Ischemic heart disease

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MYOCARDIAL ISCHEMIA

deprivation of oxygen to the myocardium accompanied by inadequate removal of metabolites secondary to decreased perfusion

RISK FACTORS OF MYOCARDIAL ISCHEMIA AND ATHEROSCLEROSIS

- ***CLASSIC***
- age (≥ 45 ♂, ≥ 55 ♀); sex (♂)
- hypertension (STK > 120)
- DM
- positive family anamnesis (< 55 ♂, < 45 ♀)
- LDL chol > 2.6 mmol/l
- HDL chol < 1.3 mmol/l)
- TG ≥ 1.14 mmol/l
- Lp(a)
- metabolic sy
- CHRI
- smoking, phys. inactivity
- left ventricle hypertrophy

- ***NEW***
- hcy
- CRP and other inflammation markers
- fibrinogen
- markers of AS plaque unstability

MECHANISMS OF MYOCARDIAL ISCHEMIA

- atherosclerosis
- nonatherosclerotic coronary artery disease (inflammation, autoimmune processes)
- coronary artery spasm
- coronary trombosis (← platelet deposition)
- coronary embolism
- increased myocardial oxygen demand

CLINICAL MANIFESTATIONS OF MYOCARDIAL ISCHEMIA

- **chronic:** stable angina pectoris
- variant angina pectoris
- silent myocardial ischemia
- arrhythmias
- cardiac insufficiency

- **acute:** unstable angina pectoris
- acute myocardial infarction
- sudden cardiac death

ACUTE MYOCARDIAL INFARCTION

acute myocardial ischemia accompanied by necrosis of a part of myocardium

- **It occurs when the supply of blood to the myocardium is reduced below a critical value.**

WHO diagnosis of AMI

- **two of the following must be present:**

- **severe chest pain longer than 20 minutes (crushing chest pain perhaps radiating to the arm, back, jaw or abdomen)**
- **ECG changes indicative of AMI**
- **cardiac markers release**

since 2000 new ESC / ACC (European Society of Cardiology / American College of Cardiology) definition

- **increase and the following decrease of biochemical markers of myocardial necrosis + presence of 1 of the following:** **typical clinical symptoms**
  ECG changes indicative of AMI

Differential diagnosis of AMI:

- another form of myocardial ischemia
- another cardiac disease
- pulmonary disease
- musculoskeletal pain
- abdominal pain (ulcers, pancreatitis, cholelithiasis etc.)

- AMI can be clinically silent, particularly in elderly, and the ECG changes may not always be typical (previous infarction, arrhythmias, pacemaker).

Biochemical markers of AMI

- If the ischemia is present, cardiac myocytes undergo rapid and reversible changes in the cellular membrane.
- Anaerobic glycolysis becomes the major source of energy. It is not sufficient to meet the needs of ATP.
- Subsequent metabolic derangement causes functional and structural lesions of membranes and **leakage of soluble molecules from the cytosol to interstitium.**
- **This reversible phase of ischemic injury lasts 5 hours.**
- If reperfusion of the injured myocardium does not take place → **irreversible necrosis follows.** This is characterised by **the lysis of cellular structures and a rise of structurally bound markers in plasma.**
- All these substances found in blood in increased amounts are called **cardiac markers.**

