**1. Physiology**

Factors determining myocardial oxygen supply and demand (Fig. 1)

- **Diastolic perfusion pressure** = \( P_{AO\ DIAST} - P_{CAP\ CORON} \)
- \( Q \sim \frac{P}{R} \)
- Max. \( Q \) during diastole

**Coronary vascular resistance**

- *External compression* of coronary branches during systole. Subendocardium subjected to greater forces, but better perfused (β2 receptors, relative ischemia). More vulnerable to diminished flow (hypotension, obstruction of epicardial arteries)

- *Intrinsic regulation of coronary tone* (autoregulation)
  
  Resistance at the level of arterioles and precapillary sphincters. Capillary recruitment in need (60-80% open in rest). Oxygen extraction 75%

Definition of myocardial ischemia:

Deprivation of oxygen & inadequate removal of metabolites owing to reduced perfusion

Most typical presentation: Angina pectoris (“strangling in the chest”)

Local metabolites

- \( O_2 \rightarrow \) vasoconstriction
- ↓ \( O_2 \) → ↑ AMP → ↑ adenosine → Ca\(^{2+}\) entry into SMC → vasodilation
- Lactate, some prostaglandins, H\(^+\) → vasodilation

Endothelium-dependent vasodilation factors

\[ \text{ADP, ATP, histamine, acetylcholine} \rightarrow \text{endothelium-derived relaxing factor (EDRF)} \rightarrow \text{cGMP} \rightarrow \text{Ca}\(^{2+}\) release from SR \rightarrow \text{vasodilation} \]
Pathologically changed endothelia → activation of platelets → TXA2 → vasoconstriction → reversal of the effects of endothelium-dependent vasodilation factors

Neural factors
Parasymp. of little influence
Epicardial vessels - α adrenergic receptors → temporary vasoconstriction
Subendocardial vessels → β2-adrenergic receptors → vasodilation
Autoregulation is sufficient to 60 mmHg in aorta.
Advanced AS → maximal dilation → loss of regulation

Coronary collateral vessels important mainly in situation of obstruction
O2-carrying capacity (Hb + lungs) - usually constant

2. Mechanisms of myocardial ischemia

Lesion → ↓perfusion (Fig. 2)

↓ lumen radius to 50%
(= ↓cross-sectional area to 25%)
+ exercise and psych. stress
(= clinically important narrowing)
↓ lumen radius to 10% in rest → ischemia

1. Atherosclerosis
most common
in proximal segments or rarely diffuse
radius below 50% → stable angina, below 10% → angina in rest

2. Nonatherosclerotic coronary artery diseases - inflammatory (autoimmune) processes in small branches:
  • polyarteritis nodosa
  • systemic lupus erythematosus
  • rheumatoid arthritis
  • diabetes

Coronary collateral vessels important mainly in situation of obstruction
O2-carrying capacity (Hb + lungs) - usually constant

2. Heart rate: β-blocker therapy → ↓HR
   Most important parameter for oxyg. consumption:
   HR * BPSYST

3. Contractility: catecholamines → ↑O2 consumption
   β-blockers → ↓O2 consumption
3. Coronary thrombosis and platelet aggregation

- Fissure of an AS plaque → intraintimal thrombosis → unstable angina or IM (Fig. 3)

Spasmus/obstruction ratio (Fig. 4)

5. Coronary embolism from the left heart, rare

6. Diminished coronary flow reserve without a morphological changes of coronary arteries

Def. of C.F.R.: maximum flow ÷ resting flow

Fig. 5 I, II

7. Increased myocardial oxygen demand (see above)
3. Acute adaptations to ischemia

Ischemia → ↓ creatine phosphate → ↓ ATP → ↓ contractility
→ anaerobic glycolysis → ↑ ATP
→ intracellular acidosis → activation of lysosomes
→ tissue destruction
→ ↓ contractility (H+ replace Ca²⁺)

Acute defense – Fig. 6

4. Ischemic heart disease

Traditional types: angina pectoris and myocardial infarction. Now added: stunning, hibernation, preconditioning

Angina pectoris

Coronary ligature, angioplasty → ischemic cascade (Fig. 7)
Contractile dysfunction: damage > 40% → cardiogenic shock
Methods: angiocardiography, echocardiography, nuclear angiography

Stable angina pectoris

Exercise, emotion → pain
Discontinuation, nitroglycerin → relief
Unchanged ≥ 2 - 3 months
Severe A.S. → fixed ↓ blood supply combined with ↑ oxygen demand
Reproducible by fixed amount of exercise (HR*BP) (Fig. 5)
↓ Release of EDRF (NO⁻)
ATP → adenosin ? → pain
ECG: Horizontal or declining depression of ST interval during exercise
Large ischemia → syst. & diastolic dysfunction (↑ EF)
↑ Arterial tone → ↓ coronary flow reserve → → S.A.P. without CAD (= syndrome X)
Unstable angina pectoris

Types:
1. Progressive angina after a period of stable angina
2. Recent, minimal exercise ("immediately serious")
3. Intermediate coronary syndrome: > 15 min at rest
4. ≤4 weeks after IM

Mechanisms: rupture of an AS plaques → platelet aggregation → thrombus;
rupture ⇔ coronary spasm
Both → ↓ coronary flow reserve (Fig. 5 III)
Same as in IM, only milder
Therapy: heparin, aspirin

Variant angina pectoris (= variant = Prinzmetal)

Pain at rest with ST denivelation, intraindividually variable response to exercise, some patients without AS
Focal spasm of epicardial coronary artery (local hypersensitivity ?, Fig. 5 II)
IM seldom

Mixed angina pectoris

Spasms, platelet aggregation, thrombosis at the site of a plaque → mixed symptomatology (tolerance varies during a day etc.)

