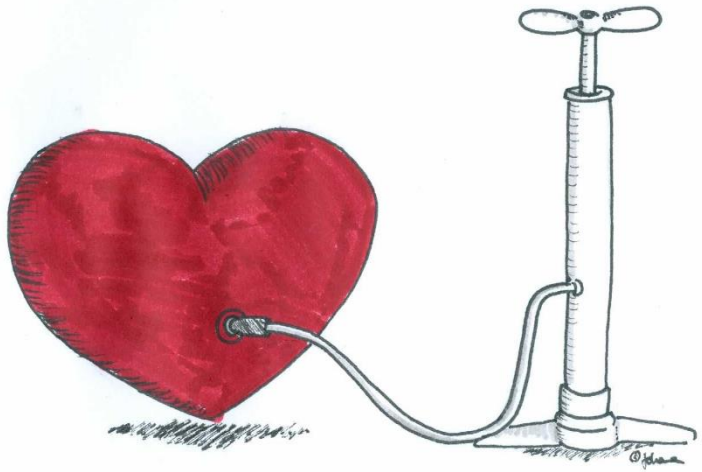
# PP of circulatory system – part I:

Heart is a pump in need of energy!
Myocardial blood supply & metabolism
Etiopathogenesis of atherosclerosis
Myocardial ischemia – compensation
Coronary artery/heart disease (CAD/CHD)



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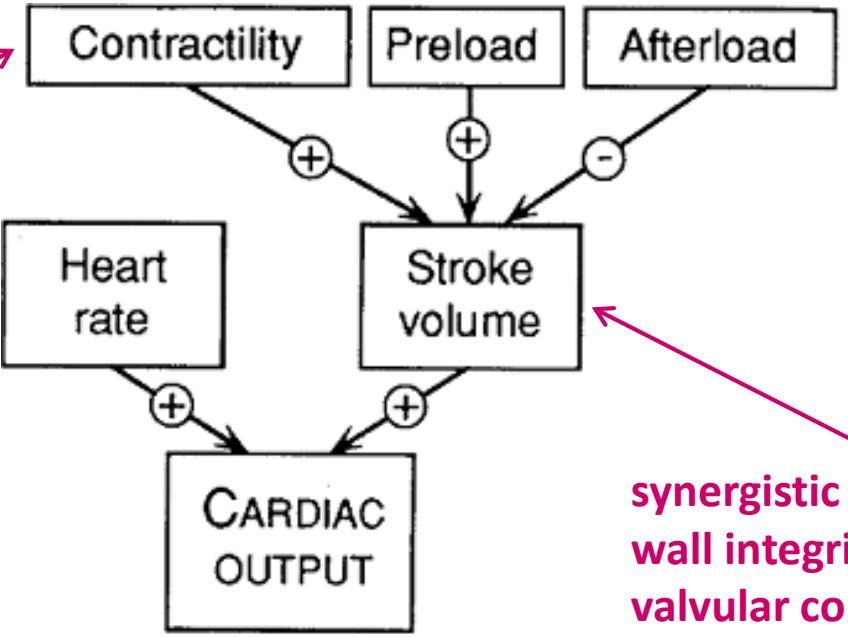
# Heart needs a lot of energy (= ATP) to continually perform as a pump (~7,500 L/day, ~ 40 mil beats/year)

venous return (i.e. circulating volume)

systemic vascular resistance (i.e. blood pressure or valve obstruction)




sympathetic nervous system

parasympathetic nervous system

synergistic LV contraction
wall integrity
valvular competence

- quantitatively
  - heart rate ~70/min
  - SV ~70ml
  - CO 70 × 70 = 4,900 ml/min ~ 5 L/min at rest
  - **CO ~ 20 - 25L/min during exercise!!!!**
- influenced by
  - autonomic nervous system activity
  - hormones
  - age
  - gender
  - genetics
  - drugs
  - fitness
  - anatomy/size of the heart

**SV × f = CO** → 70mL × 70 bpm = ~ 5 L/min

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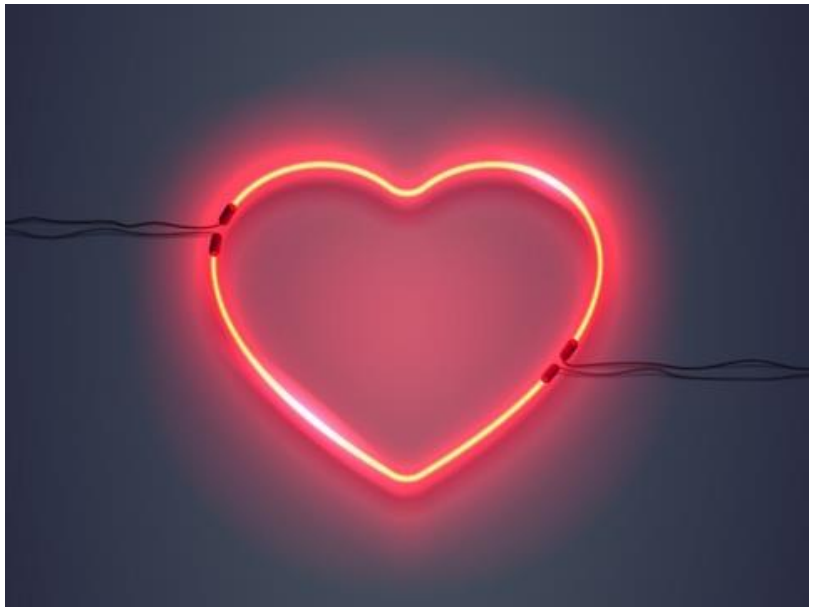

# MYOCARDIAL METABOLISM

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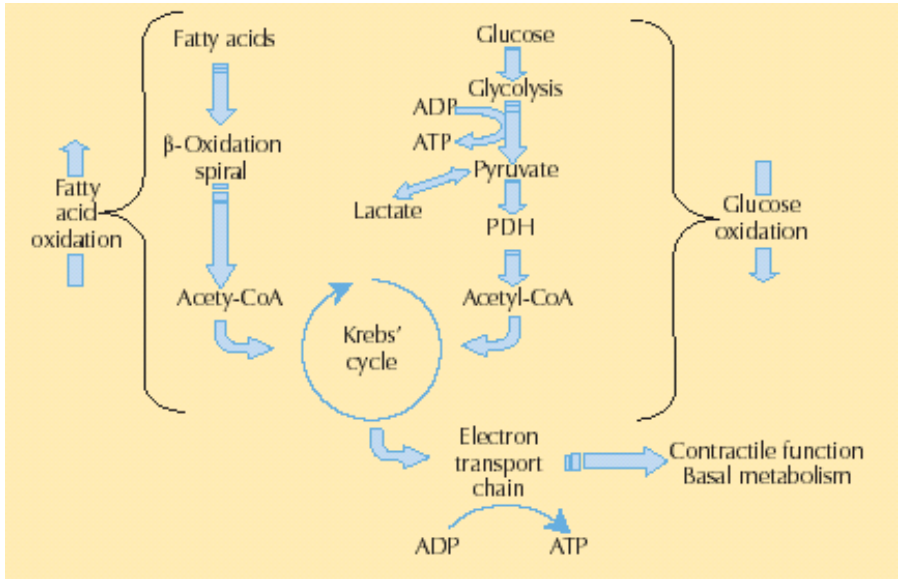
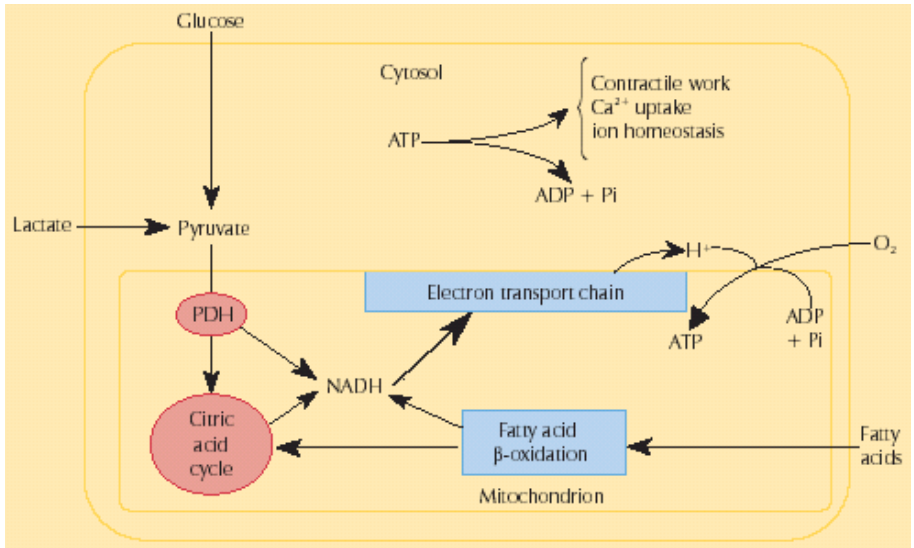
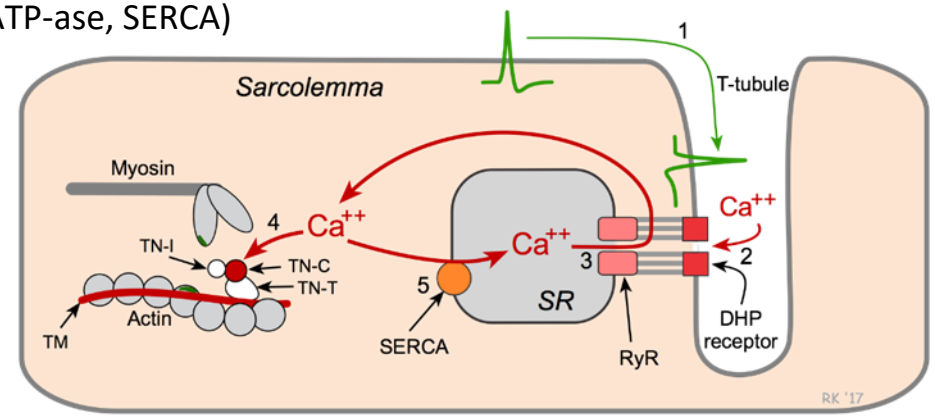
# Myocardial metabolism – a lot of ATP is needed




- heart is a **pump** that has to continually perform 2 processes:
  - **(1) automacy** = generation of action potential in order to perform
  - **(2) contraction**
- myocardium thus has a very high demand for **ATP** even in the resting state
  - for contraction
    - actin/myosin – ATP
    - $Ca^{2+}$ handling ($Ca^{2+}$-ATP-ase, SERCA)
  - for repolarisation
    - $Na^{+}/K^{+}$-ATP-ase




- ATP is produced by oxidation of substrates
  - FFA - preferentially
  - glucose (glycogen)
  - ketone bodies and lactate
- since myocardium requires **large amounts of $O_2$** it must be, therefore, well perfused !!

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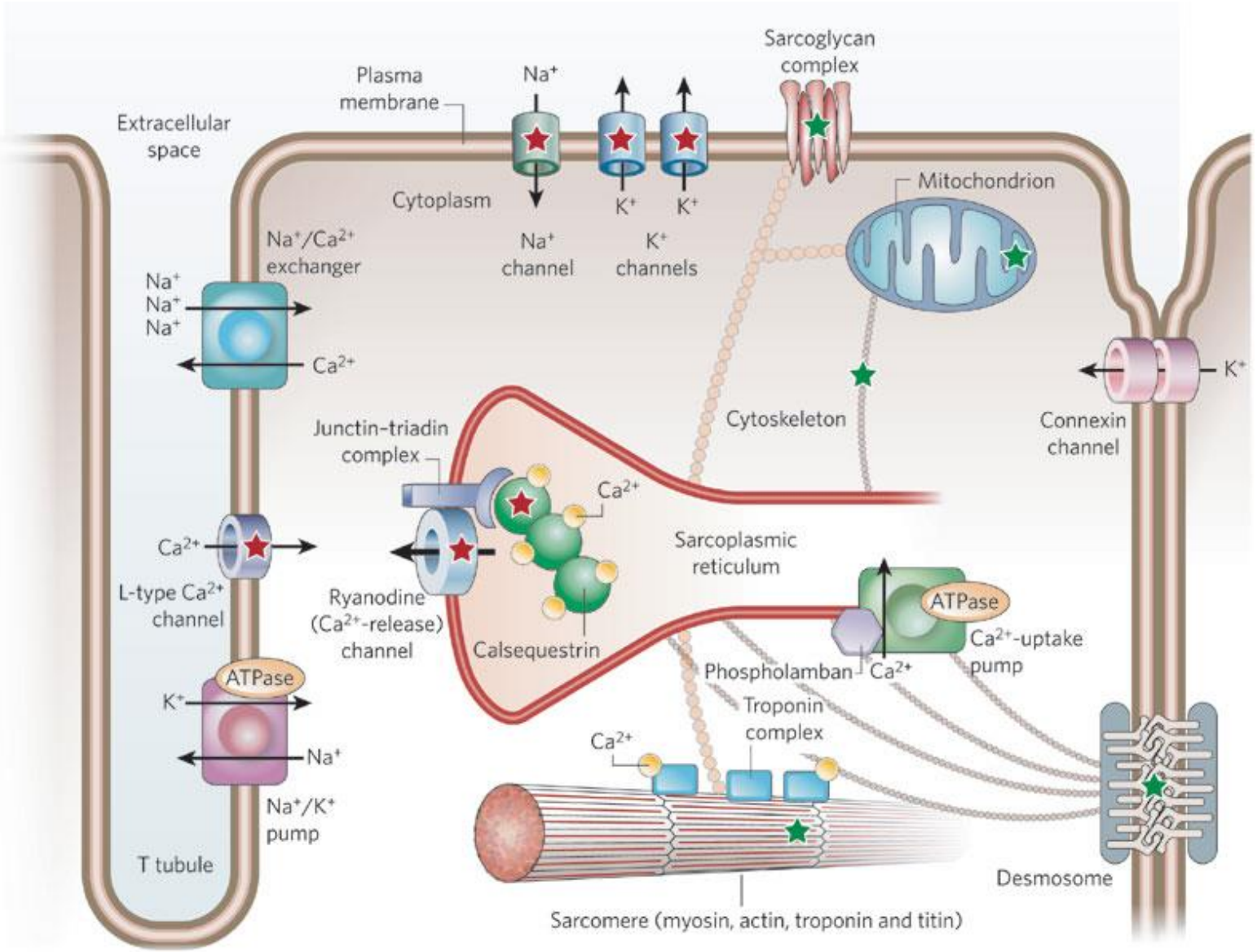
# Excitation-contraction coupling in a ventricular cardiomyocyte




- The initial event in the cardiac cycle is membrane depolarization, which occurs with ion entry through connexin channels from a neighbouring cardiomyocyte (right) followed by opening of voltage-gated Na+ channels and Na+ entry (top).
- The resultant rapid depolarization of the membrane inactivates Na+ channels and opens both K+ channels and Ca2+ channels. Entry of Ca2+ into the cell triggers the release of Ca2+ from the sarcoplasmic reticulum through the ryanodine channel.
- Ca2+ then binds to the troponin complex and activates the contractile apparatus (the sarcomere, bottom).
- Cellular relaxation occurs on removal of Ca2+ from the cytosol by the Ca2+-uptake pumps of the sarcoplasmic reticulum and by Na+/Ca2+ exchange with the extracellular fluid.
- Intracellular Na+ homeostasis is achieved by the Na+/K+ pump.
- The molecular components that are required for normal electrophysiological activity, contractile function and cell–cell adhesion (the latter mediated by desmosomes) all need to be positioned correctly within the cell and anchored to each other and the cytoskeleton.
- Some cardiomyocyte components are not shown (for example, stretch-activated channels, and ankyrins that target channels and other proteins to their correct locations within the cell).
- Red stars indicate proteins encoded by genes that are mutated in primary arrhythmia syndromes; many of these proteins form part of macromolecular complexes, so mutations in several genes could be responsible for these syndromes.
- Green stars indicate protein complexes in which mutations in multiple genes cause cardiomyopathies often associated with arrhythmias; these complexes include the sarcomere (in hypertrophic cardiomyopathy), the desmosome (in arrhythmic right ventricular cardiomyopathy), and the cytoskeleton, sarcoglycan complex and mitochondrion (in dilated cardiomyopathy).

