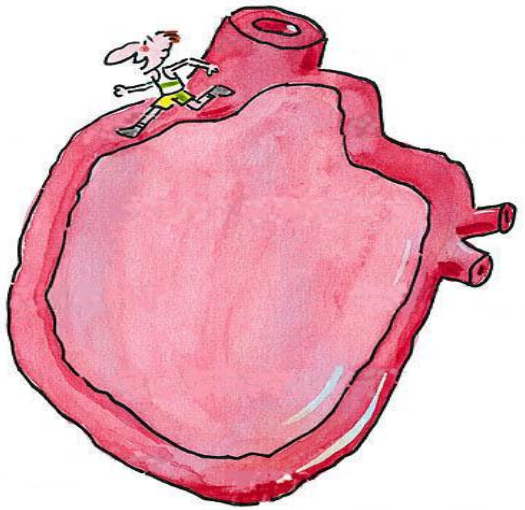
PP of circulatory system – part II:

Myocardial ischemia – compensation
Clinical forms of CAD – angina, MI, sudden death
Ischemic heart disease as a consequence of CAD



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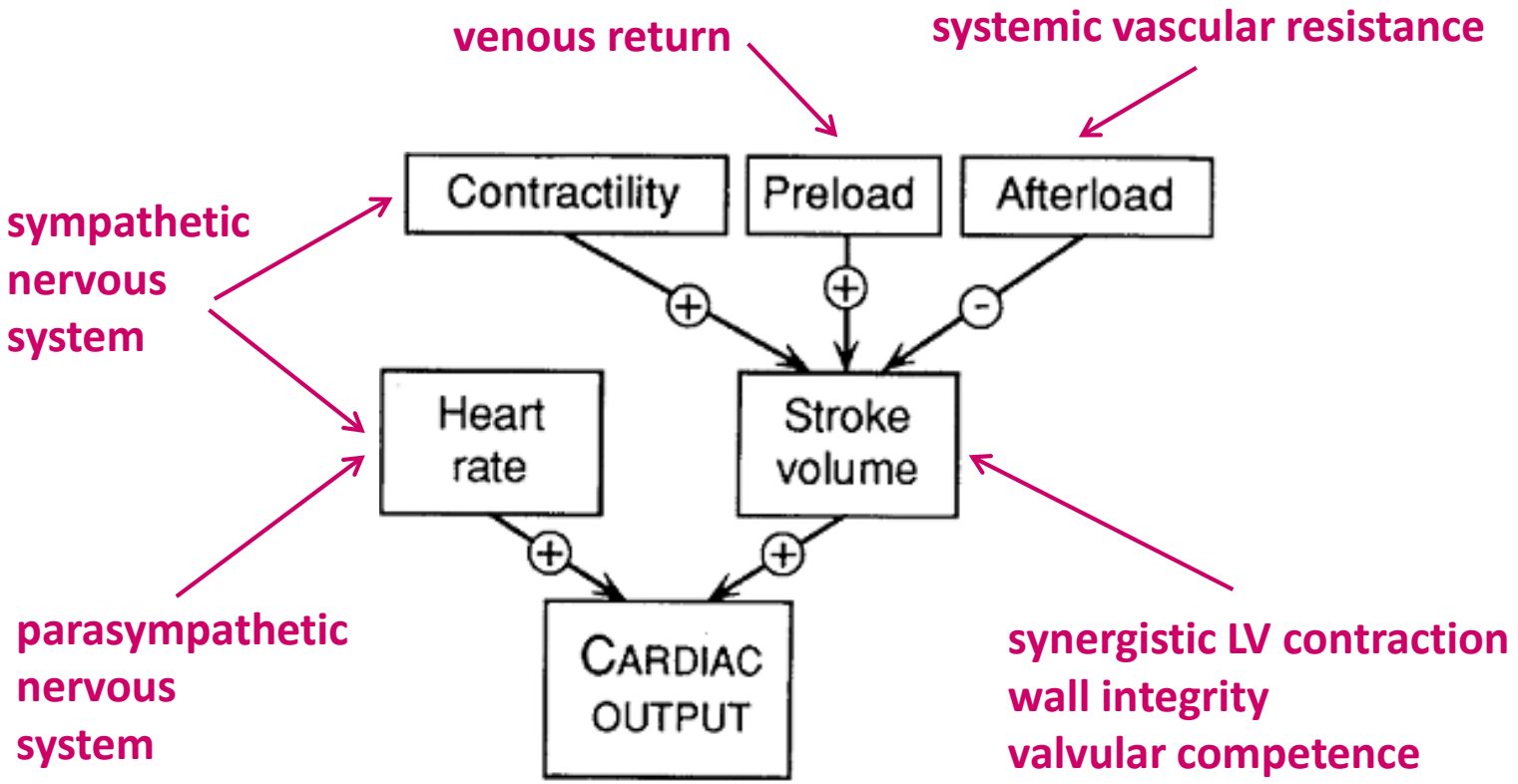
Heart needs a lot of energy (= ATP) to continually perform as a pump (~7,500 L/day, ~ 40 mil beats/year)



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

$$CO = SV \times f$$

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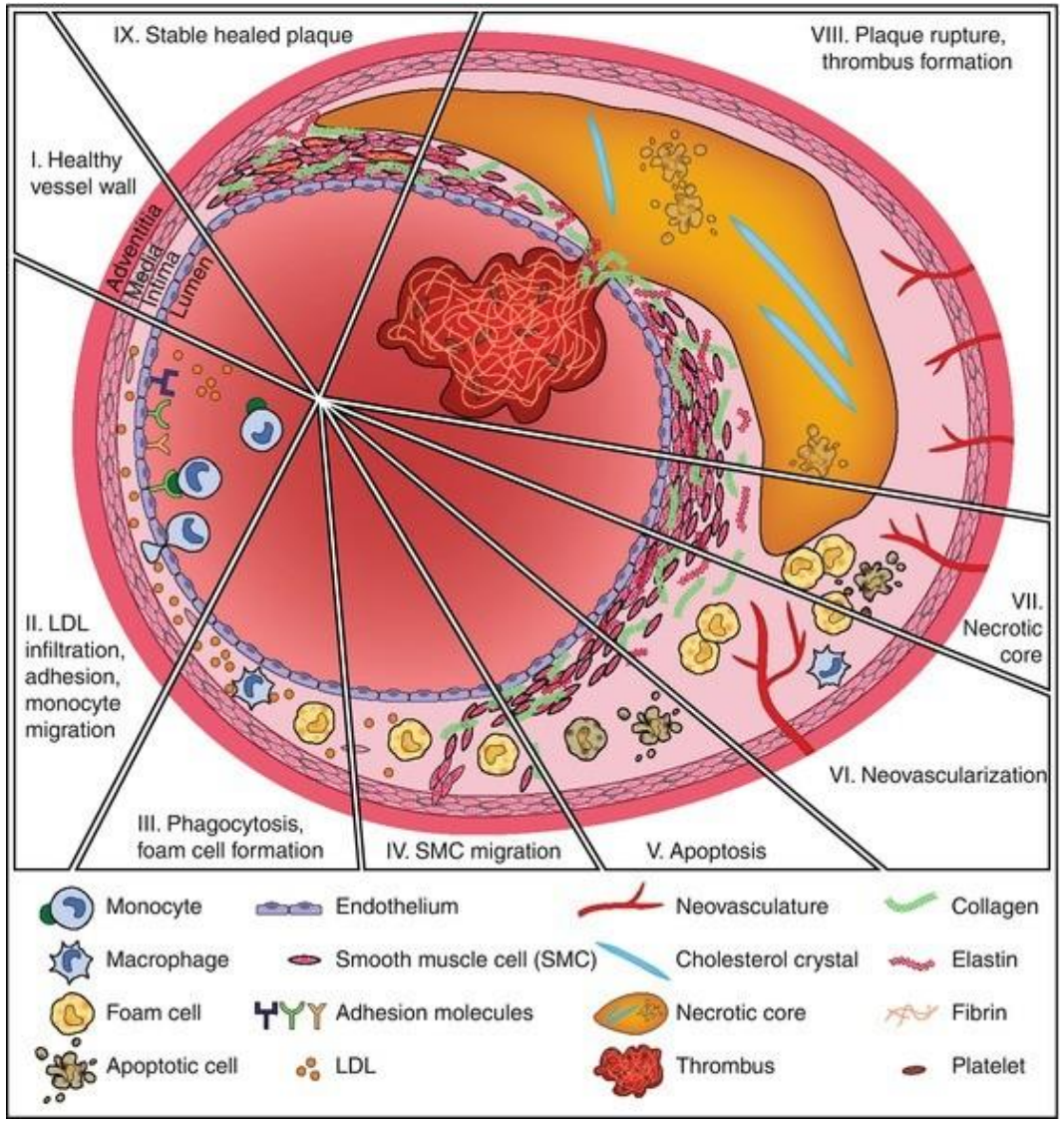
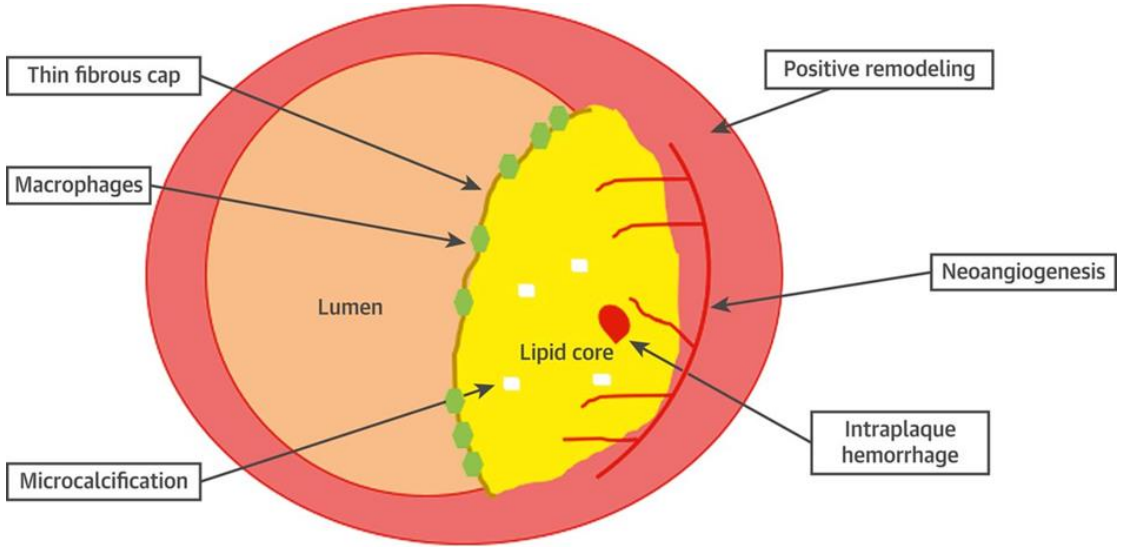
Initiation and progression of AS / vulnerable plaque





- Typical adverse plaque characteristics include
  - macrophage accumulation
  - a large lipid core
  - positive remodelling
  - a thin fibrous cap
  - microcalcification
- Intraplaque microvessels result from angiogenesis driven by hypoxia and inflammatory stimuli within the necrotic core
  - these vessels can result in intraplaque hemorrhage, which increases the risk of plaque destabilization

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Vulnerable plaque vs. vulnerable patient

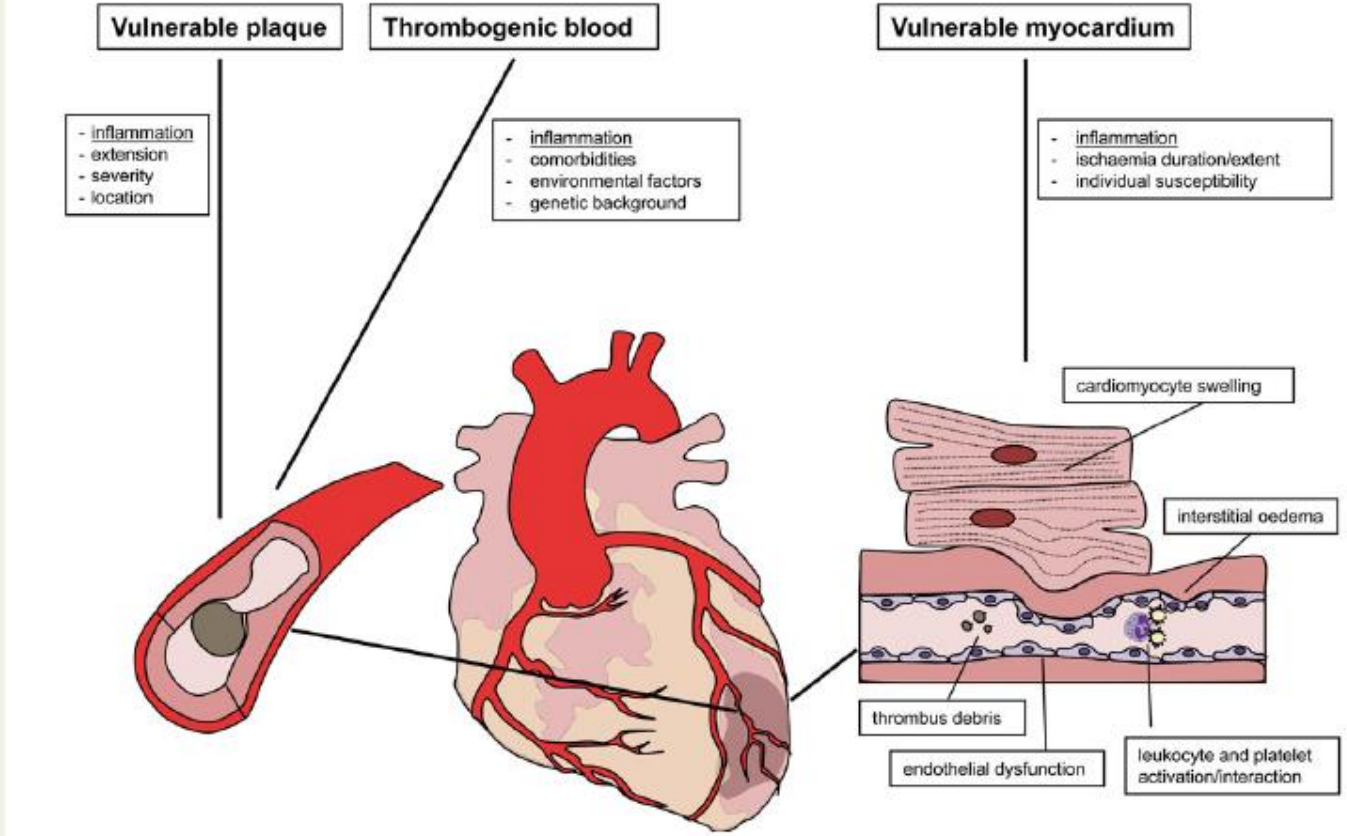

Figure 1 Critical determinants of myocardial infarction injury. The overlapping of vulnerable plaque and thrombogenic blood are critical determinants for myocardial infarction occurrence and extension. In addition, myocardium vulnerability, which is largely due to coronary microvascular dysfunction, contributes to extension and severity of ischaemic injury. In the most severe form (known as no-reflow), structural and functional impairment sustain vascular obstruction. Endothelial dysfunction triggers leukocyte and platelet activation/interaction, whereas thrombus debris may worsen the obstruction. Furthermore, cardiomyocyte swelling, interstitial oedema, and tissue inflammation promote extravascular compression.

