MUNI
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# Atherosclerosis and IHD

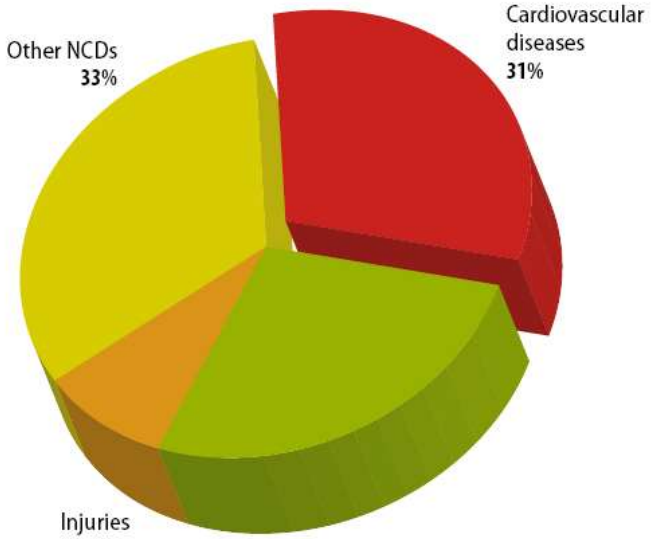
# Atherosclerosis definition

- Athera – the mush, sclerosis – hardening
- It is an inflammatory disease of arterial wall, characterised by lipid acumulation in altered macrophages – foam cells
- This leads into atherosclerotic plaque that may, according to its stability, cause acute or chronic arterial occlusion

# Atherosclerosis - epidemiology

- Cardiovascular diseases are responsible for aproximately 1/3 of mortality worldwide (most common cause
- In Czech Republic and Europe the number reaches cca ½
- 80% of CVD are caused by atherosclerosis, especially vascular disease of brain and heart
- It is also the most common cause of morbidity and invalidity
- In women, the onset is delayed by ~10 years, but overall prevalence and mortality are similar to men

Distribution of major causes of death including CVDs (*1*).



# IHD and CVD – mortality (WHO 2012)

Figure 27 World map showing ischemic heart disease mortality rates (age standardized, per 100 000) (1).

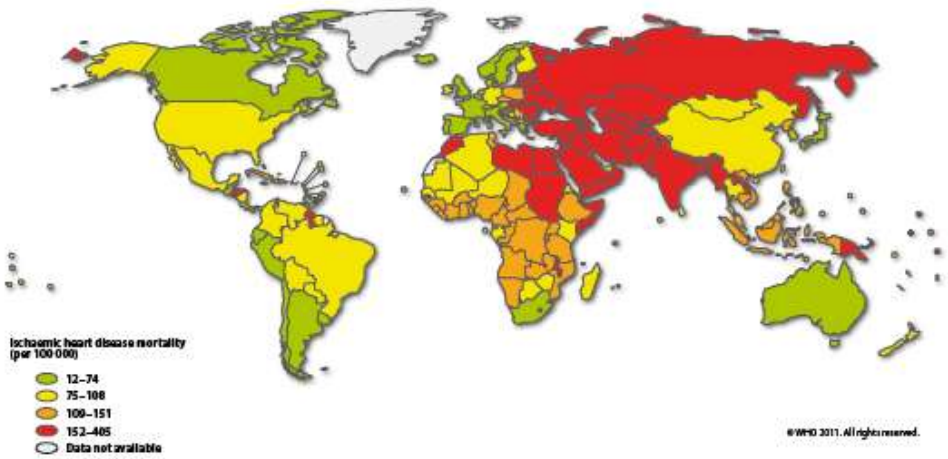
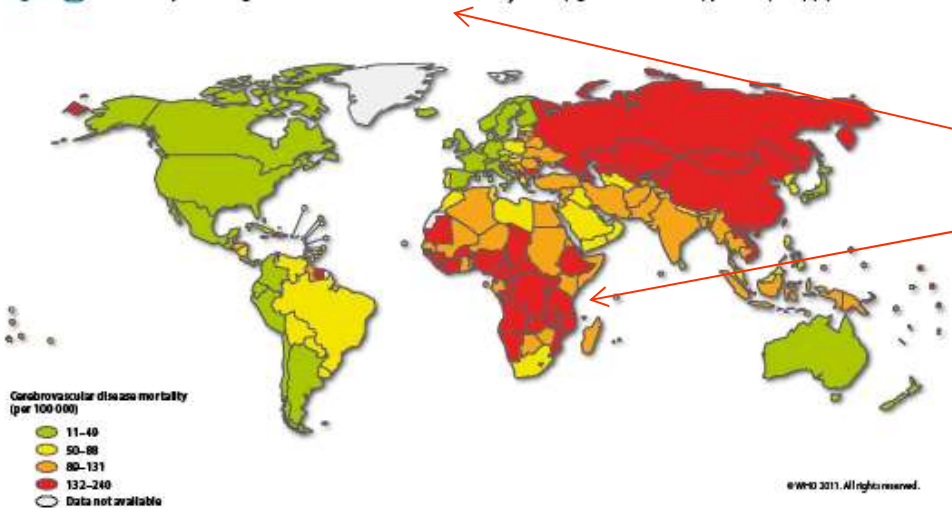
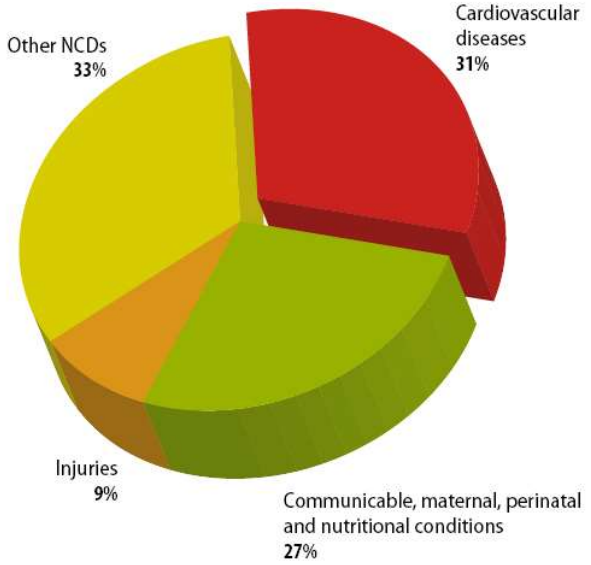



Figure 28 World map showing cerebrovascular disease mortality rates (age standardized, per 100,000) (1).




Global Atlas on Cardiovascular Diseases Prevention and Control

Distribution of major causes of death including CVDs (1).




incl. hemorrhagic stroke

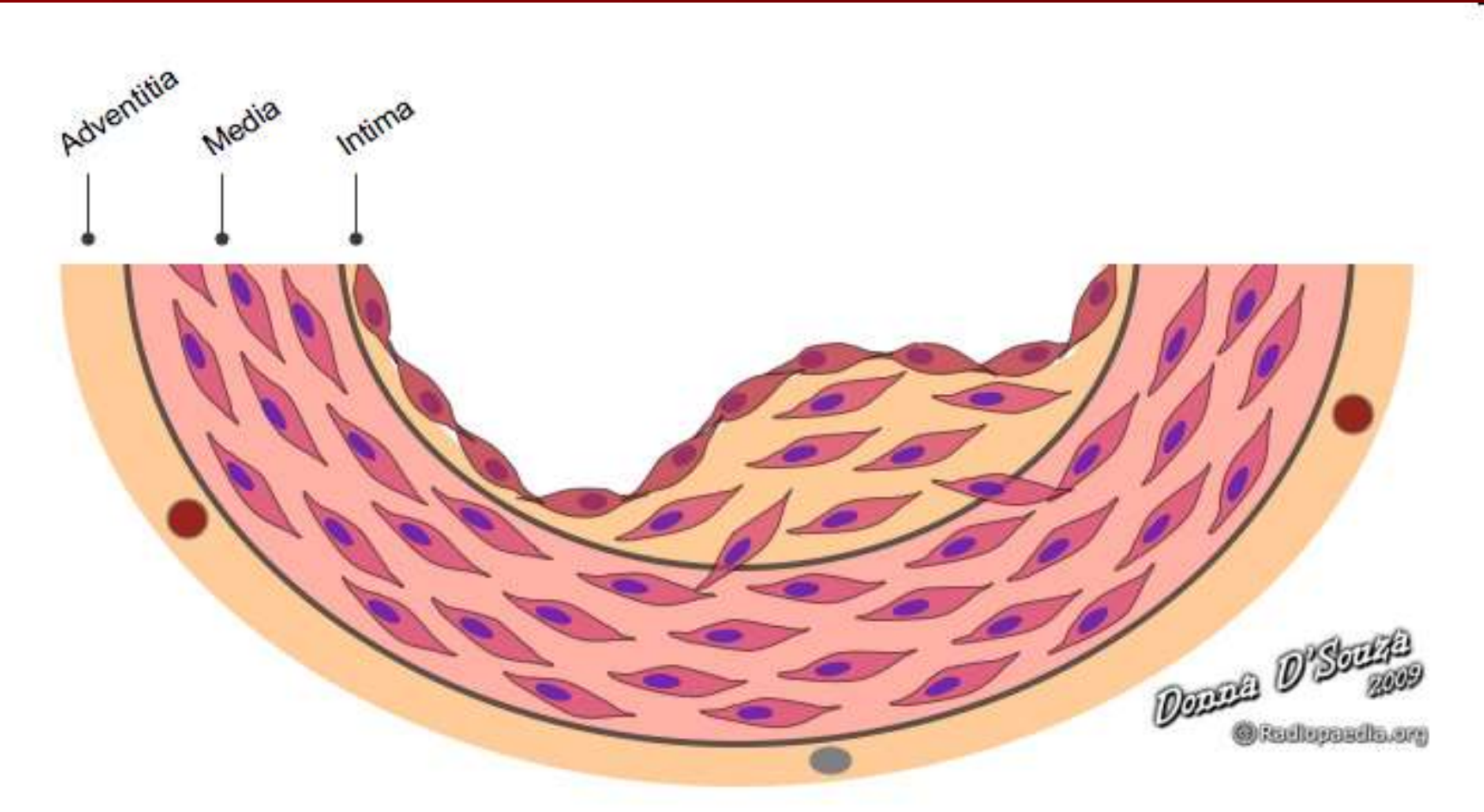
WHO (2011), 'World Health Organization - Global atlas on CVD prevention and control, URL: http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf'.

