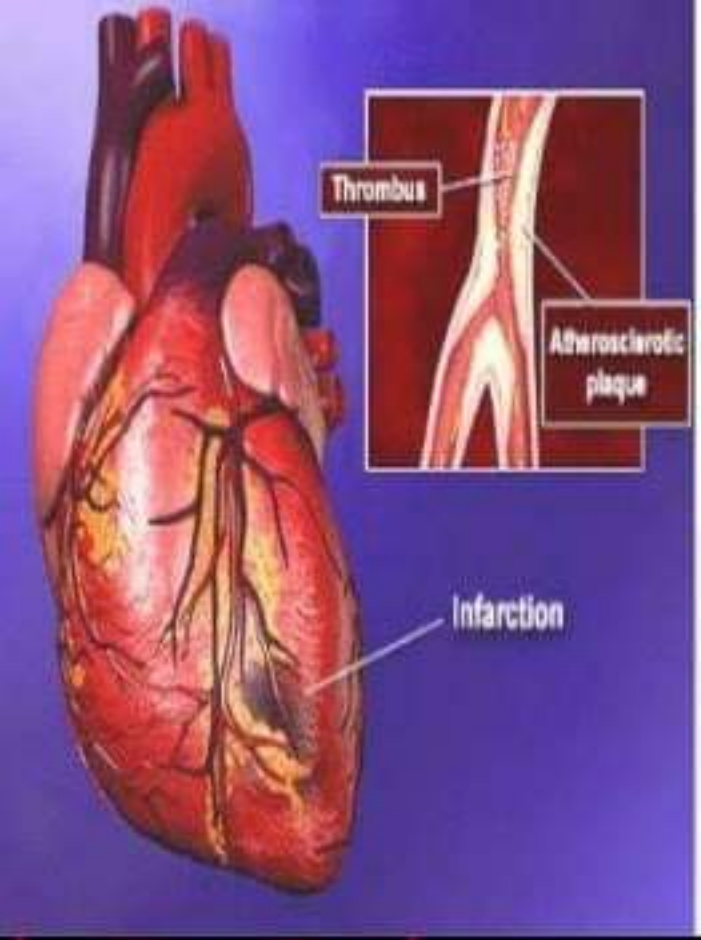


Myocardial Infarction

Gandham. Rajeev

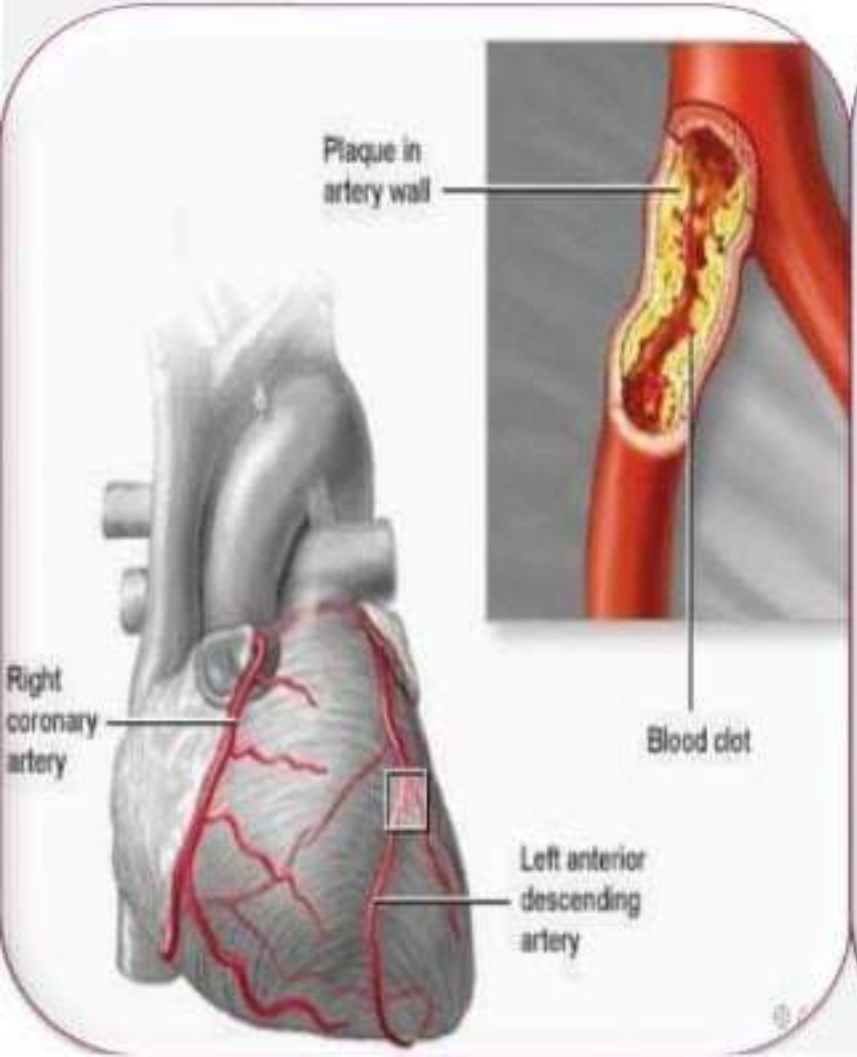
Introduction

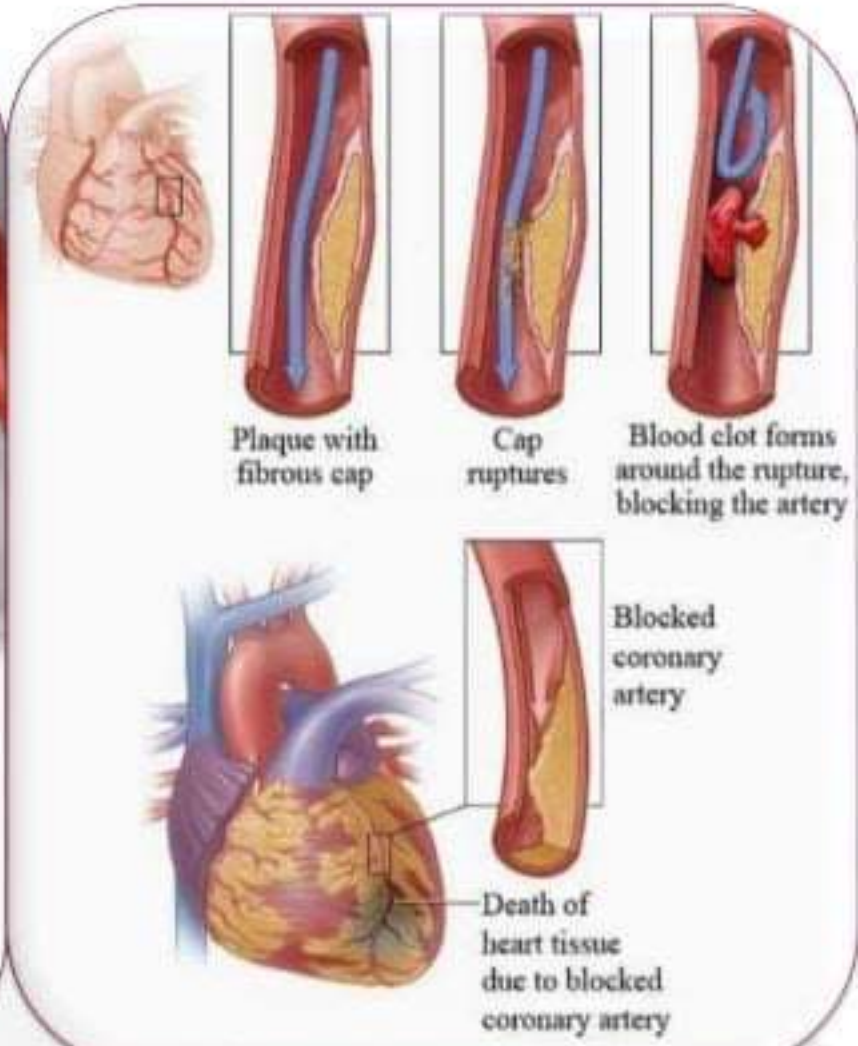
- What is MI
- Mechanism of Atherosclerosis
- Diagnosis of MI
- Cardiac Biomarkers
- Summary

Myocardial Infarction (MI)

- MI is caused by reduced blood supply to the myocardium resulting in death of cardiac myocytes.
- This results from rupture of plaque & thrombosis in the area of coronary atherosclerosis.
- Features:
- More severe chest pain, sweating, anxiety & nausea.
- Complications:
- Shock & conduction disturbances resulting in arrhythmias.

Myocardial Infarction (MI)





Atherosclerosis

- The most common vascular disease.
- Characterized by thickening or hardening of medium & large sized arteries due to the accumulation of cholesterol & other lipids, leads to formation of plaque & results in endothelial damage.
- Atherosclerosis is a progressive disorder that narrows & ultimately blocks the arteries.

Risk factors

Conventional risk factors	
Modifiable life style characteristics	Diet, High in saturated fat, Cholesterol & calories, Excess alcohol consumption, Physical inactivity, Cigarette smoking
Modifiable Biochemical or Physiological characteristics	Elevated Cholesterol, LDLC, Low levels of HDLC, DM, Obesity, Met S
Non-modifiable personal characteristics	Genetic, Age & Male sex
Newer (novel) risk factors	Left ventricular hypertrophy, Hyperhomocysteinemia, Fibrinogen, CRP, Lipoprotein (a) excess, Plasminogen activator inhibitor -1(PAI-1), Oxidative stress, Hypertriglyceridemia, Infectious agents

Mechanism of Atherosclerosis

- **Stage I:**
- **Formation of foam cells: Increased levels of cholesterol for prolonged periods will favour deposits in the subintimal region of arteries.**
- **Aorta, coronary arteries & cerebral vessels are predominantly affected by this process.**
- **LDLC, especially oxidized LDL particles are deposited in the walls of arteries.**

- The oxidized LDLC is taken up by macrophages of immune system.
- Free radical induced oxidative damage of LDL will accelerate this process.
- These macrophages are overloaded with lipid (cholesterol & oxi-LDLC) & these are called as "foam cells".
- These form the hallmark of atherosclerotic plaques.