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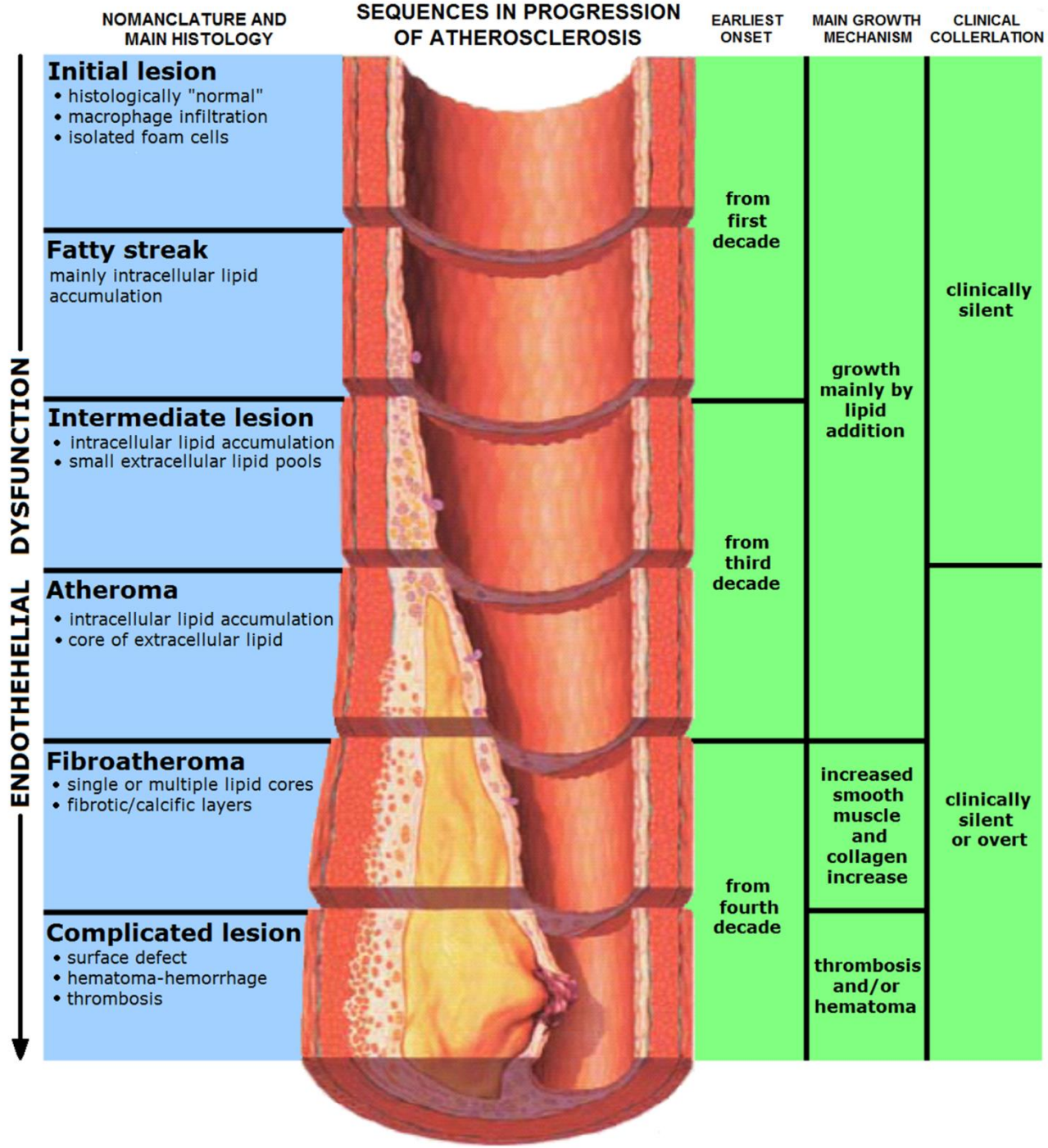
NOMANCLATURE AND MAIN HISTOLOGY
SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS
EARLIEST ONSET
MAIN GROWTH MECHANISM
CLINICAL COLLERLATION
ENDOTHEHELIAL DYSFUNCTION
Initial lesion
• histologically "normal"
• macrophage infiltration
• isolated foam cells
Fatty streak
mainly intracellular lipid accumulation
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

MYOCARDIAL ISCHEMIA AS A CONSEQUENCE OF CHD

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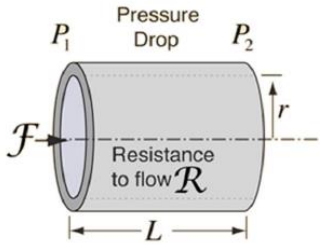
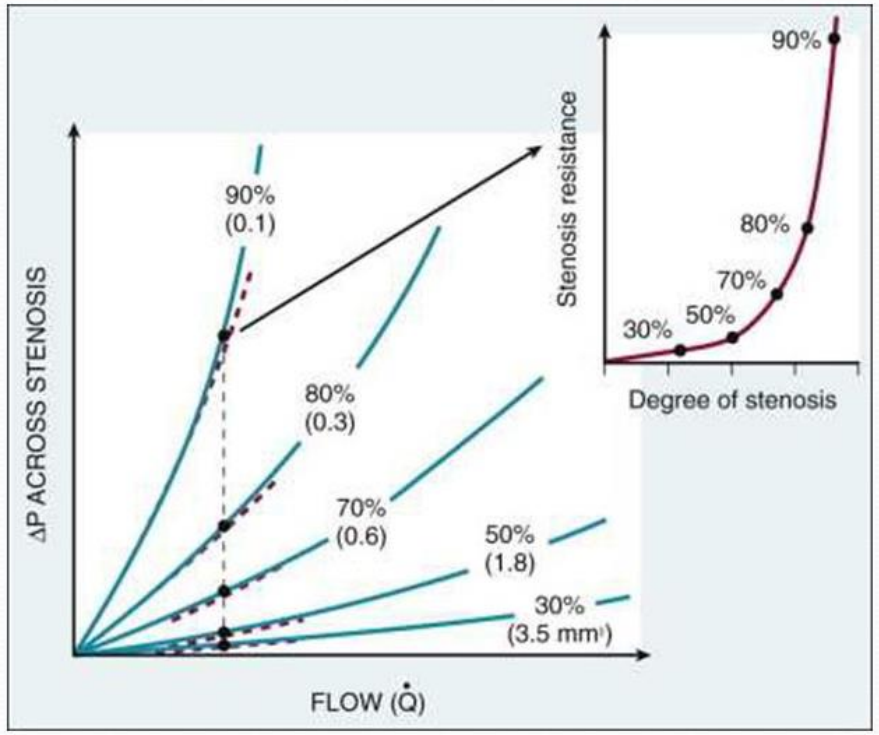
Coronary artery stenosis – haemodynamic consequences

Poiseuille's Law

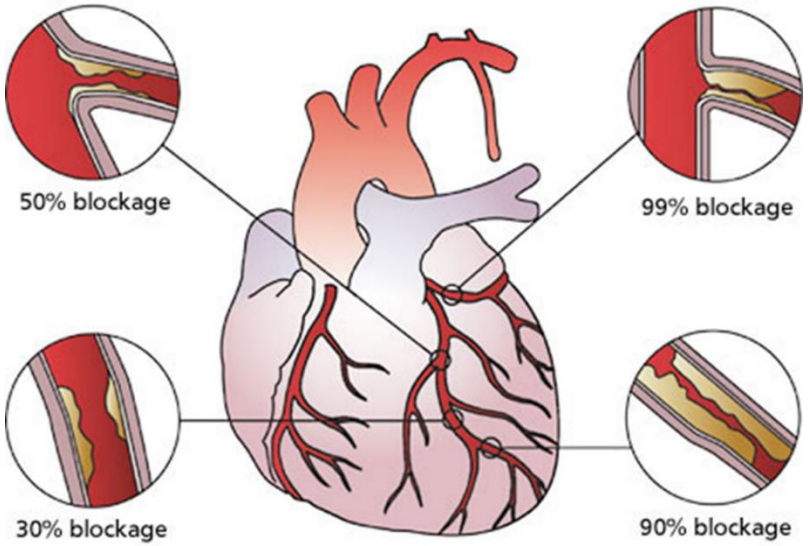
Volume Flowrate $= \mathcal{F} = \frac{P_1 - P_2}{\mathcal{R}}$

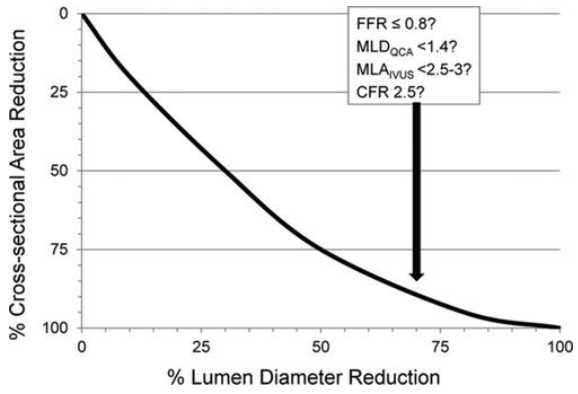
Resistance to Flow $\mathcal{R} = \frac{8\eta L}{\pi r^4}$





- change in vessel **diameter** (i.e. cross-sectional luminal area) produces by far the most significant effect
  - haemodynamically significant stenosis manifests usually after a significant (>50%) reduction in cross-sectional luminal area
  - concomitant factors modify the **severity of myocardial ischemia** significantly
    - condition of microcirculation (endothelial dysfunction)
    - heart rate
    - hypoxia/anemia, hypovolemia
    - aortic stenosis, LV hypertrophy
    - dynamic stenosis (thrombus, excentric plaque, vasospasm)





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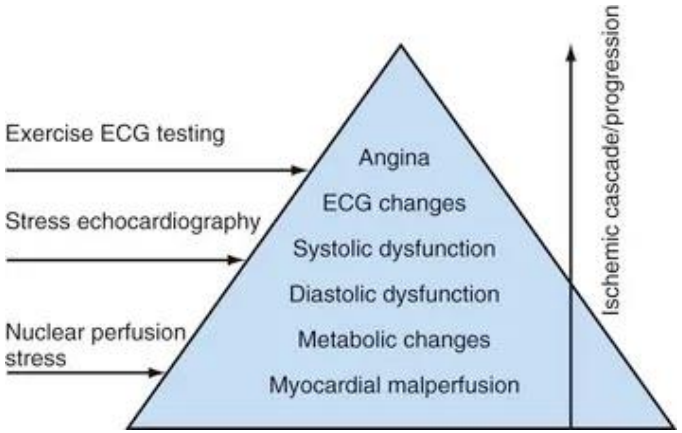
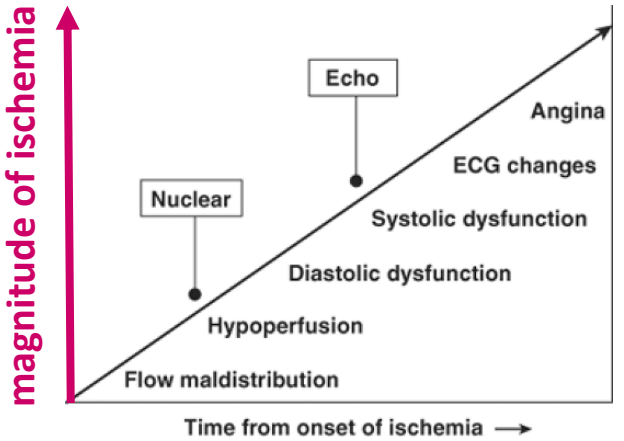
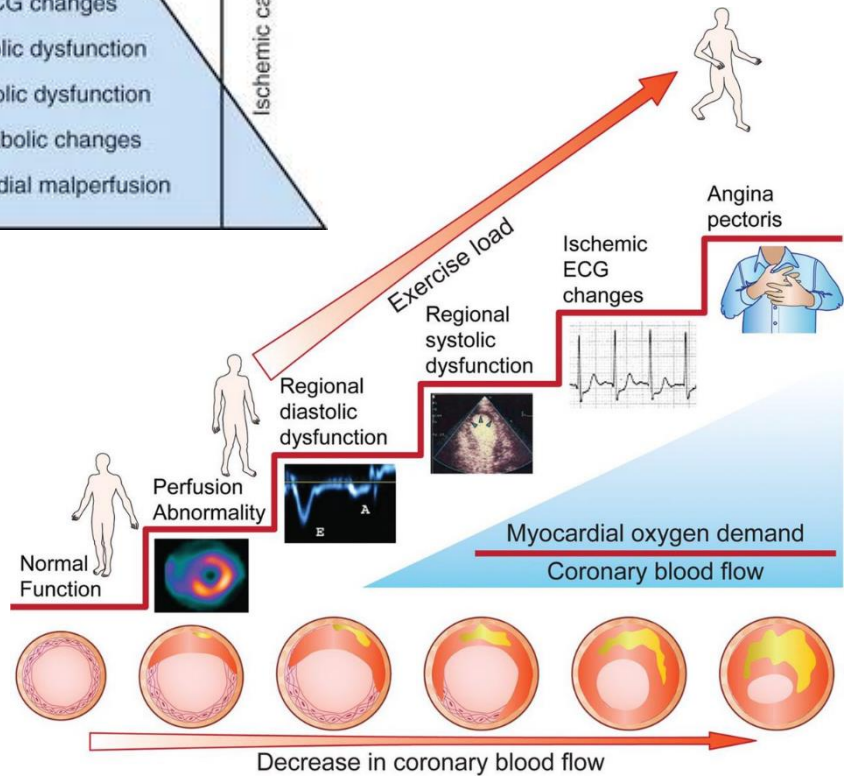
Metabolic and functional consequences of ischaemia