# Pathogenesis – theories

- Several mechanisms are employed in the pathogenesis of atherosclerosis
- Thus, there are several different points of view, e.g.:

1) „endothelial theory" („response to injury" – atherosclerosis as a result of endothelial damage and subsequent inflammatory response) - Russell Ross, 1973
2) „autoimmune theory" (cellular type – infiltration of subendothelial space by leukocytes, especially macrophages, domination of proinflammatory molecules and cytokines, uptake of oxidated lipoproteins by macrophages and their change into foam cells, migration of smooth muscle cells) – Rudolf Virchow, 1856
3) „tumour theory" (proliferation and clonal selection esp. in SMC) - Benditt & Benditt, 1973
4) „lipid theory" (damage of vascular endothelium by oxidated lipoprotein particles, especially LDL, or chylomicron and VLDL remnants, propagation of atherosclerosis because of their retention and receptor binding) – Nikolai Anitschkow, 1913

# Arterial wall



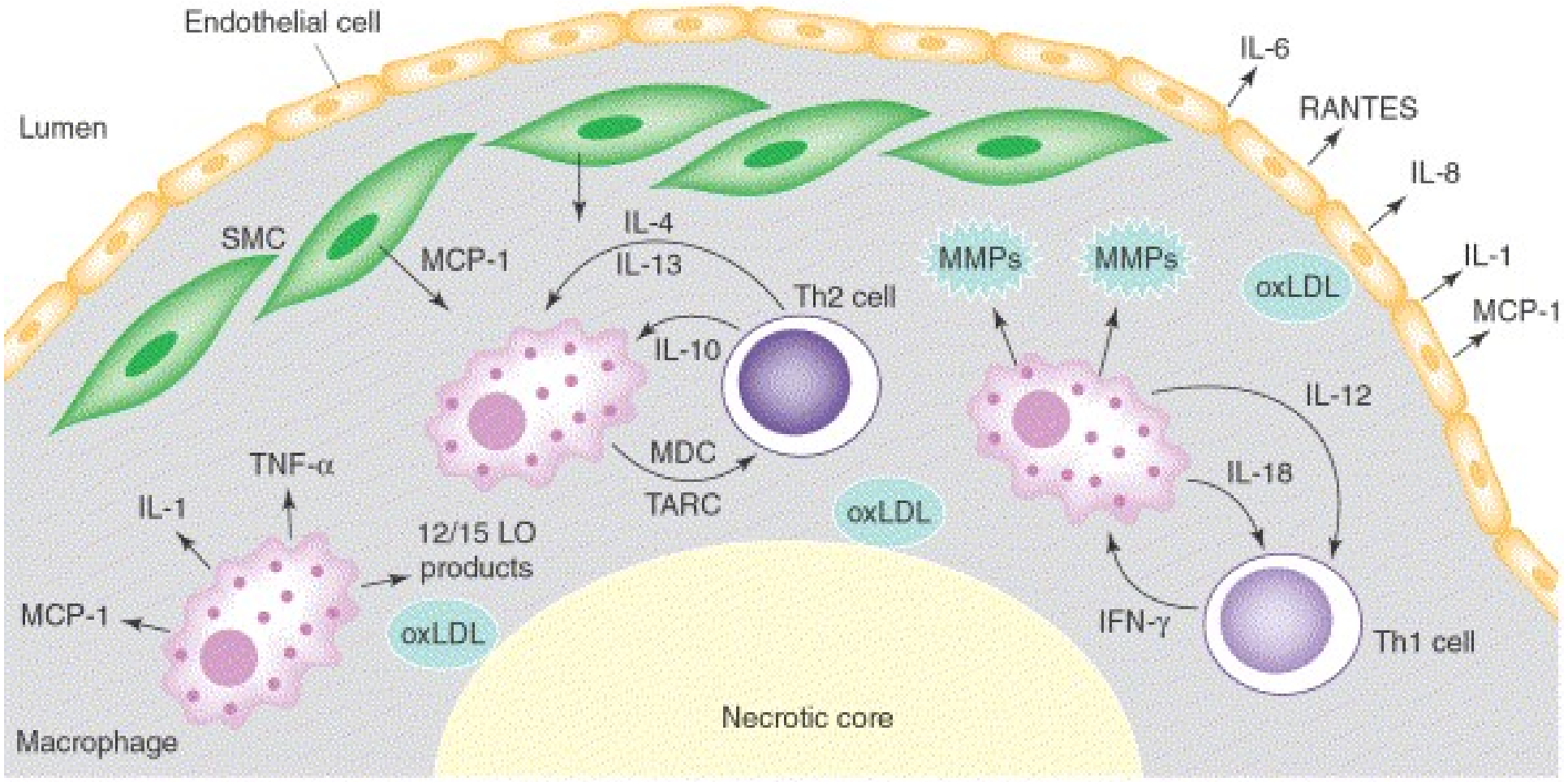

Intima/media thickness (IMT) is an important marker of atherosclerosis

# Endothelial damage and dysfunction

- Endothelial dysfunction is present already in initial stages of atherosclerosis
- Important consequence is lower synthesis of NO (endothelial relaxating factor) or anticoagulant factors (TFPI, thrombomodulin)
- „Leaky junctions" allow the passage of LDLs into the subendothelial space
- Damaged endothelium produces chemoattracting factors and adhesive molecules (ICAM, VCAM)
- Following risk factors are linked to endothelial damage:

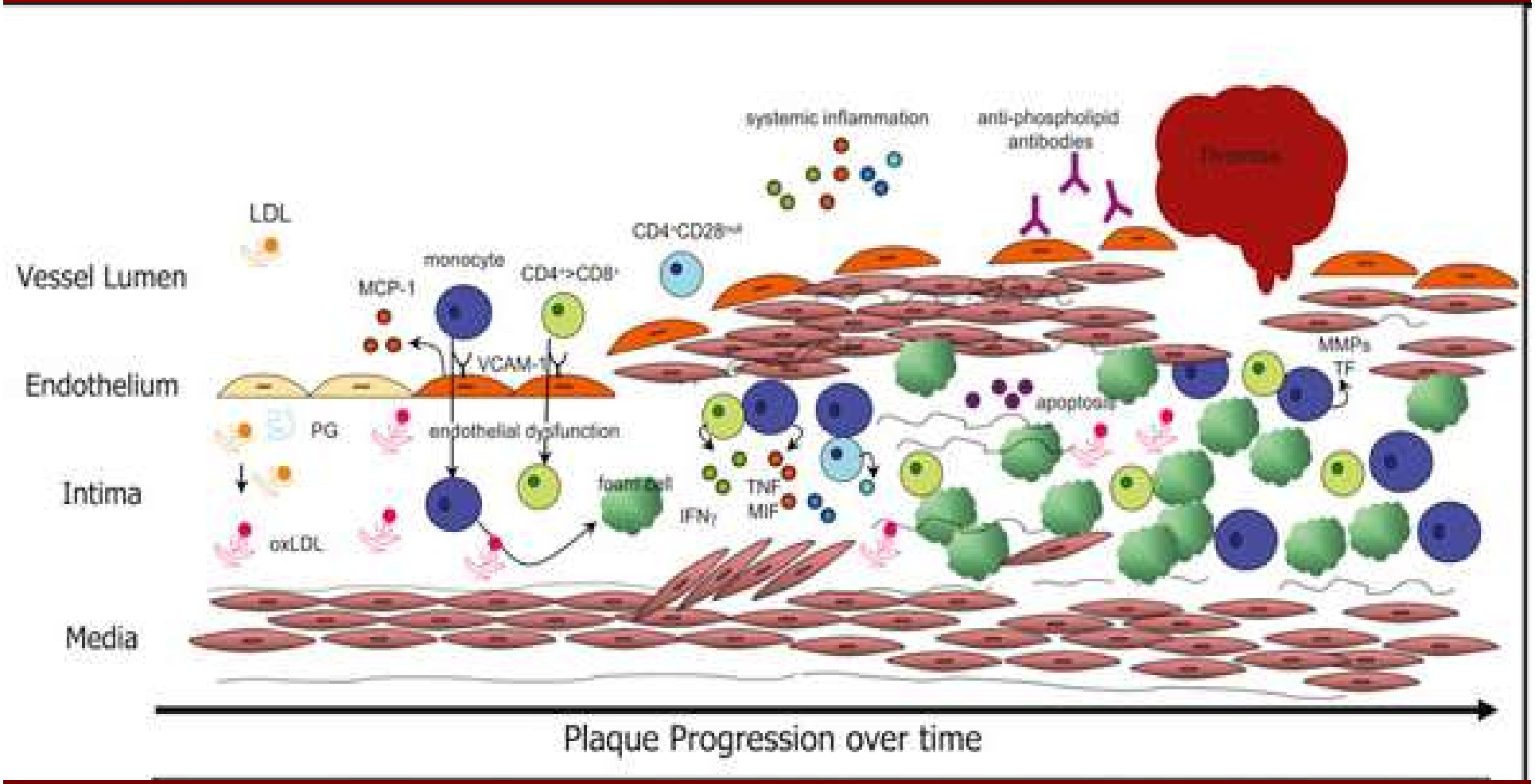
1) Mechanical stress in hypertension
2) Low an/or variable shear stress of vessel wall – points to localities at risk
3) Non-enzymatic glycation of endothelial proteins in hyperglycaemia
4) Components of cigarette smoke (esp. tar) – most important risk factor in the atherosclerosis of lower extremities
5) Low grade inflammation
6) Lipotoxicity – damage by oxidated lipoproteins, especially LDL – they subsequently pass into subendothelial space

# inflammation in arterial wall




TRENDS in Immunology

# Endothelial dysfunction, oxLDL and inflammation




Full, L. E., Ruisanchez, C., Monaco, C. (2009), 'The inextricable link between atherosclerosis and prototypical inflammatory diseases rheumatoid arthritis and systemic lupus erythematosus', *Arthritis Res Ther,* 11 (2), 217.

