Myocardial ischemia and infarction

1. Physiology
   Factors determining myocardial oxygen supply and demand
   Myocardial oxygen demand
2. Mechanisms of myocardial ischemia
3. Acute adaptations to ischemia
4. Ischemic myocardial disease
5. Myocardial infarction

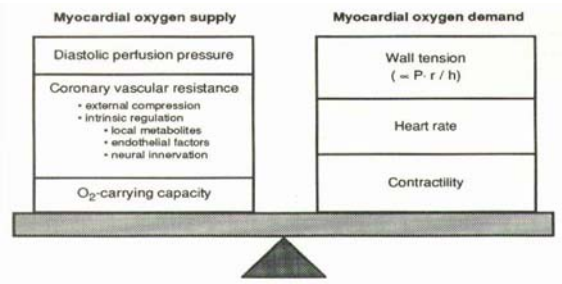
Definition of myocardial ischemia :

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

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

1. Physiology

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



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Diastolic perfusion pressure = $P_{AO\ DIAST}$ - $P_{CAP\ CORON}$

$\dot{Q} \sim P/R$

max. $\dot{Q}$ during diastole

during systole → Venturi effect at coronary ostia → ↓ $P_{AO\ SYSTOLIC}$

during systole → Compression of coronary branches inside myocardium

aortic regurgitation → ↓$P_{AO\ DIAST}$

aortic stenosis → ↓pressure gradient aorta/myocardium

↑EDP → ↓coronary perfusion

Coronary vascular resistence

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)

Resistence at the level of arterioles and precapillary sphincters. Capillary recruitment in need (60-80% open in rest). Oxygen extraction 75%

Local metabolites

O_2 → vasoconstriction

↓ O_2 → ↑AMP → ↑ adenosine ¬ Ca^{2+} entry into SMC → vasodilation

Lactate, some prostaglandins, H^+ → vasodilation

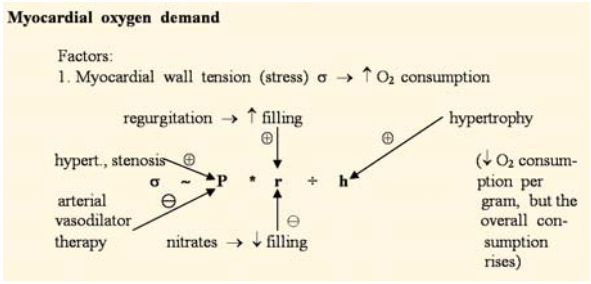
Endothelium-dependent vasodilation factors

ADP, ATP, bradykinin, histamine, acetylcholine → endothelium-derived relaxing factor (EDRF) ≡ NO· + PGI_2 ≡ prostacycline → ↑cGMP → ⊥ Ca^{2+} release from SR → ↓ vasodilation

Pathologically changed endothelia
→ activation of platelets → TXA2 → vasoconstriction
→ reversal of the effects of endothelium-dependent vasodilation factors

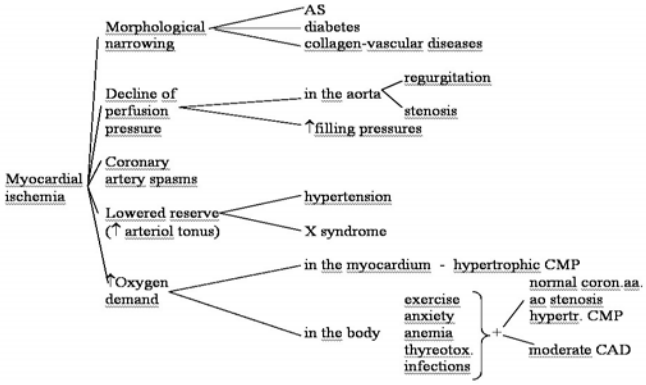
Neural factors
Parasymp. of little influence
Epicardial vessels - α adrenergic receptors → temporary vasoconstriction
Subendocardial vessels → β2-adrenergic receptors → vasodilatation
Autoregulation is sufficient to 60 mmHg in aorta.
Advanced AS → maximal dilation → loss of regulatior