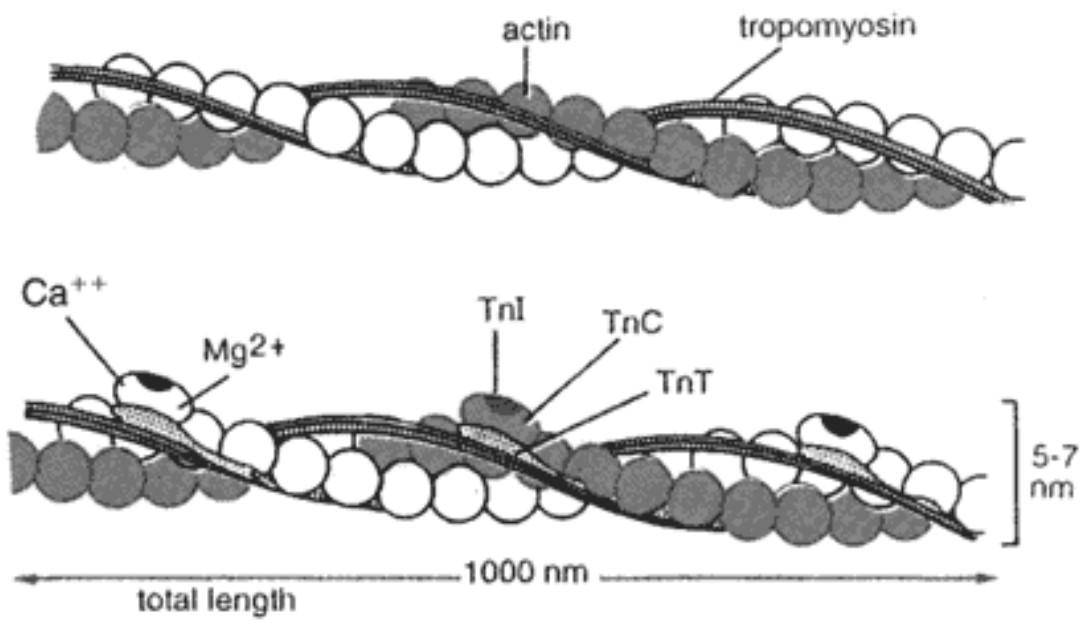
Cardiac markers

- **old markers**
- **enzymes**
- **AST**
- **CK**
- **CK-MB**
- **LD**
- **HBD**

- **new markers**
- **CK-MB mass**
- **myoglobin**
- **troponins**

Troponin

- Togeher with actin and tropomyosin is one of proteins making up the cardiac muscle fibre. It is a complex of three polypeptides - Tn C, Tn T and Tn I.



Tn T binds the troponin complex to tropomyosin molecule

Tn I is the ATPase inhibitor

Tn C binds Ca^{2+}

TnT and TnI are used in AMI diagnosis

- **Cardiac-specific isoforms of both have been identified, beeing highly specific and sensitive for myocardial damage.**
- **Their greatest use is to exlude cardiac damage in a patient with chest pain: AMI is highly unlikely if there is no increase in troponins.**
- **The soluble fraction of Tn I and T is released together with the other cytosolic markers during the reversible phase of mycardial injury. The insoluble fraction of Tns is released after the irreversible necrosis when there is a decline in the concentration of cytosolic markers.**

TnT

- cardiac-specific isoform **cTnT** different from TnT of cross-striated muscle cells

- !: **re-expression of cTnT during regeneration and degenerative changes in skeletal muscles**
  (dermatomyositis/polymyositis, Duchene muscular dystrophy, post-traumatical regeneration of muscles)
  dialysed patients (↑ cTnT in 30%)