# Local inflammation of vessel wall

- Macrophages in vessel wall uptake damaged (oxidized) lipoproteins (esp. LDL, eventually CM remnants or IDL) by their scavenger receptors
- That leads into foam cells, producing many pro-inflammatory factors
- Heat shock proteins (esp. Hsp 60) are another autoantigen involved in atherosclerosis
- Foam cells support migration of other leukocyte types (e.g. Th1, Th 17 cells) and smooth muscle cells
- Smooth muscle cells are oligoclonal and some of them originate from circulating progenitors
- Some leukocyte populations can be inflammation-suppressing – CD25+ lymphocytes (Treg)
- Neutrophils are also present in advanced atherosclerotic plaque

# Infectious pathogens associated with atherosclerosis development (chronic low-grade inflammation)

Chlamydia (may play a causal role in vascular inflammatory reaction – „infectious hypothesis“ – Pekka Saiku, 1992)

HIV

CMV (Cytomegalovirus)

Staphyloccocus

Salmonella

Pneumococcus

Proteus

Herpes Simplex

Klebsiella

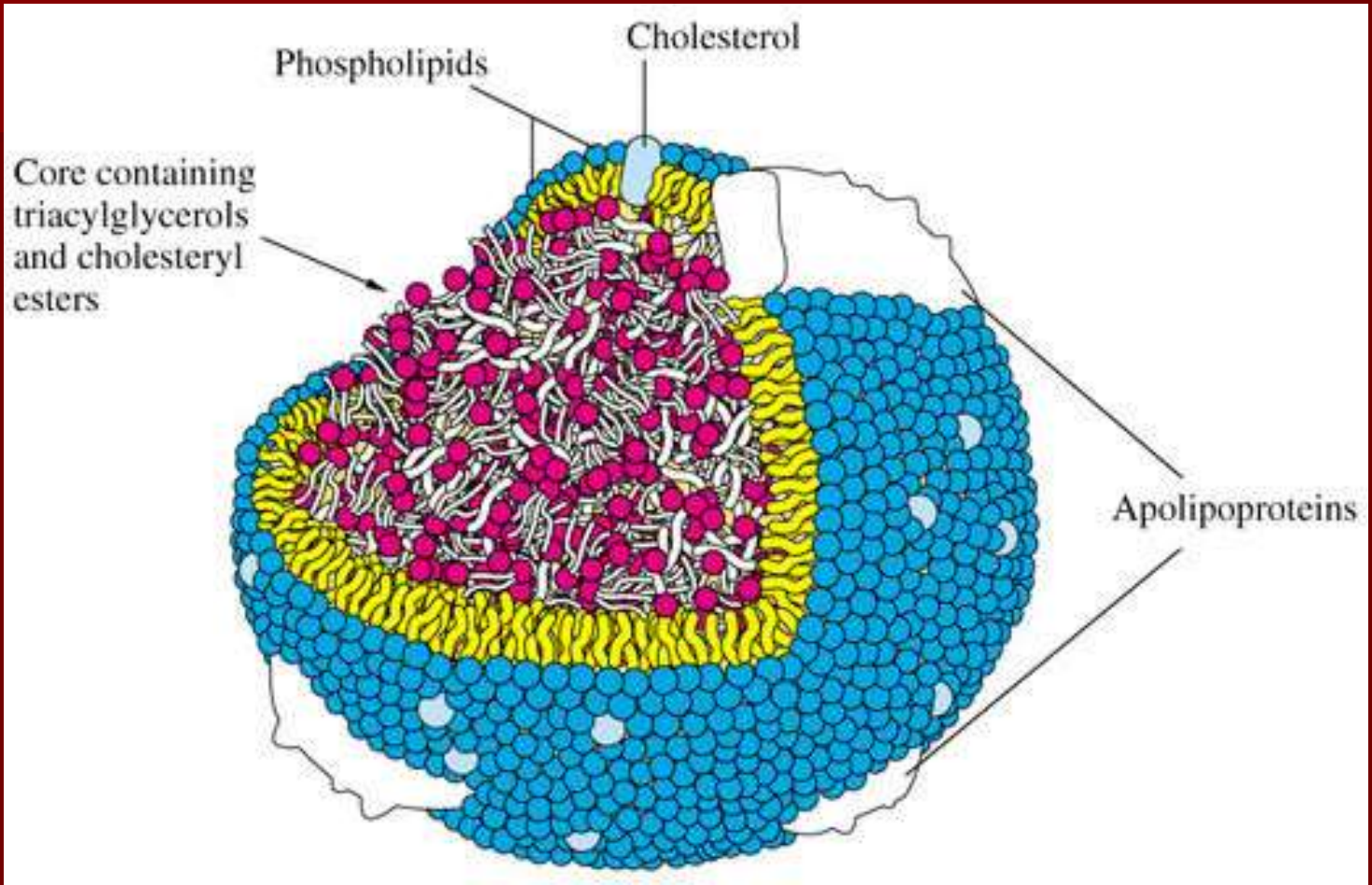
Meningococcus

Helicobacter Pylori

Hepatitis- C

Mycobacterium TB

# Lipids in atherosclerosis

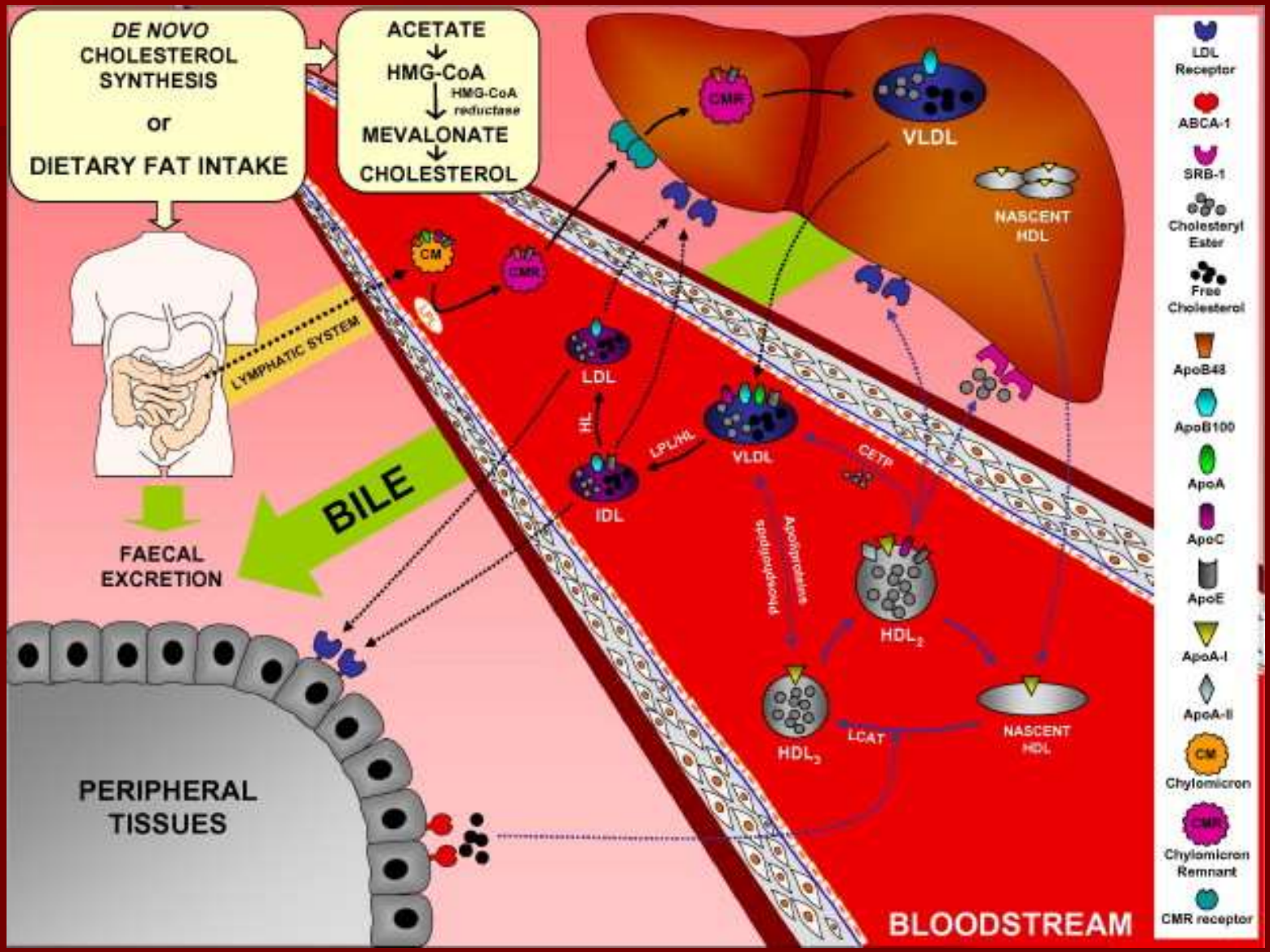



Lipoprotein structure

# Lipoprotein factions

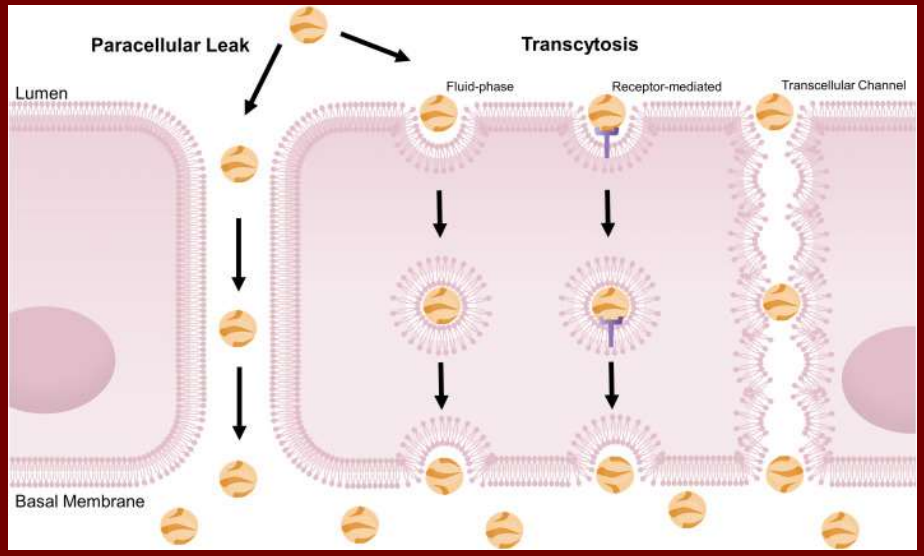
- Atherogenic: LDL, remnants of chylomicrons, IDL, Lp (a)
- Atherogenic modifications (oxidation, glycation, aggregation)
  - in the circulation
  - in the subendothelial space
- Antiatherogenic: HDL
- Mutations in apolipoproteins, their receptors or related enzymes can cause monogenic forms of atherosclerosis