Coronary collateral vessels important mainly in situation of obstruction
O_2-carrying capacity (Hb + lungs) - usually constant

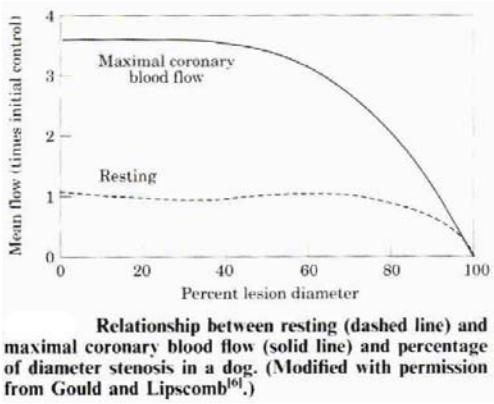


2. Heart rate: β-blocker therapy → ↓ HR
Most important parameter for oxyg. consumption: HR * BPSYST
3. Contractility: catecholamines → ↑ O_2 consumption
β-blockers → ↓ O_2 consumption

2. Mechanisms of myocardial ischemia



Lesion → ↓perfusion (Fig. 2)



Relationship between resting (dashed line) and maximal coronary blood flow (solid line) and percentage of diameter stenosis in a dog. (Modified with permission from Gould and Lipscomb[6].)

↓ lumen radius to 50%
(= ↓ cross-sectional area to 25%)
+ exercise and psychol. 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:

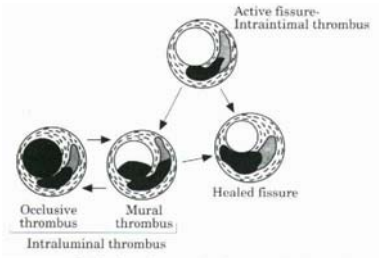
- polyarteritis nodosa
- systemic lupus erythematosus
- scleroderma

→ **collagen-vascular diseases**

- rheumatoid arthritis
- diabetes

3. Coronary thrombosis and platelet aggregation

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



Evolution of an active fissure with intraintimal thrombosis to either healing with aggravation of the stenosis or occlusive thrombosis and subsequent myocardial infarction.

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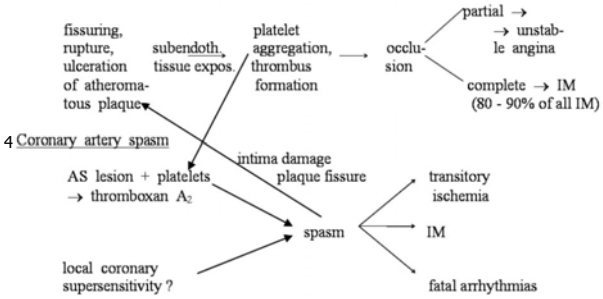
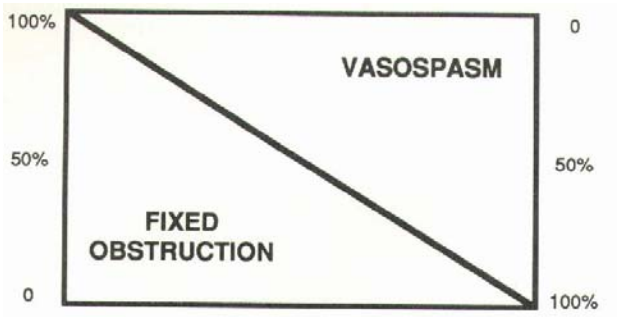


Spasmus/obstruction ratio (Fig.4)



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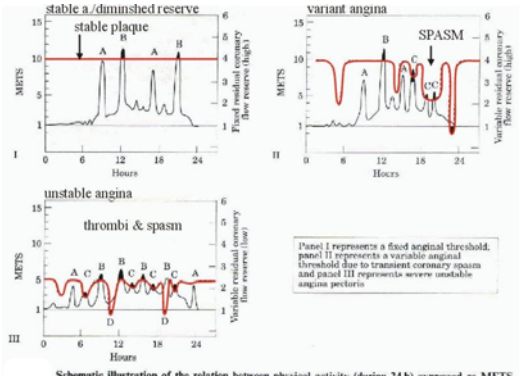
5. Coronary embolism from the left heart, rare

