Coronary heart/artery disease (CHD/CAD)

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

Myocardial metabolism

- heart has to continually perform 2 processes:
  - **autonomy** = 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
    - 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!!

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
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

Factors influencing myocardial O2 consumption

- (1) wall tension
  - that's why O2 demand is ↑ in pressure or volume overload
- (2) contractility
- (3) heart rate
  - that's why (i.e. 2 & 3) O2 demand is ↑ during sympathetic activation
- (4) myocardial mass
  - that's why O2 demand is ↑ in cardiac hypertrophy

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

Why hypertrophy does not ↓ O2 consumption at the end

- hypertrophy normalizes wall tension per gram of myocardium
  - initially, it does reduces O2 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 O2 increases as well
  - myocardial hypertrophy is not paralleled by similar growth of coronary bed

Coronary blood flow – quantitative aspects

- amount of oxygen supplied by the coronary blood (VO2): ~45ml O2/min
  - VO2 = Qm x CaO2
    - Qm = 210–240ml/min in the resting state (1000–1200ml/min during the exercise)
    - CaO2 = 200ml O2/l
      - for PaO2 = 13.3kPa and c[Hb] = 150g/l

- consumption in the resting state: ~30ml O2/min (65–70%)
  - very high O2 extraction (A-VO2 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
Coronary blood flow - autoregulation

- autoregulation tightly coupled to the oxygen demand
  - between 60 to 200 mm 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

- factors:
  - (1) 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
  - (2) nitric oxide
    - an important regulator of coronary blood flow, produced by endothelial nitric oxide synthase
  - (3) sympathetic activation
    - ß1-receptor (more than ß1-receptor) activation results in coronary vasodilation (plus increased heart rate, contractility)

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

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 disease (CAD)
    - thrombembolism
  - (2) dynamic obstruction
    - vascular spasm
  - (3) "small vessel disease"
    - diabetic angiopathy
    - polyarteritis nodosa
    - systemic lupus erythematoses
  - (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 ischaemia is the most commonly occurs as a result of coronary atherosclerosis

CHD due to atherosclerosis

- AS is a degenerative process characterized 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 (= atherosclerosis)
  - 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 ethiopathogenesis
  - (1) modified lipoproteins (LDL)
  - (2) monocyte-derived macrophages
  - (3) T lymphocytes
  - (4) normal cells of vessel wall (smooth muscle cells)
- morphologically defined stages (findings) in natural history of AS:
  - (1) fatty streak
  - (2) fibrous plaque
  - (3) complicated plaque

Risk factors of AS

<table>
<thead>
<tr>
<th>Genetic predisposition (partial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ LDL and VLDL, ↓ HDL levels</td>
</tr>
<tr>
<td>↑ lipoprotein apo(a)</td>
</tr>
<tr>
<td>hypertension</td>
</tr>
<tr>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>male gender</td>
</tr>
<tr>
<td>plasma homocystein</td>
</tr>
<tr>
<td>conc. of haemostatic factors (e.g. fibrinogen, PAI, ..)</td>
</tr>
<tr>
<td>metabolic syndrome/ins. resistance</td>
</tr>
<tr>
<td>obesity</td>
</tr>
<tr>
<td>chronic inflammation</td>
</tr>
</tbody>
</table>

Environmental factors

| smoking |
| physical inactivity |
| high dietary intake of fat |
| infection |
### Wall shear stress

- **Coronary Arteries of the Heart**
  - Right Coronary Artery
  - Left Coronary Artery
  - Circumflex
  - Obtuse Marginal
  - Diagonals
  - Acute Marginal
  - Left Anterior Descending
  - Right Anterior Descending

- **Tensile stress**
  - **Compressive stress**

### 13

**Wall shear stress**

- **Initiation – formation of fatty streak**
  - LDLs can exist in native or modified forms
    - native LDL is recognized 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 adhesion molecules (VCAM, ICAM, selectins) by EC
  - Monocytes and T lymphocytes adhere to endothelium and migrate 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 chemotactic 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
    - oxidised molecules (i.e. particular epitopes) are very often similar to PAMP

### 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 triggers reactions that influence associated SMC; these effects operate via second messenger systems
    - Phospholipase A2 (PLA2) which activate cyclooxygenase (COX) / prostacyclin synthase (PCS) to produce prostaglandins (PG) which diffuse readily through the tissue fluids to act on SMC
    - Alternatively, nitric oxide synthase (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
    - Biochemical abnormalities
    - Glucose, modified proteins incl. LDL, homocysteine
    - Oxidative stress
    - Oxygen radicals formed by smoking, inflammation
    - Certain infections (Chlamydia pneumoniae, Helicobacter pylori)

### 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**
    - 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 (PRRs)
        - SR-A, CD36, TLR (Toll-like receptor)
  - Oxidised molecules (i.e. particular epitopes) are very often similar to PAMP

---

**Note:** The diagrams include additional information that is not transcribed here. The focus is on the textual content that is relevant to understanding the processes described.
(2) progression – formation of plaque

- Immunologic interaction between macrophages and T lymphocytes (Th1 and Th2 subpopulation) 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 towards 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 extracellular matrix (collagen) → 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 → "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 → microthrombotsiation → 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
- A 50% reduction in luminal diameter causes a haemodynamically significant stenosis
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 (no ST-segment elevation)
    - transmural (ST-segment elevation)

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 degree 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)

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
    - ascendancy
    - 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

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
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 present 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 bifunctional 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.