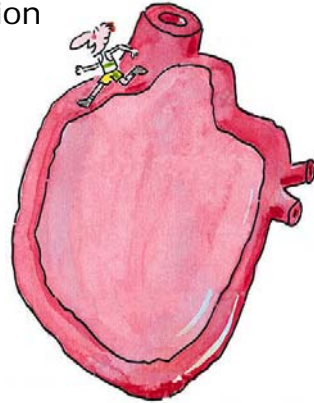
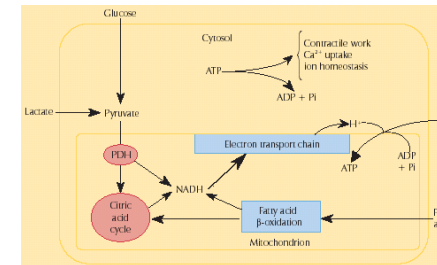
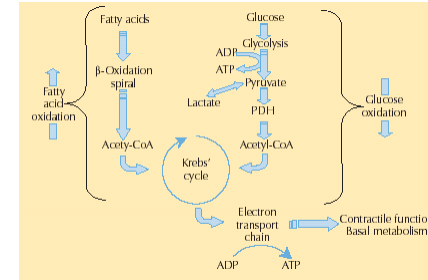


Coronary heart/artery disease (CHD/CAD)

Myocardial blood supply & metabolism
 Myocardial ischemia - compensation
 Coronary atherosclerosis
 CAD - etiopathogenesis

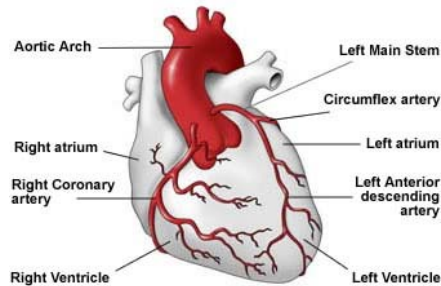


Myocardial metabolism

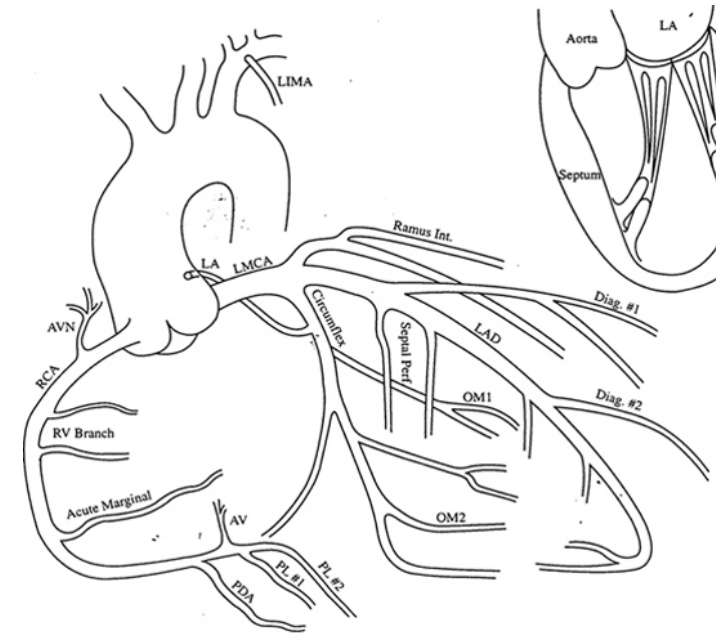


- heart has to continually perform 2 processes:
 - **automacy** = generation of action potential in order to perform
 - **contraction**
- myocardium has thus a very high demand for **ATP** even in resting state
 - for contraction
 - actin/myosin – ATP
 - Ca²⁺ handling (Ca²⁺-ATP-ase, SERCA)
 - for repolarisation
 - Na⁺/K⁺-ATP-ase
- ATP is produced by oxidation of substrates
 - FFA
 - glucose (glycogen)
 - ketone bodies and lactate
- therefore myocardium requires **large amounts of O₂** and must be, therefore, well perfused !!