- metabolic changes
  - ↓ perfusion → O2 → ↓ aerobic metabolism → ATP depletion → ↓ creatine phosphate → accumulation of lactate and other catabolites → metabolic acidosis → efflux of potassium into extracellular space → loss of membrane function and cellular integrity → cardiomyocyte death
  - accumulation of K+, lactate, serotonin and ADP causes ischemic pain (**angina**)
- functional changes
  - ↓ contractility (= systolic dysfunction)
    - ↓ EF (ejection fraction), ↓ SV (stroke volume)
  - ↓ diastolic relaxation (= diastolic dysfunction)
    - ↑ EDP (end-diastolic pressure)
- clinical signs are „tip of the iceberg“
  - earlier changes detectable diagnostically

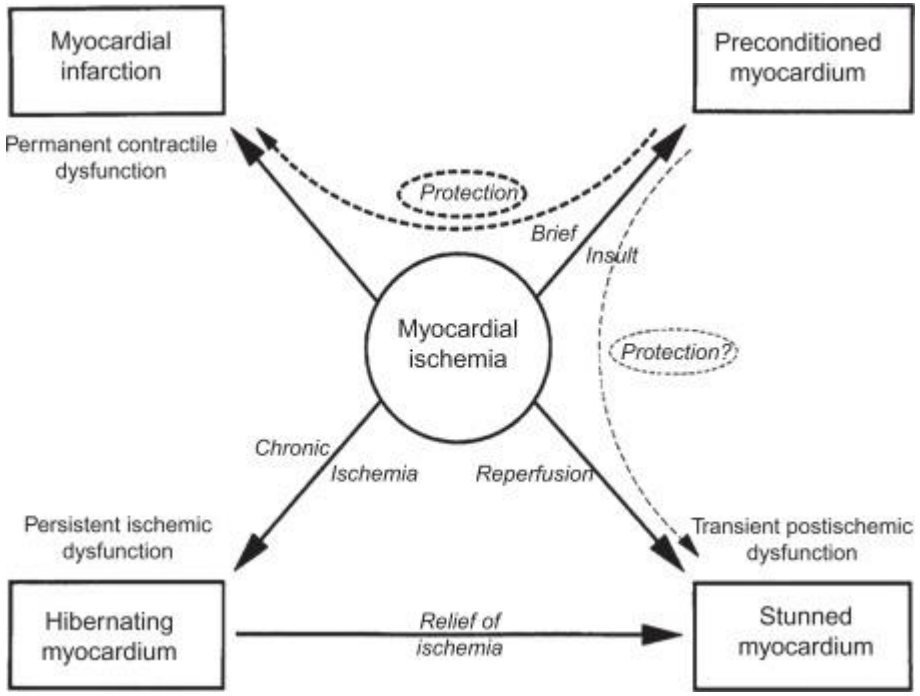






Consequences of myocardial injury – graded and often co-occurring

- reversible brief / intermittent injury (ischemia) = **preconditioning**
  - due to fixed stenosis and oxygen supply-demand mismatch or pharmacologically
  - molecular mechanisms involve iNOS, COX-2, mitochondrial K-ATP channels
- prolonged ischemia followed by reperfusion = **stunned myocardium**
  - depression of myocardial function despite restored flow
  - function spontaneously normalises in days – weeks
- chronic reduction of flow (at rest) = **hibernating myocardium**
  - myocyte apoptosis, myofilament autophagy, loss of B-adrenergic responsiveness and inhomogeneity in sympathetic activity, fibrosis
  - clinically: arrhythmia (V tachycardia and fibrillation) risk! and LV dysfunction
- irreversible injury and myocyte death = **myocardial infarction**
  - after ~20 min from occlusion coronary artery in then absence of significant collaterals
  - begins in the subendocardium and spreads as a wavefront towards epicardium
  - transmural death completed after 4 - 6 hrs
    - depends on the presence of other factors increasing oxygen consumption, such as tachycardia, anaemia, hypovolemia, and the degree of preconditioning



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Causes of myocardial ischemia other than AS

- zany condition leading to oxygen supply/demand mismatch can cause myocardial ischemia
- causes:
  - (1) reduction of coronary perfusion due to fixed mechanic obstruction
    - (a) coronary AS (with or without superimposed thrombotisation)

    by far the most common cause (~ 90%)
    - (b) thromboembolism (from distant site – e.g. atrial or ventricular thrombus, bacterial endocarditis etc.)
  - (2) dynamic obstruction due to vascular spasm
  - (3) "small vessel disease"
    - diabetic microangiopathy, polyarteritis nodosa, systemic lupus erythematosus, autoimmune vasculitis
  - (4) hypoxemia, hypoxia, hypotension
    - pulmonary disease, anaemia, abnormal haemoglobin, poisoning, shock, sepsis, …
  - (5) exaggerated oxygen demand
    - ↑↑↑ CO (e.g. thyrotoxicosis, amphetamine or cocaine abuse, …)
    - LV hypertrophy as a consequence of pressure (volume) overload
  - (6) polycythaemia, hyper-coagulation, DIC
- causes (1) and (2) affect larger arteries and branches (ischemia more epicardially)
- causes (3) to (6) smaller terminal branches and often coincide with (1) or (2)
  - note hypoxia ≠ ischemia

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CLINICAL MANIFESTATION OF CAD/CHD/IHD

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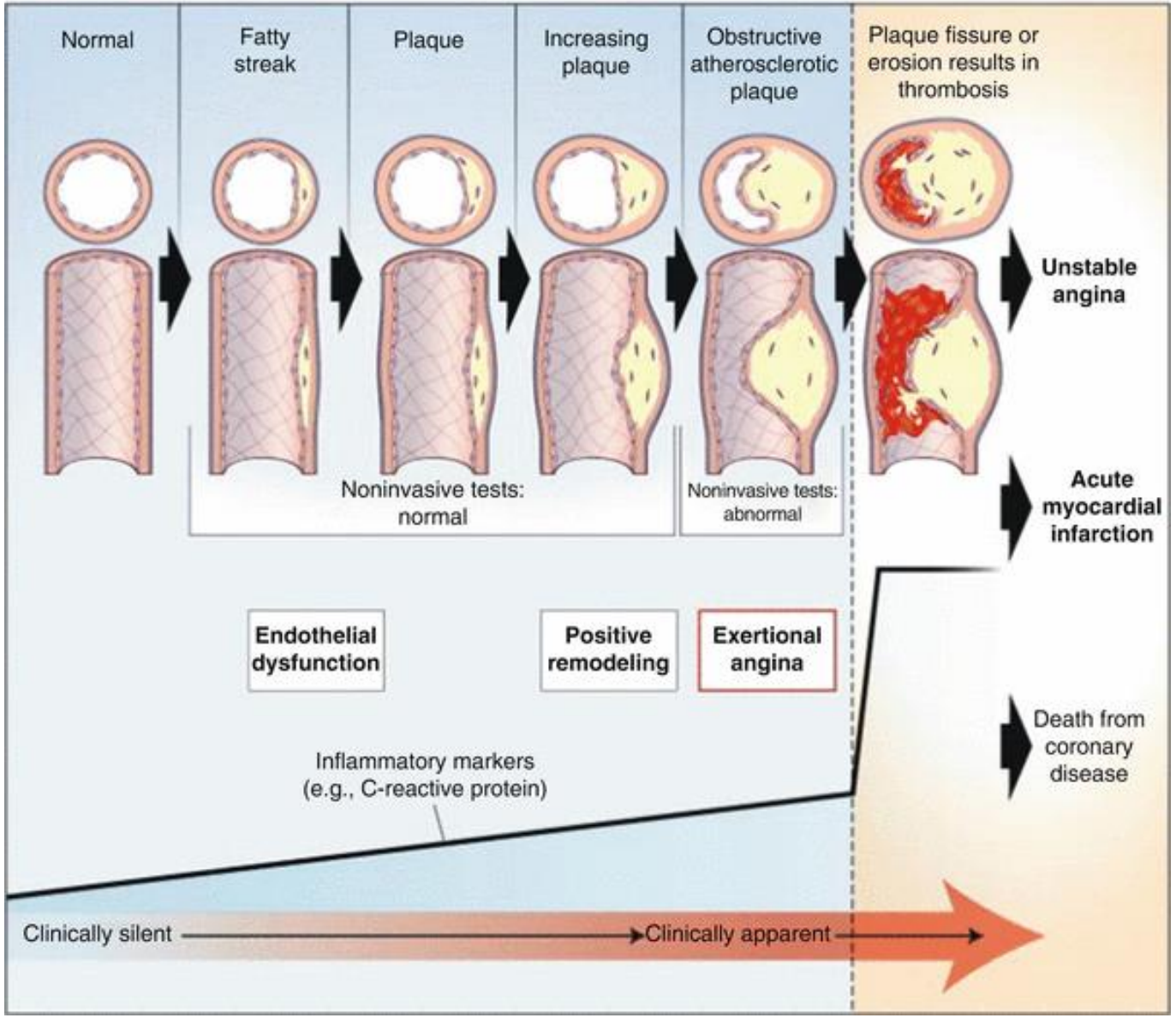
Clinical manifestation is a relatively late event



- the terms
  - coronary artery disease (CAD)
  - coronary heart disease (CHD)
  - ischemic heart disease (IHD)
- can largely be considered synonyms

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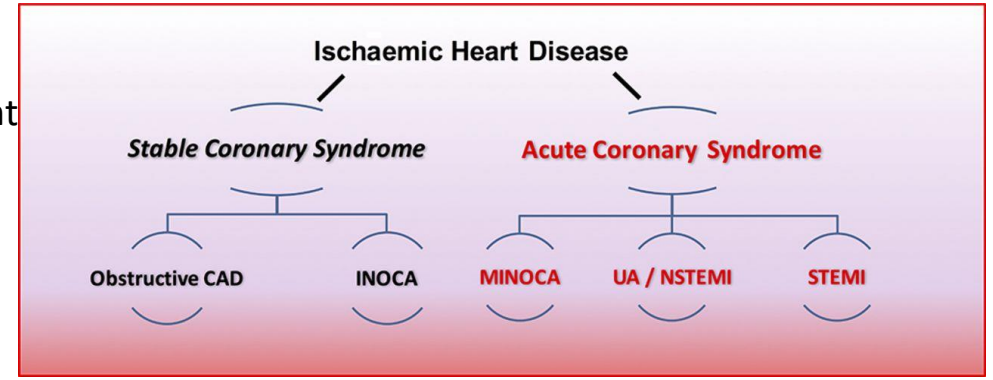
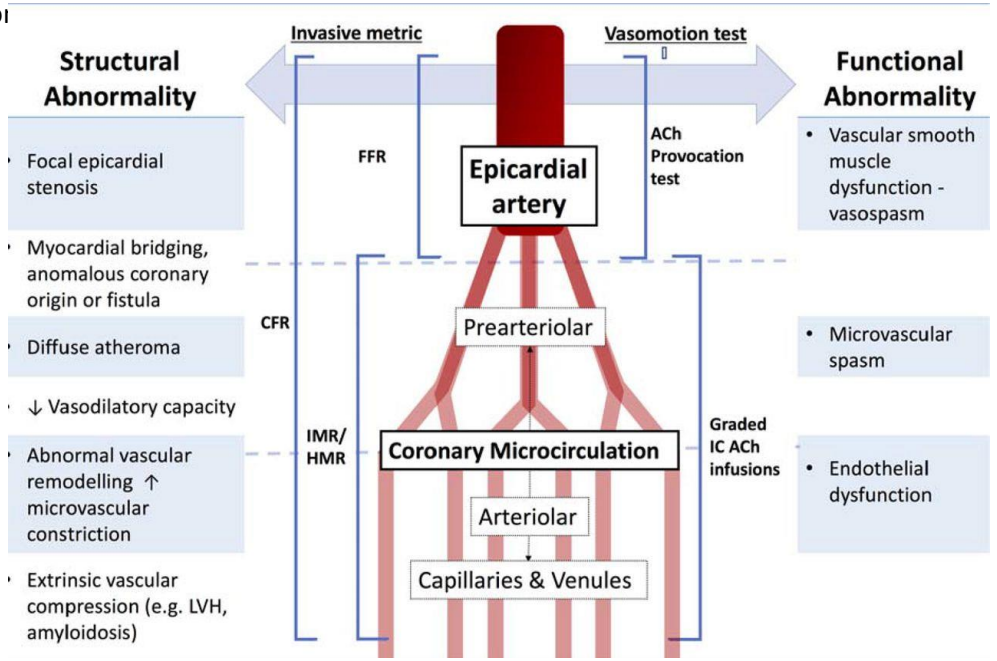
Clinical forms of CAD/CHD/IHD

