A fatty streak develops between the intima and the media.
If the blood clot enlarges to completely block the artery, all tissues supplied by that artery begin to die below the blockage.
Reversible
Stable angina occurs with increased demand on the heart.

Progressive
Unstable angina may be associated with a heart attack.

Coronary artery with stable plaque
Biomarkers and Cardiac Ischemia

By -Basil OM Saleh-

Upon completion of this lecture, the student will be able to answer

Objectives:

- List the cardiac biomarkers used in completion the diagnosis of ischemic heart disease
- Identify the time of elevation and the peak of each marker after onset of chest pain.
• State the false positive results; causes other than Ischemia in elevation of biomarkers (SPECIFICITY).
• Employ of biomarkers in differentiation between different types of cardiac injuries; unstable angina and MI.
• Choose the most sensitive and specific biomarker in completion the diagnosis of myocardial injury.
• Define the biochemical marker that aid in evaluation of heart failure.
Biochemical marker is any hormone, enzyme, antibody, or other substance that is detected in the urine, blood, or other body fluids or tissues that may serve as a sign of a disease or other abnormality.

Cardiac biomarkers, proteins released from the injured myocardium into the circulation LIKE total Creatine kinase (CK), CK-MB, Troponin ... and so, are useful for confirmation the diagnosis of Myocardial infarction (MI) according to the World Health Organization (WHO) criteria.
Ischemic heart disease (IHD) is caused by an imbalance between the myocardial blood supply and the myocardium metabolic demand of blood and O2. Reduction in coronary blood flow is mainly due to progressive atherosclerosis with increasing occlusion of coronary arteries. The Acute Coronary Syndrome (ACS) represent the following conditions:
Stable Angina (SA) is Ischemia due to stable plaque / exertion.

Unstable Angina (UA) is Ischemia due to plaque disruption / thrombus.

Acute Myocardial Infarction (AMI) is Myocardial necrosis due to prolonged ischemia

Acute Coronary Syndromes (ACS) included both Unstable Angina and Acute Myocardial Infarction
minor **Unstable angina**: there is no ST-segment change and there is *not* sufficient myocardial damage for release of a biomarker such as the troponins or CK-MB.

**Non-ST-segment Elevation Myocardial Infarction (NSTEMI)**: there is no ST-segment change but there *is* myocardial necrosis for release of a biomarker mainly the troponins.

**ST-segment Elevation Myocardial Infarction (STEMI)**: there is ST-segment elevation and myocardial necrosis with release of a biomarker such as the troponins or CK-MB.
Now, the routinely biochemical investigations of MI are **Creatine Kinase-(CK-) MB** and **Cardiac Troponin cTn**.

1. **CK or CPK**  It is protein enzyme of most abundant in the cells of skeletal & cardiac muscles and also in brain and smooth muscles like in GIT and respiratory tract. CK is resides in the cytosol of cells and facilitates movement of high energy phosphates ATP into and out of mitochondria.
There are three cytoplasmic CK-isoenzymes; **CK-MM, CK-MB, & CK-BB.** In normal healthy subject, CK-MM accounts for 95% of total CK, while CK-MB for less than 5% & CK-BB for very small quantities of total CK and is normally undetectable in blood and of no clinical value.
-CK-MM 98% in skeletal Muscle (SM) & 2% in cardiac muscle (CM)

-CK-MB 65% in SM & 35% in CM

-CK-BB present predominantly in the brain and in the smooth muscles of the GIT and genital tracts, very small amounts of total CK-no clinical utility.
Pattern of biochemical markers elevation: **BLOOD** should not be taken for cardiac enzyme or other biomarkers assay until at least (4 hr.) has been elapsed after the onset of the chest pain, the principle clinical feature of MI (all are normal in blood before 4 hr. of chest pain).
If the initial plasma CK activity is normal, a second sample should be taken about 4-6 hours later (8-12 hr. after chest pain). A rise in quantities of these biomarkers or a positive result in qualitative estimation supports the diagnosis of MI.
Serum Total CK elevation is not specific for myocardial injury; increased in a variety of non-cardiac conditions (false positive result) like; trauma, intramuscular injection, skeletal muscle breakdown (Rhabdomyolysis), muscle dystrophy, ...., .