Blood supply of the heart

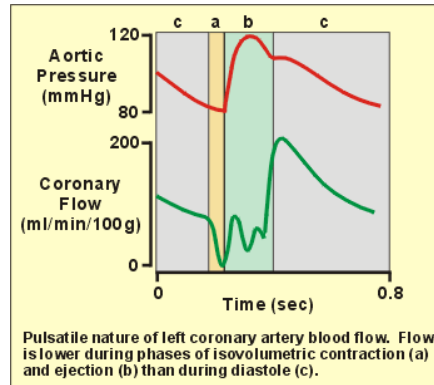


- demand for O₂ and substrates is met by heart blood vessels - **coronary arteries** - branching from the ascendant aorta
 - (1) left coronary artery
 - (a) left ant. desc. branch
 - supplies front part of the LV and RV and front part of the septum
 - (b) circumflex branch
 - supplies left and back wall of the LV
 - (2) right coronary artery
 - supplies RV



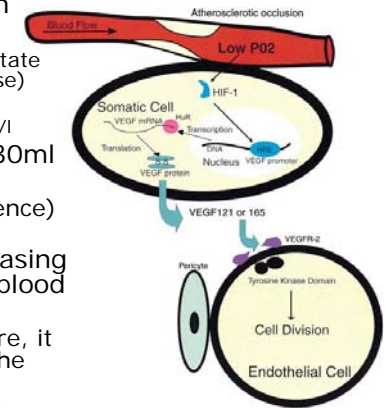
Coronary blood flow – temporal pattern

- 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
 - endocardium is more susceptible to ischemia, especially at ↓ perfusion pressures or ↑ intracardial pressure
 - tachycardia shortens diastole so there is relatively less time available for coronary flow during diastole to occur



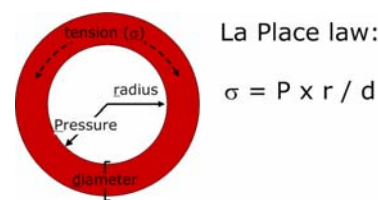
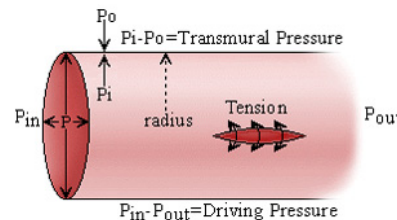
Coronary blood flow – quantitative aspects

- amount of oxygen supplied by the coronary blood (VO_2): $\sim 45\text{ml } O_2/\text{min}$
 - $VO_2 = Q_m \times CaO_2$
 - $Q_m = 210\text{--}240\text{ml/min}$ in the resting state ($1000\text{--}1200\text{ml/min}$ during the exercise)
 - $CaO_2 = 200\text{ml } O_2/\text{l}$
 - for $PaO_2 = 13.3\text{kPa}$ and $c[\text{Hb}] = 150\text{g/l}$
- consumption in the resting state: $\sim 30\text{ml } O_2/\text{min}$ (65-70%)
 - very high O_2 extraction (A- V_{O_2} 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



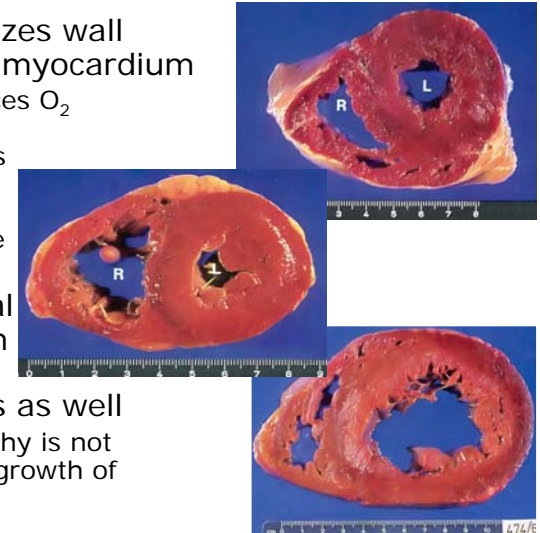
Factors influencing myocardial O_2 consumption

