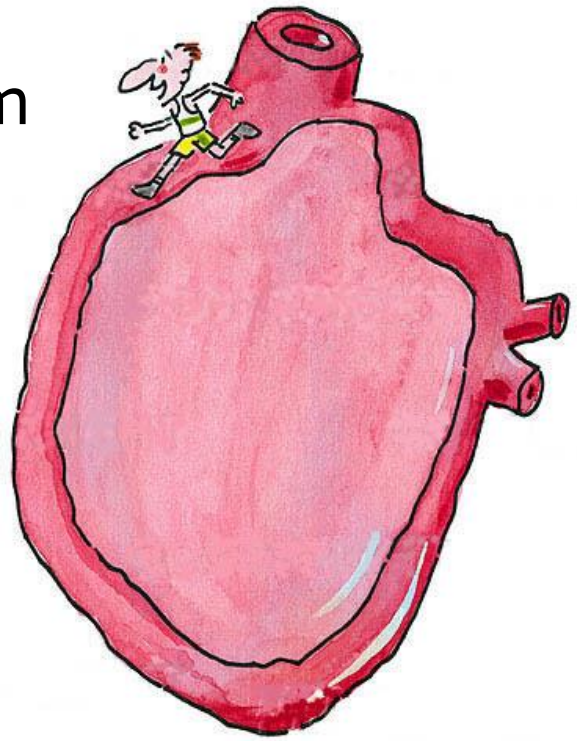
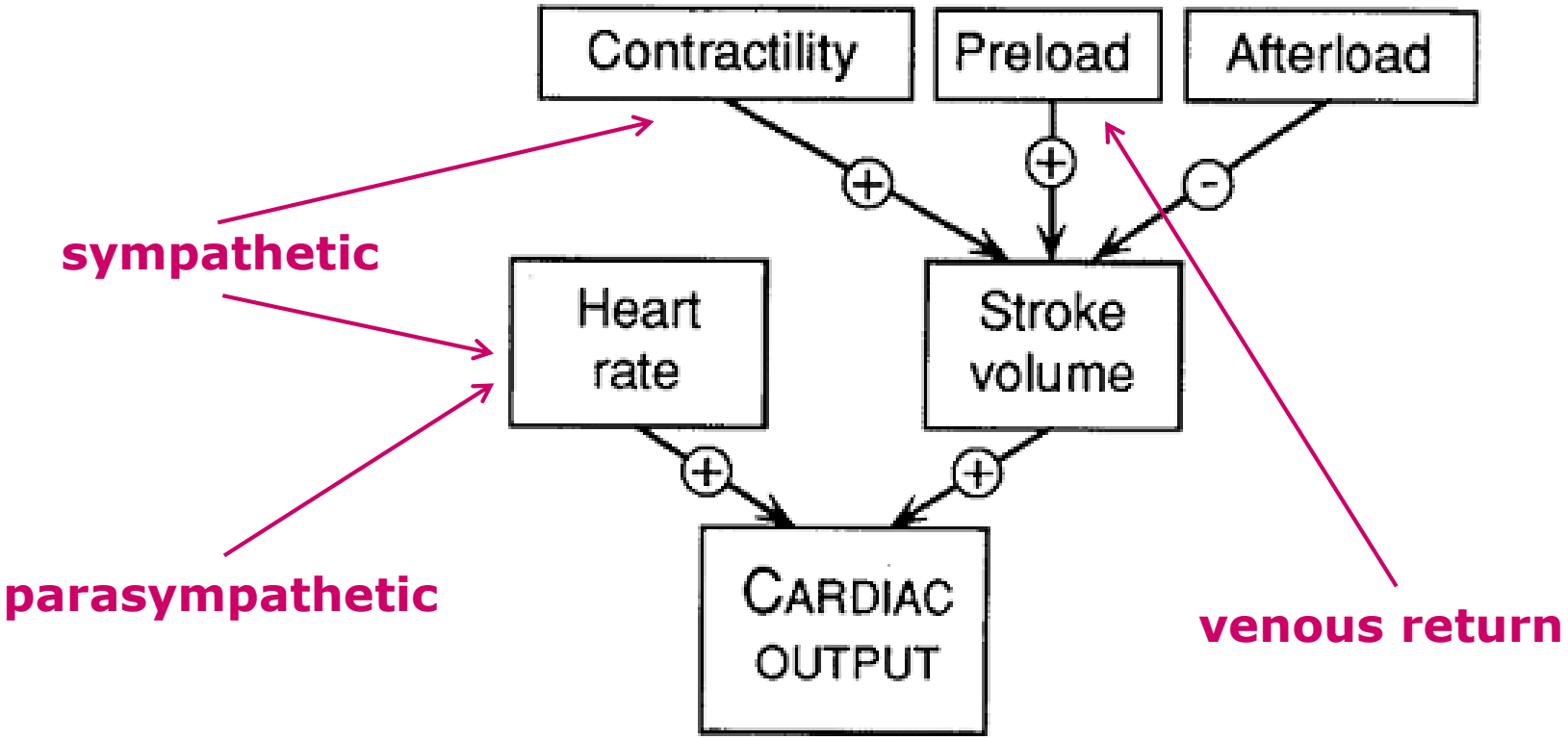
Atherosclerosis & Coronary heart/artery disease (CHD/CAD)

Myocardial blood supply & metabolism
Ethiopathogenesis of atherosclerosis
Myocardial ischemia – compensation
CAD – symptoms & outcomes

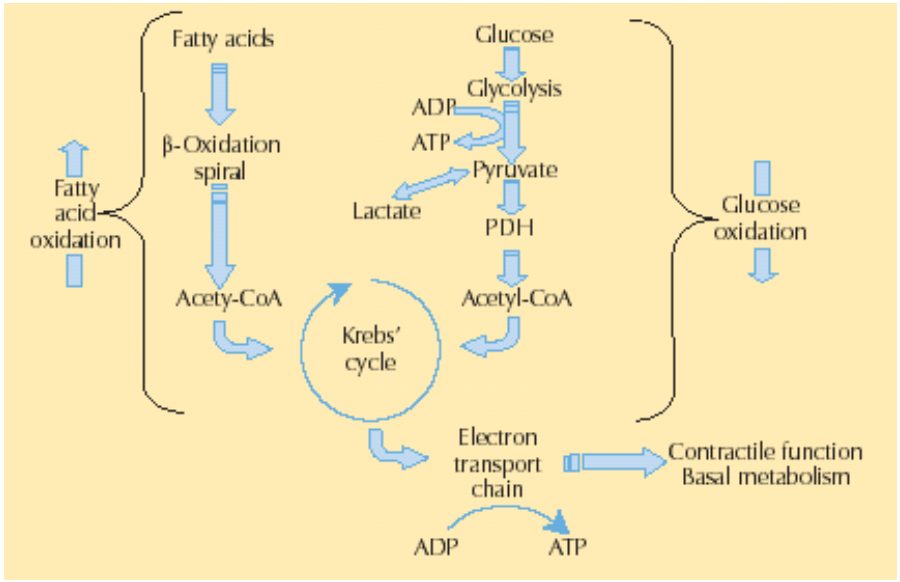


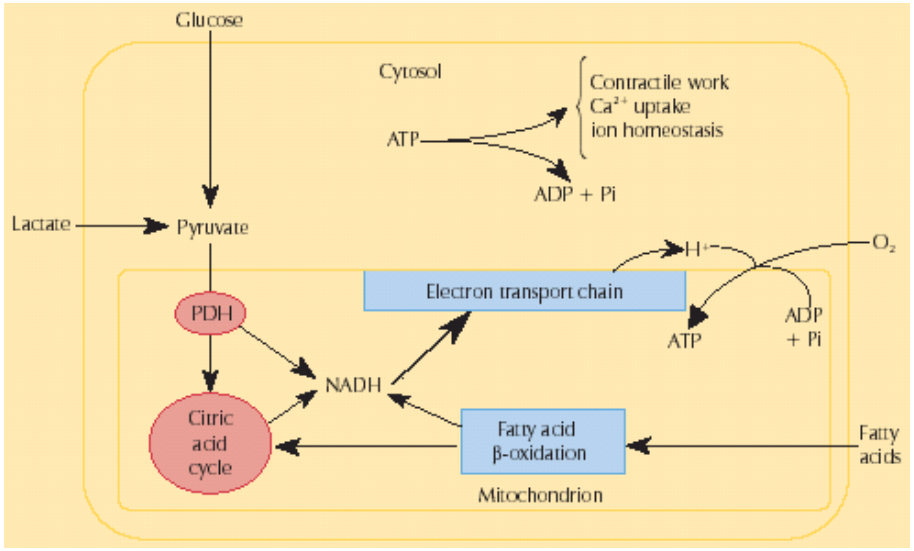
Heart needs a lot of energy to continually perform as a pump



$$CO = SV \times f$$

Myocardial metabolism





- heart is a **pump** that has to continually perform 2 processes:
  - **automacy** = generation of action potential in order to perform
  - **contraction**
- myocardium thus has a very high demand for **ATP** even in 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
  - glucose (glycogen)
  - ketone bodies and lactate
- therefore myocardium requires **large amounts of O_2** and must be, therefore, well perfused !!

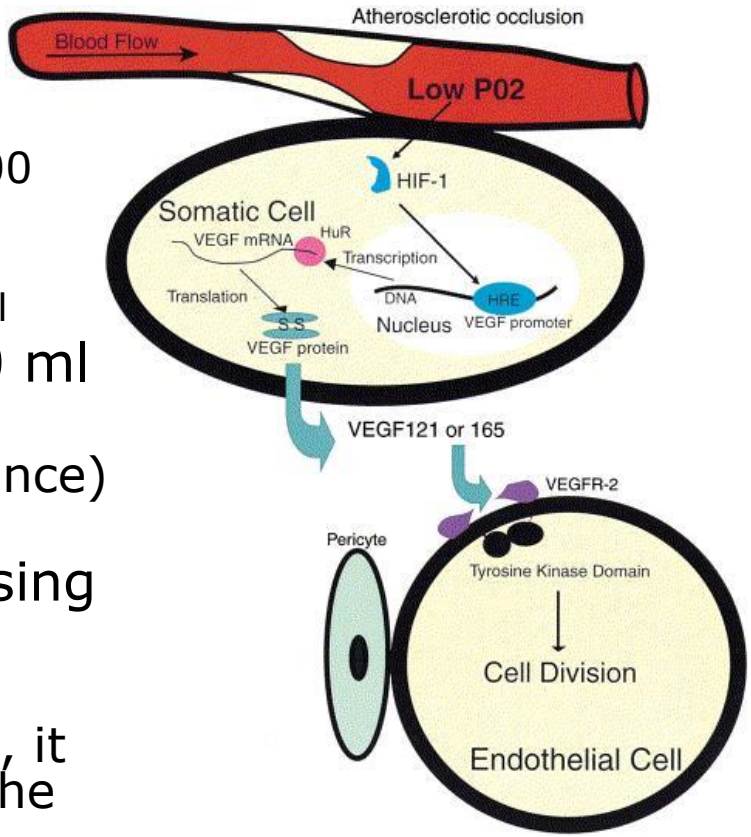
Oxygen extraction by various tissues/organs

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 %

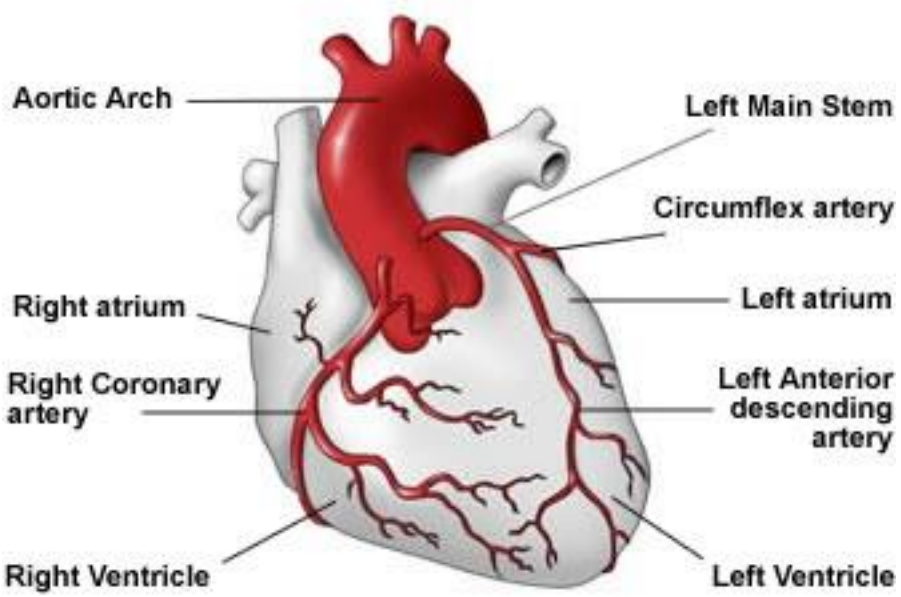
- Theoretically, the maximal amount of oxygen that can be extracted is **20 vol %** (if CaO_2 = 200 ml O_2/l)
- In reality, however, the maximal oxygen extraction is around **15 - 16 vol %** because of the kinetics of oxygen dissociation from haemoglobin
- Therefore, the heart is extracting one-half to two-thirds of the physiologically available oxygen under normal operating conditions

Oxygen consumption – quantitative aspects

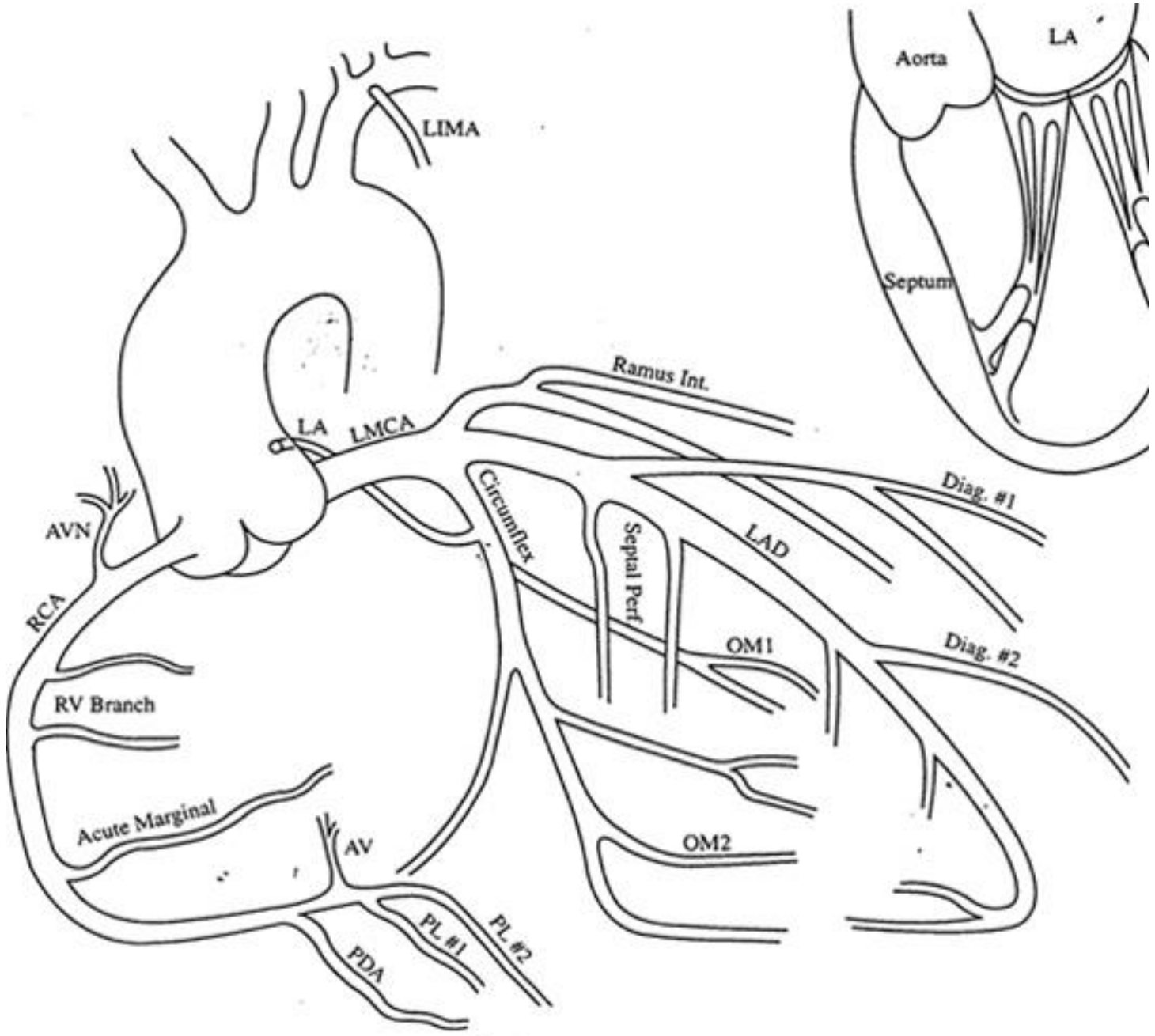
- amount of oxygen supplied by the coronary blood (VO_2): ~45 ml O_2/min
  - $VO_2 = Q_m \times CaO_2$
    - myocardial perfusion (Q_m) = 210 – 240 ml/min in the resting state (1000 – 1200 ml/min during the exercise)
    - CaO_2 = 200 ml O_2/l
      - for PaO_2 = 13.3 kPa and c[Hb] = 150 g/l
- consumption in the resting state: ~30 ml O_2/min (~65 - 70%)
  - 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 blood flow**
  - because aorta has a constant pressure, it has to be done by **vasodilatation** in the coronary bed = **coronary reserve**
  - small scale neovascularisation is also possible



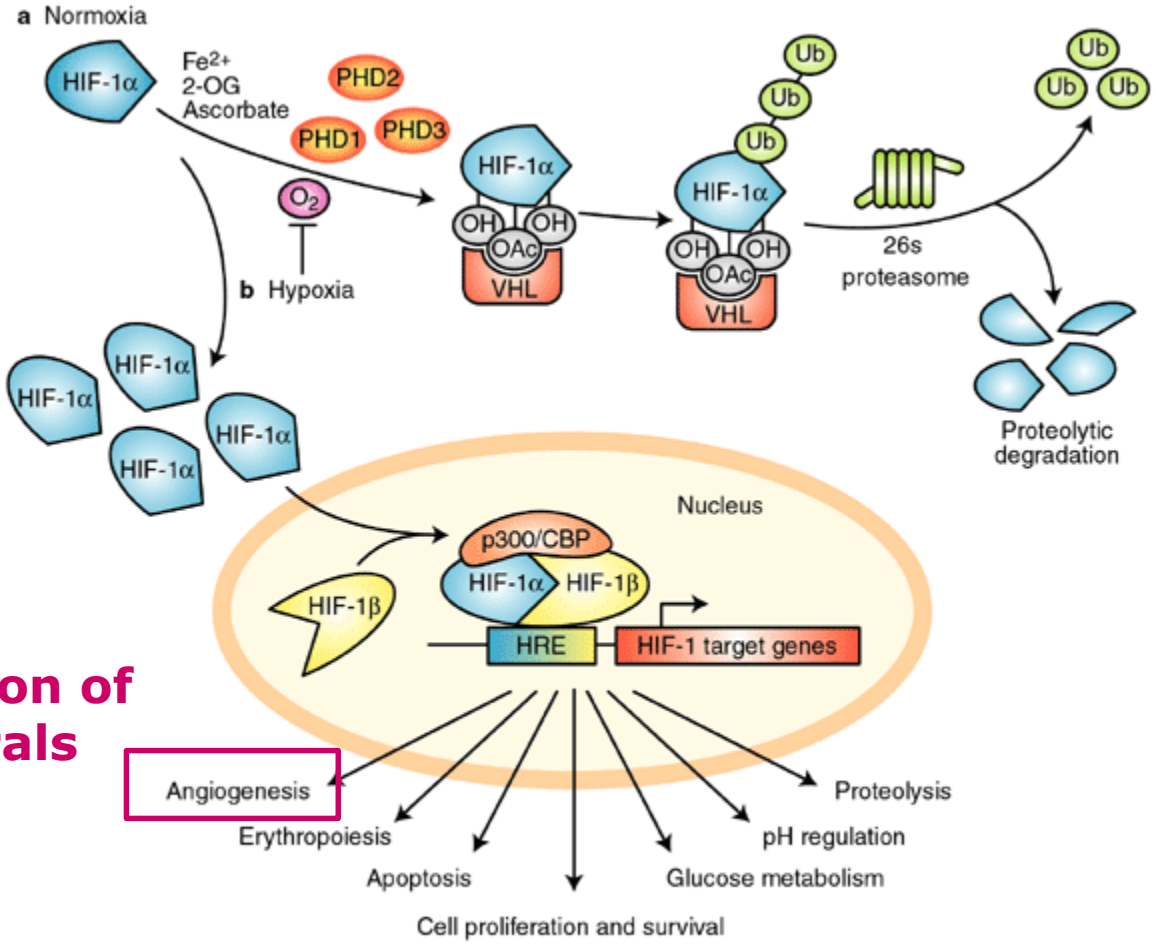
Blood supply of the heart



- 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


Aorta
LA
Septum
LIMA
Ramus Int.
LA
LMCA
Circumflex
Diag. #1
Septal Perf
LAD
AVN
RCA
OM1
Diag. #2
RV Branch
Acute Marginal
AV
OM2
PL #1
PL #2
PDA