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



Schematic illustration of the relation between physical activity (during 24 h) expressed as METS (multiple of basal metabolic oxygen consumption) and coronary flow reserve. A = exercise below level of maximal coronary flow reserve without experiencing ischaemia; B = exercise above level of maximal coronary flow reserve; C = coronary flow reserve is impaired; D = coronary flow reserve decreases so that resting flow is impaired and ischaemia occurs at rest. (Modified with permission from Maseri *et al.*[111].)

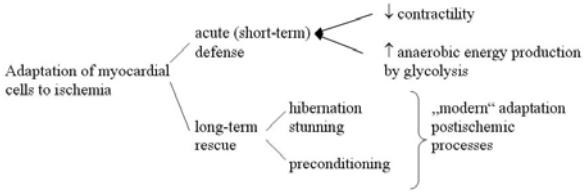
I - fixed treshold for angina pectoris (stable angina)
II - variable treshold for angina as a result of a coronary spasm (variant angina)
III - grave unistable angina pectoris

5

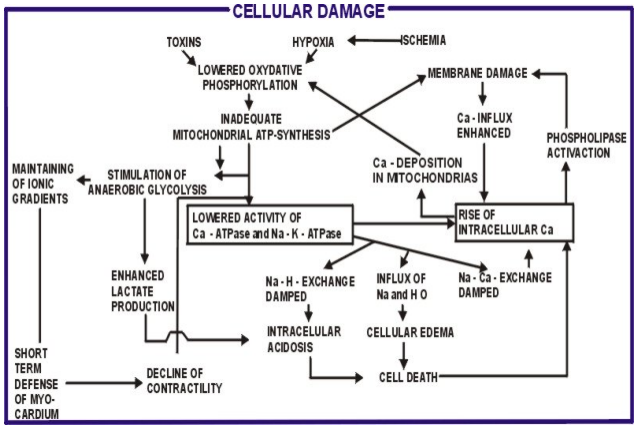
regulatory? → abnormally high resistence (arterioles) → ↓C.F.R stress → ischemia during exercise (hypertension, syndrome X = normal coronaries + exercise pain)

7. Increased myocardial oxygen demand (see above)

3. Acute adaptations to ischemia



Acute defense – Fig. 6



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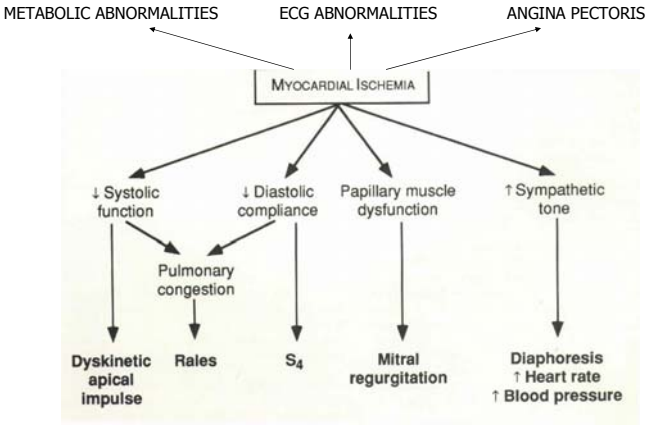
Ischemia → ↓creatine phosphate → ↓ATP → ↓contractility
→ ↑anorg. P → ↓contractility
→ anaerobic glycolysis → ↑ATP
→ intracellular acidosis → activation of lysosomes
→ tissue destruction
→ ↓contractility (H+ replace Ca^{2+})