- CAD/CHD/IHD is the leading global cause of death and lost life years in adults
  - despite reductions in morbidity and mortality in general, these are not consistent across subgroups
- classification/clinical forms
  - **stable coronary syndromes** = stable angina pectoris
    - recurrent, transient episodes of chest pain due to demand-supply mismatch
    - causes
      - obstructive CAD (angiographically proven)
      - INOCA (ischaemia and no obstructive coronary artery disease), formerly „coronary syndrom X“ (negative coronary angiography) – **10-20%**
        - due to coronary microvascular dysfunction (i.e. functional and/or structural abnormalities in the coronary microcirculation
        - due to coronary vasospasm (Prinzmetal variant angina)
        - due to other local or systemic causes (see slide 11)
        - abnormal pain perception
    - **silent myocardial ischemia** (both obstructive and INOCA)
      - sometimes mixed – some episodes of ischemia with chest pain, others silent
  - **acute coronary syndromes**
    - unstable angina
    - myocardial infarction (heart attack) = frank cardiac necrosis
      - STEMI / transmural / Q-wave MI
        - ECG: ST-segment elevation present
      - non-STEMI / subendocardial / non-Q wave MI
        - ECG: ST-segment elevation absent
    - sudden cardiac death due to MI complications (usually ventricular arrhythmias)
  - **heart failure due to IHD**





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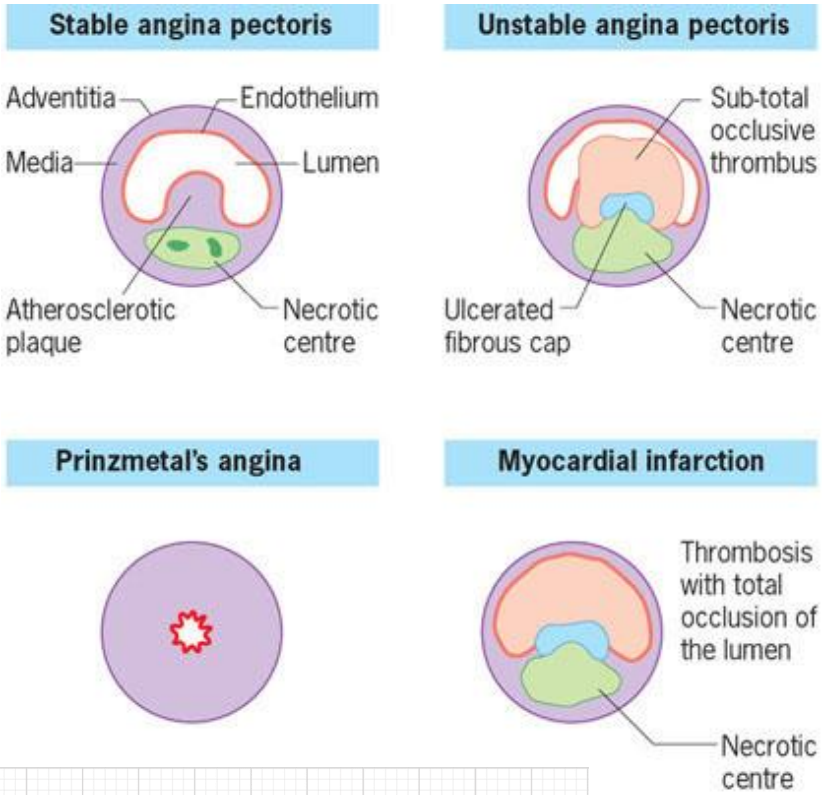
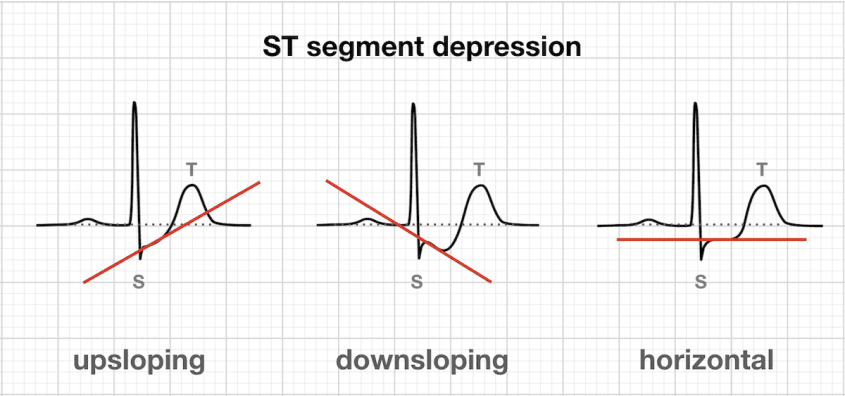
Angina pectoris

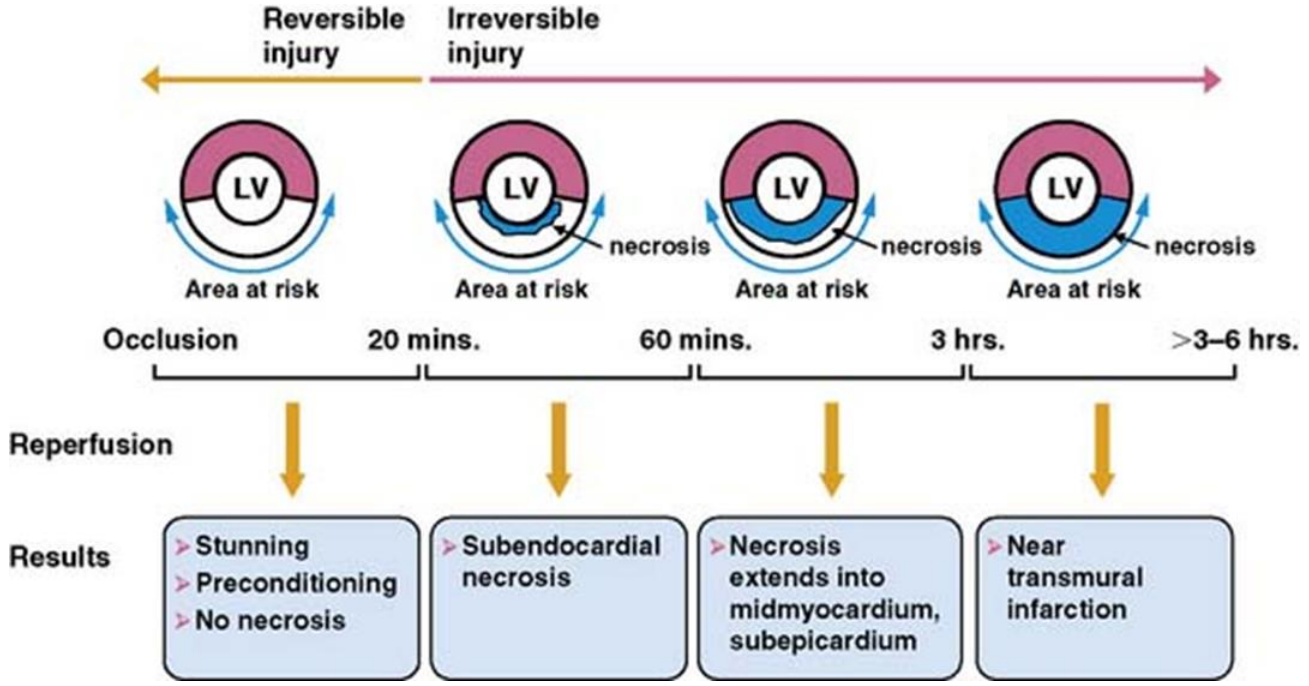
- diagnosis of angina is largely based on the clinical history
  - the chest pain/dyscomfort is generally described as 'heavy', 'tight' or 'gripping‘
  - typically, the pain is central/retrosternal and may radiate to the jaw and/or arms
  - it can range from a mild ache to a most severe pain that provokes sweating and fear, there may be associated breathlessness
  - typically exertional
  - dyspnoea can be a consequence of severe LV dysfunction (↑ LV filling pressure)
  - nocturnal angina in combination with sleep apnoea
  - grading systems
  - ECG finding tent to be normal at rest, ST segment abnormalities (typically depression) during angina
    - additional changes such as LBBB and LAFB associated with impaired LV function and indicate poor prognosis
- types – manifestation:
  - 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)
  - unstable
    - angina of recent onset (less than 1 month)
    - worsening angina (previously stable for certain time)
    - angina at rest
- causes
  - obstructive CAD
  - INOCA
    - cardiac syndrome X
      - personal history of angina + positive exercise test + angiographically normal coronary arteries
      - heterogeneous group (more common in women)
      - due to microvascular abnormalities
    - variant (Prinzmetal) angina
      - occurs without provocation, usually at rest or night, as a result of coronary artery spasm
      - more frequently in women





Myocardial infarction (MI)

- Occlusive thrombus consists of a platelet-rich core ('white clot') and a surrounding fibrin-rich ('red') clot
- The infarct develops in a typical **wave front manner**, starting in the subendocardial layers in the centre of the area at risk and progressing into subepicardial layers and to the border zones of area at risk with ongoing duration of coronary occlusion
  - timing defines the extent of necrosis
    - irreversible changes develop 20-40 min after complete occlusion of the artery – subendocardial non-STEMI
    - speads epicardially
    - in 12-24 hrs STEMI develops
- Therefore, **the size of the resulting infarction** depends on
  - (i) the size of the ischaemic area at risk
    - where the stenosis/occlusion happens
  - (ii) the duration and intermittency of coronary occlusion
    - time of reperfusion (spontaneous or induced)
  - (iii) the magnitude of residual collateral blood flow
  - (iv) preconditioned x hibernating myocardium
  - (v) the extent of coronary microvascular dysfunction
  - (vi) intensity of the pain
    - event. silent



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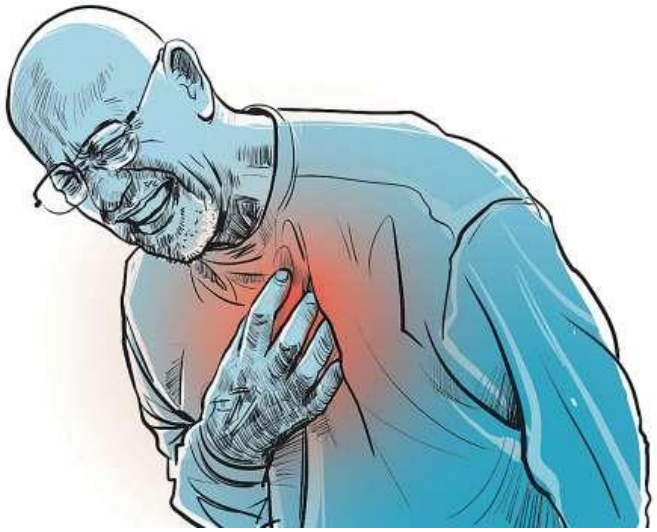
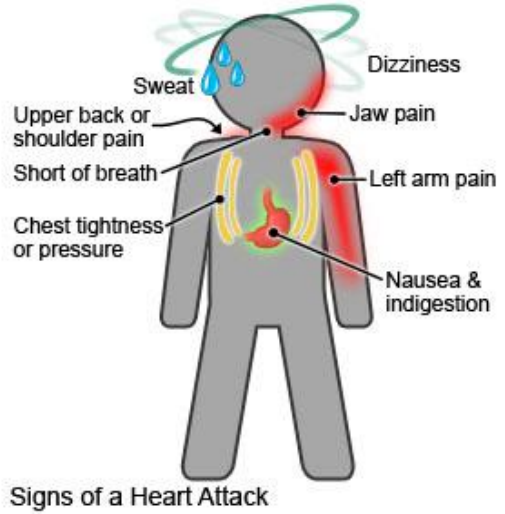
Clinical features of MI

- severe (crushing) 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
- symptoms are produced directly by MI/ischemia (heart, brain, …)
  - chest pain, dizziness,
- or, indirectly, by autonomous nervous system activation
  - sympathetic
    - sinus tachycardia and the fourth heart sound
    - sweating
    - restlessness
  - parasympathetic
    - nausea, vomiting
- pulmonary congestion
  - dyspnoea/breathlessness
- referred pain (back, jaw, shoulder, …) – important for differential diagnosis!
- modest fever (up to 38°C) due to myocardial necrosis often occurs over the course of the first 5 days