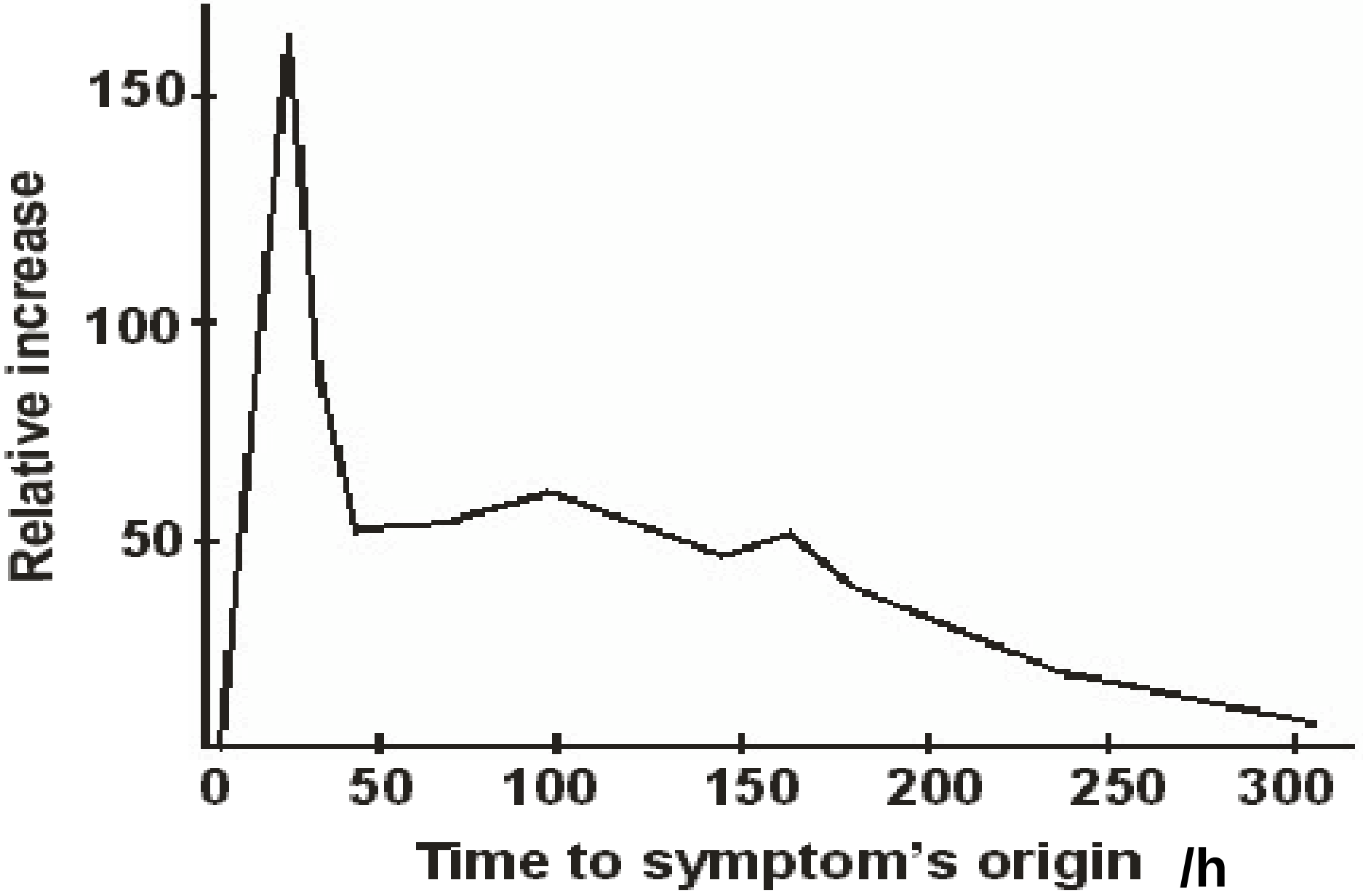
TnT

- start of plasma level elevation in 3.5-10 h
- peak around 18 hours post infarction (free troponin present in cytosol)
- remains elevated for 2-3 weeks due to its continued release from contractile apparatus

TnI

- more specific for myocardium than TnT
- cardiac-specific isoform cTnI (31 AA) is not produced by fetal cross-striated muscle cells
- increase of cTnI in dialysed patients is less often than cTnT
- start of elevation in 3.5-10 h,
  peak in 9-18 h ,
  remains elevated for 2-3 weeks