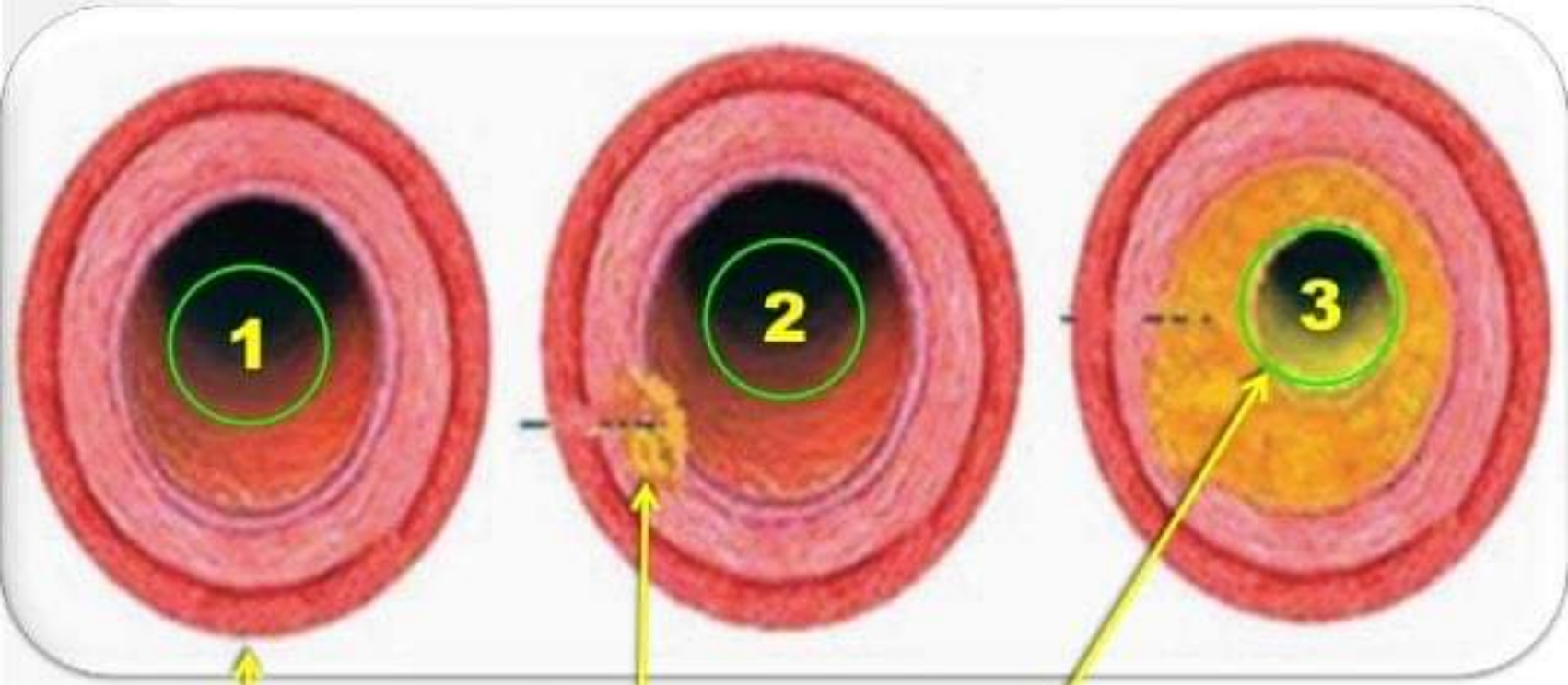
- **Stage II: Progression of atherosclerosis:**
- **Smooth muscle cells containing lipid droplets are seen in the lesion.**
- **Plaques are composed of smooth muscle cells, connective tissue, lipids & debris that accumulate in intima of arterial wall.**

- Plaque progresses with age as follows.
- Endothelial cell of the artery wall are injured either by oxidized LDL or mechanically.
- The injured area is exposed to blood & attracts monocytes which are converted to macrophages that engulf oxidized LDLC & converted to foam cells, which accumulate causing a fatty streak to develop within blood vessel.

- **Stage III:**
- **Fibrous proliferation:**
- Due to liberation of various growth factors by macrophages & platelets, lipoproteins, GAGs & collagen are accumulated.
- Thus there is a definite component of inflammation in atherosclerosis.
- This chronic inflammation leads to increased levels of plasma hs-CRP.

- Damaged endothelial cells cannot produce prostaglandins I_2 & prostacyclin (which inhibit platelet aggregation).
- Platelets begin to aggregate & release thromboxane A_2 (TXA_2).
- Thromboxane A_2 stimulate platelet aggregation.

- **Stage IV:**
- **Advancing fibrous plaque:**
- **Damaged endothelial cells also release platelet derived growth factor (PDGF).**
- **The growth factors cause proliferation of smooth muscle cells, which migrate from medial to intimal layer arterial wall & contributes to the formation of atherosclerosis plaques.**
- **This leads to narrowing of blood vessels & leads to heart attacks.**