- (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
- rough estimate of energetic demands of heart: **tension-time index (TTI)**
 - SBP x heart rate



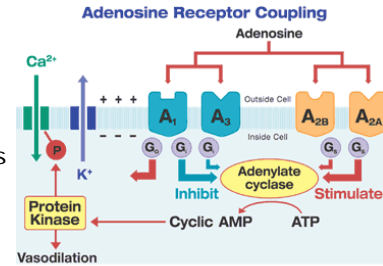
Why hypertrophy does not ↓ O_2 consumption at the end

- hypertrophy normalizes wall tension per gram of myocardium
 - initially, it does reduce O_2 consumption 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



Coronary blood flow - autoregulation

- autoregulation tightly coupled to the oxygen demand
 - between 60 to 200 mm perfusion pressure (ie. systemic pressure) helps to maintain normal coronary blood flow whenever coronary perfusion pressure changes due to changes in aortic pressure
 - during exercise

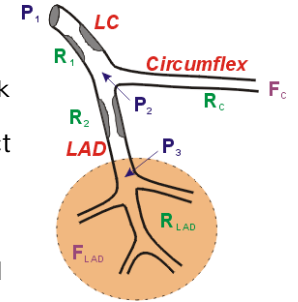


- factors:
 - adenosine**
 - the most important mediator of **active hyperemia**
 - formed from cellular AMP by 5'-nucleotidase; AMP is derived from hydrolysis of intracellular ATP and ADP
 - nitric oxide**
 - an important regulator of coronary blood flow, produced by endothelial nitric oxide synthase
 - sympathetic activation**
 - β 1-receptor (more than α 1-receptor) activation results in coronary vasodilation (plus increased heart rate, contractility)

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Consequences of O₂/ATP depletion

- ↓ contractility
 - ↓ EF (ejection fraction), ↓ SV (stroke volume)
- ↓ diastolic relaxation
 - ↑ 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 don't react to this stimulation and "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



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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:
 - reduced coronary blood flow due to a fixed mechanical obstruction
 - coronary atherosclerosis (with or without thrombus) = coronary artery disease (CAD)
 - thrombembolism
 - dynamic obstruction
 - vascular spasm
 - "small vessel disease"
 - diabetic angiopathy
 - polyarteritis nodosa
 - systemic lupus erythematoses
 - decrease of blood oxygenation or concentration of oxygen carrier
 - hypoxic hypoxia
 - anemic hypoxia
 - inadequately high demand for oxygen
 - ↑↑↑ cardiac output (e.g. thyrotoxicosis)
 - 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 ischaemia is the most commonly occurs as a result of coronary atherosclerosis**

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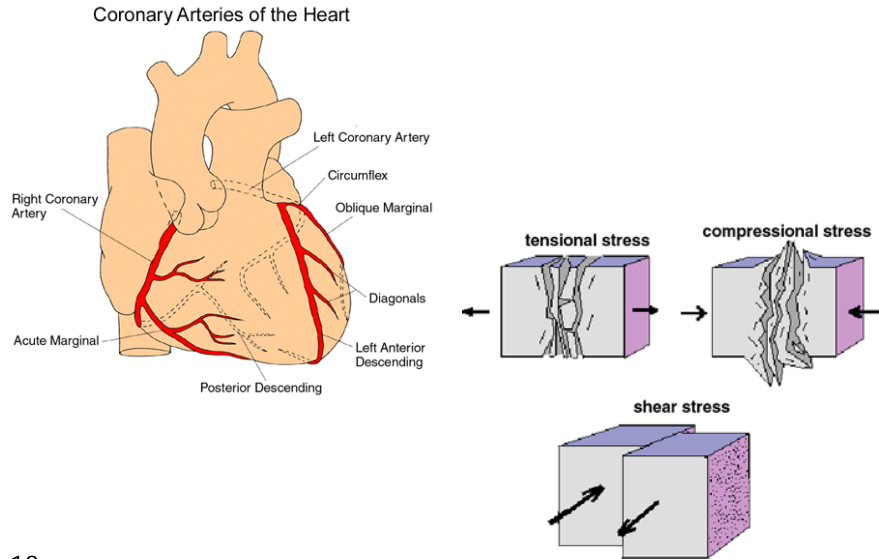
CHD due to atherosclerosis