Dynamic of TnI and TnT release at patients with AMI



TnT x TnI

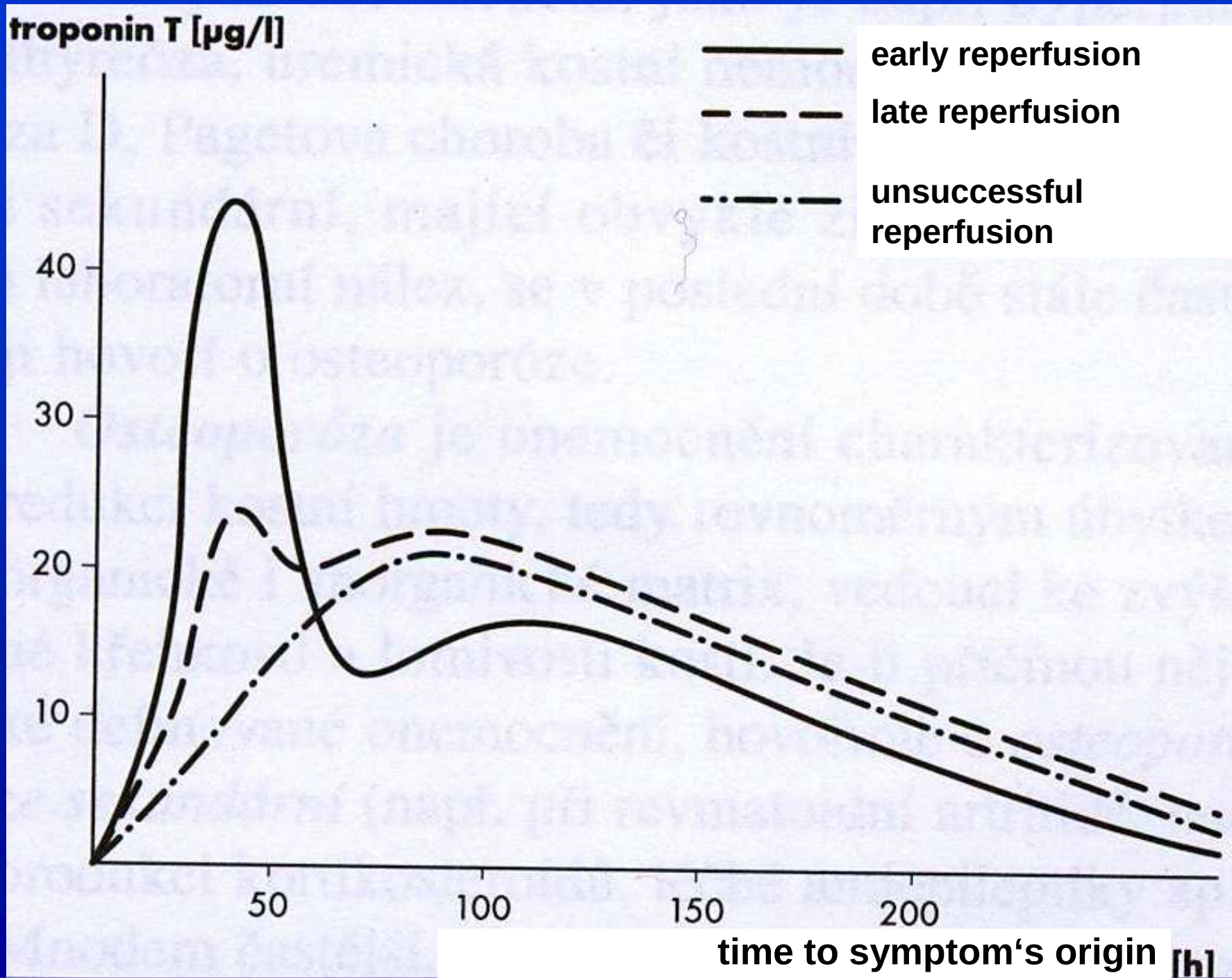
- the method for assessment of TnT is identical worldwide
- a variety of kits for different methods for assessment of TnI represent the major disadvantage of its clinical use (different cut off values, difficulties in comparison)

- TnI - more specific for myocardium
- TnT – problem with increase interpretation in patients with renal failure and systemic degenerative processes

TnT in thrombolytic therapy monitoring

- If this therapy is succesful in restoring perfusion, there is a rapid rise in plasma cardiac markers (wash-out phenomenon). The rises are slower and last longer if occlusion remains.

- Evaluation:
- T_{max}-T_0 (time to peak): fibrinolysis start - plasma value peak; < 14 h in successful reperfusion, > 14 h if occlusion remains
- c_1-c_0 (slope) or c_1/c_0 (ratio): concentration increase steepness in 1st h of therapy; c_1-c_0 > 0.2 µg/l in successful reperfusion


troponin T [µg/l]
early reperfusion
late reperfusion
unsuccessful reperfusion
40
30
20
10
50
100
150
200
time to symptom's origin
[h]

Myoglobin

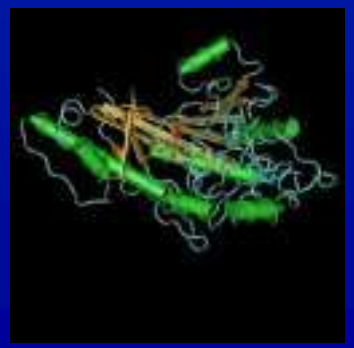
- cytosolic protein, sensitive indicator of cardiac damage, but is non-specific, being present in skeletal muscles as well
- released early following infarction. It‘s the earliest AMI indicator and, as such, is useful for decisions on thrombolytic therapy.
- start of elevation 0.5 - 2 h,
  peak in 6 - 12 h,
  return to normal values in 14 - 18 h