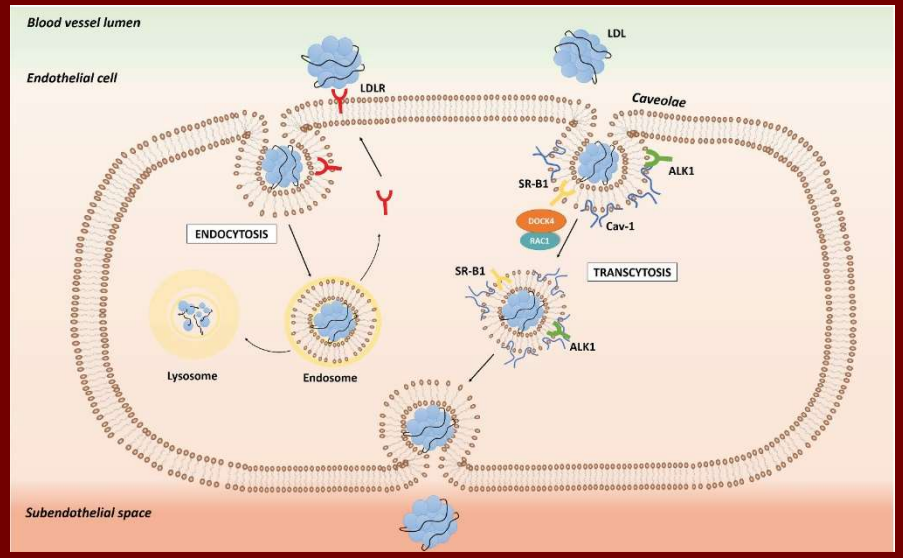
# Lipoprotein metabolism



# Aterogenic lipoprotein penetration

- They must be sufficiently small (i.e. not chylomicrons and nascent VLDL)
- Endothelium: transcellular transport (vesicles) and paracellular transport („leaky junctions")
- Scavenger receptors SR-B participate in transcellular transport (on the other hand, the binding to LDL-receptor supports lipoprotein internalization – role of previous atherogenic modifications)



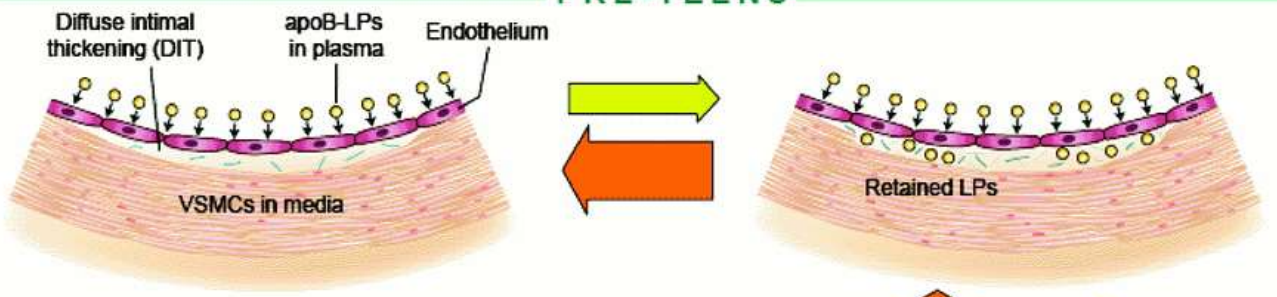
# Retention in subendothelial space

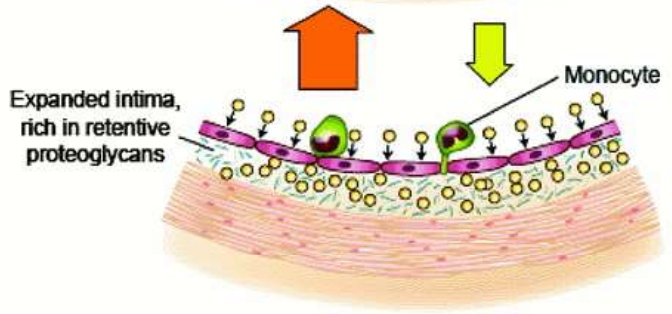
- Vesicular transport through the endothelium goes both ways
  - i.e. lipoproteins are rapidly removed from the subendothelial space
- Binding to subendothelial glycosaminoglycans → retention
- Further modification (oxidation / glycation / aggregation…) → binding to macrophage scavenger receptors (“toxic lipoproteins“)

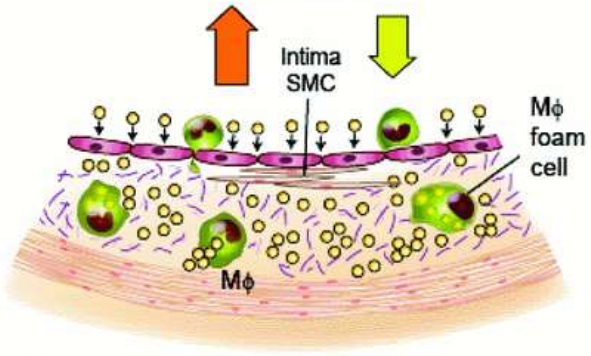
- Pre-lesional susceptible area of the arterial wall with diffuse intimal thickening (DIT)
- Lowering plasma apoB LPs and decreasing risk factors will prevent future vascular disease

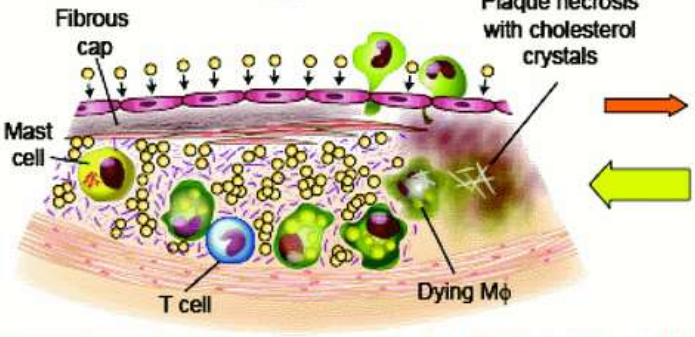
- Early lipoprotein retention
- Lowering plasma apoB LPs and decreasing risk factors will readily promote removal of atherogenic components and prevent maladaptive responses and future disease

## PRE-TEENS




Atherothrombotic vascular disease

## TEENS

- Early responses to LP retention, *e.g.*, monocyte entry
- Lowering plasma apoB LPs and decreasing risk factors will readily promote removal of atherogenic components and prevent further responses and future disease
- Future strategies to prevent LP retention are likely to be most feasible up to this stage

## TWENTIES AND BEYOND

- Advanced responses to LP retention, including maladaptive inflammation, Mϕ death, and plaque necrosis
- LP retention continues to accelerates
- Lowering plasma apoB LPs and reducing risk factors can promote removal of atherogenic components and promote regression, but reversal is more difficult and prolonged, and vascular disease may still develop

- Continued responses to LP retention, e.g., Mϕ foam cell formation and SMC migration
- LP retention starts to accelerate
- Lowering plasma apoB LPs and other risk factors can still promote removal of atherogenic components, promote regression, and prevent further responses and future disease

# Atherosclerosis development

- Initiation
- Inflammation
- Remodelatoin
- Fibrous cap formation
- Thinning/destabilization of the cap
- Plaque rupture
- Thrombosis
- In stable plaque – chronic occlusion

# Thrombosis

- Pathological activation of hemostasis in vascular lumen or in heart chambers
- In arteries, it is usually a consequence of vessel wall damage
- Ulceration or rupture of the fibrous cap

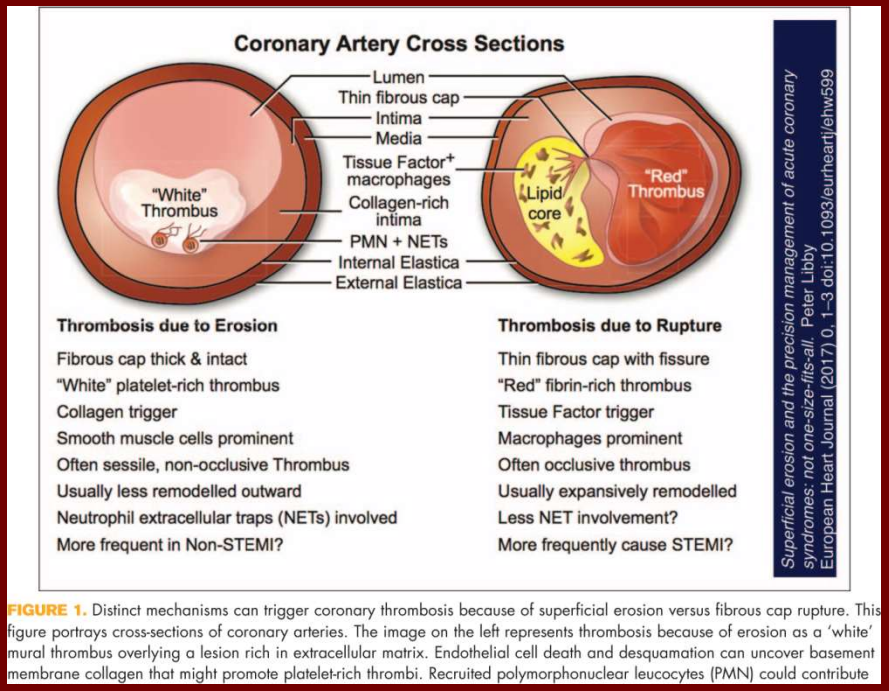


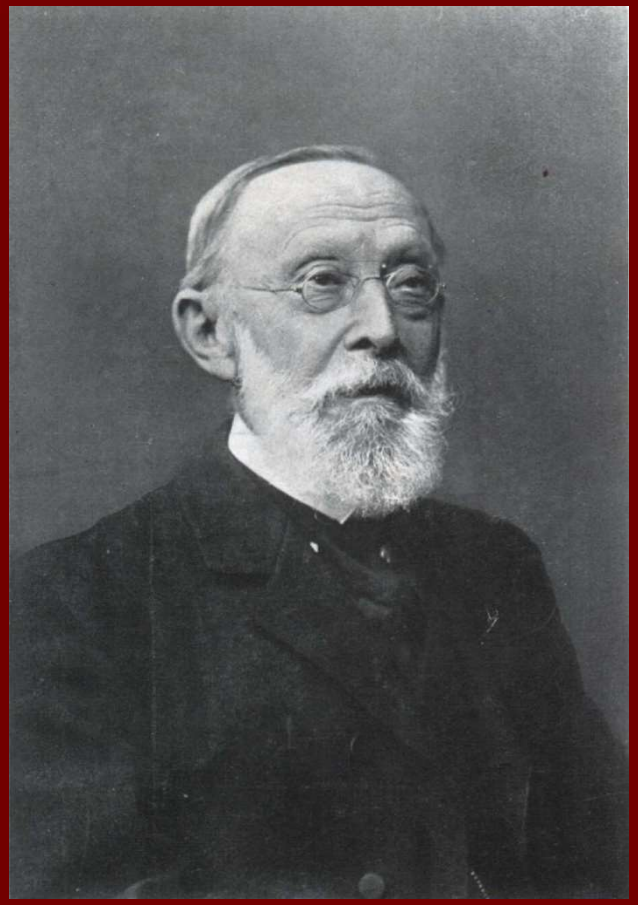

FIGURE 1. Distinct mechanisms can trigger coronary thrombosis because of superficial erosion versus fibrous cap rupture. This figure portrays cross-sections of coronary arteries. The image on the left represents thrombosis because of erosion as a 'white' mural thrombus overlying a lesion rich in extracellular matrix. Endothelial cell death and desquamation can uncover basement membrane collagen that might promote platelet-rich thrombi. Recruited polymorphonuclear leucocytes (PMN) could contribute