- 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
- 4 main players in the AS etiopathogenesis
 - modified lipoproteins (LDL)
 - monocyte-derived macrophages
 - T lymphocytes
 - normal cells of vessel wall (smooth muscle cells)
- morphologically defined stages (findings) in naturalhistory of AS:
 - fatty streak
 - fibrous plaque
 - complicated plaque

Risk factors of AS
Genetic predisposition (partial)
↑ LDL and VLDL, ↓ HDL levels
↑ lipoprotein apo(a)
hypertension
diabetes mellitus
male gender
↑ plasma homocystein
↑ conc. of haemostatic factors (e.g. fibrinogen, PAI, ...)
metabolic syndrome/ins. resistance
obesity
chronic inflammation
Environmental factors
smoking
physical inactivity
high dietary intake of fat
infection

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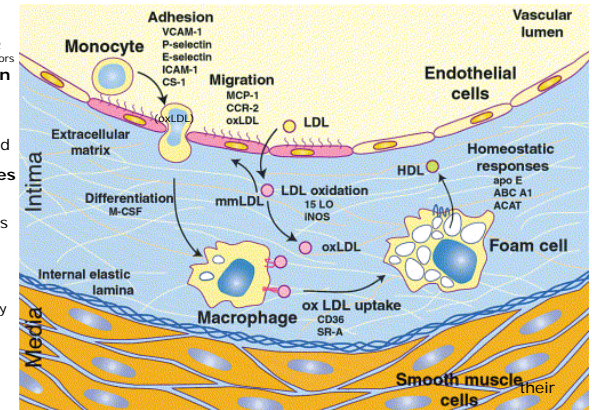
Wall shear stress



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(1) initiation – formation of fatty streak

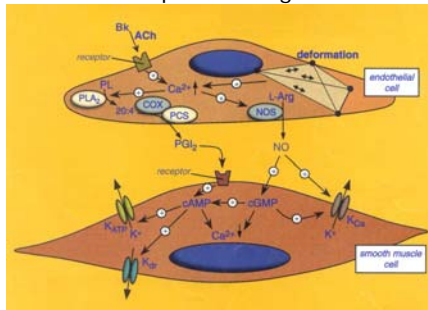
- LDLs can exist in **native** or **modified** forms
 - native LDL is recognised and bound by LDL-R
 - modified LDL is uptaken by scavenger receptors
- in vivo LDL is modified by **oxidation** (or glycation) in circulation and in subendothelial space
 - minimally at first (mmLDL), extensively later (oxLDL)
- 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 lesions are completely absent in AS, finding not entirely understood: it might be because of the particular cytokine spectrum – expression of MCP-1 (monocyte chemoattractant protein) by EC
- macrophages ingest oxLDL via scavenger receptors (SR-A and CD36) and form this was so called **"foam cells"** (= lipid-laden macrophages)
 - 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 acyltransferase) 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



