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CARDIAC BIOMARKERS IN ACUTE CORONARY SYNDROME

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Abstract

Across the globe, one of the most common reasons for admission to emergency departments (EDs) is acute coronary syndrome, or ACS. Evaluation of clinical signs and symptoms, electrocardiographic examination, and testing of cardiac circulating biomarkers are all part of the diagnosis process for acute coronary syndrome (ACS). In order to get a broad notion of the extent of muscle damage, biomarkers, which are protein molecules released into the bloodstream from cardiac muscle injured by a blocked artery, are analyzed. Aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and creatine kinase (CK) total enzyme activity tests have been used in early biomarker assessment; nevertheless, these tests have been incredibly nonspecific. the CK-MB isoenzyme (CK-MB) measured in bulk as opposed to myoglobin and activity. Therefore, specific cardiac indicators are essential for detecting AMI. These markers include cardiac troponin and creatinine kinase-MB (CK-MB), which are produced in myocardial cell injury. There are new biomarkers that can be used to diagnose acute coronary syndromes that are more sensitive and specific. From the earliest introduction of AST in the 1950s to the latest high-sensitivity troponin immunoassays in the 2010s, this article offers a chronology of the significant events that marked the growth of cardiac biomarker testing and the development of the related assays.

Keywords: Acute coronary syndrome, acute myocardial infarction, Cardiac biomarkers, Cardiac troponin.

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Introduction

Acute coronary syndrome (ACS) is a spectrum of coronary artery diseases that includeunstable angina (ACS without ST-elevation and cardiac marker elevation), ST-elevation myocardial infarction (STEMI), and non-ST-elevation myocardial infarction (NSTEMI). STEMI is further classified into Q-wave and non-Q-wave MI. NSTEMI with cardiac markers elevation is also classified into Q-wave and non-Q-wave MI.(3)ACS symptoms include chestpain, referred pain, nausea, vomiting, dyspnea, diaphoresis, and light-headedness. Cardiac biomarkers are measurable and quantifiable biological parameters which are detected in the blood and serve as indices of assessments of AMI. Cardiac biomarkers such as total creatinine kinase (total CK), CK-MB, aspartate transaminase (AST), and lactate dehydrogenase (LDH) can be used to diagnose AMI, especially for patients showing negative ECG results. Troponin-T (a component of troponin) can be found in cardiac and skeletal muscles, however, troponin isoforms in these muscles are encoded by different genes. Therefore, monoclonal antibodies against cardiac troponin-T with little or no cross-reactivity with its respective skeletal muscle isoforms have been evolved. An interesting fact is that CAD affects Indians with greater frequency and at a younger age as compared with the developed countries, as well as many other developing countries.(5)

Myocardial Infarction.

Cardiac Markers:

A biomarker is defined as a measurable substance or parameter that is an indicator of an underlying biological or pathological process.(3) Therefore, depending on the underlying process that we are referring to, cardiac markers can be classified as markers of necrosis, markers of ischemia and markers of inflammation.

Why do we Need Biomarkers for Diagnosis?

Acute coronary syndrome is the result of numerous pathophysiological events like [2]

- Plague rupture with acute thrombosis,
- Progressive mechanical obstruction,
- Inflammation,

These sensitive biomarkers guide the clinician in early management of myocardial ischemia to prevent necrosis with treatments, such as fibrinolysis, coronary artery bypass grafting, and percutaneous coronary interventions (PCIs) for improving outcomes.(5)

Criteria for IDEAL markers for MI

- Specific: It should be specific to myocardial muscle cells (no false positive)
- Sensitive: It should release rapidly on onset of attack (diagnose early cases) – It should be able to detect even minor damage – It should not miss positive cases (no false negative)
- Prognostic*:* Its level should relate with extent of damage
- Persists longer: It should stay longer in blood so that it can diagnose delayed admissions.

Types of Biochemical Markers for MI1.Cardiac enzymes (isoenzymes):

- Total CK
- CK-MB activity
- LDH
- AST 2.Cardiac proteins:
- Myoglobin
- TnI and TnT
- Pro-brain natriuretic peptide (pro-BNP)

Cardiac Enzymes:

AST (aspartate aminotransferase)

- Aspartate transaminase (AST) or aspartate aminotransferase, also known as glutamic oxaloacetic transaminase (GOT, SGOT), is a pyridoxal phosphate (PLP)-dependent transaminase enzyme that was first described by Arthur Karmen and colleagues in 1954.(3)
- AST is found in the liver, heart, skeletal muscle, kidneys, brain, red blood cells and gallbladder.