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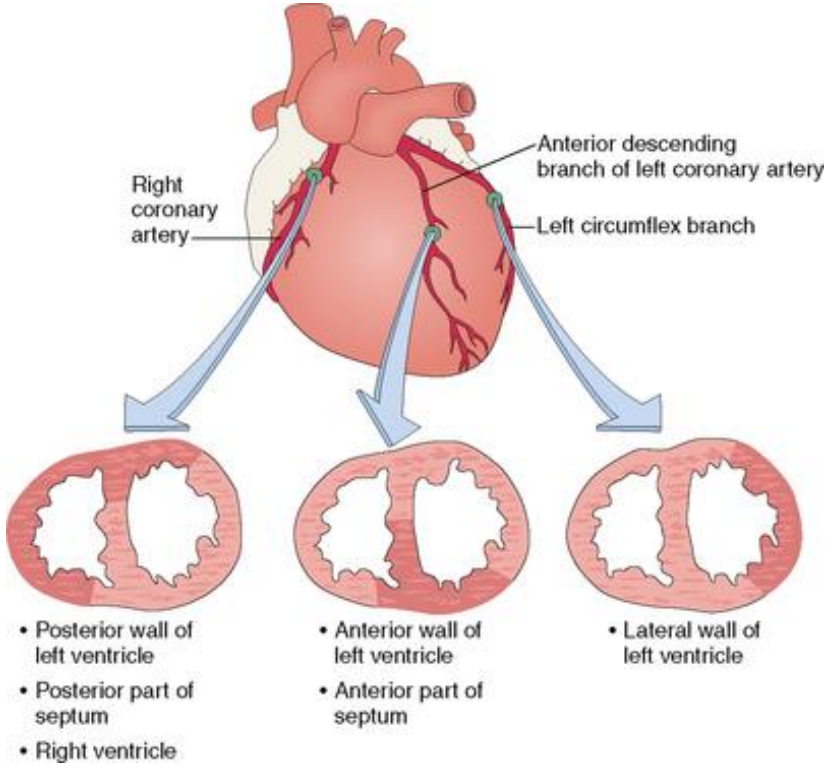
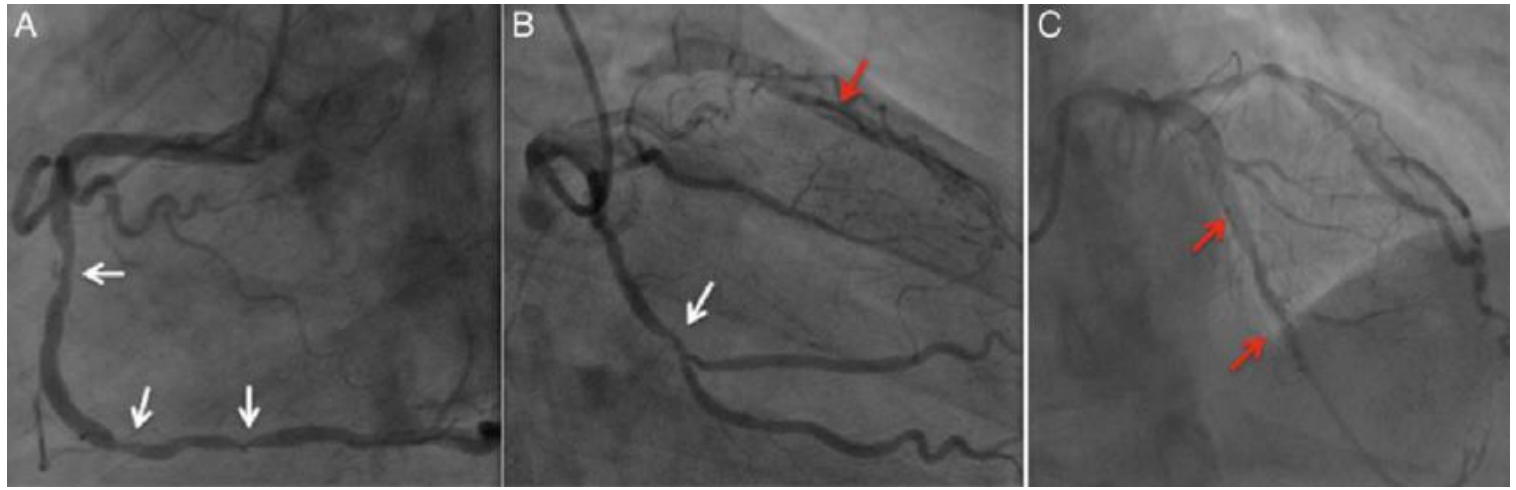
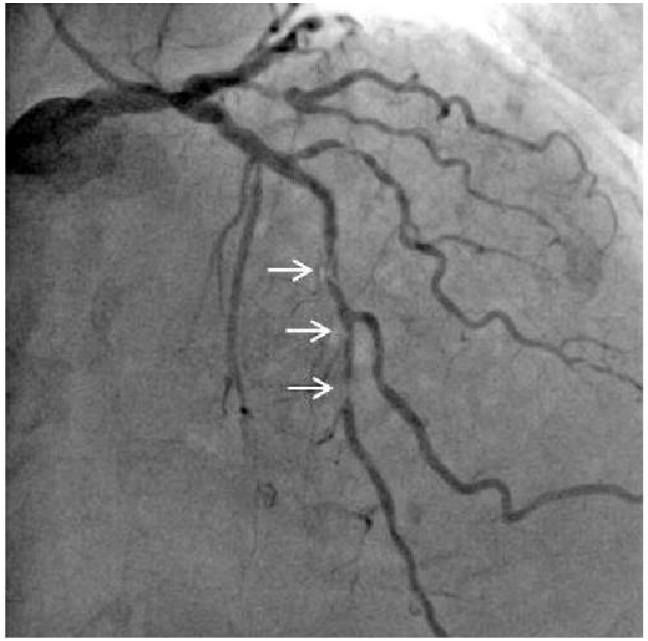
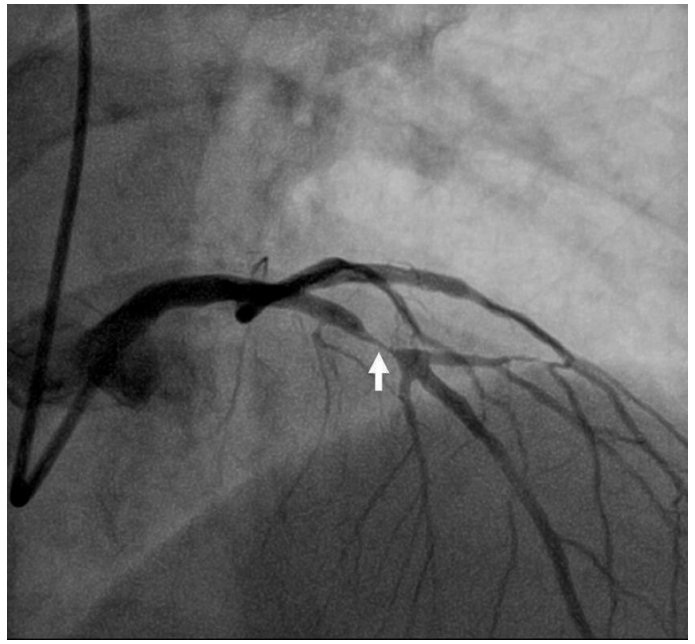
Localisation of MI depends on obstructed artery









- Majority of stenoses and subsequent **ruptures** or **erosions** of an **AS plaque** develop in proximal parts of epicardial arteries (or 1st order branches)
  - thus can be assessed by coronarography
  - stenoses in intramyocardial (penetrating) branches are rare
- LV much more commonly affected
  - 40-50% cases LAD
  - 15-20 % cases LCX
- RV and atria rarely
  - 30-40% cases RCA

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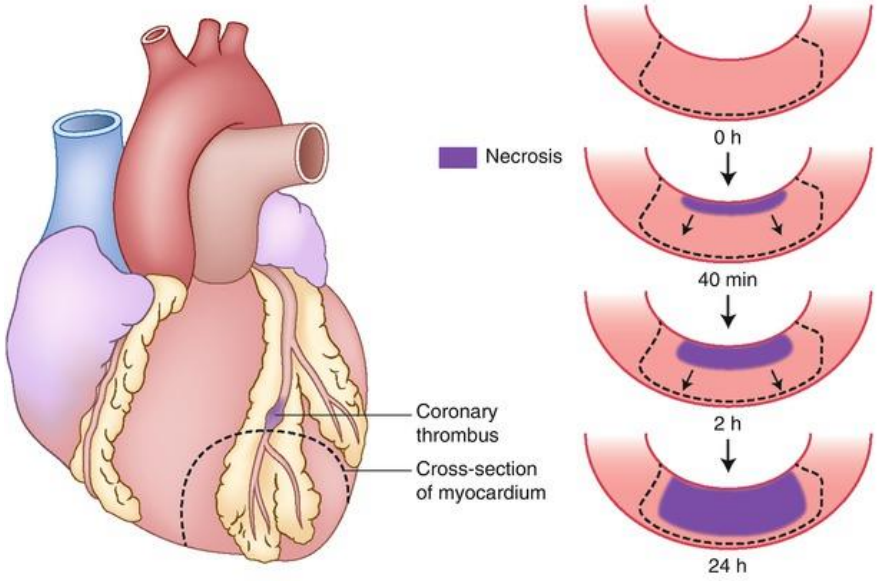
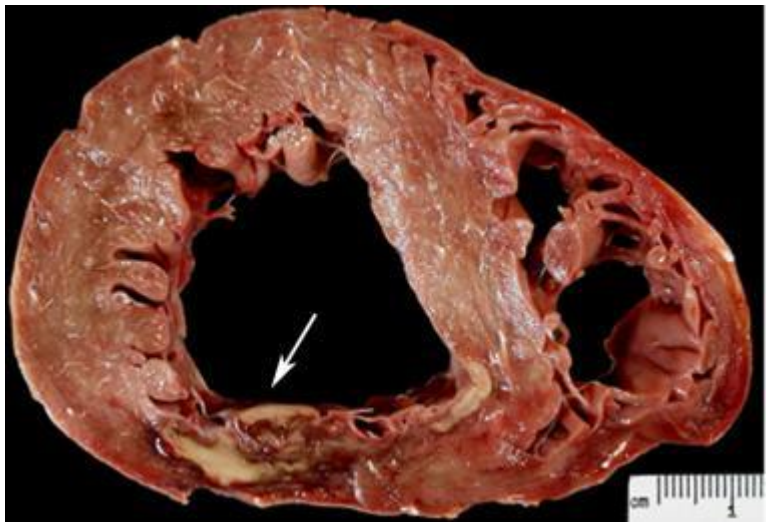
Pathology of MI

- irreversible changes develop 20-40 min after complete occlusion of the artery
  - swelling, electrolyte abnormalities
- 6 hours after the onset of infarction, the myocardium is swollen and pale
  - coagulation necrosis
- in 24 hours the necrotic tissue appears deep red owing to haemorrhage
  - LV wall in infarct zone weakened and dilated
- 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 viable myocardium





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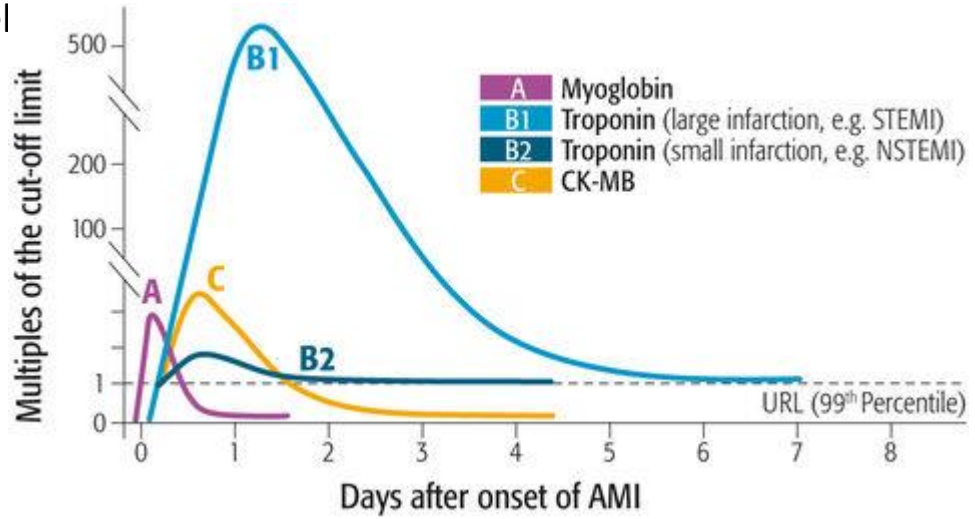
Cardiac markers of myocardial damage / acute MI

- 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 infarction size
    - possibility to detect re-infarcion
  - **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)
    - 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 – 6 hrs after onset of the chest pain, reaching peak level within 16 – 30hrs
  - **Myoglobin**
  - historically AST - aspartate aminotransferase and LDH - lactate del
    - 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 for confirming myocardial infarction in patients presenting several days after



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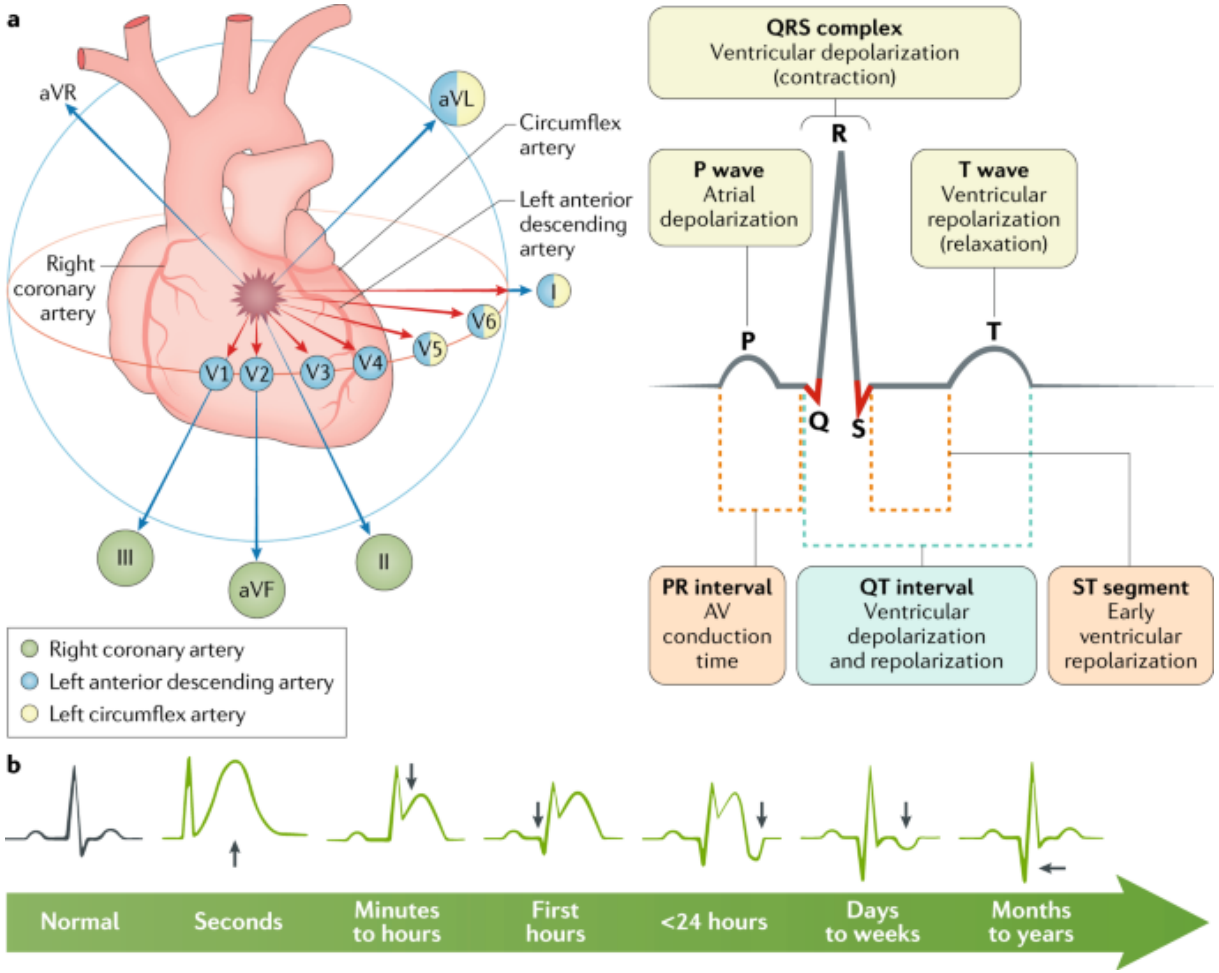
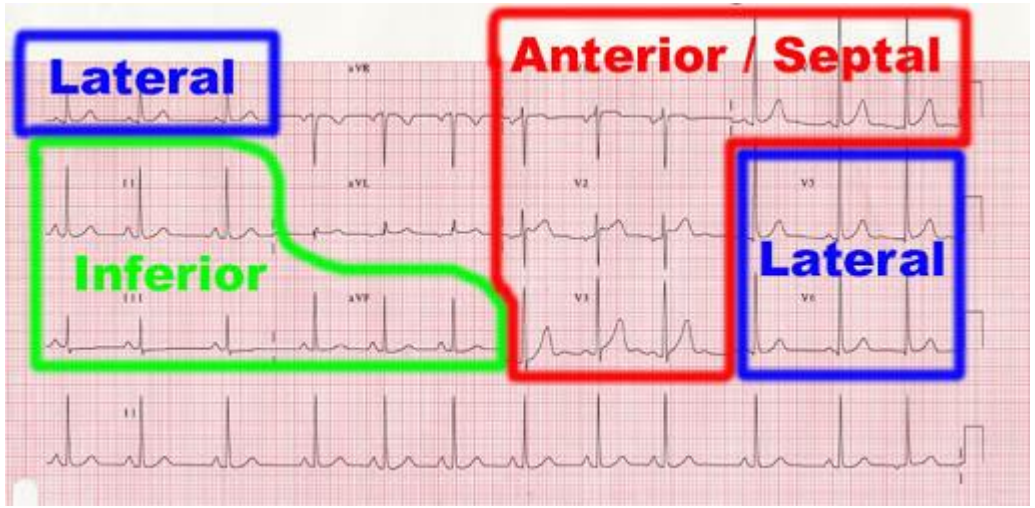
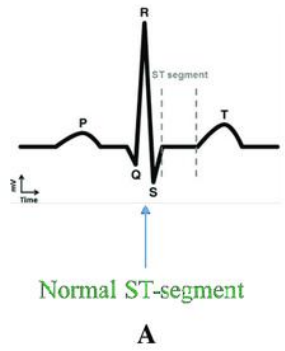
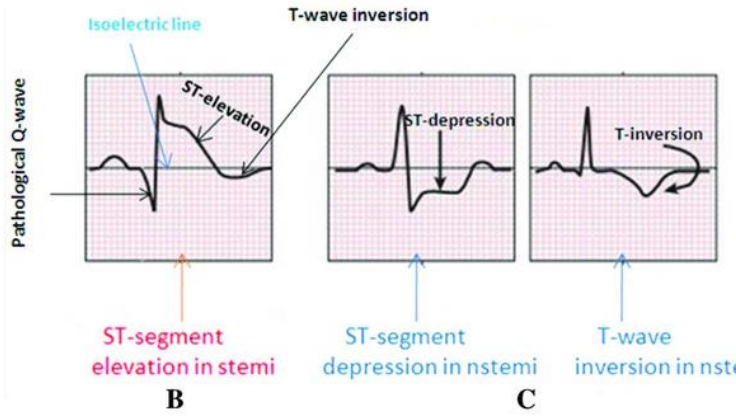
ECG changes evolve in parallel with tissue changes