AST (aspartate aminotransferase)

- **1st marker used for AMI dg**
- **aspartate + α-ketoglutarate ↔ oxalacetate + glutamate**
- **non-specific for myocardium, ↑ in skeletal muscle diseases, haemolysis, liver or pulmonary diseases etc.**
- **in AMI ratio AST/ALT >1**
- ***non recommended for AMI dg***

CK (creatin kinase)

- **creatin + ATP ↔ creatin phosphate + ADP**
- **non-specific for myocardium, high activity mainly in skeletal muscles**
- **↑ in physical activity, muscle injuries including i.m. injections etc.**
- ***non recommended for AMI dg***



CK

- 3 types of isoenzymes formed by 2 subunits: B (brain) ■ and M (muscle) ●

- each isoenzyme is a combination of 2 subunits :
- CK-BB ■ ■ typical for brain
- CK-MB ● ■ myocardium
- CK-MM ● ● muscles and myocardium

- myocardium: 42% MB, 58% MM
- skeletal muscles: 97% MM, 3% MB

- *CK-MB previously used for AMI dg*

CK-MB mass

- **imunochemical assessment of concentration in mg/l, no activity**
- **reaction with specific antibody → also determination of partly destroyed molecules without enzymatic activity → higher sensitivity than CK-MB**

LD (lactate dehydrogenase)

- **lactate + NAD^+ ↔ pyruvate + NADH + H^+**
- **non-specific for myocardium, present in all body tissues**
- ***non recommended for AMI dg, formerly used for late dg***

LD

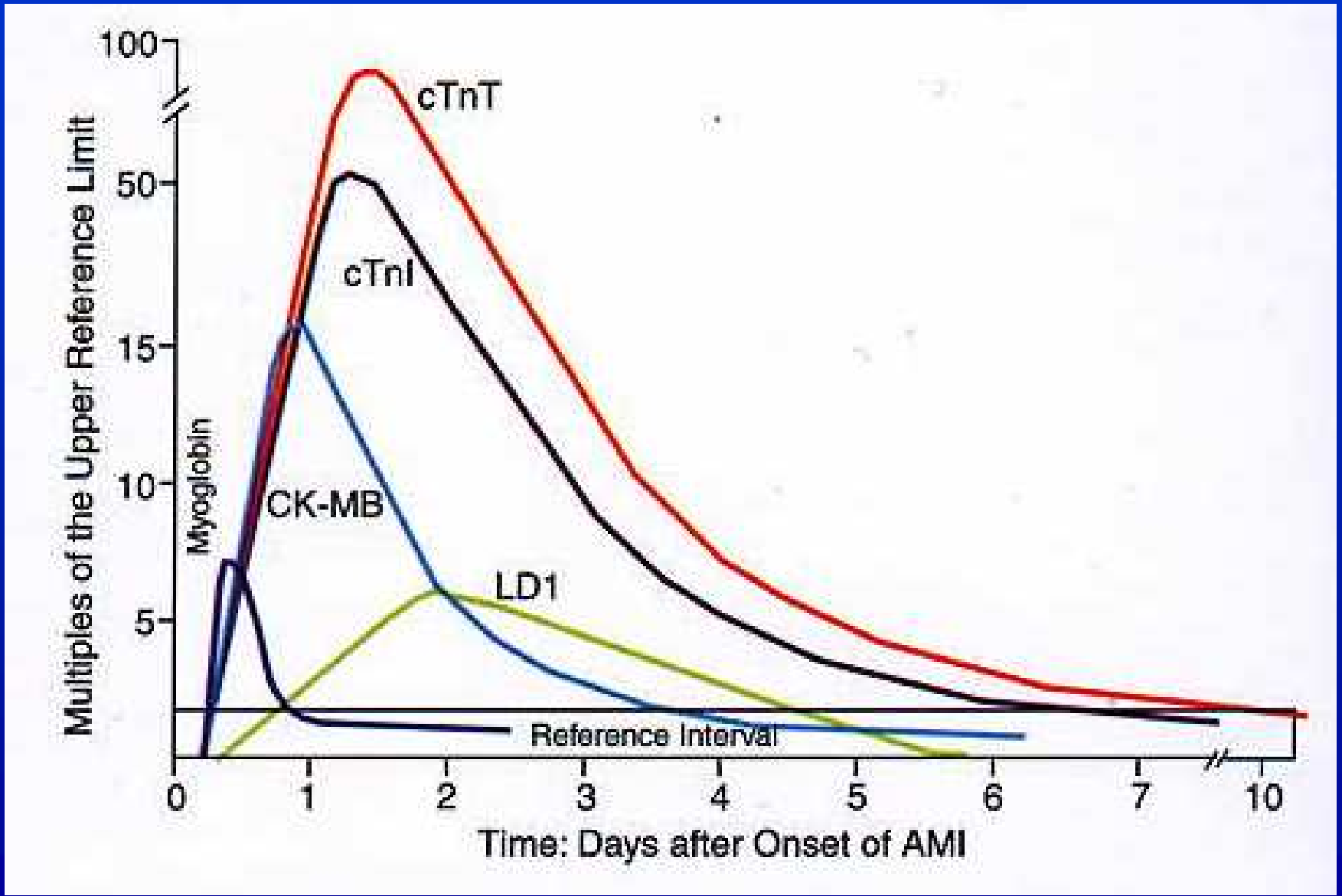
- 5 isoenzymes formed by 4 subunits, 2 types of subunits - H (heart) ● and M (muscle) ●