1. Normal artery
2. Early plaque formation
3. Advanced plaque formation

Diagnosis of MI

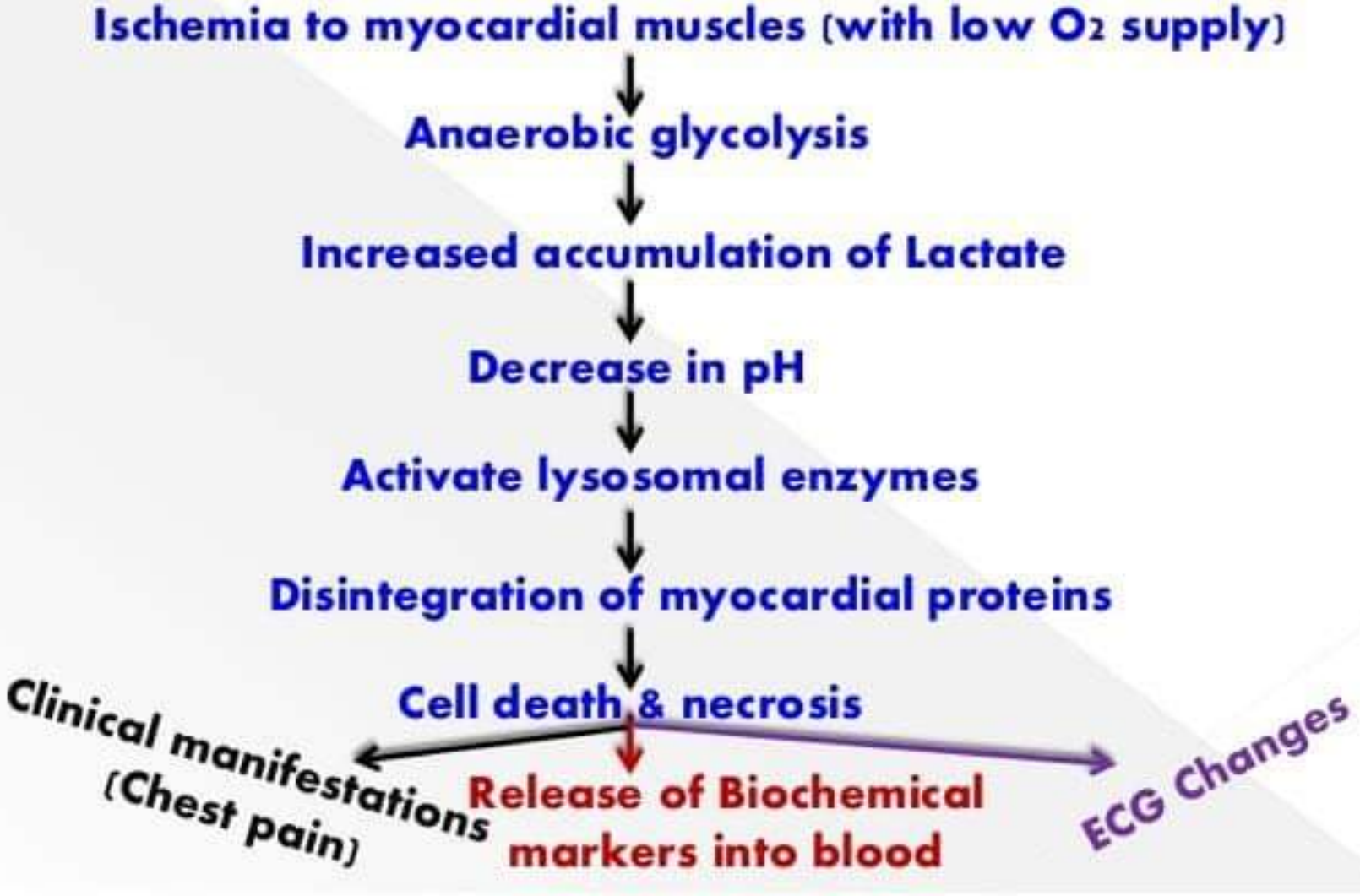
- According to WHO,
- Requires 2 of the following:

1. Clinical Manifestations
2. ECG changes
3. Elevation of Cardiac Biomarkers

Markers for cardiac diseases

- Creatine kinase & Creatine kinase -MB (CK-MB)
- Cardiac troponin I (cTI) & Cardiac troponin (cTT)
- Lactate dehydrogenase (LDH)
- Aspartate transferase (AST)
- Myoglobin (Mb)
- Brain natriuretic peptide (BNP)
- *BNP is a reliable marker of ventricular function*

Biochemical Changes in MI
(Mechanism of release of Cardiac markers)



Criteria for ideal markers for MI

- **Specific:** To myocardial muscle cells (no false positive)
- **Sensitive:** Rapid release on onset of attack (diagnose early cases) - so, can detect minor damage.
- **Prognostic:** Relation between plasma level & extent of damage.
- **Persists longer:** So, can diagnose delayed admission.
- **Simple, inexpensive:** Can be performed anywhere by low costs & no need for highly qualified personnel.
- **Quick:** *Low turnaround time.*

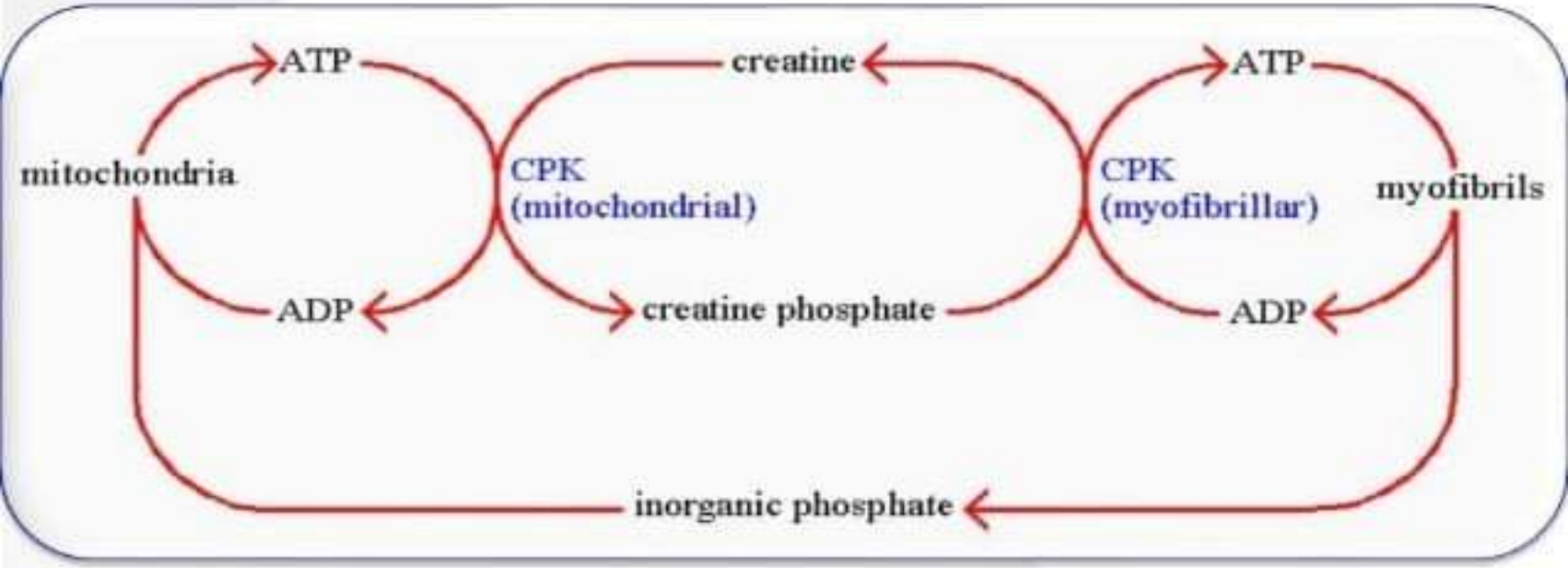
Cardiac Biomarkers

- **Enzyme markers:**
- **CK & CK-MB**
- **AST**
- **LDH, LDH_1 & LDH_2**
- **Non-enzyme markers:**
- **Myoglobin (Mb)**
- **Cardiac Troponins**