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Endothelial dysfunction

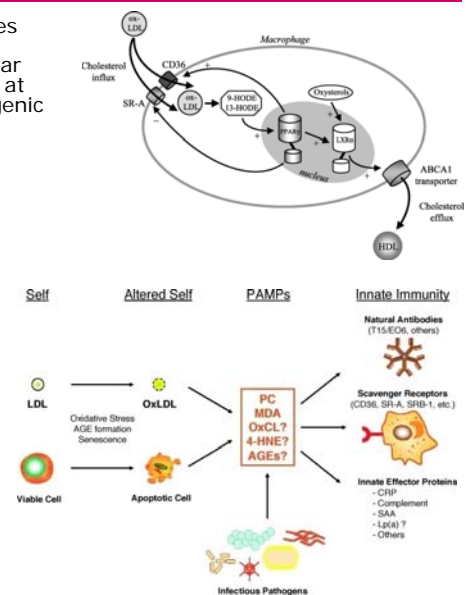
- physiological role of EC
 - smooth muscle cells (SMC) in blood vessels - notably arterioles - work in close association with the overlying ECs
 - action of hormones, neurotransmitters (**ACh**) or deformation of the ECs by flow of blood trigger reactions that influence associated SMC, these effects operates via second messenger systems
 - phospholipase A₂ (**PLA₂**) which activate cyclooxygenase (**COX**) / prostacyclin synthase (**PCS**) to produce prostaglandins (**PGI₂**) 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
- 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, homocystein
 - oxidative stress
 - oxygen radicals formed by smoking, inflammation
 - certain infections (Chlamydia pneumoniae, Helicobacter pylori)



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Role of macrophages

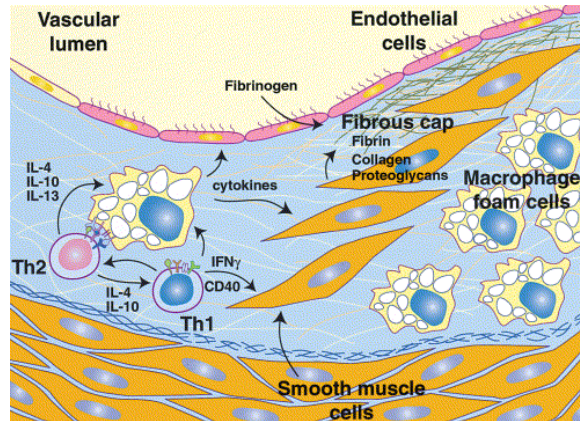
- scavenger receptors** of macrophages for modified macromolecules play physiologically important role in cellular defence against cytotoxic agents, but at the same time they can act as pathogenic mechanisms under the:
 - high CH levels
 - its increased modification
 - oxidation, glycation
 - defective 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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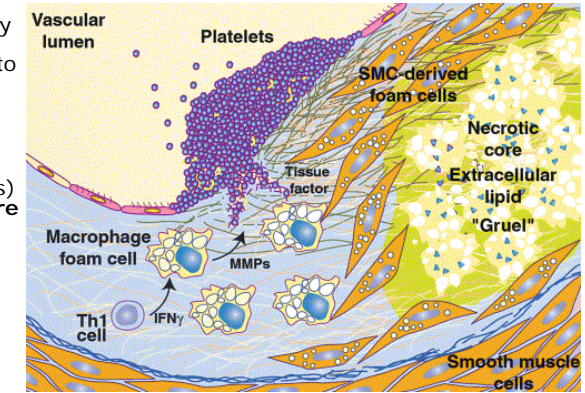
(2) progression – formation of plaque

- 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 typically modified by many factors
- macrophages as antigen-presenting cells help to activate B lymphocytes to wards production of **auto-antibodies** against oxLDL \rightarrow formation of immune complexes \rightarrow inflammation
- cytokines stimulate other cells, mainly **SMCs** of media, to migrate into intima, proliferate (\rightarrow intima thickening) and secrete proteins of extracelullular matrix (**collagen**) \rightarrow **fibrose plaque**
- pathologic **calcification** of atherosclerotic vessel wall is not a passive consequence but result of changed gene expression in macrophages (osteopontin)



