# Clinical Laboratory Tests in Cardiovascular Diseases

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- The heart is divided by a septum into two halves. The halves are in turn divided into chambers.
- The upper two chambers of the heart are called atria, the lower two chambers are called ventricles.
- Valves allow blood to flow in one direction between the chambers of the heart.

# Diseases of the heart

- The diseases and conditions affecting the heart are collectively known as heart disease.
- The heart consists of a muscle that pumps blood, arteries that supply blood to the heart muscle, and valves that ensure that the blood within the heart is pumped in the correct direction.
- Problems can arise in any of these areas.
- Like cardiovascular disease, heart disease is a term that's somewhat loose and broad, it's often used in that way.

# Types Of Cardiovascular Disease

- Atherosclerosis
- Coronary heart disease (CHD)
- Chest pain (angina pectoris)
- Irregular heartbeat (arrhythmia)
- Congestive heart failure (CHF)
- Congenital and rheumatic heart disease
- Stroke

# Acute Myocardial Infarction

- Acute myocardial infarction is the rapid development of myocardial necrosis caused by a critical imbalance between the oxygen supply and demand of the myocardium.
- It is an irreversible myocardial injury from prolonged ischemia.
- Accurate and early diagnosis is important in minimizing cellular damage and, consequently, in obtaining a successful outcome for the patient

# Plaque formation

- **Risk Factors:**

Hyperlipiemia-LDL

Diabetes

Hypertension

Smoking

Obesity

## Initiation of atherosclerosis

Expression of adhesion molecules that allows the leukocytes to stick to the arterial wall.

## Early lesion- Fatty streak

Upon entry into the arterial wall blood monocytes begin to scavenge lipids and become foam cells.

- Stable atherosclerotic plaque

  Foam cells release further cytokines and effector molecules that stimulate smooth muscle cell migration from the arterial intima into the media, as well as smooth cell proliferation. Smooth muscle cells together with lipd core and matrix form a stable atherosclerotic plaque that will remain asymptomatic until it becomes large enough to obstruct arterial flow.

- Vulnerable plaque

  Inflammatory cell infiltrate, smooth muscle cell death through apoptosis and matrix degradation by matrix metalloproteinases generate a plaque with a thin fibrous cap and lipid-rich necrotic core. It is called a vulnerable plaque and it can rupture. Plaque rupture will expose its contents to blood and trigger platelet aggregation and thrombosis. It will result in partial or complete obstruction of the blood vessel leading to ischemia or infarction

- Ruling out AMI requires a test with high diagnostic sensitivity.
- Ruling in AMI requires a test with high specificity.
- A single test that will quickly and accurately assess AMI (acute myocardial infarction) does not exist.

- A combination of markers is used :
  - An early marker that increases within 6 hr. after onset of symptoms
  - A definite marker that increases after 6-9 hrs. and remains high for several days

# Cardiac Markers

**Cardiac markers should be:**

- absolutely heart specific
- highyl sensitive
- able to differentiate irreversible damage from reversible
- able to detect reocclusion and reinfarction
- able to monitor reperfusion therapy

- able to estimate size of infarct and prognosis
- stable
- able to make measurements rapidly
- easy to perform
- cost effective

# Enzymes as Cardiac Markers

- Creatine kinase (CK or CPK)
- Aspartate aminotransferase (AST)
- Lactate dehydrogenase (LDH or LD)

# Cardiac Proteins

- Myoglobin
- Troponins

# Creatine kinase

- Creatine kinase is an enzyme (cytoplasmic & mitochondrial)
- CK catalyses the conversion of creatine
- Uses ATP to create phosphocreatine (PCr) and ADP.
- This CK enzyme reaction is reversible, such that also ATP can be generated from PCr and ADP.
- **PCr serves as an energy reservoir for the rapid buffering and regeneration of ATP in situ and for intracellular energy transport**

- Total CK is %40 sensitive and %80 specific
  - CK-1(BB) : Brain
  - CK-2(MB) :Myocardium
  - CK-3(MM) :Skeletal muscle ,heart
- CK-3 has 3 isoforms :$CK\text{-}3_1$, $CK\text{-}3_2$ and $CK\text{-}3_3$ (posttranslational products)
- CK-2 has 2 isoforms

- CK-MB (CK-2) has the most specificity for cardiac muscle (>%85)
- CK-MB (CK-2) accounts for only 3-20 % of total CK activity in heart
- Normal skeletal muscle contains 1 % CK-2

# Creatine kinase MB isoenzyme is present in:

- Myocardium
- 1-2% in
  - Skeletal Muscle
  - Tongue
  - Small intestine
  - Diaphragm

# Factors increasing CK levels

- **Myocardial infarction**
- Cardioversion
- Cardiac Surgery
- Rapid Tachycardia
- Hypothyroidism
- Extensive Trauma
- Rhabdomyolysis (severe muscle breakdown)
- Muscular dystrophy
- Myopericarditis
- Recent **cocaine use**

CK-2 is increased in severe skeletal muscle injury (trauma/ surgery ),chronic muscle disease (muscular dystrophy, polymyositis ) and extreme exercise.