4. Ischemic heart disease

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

<u>Angina pectoris</u>

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



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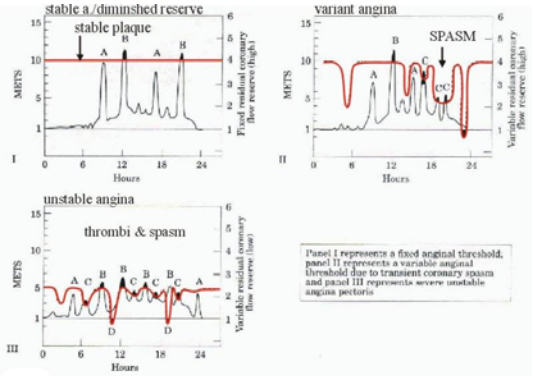
Stable angina pectoris
Exercise, emotion → pain
Discontinuation, nitroglycerin → relief
Unchanged ≥ 2 - 3 months
Severe A.S. → fixed ↓ blood supply combined with ↑oxygen demand
Reproducible by fixed amount of exercise (HR*BP) (Fig. 5 I)
↓ Release of EDRF ($NO^{\cdot}$)
ATP → adenosin ?→ pain
ECG : Horizontal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



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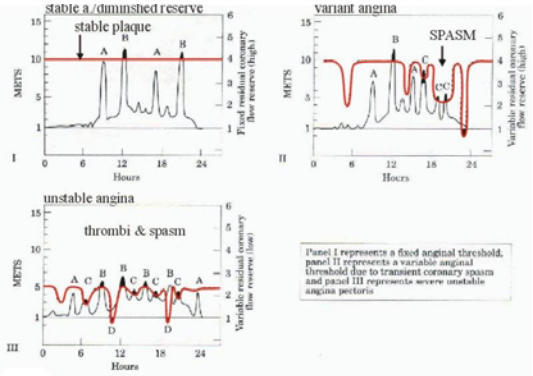
Unstable angina pectoris

Types :
1. Progressive angina after a period of stable angina
2. Recent, minimal exercise („immediately serious")
3. Intermediate coronary syndrom: > 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



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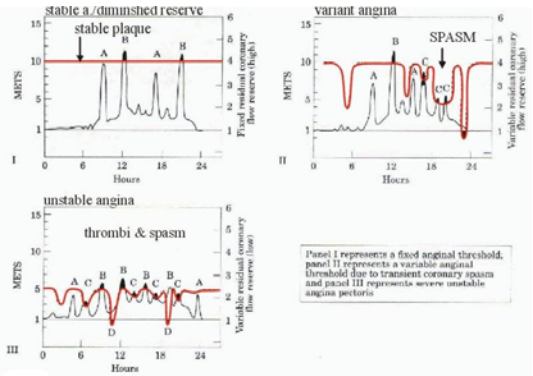
Variant angina pectoris (= variant = Prinzmetal)

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



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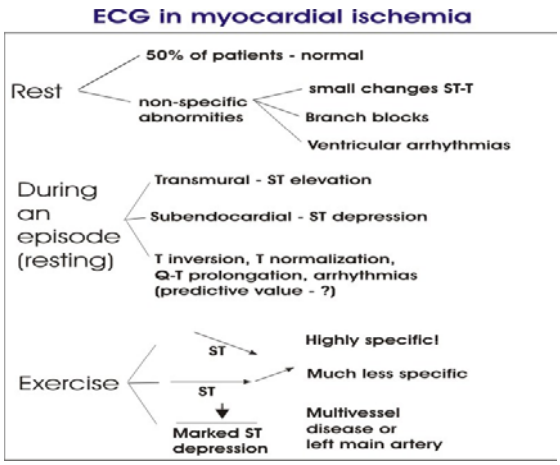
Mixed angina pectoris

Spasmus, 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 Thalium 201 abnormalities in the absence of symptoms
↑pain threshold ?
Prognosis?