Hypoxia

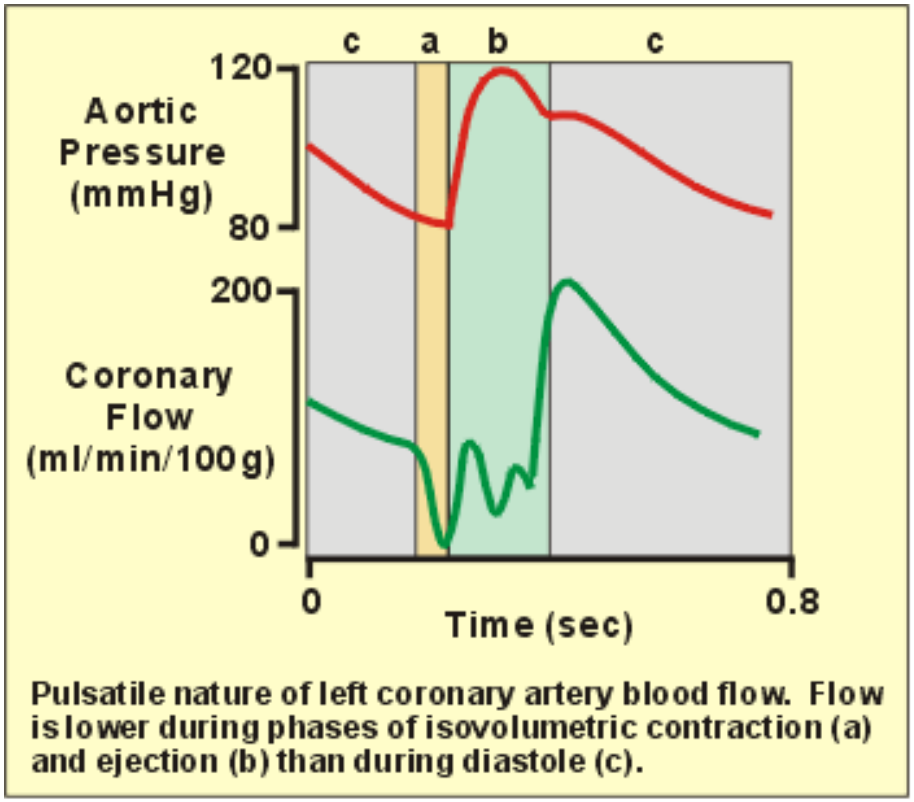


formation of collaterals

HIF-1α regulation by proline hydroxylation

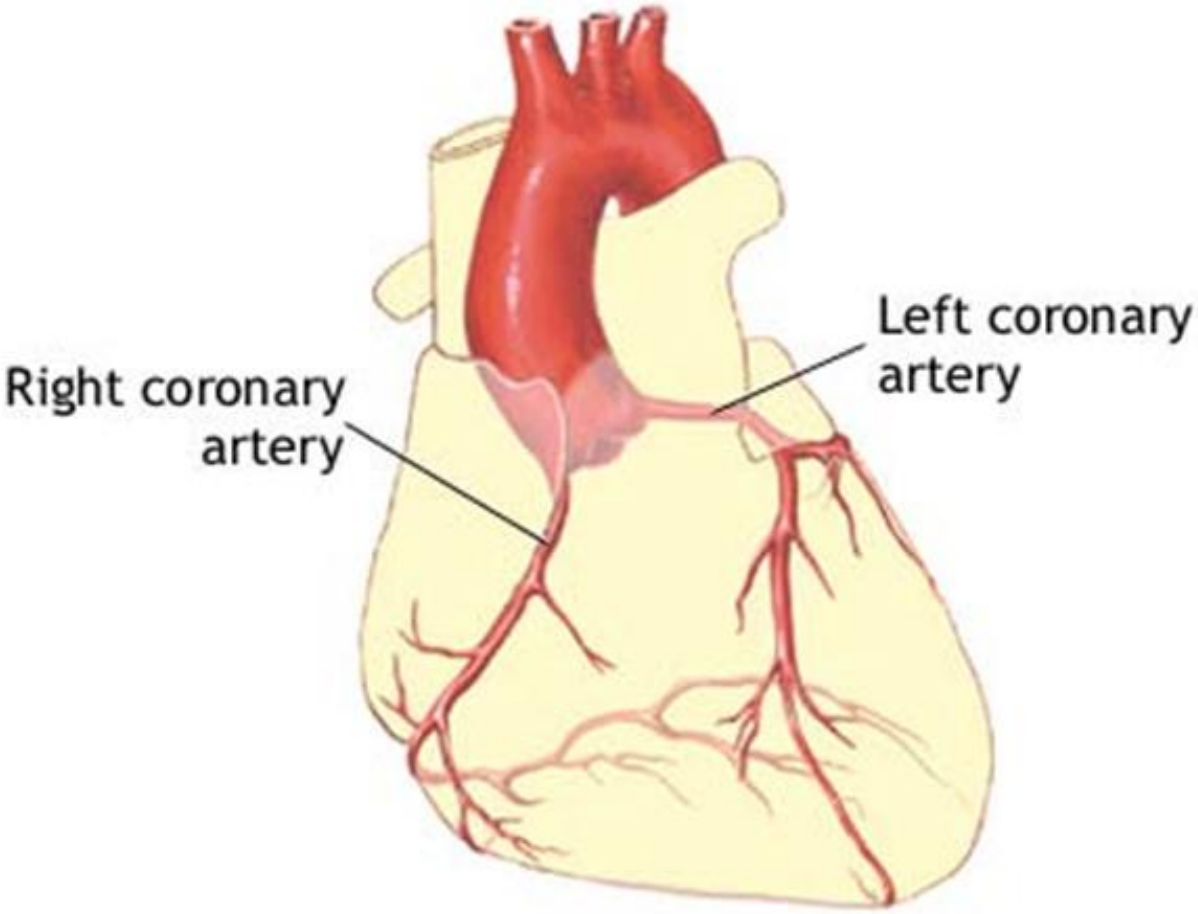
Coronary blood flow – temporal pattern

- blood flow is diminished during the systole due to:
  - (1) temporal blocking of coronary ostia by opened aortic valves
  - (2) high flow during systole which "sucks" the blood out (= Venturi effect)
  - (3) compression of vessels during the systolic contraction
- therefore most of the coronary **flow occurs during diastole**
  - **tachycardia** shortens diastole so there is relatively less time available for coronary flow during diastole to occur
- coronary arteries penetrates myocardium from surface (epi-cardium) to the internal chamber lining (endocardium) direction
  - therefore, endocardium is more susceptible to ischemia, especially at
  - ↓ **perfusion pressures** (e.g. atherosclerosis)
  - or ↑ **intracardial pressure** (e.g. heart failure)



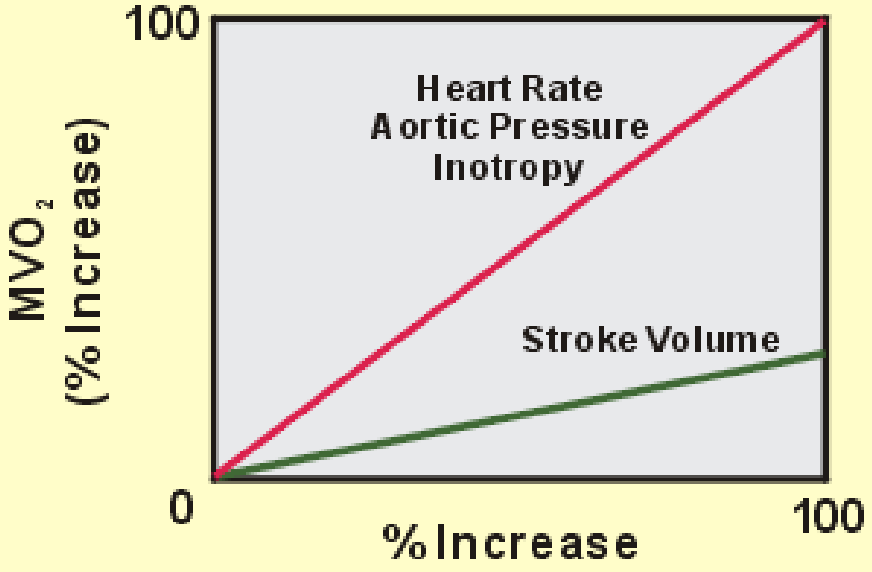
Pulsatile nature of left coronary artery blood flow. Flow is lower during phases of isovolumetric contraction (a) and ejection (b) than during diastole (c).

(Problematic) anatomy of coronary arteries



Factors influencing myocardial O_2 consumption (MVO_2)

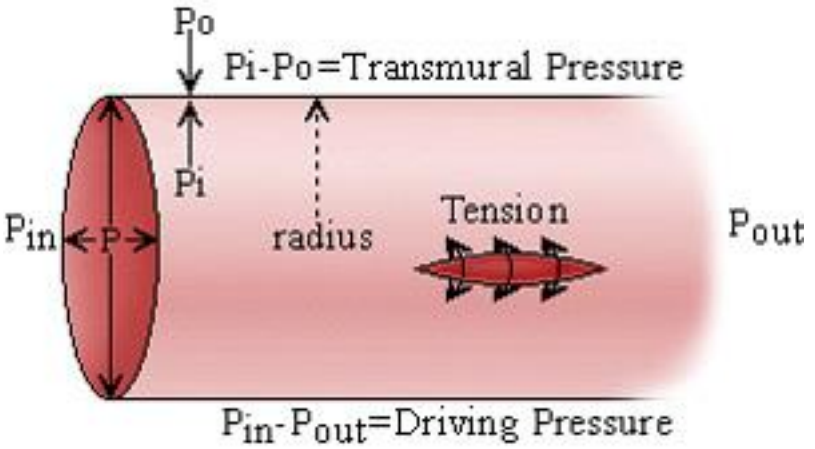
- (1) wall tension
  - that's why O_2 demand is ↑ in pressure or volume overload
- (2) contractility
- (3) heart rate
  - that's why (i.e. 2 & 3) O_2 demand is ↑ during sympathetic activation
- (4) myocardial mass
  - that's why O_2 demand is ↑ in cardiac hypertrophy (esp. maladaptive)
- rough estimate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

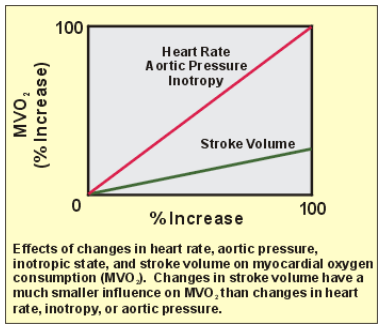


Effects of changes in heart rate, aortic pressure, inotropic state, and stroke volume on myocardial oxygen consumption (MVO_2). Changes in stroke volume have a much smaller influence on MVO_2 than changes in heart rate, inotropy, or aortic pressure.

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)
- $V = 4/3\pi \times r^3$
- $r = \sqrt[3]{V}$
- $\sigma = P \times \sqrt[3]{V} / d$
  - 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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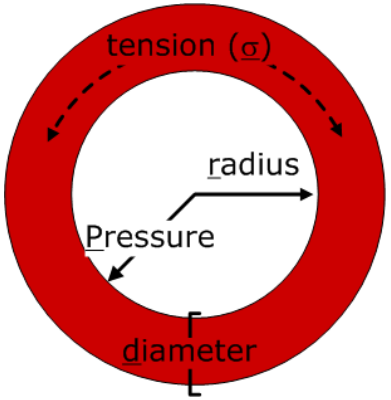
for detail see previous slide

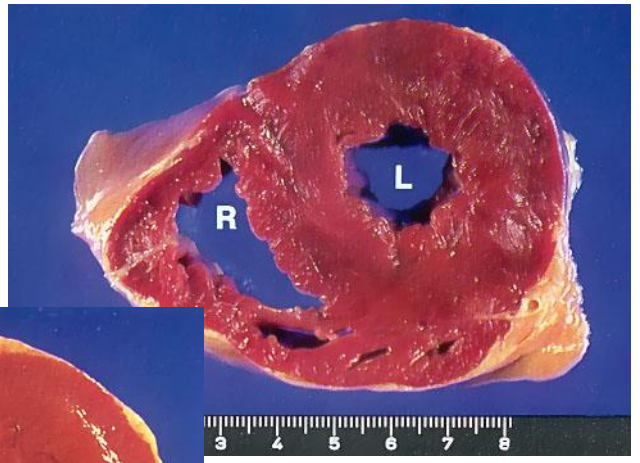


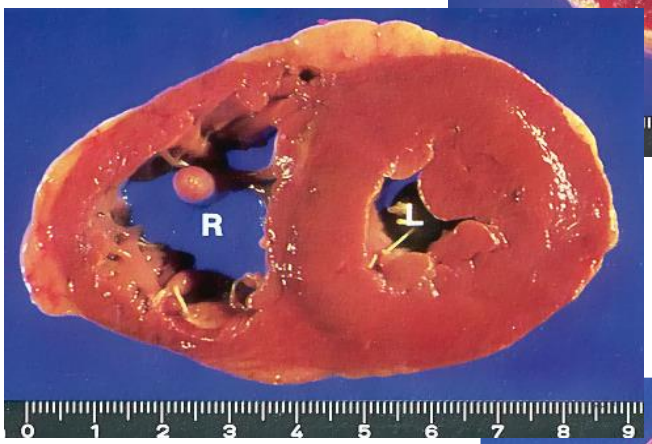
La Place law:

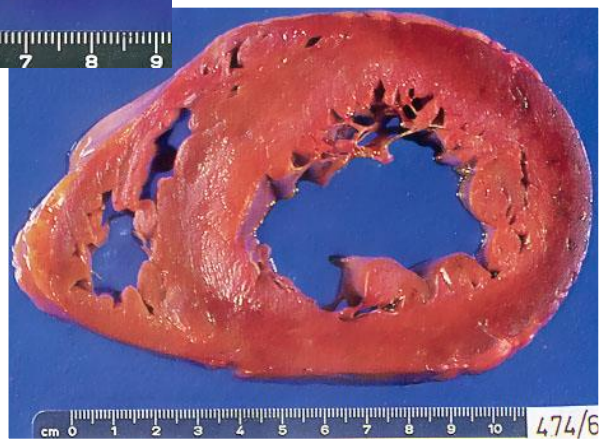
$\sigma = P \times r / d$

Why hypertrophy does not ↓ O_2 consumption at the end

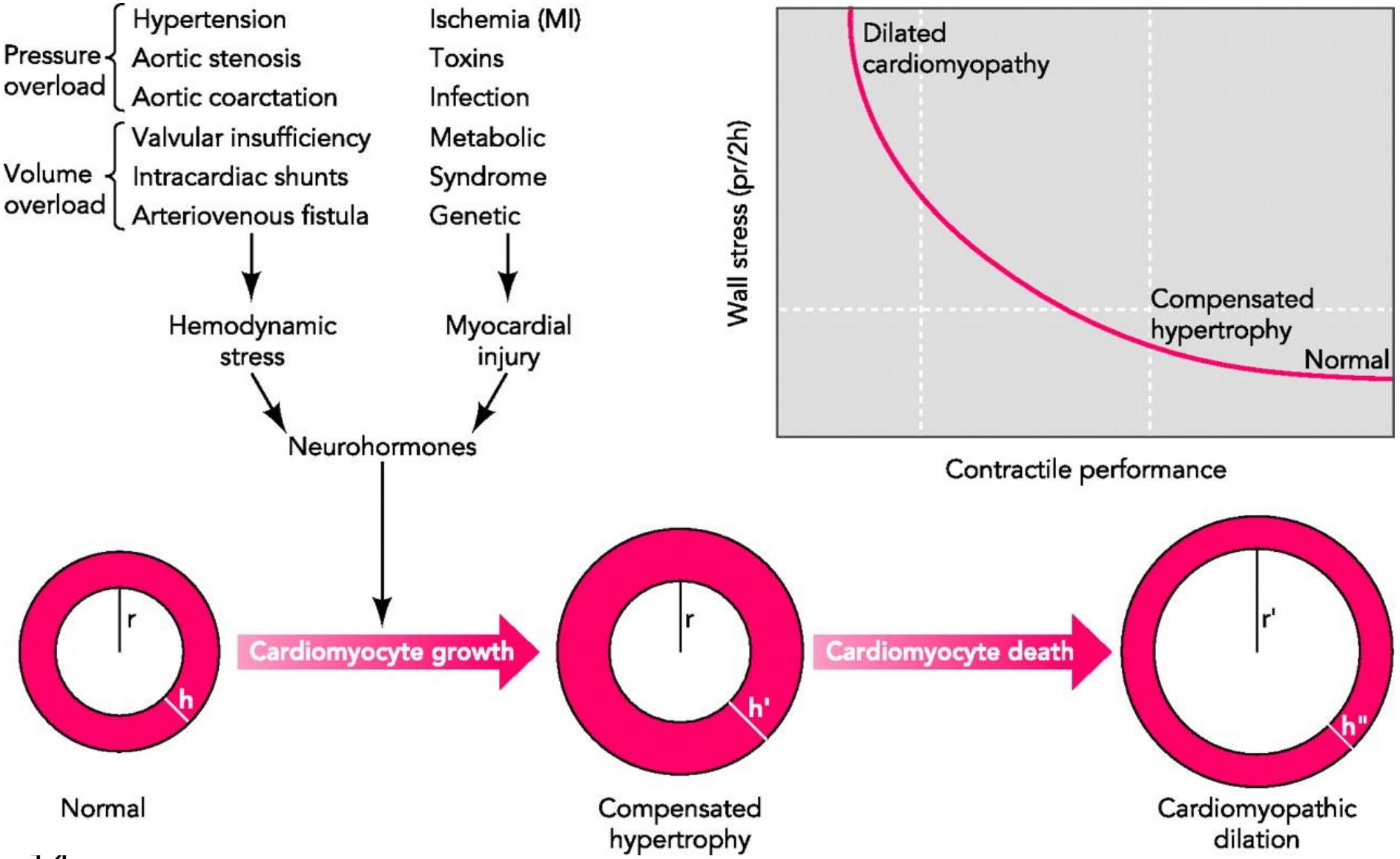
- hypertrophy (↑ **d**) normalizes wall tension (σ) per gram of myocardium in case of pressure or volume overload
  - $\sigma = \mathbf{P} \times \mathbf{r} / \mathbf{d}$
  - initially, it does reduces MVO_2 when wall tension increases and heart has to generate higher pressure to overcome V or P overload
- 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