isoenzyme	tissue
LD_1 ● ● ● ●	myocardium, ercs, kidneys
LD_2 ● ● ● ●	myocardium, ercs, kidneys
LD_3 ● ● ● ●	muscles, lymphatic tissue, leukocytes
LD_4 ● ● ● ●	liver, muscles
LD_5 ● ● ● ●	liver, muscles

- myocardium typical isoenzymes LD_1 and LD_2 are called *HBD* (2-hydroxybutyrate dehydrogenase (↑ substrate afinity to 2-OHbutyrate than lactate)

enzyme	start of elevation	peak	return to normal values
AST	4-8 h	16-48 h	3-6 d
CK	3-6 h	16-36 h	3-5 d
LD	6-12 h	24-60 h	7-15 d

Dynamic of selected cardiac markers



Physiological or cut off values of cardiac markers

- **TnT** ≤ 0.03 µg/l
- **TnI** from ≤ 0.01 to ≤ 1.5 µg/l (different methods)
- **Mb** ♂ 16-76 µg/l ♀ 7-64 µg/l
- **CK-MB mass < 5 µg/l**

- **AST** ♂ ≤ 0.7 µkat/l ♀ ≤ 0.6 µkat/l
- **CK** ♂ 0.41-3.16 µkat/l ♀ 0.41-2.83 µkat/l
- **CK-MB** ≤ 0.4 µkat/l, or 6% of total CK
- **LD** ♂ 3.3-7.5 µkat/l ♀ 3.3-6.3 µkat/l
- **HBD** ≤ 3.0 µkat/l

OTHER BIOCHEMICAL AND HAEMATOLOGICAL TESTINGS IN AMI

- WBC
- sedimentation rate, CRP
- glycaemia
- Na, K, Cl, Ca, Mg
- cholesterol, triglycerides
- FBG
- coagulation
- acid-base balance
- urea, kreatinin
- uric acid, bilirubin
- ALT, AST, ALP, GMT, LD

OTHER MARKERS IN DG OF ACUTE CORONARY SYNDROMES

- ***GPBB*** ***(cardiac-specific BB isoenzyme of glycogen phosphorylase)***
- **glycogen phosphorylase – enzyme of glycogenolysis**
- **3 isoenzymes formed by 2 subunits, 3 types of subunits– B, M, L:**

• **isoenzyme**	**BB**	**brain and myocardium**
	MM	**skeletal muscles**
	LL	**liver**