# Virchow's triad

- Three main factors predisposing to thrombosis
  1) slowing of the blood flow

     - e.g. stasis during the immobilization, atrial fibrillation, heart failure
  2) Damage of the vessel wall

     - e.g. ruptured atherosclerotic plaque, artificial surfaces, endothelial damage - ↓trombomodulin
  3) Thrombophilic states

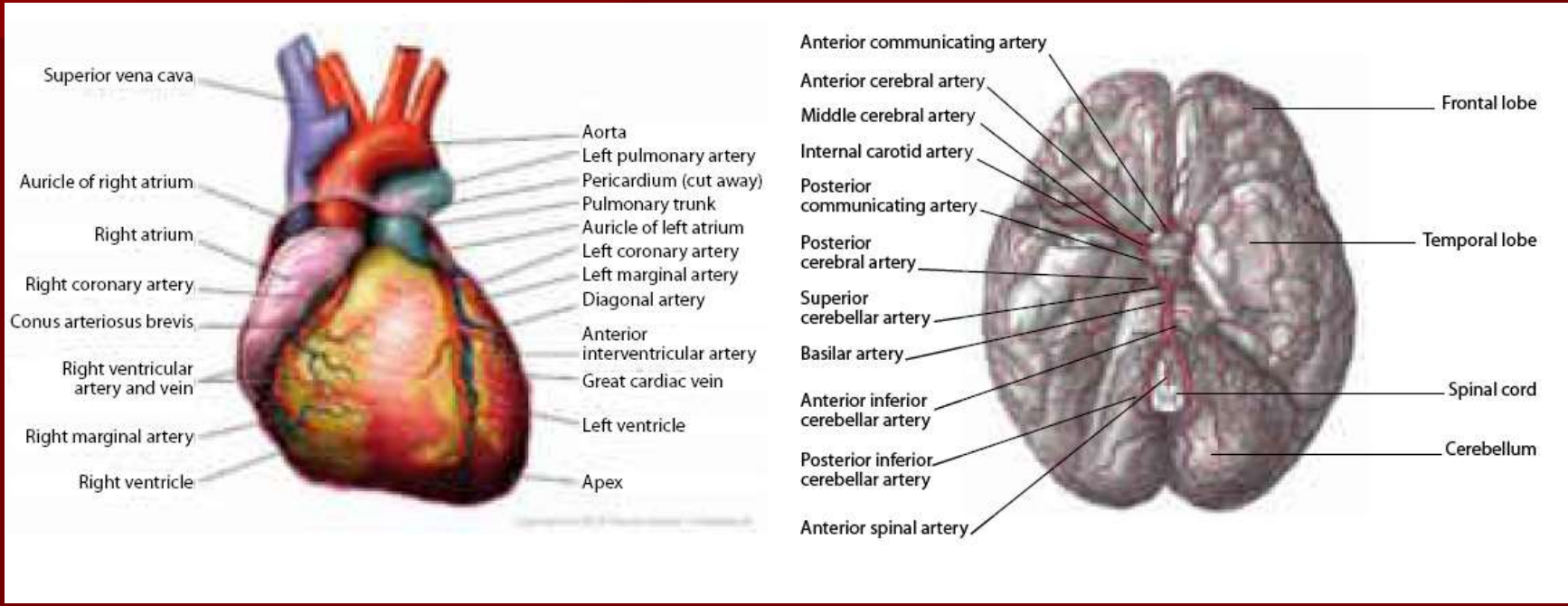


Rudolf Virchow (1821-1902), German pathologist and politician

# Genetics of atherosclerosis

- Overall heritability of coronary artery disease and cerebrovascular atherosclerosis is around 50%
- The heritability is lower in peripheral artery disease (20-30%)
- Polygenic heritability (with an exception of inborn lipid metabolism disorders and vasculopathies of purely immunopathological background)
- „Thrifty genotype hypothesis" – primary setting of human organism is obesitogennic and pro-inflammatory (set in „age of plague and famine")
- Cca 300 candidate genes, common variants have small effects
- Genetic studies (including genome-wide) explain only about 25% of total heritability – similar to other complex diseases – rest is „missing heritability"