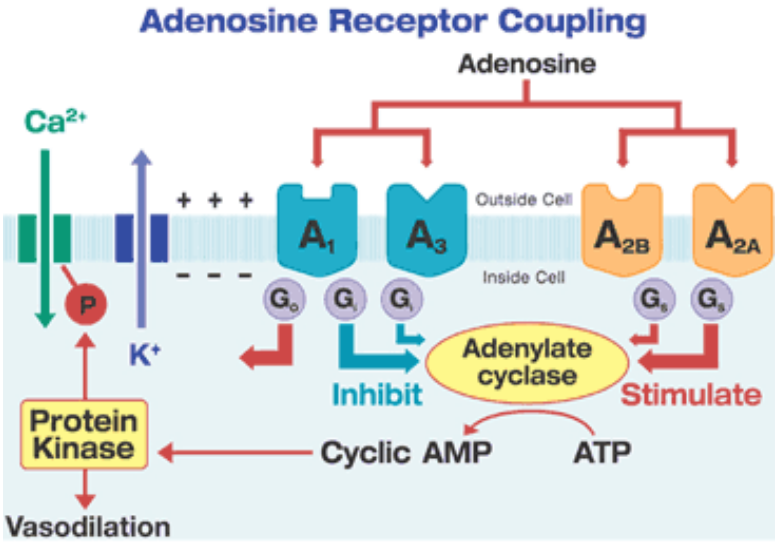


Hypertrophy development



Coronary blood flow - autoregulation

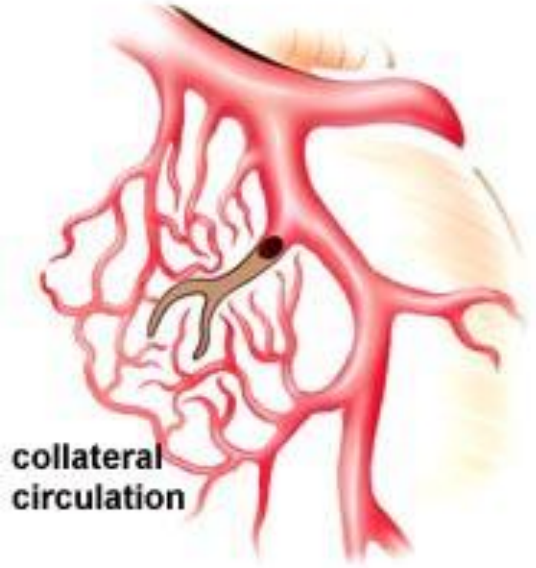
- autoregulation tightly coupled to the oxygen demand
  - between 60 to 200 mmHg of the perfusion pressure (i.e. systemic pressure) helps to maintain normal coronary blood flow whenever coronary perfusion pressure changes due to changes in aortic pressure
  - during exercise maximal flow can be reached (**"coronary reserve"**)

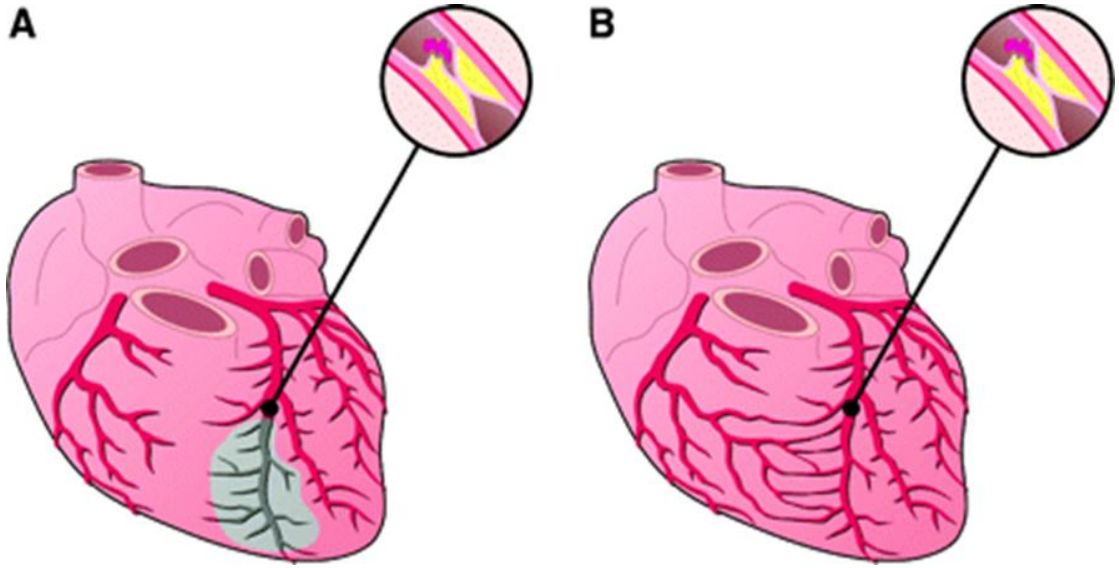


- factors:
  - (1) **adenosine**
    - the most important mediator of **active hyperemia**
    - metabolic coupler between oxygen consumption and coronary blood flow = formed from cellular AMP by 5'-nucleotidase
      - AMP is derived from hydrolysis of intracellular ATP and ADP
  - (2) **nitric oxide**
    - an important regulator of coronary blood flow, produced by endothelial nitric oxide synthase
  - (3) **sympathetic activation**
    - 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

Coronary collaterals & angiogenesis

- enhancement of blood flow to ischaemic myocardium can result from
  - (1) recruitment of pre-existing coronary collaterals
    - variable density among people?
  - (2) true angiogenesis/arteriogenesis
- angiogenesis = budding of capillaries that leads to the formation of new microvessels from pre-existing vascular structu
  - due to hypoxia (HIF-1/VEGF)
  - failure of concomitant angiogenesis in hypertrophic myocardium

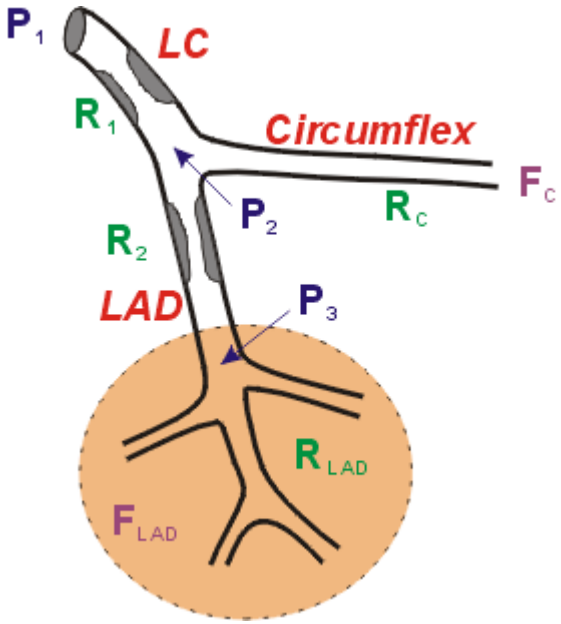




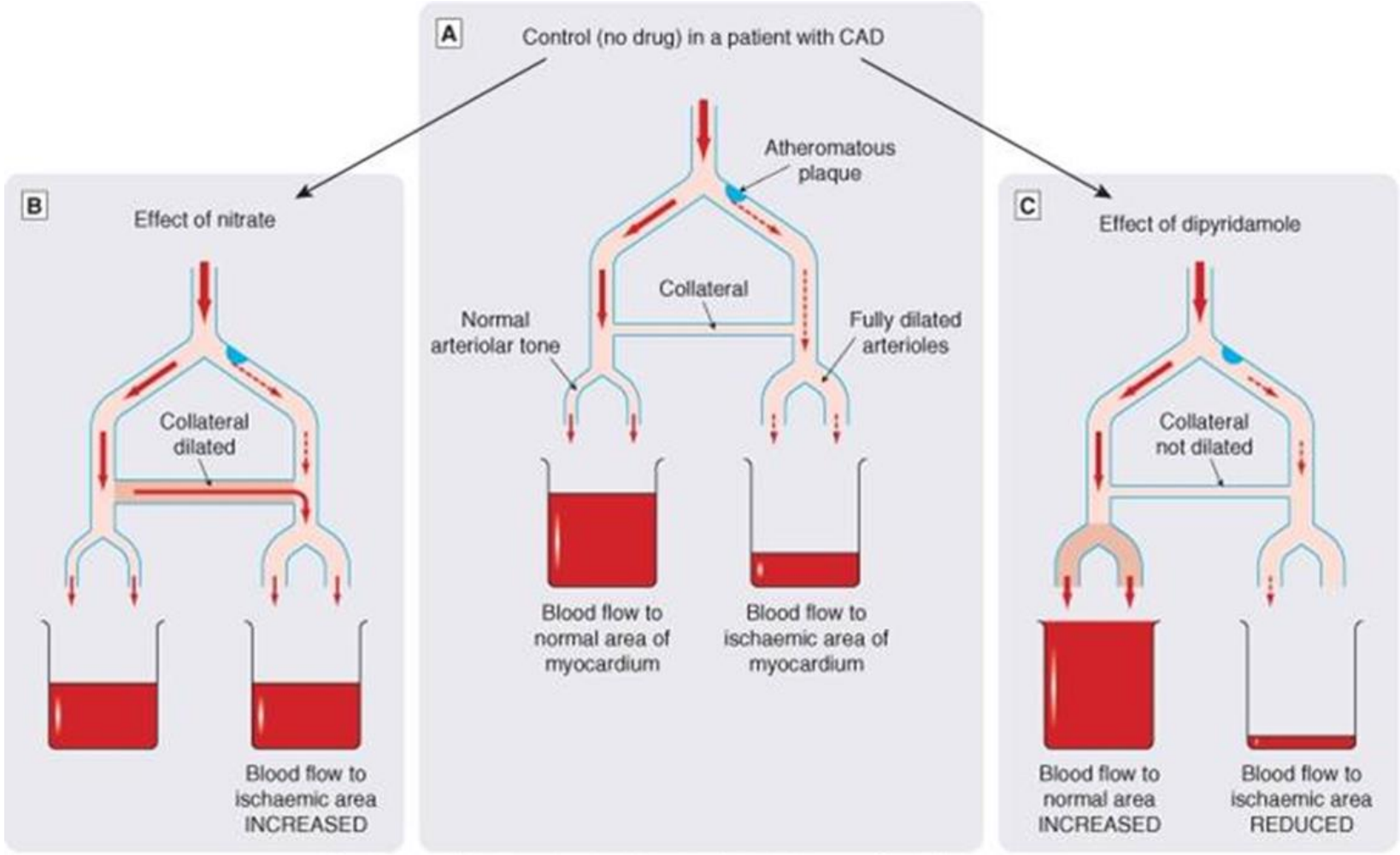
Consequences of O_2/ATP depletion

- ↓ 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 fjurther "steal" the blood from already ischemic region
- accumulation of K^+, lactate, serotonin and ADP causes **ischemic pain** (angina)
- in the less advanced form above mentioned processes appear only during the exercise, later also in the rest



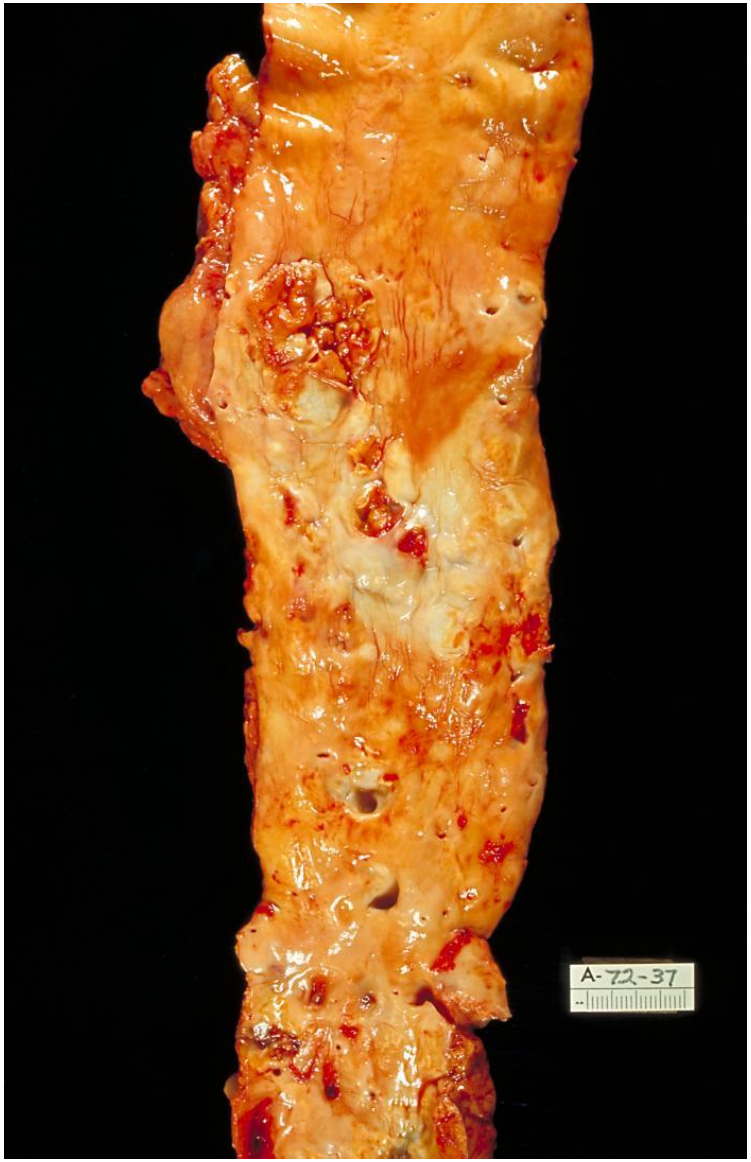
Nitrates restore „vascular steal" by dialation of collaterals

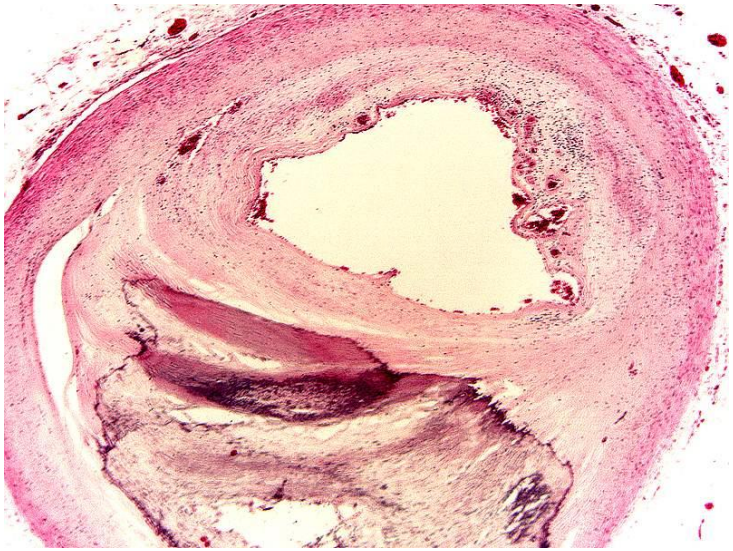


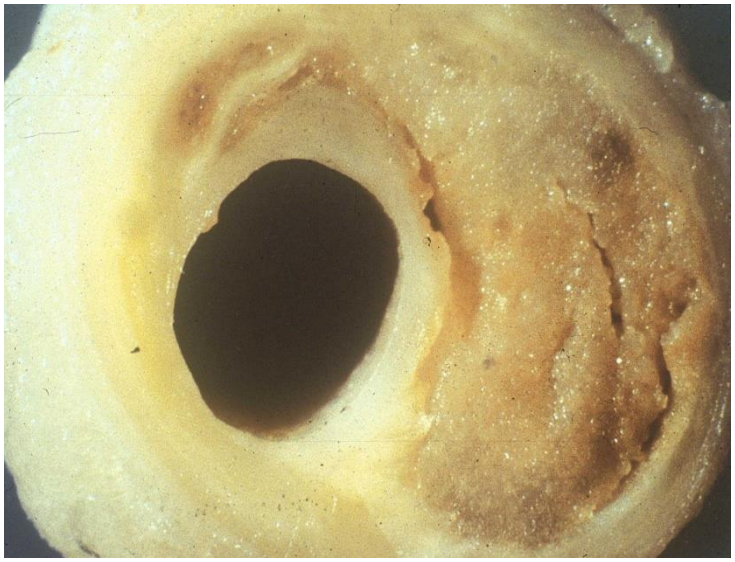
Causes of myocardial ischemia

- myocardial ischemia = imbalance between supply of the oxygen (and other essential myocardial nutrients) and the myocardial demand for these substances
- causes:
  - (1) reduced coronary blood flow due to a fixed mechanical obstruction
    - coronary atherosclerosis (with or without thrombus) = coronary artery/heart disease (CAD/CHD)
    - thrombembolism
  - (2) dynamic obstruction
    - vascular spasm
  - (3) "small vessel disease"
    - diabetic angiopathy
    - polyarteritis nodosa
    - systemic lupus erythematodes
  - (4) decrease of blood oxygenation or concentration of oxygen carrier
    - hypoxic hypoxia
    - anemic hypoxia
  - (5) inadequately high demand for oxygen
    - ↑ ↑ ↑ cardiac output (e.g. thyreotoxicosis)
    - myocardial hypertrophy (due to pressure or volume overload)
- (1) and (2) affect larger artery branches (epicardially), (3) to (5) smaller terminal branches and very often superimpose on the previous two processes
- **myocardial ischemia is the most commonly occurs as a result of coronary atherosclerosis (AS)**

Vessels affected by AS

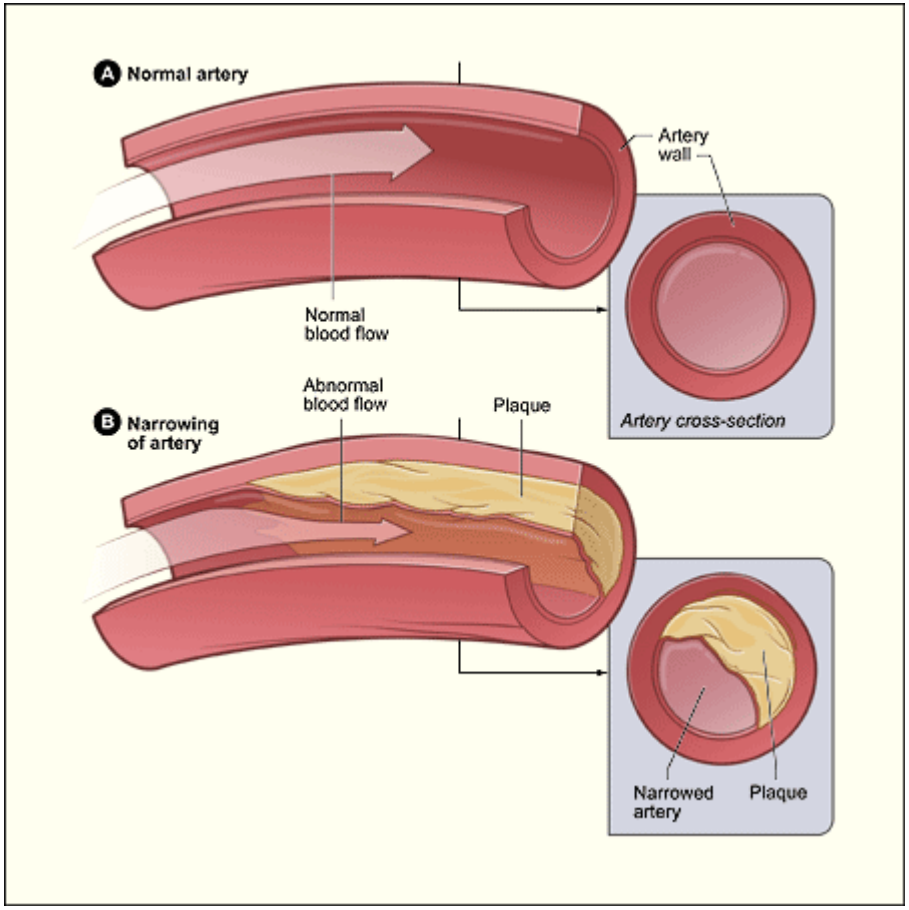






CAD due to AS – main facts

- 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, renal artery, truncus coeliacus, 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