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# Oxygen extraction by various tissues/organs

| 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 body | | 20 – 30 % |

- Theoretically, the maximal amount of oxygen that can be extracted is **20 vol %** (if $CaO_2$ = 200 ml $O_2$/l )
- In reality, however, the maximal oxygen extraction is around **15 - 16 vol %** because of the kinetics of oxygen dissociation from haemoglobin
- Therefore, the heart is extracting one-half to two-thirds of the physiologically available oxygen under normal operating conditions
- Meeting increased demands (during exercise) is only possible by increasing coronary perfusion (= **coronary flow reserve, CFR**)

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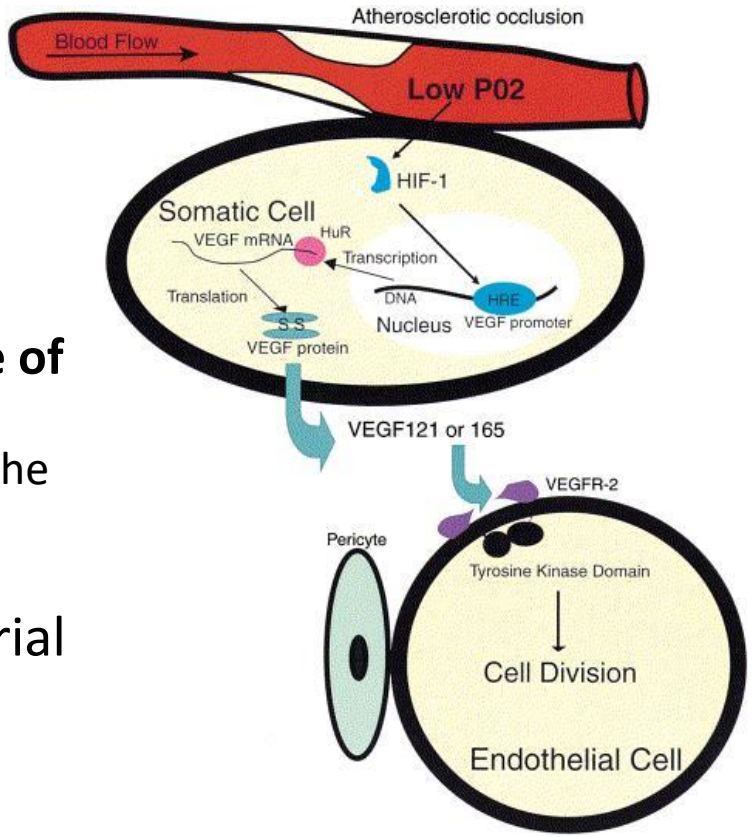
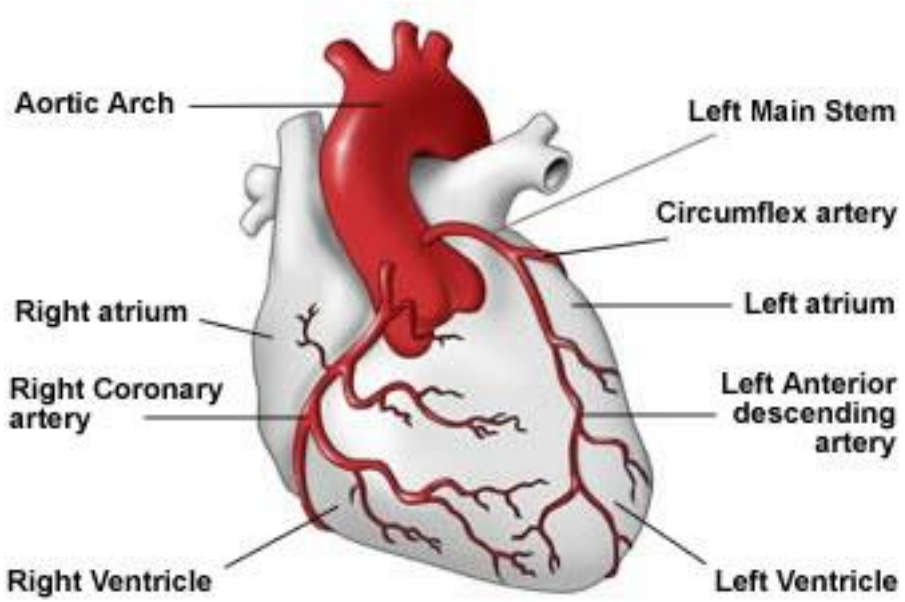
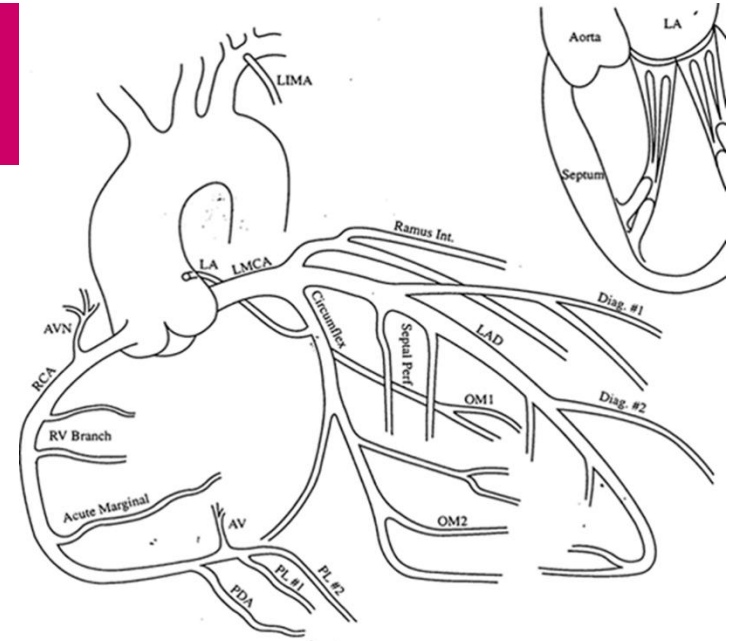
# Oxygen consumption – quantitative aspects

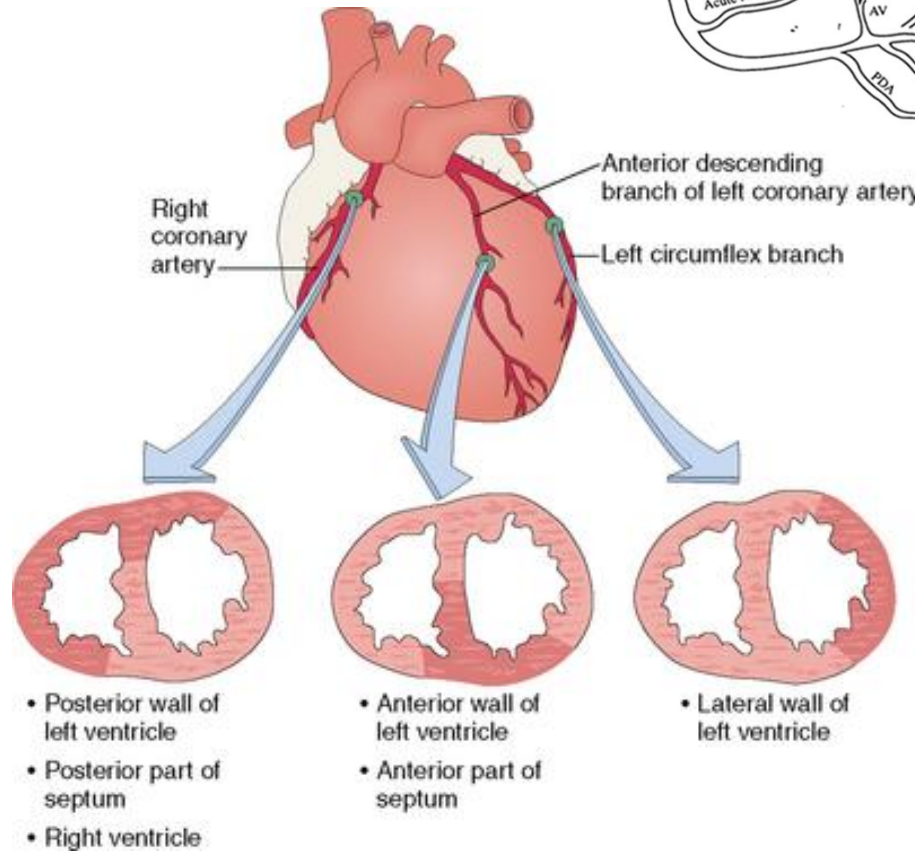
- amount of oxygen supplied by the coronary blood ($VO_2$): ~ 45 ml $O_2$/min
  - $VO_2 = Q_m \times CaO_2$
    - myocardial perfusion ($Q_m$) = 210 – 240 ml/min in the resting state
    - but 1000 – 1200 ml/min during the exercise
    - $CaO_2$ = 200 ml $O_2$/l
      - for $PaO_2$ = 13.3 kPa and c[Hb] = 150 g/l
- consumption in the resting state: ~ 30 ml $O_2$/min (~60 - 80%)
  - very high $O_2$ extraction (A - $V_{O2}$ difference) compared to other organs
- therefore, the only mechanism increasing the oxygen supply is **an increase of coronary blood flow**
  - because aorta has a constant pressure, it has to be done by **vasodilatation** in the coronary bed = **CFR**
  - small scale neovascularisation is also possible
- majority of oxygen is **consumed by LV** (generating much larger arterial pressure compared to right heart supplying pulmonary circulation)
  - therefore **CBF is a critical determinant of** its function (i.e. **contractility** mainly)



# Blood supply of the heart




- demand for $O_2$ and substrates is met by heart blood vessels - **coronary arteries** - branching from the ascendant aorta
  - (1) left coronary artery
    - (a) left ant. desc. branch
      - supplies front part of the LV and RV and front part of the septum
    - (b) circumflex branch
      - supplies left and back wall of the LV
  - (2) right coronary artery
    - supplies RV

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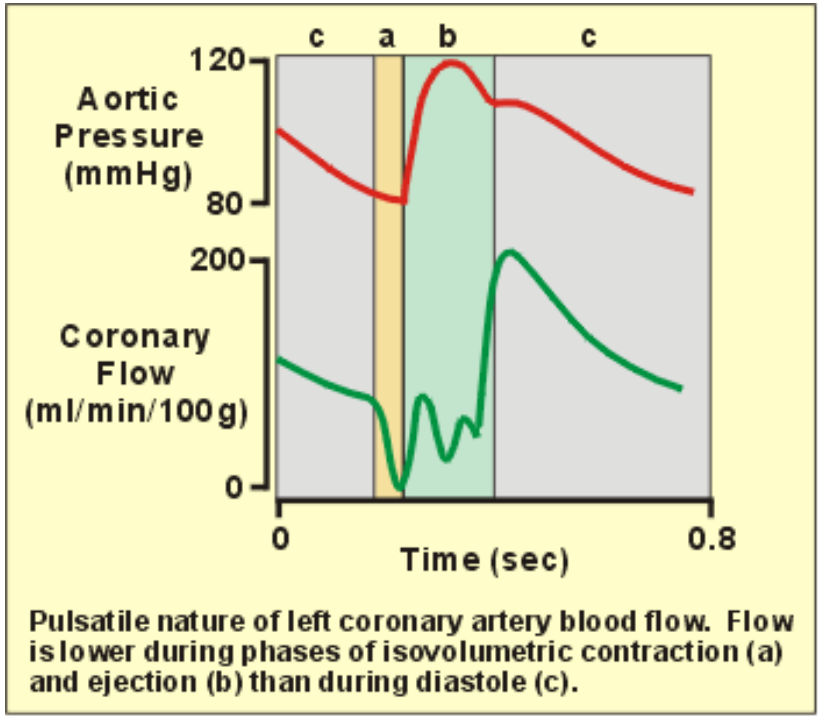
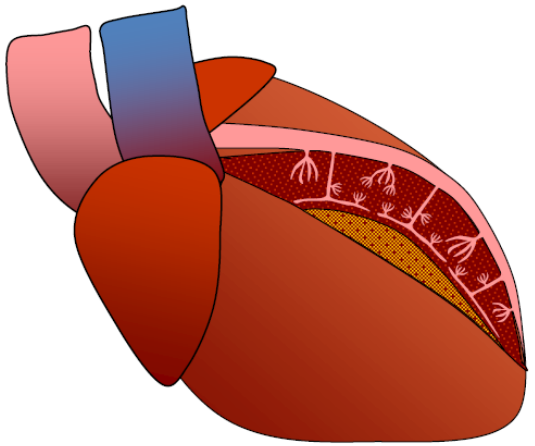
# Coronary blood flow (CBF) – a temporal and spatial pattern

- **marked phasic variations** = blood flow is diminished during the systole due to:
  - (1) temporal blocking of coronary ostia by opened aortic valves
    - „problematic“ anatomy of coronary arteries
  - (2) high flow in aorta during the systole
    - which “sucks” the blood out (= Venturi effect)
  - (3) compression of vessels (microvasculature) during the systolic contraction
    - less blood in through arteries, more blood out through veins
- therefore most of the coronary flow occurs during diastole
  - tachycardia has adverse effect since it shortens diastole so there is relatively less time available for coronary flow during diastole to occur
- moreover, **subendocardium is much more susceptible to ischemia than epicardium** due to several reasons:
  - coronary arteries penetrates myocardium from surface (epicardium) to the internal chamber lining (endocardium) direction
    - decrease in diameter and oxygen tension
    - ↓ perfusion pressures in pathological conditions (e.g. epicardial artery stenosis due to atherosclerosis)
  - systolic compression too is nor evenly distributed
    - more at subendocardium
    - ↑ intracardial pressure due to congestion in pathological conditions (e.g. heart failure)
  - lesser capillary density in subendocardium compared to epicardium



Pulsatile nature of left coronary artery blood flow. Flow is lower during phases of isovolumetric contraction (a) and ejection (b) than during diastole (c).



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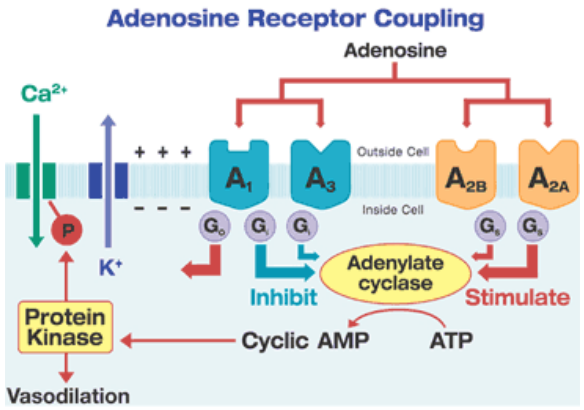
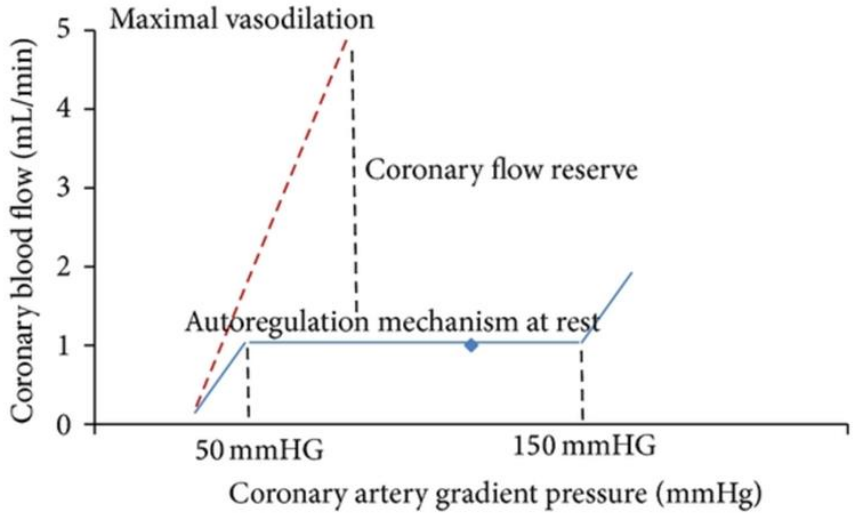
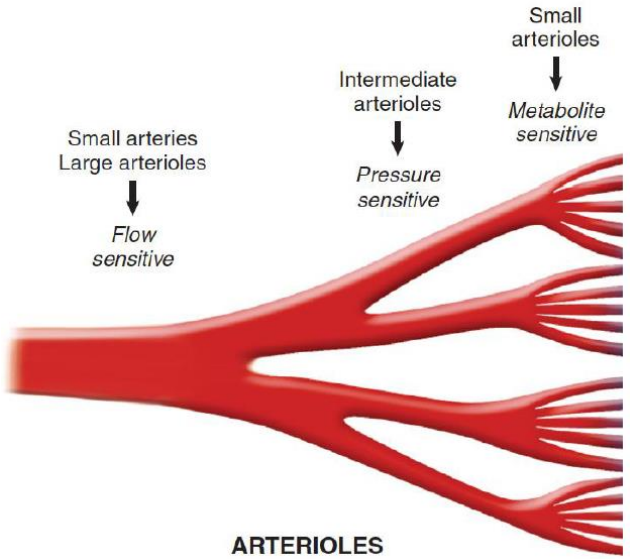
# CBF autoregulation - tightly coupled to the oxygen demand

- autoregulation between 60 to 200 mmHg of the perfusion pressure (i.e. systemic arterial pressure) helps to maintain normal coronary blood flow whenever coronary perfusion pressure changes due to changes in aortic pressure
  - resistance coronary arteries (100-400 µm diameter) – haemodynamic regulation
    - shear-stress (flow-induced) mediated intraluminal control – dilation by endothelial NO
    - myogenic regulation as a response to transmural pressure/wall stress mediated by stretch-activated L-type Ca channels (Ca2+ in influx)
  - arterioles - metabolic regulation
    - adenosine as the most important mediator of active hyperaemia
      - a metabolic coupler between oxygen consumption and coronary blood flow = formed from cellular AMP by 5'-nucleotidase
      - AMP is derived from hydrolysis of intracellular ATP and ADP




  - neural regulation – negligible at rest
    - during sympathetic activation (mainly β-adrenergic) vasodilation
    - β1-receptor (more than α1-receptor) activation results in coronary vasodilation (plus increased heart rate, contractility)
      - "functional sympatholysis": sympathetic activation to the heart results in coronary vasodilation and increased coronary flow due to increased metabolic activity (increased heart rate, contractility) despite direct vasoconstrictor effects of sympathetic activation on the coronaries
    - + Ach induced vasodilation too (though the role of parasympathetic system is less obvious)