Ischemic ECG – Fig. 8



Stunned myocardium

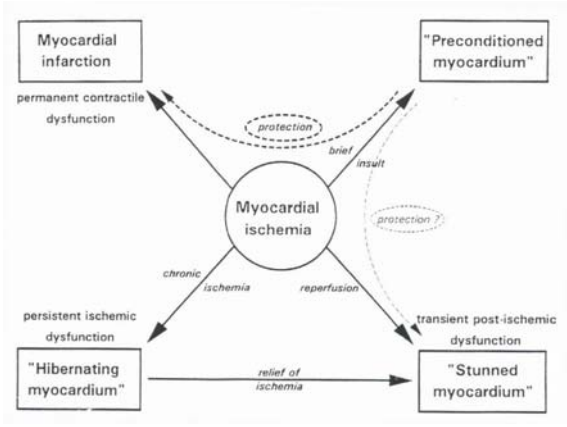


Fig. 9

Reperfusion damage: ventricular arrhythmias and stunned myocardium

Definition: Postischemic dysfunction of the myocardium with a brelatively normal perfusion

15´ - 20´ ischemia → hrs od days of stunning

Reversible!

2 hypotheses:

- free radicals (scavengers helpful if on the spot immediately)
- Ca^{2+} 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:

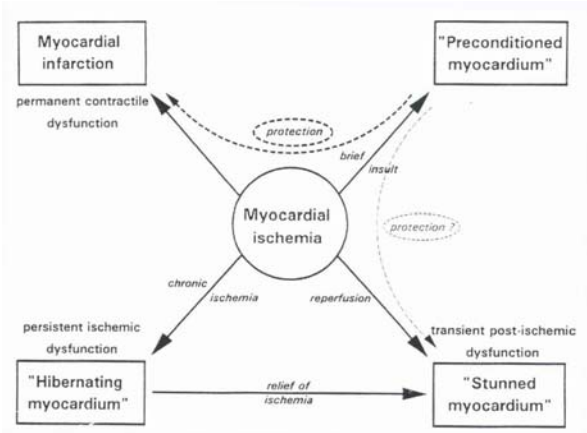
- original authors: chronic resting hypoperfusion, *adaptive* lowering of O2 consumption
- now: *basal* perfusion is OK, ↓coronary reserve. Perfusion is not lowered so much as to explain the degree of dysfunction → important stunning component: CAD → ↓coronary reserve → → repeated stunning several times a day

However, stunning and hibernation are different phenomena (Tab. 1)

Characteristics of Stunned and Hibernating Myocardium

	Stunning	Hibernation
Clinical condition	Cardiac surgery Reperfusion after acute regional ischemia	(Stable) angina
Coronary blood flow	Restored	Reduced
Experimental model	Reperfusion	None
Pathophysiology	Generation of oxygen radicals Calcium overload	?
Histologic findings	No necrosis	No necrosis
Recovery	Slow	Rapid to slow
Therapy	Prevention: Oxygen radical scavengers? Calcium channel blockers?	Restoring oxygen supply/demand balance: Revascularization Interventional recanalization Nitrates

Tab.1

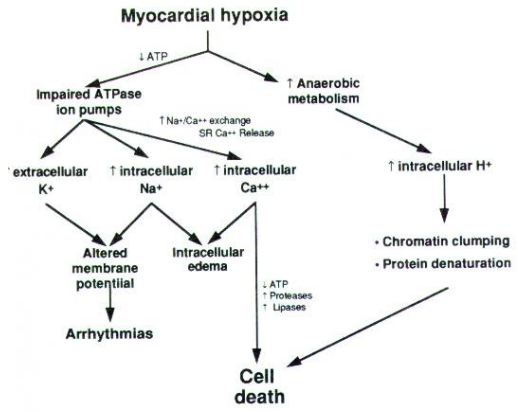


Preconditioning

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) → slowering of metabolism
Protective effect lasts several hrs – 1 day
In clinics: repeated coronary angioplasty
Profylactic 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)
Extention of IM :
Complete occlusion → transmural IM
Incomplete occlusion → nontransmural IM
Vulnerable subendoc. zone → subendocardial IM
Pathogenesis: ischemia → IM (Fig. 11)
↑cytosolic Ca^{2+} → irreversibility



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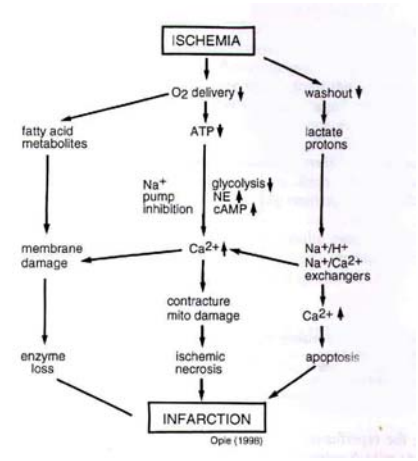