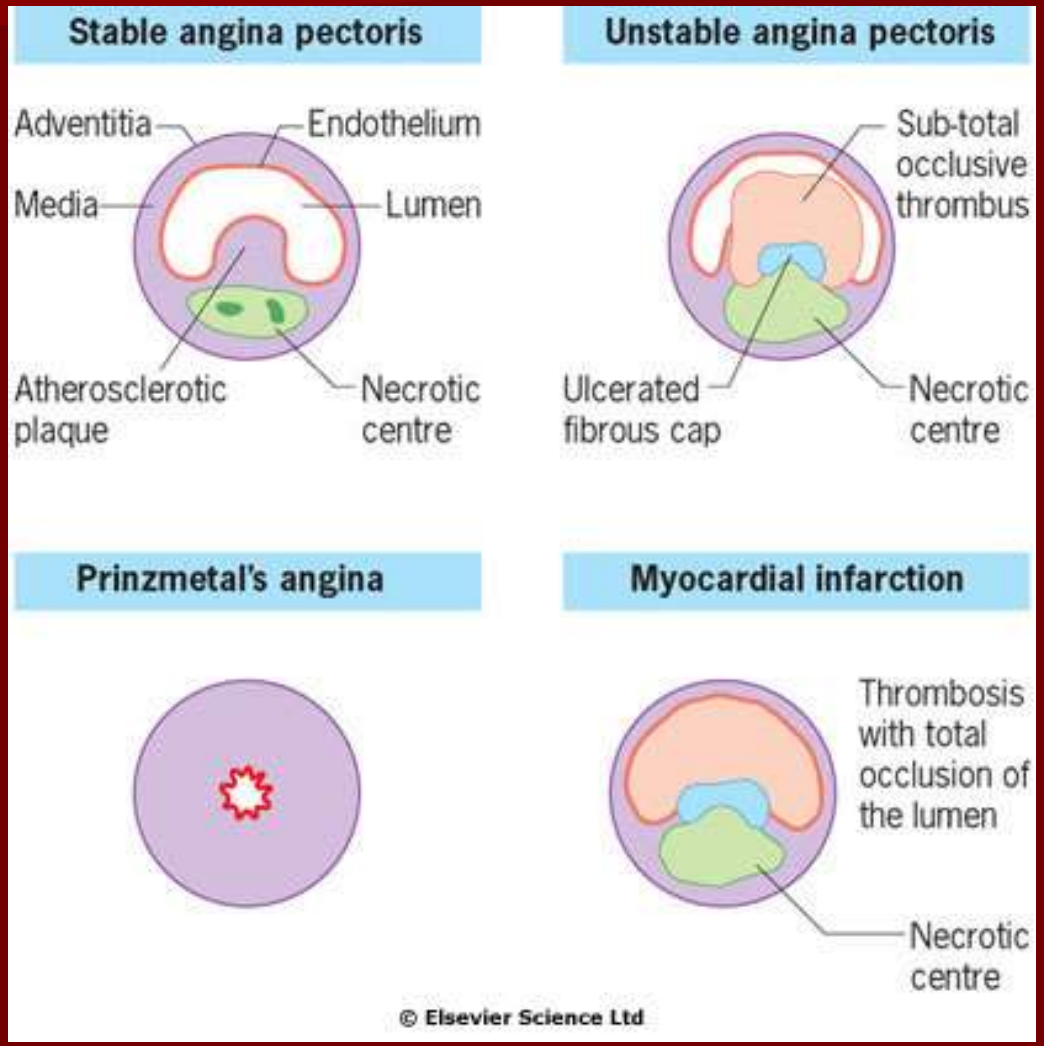
# Atherosclerotic diseases



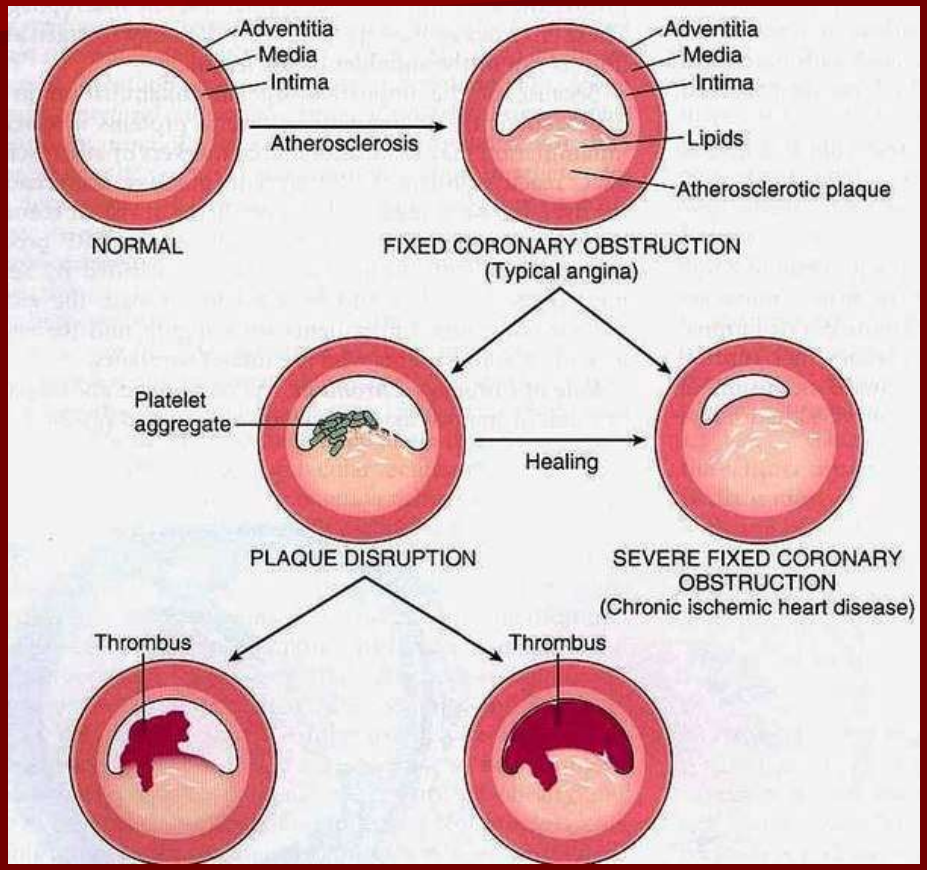

Myocardial infarction
Angina pectoris
Heart failure

Ischemic cerebral stroke
Vascular dementia

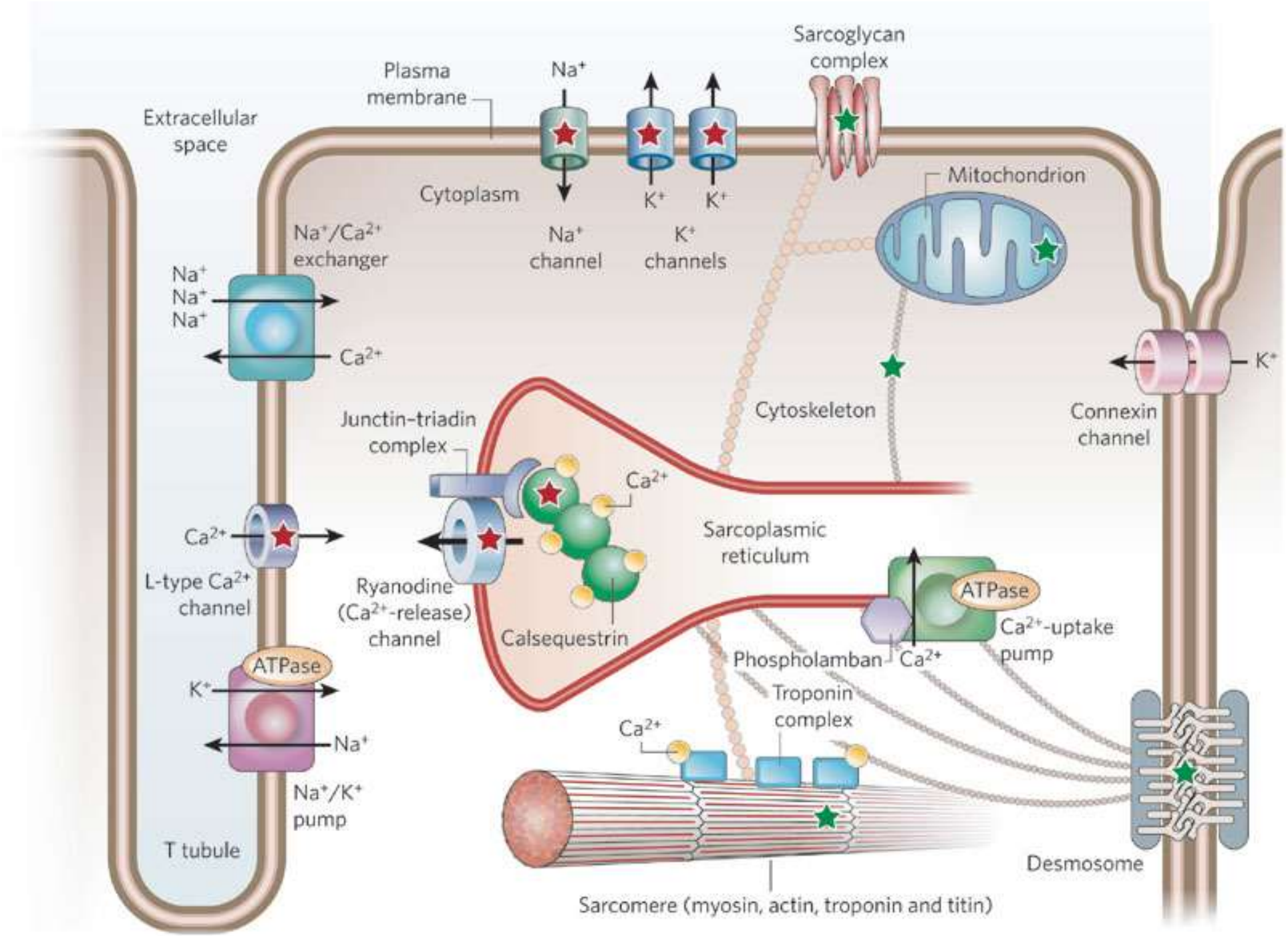
# Forms of atherosclerosis in coronary vessels:



# Stable and unstable plaque in IHD




- Stable angina pectoris
  - Chest pain during effort
- Unstable angina pectoris
  - accelerated AP, or pain at rest, diminished reaction to vasodilatants
  - Form of acute coronary syndrome
- Minimal myocardial damage
  - Chest pain + laboratory markers of MI
  - No ECG finding or impaired contractility in imaging methods
- Non-STEMI
  - theoretically ~ non-QIM ~ subendocardial IM)
- STEMI
  - theoretically ~ QIM ~ transmural IM)


Sarcoglycan complex
Plasma membrane
Na+
Extracellular space
Cytoplasm
K+
K+
Mitochondrion
Na+/Ca2+ exchanger
Na+ channel
K+ channels
Na+
Na+
Na+
Ca2+
K+
Cytoskeleton
Connexin channel
Junctin-triadin complex
Ca2+
Sarcoplasmic reticulum
Ca2+
L-type Ca2+ channel
Ryanodine (Ca2+-release) channel
Calsequestrin
ATPase
Ca2+-uptake pump
Phospholamban
Ca2+
ATPase
K+
Troponin complex
Ca2+
Na+
Na+/K+ pump
T tubule
Desmosome
Sarcomere (myosin, actin, troponin and titin)

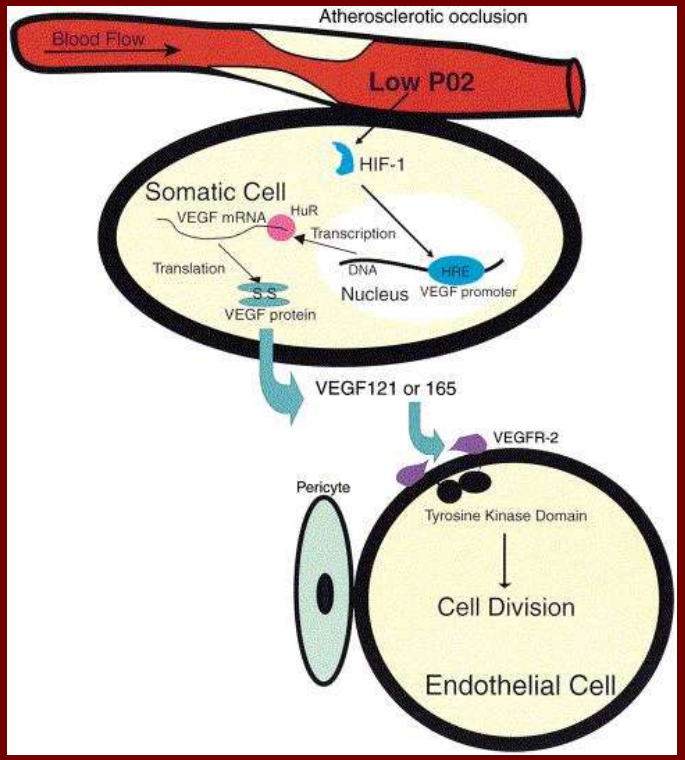
# $O_2$ extraction by various tissues/organs

| Tissue/organ | $CaO_2$ - $CvO_2$ (vol %) | % extraction |
|---|---|---|
| heart | 10 – 12 | **65 – 70** |
| skeletal muscle (resting) | 2 – 5 | 13 – 30 |
| kidney | 2 – 3 | 13 – 20 |
| intestine | 4 – 6 | 25 – 40 |
| skin | 1 – 2 | 7 – 13 |
| whole organism | | 20 – 30 % |

- Theoretically, a maximal amount of $O_2$, which could be extracted in a given tissue ($CaO_2$ - $CvO_2$) is approx. 20 vol % (with $CaO_2$ = 200 ml $O_2$/l = 20 vol %)
- In fact the maximal extraction of oxygen is 15 - 16 vol % because of a nature of Hb dissociation curve
- Because of that, a healthy heart extracts two thirds of physiologically available oxygen already at rest (10 - 12%)
- During exercise, blood flow through myocardium must be increased (**coronary flow reserve**), significant increase of the extraction (e.g. by shift of Hb dissociation curve) is impossible

# Coronary blood flow – quantitative aspects

- Oxygen flow in coronary blood ($VO_2$):
  - ~45 ml $O_2$/min
  - $VO_2 = Qm \times CaO_2$
    - myocardial blood flow (Qm) = 210 – 240 ml/min at rest
    - but 1000 – 1200 ml/min during stress
    - $O_2$ concentration in coronary blood ($CaO_2$) = 200 ml $O_2$/l
      - for $PaO_2$ = 13.3 kPa and c[Hb] = 150 g/l
- **Consumption at rest**: ~30 ml $O_2$/min, i.e. **~65 - 70% of available $O_2$**)
  - Very high extraction of $O_2$ (A - $VO_2$ difference) compared with other organs
- In such level of extraction, the only mechanism that may increase the oxygen supply to myocardium is an **increase of the blood flow**
    - Increasing of extraction from Hb through acidosis, temperature etc. (i.e. right shift of the disociation curve) is not eficient here
  - With constant intraaortic pressure, this can only be achieved through vasodilation of coronary = **coronary flow reserve** (normal values are around 5-6 times)



# Biochemical changes in cardiac ischemia

- 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

# Changes on the cellular level

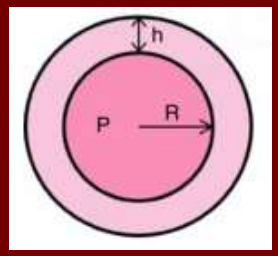
- Proliferation factors reach the overloaded cardiomyocytes (catecholamines, angiotesin II, endothelin-1
- Expression of fetal genes (protooncogenes) → fetal phenotype
- Cardiomyocyte hypertrophy
  - ↑ $O_2$ consumptions
  - microvascular compression } hypoxia
  - hypoxia changes the shape of some cells' action potentials → ↑ arrhythmia risk
  - apoptosis → myocardium replacement by fibrous tissue → impaired inotropy and lusitropy (vicious circle – see later)
- Smooth muscle cells hypertrophy → ↑ resistence (including coronary arteries)