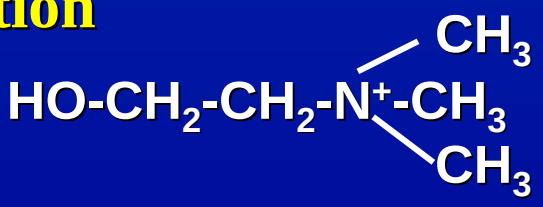
- **very sensitive and early indicator of myocarial injury**
- **↑ in 0.5-2 h, return to normal values in 2 days**
- **peak about 20times the amount of the physiological value**

OTHER MARKERS IN DG OF ACUTE CORONY SYNDROMES

- **IMA (ischemia-modified albumin)**
- modified N-terminal → modified ability of microelements binding
- very early non-specific marker ~ in serum occurs minutes after attack, peak in 1 or more h, return to normal values in 6-12 h

- **HFABP (heart fatty acids binding protein)**
- common marker as GPBB

- **WBCHO (whole blood cholin)**
- considering the risk of AS plaque destabilisation
- ↑ in liver and renal failure and tumors



- research

Cardiac failure

fale of the heart to pump enough blood to satisfy the needs of the body

- ***old markers:*** **CK and CK-MB are normal**
- **AST, ALT, and LD_5 are elevated as a result of liver congestion**

- ***new markers:*** **natriuretic peptides**

Natriuretic peptides

hormones synthesized, stored and released by cardiomyocytes

- **vasorelaxation and natriuretic effects**

- **secretion stimulated by: atrial distension or hypertrophy, ventricle overload, myocardial ischemia, blood volume expansion, glucocorticoids, hypoxia, thyroideal dis.**

ANP (atrial NP)

- 28 AA peptide with a 17 AA ring formed by a disulfide bond in the middle of the molecule

- produced, stored and released by atrial myocytes in response to:
  - atrial distention
  - stretching of the vessel walls
  - sympathetic stimulation of β–rec.
  - hypernatremia
  - ANGT-II
  - endothelin (vasoconsrtictor)

Physiological effects of ANP

- **Renal**
- ↑ the glomerular filtration rate (GFR), resulting in greater excretion of Na^+ and water
- ↓ Na^+ reabsorption
- inhibits renin secretion, thereby inhibiting the RA system
- ↓ aldosterone secretion
- **Cardiovascular**
- relaxes vascular smooth muscle by: ↑ of vascular smooth muscle cGMP and inhibition of the effects of catecholamines
- inhibits maladaptive cardiac hypertrophy
- **Adipose tissue**
- ↑ the release of free fatty acids from adipose tissue
- ↑ intracellular cGMP levels that induce the phosphorylation of a hormone-sensitive lipase

Tests showing elevated levels of BNP or NT-proBNP in the blood are used as a diagnosis of heart failure and may be useful to establish prognosis in heart failure, as both markers are higher in patients with worse outcome.

Both BNP and NT-proBNP have been approved as a marker for acute congestive heart failure. The plasma/serum concentrations are increased in patients with asymptomatic and symptomatic left ventricular dysfunction.

BNP (brain NP)

- originally identified in extracts of porcine brain, but in humans it is produced mainly in the cardiac ventricles
- 32 AA polypeptide secreted in response to excessive stretching of ventricular myocytes
- synthesized as pre-pro-hormone → proBNP (AA 1-108) - cleavage → BNP (AA 77-108) and inactive NTproBNP (AA 1-76)

BNP /P

- Binds to and activates NP receptor system in a similar fashion to ANP but with 10-fold lower affinity; its biological half-life is, however, twice as long.

- **Effects:** ↓ in systemic vascular resistance and central venous pressure → ↑ in natriuresis
  ↓ in cardiac output and ↓ in blood volume
  renin and aldosterone synthesis inhibition

- **cut off = 100 ng/l** = 28.90 pmol/l
- (1 pmol/l = 3.460 ng/l; 1 ng/l = 0.289 pmol/l)

NTproBNP (N-terminal) /S

- 76 AA N-terminal fragment co-secreted with BNP
- synthesized as pre-pro-hormone → proBNP (AA 1-108) - cleavage → BNP (AA 77-108) and inactive NTproBNP (AA 1-76)

- cut off = 125 ng/l = 14.75 pmol/l
- (1 pmol/l = 8.457 ng/l; 1 ng/l = 0.1182 pmol/l)