
  - **cardiogenic or hydrostatic pulmonary edema** results from high pulmonary capillary hydrostatic pressures
  - **non-cardiogenic or high permeability edema** is characterized by injury to the alveolar-capillary barrier with leakage of protein-rich fluid into the interstitium and air spaces
- Studies based on the ratio of edema fluid protein to serum protein in patients with cardiogenic and noncardiogenic pulmonary edema have shown that frequently there is a combination of high hydrostatic pulmonary capillary pressure and high permeability of the alveolar-capillary barrier, leading to a significant overlap between the two groups
  - if increased hydrostatic pulmonary capillary pressure per se were responsible for pulmonary edema formation, protein concentration of the alveolar lining fluid would be expected to decrease due to the influx of plasma ultrafiltrate
  - paradoxically, it nearly doubles

$$IFA = K[P_c - P_{if}] - x[O_c - O_{if}] - Q_{lymph}$$



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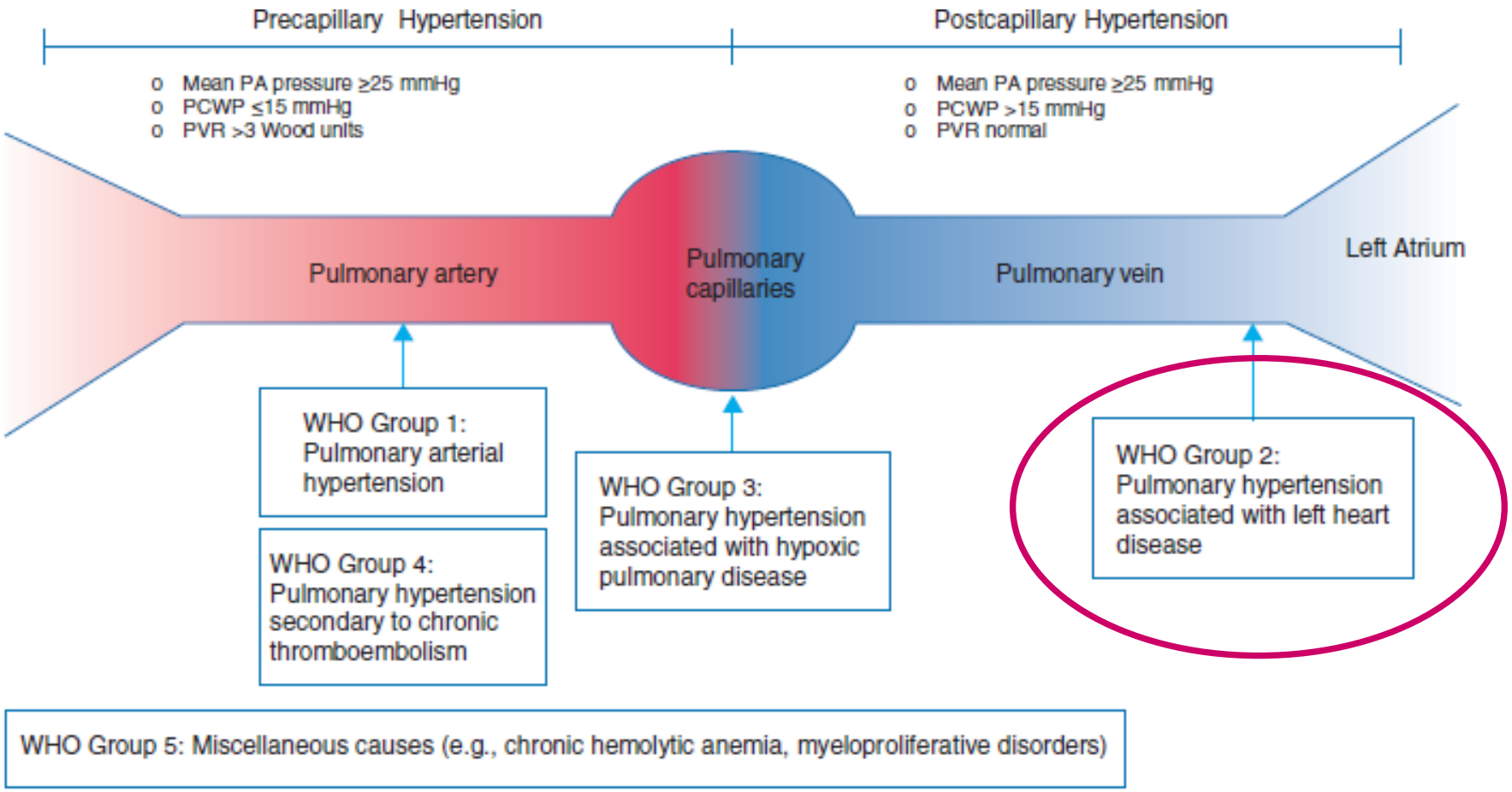
Pulmonary hypertension