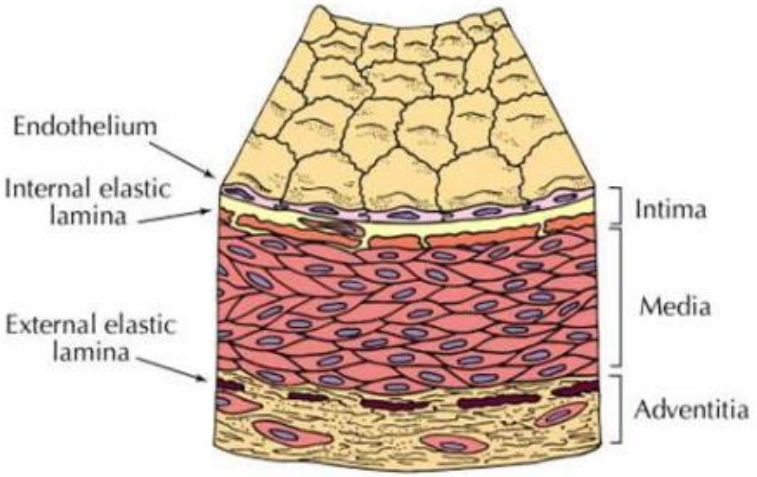
Cardiovascular risks

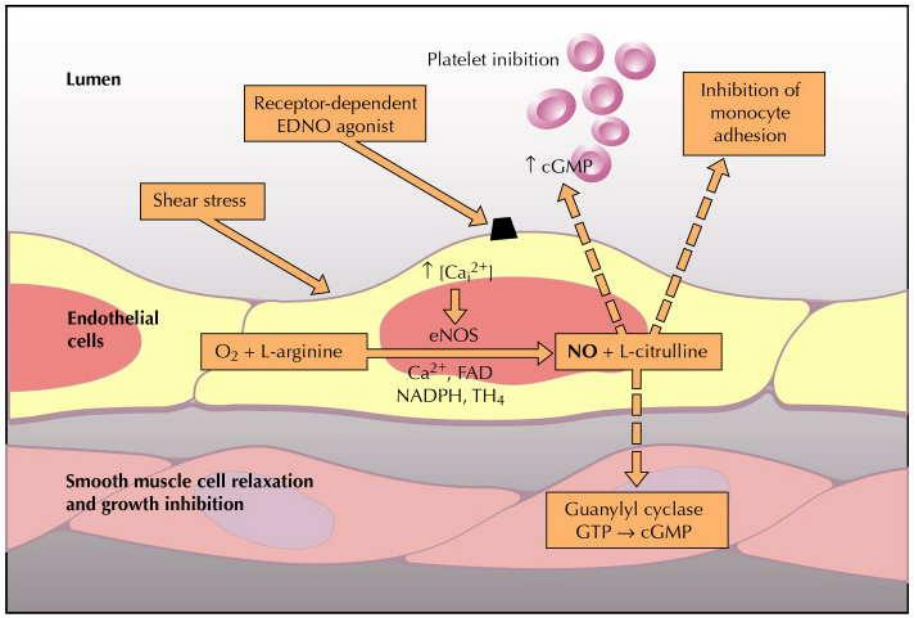
- identification of the main CV risks by prospective epidemiologic studies
  - **Framingham study** = ↑ TK, ↑ cholesterol, ↑ triglycerides, ↓ HDL, smoking, obesity, diabetes, physical inactivity, ↑ age, gender (male) and psychosocial factors
    - original cohort (from 1948)
      - 5,209 subjects (aged 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
  - late clinical manifestation of long-term untreated / decompensated hypertension:
    - **heart attack, stroke (→ atherosclerosis)**
    - heart failure (→ left ventricular hypertrophy)
    - renal failure (→ hyperfiltration, nephrosclerosis)
    - retinopathy

Risk factors of AS
Signif. contribution of genetics
↑ plasma LDL and VLDL, ↓ HDL
↑ lipoprotein apo(a)
hypertension
diabetes mellitus
male gender
↑ plasma homocysteine
↑ plasma haemostatic factors (e.g. fibrinogen, PAI, ..)
metabolic syndrome/ins. resistance
obesity
chronic inflammation
Environment / non-genetic
smoking
physical inactivity
high fat intake in diet
certain infections

Endothelium - physiological role of ECs

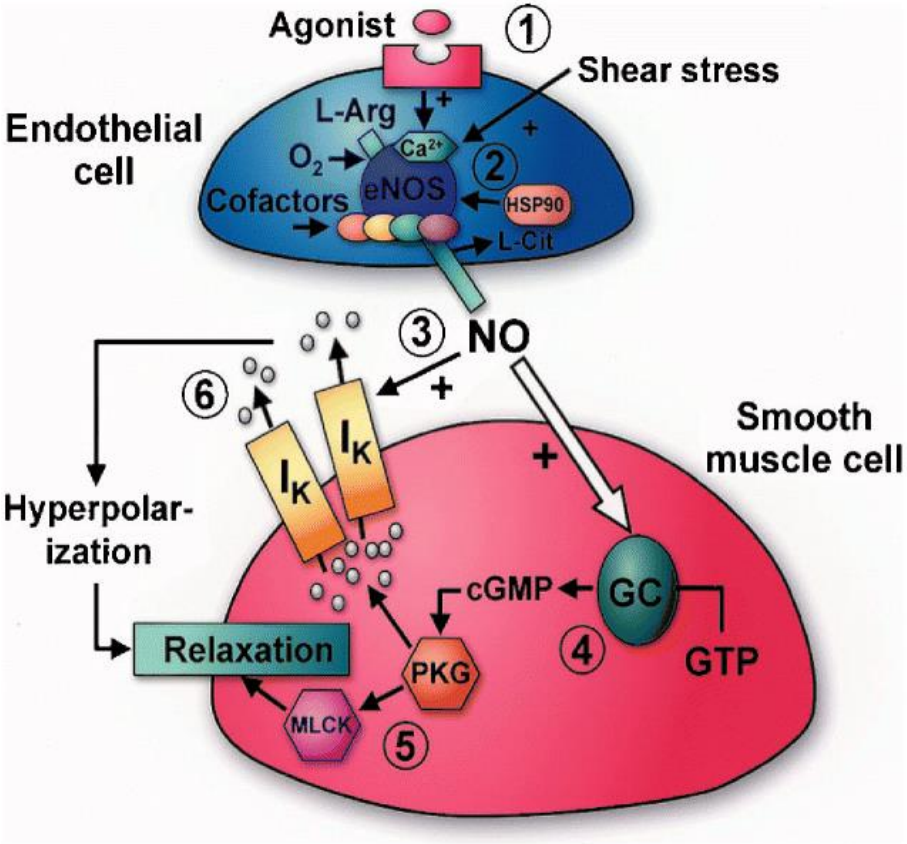
- (1) **vasodilation**
  - smooth muscle cells (SMC) in blood vessels - notably arterioles - work in close association with the overlying ECs
  - action of hormones, neurotransmitters (**ACh**) or deformation of the ECs by flow of blood (shear stress) trigger reactions that influence associated SMC, 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



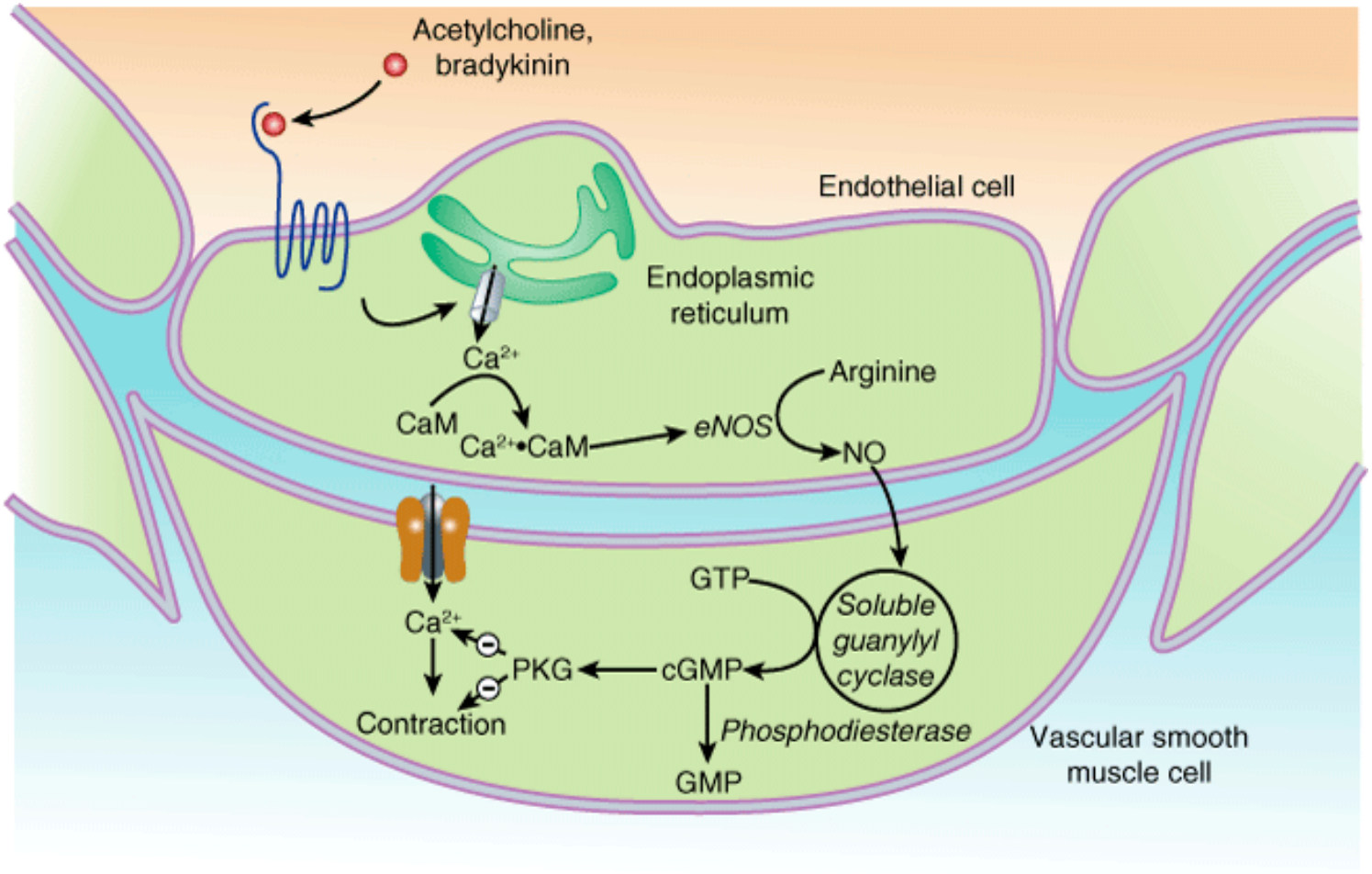


NO-mediated vasodilation

- 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 byproduct. 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 (I_K; 6), thereby increasing cell membrane hyperpolarization and causing relaxation

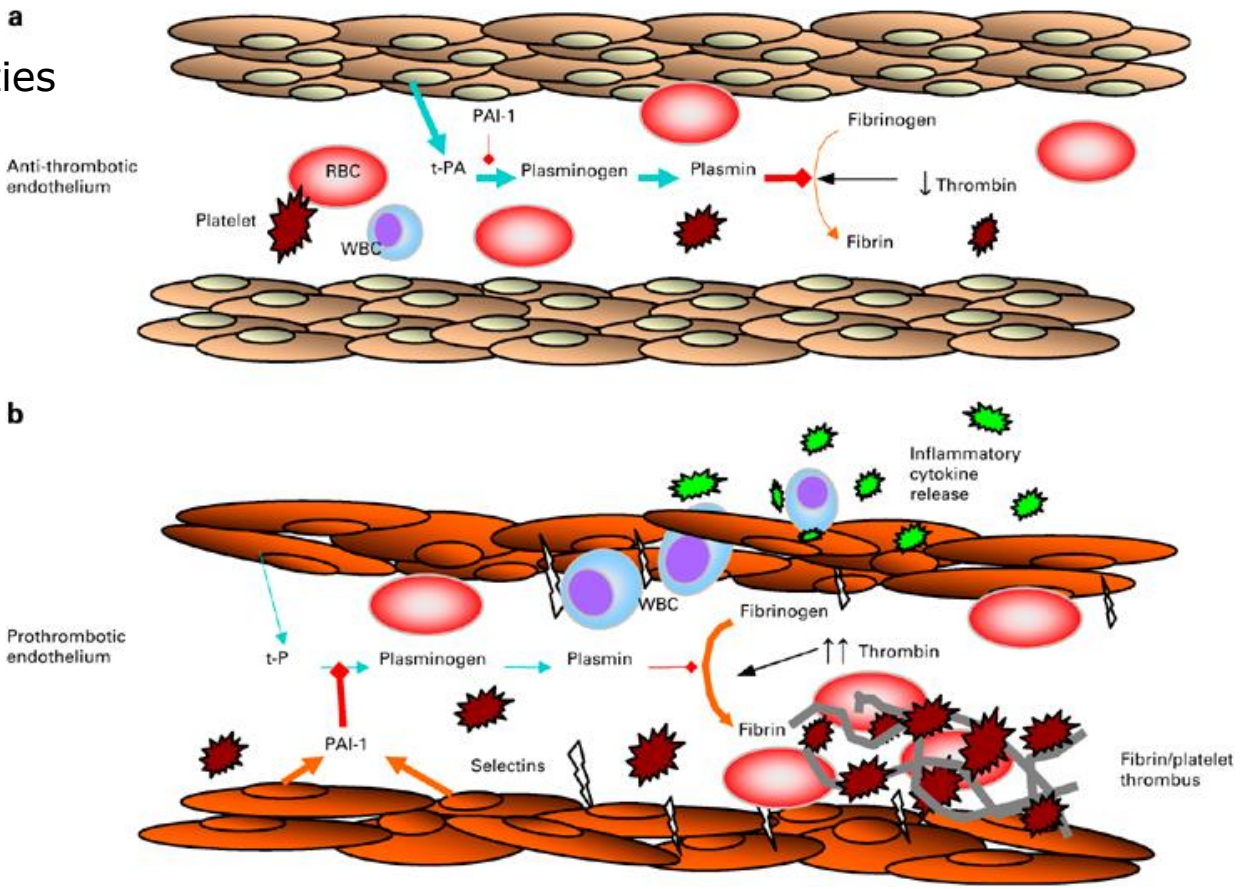


Action of agonists on NO production

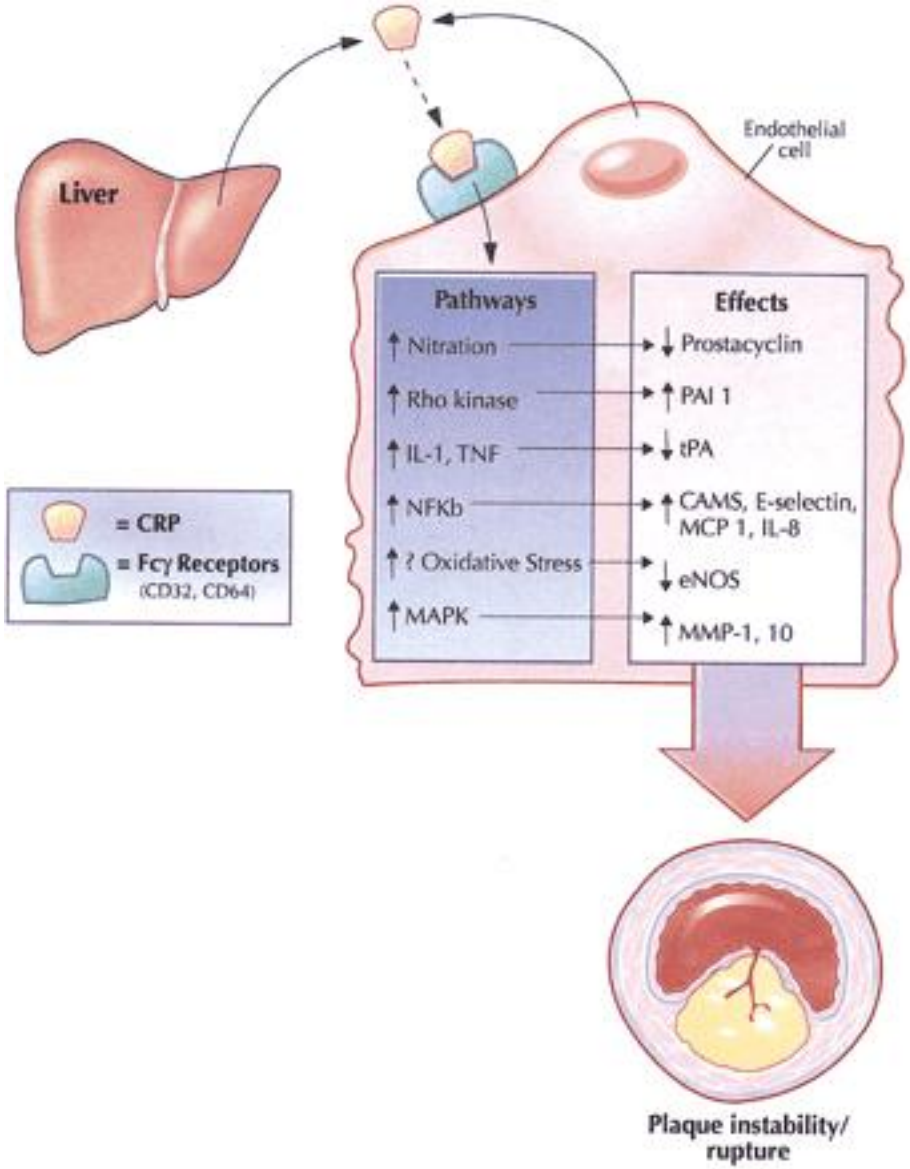


Endothelial dysfunction

- 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



Effect of inflammation on EC

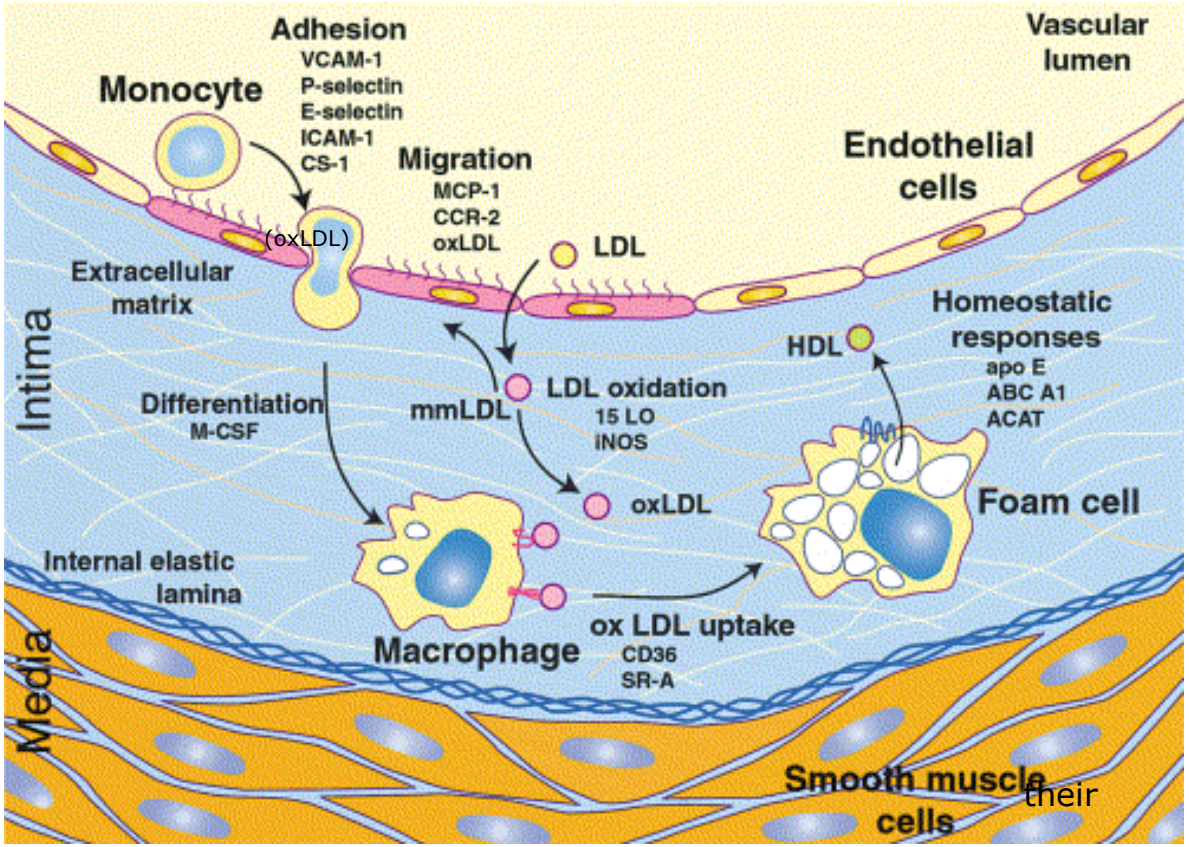


Endothelium - summary

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

(1) Initiation – formation of fatty streak

- **LDLs** can exist in **native** or **modified** forms
  - native LDL is recognised and bound by LDL-R
  - modified LDL is uptaken 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