# Cardiac hyperthrophy

- Primarily a compensatory process to meet the requirements for circulatory system in:
  - a) failing cardiac function (e.g. in IHD)
  - b) increased workload
    - volume overload
    - pressure overload
- Driven by proliferation factors (endothelin-1, angiotensin II, mineralocorticoids…)
- Increases the risk of arrhythmias, ischemic damage (e.g. in myocardial infarction), ↓ lusitropy (diastolic dysfunction)

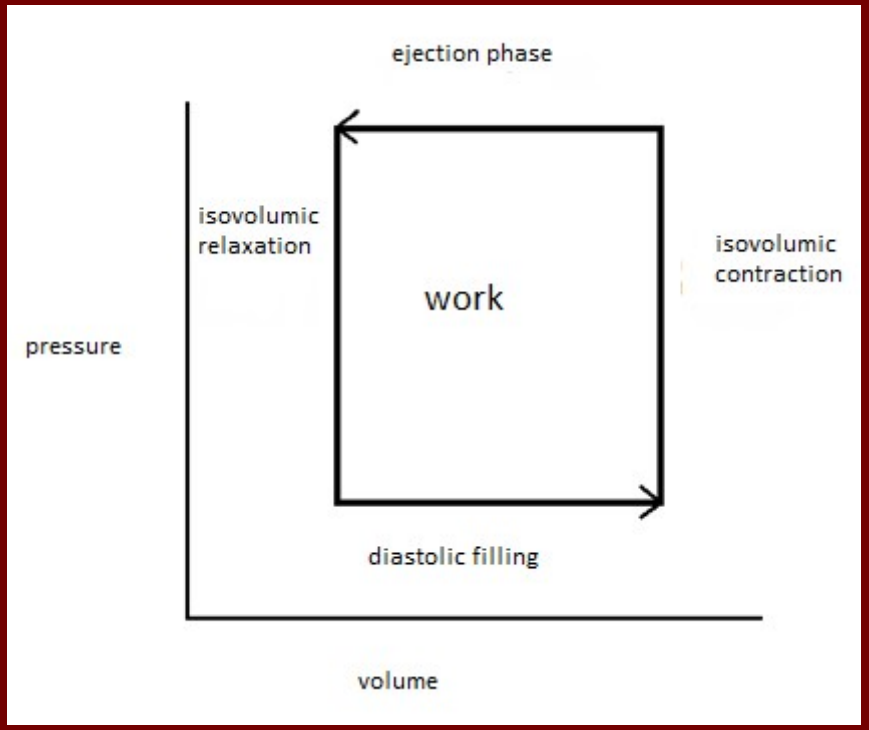
# Wall tension in heart

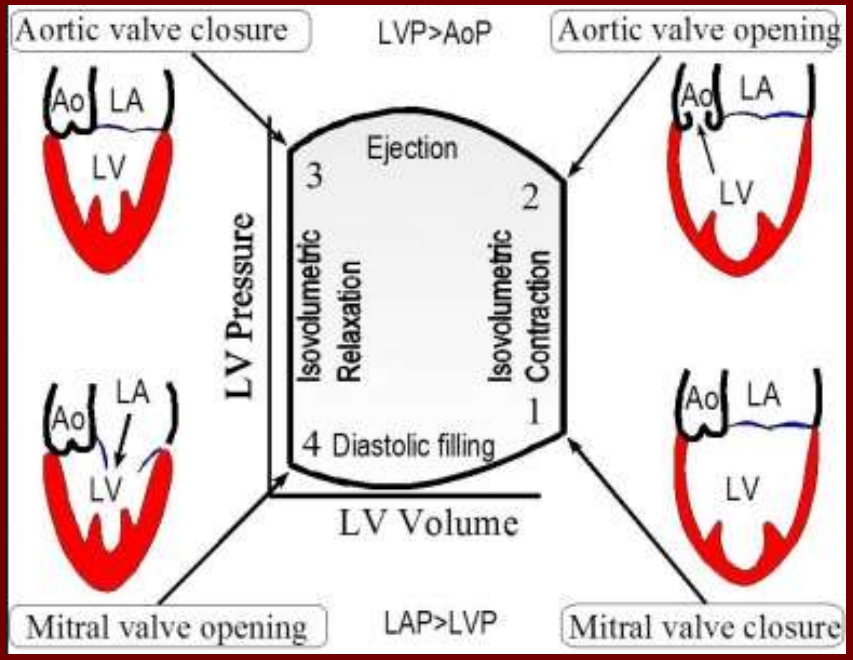
- Law of Laplace for wall tension in a hollow sphere: $\sigma = \frac{P \times r}{2h}$, where:
  P….pressure inside the sphere
  r….inner radius
  h….wall thickness



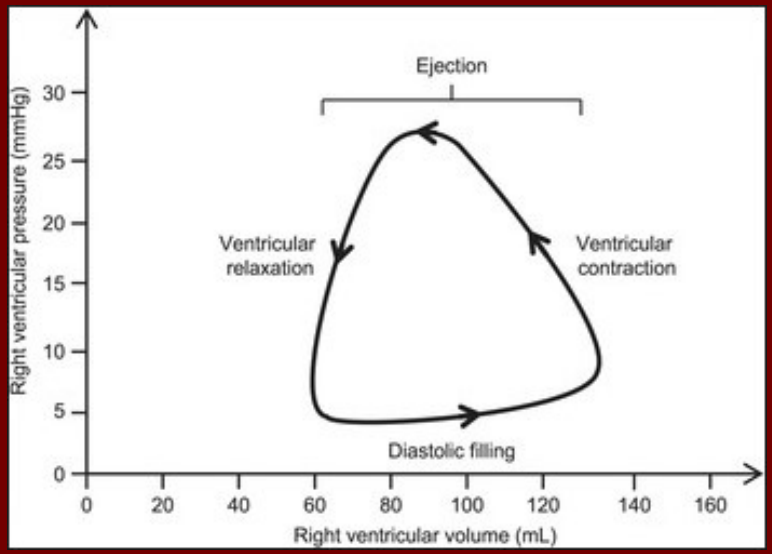

- Preload – wall tension ($N.m^{-2}$ = Pa – force per area) before the systole
  - The main factor is venous return → filling of cardiac ventricles
- Afterload – increase in wall tension during the systole
  - The main factor is a peripheral resistence, or pumonary vascular resistence in a case of the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

# Muscular work of the heart – P-V diagram:



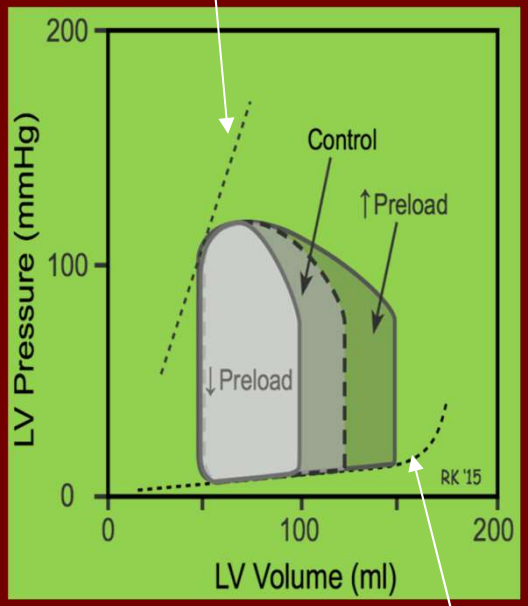



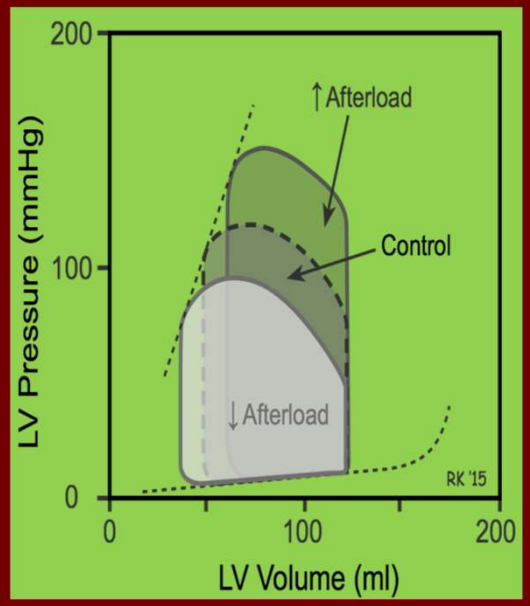
# P-V diagram in the right ventricle



# P-V diagram during changes of preload or afterload

Endsystolic P-V curve

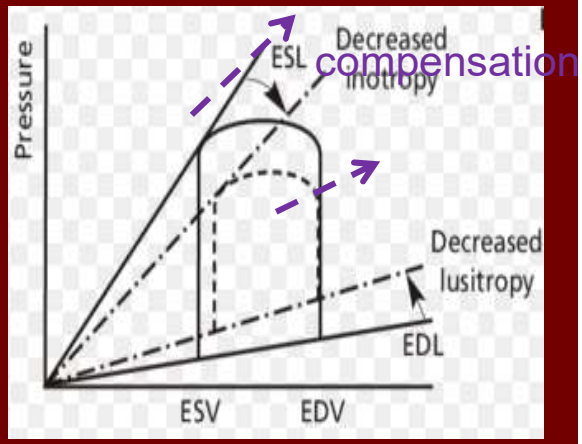


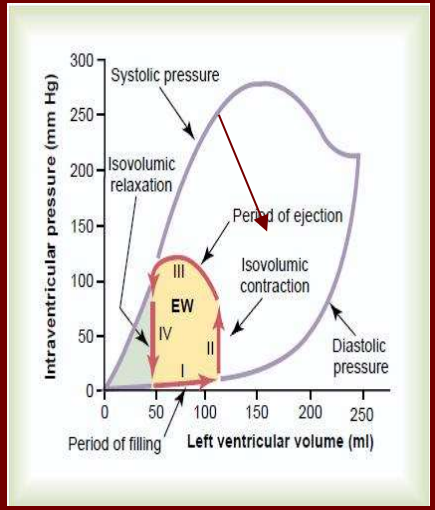

Enddiastolic P-V curve

# 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
  - The relaxation process is ATP-dependent – as well as it is enabled by pumping out the cytosolic $Ca^{2+}$
- ↓ inotropy or lusitropy decrease an area of P-V diagram (i.e. the cardiac work decreases – compensation by RAAS and SNS linked to an increase of preload and afterload follows)
- ↑ preload and ↑afterload, however, support hypertrophy