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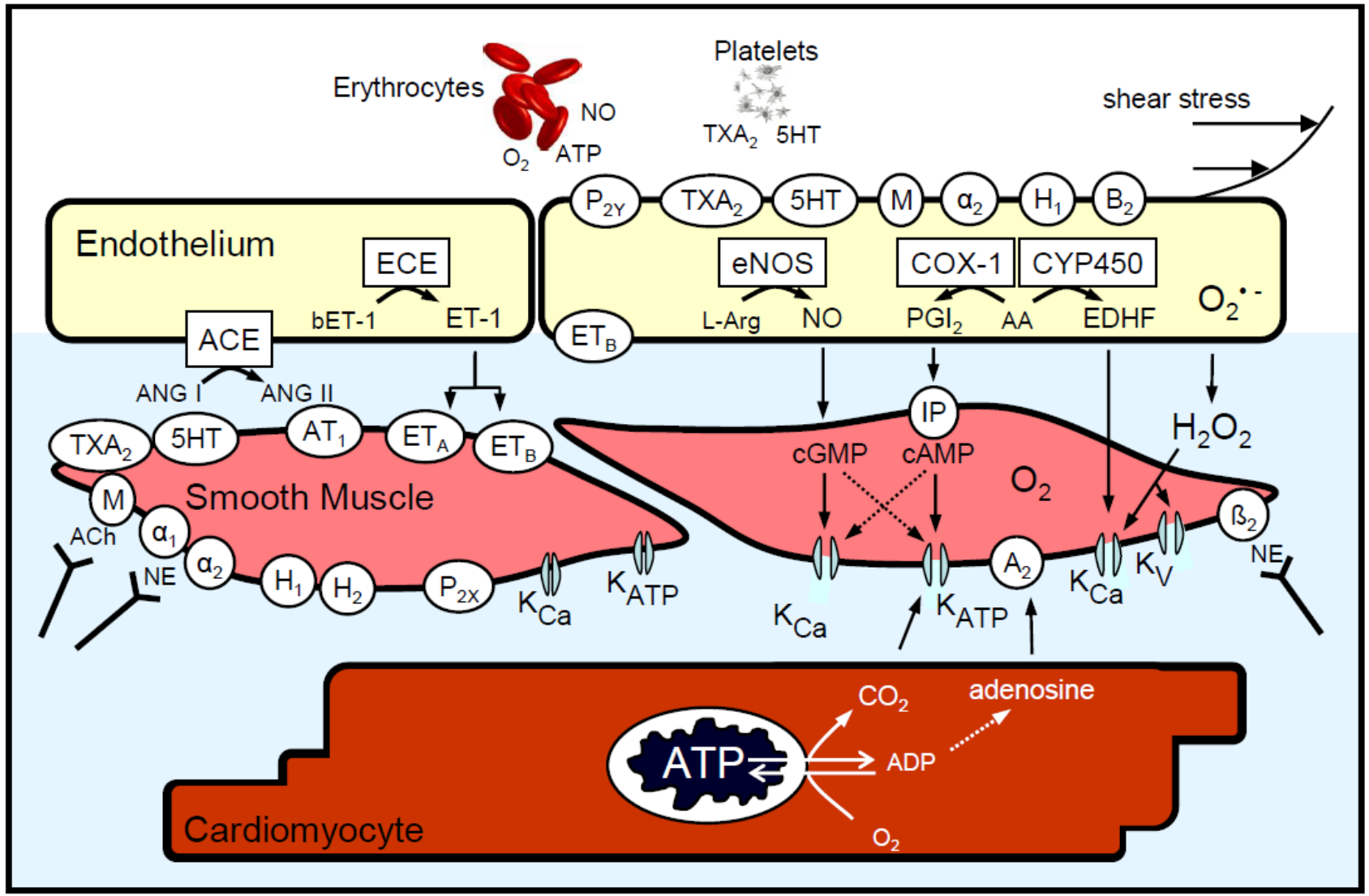
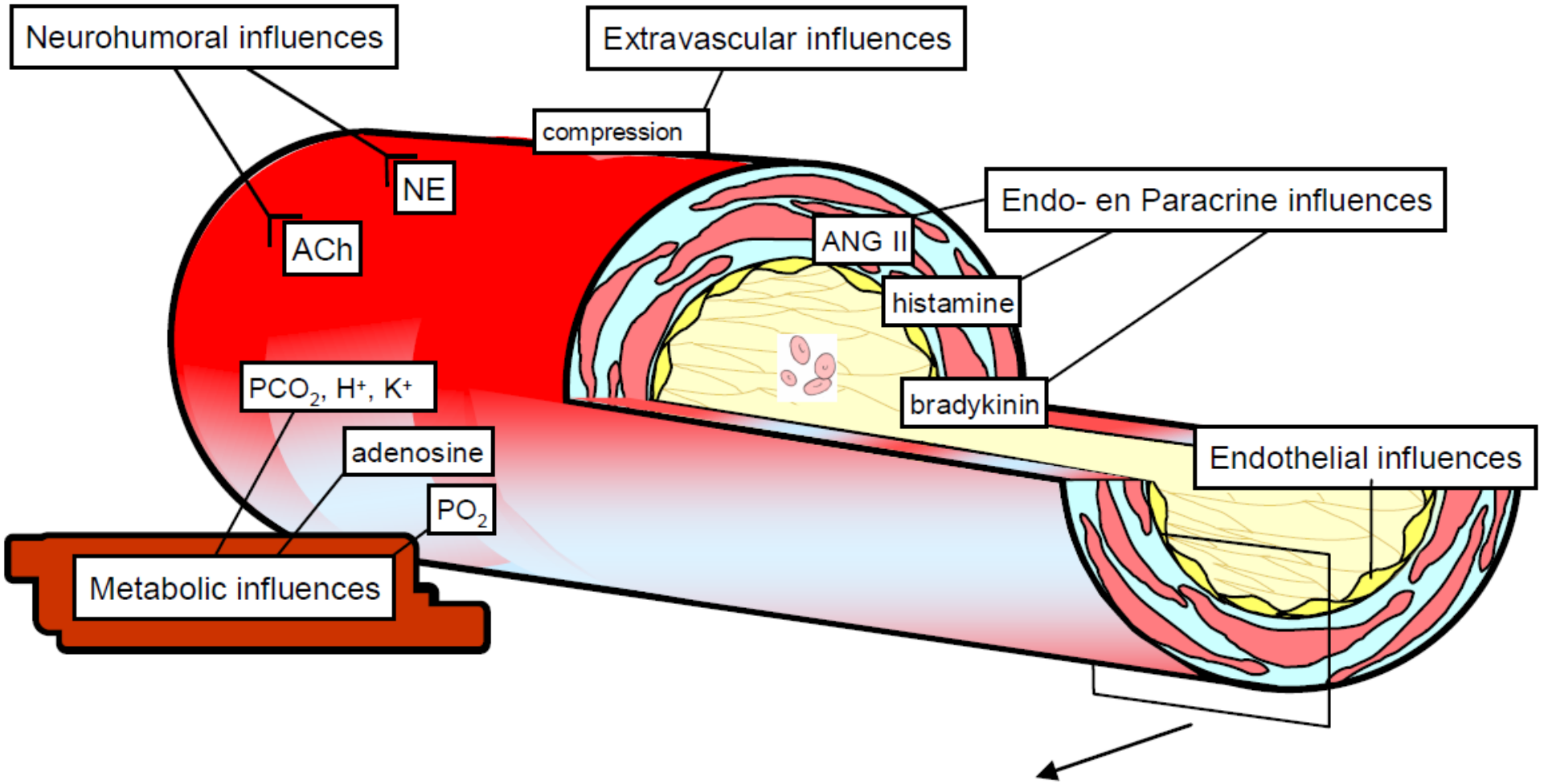
# Control of Coronary Microvascular Tone






*Laughlin et al Compr Physiol 2012*

# Summary of control mechanisms of coronary microvasculature tone






*Duncker & Bache Physiol Reviews 2008*

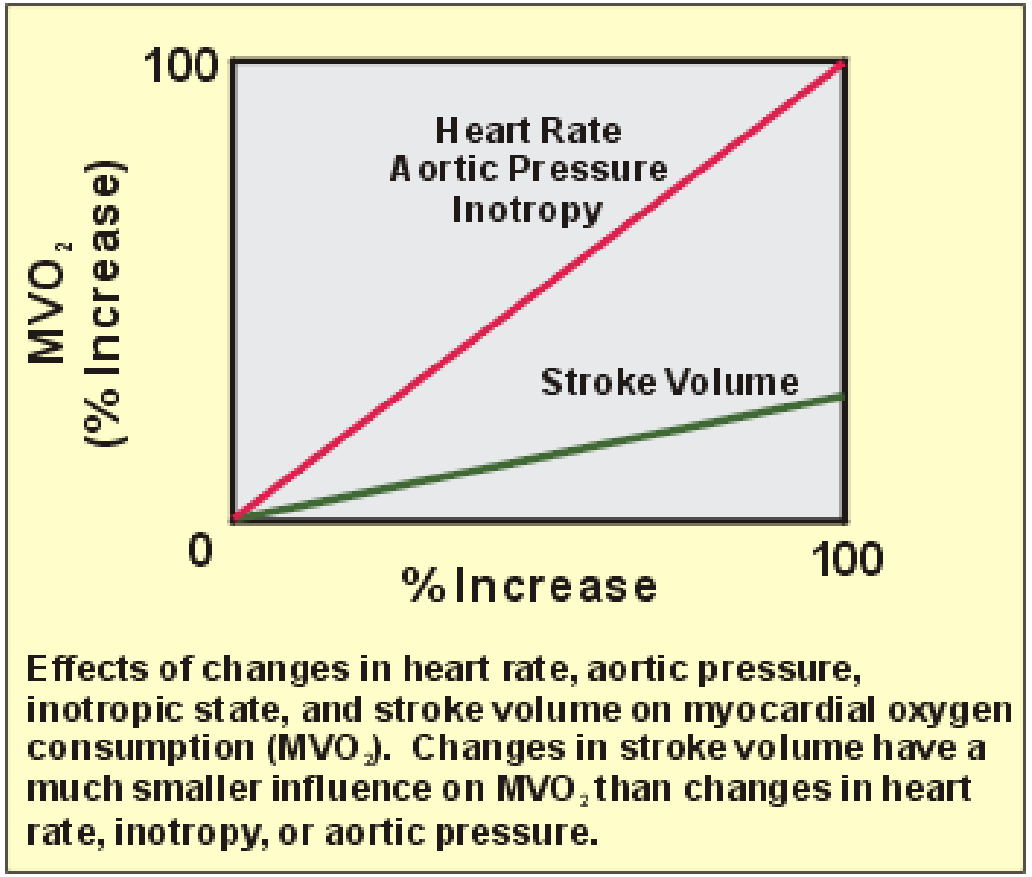
# Factors influencing myocardial $O_2$ consumption ($MVO_2$)

- (1) heart rate
  - more cardiac cycles = more ATP consumption
- (2) contractility
  - that's why (i.e. 1 & 2) $O_2$ demand is ↑ during sympathetic activation
    - positive chrono- and inotropic effect
- (3) wall tension (see La Place law)
  - that's why $O_2$ demand is ↑ in pressure or volume overload, but the extent is not the same!
    - effect of ↑ afterload is much greater than that of ↑ preload

$$T \propto P \cdot r$$

$$T \propto P \cdot \sqrt[3]{V}$$

- (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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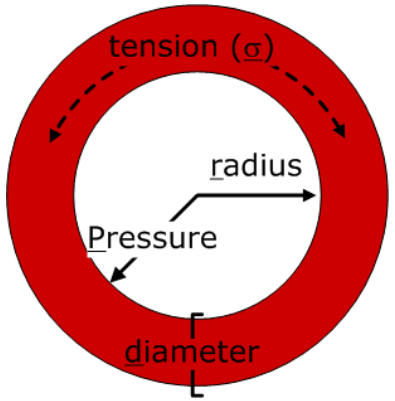
# Wall tension x pressure or volume overload x $MVO_2$

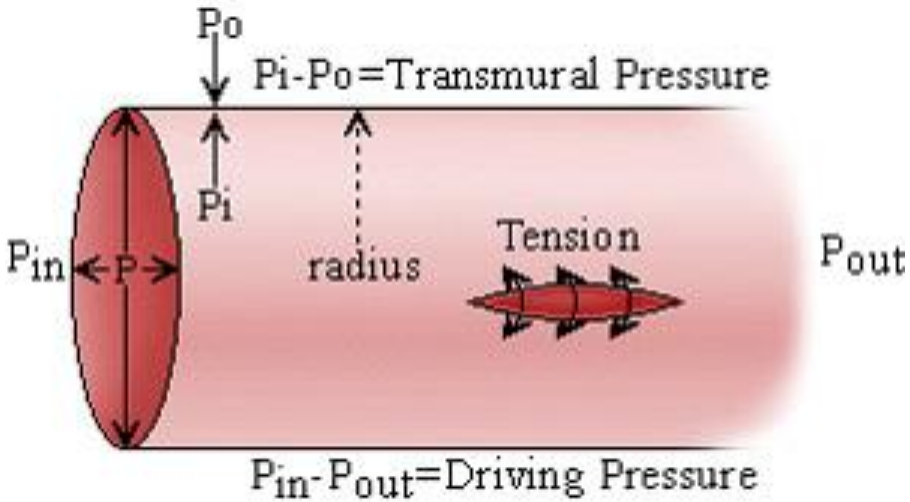
- wall tension ($\sigma$) = tension generated by myocytes that results in a given intraventricular pressure at a particular ventricular radius
- pressure and volume overload have very various effects on $MVO_2$
  - afterload = pressure
  - preload = volume (filling ~ end-diastolic pressure)
- $V = 4/3\pi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

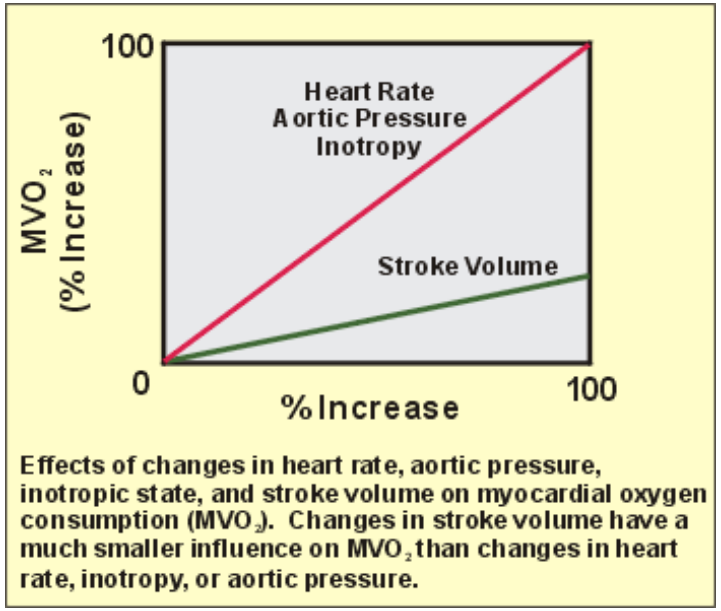



La Place law:

$\sigma = P \times r / d$

*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 ($\sigma$) by only 26%
- in contrast, increasing intraventricular pressure (P) by 100% increases wall tension ($\sigma$) by 100%!

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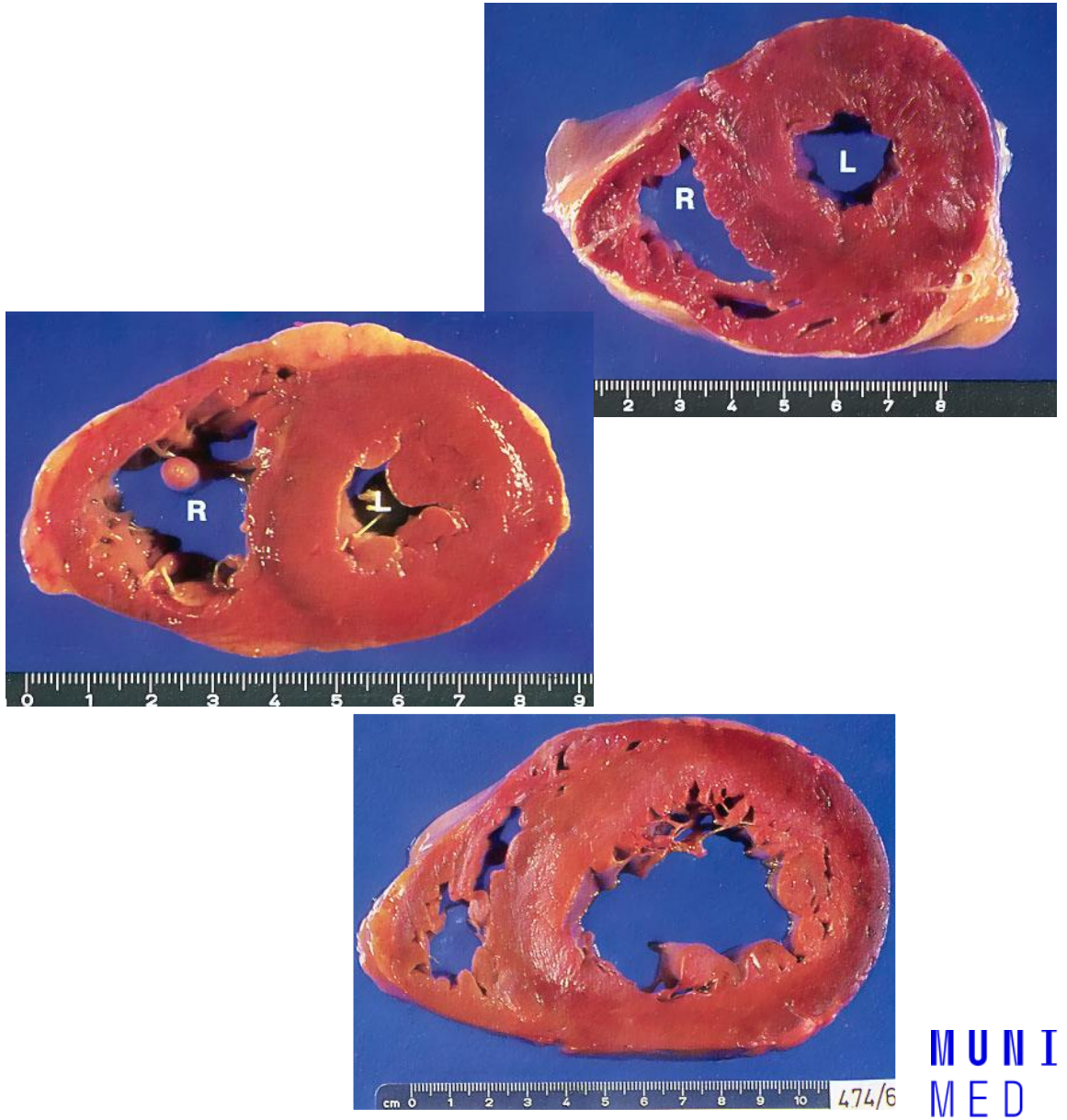
# Why hypertrophy does not ↓ $O_2$ consumption at the end

- 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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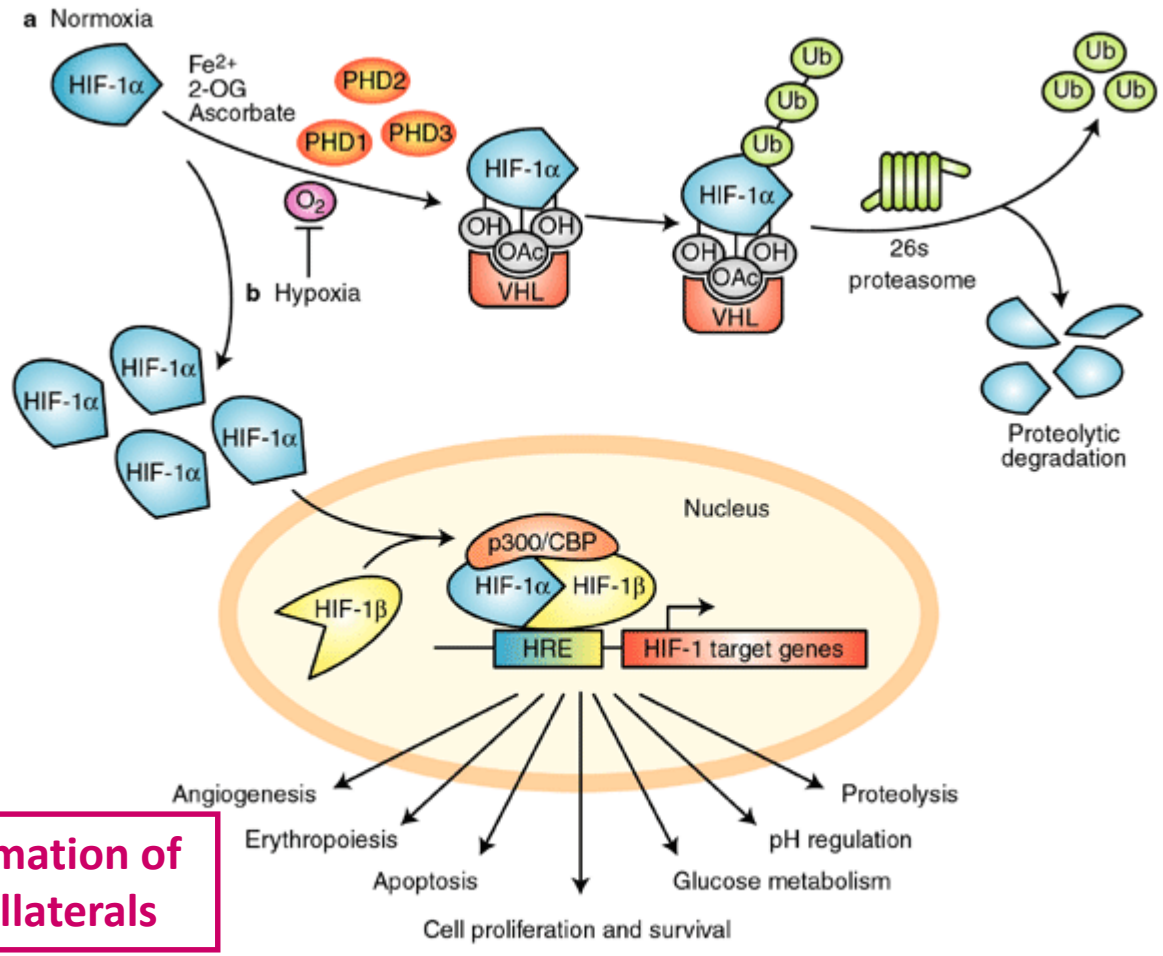
# Hypoxia ≠ ischemia