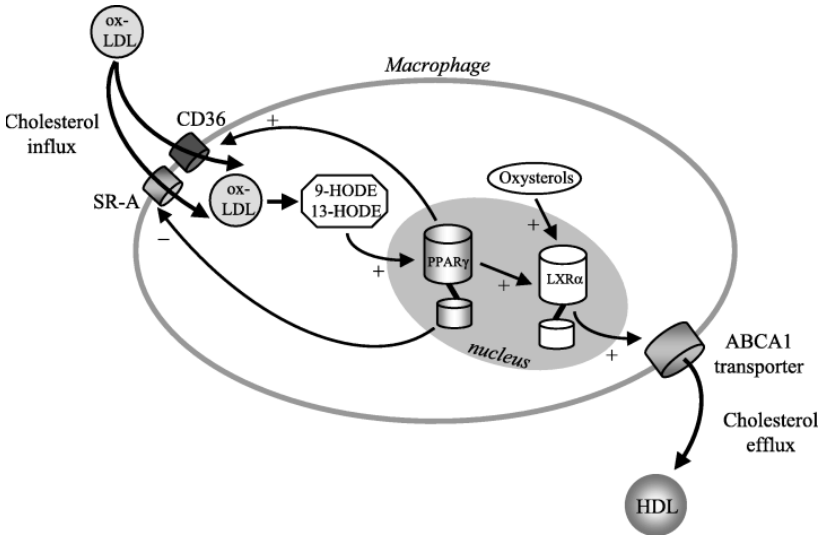


- macrophages ingest oxLDL via scavenger receptors (SR-A and CD36) and form this was so called **"foam cells"** (= lipid-laden macropghges)
  - macroscopically seen as a yellowish dots or streaks in subendothelium, hence **"fatty streaks"**
- free cholesterol from oxLDL in macrophages is again esterified by ACAT-1 (acyl-CoA cholesterol acylransferase) 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 crucial anti-atherogenic mechanism

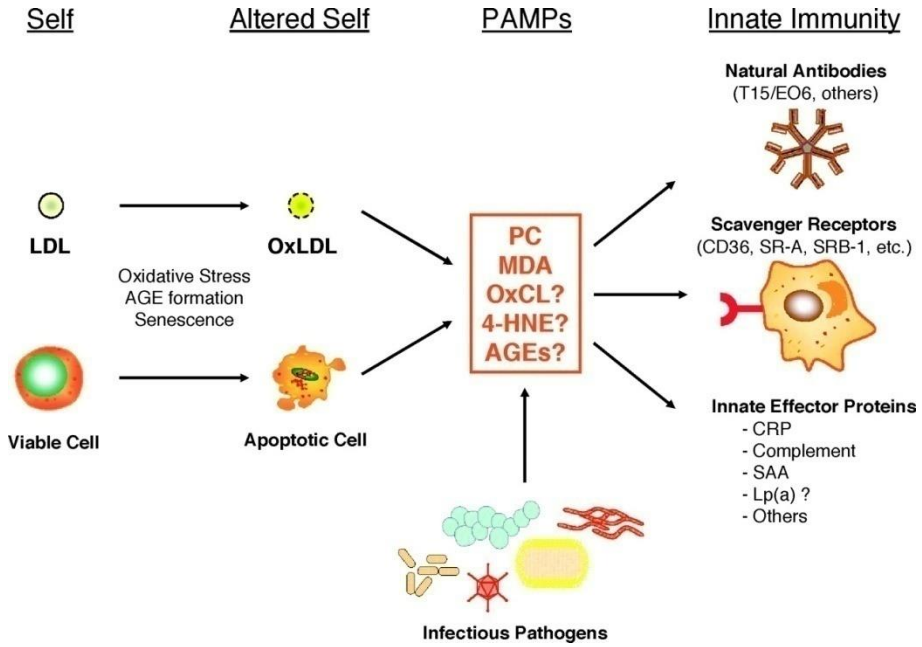
their

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

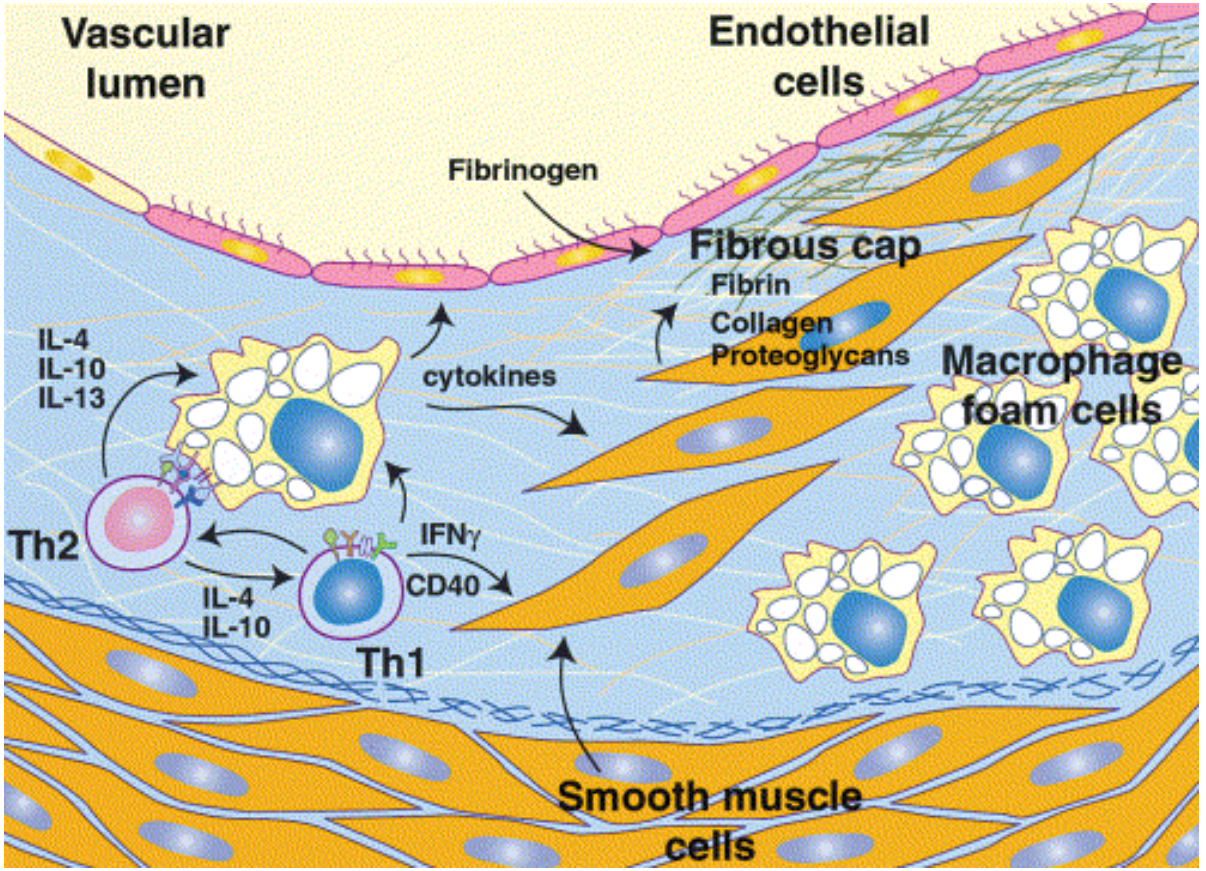


- scavenger receptors are part of the **innate immunity**
  - both natural antibodies and scavenger receptors developed during evolution under the frequent stimulation by certain pathogens
  - (1) natural antibodies (IgM)
    - against bacterial pathogen-associated molecular patterns [PAMPs]
  - (2) pattern-recognition receptors (PPRs)
    - SR-A, CD36, TLR (Toll-like receptor)
- oxidised molecules (i.e. particular epitopes) are very often similar to PAMP !!!



(2) Progression – formation of plaque

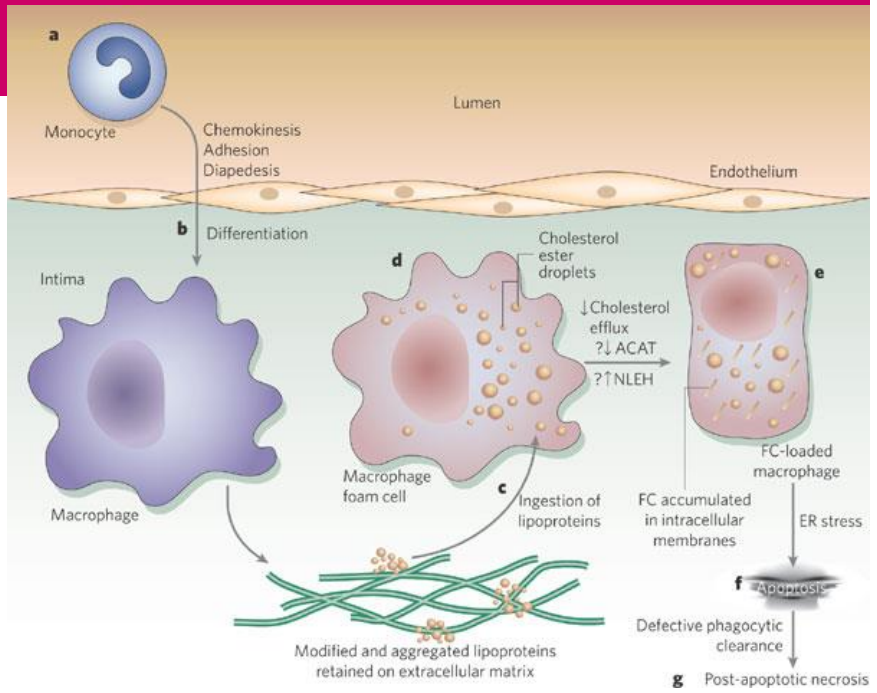
- immunologic interaction between **macrophages** and **T lymphocytes** (Th1 and Th2 sub-population) locally maintains the **chronic inflammation**
  - production of both pro-atherogenic Th1 **cytokines** (MCP-1, IL-6, TNF-α, …) and anti-atherogenic Th2 (IL-4)
  - mutual balance between Th1 and Th2 is topically modified by many factors

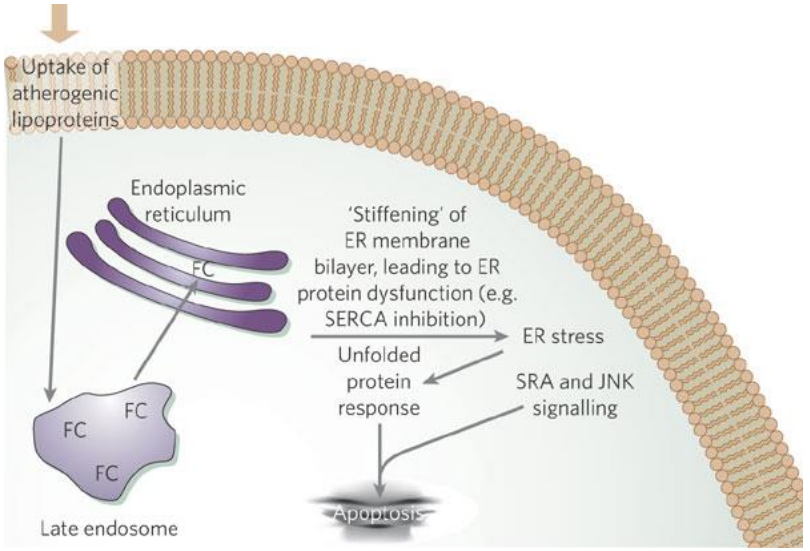


- macrophages as antigen-presenting cells help to activate B lymphocytes to wards production of **auto-antibodies** against oxLDL → formation of immune complexes → inflammation
- cytokines stimulate other cells, mainly **SMCs** of media, to migrate into intima, proliferate (→ intima thickening) and secrete 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)

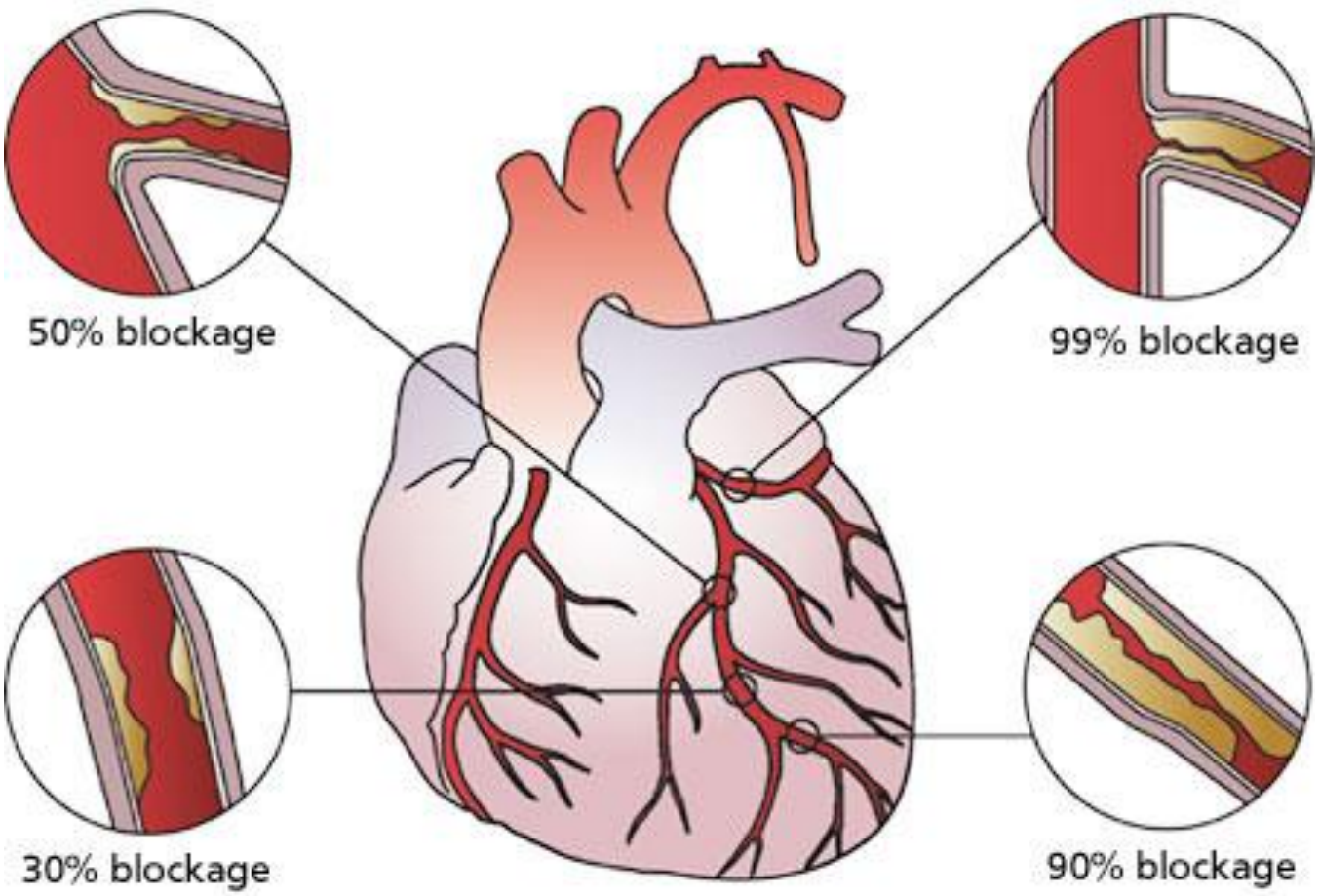
Macrophages in advanced AS – role in AS progression