Creatine phosphokinase (CPK)

- It catalyses formation of creatine phosphate from creatine & ATP.
- Biological reference interval:
- Males :15-100 U/L
- Females: 10-80 U/L
- CPK consists of 3 isoenzymes.
- Each isoenzyme of CK is a dimer & MW of 40 kD.
- Subunits are called B for brain (chromosome -14) & M for muscle (chromosome -19)

Creatine Phosphokinase (CPK)



- It is an important enzyme in energy metabolism.
- Immediate source of ATP in contracting muscle.

- Iso-enzymes are separated by electrophoresis.
- CPK-1 (also called CPK-BB) is found mostly in the brain & lungs.
- CPK-2 (also called CPK-MB) is found mostly in the heart (heart iso-enzyme)
- CPK-3 (also called CPK-MM) is found mostly in skeletal muscle.
- CK-MB released after 3-6 hrs after onset of MI

Creatine phosphokinase isoenzymes

Isoenzymes	Sub-Unit	Tissue of Origin	% In Blood
CK1 Fast moving	BB	Brain	1%
CK2 Intermediate	MB	Heart	5%
CK3 Slow moving	MM	Skeletal muscle	80%

Clinical significance of CPK

- **CPK & heart attack:**
- **CPK_2 iso-enzymes is very small, (5% of total CPK activity).**
- **In myocardial infarction (MI), CPK_2 levels are increased within 4 hrs, then falls rapidly.**
- **Total CPK level is elevated up to 20-folds in MI.**
- **CK level is not increased in hemolysis.**

CPK & Muscle diseases

- CPK level is elevated in muscular dystrophy (500-1500U/L)
- CPK level is highly elevated in crush injury, fracture & acute cerebrovascular accidents.
- Estimation of total CPK is employed in muscular dystrophies & CPK-MB isoenzyme is estimated in myocardial infarction.

Atypical forms of CK

- Two atypical isoforms.

1. **Macro-CK (CK-macro)**

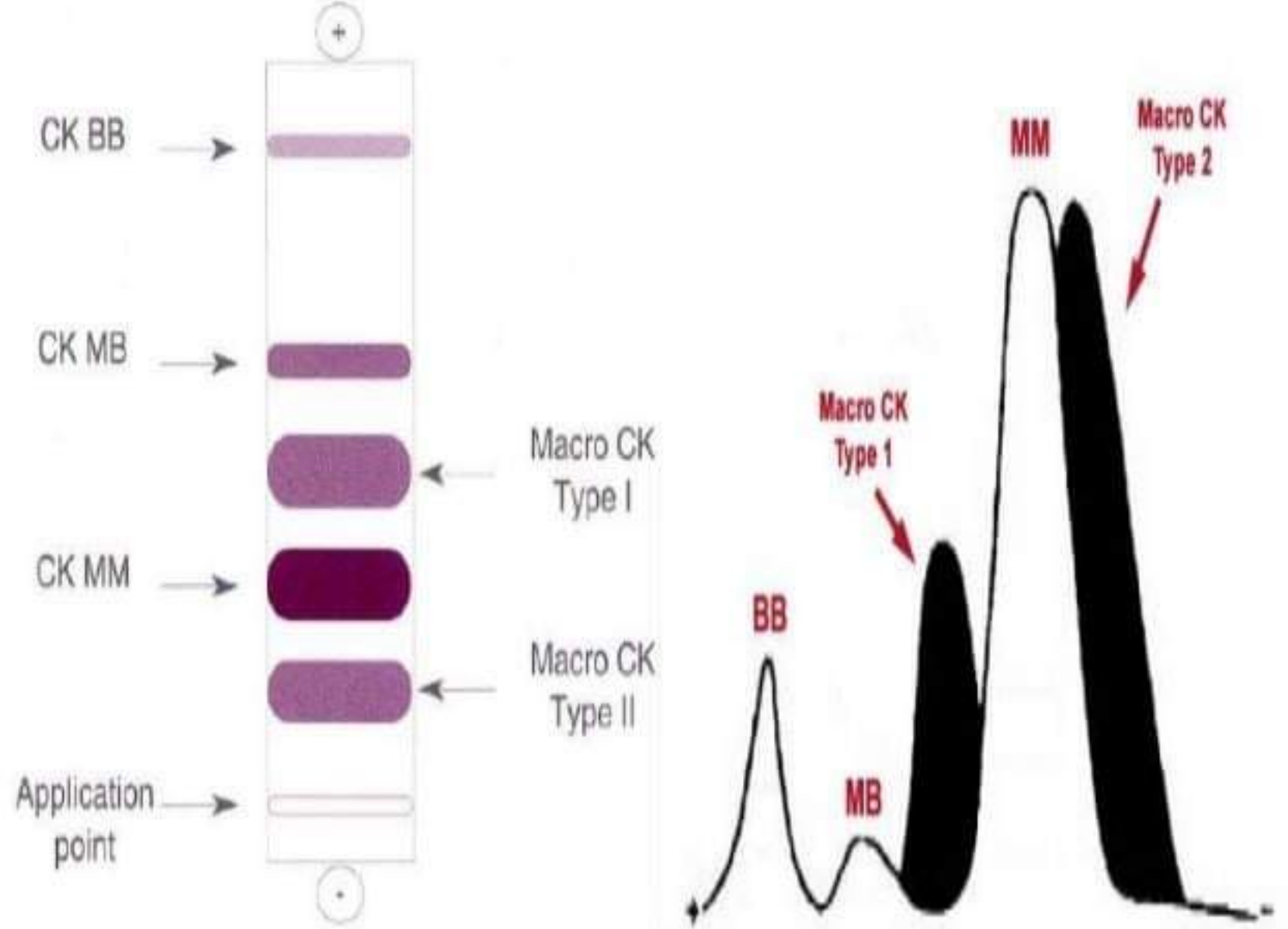
- Formation:
- Formed by aggregation CK-MB with IgG, sometimes IgA.
- Also formed by complexing CK-MM with lipoproteins.
- Electrophoretically migrates between CK-MB & CK-MM.
- Occurs frequently in women above 50 years.
- Significance:
- Not significant.