HIF-1α regulation by proline hydroxylation

**formation of collaterals**

- hypoxia is a common situation both pre- and postnataly driving the tissue homeostasis
  - morphogenesis, wound healing, cancer progression, …
- stimulates HIF-1 driven transcription programme

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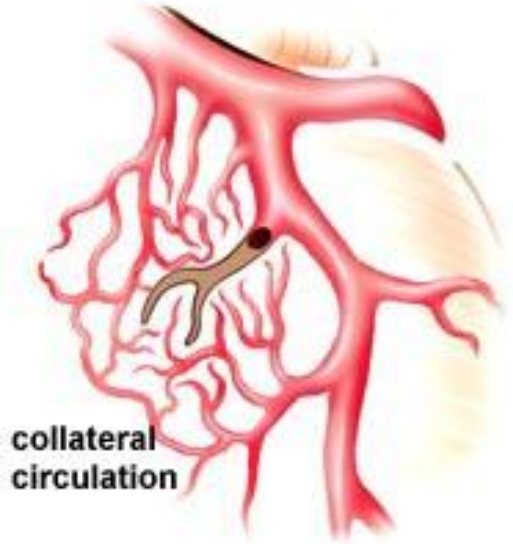
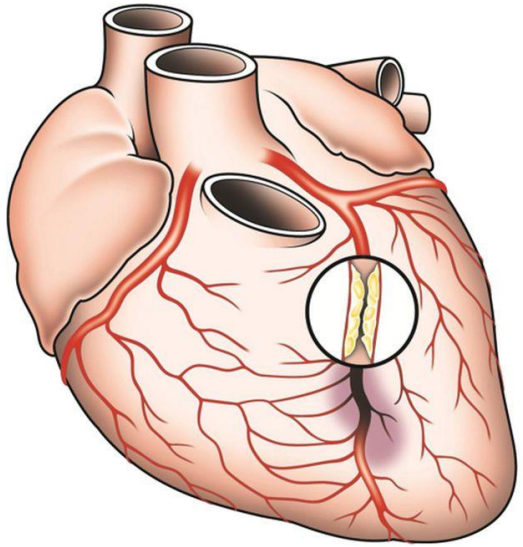
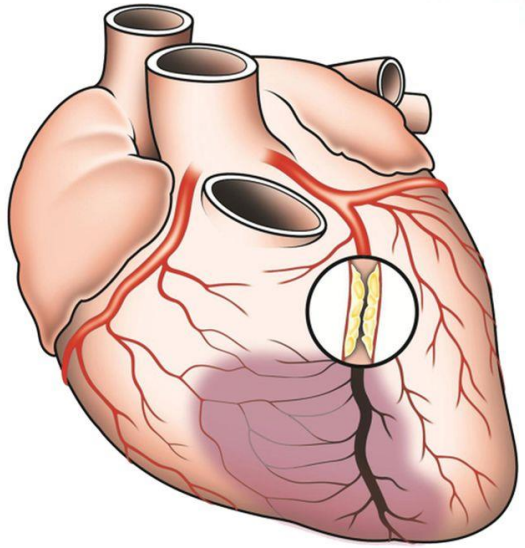
# Coronary collaterals & angiogenesis

- enhancement of blood flow to ischaemic myocardium can result from
  - (1) recruitment of pre-existing coronary collaterals (= **arteriogenesis**)
    - variable density among people?
  - (2) de novo **angiogenesis**
    - angiogenesis = budding of capillaries that leads to the formation of new microvessels from pre-existing vascular structures
- orchestrated by hypoxia (HIF-1/VEGF)
- prominent interinidividual variability
- failure of concomitant angiogenesis in hypertrophic myocardium





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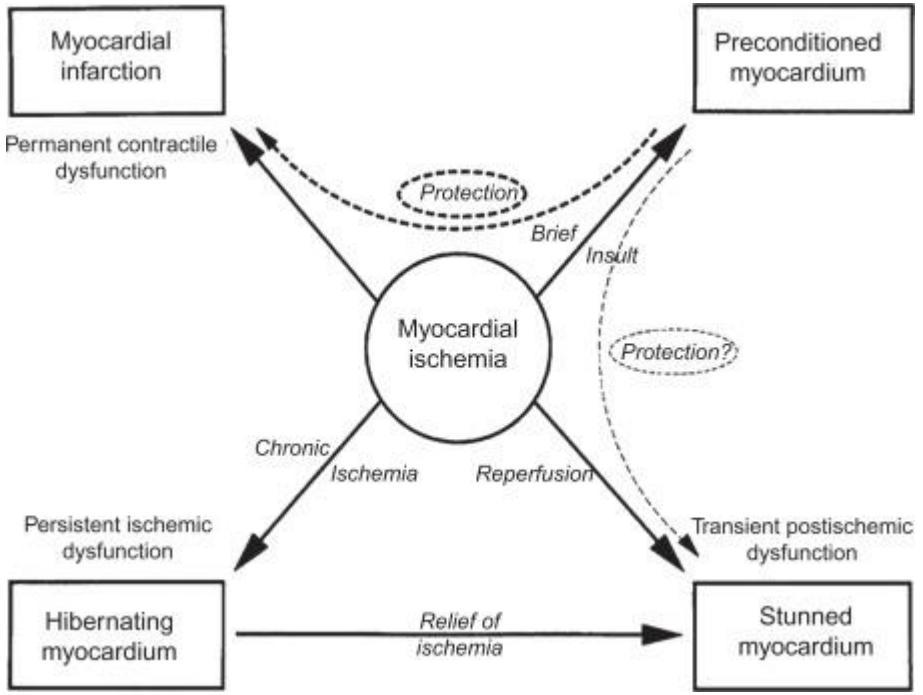
# Metabolic and functional consequences of ischemia

- metabolic changes
  - ↓ perfusion → $O_2$ → ↓ aerobic metabolism → ATP depletion → ↓ creatine phosphate → accumulation of lactate and other catabolites → metabolic acidosis → efflux of potassium into extracellular space → loss of membrane function and cellular integrity → cardiomyocyte death
  - accumulation of $K^+$, lactate, serotonin and ADP causes **ischemic pain** (angina)
- functional changes
  - ↓ contractility (= systolic dysfunction)
    - ↓ EF (ejection fraction), ↓ SV (stroke volume)
  - ↓ diastolic relaxation (= diastolic dysfunction)
    - ↑ EDP (end-diastolic pressure)
- in summary … **↓ CO (cardiac output)**
  - in the most serious form = cardiogenic shock
- (auto)regulatory and systemic regulatory mechanisms cause vasodilation in the intact part of coronary bed - **vascular steal**
  - stenotic arteries do not react to this stimulation and healthy ones further "steal" the blood from already ischemic region
- the extent of perfusion limitation decides whether the above mentioned processes appear only during the exercise, also in the rest or whether myocardial necrosis develops and what is its extent

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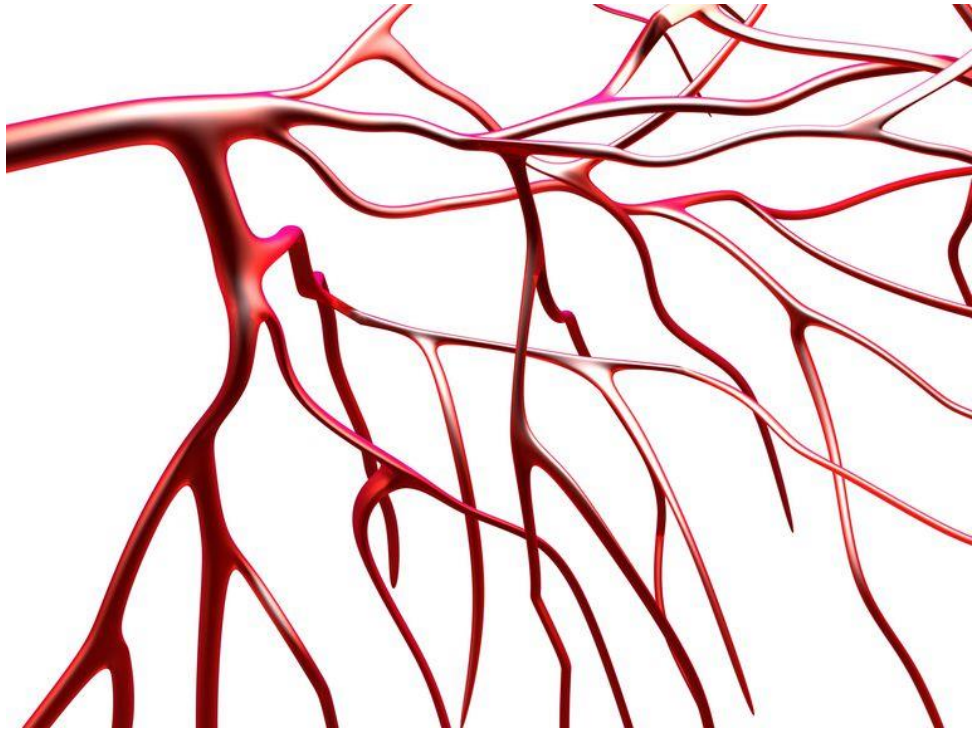

# ENDOTHELIAL DYSFUNCTION AS A TRIGGER OF ATHEROSCLEROSIS

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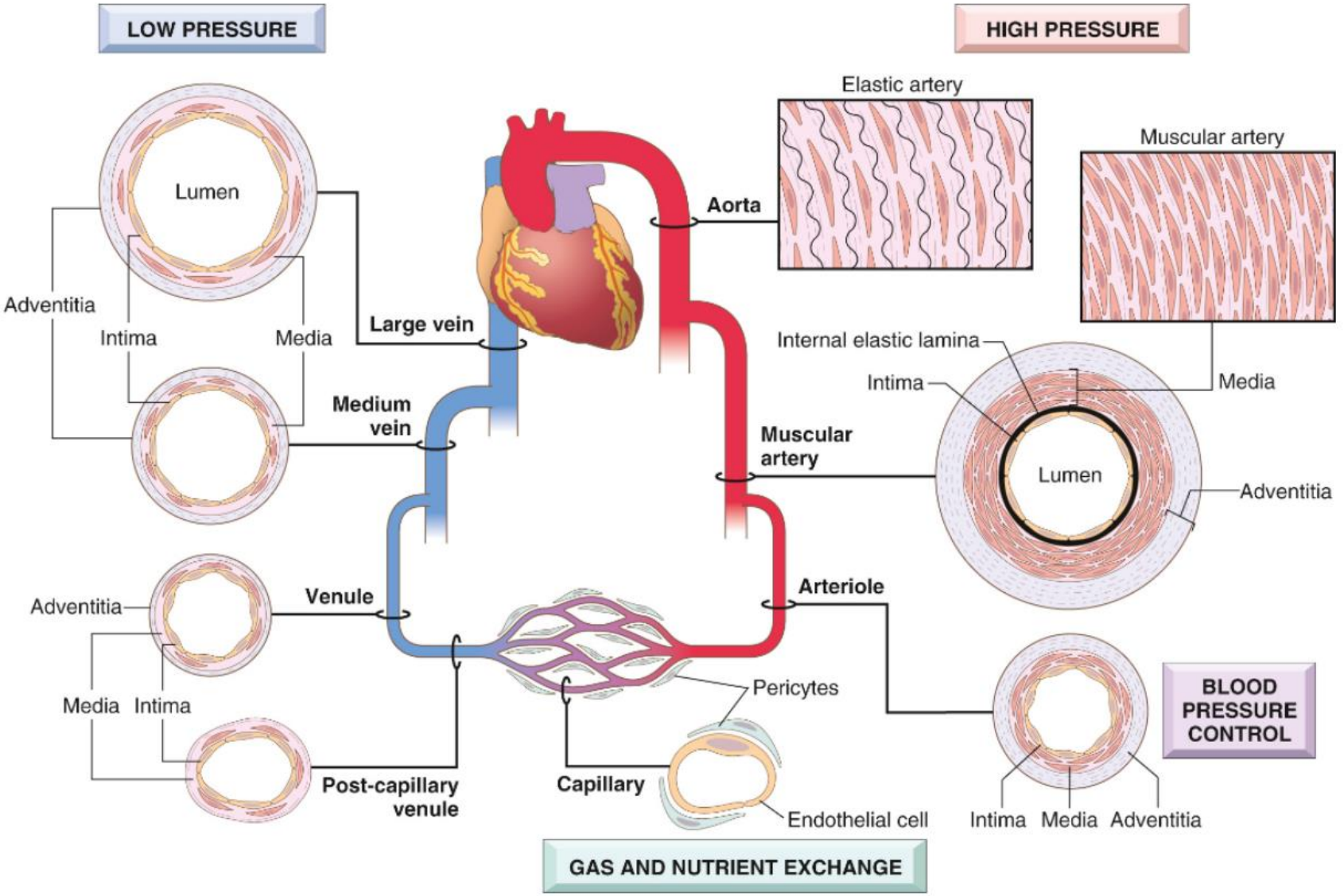
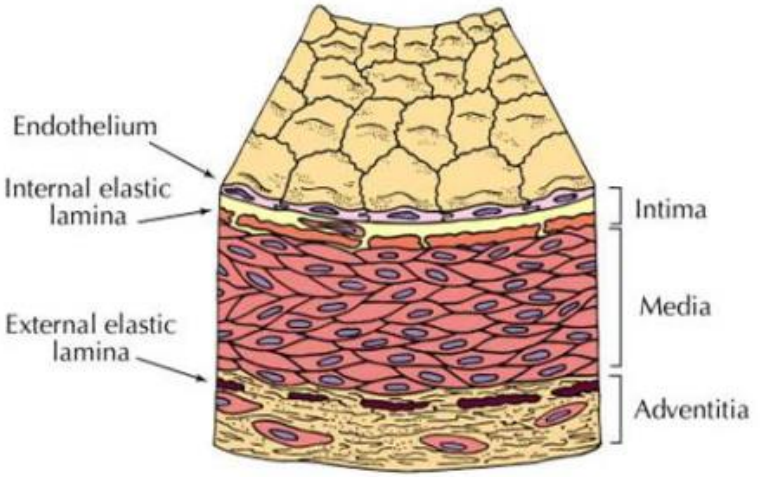
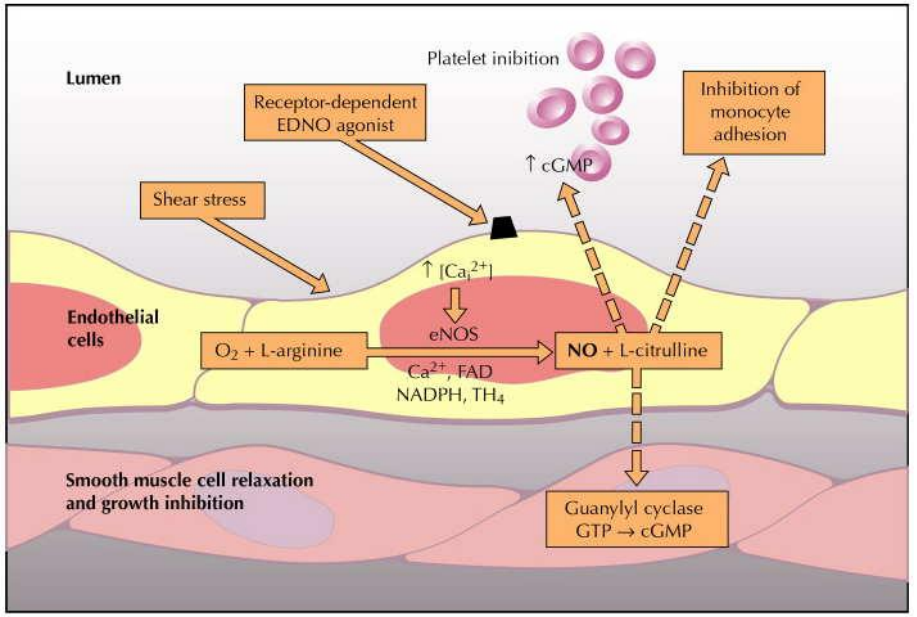
# Vessels – types and function



# Endothelium - physiological role of ECs

- (1) **vasodilation**
  - smooth muscle cells (SMC) in blood vessels - notably arterioles - work in close association with the overlying ECs
  - action of hormones, neurotransmitters (**ACh**) or deformation of the ECs by flow of blood (shear stress) trigger reactions that influence associated SMC, these effects operates via second messenger systems
    - phospholipase A2 (**PLA2**) which activate cyclooxygenase (**COX**) / prostacyclin synthase (PCS) to produce prostaglandins (**$PGI_2$**) which diffuse readily through the tissue fluids to act on SMC
    - alternatively, nitric oxide synthase (L-arginase) (**NOS**) produces highly diffusible gaseous "neurotransmitter„ **NO** acting on SMC either through G-protein systems or directly on ion channels
- (2) **antiadhesive /anti-inflammatory action**
  - no VCAM, ICAM, selectins, …
- (3) **antithrombotic, antiagregant** and **fibrinolytic action**
  - heparansulphate
  - thrombomodulin
  - tPA