(3) complication – rupture and thrombosis

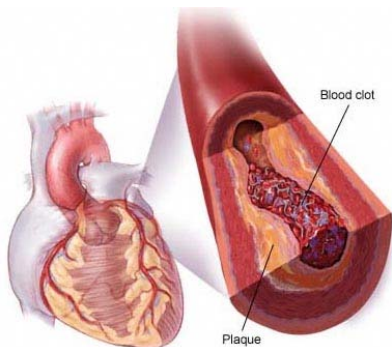
- plaque can grow and slowly obstruct lumen or it can become instable and lead to thrombosis and acute complete obstruction \rightarrow **“complicated plaque”**
- intimal macrophages and SMC die (necrosis and cytokine-induced apoptosis) and establish **necrotic core of the plaque** with accumulated extracellular CH
- stimulated and hypoxic macrophages produce proteolytic enzymes degrading extracellular matrix proteins (**matrix metalloproteinases, 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 \rightarrow microthrombotisation \rightarrow fibrinolysis \rightarrow healing = **“instable plaque”**



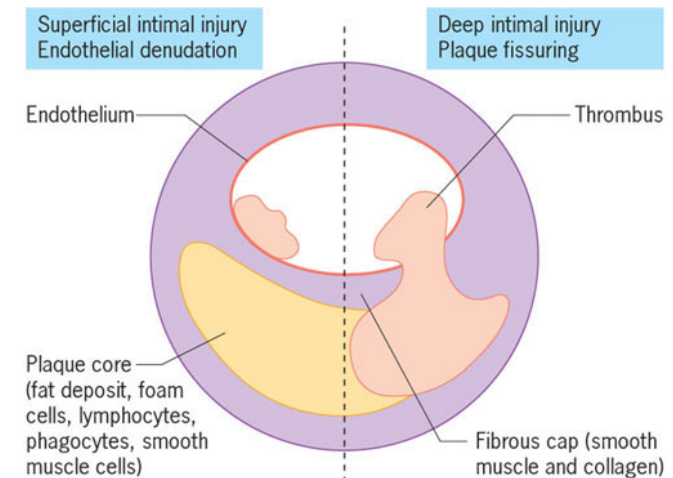
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Thrombosis of the plaque

- 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
- A 50% reduction in luminal diameter causes a **haemodynamically significant stenosis**



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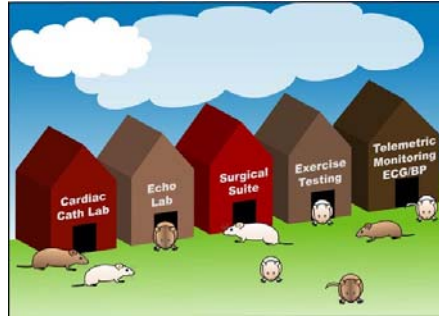


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Animal models of AS - mouse

- 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



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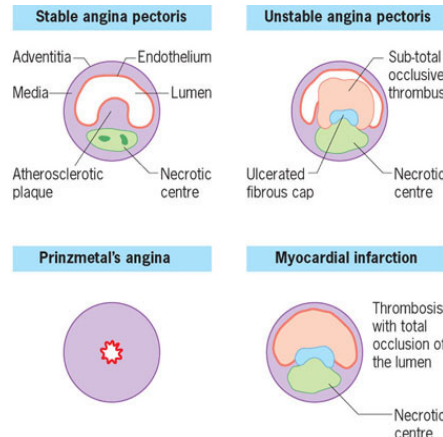
Clinical manifestation of CHD

- chronic ischemic heart disease
 - stable angina pectoris
 - variant/vasospastic angina
 - silent myocardial ischemia
- acute coronary syndromes
 - unstable angina
 - myocardial infarction
 - subendocardial (no ST-segment elevation)
 - transmural (ST-segment elevation)