CK-Mi (Mitochondrial CK-Isoenzyme)

- **Formation:**
- **Present**, bound to the exterior surface of inner mitochondrial membrane of muscle, liver & brain.
- **It** exist in dimeric form or oligomeric aggregates & molecular weight 35,000
- **Electrophoretically**, migrates towards cathode & is behind CK-MM band.

Clinical significance

- It is present in serum when there is extensive tissue damage causing breakdown of mitochondrial & cell wall.
- Its presence in serum indicate severe illness & cellular damage.
- It has been detected in cases of malignant tumours.


+
CK BB
CK MB
CK MM
Application point
-
Macro CK Type I
Macro CK Type II
BB
MB
Macro CK Type 1
MM
Macro CK Type 2

Cardiac troponins (CTI/CTT)

- They are not enzymes, accepted as reliable markers for MI
- One of the main tests in early detection of an ischemic episode & in monitoring the patient.
- The troponin complex consists of 3 components
- Troponin C (calcium binding subunit),
- Troponin I (actomyosin ATPase inhibitory subunit)
- Troponin T (tropomyosin binding subunit)

Cardiac troponin I

- Troponin I (TnI) is encoded by 3 different genes, giving rise to 3 isoforms; the "slow" & "fast" moving forms are skeletal variety.
- Cardiac isoform is specific for cardiac muscle; the amino acid sequence is different in skeletal muscle isoform.
- Cardiac isoform of CTnT & CTnI are mainly (95%) located in myofibrils & 5% is cytoplasmic.

- Troponins are seen in skeletal & cardiac muscles, but not in smooth muscles.
- Human cTnI contains 30 amino acid residues.
- Troponin I is released into the blood within 4 hours after the onset of symptoms of myocardial ischemia; peaks at 14-24 hours & remains elevated for 3-5 days post-infarction.
- CTI is very useful as a marker at any time interval after the heart attack.

- It is not increased in muscle injury.
- The initial increase is due to liberation of the cytoplasmic fraction and sustained elevation is due to the release from myofibrils.

Cardiac troponin T

- Cardiac Troponin T has an unique 11 amino acid sequence.
- Serum level of Troponin T (TnT) increases within 6 hrs of myocardial infarction, peaks at 72 hours and then remains elevated up to 7-14 days.

High sensitive cardiac troponin T (hs-TnT)

- Elevated cTn levels indicate cardiac injury, includes ACS, stroke, pulmonary embolism, sepsis, acute perimayocarditis, acute heart failure & tachycardia.
- hs-cTnT determines very low cTn concentrations.
- It allows identification of AMI patients in first 3 hrs following symptoms.
- Even small increases are associated with higher risk of death.

Troponin I and T

Cardiac Specific Marker

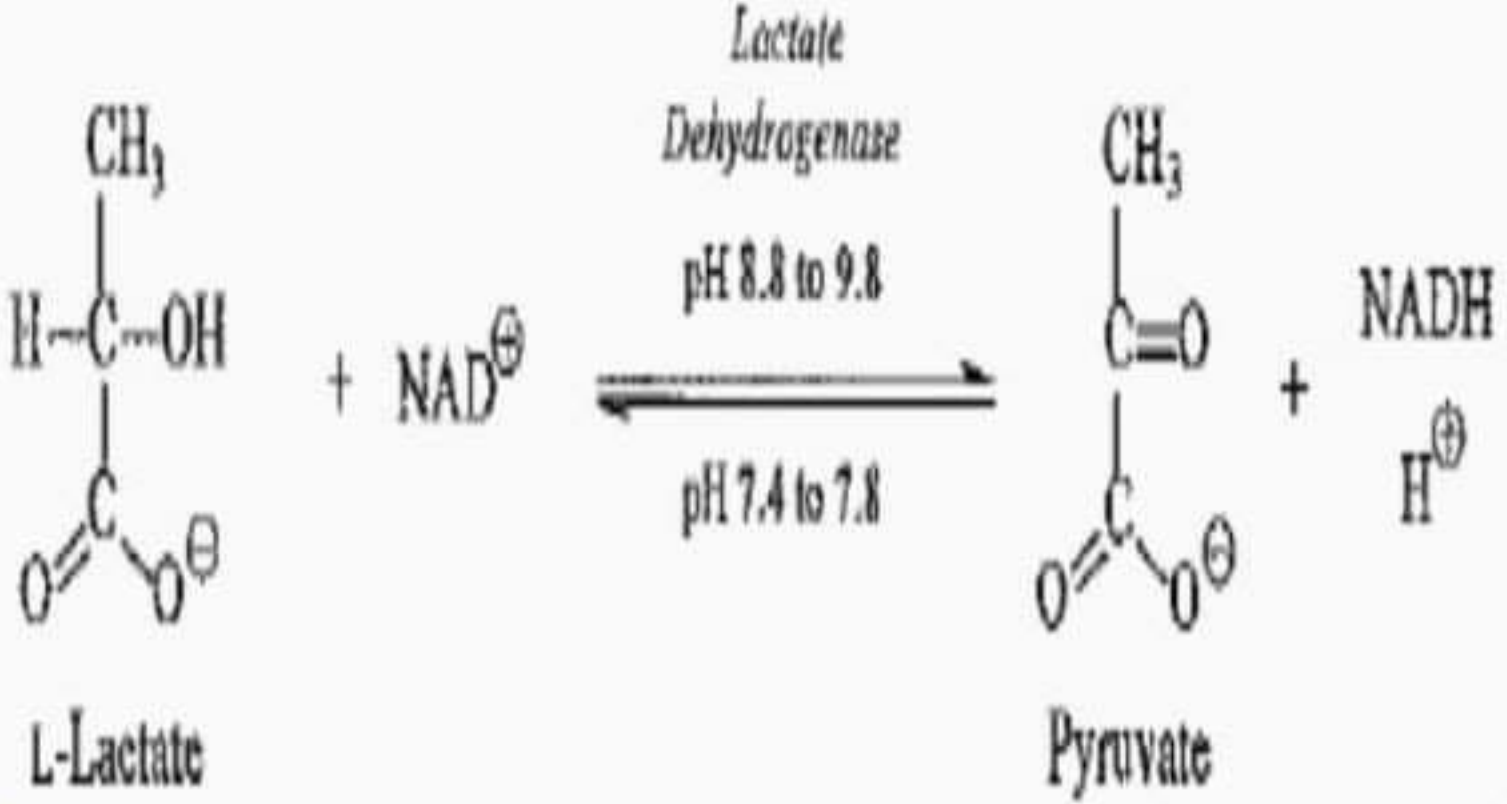
Post AMI		Troponin I	Troponin T	CKMB
Increase	Hrs	4-6	3-6	4-6
Peak	Hrs	14-24	10-24	10-24
Return to Normal	Days	5-7	6-10	2-3