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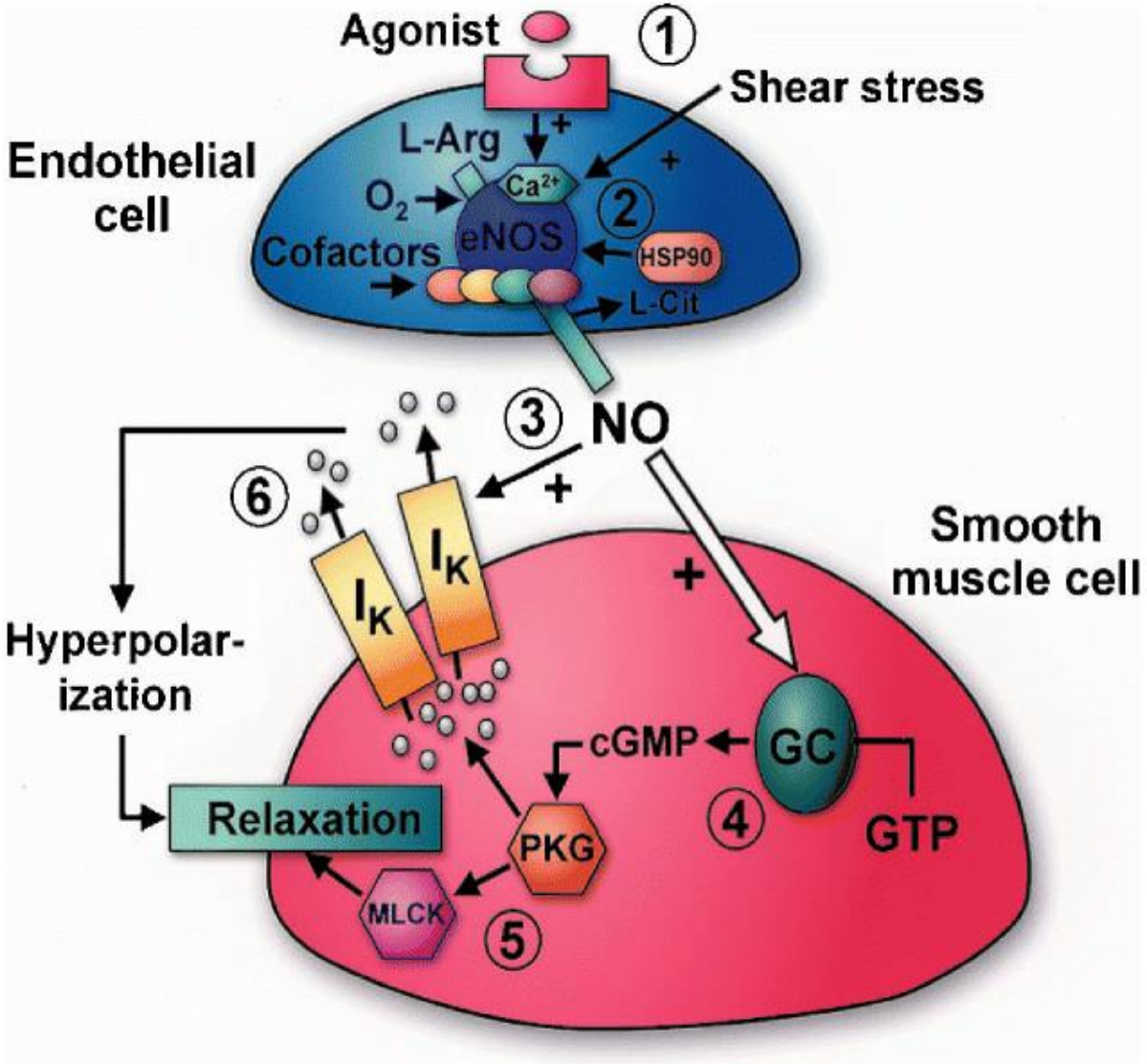
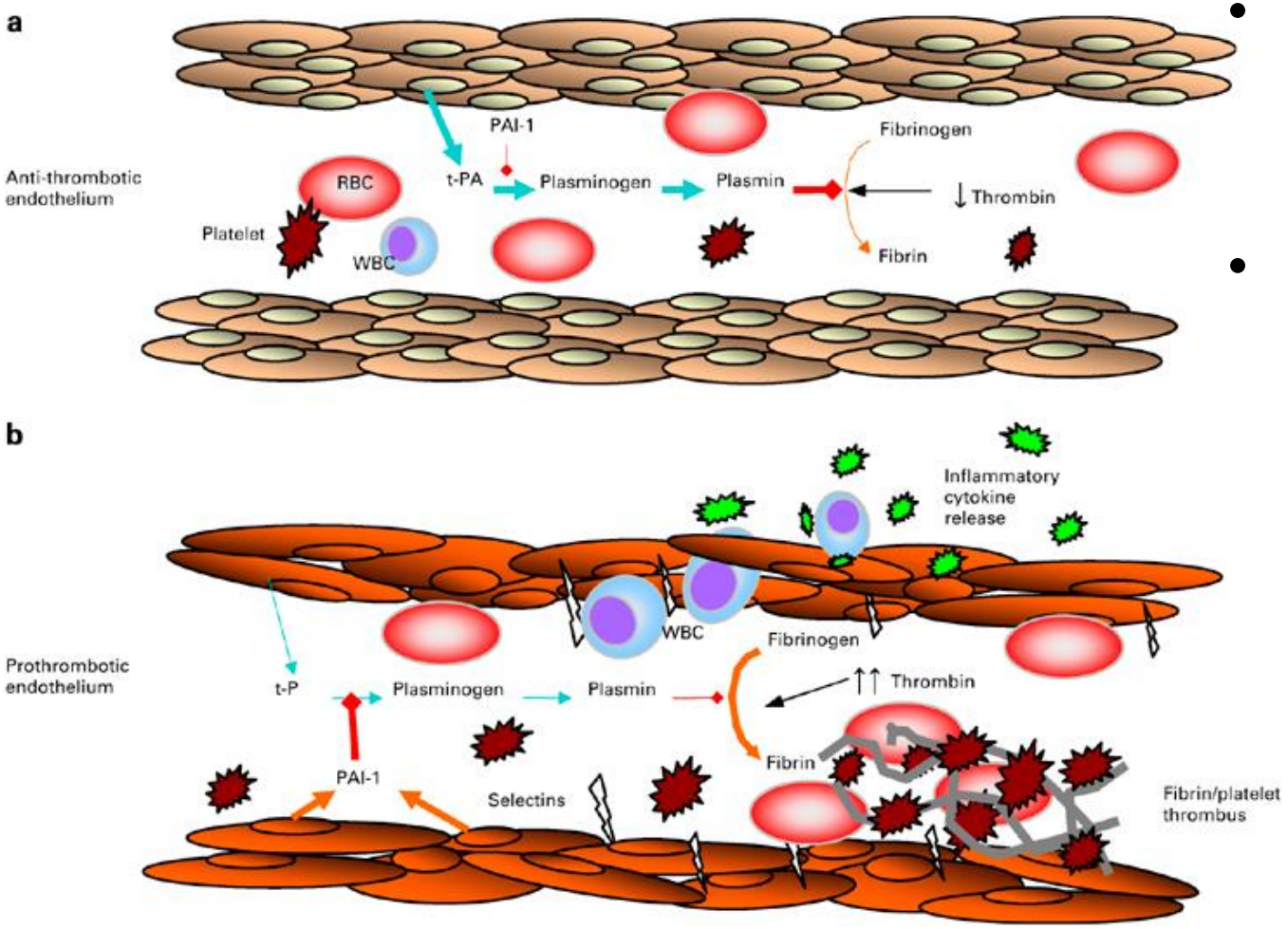
# NO-mediated vasodilation

- biosynthesis of the key endogenous vasodilator NO is principally performed by the calcium-dependent endothelial isoform of nitric oxide synthase (eNOS)
- this is triggered by the binding of agonists or by shear stress (1) and facilitated by a variety of cofactors and the molecular chaperone heat-shock protein 90 (HSP90)
- amino acid L-Arg is converted by eNOS into NO (2), with L-citrulline as a by-product. NO diffuses into adjacent smooth muscle cells (3) where it activates its effector enzyme, guanylate cyclase (GC)
- GC (4) converts GTP into the second messenger cyclic guanosine monophosphate (cGMP), which activates protein kinase G (PKG) (5), leading to modulation of myosin light chain kinase and smooth muscle relaxation.
- PKG also modulates the activity of potassium channels (IK; 6), thereby increasing cell membrane hyperpolarization and causing relaxation



# Endothelial dysfunction




- given the essential role of endothelial integrity in maintenance of normal vessel morphology endothelial dysfunction act as a pro-atherogenic factor increasing adhesivity, permeability and impairing vasodilatation
- causative factors:
  - increase BP (hypertension)
  - mechanical shear stress
    - turbulent flow
    - bifurcations
  - biochemical abnormalities
    - glucose
    - modified proteins
      - incl. LDL
    - homocysteine
  - oxidative stress
    - oxygen radicals
      - formed by smoking
      - inflammation
  - certain infections
    - Chlamydia pneumoniae?
    - Helicobacter pylori??

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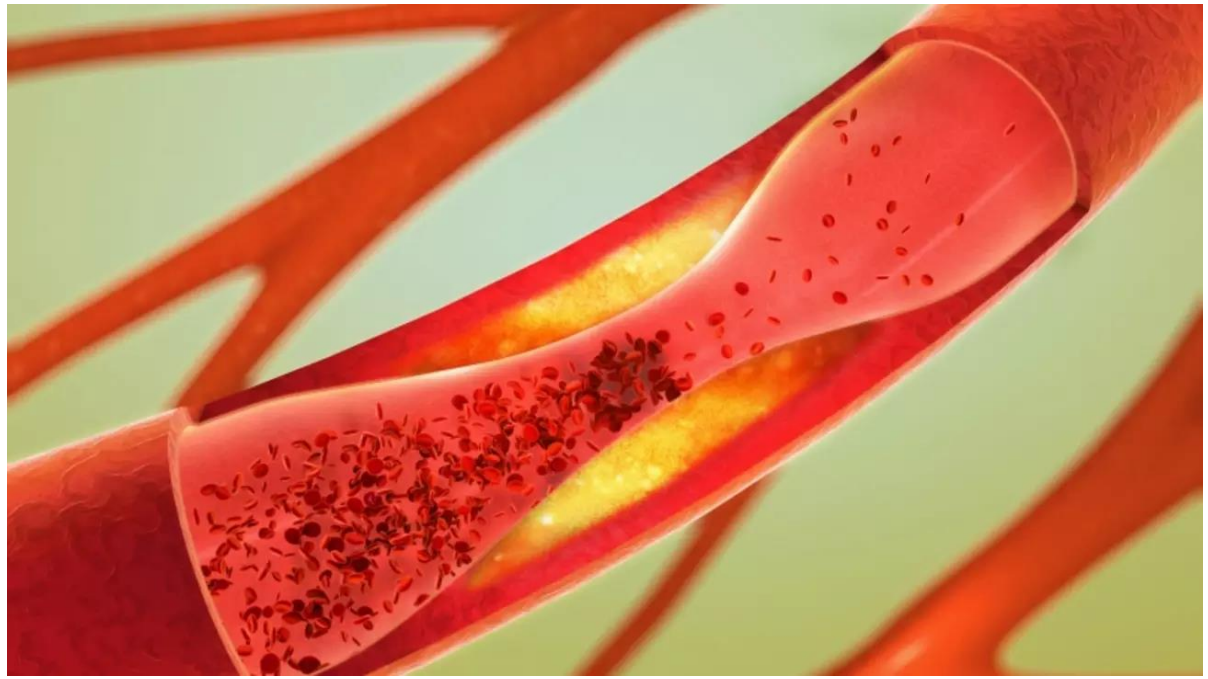
# Endothelium - summary

| Functional | Dysfunctional |
| --- | --- |
| constant vasodilation due to mechanical stimuli (shear stress) and mediators (Ach, bradykinine) mediated by NO, $PGI_2$ (event. adenosine) | increased sensitivity to paracrine constrictive mediators (epinephrine, norepinephrine, AT II, serotonin) and active formation of vasoconstrictors (ET-1) |
| anti-adhezive / anti-inflammatory state (NO, $PGI_2$), inhibition of expression of adhezive proteins | expression of adhesive molecules (ICAM, VCAM, selectins), production of cytokines (e.g. MCP-1) attracting migration of inflammatory cells into subendothelial space |
| constant local anticoagulant production (heparansulphate, thrombomoduline), antiagregant and thrombolytic state (tPA) | prothrombotic (vWf, TF), anti-fibrinolytic (PAI-1) phenotype |



# CORONARY ATHEROSCLEROSIS

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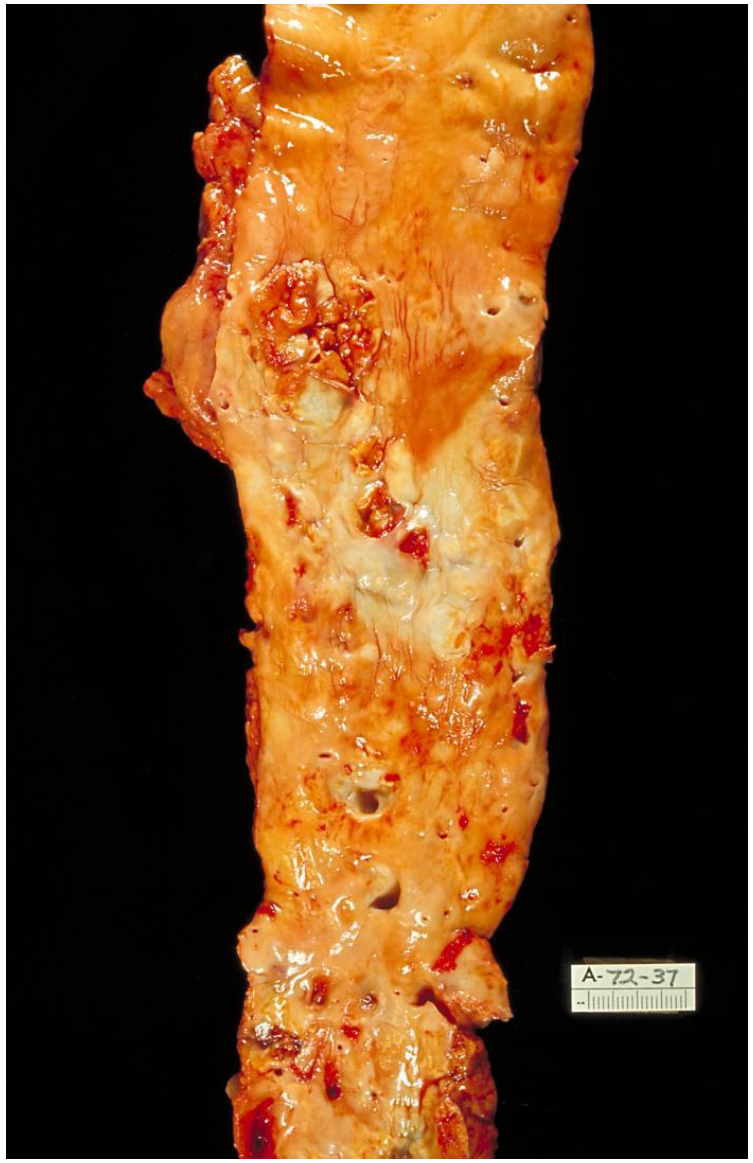
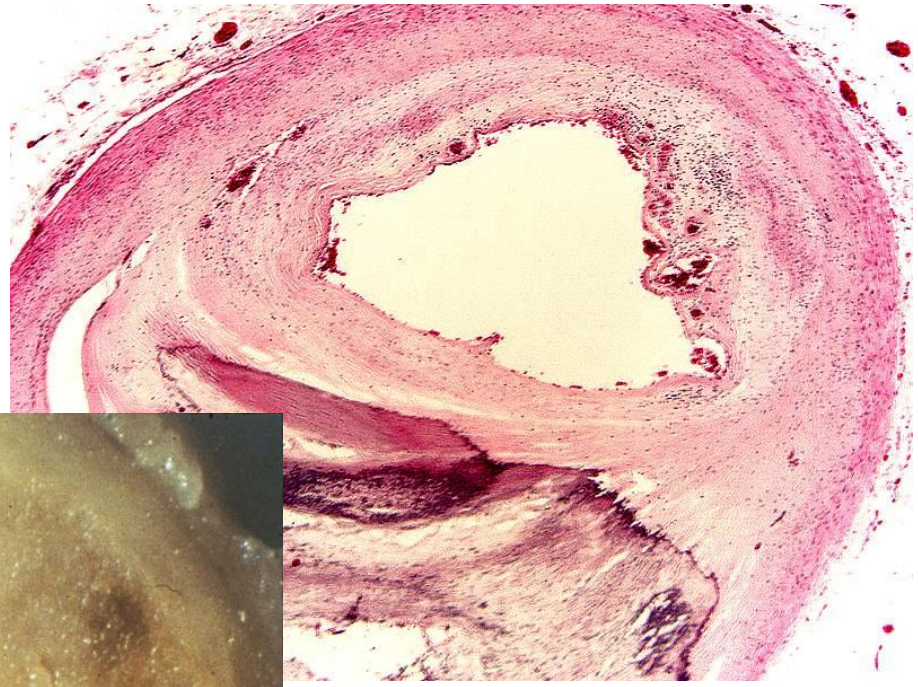
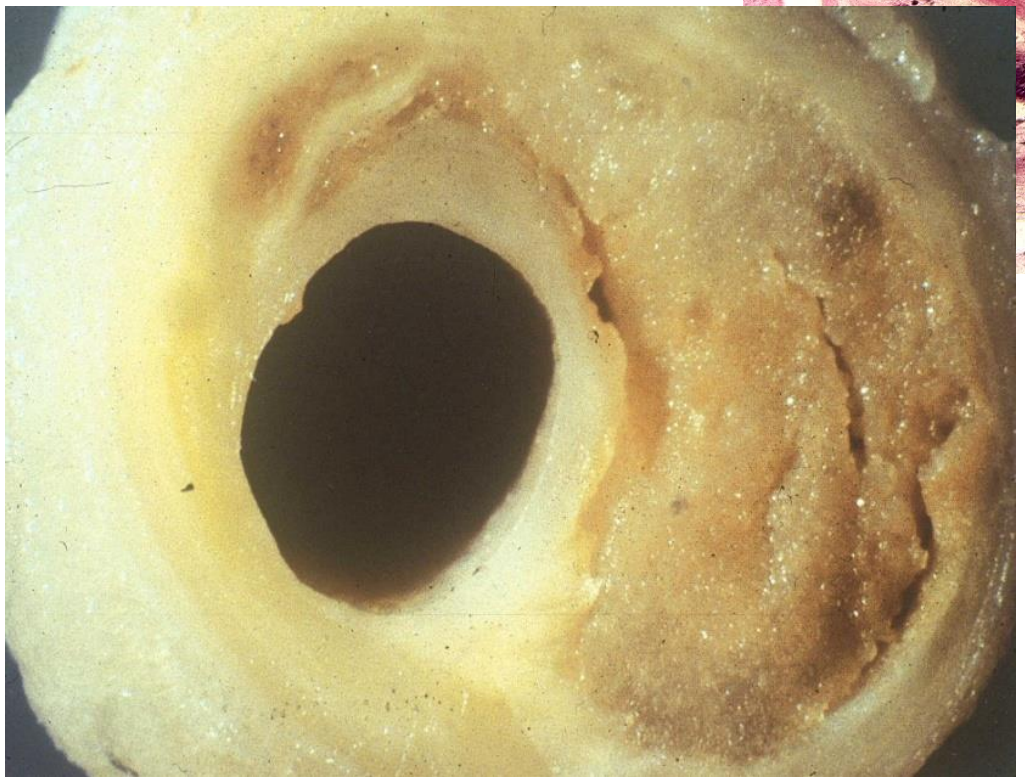
# Vessels affected by AS