- 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



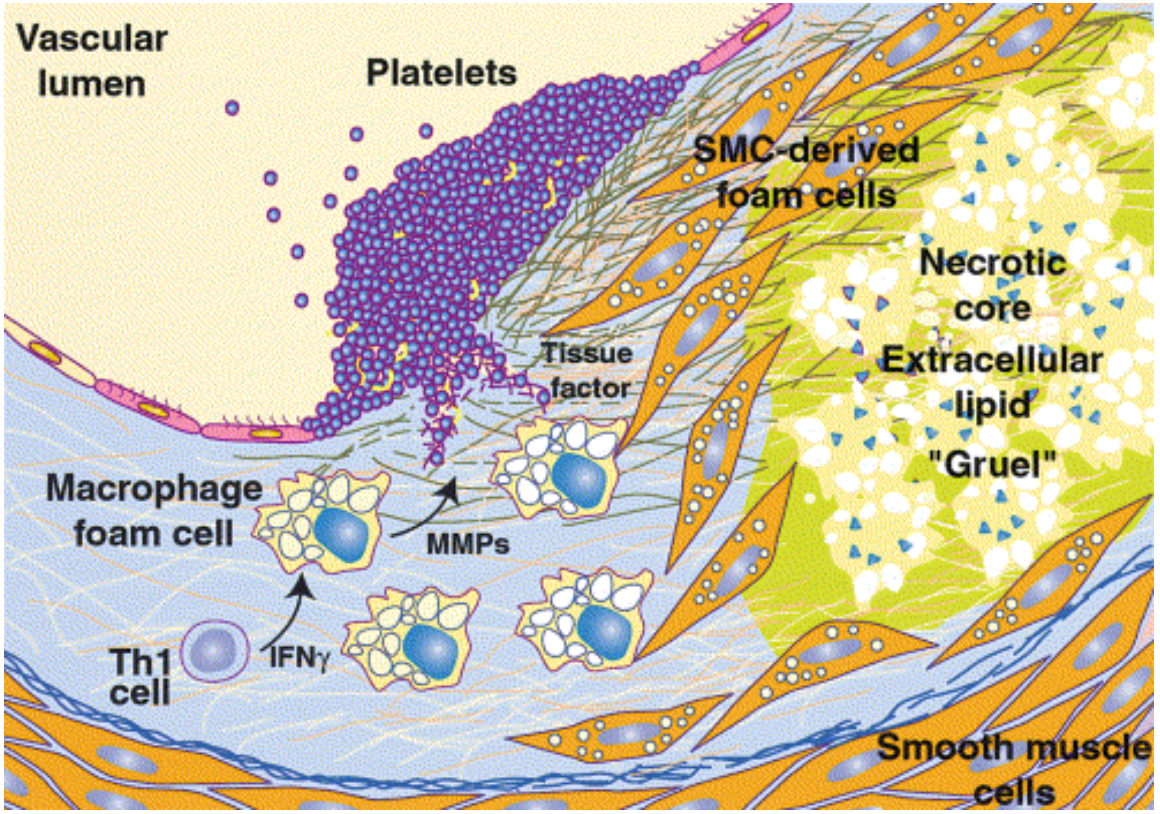


Haemodynamically significant stenosis manifests ususally after a significant (>50%) reduction in luminal diameter



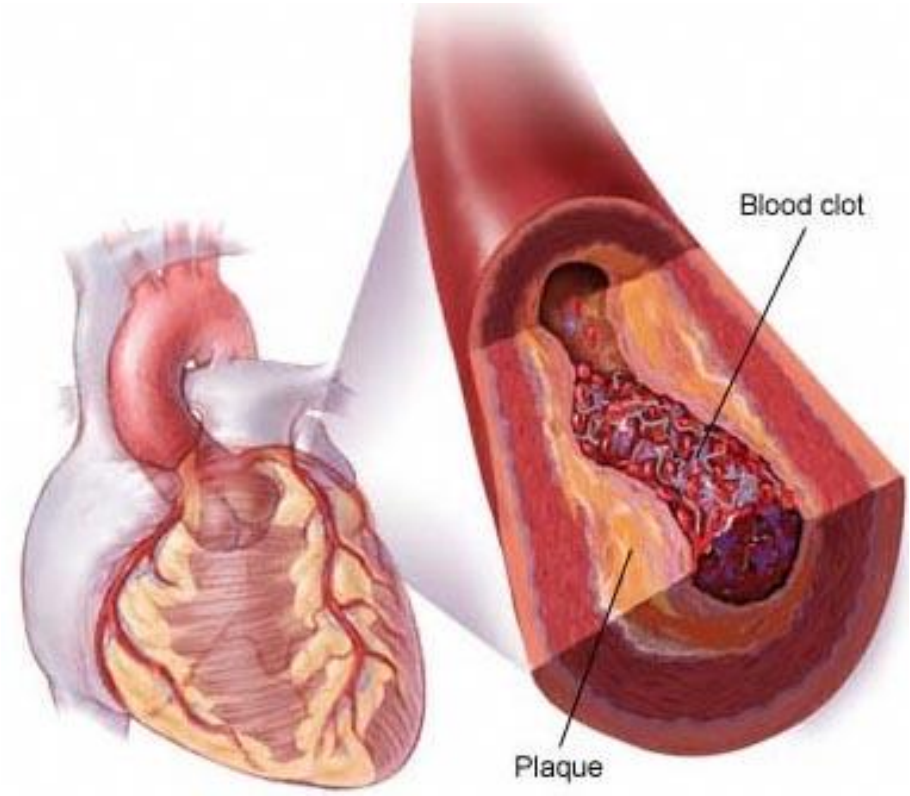
(3) Complication – rupture and thrombosis

- plaque can grow and slowly obstruct lumen or it can become instable and lead to 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 accu-mulated extracellular CH
- stimulated and hypoxic macrophages produce proteolytic enzymes degrading extracellular matrix proteins (**matrix metaloproteinases, MMPs**) which further weaken the plaque

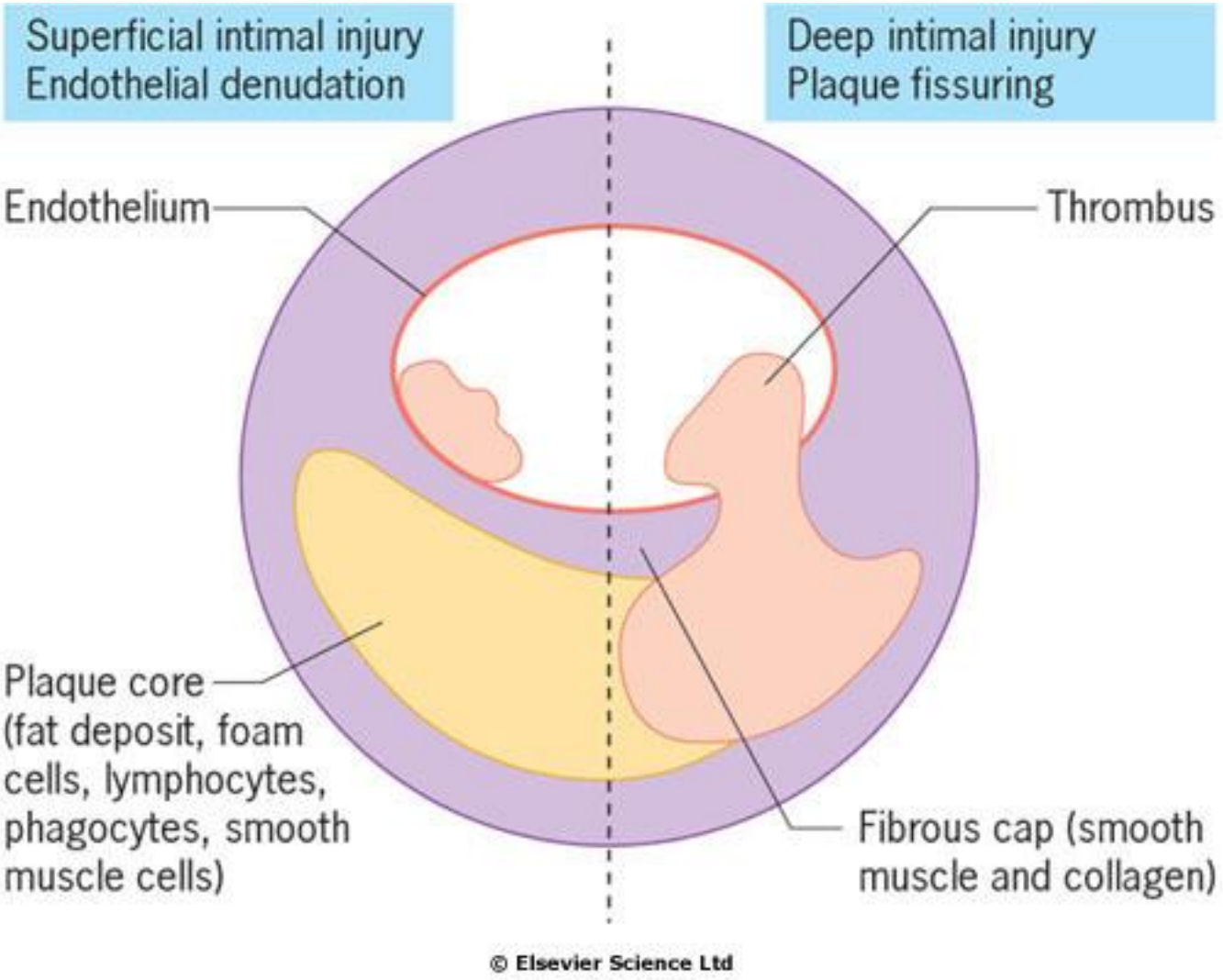


- plaque rupture (often eccentric and CH-rich), typically in the plaque "shoulder" lead to exposure of accumulated lipids and tissue factors to platelets and coagulation factors and cause **thrombosis**
- this can be manifested as a complete vessel occlusion and thus lead to tissue necrosis (e.g. myocardial infarction or stroke) or incomplete occlusion as a consequence of repeated cycles of rupture → microthrombotisation → fibrinolysis → healing = **"instable plaque"**

Thrombosis of the plaque



- Two different mechanisms are responsible for a thrombosis on the plaque:
  - (1) **denudation of endothelium** covering the plaque
    - subendothelial connective tissue is exposed - platelet adhesion occurs - thrombus is adherent to the surface of the plaque
  - (2) deep endothelial **fissuring of the advanced plaque** with a lipid core
    - plaque cap tears (ulcerates, fissures or ruptures), allowing blood from the lumen to enter the inside of the plaque itself (the core with lamellar lipid surfaces, tissue factor (triggering platelet adhesion) produced by macrophages and exposed collagen, is highly thrombogenic
    - thrombus forms within the plaque, expanding its volume and distorting its shape


Superficial intimal injury
Endothelial denudation
Deep intimal injury
Plaque fissuring
Endothelium
Thrombus
Plaque core
(fat deposit, foam
cells, lymphocytes,
phagocytes, smooth
muscle cells)
Fibrous cap (smooth
muscle and collagen)
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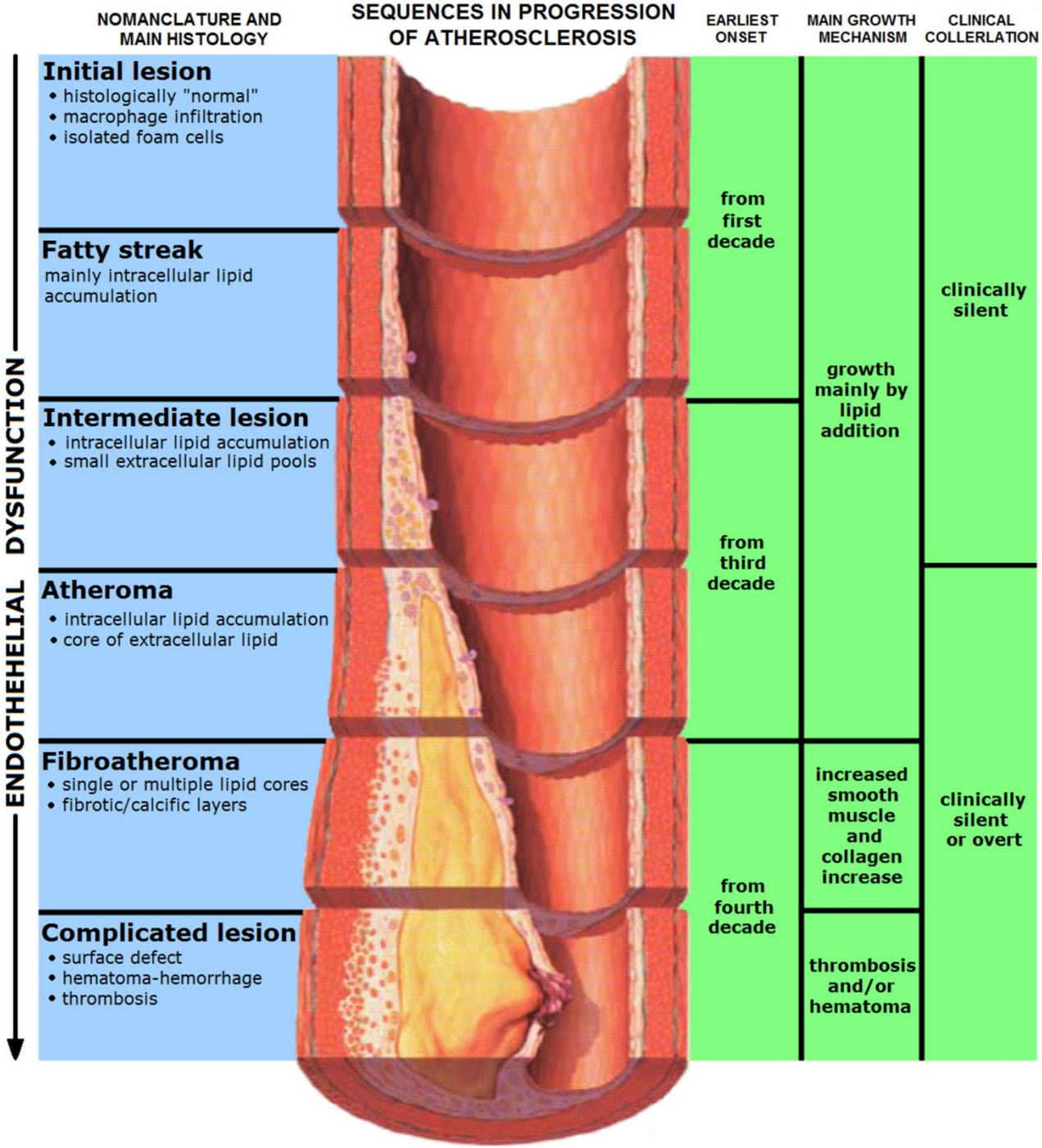
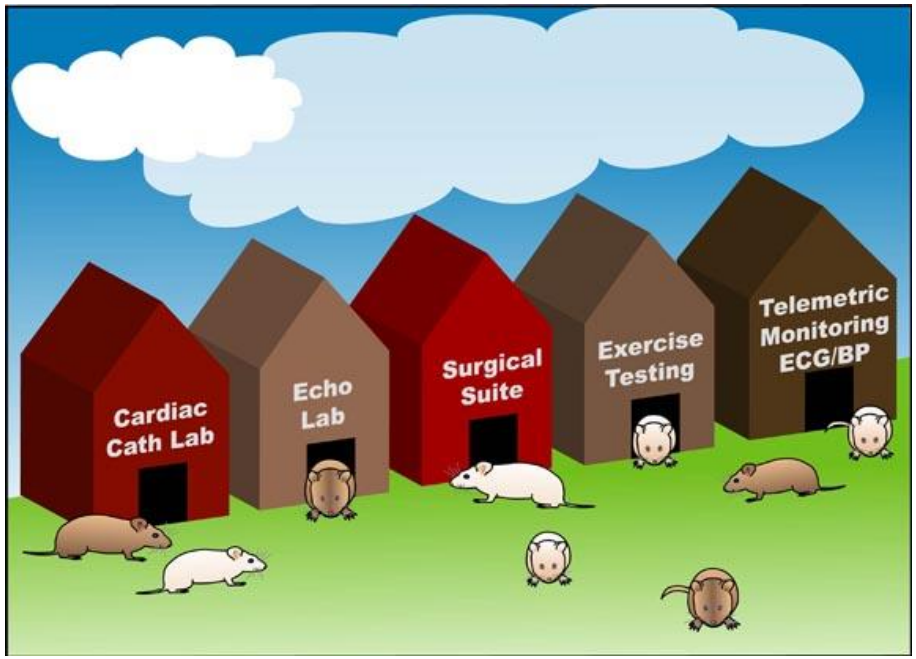

NOMANCLATURE AND MAIN HISTOLOGY
SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS
EARLIEST ONSET
MAIN GROWTH MECHANISM
CLINICAL COLLERLATION
ENDOTHEHELIAL DYSFUNCTION
Initial lesion
• histologically "normal"
• macrophage infiltration
• isolated foam cells
Fatty streak
mainly intracellular lipid accumulation
Intermediate lesion
• intracellular lipid accumulation
• small extracellular lipid pools
Atheroma
• intracellular lipid accumulation
• core of extracellular lipid
Fibroatheroma
• single or multiple lipid cores
• fibrotic/calcific layers
Complicated lesion
• surface defect
• hematoma-hemorrhage
• thrombosis
from first decade
from third decade
from fourth decade
growth mainly by lipid addition
increased smooth muscle and collagen increase
thrombosis and/or hematoma
clinically silent
clinically silent or overt

Animal models of AS - mouse

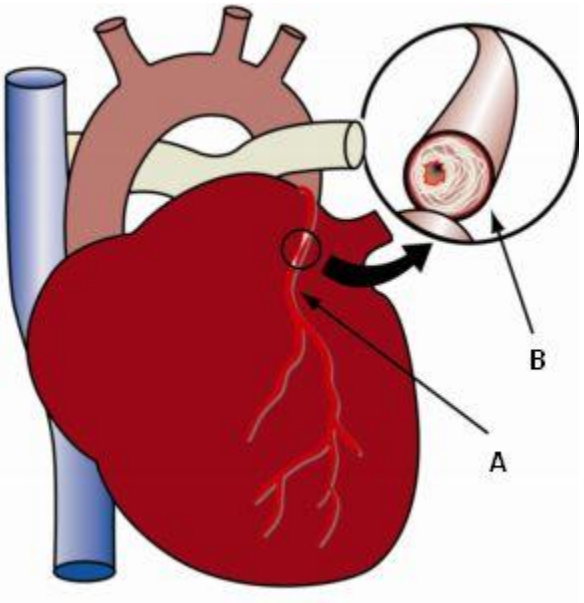
- generally, it is extremely difficult to simulate AS in animals, even those kept in captivity
  - in this aspect Homo sapiens is quite unique in their susceptibility to damage of vessel wall
- although mice is the most studied model, exp. induced AS is not entirely similar to man

- exp. model of AS
  - induced
    - high CH diet + endothelial denudation + hypertension (ligation of a. renalis)
  - spontaneous (knock-out)
    - ApoE -/- mouse
    - LDL-R -/- mouse
- exp. model spontaneous IM
  - induced
  - ligation of coronaries
  - spontaneous
    - comb. apoE/LDL-R -/- + mental stress + hypoxia



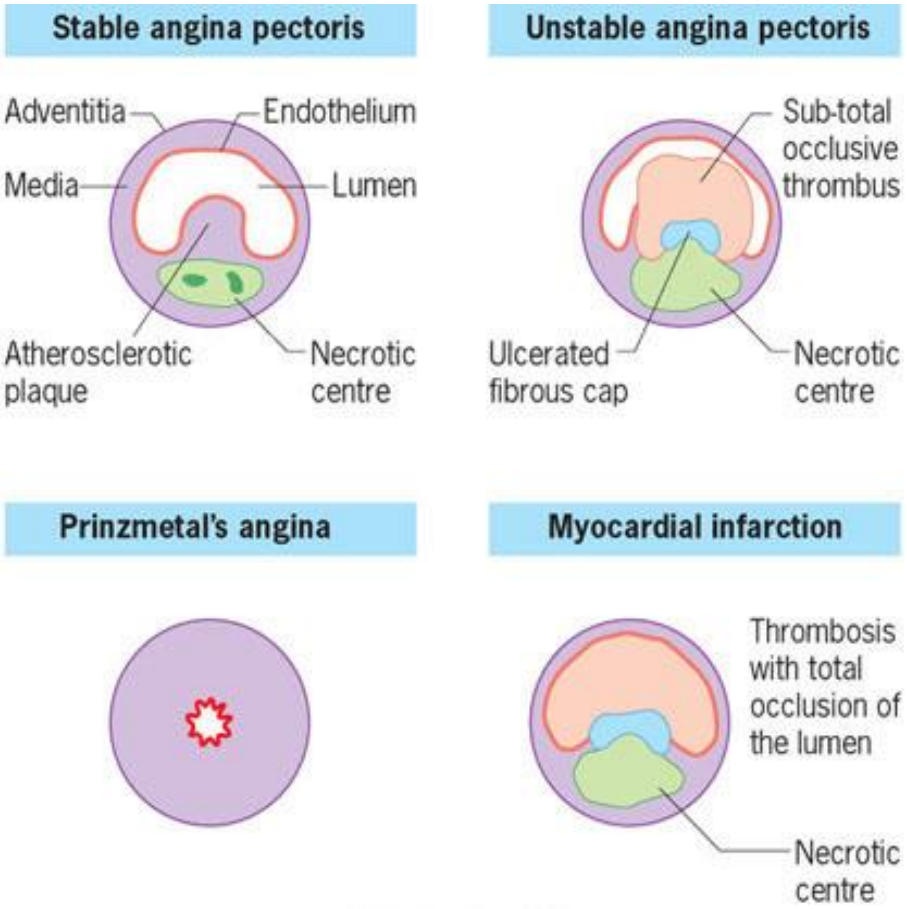
Clinical manifestation of CHD

- chronic ischemic heart disease
  - stable angina pectoris
  - variant/vasospasctic angina
  - silent myocardial ischemia
- acute coronary syndromes
  - unstable angina
  - myocardial infarction
    - subendocardial (non-Q)
      - ECG: ST-segment elevation absent (non-STEMI)
    - transmural (Q)
      - ECG: ST-segment elevation present (= STEMI)