Silent myocardial ischemia

Holter: ST denivelation and/or ↓ ejection fraction and Thallium 201 abnormalities in the absence of symptoms
↑ pain threshold?
Prognosis?
Ischemic ECG – Fig. 8
Reperfusion damage: ventricular arrhythmias and stunned myocardium
Definition: Postischemic dysfunction of the myocardium with a relatively normal perfusion
15’ - 20’ ischemia → hrs or days of stunning
Reversible!
2 hypotheses:
- free radicals (scavengers helpful if on the spot immediately)
- Ca²⁺ overload (free radicals → damage of SR and sarcolemma); Ca-blockers promising
Clinical demonstration difficult – local perfusion cannot be measured easily. Hypothetically after: operations, angioplasty, angina pectoris and IM → however, lasting ischemia?
Tab. 1: Characteristics of stunned and hibernating myocardium

Hibernating myocardium
Fig. 9
Myocardial dysfunction could be dramatically amended by inotropic agents, bypass or ↓O₂ consumption
Def.: Chronic reversible dysfunction of LV due to coronary disease, responding to inotropic stimuli. Residual contractile reserve can be demonstrated by them
Could be presupposed in IM not explaining the degree of LV failure Histopathology: loss of sarcomeres, SR etc.
2 hypotheses:
- original authors: chronic resting hypoperfusion, adaptive lowering of O₂ consumption
- now: basal perfusion is OK, ↓coronary reserve. Perfusion is not lowered so much as to explain the degree of dysfunction → important stunning component: CAD → ↓coronary reserve → repeated stunning several times a day
However, stunning and hibernation are different phenomena (Tab. 1)
Preconditioning

Definition: Fast adaptive response to a short (> 2 minutes) ischemic damage lowering the decay of cells during a further protracted period of ischemisation → ↓ infarction zone
Diffusion of endogene humoral factors (adenosine, [nor]epinephrine, activation of α1-receptor, activation of A1 receptor for adenosine, opening of the KATP channel) → slowing of metabolism
Protective effect lasts several hrs – 1 day
In clinics: repeated coronary angioplasty
Prophylactic preconditioning?

4. Myocardial infarction

Definition: Condition of irreversible necrosis or apoptosis of the muscle that results from prolonged (40~60’) ischemia
Fissure (rupture) of an AS plaque → thrombosis → obturation of a CA (Fig. 10)
Dynamic: By 8 - 10 days necrosis removed, by 2 - 3 months scar formed (its strengthen with time)
Extension of IM:
Complete occlusion → transmural IM
Incomplete occlusion → nontransmural IM
Vulnerable subendoc. zone → subendocardial IM
Pathogenesis: ischemia → IM (Fig. 11)
↑ cytosolic Ca2+ → irreversibility

Remodeling of a ventricle and complications (Fig. 12)
Remodeling = change of ventricle geometry by a scar and hypertrophy → ↓ compliance, dilation, failure
Myocardial rupture → hemopericardium → tamponade → death
Rupture of papillary muscle → pulm. edema
Reentry, ↑automaticity, late afterdepolarization, microembolisation into the myocardium → ventricular arrhythmias → sudden cardiac death
Ventric. aneurysm → thrombembolization, arrhythmias
ECG in IM (Fig. 13)

ST interval
Hypoxia of cell → loss of rest voltage → cell surface relatively negative → injury current from infarction focus to center of heart → depression of TQ (=TP+PQ) on nearby electrode. Injury current disappears at ventricle’s depolarization (ST interval) → ST interval in normal position → it presents as being elevated compared to depressed TQ. Reciprocal findings are present on distant electrode. Start of ST interval returns to “isoelectric” line after hours, ST remains elevated and convex upward, normalization of ST after 2 - 3 weeks.

T wave
Ischemic zone bordering necrosis repolarizes slowly → T wave inversion outlasting ST normalization

Q wave (Fig. 14)
Propagation of excitation is lacking in necrotic zone → vectors oriented contrarilywise (of opposite wall) prevail → deep & wide Q on the nearby electrode. Lasts indefinitely

Subendocardial (= non Q) IM → necrotic focus turned away from all electrodes → ST depression in all electrodes, i.e., a nonspecific sign

Serum enzymes in acute IM (Fig. 15)

Therapy of IM
Thrombolytic (last 20 ye)
tissue plasminogen activator streptokinase
Conventional therapy
bed rest, psychother., sedation pain relief - nitrates, morphine β - blockers → ↓ sympathetic drive aspirin → ↓ platelet adhesiveness anticoagulants - heparin ACE inhibitors diuretics in pulmonary edema balloon angioplasty
Cardiogenic shock after IM inotropic agents
when ↑ TPVR → vasodilators
when ↓ preload → liquids i.v.
 intra-aortic balloon pump

Therapy of myocardial ischemia
- Nitrates → ↓ venous return
- β - blockers → ↓ heart rate
- Ca - channel blockers → ↓ afterload, → ↓ O₂ consumption
- Coronary dilation

Revascularization procedures