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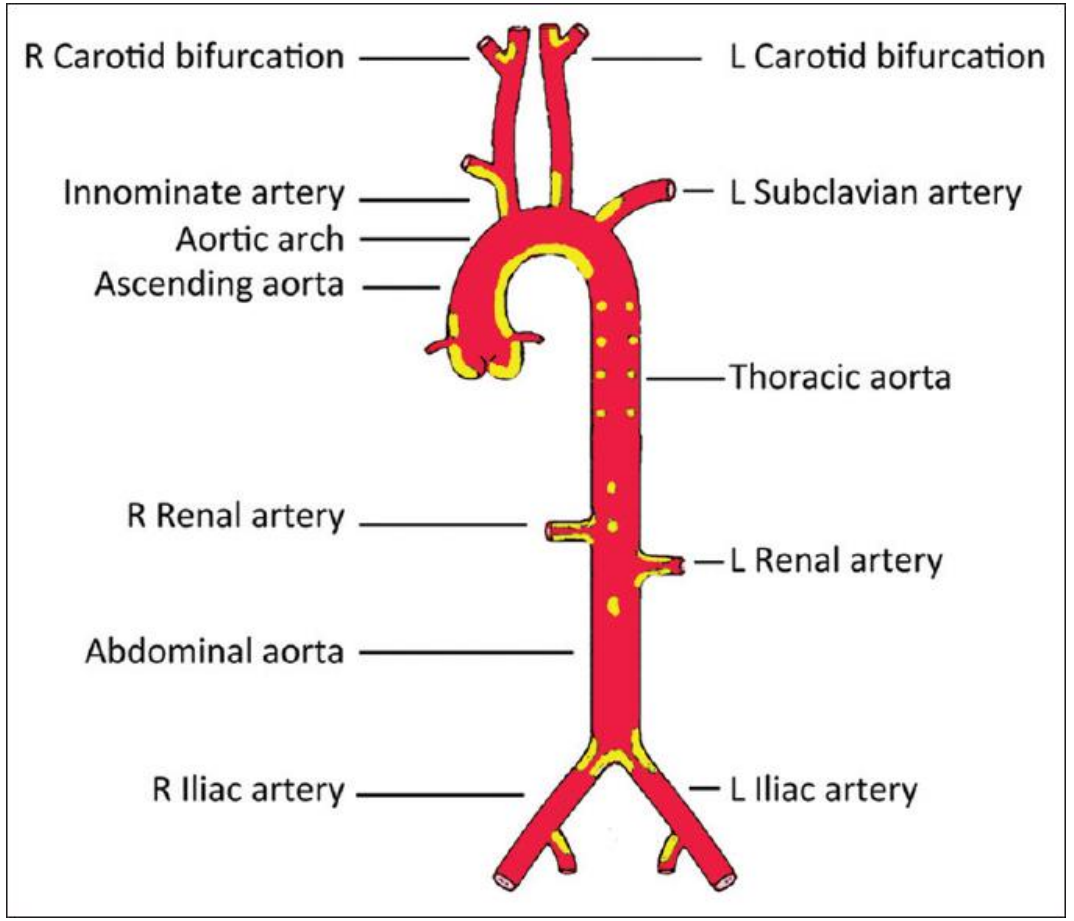
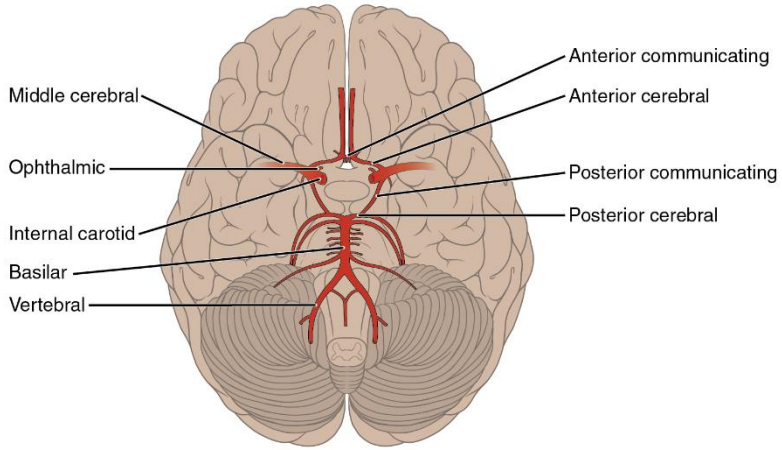
# CAD due to AS – main facts

- AS is a degenerative process characterised by **chronic inflammation** of the vessel wall
- AS represents **multifactorial disease** due to endogenous (typically with significant genetic component) and environmental factors
- AS can theoretically affect any vessel, in reality AS is limited only to arteries (= arteriosclerosis)
  - due to the role of **blood pressure** as a pathogenic factor
  - moreover, not all arteries are equally affected, but most often those in **predilections** (bifurcations, non-laminar flow)
    - coronary and cerebral bed, carotids, renal artery, lower extremities artery bifurcations
- main players in the AS ethiopathogenesis
  - (1) modified lipoproteins (LDL)
  - (2) monocyte-derived macrophages
  - (3) normal cells of vessel wall (smooth muscle cells)
- morphologicaly defined **stages** (findings) in naturalhistory of AS:
  - (1) endothelial dysfunction
  - (2) fatty streak
  - (3) fibrous plaque
  - (4) complicated plaque

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# Cardiovascular (AS) risks

- identification of the main CV risks by prospective epidemiologic studies
  - **Framingham study** = ↑ TK, ↑ cholesterol, ↑ triglycerides, ↓ HDL, smoking, obesity, diabetes, physical inactivity, ↑ age, gender (male) and psychosocial factors
    - original cohort (from 1948)
      - 5,209 subjects (aged 32 – 60 yrs) from Framingham, Massachusetts, USA
      - detail examination every 2 years
    - II. cohort (from 1971)
      - 5,124 adult offspring
    - III. cohort
      - 3,500 grandchildren of original participants
  - identified late clinical manifestation of long-term untreated / decompensated hypertension as well:
    - **heart attack, stroke (→ atherosclerosis)**
    - heart failure (→ left ventricular hypertrophy)
    - renal failure (→ hyperfiltration, nephrosclerosis)
    - retinopathy

| | Risk factors of AS | |
|---|---|---|
| significant genetic contribution | **Major** | |
| | dyslipidaemia (↑ LDL and VLDL, ↓ HDL) | metabolic syndrome driven by obesity |
| | hypertension | |
| | diabetes mellitus | |
| | male gender | |
| | **Minor** (20% of CV events occur in subjects without major risks) | |
| | ↑ plasma homocysteine | |
| | ↑ plasma haemostatic factors (e.g. fibrinogen, PAI, ..) | |
| | ↑ Lipoprotein (a) – Lp(a) | |
| | chronic inflammation (CRP as a surrogate) | |
| non-genetic | **Environmental** | |
| | smoking (major risk!) | |
| | physical inactivity | |
| | diet | |
| | certain infections | |

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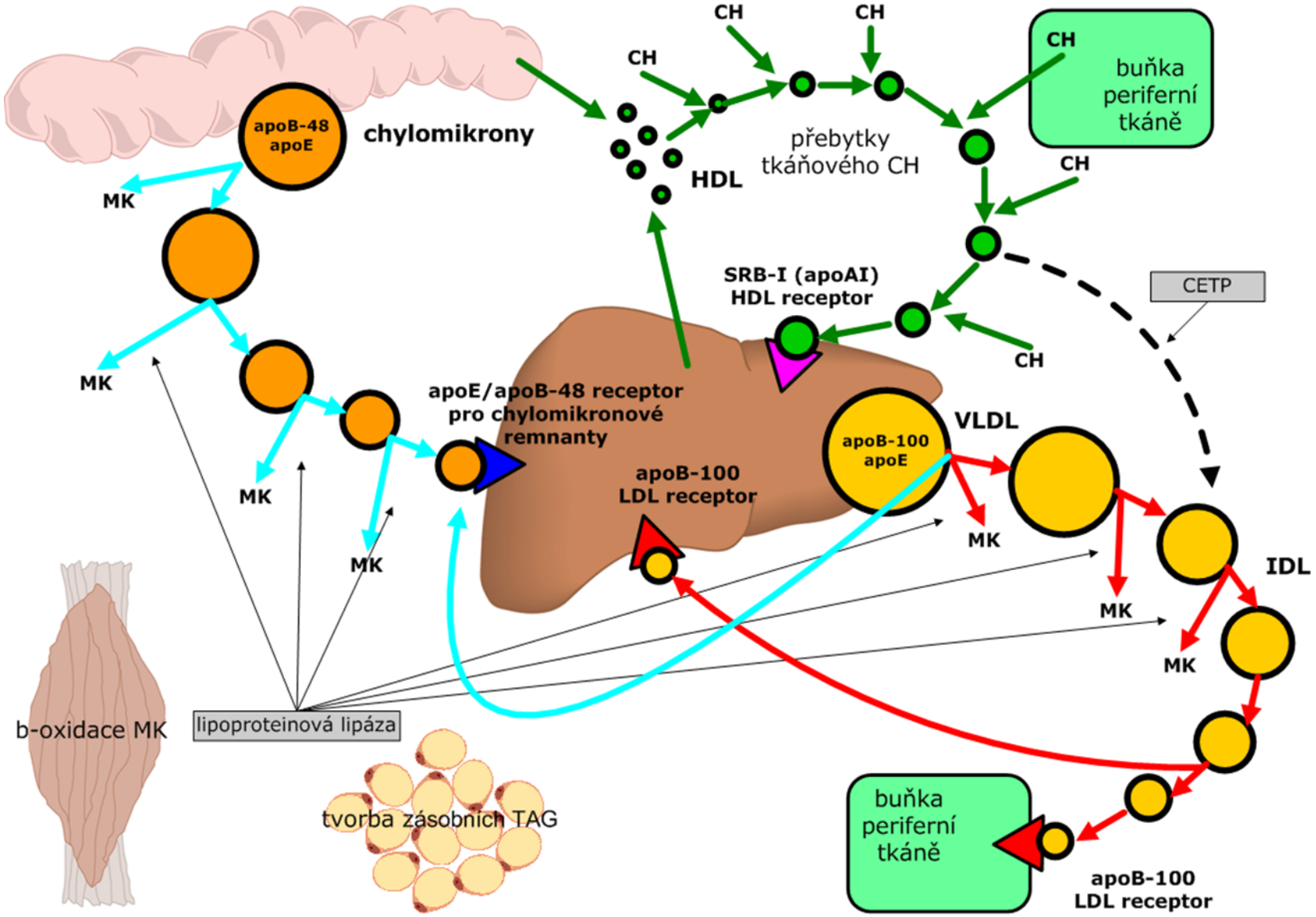
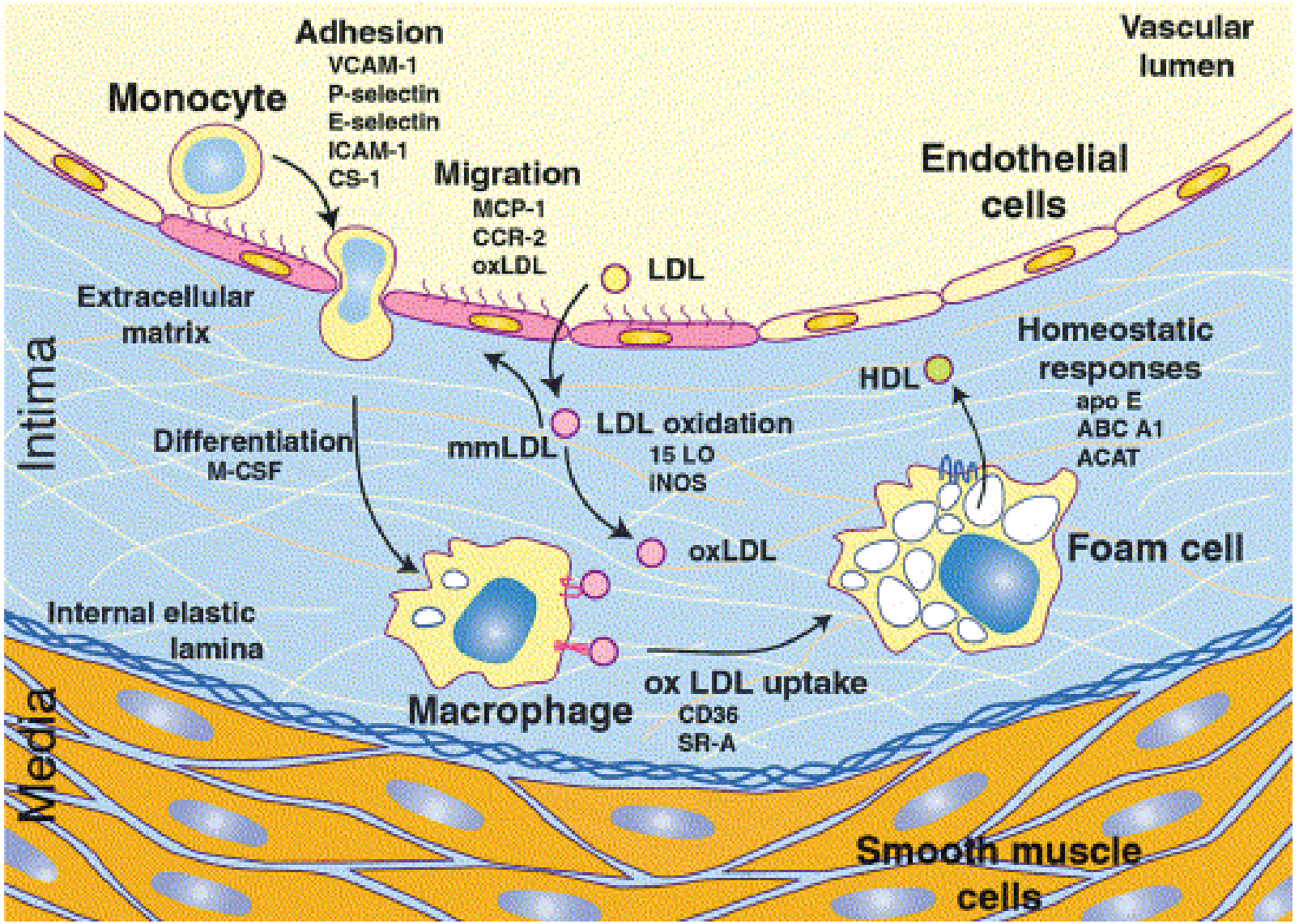
# Lipoprotein metabolism / lipid transport overview



# (1) Initiation – formation of fatty streak




- **LDLs** can exist in a native or modified forms
  - native LDL is recognised and bound by LDL-R
  - modified LDL is up-taken by scavenger receptors
- in vivo LDL is modified by oxidation (acetylation or glycation) in circulation and in subendothelial space
  - minimally at first (mmLDL), extensively later (oxLDL)
- mmLDL and oxLDL are cytotoxic and pro-inflammatory, they increase expression of adhesive molecules (VCAM, ICAM, selectins) by EC
- monocytes and T lymphocytes adhere to endothelium and migrates to subendothelial space, here monocytes transform to macrophages
  - interestingly, neutrophils that are constant cell type present in inflammatory lessions are completely absent in AS, finding not entirely understood; it might be because of the particular cytokine spectrum – expression of MCP-1 (monocyte chemotactic protein) by EC
- macrophages ingest oxLDL via their scavenger receptors (SR-A and CD36) and form this was so called **"foam cells"** (= lipid-laden macropghges)
  - macroscopically seen as a yellowish dots or streaks in subendothelium, hence **"fatty streaks"**
- free cholesterol from oxLDL in macrophages is again esterified by ACAT-1 (acyl-CoA cholesterol acyl-transferase) and stored together with lipids, inversely, it can be transform into soluble form by hormone-sensitive lipase, inbuilt into plasma membrane and exported from the cell (by transporter ABCA1 and HDL)
  - reverse CH transport via HDL is a crucial anti-atherogenic mechanism

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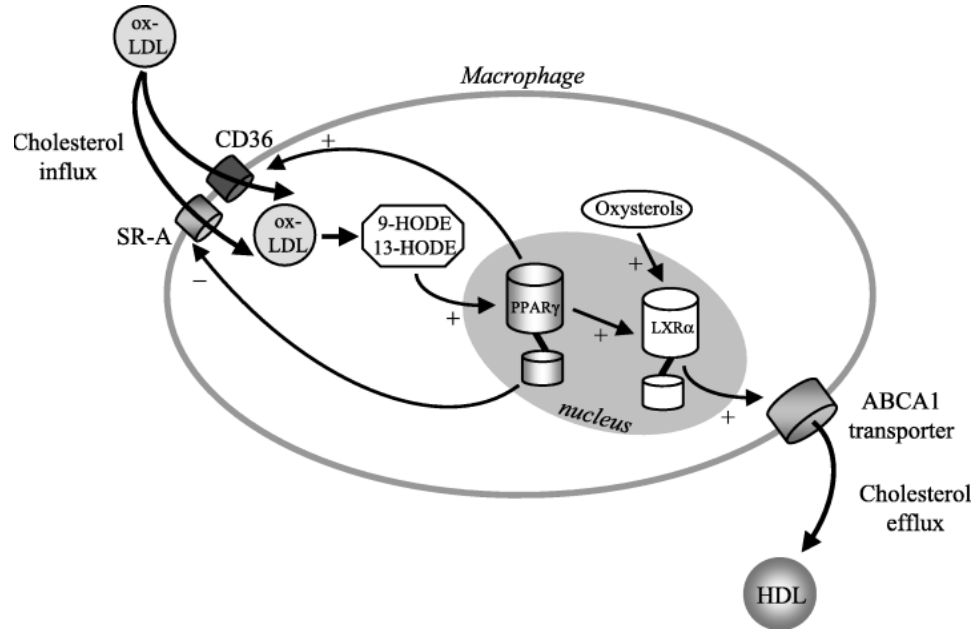
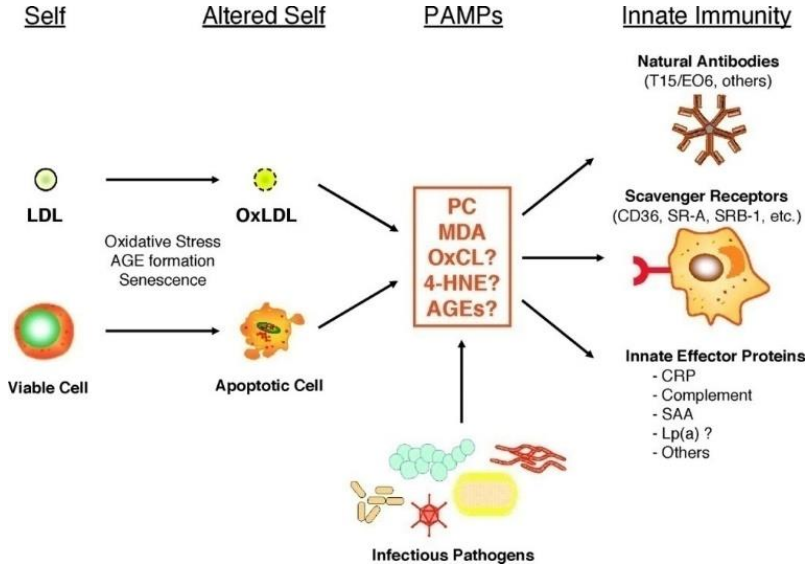
# Role of macrophages in AS initiation

- scavenger receptors of macrophages for modified macromolecules play physiologically important role in cellular defence against cytotoxic agents, but at the same time, they can act as pathogenic mechanisms under the:
  - high CH levels
  - its increased modification
    - oxidation, glycation
  - defective reverse CH transport
    - Tangier disease (mutation in ABCA1)
  - abnormal stimulation of monocytes
- **scavenger receptors are part of the innate immunity**
    - both natural antibodies and scavenger receptors developed during evolution under the frequent stimulation by certain pathogens
  - (1) natural antibodies (IgM)
    - against bacterial pathogen-associated molecular patterns [PAMPs]
  - (2) pattern-recognition receptors (PPRs)
    - SR-A, CD36, TLR (Toll-like receptor)
- oxidised molecules (i.e. particular epitopes) are very often similar to PAMP !!