Lactate Dehydrogenase

- LDH is an enzyme present in a wide variety of organisms
- Molecular weight- 32 kD & it is tetramer
- M (A) -muscle –chromosome 11
- H (B) -heart – chromosome 12
- Lactate dehydrogenase, reversibly converts lactate to pyruvate, in different tissues.

- **Hemolysis will result false positive.**
- **LDH consists of 5 iso-enzymes – LDH_1, LDH_2, LDH_3, LDH_4 & LDH_5**
- **These isoenzymes are separated by cellulose acetate electrophoresis at pH 8.6**
- **Biological reference interval:**
- **Serum -100 -200 U/L**
- **CSF - 7 -30 U/L**
- **Urine - 40 -100 U/L**

LDH reaction



Isoenzymes of lactate dehydrogenase	Highest levels found in the following:	Isoenzymes of lactate dehydrogenase	Highest levels found in the following:
		 H_2M_2 (LDH_3)	Brain, lung, white blood cells
 H_4 (LDH_1)	Heart, kidneys	 HM_3 (LDH_4)	Lung, skeletal muscle
 H_3M (LDH_2)	Red blood cells, heart, kidney, brain	 M_4 (LDH_5)	Skeletal muscle, liver

LDH Isoenzymes

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LDH Isoenzymes

LDH isoforms

Isoenzyme	Composition	Electrophoretic migration	Present in	Elevated in
LDH 1 Heat resistant	(H_4)	Fastest moving	Myocardium, RBC, kidney	myocardial infarction
LDH2 Heat resistant	(H_3M_1)	Faster	Myocardium, RBC, kidney	Kidney disease, megaloblastic anemia
LDH3	(H_2M_2)	Fast	brain	Leukemia, malignancy
LDH4 Heat labile	(H_1M_3)	Slow	Lung, Liver	Pulmonary infarction
LDH5 Heat labile Inhibited by urea	(M_4)	Slowest moving	Skeletal muscle, Liver	Skeletal muscle & liver diseases

Clinical significance of LDH

- In normal serum, LDH_2 (H_3M) predominant isoenzyme & LDH_5 is rarely seen.
- In myocardial infarction, LDH_1(H_4) levels are greater than LDH_2, called flipped pattern
- Megaloblastic anemia (50 times upper limit of LDH 1 and LDH 2)
- Muscular dystrophy, LDH_5 (M_4) is increased.
- Toxic hepatitis with jaundice (10 times more LDH_5)