Total CK is less sensitive than CK-MB.

The CK-MB is the choice instead of total CK for assessment of MI ?(35% CM).
Pattern of elevation of serum CK-MB: It released in blood from injured CM after 3-4 hr. of onset chest pain (MI), peak 24 hr., and returned to normal 48-72 hr. after chest pain. CK-MB is also useful for assessment of reinfarction or extensive of an MI because it begins to fall after 48 hr., so subsequent elevations are indicative of another event of MI. However, it cannot be used for late diagnosis of acute MI.
2. **Troponins**: Troponin, a complex of three contractile regulatory proteins, troponin C, T and I, controls the calcium-mediated interactions between actin and myosin in cardiac and skeletal muscles. **Troponin-I and T are specific to cardiac muscles**, unlike troponin-C which is associated with both cardiac and skeletal muscles.
A patient who had suffered from a myocardial infarction would have an area of damaged heart muscle and so would have elevated cardiac Troponin levels in the blood.
Troponin is the most sensitive and specific test for myocardial damage MI. Because it has increased specificity (increased mainly in MI) compared with CK-MB, Troponin is a superior marker for myocardial injury. They are also measured in the blood to differentiate between unstable angina and myocardial infarction (heart attack) in patients with chest pain.
Pattern of elevation: After cardiac myocyte injury MI, troponin is released in 4-6 hr., peak 24-48 hr. and persists for up to 5-14 days.

They are highly specific for myocardial injury--more so than CK-MB--and help to exclude elevations of CK with skeletal muscle trauma.
Troponins will remain elevated longer than CK-MB up to 5 to 10 days for troponin I and up to 2 weeks for troponin T. This makes troponins a superior marker for diagnosing myocardial infarction in the recent past—better than other markers. However, this continued elevation has the disadvantage of making it more difficult to diagnose reinfarction or extension of infarction in a patient who has already suffered an initial MI.
Troponin T lacks some specificity because elevations can appear with renal failure, severe pulmonary embolism, congestive heart failure & myocarditis.

3. Lactate dehydrogenase (LDH) catalyses the conversion of pyruvate to lactate. LDH-1 isoenzyme is normally found in the heart muscle and LDH-2 is found predominately in blood serum. A high ratio of LDH-1 level to LDH-2 suggest MI. LDH levels are also high in tissue breakdown or hemolysis, cancer
meningitis, encephalitis, or HIV. LDH is usually back to normal 10–14 days. LDH is not as specific as troponin. peak 72 hours. LDH measurement for MI is now stopped.

4. Myoglobin (Mb) low specificity for myocardial infarction. Myoglobin is used less than the other markers. Myoglobin is the primary oxygen-carrying pigment of muscle tissue. It is high when cardiac muscle tissue is damaged but it lacks specificity. It has the advantage of responding very rapidly, rising within 2 hr. after MI and falling earlier than CK-MB or troponin.
5. Brain natriuretic peptide (BNP) is a 32-amino acid polypeptide secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells (cardiomyocytes). BNP is named as such because it was originally identified in extracts of porcine brain.
In humans it is produced mainly in the cardiac ventricles. BNP is secreted along with a 76-amino acid N-terminal fragment (NT-proBNP) that is biologically inactive. BNP and NT-ProBNP are increased in patients with heart failure. It has been approved as a marker for acute congestive heart failure.
Cardiac Markers: Approximate Levels vs. Time of Onset Post MI
Summary

1. CK-MB and cTn are the confirmatory biochemical markers in diagnosis of MI.
2. Serum cTn is the best biomarker in assessment of MI.
3. Also, cTn is the biomarker that aid in differentiating between MI and unstable angina.
4. The pattern of biomarker elevation is important for the choice of the best one in accordance with time of MI occurrence as well as for reinfarction.
5. Serum BNP and NT-proBNP are the best biomarkers for heart failure assessment.