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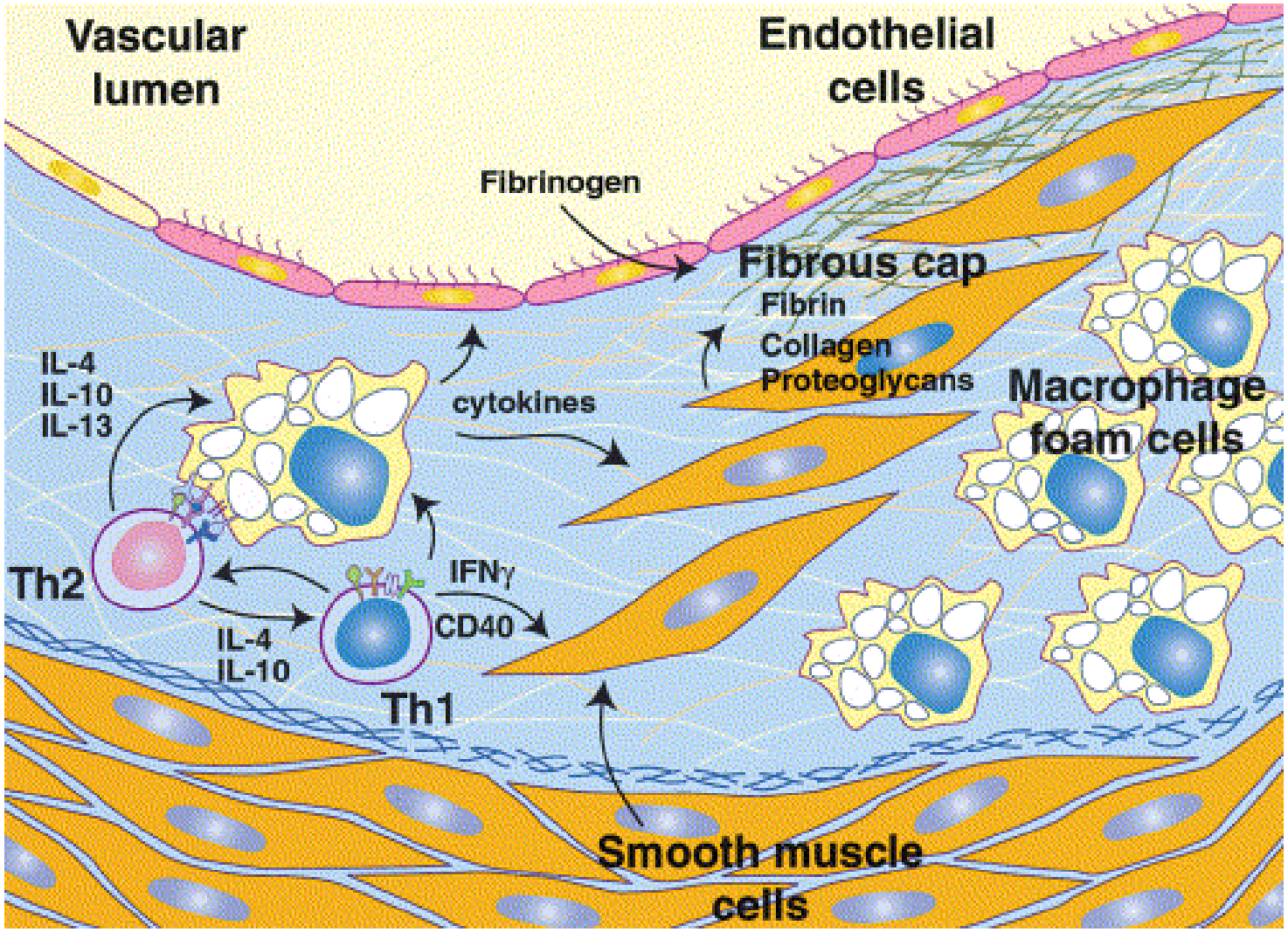
# (2) Progression – formation of plaque




- immunologic interaction between macrophages and T lymphocytes (Th1 and Th2 sub-population) locally maintains the chronic inflammation
  - production of both pro-atherogenic Th1 cytokines (MCP-1, IL-6, TNF-α, …) and anti-atherogenic Th2 (IL-4)
  - mutual balance between Th1 and Th2 is topically modified by many factors
- macrophages as antigen-presenting cells help to activate B lymphocytes to wards production of auto-antibodies against oxLDL → formation of immune complexes → inflammation
- cytokines stimulate other cells, mainly SMCs to migrate from media into intima, proliferate (→ intima thickening) and secrete proteins of extracelullular matrix (collagen) → fibrose plaque
- pathologic calcification of atherosclerotic vessel wall is not a passive consequence but result of changed gene expression in macrophages (osteopontin)

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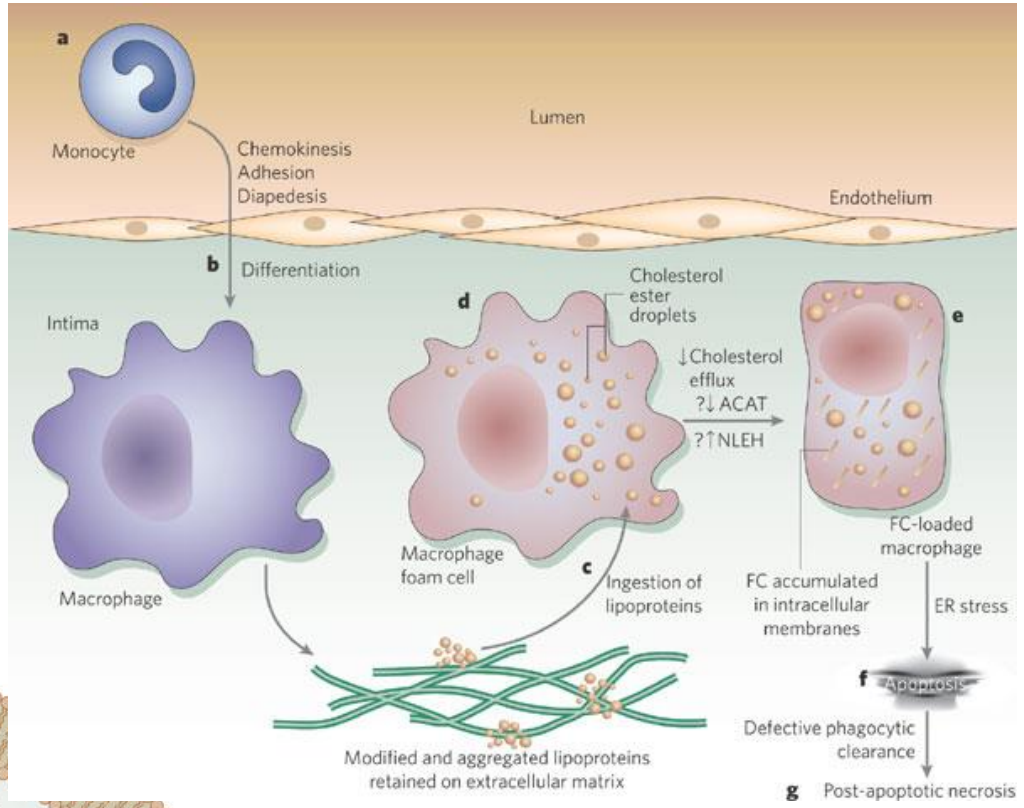
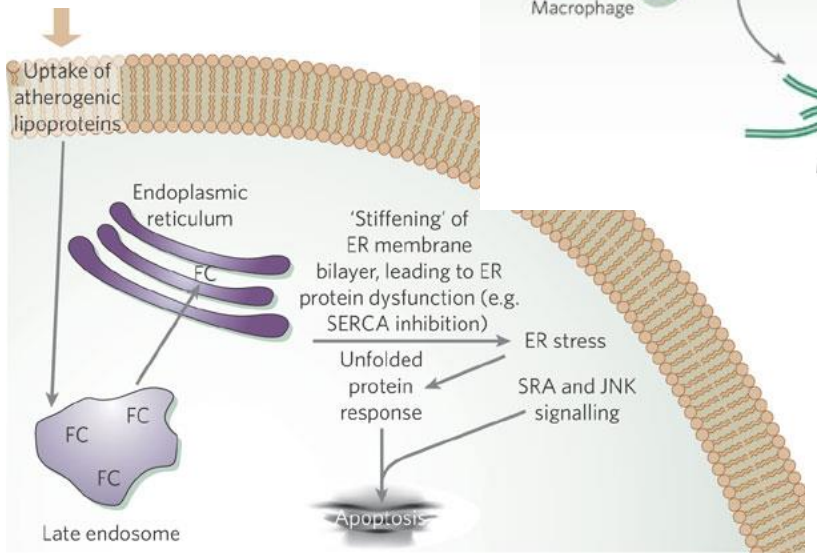
# Macrophages in advanced AS – role in AS

- M in early lesions
  - majority of Ch in the form of esters (enzyme ACAT)
    - non-thrombogenic
  - HDL reverse transport works
- M in advanced lesion
  - accumulation of free Ch (FCH)
    - highly thrombogenic
  - FCH in membranes of endoplasmic reticulum changes its permeability and Ca concentration inside → ER stress → apoptosis of macrophages → more of FCH extracellularly → increased thrombogenicity of atheroma
  - production of MMPs

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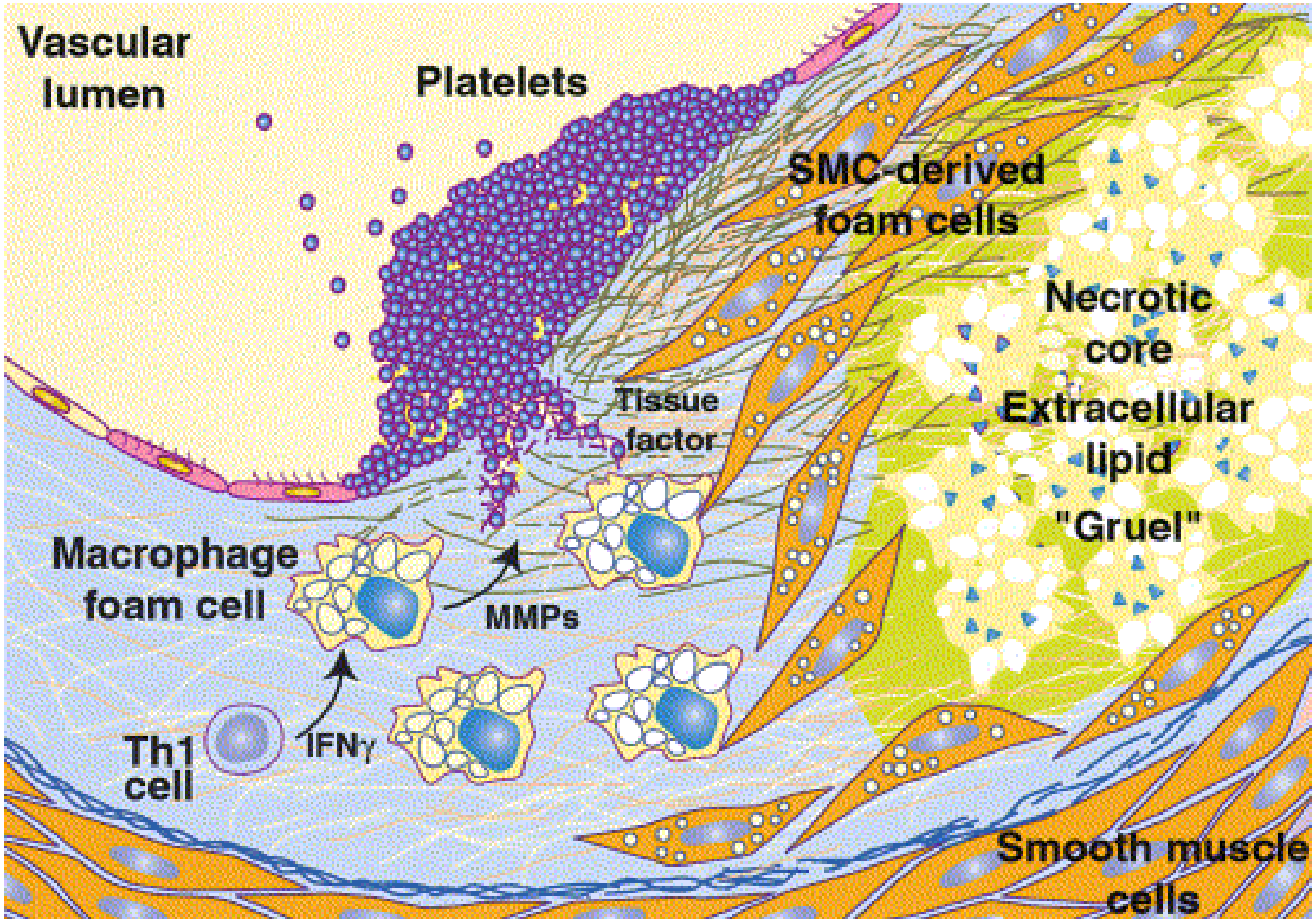
# (3) Advanced AS plaque




- plaque can grow and slowly obstruct lumen or it can become unstable and lead to rupture/fissuration and thrombosis and acute complete obstruction → "complicated plaque"
- intimal macrophages and SMC die (necrosis and cytokine-induced apoptosis) and establish necrotic core of the plaque with accumulated extracellular CH
- stimulated and hypoxic macrophages produce proteolytic enzymes degrading extracellular matrix proteins (matrix metaloproteinases, MMPs) which further weaken the plaque
- plaque rupture (often eccentric and CH-rich), typically in the plaque "shoulder" lead to exposure of accumulated lipids and tissue factors to platelets and coagulation factors and cause thrombosis
- this can be manifested as a complete vessel occlusion and thus lead to tissue necrosis (e.g. myocardial infarction or stroke) or incomplete occlusion as a consequence of repeated cycles of rupture → microthrombotisation → fibrinolysis → healing = "unstable plaque" or angina
- vulnerable plaque (i.e. rupture-prone) vs. vulnerable patient
  - see further

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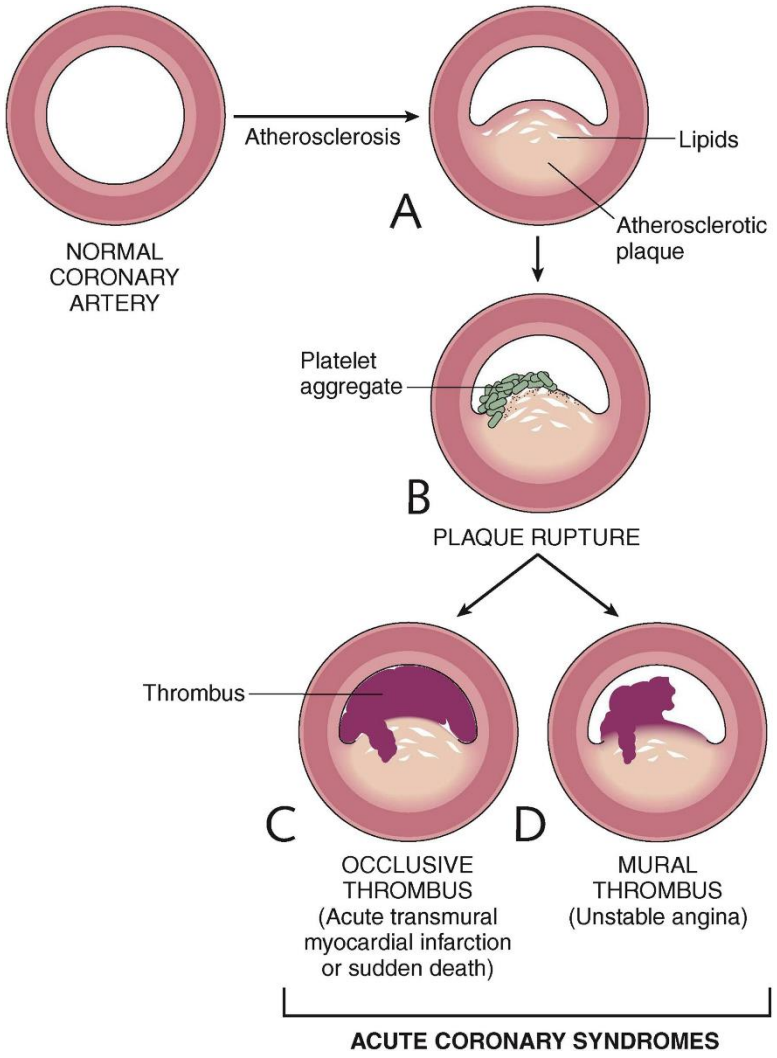
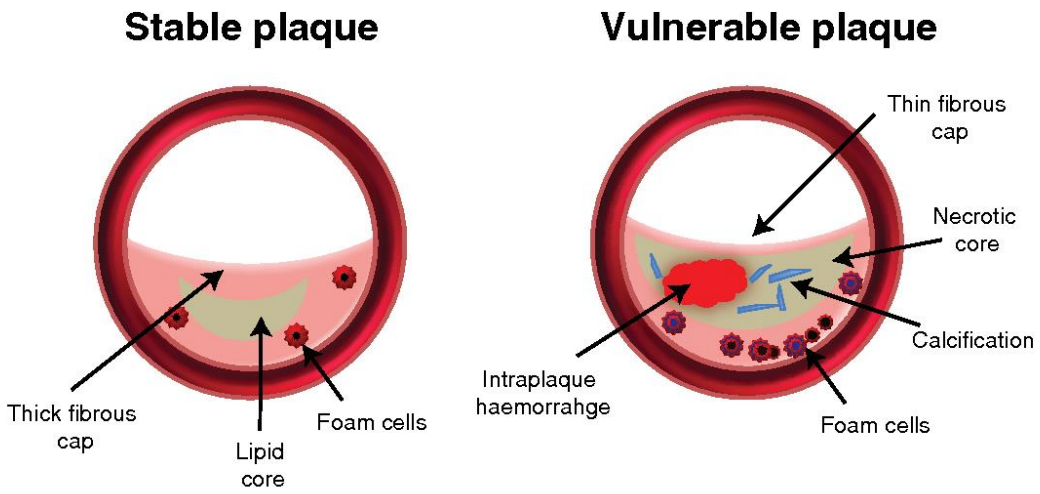
# Fate of advanced AS plaque - rupture an thrombosis