Reason:Regeneration process of muscle (reexpression of CK-MB genes )

In AMI,CK-MB increases at least 4-6 hr.after onset of chest pain,makes a peak at 12-24 hr. and returns to baseline level in 2-3 days (t 1/2 is 10-12 hr )

# Total CK can be elevated

- **IM injection**
- **Traumatic damage to skeletal muscle**
- **Hypothermia**
- **Exercise**
- **Intoxication**
- **Dose-related side effect in statin treatment**

# CK-MB FRACTION

- CK-MB fraction= CKMB /total CK
- **Rationale for using CK-MB fraction**
  - CK-MB fraction greater than 2.5% is suggestive of myocardial injury

# Aspartate aminotransferase (AST )

- Widely distributed in many tissues
- Highest concentrations are found in cardiac tissue, liver and skeletal muscle.
- Clinical utility in hepatocellular disorders and skeletal involvement.
- Unuseful in diagnosis of AMI
- Beginsto rise within 6-8 hr.
- Makes a peak at 24 hr.
- Generally returns to normal within 5 days.

# Lactate Dehydrogenase (LDH)

- A cytoplasmic enzyme found in skeletal, muscle, liver, heart, kidney and red blood cells
- 5 izoenzymes, composed of 4 subunit peptides of 2 distinct types:M (muscle ), H (heart)

- LDH isoenzyme determination increases specificity for cardiac tissue.
  - LD1 (HHHH):moves fastest towards anode
  - LD5 (MMMM):moves closest towards cathode
  - LD2 (HHHM )
  - LD3 (HHMM )
  - LD4 (HMMM )
  - LD1 in heart,kidney(cortex), red blood cells
  - LD5 in liver,skeletal muscle

- Not a tissue specific enzyme
- In AMI total LD -elevation at 12-18 hr
  - peak at 48-72 hr
  - return to baseline level after 6-10 days

- LD 1 (heart)
  - elevation at 10-12 hr
  - clinical specificity 85-90 in patients suspected of AMI
  - peak at 72-144 hr
  - return to normal >10 days

- Total LD patern ≈LD1 pattern (contrast with total CK and CK-2 pattern)
- Because of its prolonged half life, LD-1 is a clinically sensitive (%90) marker for infarction when measured after 24 hr.

# Cardiac Proteins

- Troponins
- Myoglobin

# Troponins

**Troponin is a regulatory complex of 3 protein subunits located on the thin filament of the myocardial contractile apparatus. Its function is the regulation of striated and cardiac muscle contraction. The complex regulates the calcium-modulated interaction between actin and myosin on the thin filament.**

- **Troponin C (18 kd)**
- **• Calcium-binding subunit**
- **• No cardiac specificity**
- **• Troponin I (26.5 kd)**
- **• Actomyosin-ATP-inhibiting subunit**
- **• Cardiac-specific form**
- **• Troponin T (39 kd)**
- **• Anchors troponin complex to the Tropomyosin strand**

- In the absence of calcium ions, tropomyosin blocks access to the mysosin binding site of actin. When calcium binds to troponin, the positions of troponin and tropomyosin are altered on the thin filament and myosin then has access to its binding site on actin..

- When the calcium level decreases, troponin locks tropomyosin in the blocking position and the thin filament slides back to the resting state.

# Tissue Specificity of Troponin Subunits

- **Troponin C is the same in all muscle tissues**
- **Troponins I and T have cardiac-specific forms, cTnI and cTnT**
- **cTnI and cTnT remain elevated for 10 to 14 days**

# Elevated troponin

- Acute infarction,
- Renal failure
- Severe pulmonary embolism causing acute right heart overload
- Heart failure
  - Myocarditis.
  - Tachy- or bradyarrhythmias, or heart block
  - Hypertrophic cardiomyopathy
  - Cardiac contusion or other trauma including surgery, ablation, pacing, implantable cardioverter-defibrillator shocks, cardioversion, endomyocardial biopsy, cardiac surgery, following interventional closure of atrial septal defects
  - Aortic dissection
  - Aortic valve disease
  - Apical ballooning syndrome - Takotsubo Cardiomyopathy
  - Rhabdomyolysis with cardiac injury
- Critically ill patients,
  - especially with diabetes, respiratory failure or sepsis
- Acute neurological disease
  - stroke or subarachnoid hemorrhage
- Infiltrative diseases
  - amyloidosis, hemochromatosis, sarcoidosis, and scleroderma
- Inflammatory diseases
  - myocarditis or myocardial extension of endo-/pericarditis, Kawasaki disease
- Burns, especially if affecting >25 percent of body surface area
- Extreme exertion

# Myoglobin

- $O_2$ binding protein of cardiac and skeletal muscle.
- Low molecular weight and cytoplasmic location-early appearance in circulation after muscle injury
- Cleared rapidly by kidney→unreliable as a long term marker of cardiac damage

Cardiac muscle trauma, skeletal muscle trauma, Crush injury and AMI cause an increase in myoglobin levels

- reference intervals vary according to age, rate and sex

  1. age ↑ → myoglobulin ↑

  2. male > female

  3. black > white

- very sensitive early diagnostic marker for AMI (%90-100) ,poor clinical specificity (%60-95)
- rises as early as 1 hr. after AMI, peaks in 4-12 hr → reflects the early course of myocardial necrosis, lasts for 24 hr.
- the role of myoglobin in the detection of AMI is within 0-4hr. (CK-2 is within its reference level).

- To improve clinical specificity,carbonic anhydrase III (CAIII) should be measured.
- After AMI, CK-2 and myoglobin increase,but CA III remains unchanged.In severe skeletal muscle trauma (exercise, shock and i.m injection ), CK-2, myoglobin and CAIII increase.

- If myoglobin remains unchanged and within reference levels on multiple,early samplings within 3-6 hr. after onset of chest pain,there is 100 %certainty that muscle (either skeletal or cardiac ) injury has NOT occurred recently—Negative predictor

# References


- Clinical Biochemistry (Fundamentals of Biomedical Science), Editor: Nessar Ahmed
- Handbook of Clinical Biochemistry, 2nd Edition, R. Swaminathan