Source: Navin Kumar, Anica Law: Teaching Rounds: A Visual Aid to Teaching Internal Medicine Pearls on the Wards
www.accessmedicine.com

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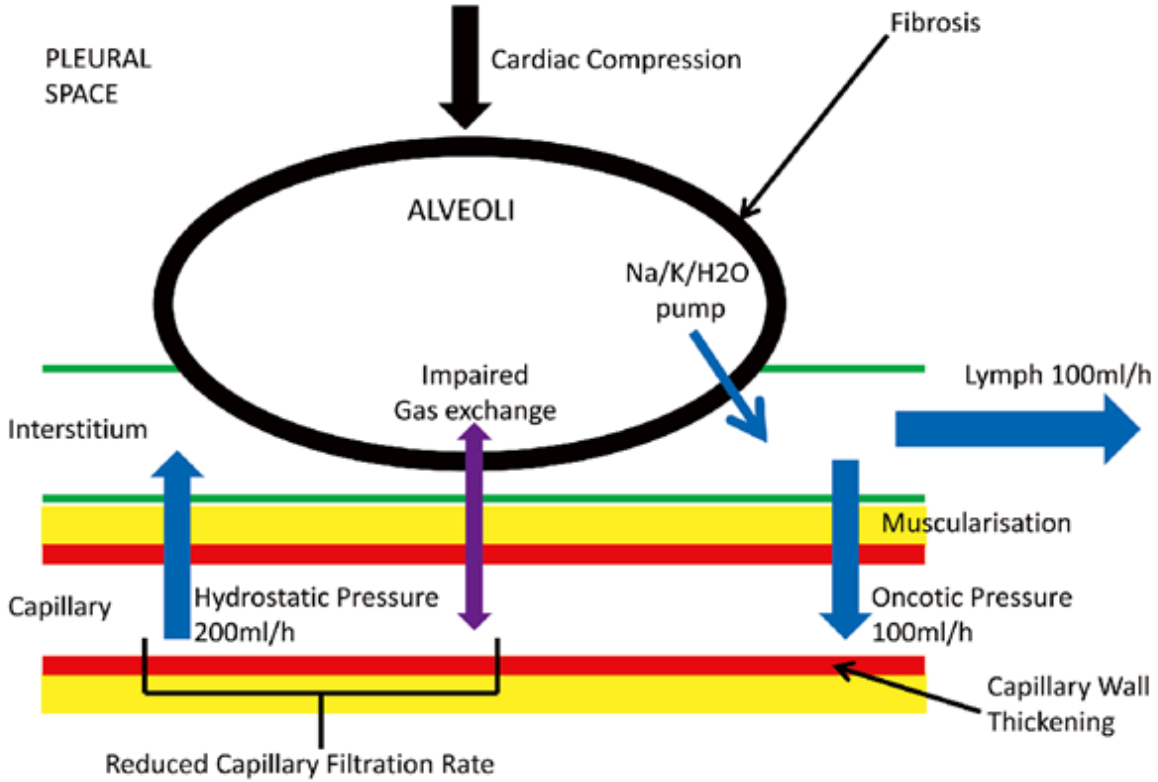
Alveolar-capillary barrier dysfunction

- whether a rise in the pulmonary capillary wedge pressure (PCWP) results in pulmonary oedema seems to depend on the rate at which this pressure rises
  - rapid rises in PCWP (as in acute HF) can result in pulmonary oedema at relatively low pressures
  - whilst those with longstanding pulmonary hypertension can tolerate remarkably high pressures without production of pulmonary oedema
- two fundamental processes may lead to alveolar-capillary barrier dysfunction in AHF
  - mechanical injury of the barrier due to increased hydrostatic pulmonary capillary pressures
  - inflammatory and oxidative lung injury
- ACM remodelling process (mainly excessive deposition of collagen type IV) may be protective against further high pressure damage and may increase resistance of the lung to the development of pulmonary edema in chronic HF patients
  - increased capillary basement membrane thickness and capillary dilatation, whilst overall capillary density falls 2
  - intimal thickening of the arteries and veins with muscularisation of the arterioles and venules
  - circumferential fibrosis of both veins and arteries
  - alveolar wall changes including increased interstitial tissue, interstitial pericapillary oedema, haemosiderin deposition and alveolar wall thickening due to excess collagen, cuboidal (as opposed to flat) epithelium and increased type II pneumocytes
  - compression of the peripheral airways by increased amounts of connective tissue 6. Bronchial smooth muscle hypertrophy



- **problems with breathing and gas exchange**
  - effect of posture on lung function
    - in the supine position (fluid from lower limbs to lungs)
  - restrictive ventilatory deficit (↓ FVC) with impaired diffusing capacity
    - airway obstruction (↓ FEV1, ↑RV) by excess fluid possible too
  - central sleep apnoea (CSA)
    - known as Cheyne-Stokes respiration or periodic breathing

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Thank you for your attention !

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