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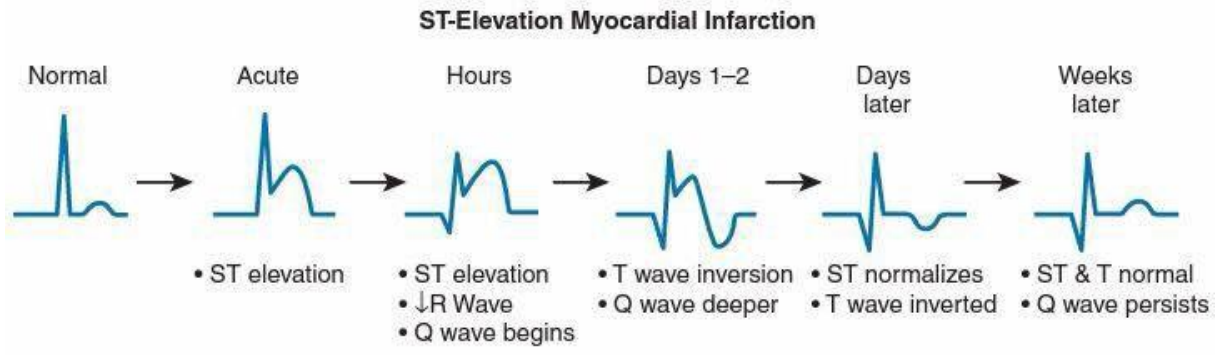
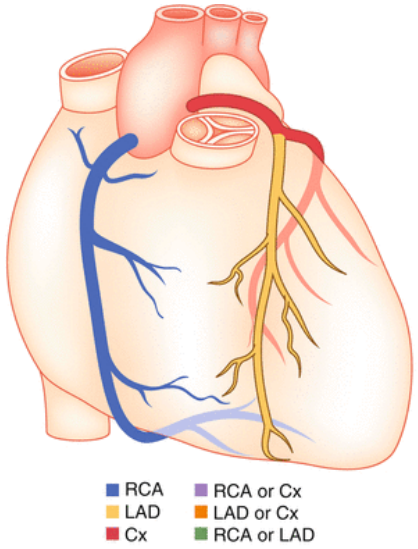
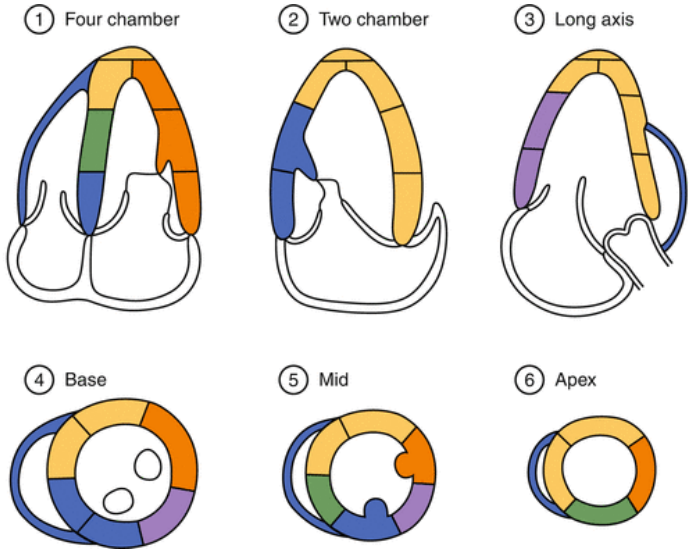
Evolution of STEMI

- **STEMI** is a dynamic process that **does not occur in instant**
  - changing ECG and echocardiography pattern parallels the evolution
- substantial **area at risk** (30–50%) is still viable and therefore **salvageable** by reperfusion after some time from the onset of angina symptoms
- early and late complication of MI are function of its size
  - recent meta-analyses emphasized the pivotal importance of infarct size within 1 month after MI as a determinant of all-cause mortality and hospitalization for heart failure at 1 year
- spontaneous reperfusion begins after 12-24 hrs
- to salvage at risk and stunned myocardium **reperfusion therapy** should be initiated as soon as possible
    - first line therapy nowadays together with strategies decreasing myocardial oxygen demands
  - pharmacological = thrombolysis / fibrinolysis
    - time! decreased efficacy as coronary thrombi mature
    - administration of t-PA
  - mechanical = PCI (percutaneous coronary intervention)
    - balloon angioplasty
    - stent deployment







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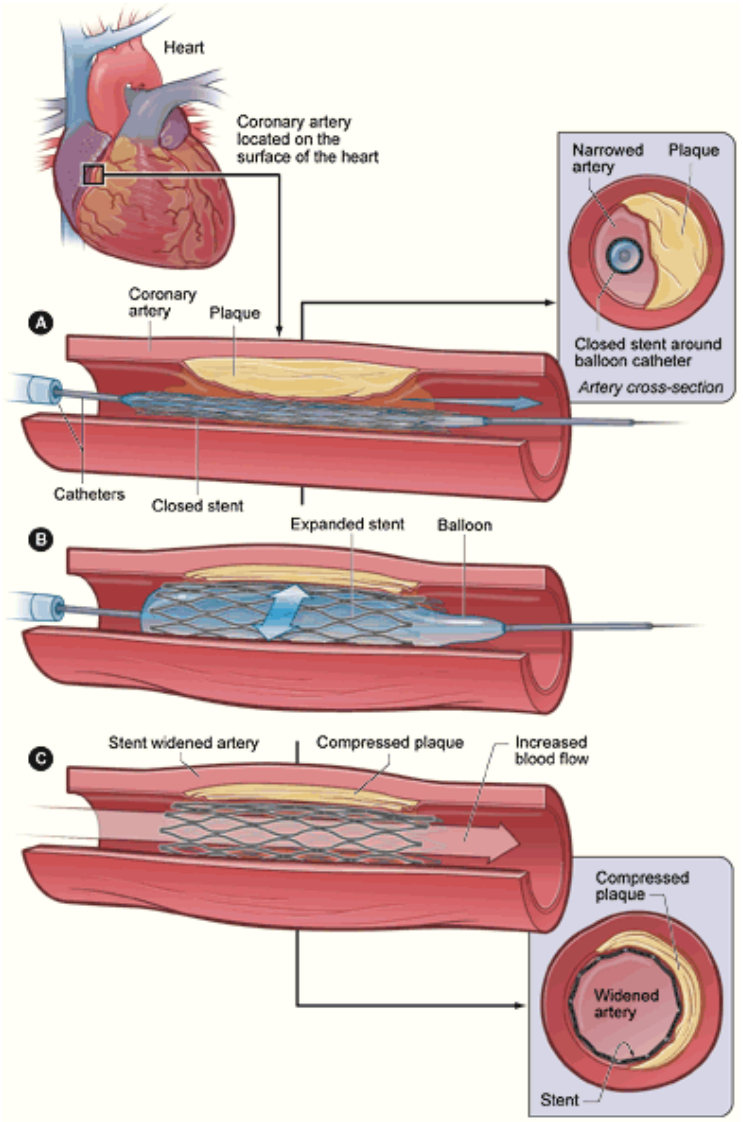
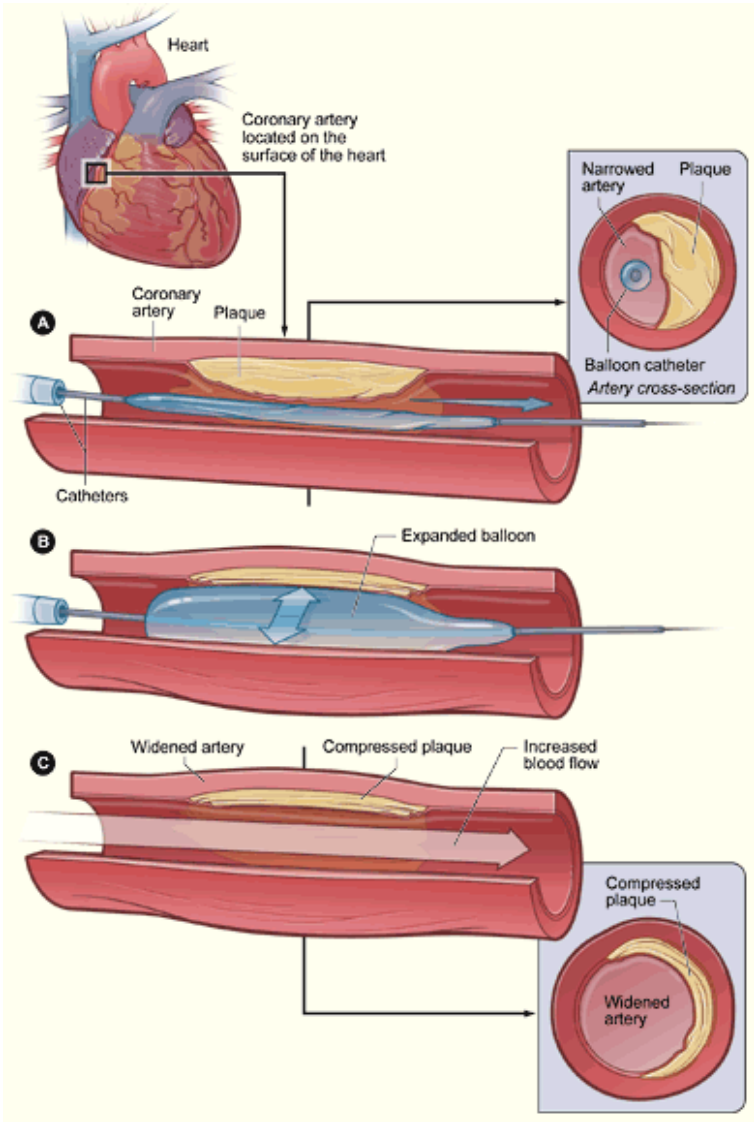
Acute interventions – stenting & angioplasty