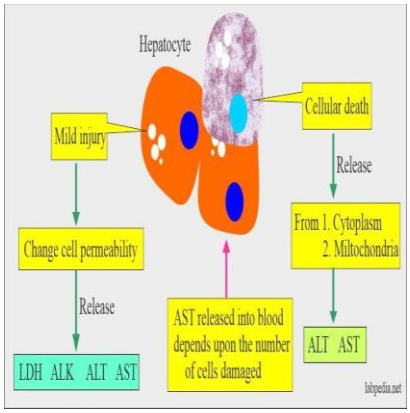

Figure:1

LDH (lactate dehydrogenase)

- A cytoplasmic enzyme found in skeletal, muscle, liver, heart, kidney, red blood cells.
- It is not a tissue – specific enzyme.
- Lactate dehydrogenase is an enzyme of anaerobic metabolism which converts pyruvateto lactate. It has 5 enzymes: LDH1, LDH2, LDH3, LDH4, LDH5
- LDH-1(4H)- in the heart
- LDH-2(3H1M)-in the reticuloendothelial system
- LDH-3(2H2M)-in the lungs
- LDH-4(1H3M)-in the kidneys
- LDH-5(4M)- in the liver and straited muscle
- Normally LDH1 concentration is less than LDH2. Ratio of LDH1 to LDH2 is <0.7. But in MI LDH1 concentration increases and LDH1 to LDH2 ratio becomes >1.

Total creatinine kinase levels:

- It is a cytoplasmic and mitochondria enzyme of all body muscles. Thus, it is nonspecificto cardiac tissue (available in skeletal muscles also). It was in 1960 that the CK activity was shown to be a potential biomarker of cardiac muscle injury.(16)

  They are:

  — CK-1 (BB): Brain

  — CK-2 (MB): Myocardium

  — CK-3 (MM): Skeletal muscle, heart
- Limitations—nonspecific; it also gets elevated in any muscle disease, skeletal trauma,alcohol intoxication, seizures, vigorous exercise, thoracic outlet syndrome, kidney disease, and pulmonary embolism.

1.1 CK-MB isoenzyme activity

- In 1972, Roe et al26 developed a zone electrophoresis method for the identification and quantification in serum or plasma of the CK-MB isoenzyme.(13)
- Therefore, skeletal muscle damage can be found in the diagnosis of an MI, as CK-MBcan be released. The following are examples:
- Myocardial injury after cardiopulmonary resuscitation
- Cardioversion
- Defibrillation
- Advantages: It is useful for early diagnosis of MI. – It is useful for diagnosis of reinfarction
- Disadvantages: It is not used for delayed admission (more than 2 days)

Cardiac Proteins:

Myoglobin:

- Myoglobin is an iron- and oxygen-binding protein found in muscle tissue. It is only found in the blood stream when it is released following muscle injury.(8)
- In 1978, myoglobin was detected for the first time.

- Time sequence after infarction: It rises as fast as 2 hours, peaks at 6 to 8 hours, and returns to normal in 20 to 36 hours.[8]
- Due to its quick release, myoglobin was once the best marker for early detection of myocardial infraction.
- Advantages: It has a high negative predictive value in the early phase.

Troponin Isoforms:

- In 1971, Greaser and Gergely demonstrated that troponin is a complex of 3 proteins which regulates interaction between thick and thin filaments during muscle contraction.

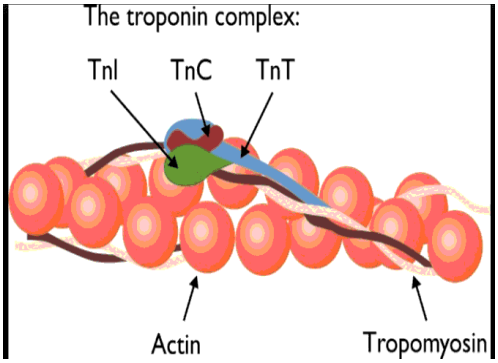

Figure 2: Cardiac troponins and their detailed structure

Duration after MI

— Appears in 2 to 6 hours

— Peak in 12 to 16 hours

— Stays elevated for 5 to 14 days

— Early peaking in reperfusion

- Normal values

TnT—0.1 to 0.2 ng/mL, TnI—0.6 ng/mL

(a) Sensitivity and sensitivity of cardiac troponins

- The sensitivity is 33% from 0-2 hours, 50% from 2-4 hours, 75% from 4-8 hours and approaching 100%from 8 hours after onset of chest pain. The specificity is close to 100%. The following is a list of some of the causes for the elevation of troponin in the absence of a thrombotic occlusion of the coronary artery.(23)
- Trachy-or bradyarrhythmia's heart block
- Critically ill patients, especially with diabetes, respiratory failure or sepsis
- Coronary vasospasm

(b) Prognostic Marker -there is a relation between its level in blood and extent of cardiac damage.