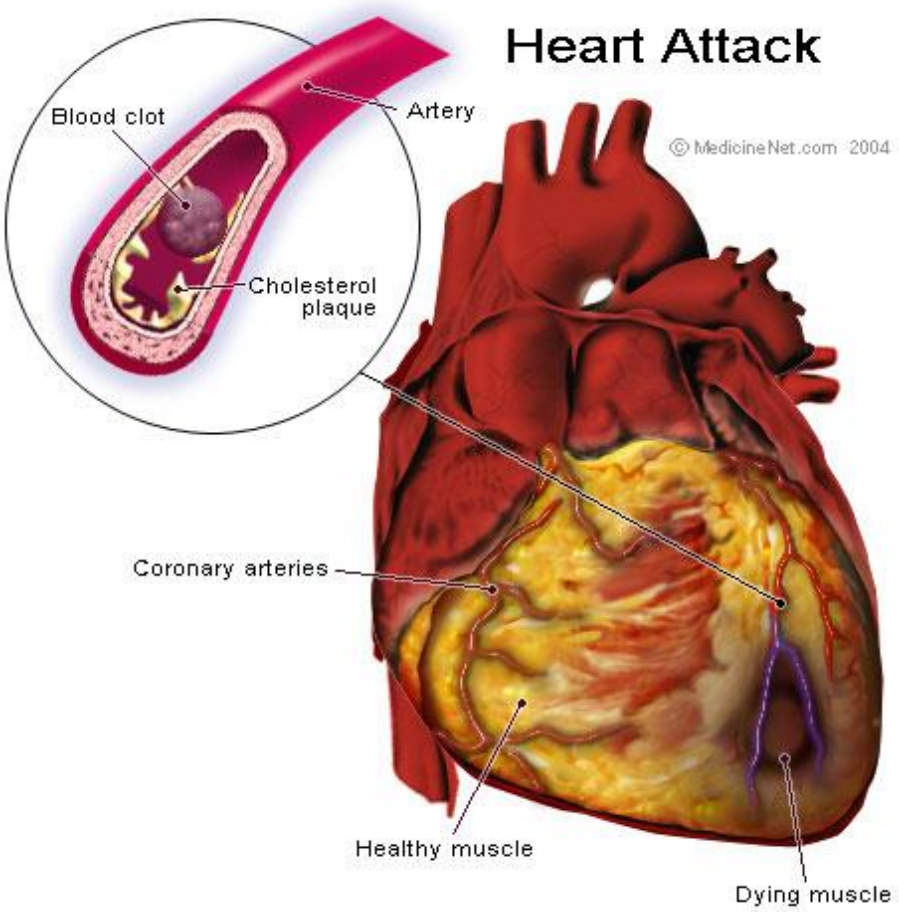
Angina pectoris

- diagnosis of angina is largely based on the clinical history
  - the chest pain is generally described as 'heavy', 'tight' or 'gripping'
  - typically, the pain is central/retrosternal and may radiate to the jaw and/or arms
  - it can range from a mild ache to a most severe pain that provokes sweating and fear, there may be associated breathlessness
- types:
  - (1) stable
    - provoked by physical exertion, especially after meals and in cold
    - aggravated by anger or excitement
    - pain occurs predictably at a certain level of exertion and fades with rest (the threshold for developing pain is variable depending on the extent of the stenosis)
  - (2) unstable
    - angina of recent onset (less than 1 month)
    - worsening angina (previously stable for certain time)
    - angina at rest
  - (3) variant (Prinzmetal's) angina
    - occurs without provocation, usually at rest or night, as a result of coronary artery spasm
    - more frequently in women
  - (4) cardiac syndrome X
    - personal history of angina + positive exercise test + angiographically normal coronary arteries
    - heterogeneous group (more common in women)
    - due to microvascular abnormalities



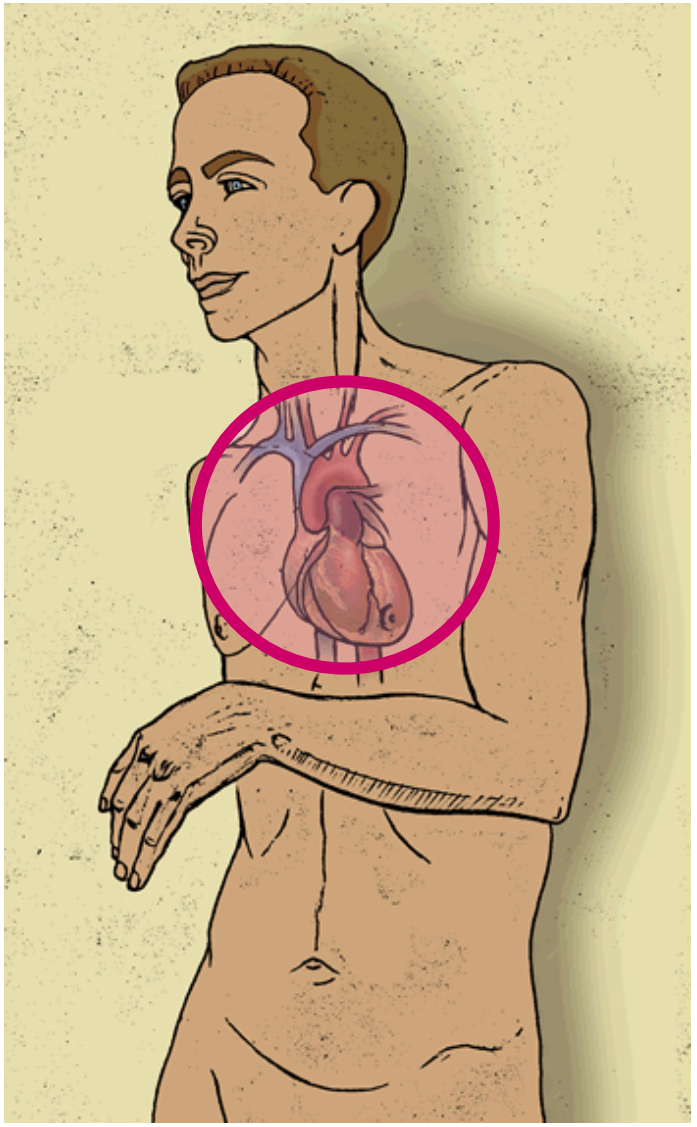
Myocardial infarction (MI)

- result of the plaque rupture with superadded thrombus
  - occlusive thrombus consists of a platelet-rich core ('white clot') and a surrounding fibrin-rich ('red') clot
  - irreversible changes develop 20-40 min after complete occlusion of the artery
  - 6 hours after the onset of infarction, the myocardium is swollen and pale
  - in 24 hours the necrotic tissue appears deep red owing to haemorrhage
  - during the next few weeks, an inflammatory reaction develops and the infarcted tissue turns grey and gradually forms a thin, fibrous scar
  - late remodelling
    - alteration in size, shape and thickness of both the infarcted myocardium (which thins and expands) and the compensatory hypertrophy that occurs in other areas of the myocardium

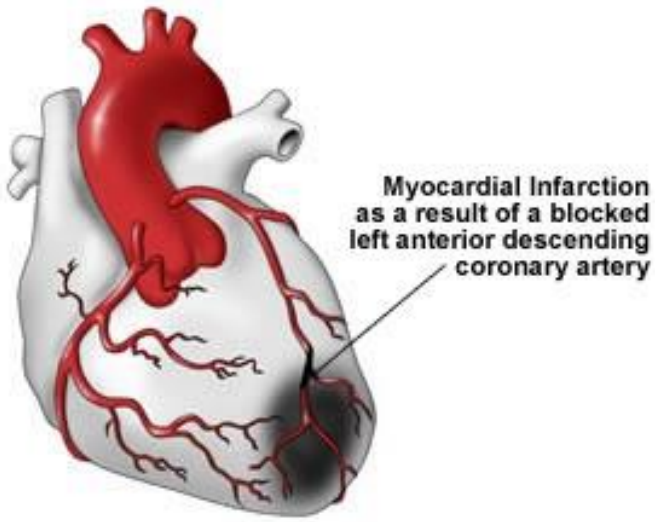


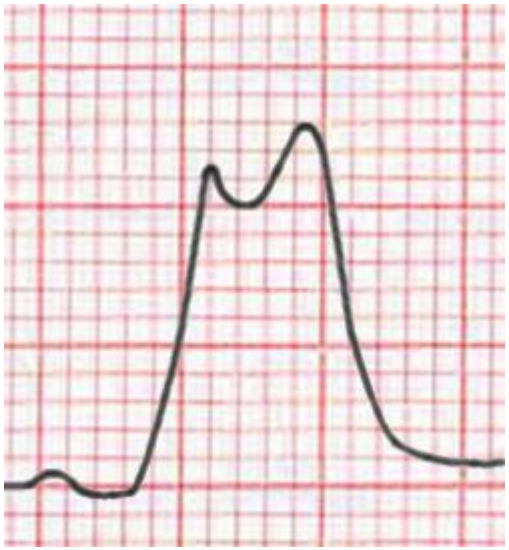
Clinical features of MI

- severe chest pain
  - onset is usually sudden, often occurring at rest, and persists fairly constantly for some hours
  - however, as many as 20% of patients with MI have no pain
    - so-called 'silent' myocardial infarctions are more common in diabetics and the elderly
- MI is often accompanied by sweating, breathlessness, nausea, vomiting and restlessness
  - differential diagnosis!
- sinus tachycardia and the fourth heart sound are common
- modest fever (up to 38°C) due to myocardial necrosis often occurs over the course of the first 5 days



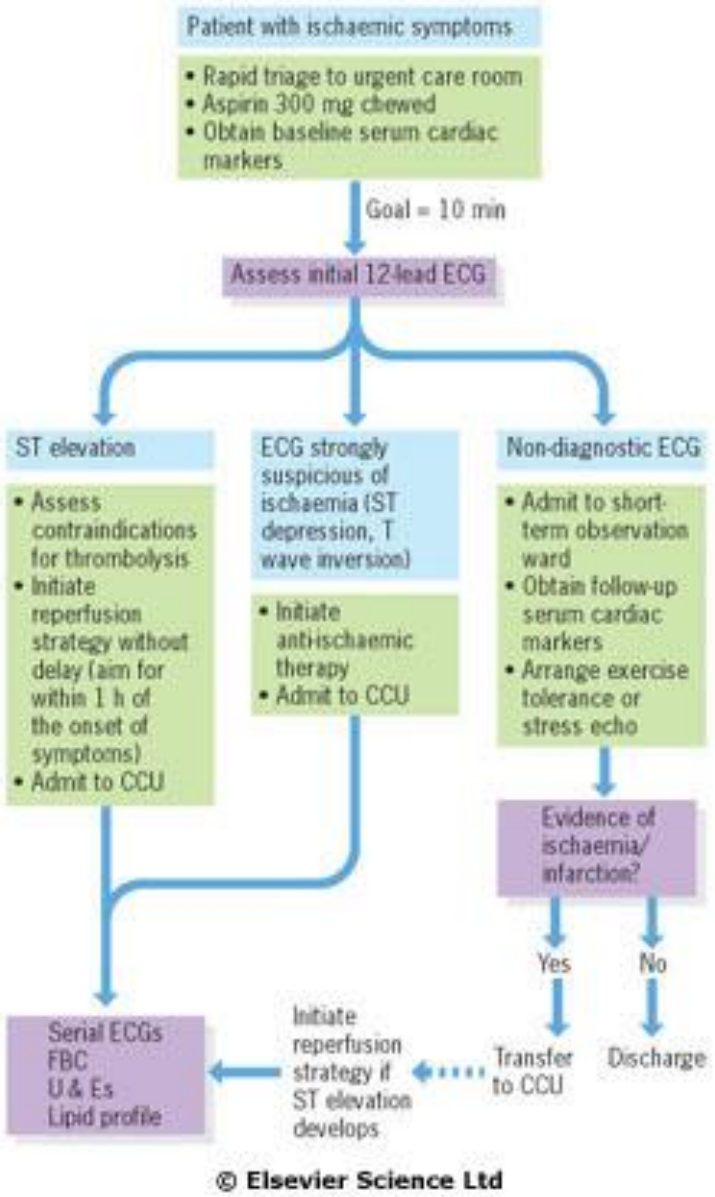
Localisation and extent of MI





- branch of coronary arteries
  - LCA
    - ascendant
    - circumflex
  - RCA
- stenosis/occlusion
  - epicardial
  - subendocardial

MI diagnosis



- requires at least two of the following:
  - a history of chest pain
  - evolving ECG changes in respective leads
  - a rise in cardiac enzymes or troponins

Typical ECG changes in myocardial infarction

Infarct site	Leads showing main changes
Anterior	
Small	V_3–V_4
Extensive	V_2–V_5
Anteroseptal	V_1–V_3
Anterolateral	V_4–V_6, I, AVL
Lateral	I, II, AVL
Inferior	II, III, AVF
Posterior	V_1, V_2 (reciprocal)
Subendocardial	Any lead
Right ventricle	VR_4

STEMI vs. non-STEMI

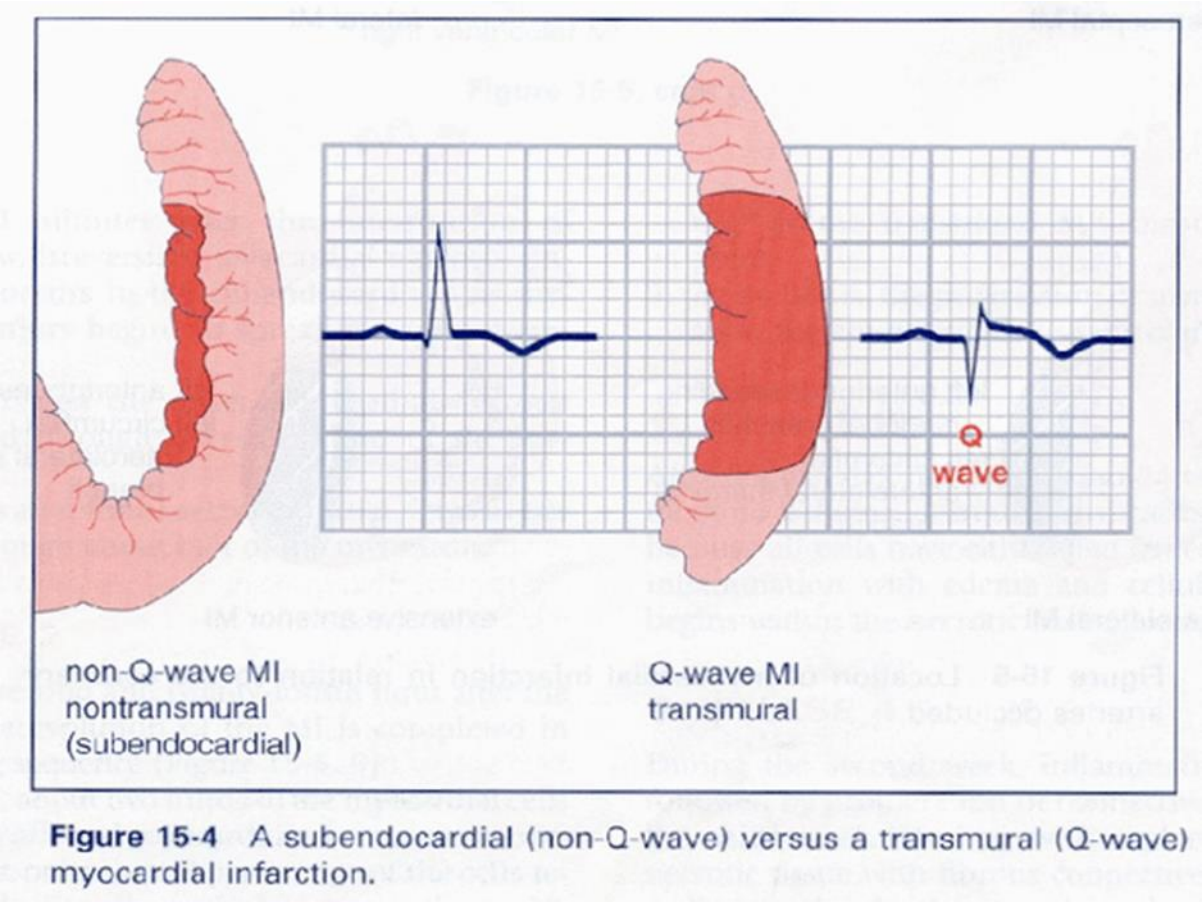
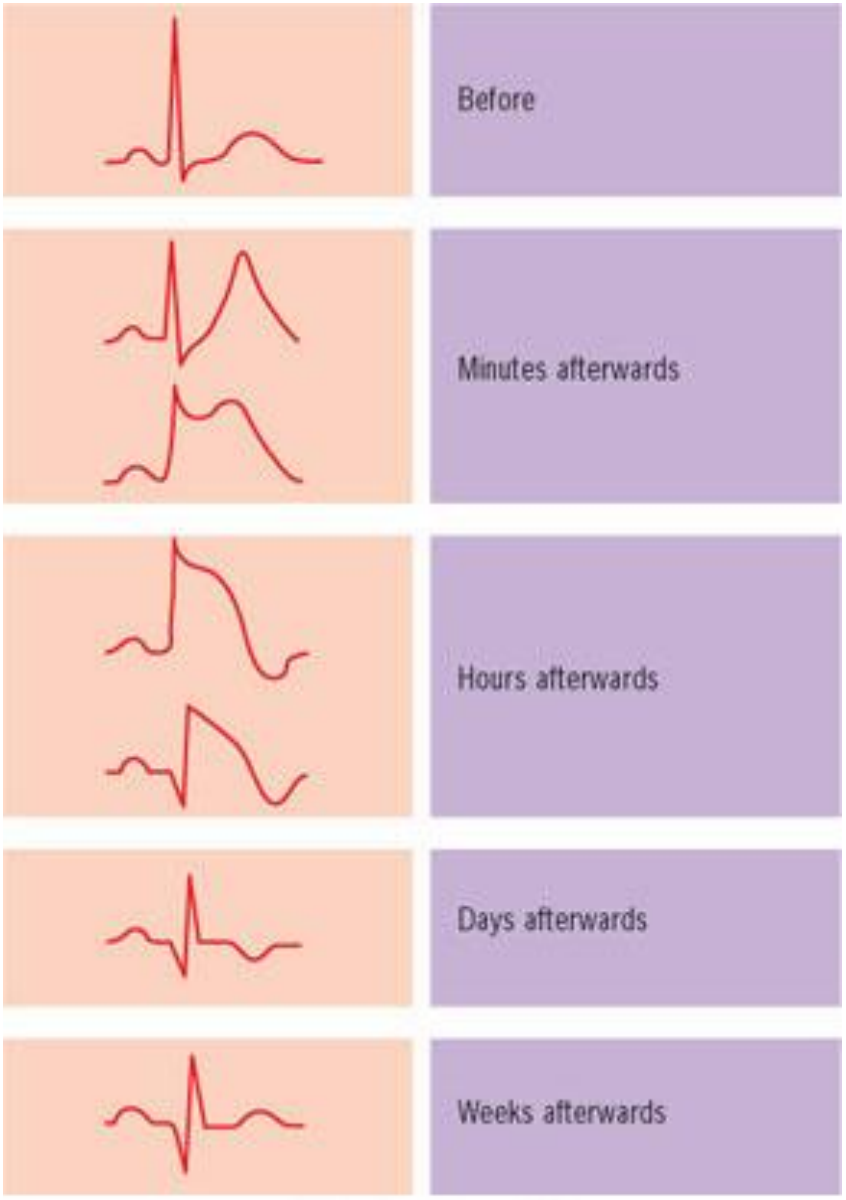
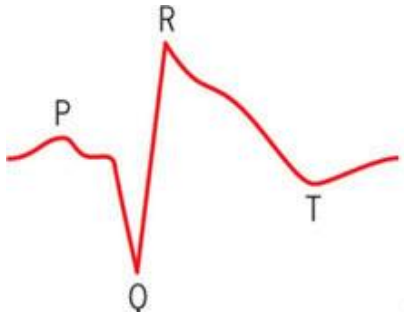


Figure 15-4 A subendocardial (non-Q-wave) versus a transmural (Q-wave) myocardial infarction.