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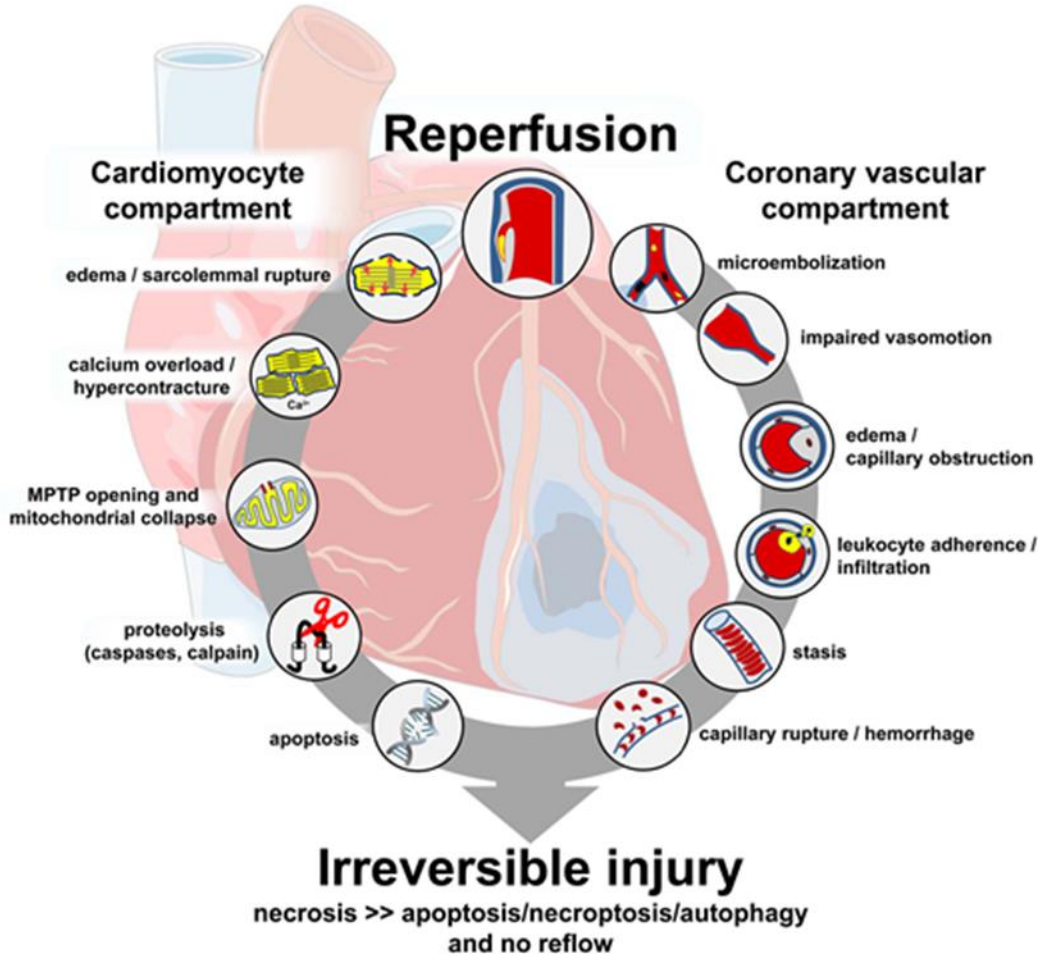
Limitation of infarct size - reperfusion

- BUT reperfusion also inflicts additional damage!
- **reperfusion injury** – damage due to restoration of blood flow
- mechanisms
  - reversible
    - stunned myocardium
      - prolonged period of contractile dysfunction in salvaged myocytes
    - reperfusion arrhythmias
    - microvascular damage
  - irreversible = increase of infarction size
    - no-reflow phenomenon as an extreme reperfusion injury
- ongoing modification of reperfusion techniques in order to perform ‘safe’ gentle reperfusion
  - ischemic post-conditioning
    - alternating cycles of reperfusion and coronary re-occlusion
  - pharmacological



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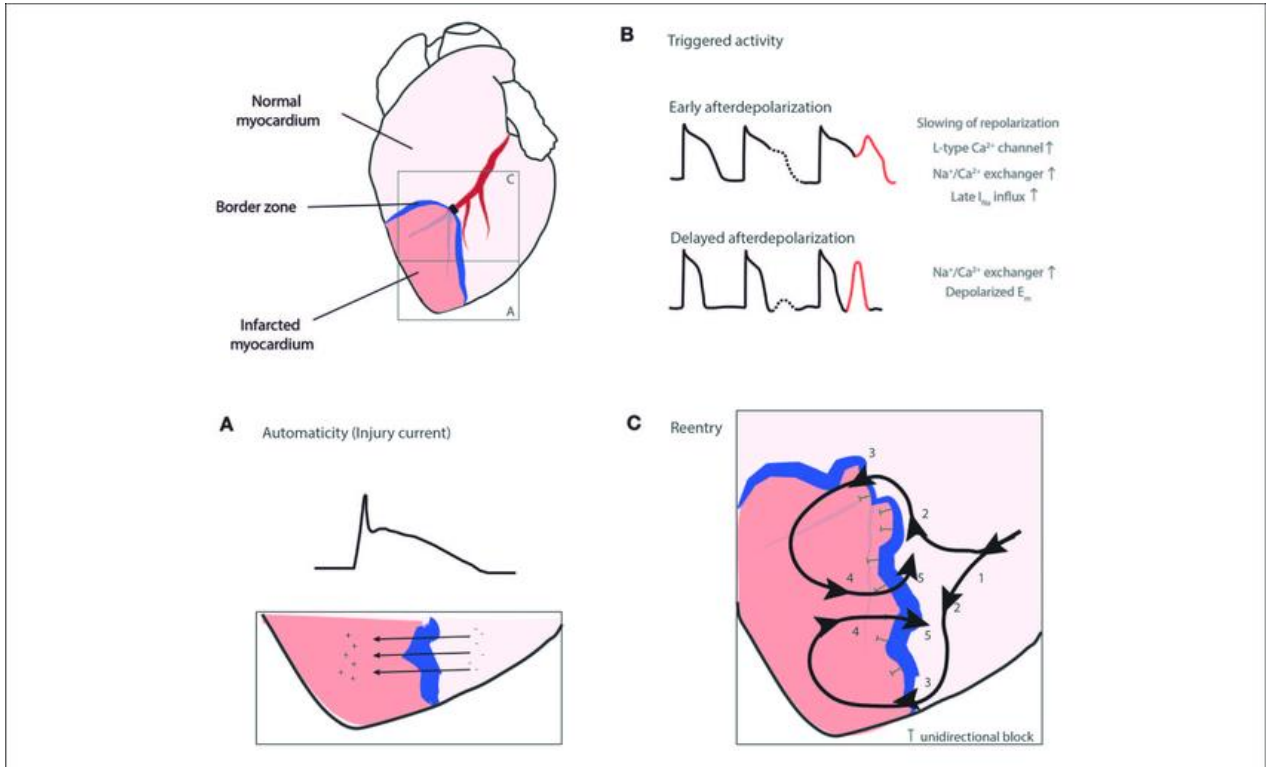
Sudden cardiac death

- cardiogenic shock
  - due to single massive MI or MI superimposed on multiple prior MIs
    - area of abnormal contraction > 25% results in HF
    - area of abnormal contraction > 40% results in cardiogenic shock
- ventricular arrhythmias
  - leading mechanism in acute phase is re-entry
- LV wall rupture
  - death from hemopericardium and cardiac tamponade
  - occasionally pseudoaneurysm
- rupture of the papillary muscle
  - from inferior wall MI
  - massive regurgitation



- The three mechanisms, automaticity (A), triggered activity (B), and reentry (C) can play a role in arrhythmogenesis during ischemia.
  - (A) Injury current across the border zone leading to ST elevation in the electrocardiogram,
  - (B) Triggered activity mainly caused by Ca 2+ overload in cardiomyocytes or Purkinje fibers.
  - (C) Reentry.
- Electrical activation wave front (1) is deflected at the border zone due to unidirectional block (T) into two wave fronts (2), eventually passing the border zone (3) and exciting the infarct zone (4) and finally passing the unidirectional block re-exciting the area in front of the block (5). I to , transient outward potassium current; [K +] o , extracellular potassium concentration; [Na +] i , intracellular sodium concentration.

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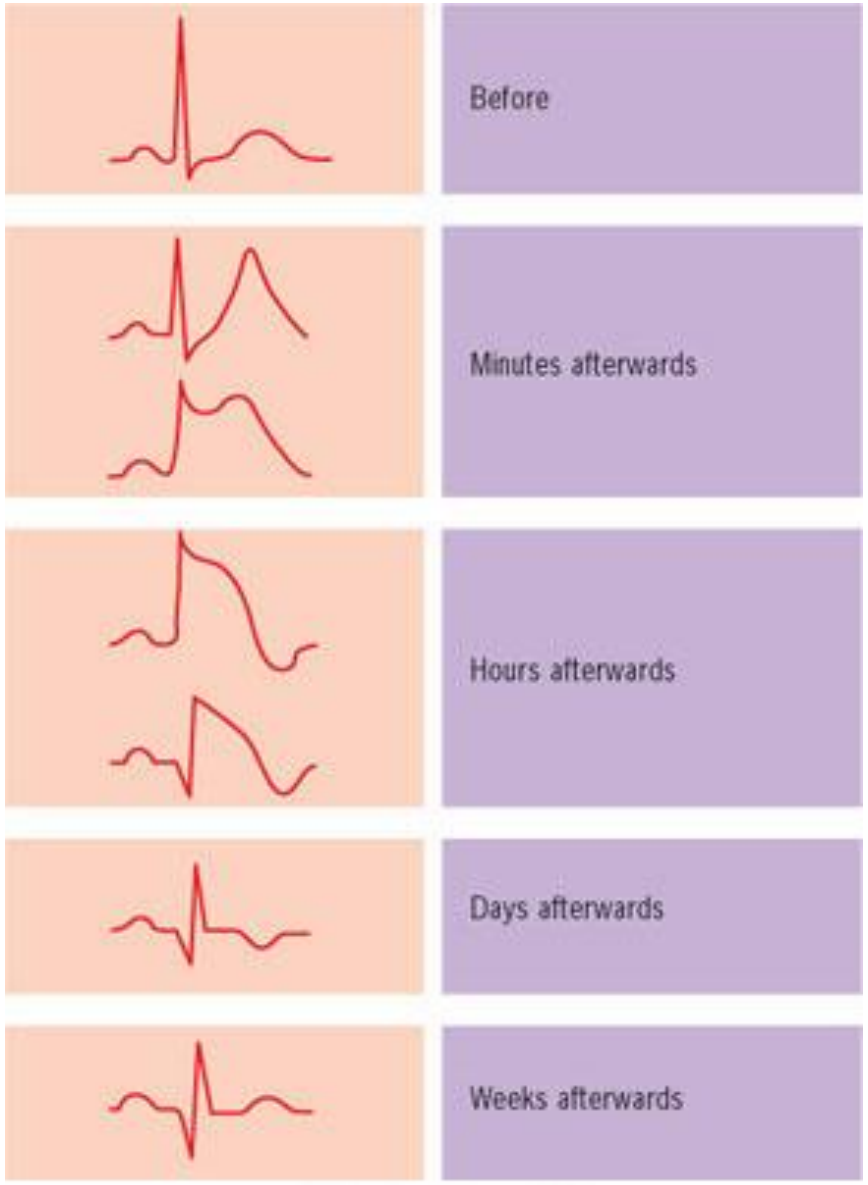
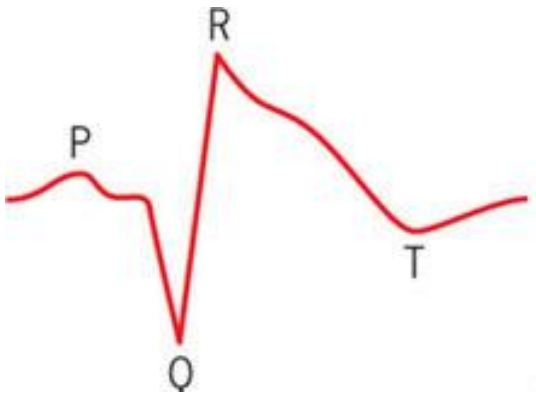
ECG changes during STEMI



- 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)

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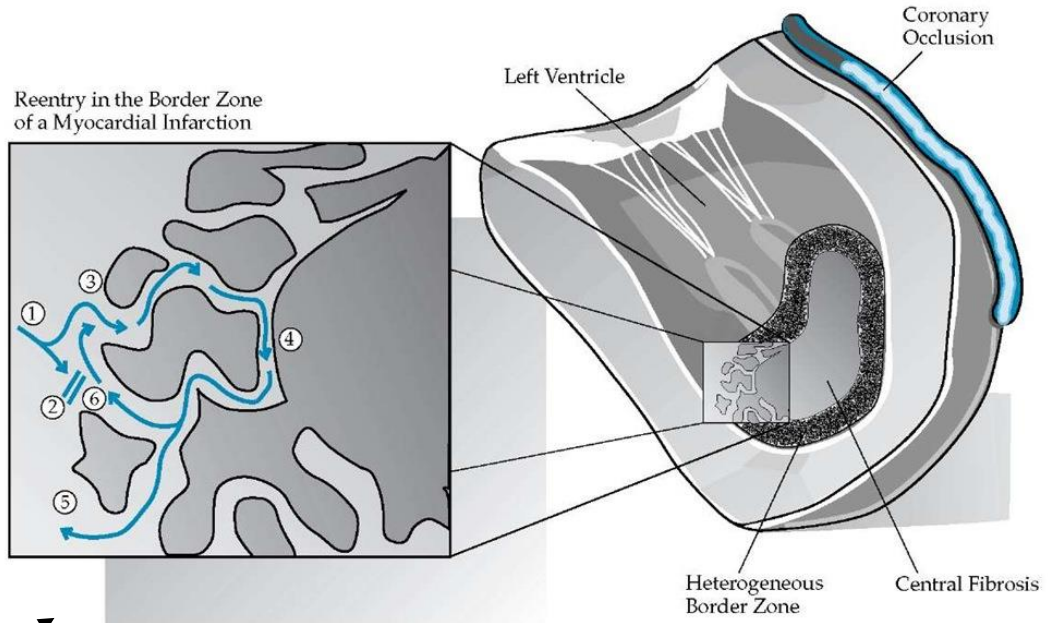
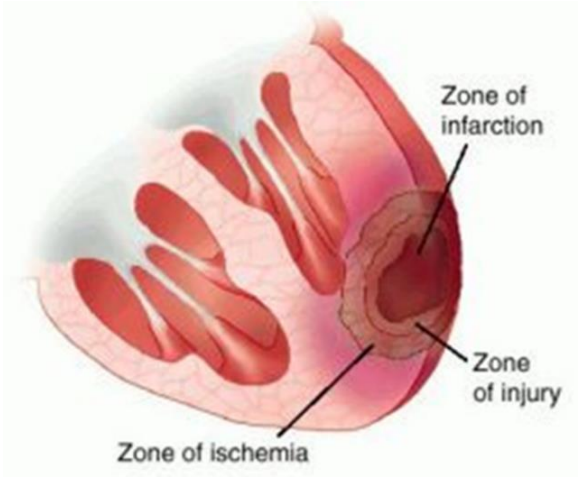
Complications of MI