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Angina pectoris

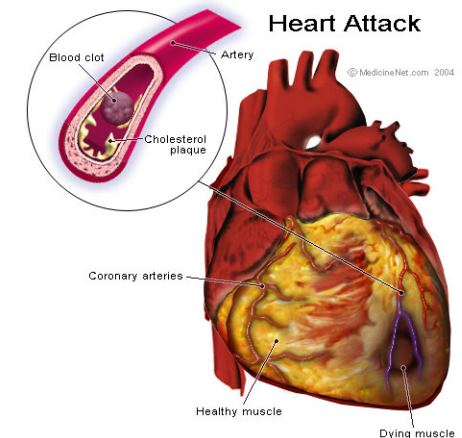
- diagnosis of angina is largely based on the clinical history
 - the chest pain is generally described as 'heavy', 'tight' or 'gripping'
 - typically, the pain is central/retrosternal and may radiate to the jaw and/or arms
 - it can range from a mild ache to a most severe pain that provokes sweating 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)



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Myocardial infarction (MI)

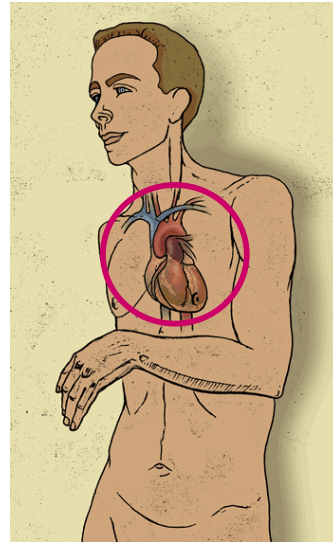
- result of the plaque rupture with superadded thrombus
 - occlusive thrombus consists of a platelet-rich core ('white clot') and a surrounding fibrin-rich ('red') clot
 - irreversible changes develop 20-40 min after complete occlusion of the artery
 - 6 hours after the onset of infarction, the myocardium 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



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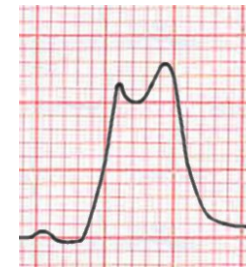
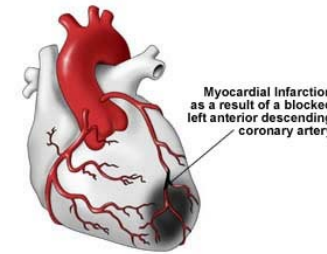
Clinical features of MI

- 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



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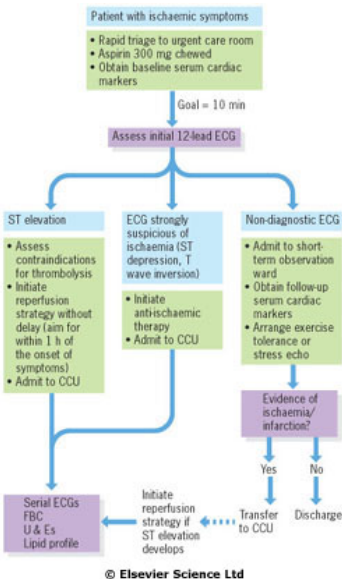
Localisation and extent of MI



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

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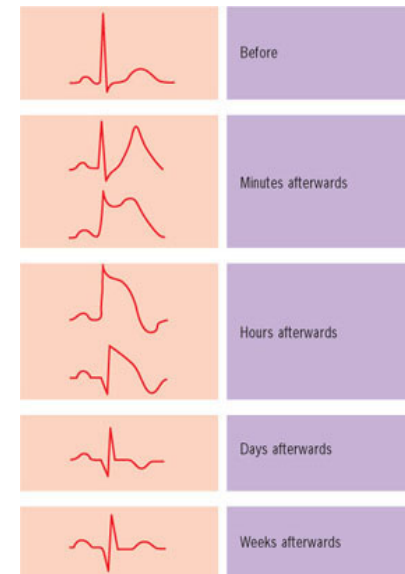
MI diagnosis