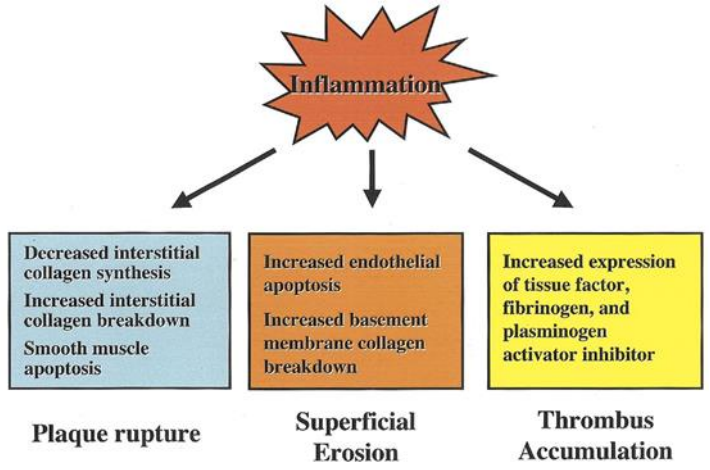
- Pathophysiological scenarios
  - (1) progressive growth of the plaque
    - asymptomatic until >50% of diameter reduction (= >75% cross-sectional area reduction)
    - typical cause of stable angina
  - (2) superficial erosion
    - denudation/apoptosis od ECs – mural platelet thrombi – healing – further lumen reduction
  - (3) plaque rupture and thrombosis
    - clinically leads to acute coronary event (MI or sudden death) in case of total occlusion of the vessel or unstable angina or no symptoms in case of a healing
    - very often happens in haemodynamically insignificant stenosis
    - plaque composition rather than plaques size matters
    - can happen due to the fracture of the fibrous cap or in the „shoulder“
      - imbalance between forces/mechanical strength



# Vulnerable plaque - thin cap fibroatheroma

- Typical features
  - a thin fibrous cap
  - extensive inflammatory infiltration by macrophages and T lymphocytes
  - large lipid core
  - small numbers of SMCs
  - intra-plaque haemorrhage
- inflammation is the most important part of progression and destabilization of an atherosclerotic plaque
  - release of proinflammatory cytokines and matrix metalloproteinases contributes to degradation of collagenous components in the fibrous cap of the atheroma
  - apoptosis of collagen synthesizing SMCs
  - tissue factor produced by intra-plaque inflammatory cells
- identification of vulnerable plaque (= prone to rupture) is clinically extremely important

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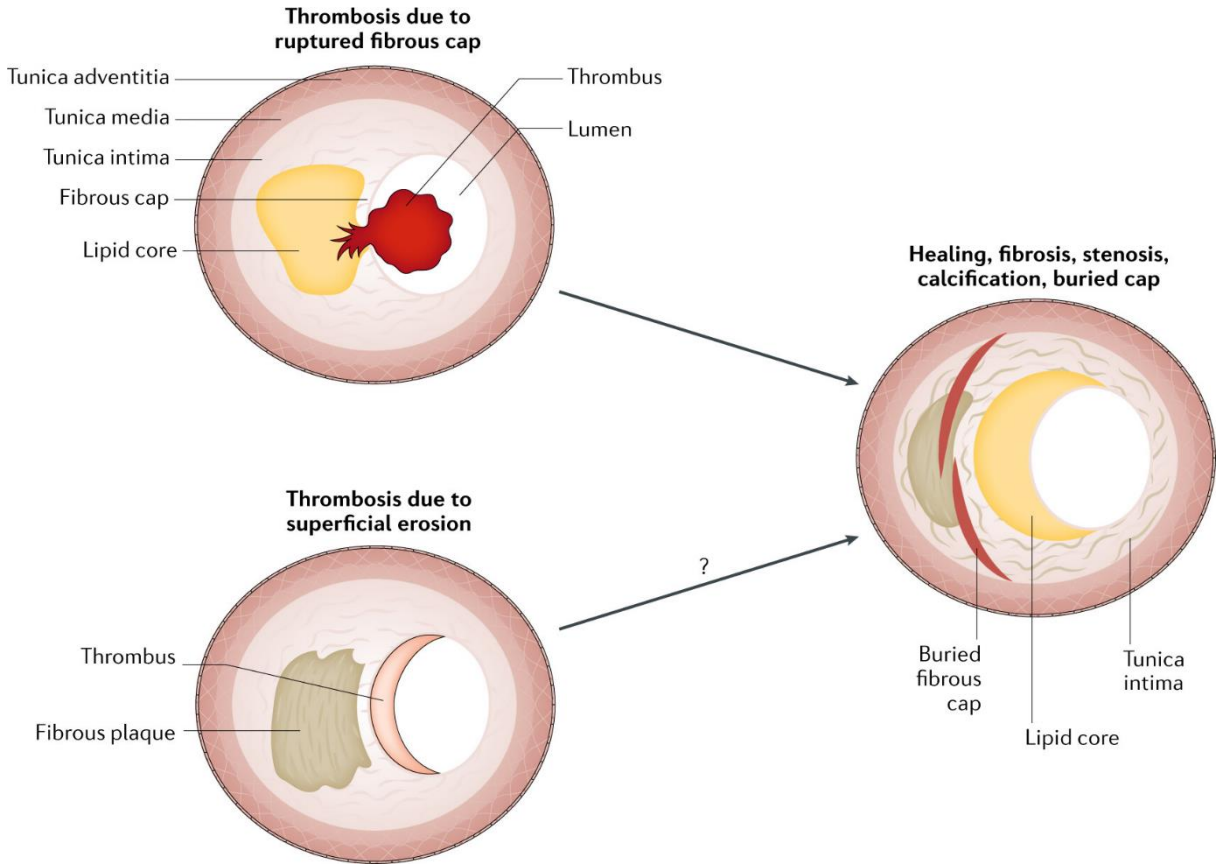
# Summary of AS etiopathogenesis – stages




Atheroma complication: disruption and healing.The fracture of the fibrous cap of the atherosclerotic plaque permits blood coagulation components to access to the core of the plaque. Pro-coagulant substances such as tissue factor can trigger thrombosis, which can cause occlusion of the vessel and lead to an acute ischaemic event. Many mural thrombi may not totally occlude the vessel or may undergo lysis due to endogenous fibrinolytic defences. The resorbing thrombus, a source of transforming growth factor-β (TGFβ) and platelet-derived growth factor elaborated by activated platelets, can stimulate smooth muscle cell migration and extracellular matrix production. These processes lead to increased lesion volume and eventual encroachment upon the arterial lumen. Pathological studies of advanced human atherosclerotic plaques showed ‘buried caps’ that provide evidence for prior rupture and healing. Plaques that lack a well-defined lipid core and have abundant rather than sparse extracellular matrix can provoke coronary thrombi due to a process known as superficial erosion. The clots associated with superficial erosion have characteristics of platelet-rich ‘white’ thrombi; by contrast, ‘red’ thrombi are rich in fibrin and trapped erythrocytes and associate with plaque rupture

*(cit. Libby, P., Buring, J.E., Badimon, L. et al. Atherosclerosis. Nat Rev Dis Primers 5, 56 (2019). https://doi.org/10.1038/s41572-019-0106-z)*

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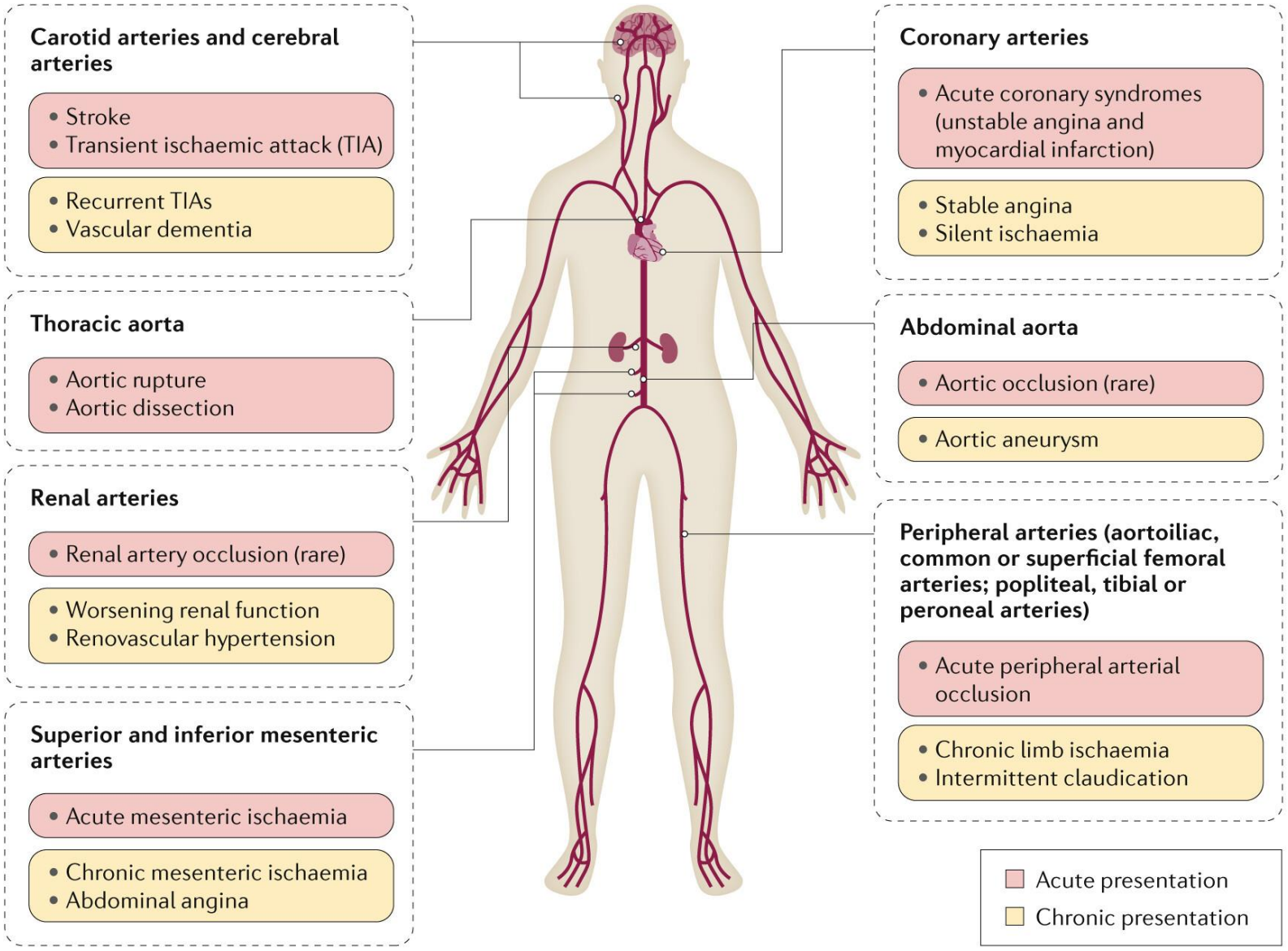
# Clinical manifestations of AS in different predilection sites




- AS is a systemic disease that may involve multiple vessels
- Consequently, the clinical manifestations vary widely according to the vascular territory involved
- Despite the systemic nature of many risk factors such as hypercholesterolaemia, hypertension, diabetes mellitus and smoking, AS tends to involve primarily specific regions of the arterial tree
- Arterial areas subjected to either disturbed flow or low shear stress have particular susceptibility to atheroma formation
- These conditions prevail at branch points in the arterial tree.

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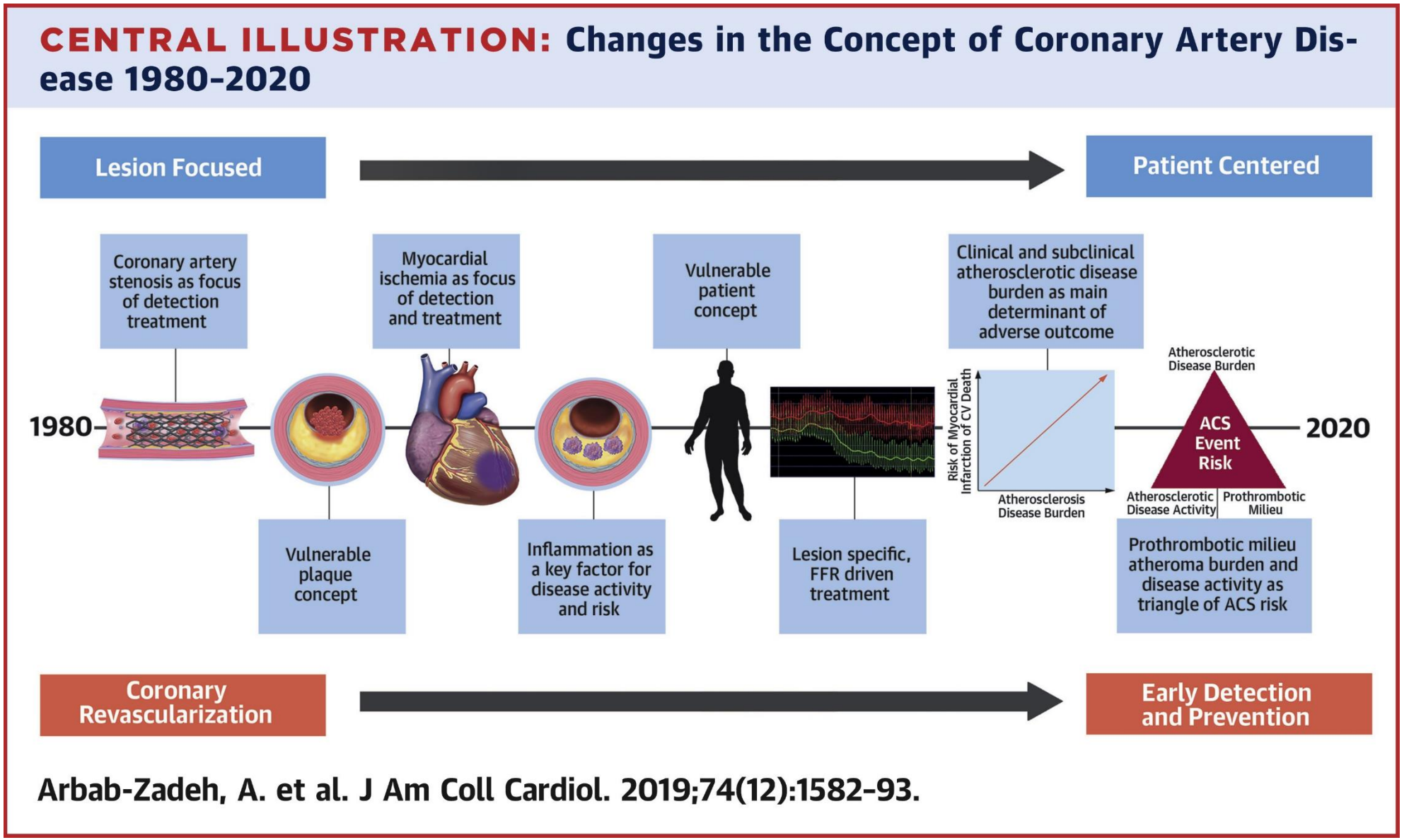
# Shift from „vulnerable plaque“ to „vulnerable patient concept“




Arbab-Zadeh, A. et al. J Am Coll Cardiol. 2019;74(12):1582-93.

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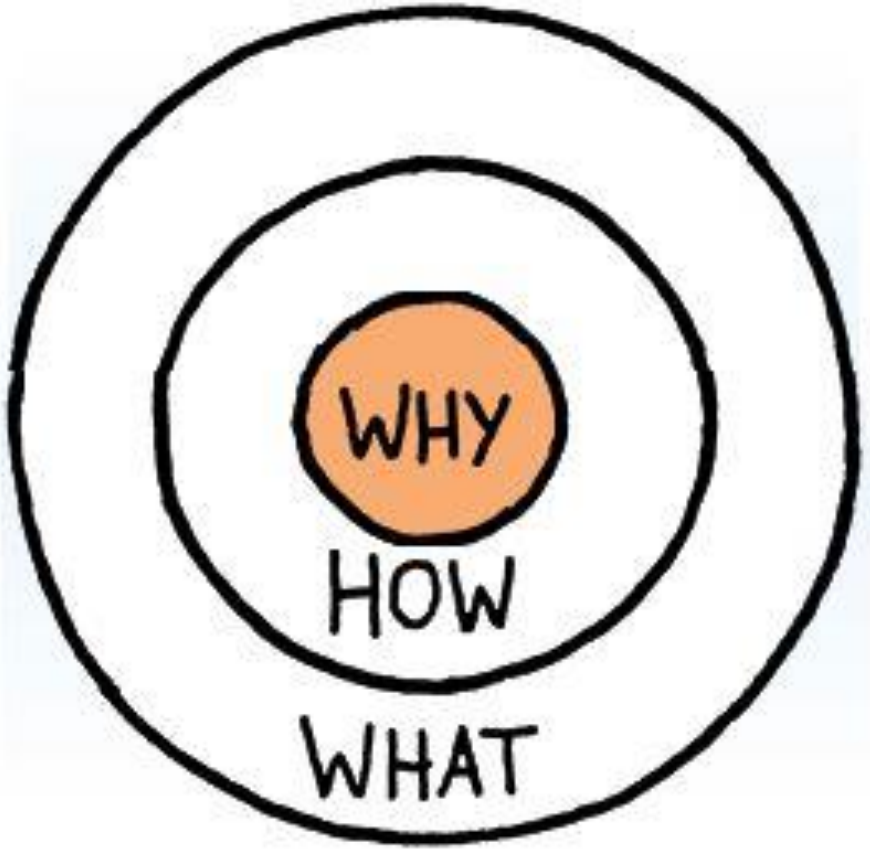
# Essential PP questions:

- How?
- Why???




Thank you for your attention

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