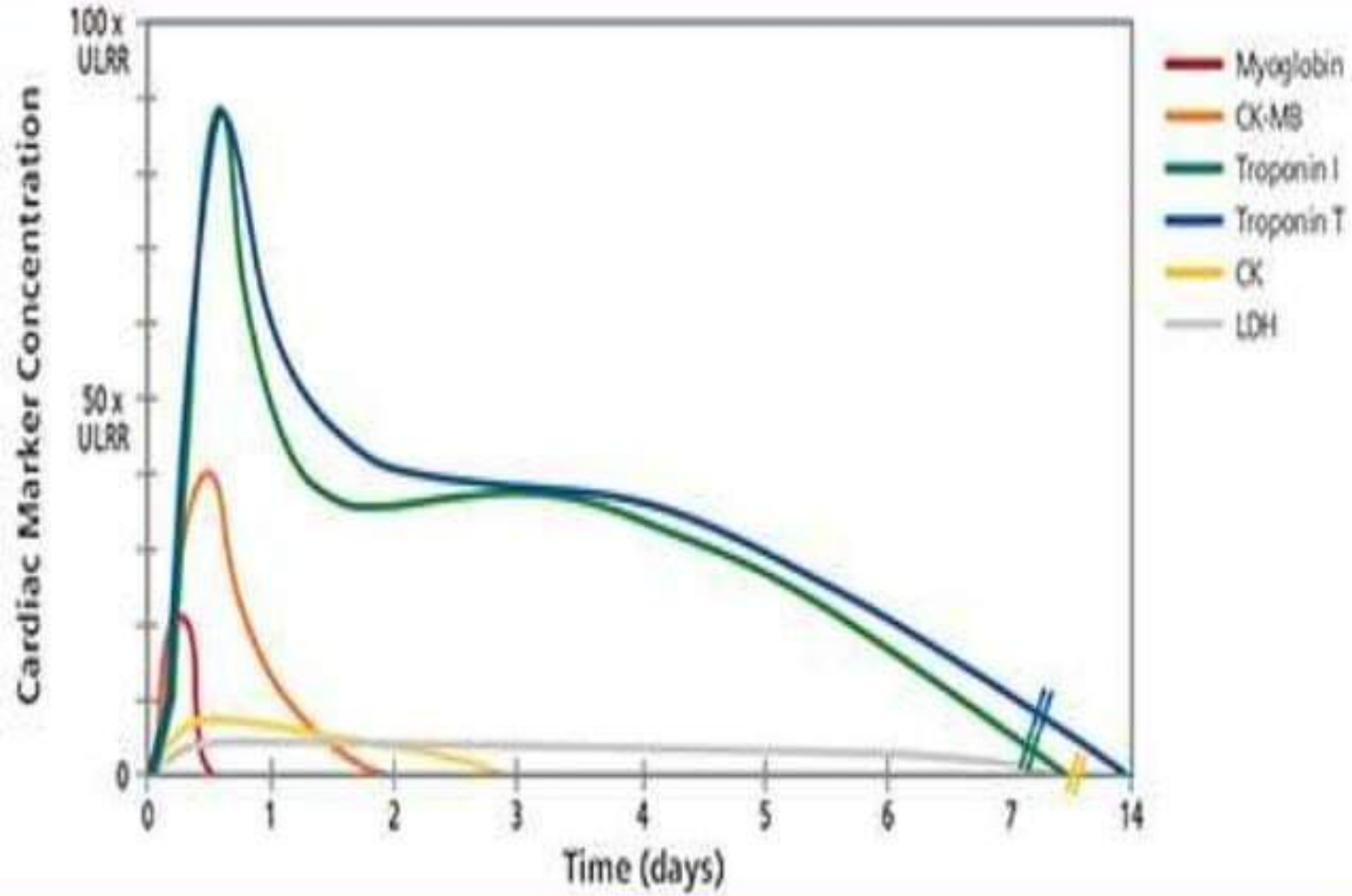
Aspartate aminotransferase (AST)

- Serum glutamate oxaloacetate transaminase (SGOT).
- AST needs PLP (vitamin B_6) as co-enzyme.
- Biological reference interval: 8 to 45 U/L.
- It is a marker of liver injury & shows moderate to drastic increase in parenchymal liver diseases like hepatitis & malignancies of liver.
- AST was used as a marker of myocardial ischemia in olden days.
- Significantly elevated in myocardial infarction.
- But troponins have replaced AST as a diagnostic marker in IHD

Myoglobin (Mb)

- Raised after MI.
- Non specific & increased in muscular injuries.
- A negative value will exclude MI.
- Useful in early hours of chest pain.

Cardiac Markers: Approximate Levels vs. Time of Onset Post MI



Brain Natriuretic Peptide (BNP)

- Natriuretic peptide family consists of 3 peptides:
- Atrial natriuretic peptide (ANP),
- Brain natriuretic peptide (BNP)
- C-type natriuretic peptide (CNP).
- The clinical significance of CNP is not clear.
- ANP is produced primarily in the cardiac atria.
- BNP is present in human brain, but more in the cardiac ventricles.

- Human pro-BNP contains 108 amino acids.
- It is cleaved by enzymes within cardiac myocytes into the active C-terminal BNP (32 amino acids) and an inactive peptide (proBNP 1–76).
- Both are seen in circulation.
- The active BNP is secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells (cardiomyocytes).

Clinical Significance

- Patients with congestive heart failure have high plasma concentrations of ANP and BNP.
- The concentrations are correlated with the extent of ventricular dysfunction.
- High concentrations of BNP predict poor long-term survival.
- In breathlessness, BNP test helps in the differentiation of the cause as heart failure or obstructive lung disease.
- The best marker of ventricular dysfunction is pro-BNP.

Other markers for MI

- **Myeloperoxidase (MPO):**
- **Marker for inflammation & oxidative stress.**
- **Produced by neutrophils, monocytes & endothelial cells.**
- **MPO levels predict mortality in patients with chronic heart failure.**
- **Involved in the development of atherosclerosis.**

- **Ischemia modified albumin (IMA):**
- **Myocardial ischemia alters the N-terminus of albumin.**
- **IMA measures ischemia in blood vessels.**
- **It has low specificity.**
- **Negative value is highly useful, it rules out the possibility of MI.**
- **Glycogen phosphorylase BB (GPBB):**
- **Glycogen phosphorylase exist in 3 forms.**
- **GP-BB isoform exist in heart & brain.**

- During ischemia, GP-BB is converted into a soluble form & released into blood.
- Rapid rise in blood is seen in MI & unstable angina.
- GP-BB levels elevated 1-3 hrs after ischemia.
- Pregnancy-associated plasma protein A (PAPP-A):
- PAPP-A is a zinc metalloproteinase.
- Increased levels of PAPP-A correlates with poor outcome in ACS & in stable CAD.

- **Homocysteine**
- **Levels increased in CVD.**
- **hs-CRP:**
- **Increased in inflammatory diseases**
- **Corin:**
- **Biomarker for heart failure**

Summary

- MI
- Lipid Levels
- Life style modifications.

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