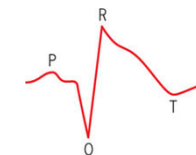
- requires at least two of the following:
 - a history of chest pain
 - evolving ECG changes in respective leads
 - a rise in cardiac enzymes or troponins

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

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 ≥ 1 mm 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 - creatin kinase**

- 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

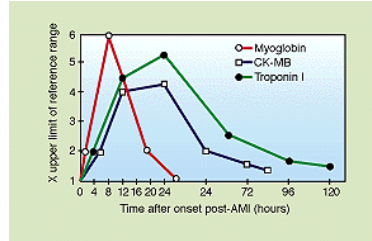
– **Troponins I and T**

- 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

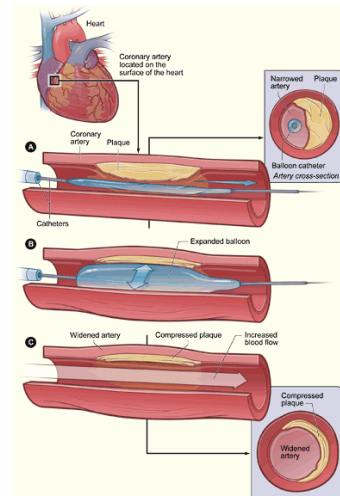
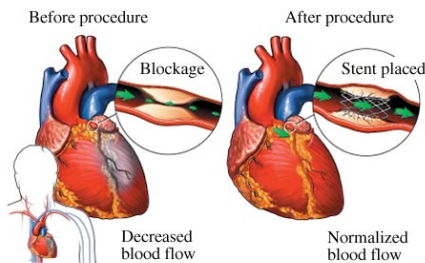
later

- recurrent infarction
- unstable angina
- thromboembolism
- mitral valve regurgitation
- ventricular septal or free wall rupture

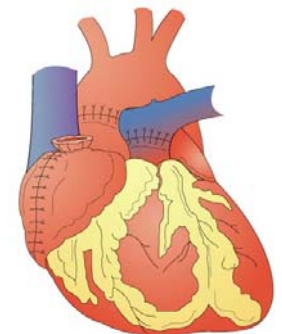
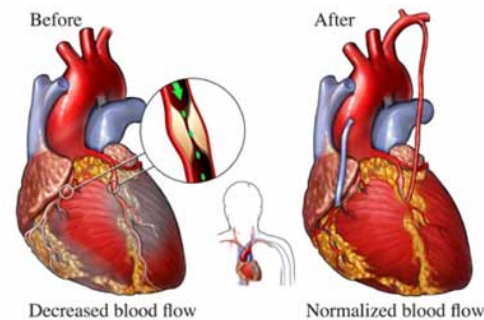
late complications

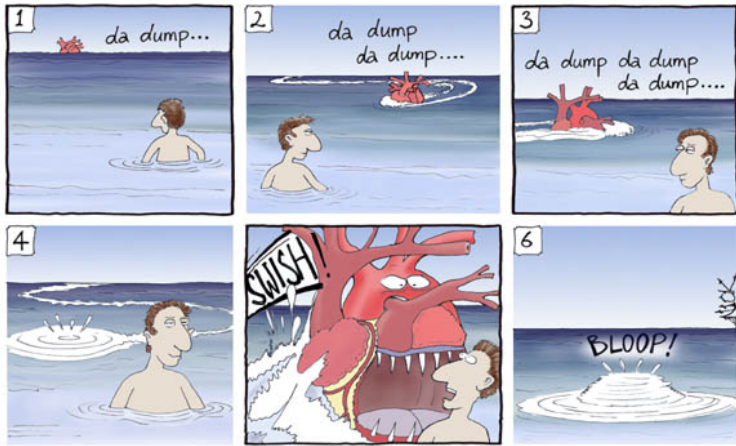
- post-MI syndrome (Dressler's syndrome)
- ventricular aneurysm
- recurrent cardiac arrhythmias

Acute interventions



Follow-up interventions





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