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



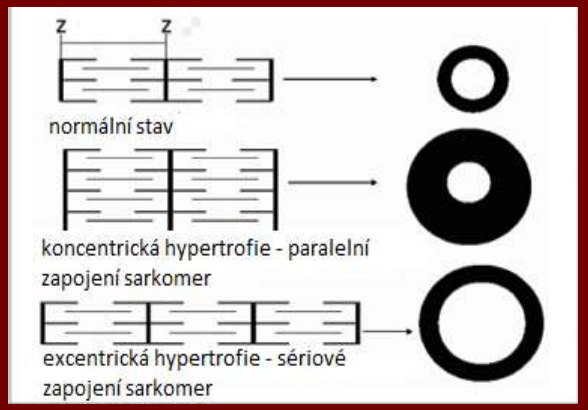

Passive contraction by elastic fibres (relaxation ability decreases)

# „Interests“ of the heart and perfused tissues

- From the heart‘s viewpoint, ↓ preload and ↓ afterload ere advantageous, regarding the blood supply to key organs they may be linked to circulatory failure (compensatory mechanisms increase preload and afterload)
- Cardiac causes of circulatory failure
  - ↓ inotropy
  - ↓ lusitropy
  - ↓ HR

# Cardiac remodelation in ↑ preload and ↑ afterload

- Volume overload – excentric hypertrophy (e.g. valvular regurgitation)
  - Wall stress is high (law of Laplace), but lusitropy increases
- Pressure overload – cncentric hypertrophy (e.g. Valvular stenosis, hypertension)
  - Wall stress decreases - ↓ consumption of $O_2$, but impaired lusitropy



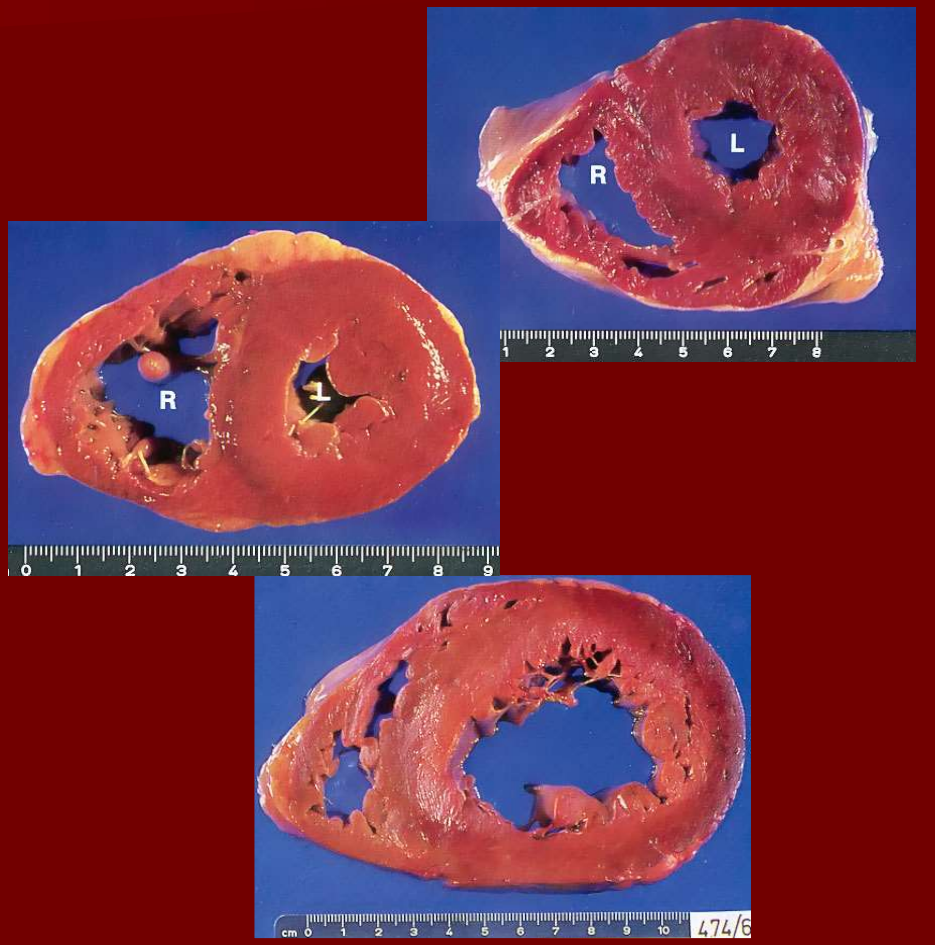

- h/r ratio is physiologically 0.3 – 0.4, increasing during exercise
- above 1.5 or below 0.2 the CO decreases

# Further causes of cardiac hypertrophy

- Excentric: dilated or inflammatory cardiomyopathy
- Concentric: hypertrophic cardiomyopathy
- Mixed: IHD, reactive hypertrophy following myocardial infarction (excentric in the ischemic area, concentric in unaffected parts of heart – i.e. combined systolic and diastolic dysfunction)
- Sport: excentric in aerobic disciplines, concentric in power disciplines (CAVE anabolics) – usually reversible
  - high coronary flow reserve

# Why the 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
  - patological hypertrophy is not followed by adequate ”densing” of coronary vessels



# Other atherosclerotic diseases

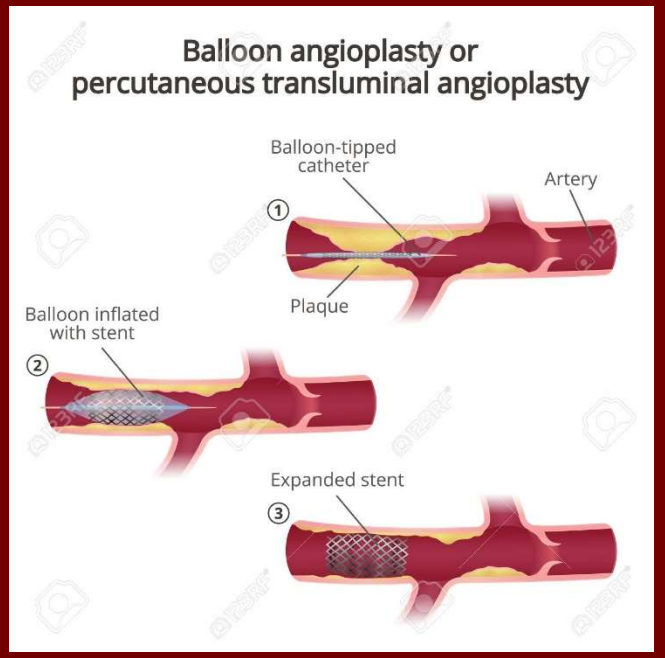
- Lower limb ischemia
- Renovascular hypertension (unilateral/bilateral stenosis – Goldblatt model)
- Steal syndromes
- Intestinal infarction, renal infarction, abdominal angina…

# Treatment of atherosclerosis

- Treating risc factors (lifestyle intervention, antihypertenzives, antidiabetics)
- Systemic
  - Treatment of lipid metabolism disorders
    - Statins (block cholesterol synhesis)
    - Ezetimib (blocks cholesterol absorbtion)
    - PCSK9 inhibitors (upregulate LDL-R)
    - Fibrates (decrease VLDL production)
    - Gene therapy in monogennic dyslipidemia
  - Treatment of inflammatory response
    - IL-1 blockers

# Treatment 2

- Local
  - PTA – percutaneous transluminal angioplasty
    - POBA: plain old baloon angioplasty
    - BMS: bare metal stent
    - DES: drug-eluted stent
      - covered by a **cytostatic** to prevent neointimal hyperplasia and restenosis
    - BVS: bio-vascular scaffold
      - degradable, lower inflamatory response and risk of thrombosis
  - Bypass
    - Arterial
    - Venous graft

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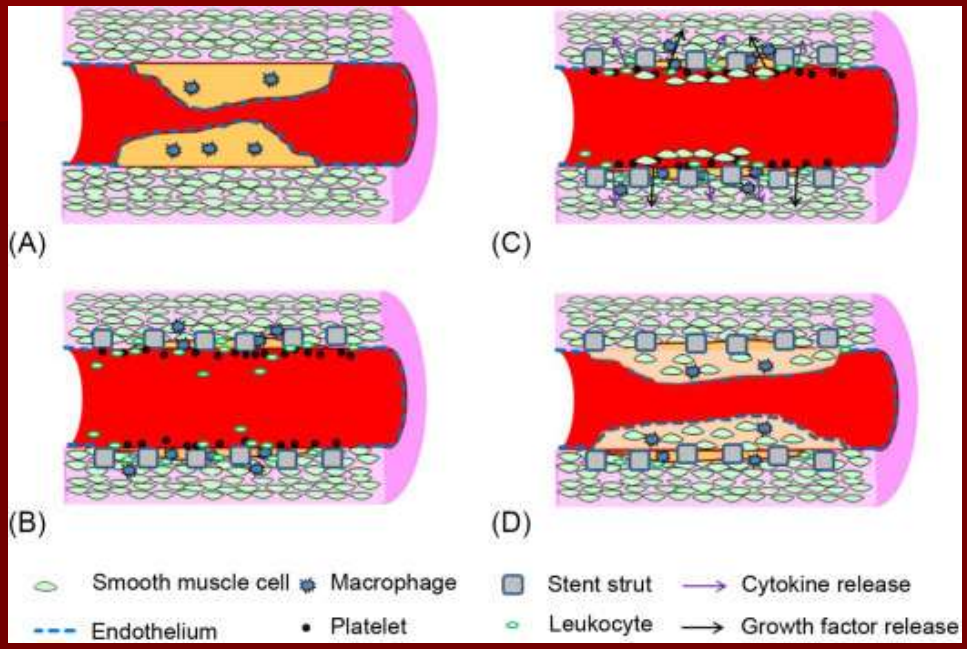
# In-stent restenosis




- Result of smooth muscle cells proliferation
- But: some degree of proliferation is necessary to cover the stent and stabilize the subendothelial space, otherwise the risk of thrombosis increases
- ↓ risk of restenosis in DES is accompanied by ↑ risk of thrombosis in early phase, local cytostatics are clinically efficient only in a range of years

Thank you for your attention