11

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, micro-embolisation into the myocardium → ventricular arrhythmias → sudden cardiac death
Ventric. aneurysm → thrombembolization, arrhythmias

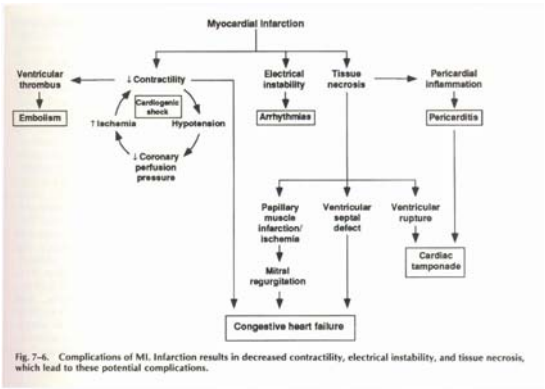
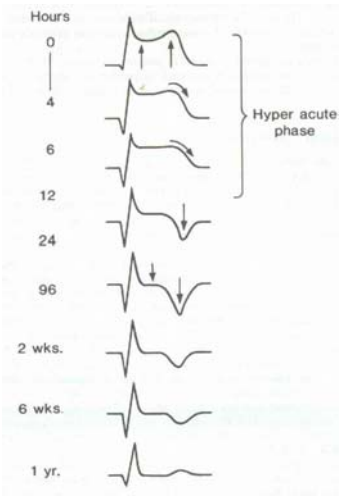


Fig. 7-6. Complications of MI. Infarction results in decreased contractility, electrical instability, and tissue necrosis, which lead to these potential complications.

12

ECG in IM (Fig. 13)



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ST interval

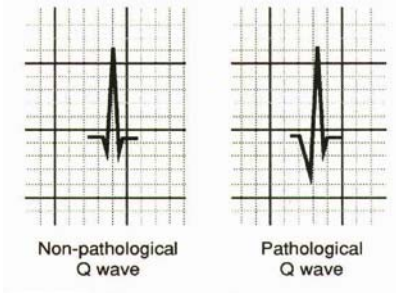
Hypoxia of cell → loss of rest voltage → cell surface relatively negative → injury current from infarction focus to center of heart → depression of TQ (=TP+PQ) on nearby electrode. Injury current disappears at ventricle´s depolarization (ST interval) → ST interval in normal position → it presents as 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 contrarywise (of opposite wall) prevail → deep & wide Q on the nearby electrode. Lasts indefinitely



Compared to small Q waves generated during normal depolarization, pathologic Q waves are more prominent: the width is ≥1 mm (1 small box) and its depth >25% of the height of the QRS complex.

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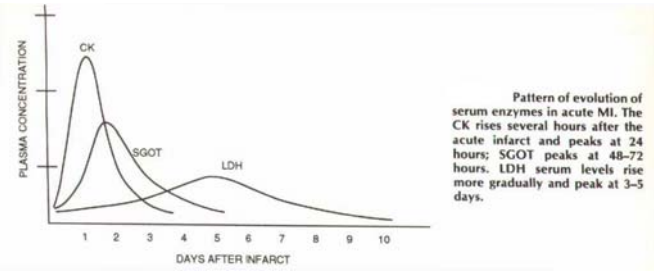
Subendocardial (≡ non Q) IM → necrotic focus turned away from all electrodes → ST depression in all electrodes, i. e., a nonspecific sign

Serum enzymes in acute IM (Fig. 15)



Pattern of evolution of serum enzymes in acute MI. The CK rises several hours after the acute infarct and peaks at 24 hours; SGOT peaks at 48–72 hours. LDH serum levels rise more gradually and peak at 3–5 days.

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 ↓ contractility
Ca - channel blockers	→	↓ afterload, → ↓ O_2 consumption coronary dilatation

Revascularization procedures