- 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





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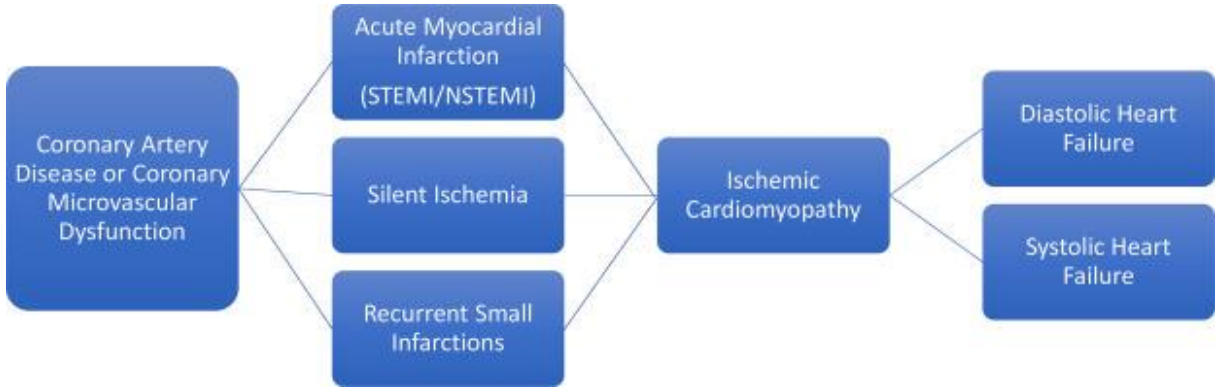
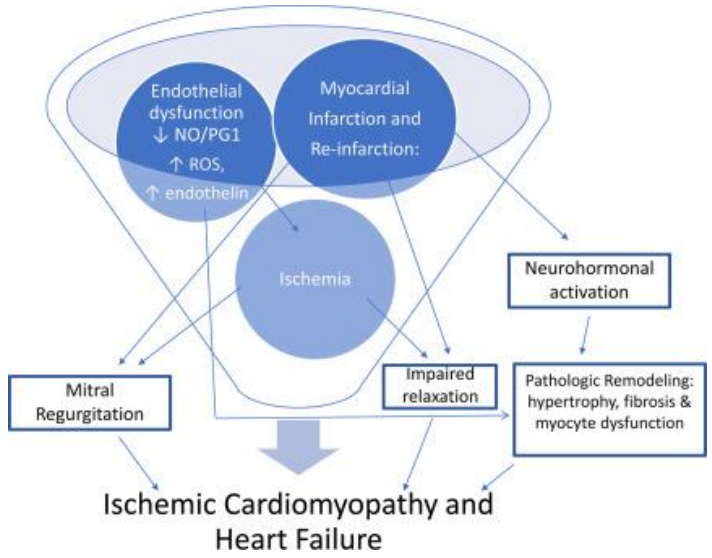
Ischemic cardiomyopathy / heart failure

- the most common aetiology of HF
  - accounts for more than 60% of cases of congestive heart failure
- results from
  - myocardial ischemia – hibernating myocardium
    - the larger the contribution the better the effect od revascularisation
  - diffuse fibrosis and LV remodelling
  - event. plus multiple scaring due to MI
  - event. mitral regurgitation due to papillary muscle dysfunction
  - event. LV aneurysm
- angina might or may not be present
  - silent ischemia and confusion with dilated cardiomyopathy





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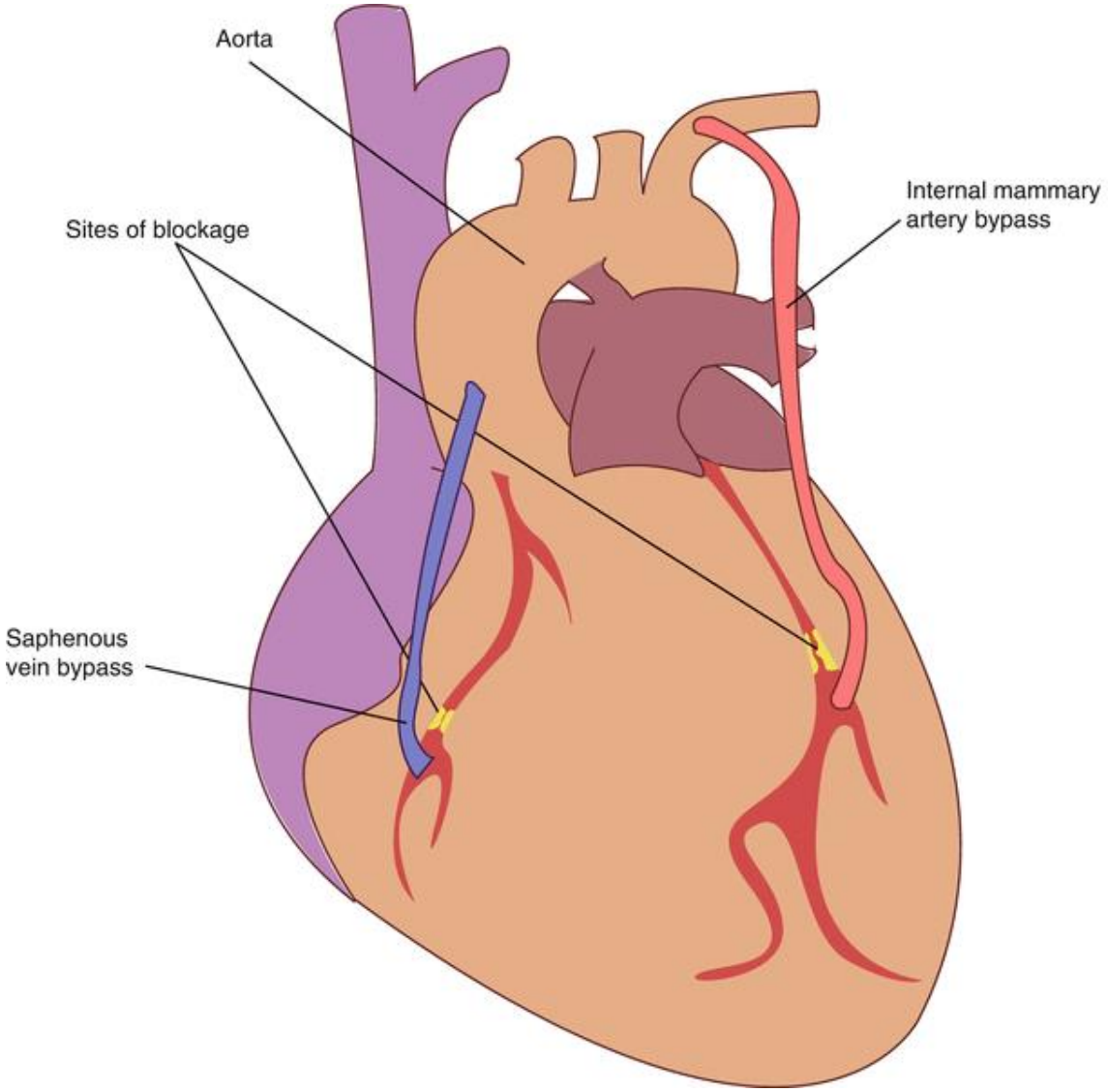
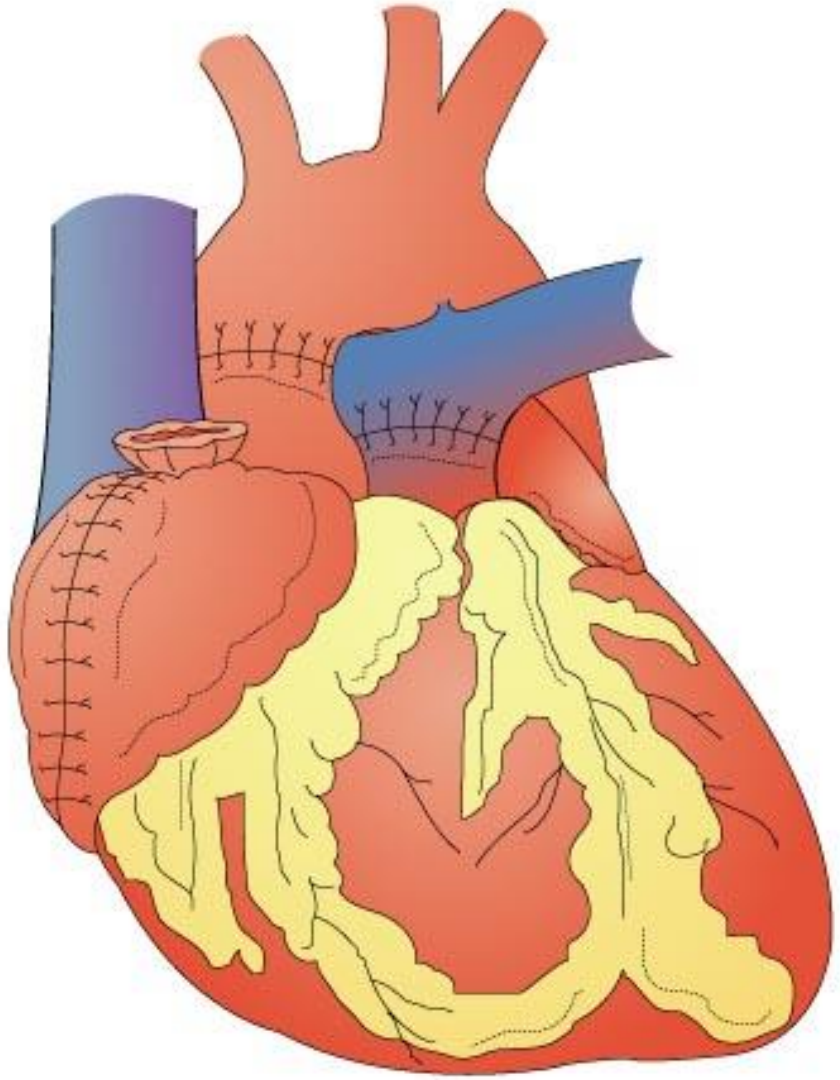
Follow-up interventions – by-pass surgery &





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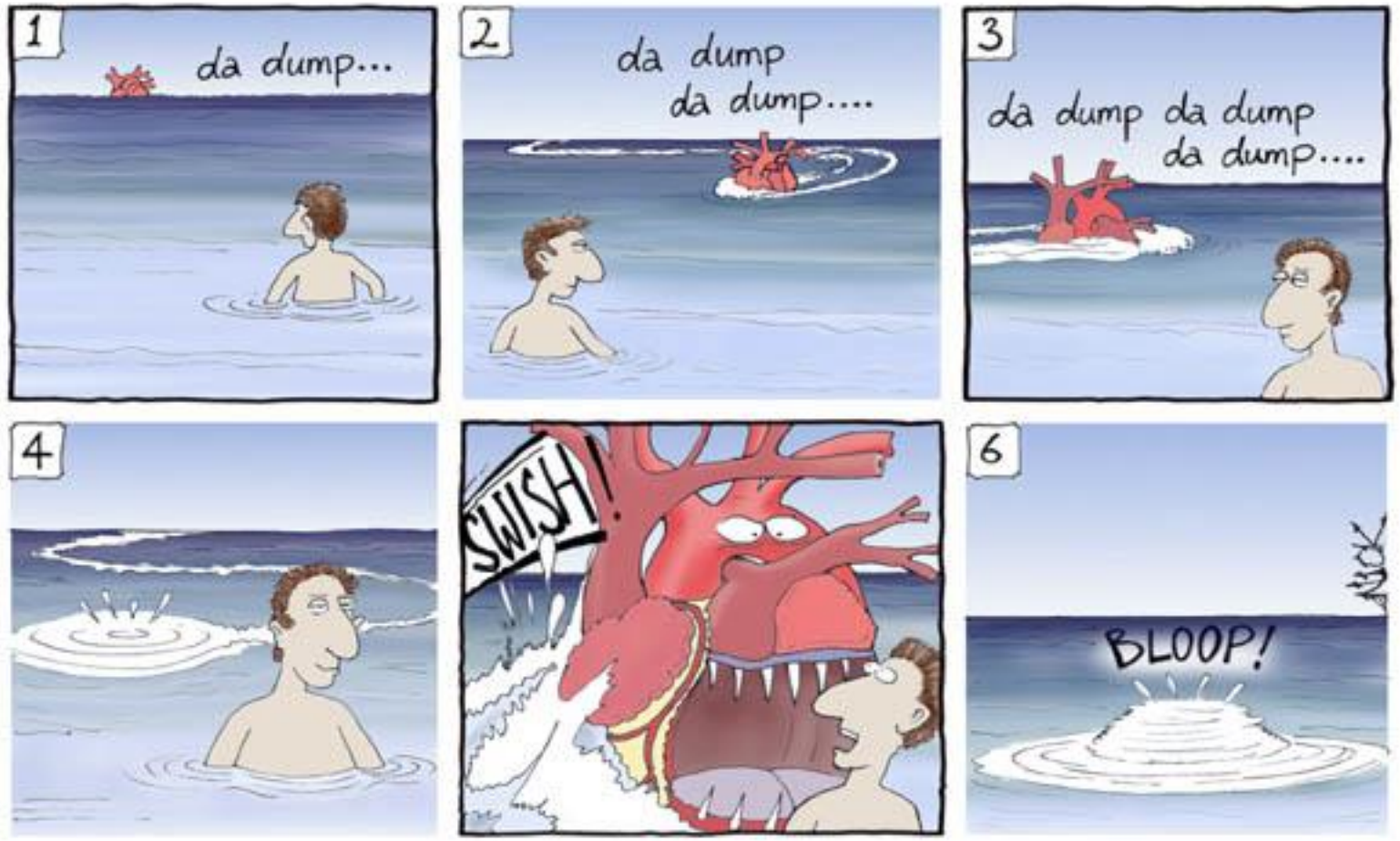

TOO BAD DESMOND HAD NEVER LEARNED TO RECOGNIZE
THE EARLY WARNING SIGNS OF A HEART ATTACK.