ECG changes during Q-MI



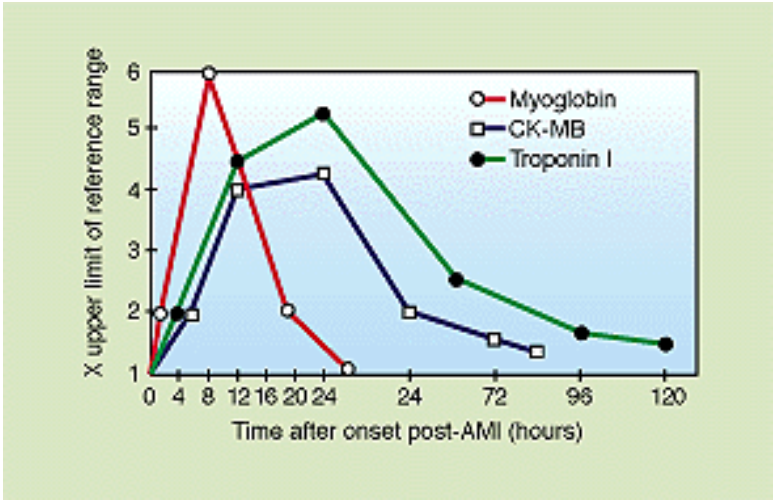
- first few minutes – tall spiked T waves
- during first hours - ST segment elevation develops (Parde waves)
- after the first few hours - the T wave inverts
- during days after onset - the R wave voltage is decreased and Q waves develop
- after a few days - the ST segment returns to normal
- after weeks or months - the T wave may return to normal
- deep Q wave remains forever



Q ≥ 1mm wide (0.04 s)
and/or
Q ≥ 2 mm deep (0.2 mV)

Cardiac markers of acute MI

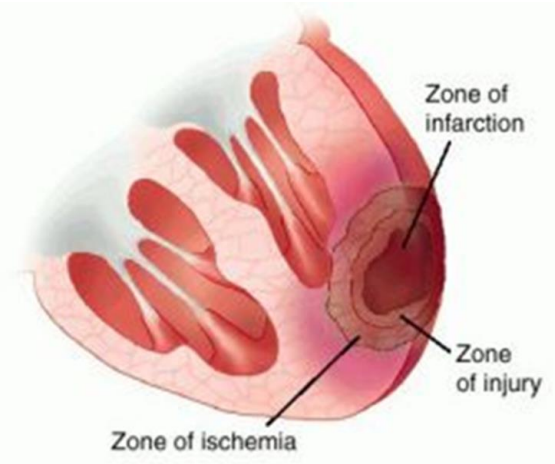
- necrotic cardiac tissue releases several enzymes and proteins into the serum:
  - **CK - creatinkinase**
    - peaks within 24hrs and is usually back to normal by 48hrs (also produced by damaged skeletal muscle and brain)
    - **cardiac-specific isoforms (CK-MB)** allows greater diagnostic accuracy
    - the size of the enzyme rise is broadly proportional to the infarct size



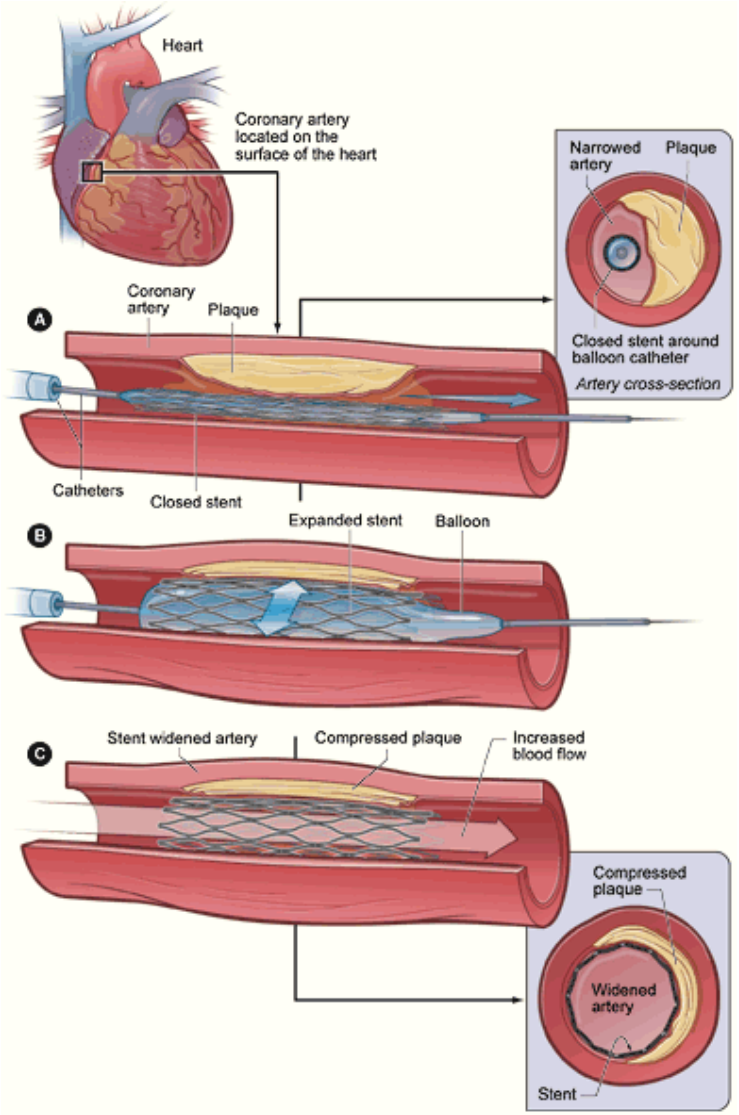
  - **Troponins I and T**
    - consists of three subunits, troponin I (TnI), troponin T (TnT) and troponin C (TnC), each subunit is responsible for part of troponin complex function
      - TnI inhibits ATP-ase activity of acto-myosin. TnT and TnI are presented in cardiac muscles in different forms than in skeletal muscles
      - only one tissue-specific isoform of TnI is described for cardiac muscle tissue (cTnI)
    - it is considered to be more sensitive and significantly more specific in diagnosis of MI than the CK-MB and LDH isoenzymes
    - cTnI can be detected in blood 3–6hrs after onset of the chest pain, reaching peak level within 16–30hrs
  - **Myoglobin**
  - historically AST - aspartate aminotransferase and LDH - lactate dehydrogenase
      - AST and LDH rarely used now for the diagnosis of MI
      - LDH peaks at 3-4 days and remains elevated for up to 10 days and can be useful in confirming myocardial infarction in patients presenting several days after an episode of chest pain

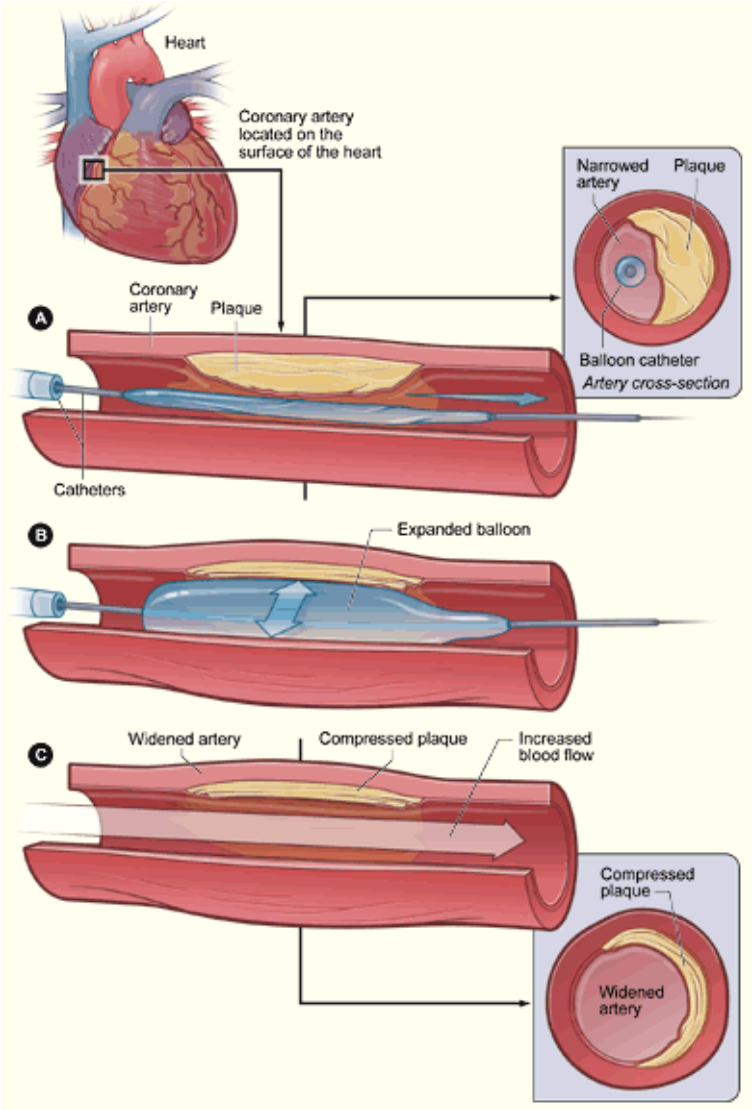
Complications of MI

- early phase (days after MI)
  - arrhythmias
    - ventricular extrasystoles
    - ventricular tachycardia (may degenerate into ventricular fibrillation)
    - atrial fibrillation (in about 10% of patients with MI)
    - sinus bradycardia (associated with acute inferior wall MI)
      - escape rhythm such as idioventricular rhythm (wide QRS complexes with a regular rhythm at 50-100 b.p.m.) or idiojunctional rhythm (narrow QRS complexes) may occur
    - sinus tachycardia
    - AV nodal delay (first-degree AV block) or higher degrees of block
      - may occur during acute MI, especially of the inferior wall (the right coronary artery usually supplies the SA and AV nodes)
      - acute anterior wall MI may also produce damage to the distal conduction system (the His bundle or bundle branches)
      - development of complete heart block usually implies a large MI and a poor prognosis
  - cardiac failure
  - pericarditis
- later
  - recurrent infarction
  - unstable angina
  - thromboembolism
  - mitral valve regurgitation
  - ventricular septal or free wall rupture
- late complications
  - post-MI syndrome (Dressler's syndrome)
    - chronic v.s. autoimmune pericarditis
  - ventricular aneurysm
  - recurrent cardiac arrhythmias

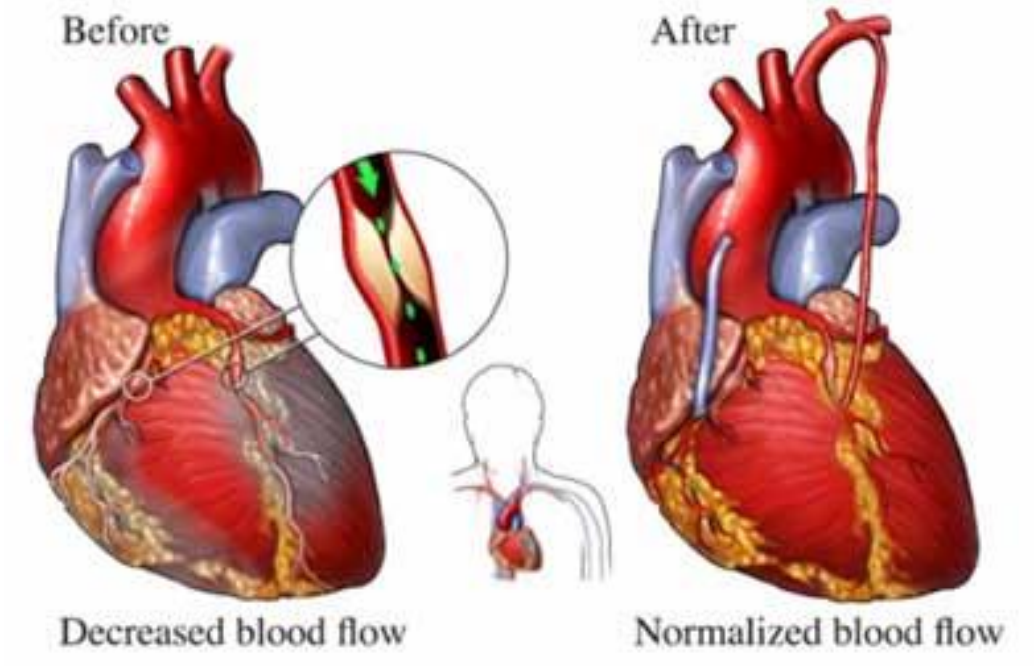


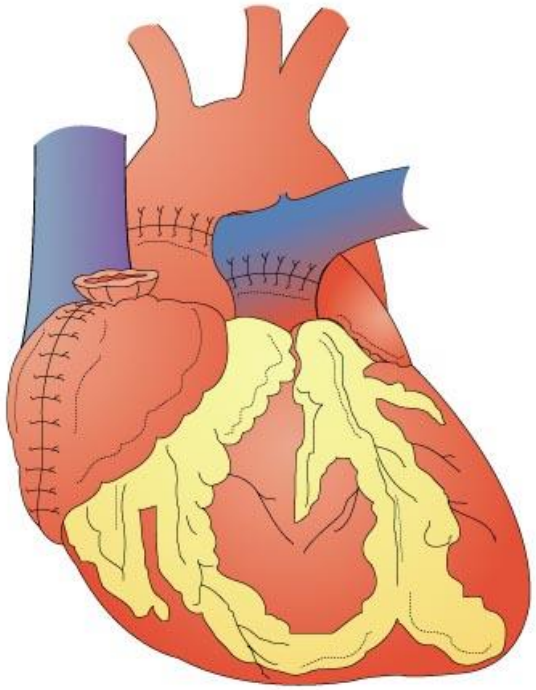
Acute interventions – stenting & angioplasty (PTCA)

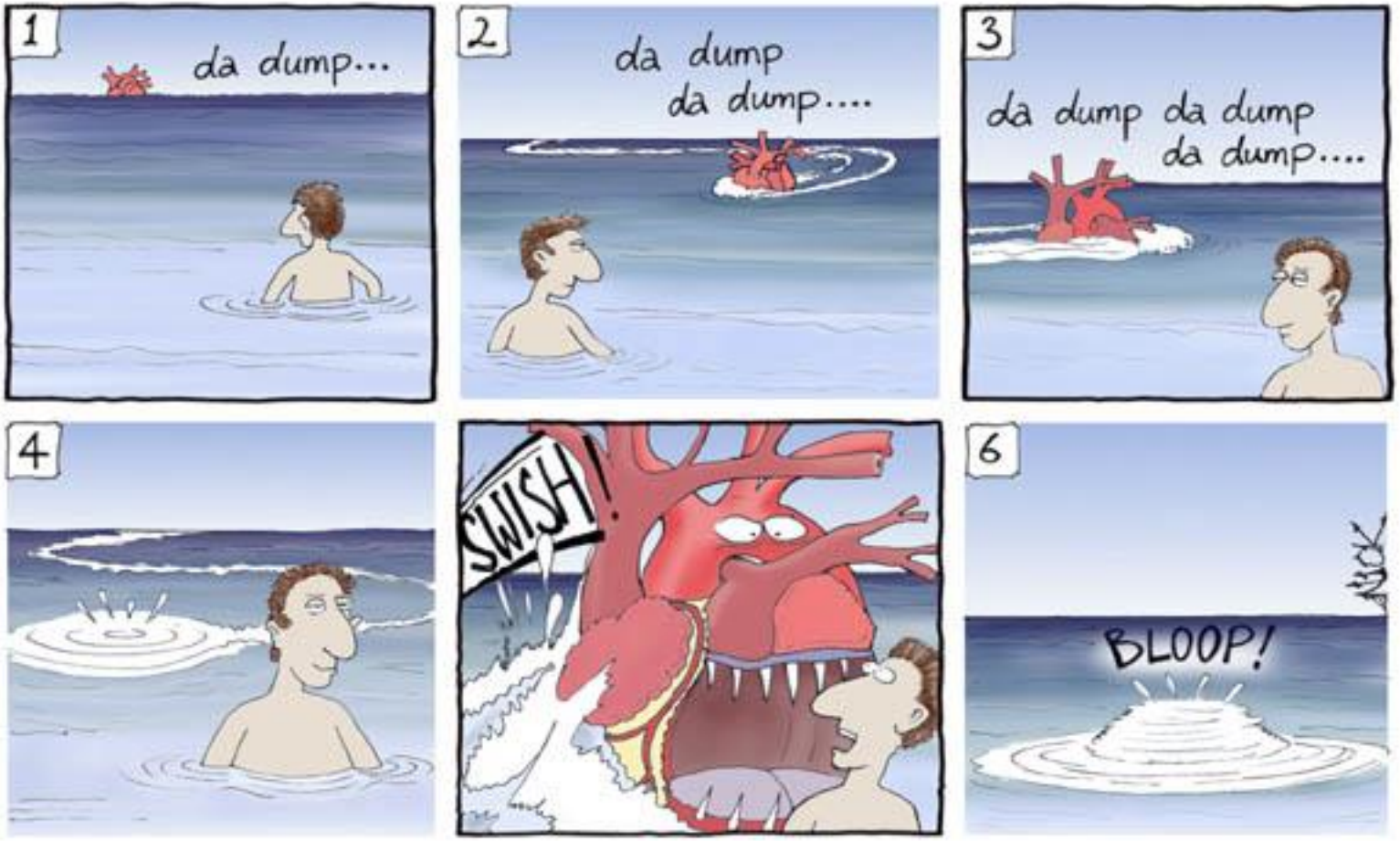




Follow-up interventions – by-pass surgery & transplantation







TOO BAD DESMOND HAD NEVER LEARNED TO RECOGNIZE THE EARLY WARNING SIGNS OF A HEART ATTACK.