- Specially, data from a meta-analysis indicated that an elevated troponin level in patients without ST-segment elevation is associated with a nearly 4-fold increase in the cardiacmortality rate.

Future Markers:

Myeloperoxidase:

- Myeloperoxidase (MPO) is a haemoprotein that is abundantly expressed inpolymorphonuclear cells (neutrophils) and secreted during their activation.
- This reactive oxygen species is involved in the development of atheroma and plaquestability. Increased Myeloperoxidase is a marker of plaque instability.(11)
- MPO plays an important role in neutrophil microbial action through catalysing chlorideion oxidation to hypochlorous acid, which is a potent antimicrobial.

Copeptin:

- Pre-Pro vasopressin is the precursor peptide for antidiuretic hormone, copeptin andneurothelin.
- Copeptin, the C-terminal part of the arginine vasopressin precursor peptide.
- At a cut off level of 14.0 p mol/L, copeptin is combinedly measured along with Troponin T had sensitivity of 98.8% and specificity of 77.1% when compared with cTnT alone or with combination of other biomarkers without copeptin. (6)

Growth differentiation Factor:

- GDF-15 is a member of the transforming growth factor beta cytokine superfamily. Studies conducted by Nora Schaub et al showed that GDF-15 has additional prognostic value when used in combination along with highly sensitive cardiac Troponin T. (4)

Heart Type Fatty Acid:

- H-FABP is a small low molecular weight (i.e., 15 k Da), 132 amino acid, soluble protein, with general characteristics resembling myoglobin.
- Heart-type fatty acid -binding protein (H-FABP) is a cytosolic, low-molecular-weight protein involved in fatty acid transport and metabolism.

Highly Sensitive C-Reactin Protein:

- CRP is an acute-phase protein produced by the liver that is upregulated in conjunction with the inflammatory response.
- C-reactive protein (CRP), an acute-phase reactant produced by hepatocytes in responseto stimulation by inflammatory cytokines, primarily IL-6, is the most widely used inflammatory marker.
- The American heart association has defined risk groups as follows: less than 1.0mg/L, Average risk: 1.0 to 3.0mg/L, and High risk: above 3.0mg/L.
- Control and Prevention issued a scientific statement that suggested the use of high-sensitivity CRP as an optional risk factor measurement in patients with ACS.(8)

Placental Growth Factor:

Placental growth factor is a member of VEGF (vascular endothelial growth factor) subfamily

— A key molecule in angiogenesis and vasculogenic, in particular during embryogenesis.(37)Placental growth factor expression within human atherosclerotic lesions is associated with plaque inflammation and neovascular growth PGF was recently shown that it is upregulated in all forms of atherosclerotic lesions. PGIF includes the following

- Vascular smooth muscle cell growth.
- Recruit's macrophages into atherosclerotic lesions.
- Up regulates production of TNF alpha.

Pregnancy Associated Plasma Protein (PAPP):

- PAPP-A was originally identified in the serum of pregnant women. PAPP-A is producedby placental tissue.
- PAPP-A is a metalloprotease produced by synaptic trophoblasts of placenta, fibroblasts, vascular smooth muscle cells. It has an active role in atherosclerotic plaque rupture.

Ischemia Modified Albumin:

- Ischemia-modified albumin (IMA) released during ischemic conditions, so it enables prior detection of ischemia and comes to baseline within 6-12 hours.
- The only ischemia marker that has been approved by the FDA is the modified albumin (IMA) using the albumin cobalt binding test (ACB) for assessment of myocardial ischemia. (15)

Matrix Metalloproteinases:

MMP are endogenous zinc dependent endopeptidase required for structural integrity of extracellular matrix of myocardium. TIMP (tissue inhibitors of metalloproteinases) regulates MMP. MMPs may degrade myocardial ECM leading to the development of LV dilation and heart failure and their inhibition in experimental models of AMI has been associated with reduced LV dilatation and wall stress.(10)

Reccomendation for use of biochemical Markers for Diagnosis of MI:

Recommended for all patients complaining of chest pain (with clinical examination and ECG) (16)

Sample timing: on admission 3 to 6 hours later (only when uncertainty exists) Test should be with low turnaround time: less than 1 hour accepted less than half an hour is preferred

- Types of markers used:

  Early markers: as myoglobin and CK-MB; these appear in blood early within<4hours) but not specific and does not persist for long periods (less than 2 days)

  Definitive markers: Troponin- it appears in blood later than myoglobin (within 6 hours) but 100% specific, prognostic, and stays longer (1 week). Its value should be above the 99th percentile of URL.

- Troponin currently the marker of choice -It should be available in all cardiac and emergency centres (if not, CK-MB mass method for isoforms is the second choice) (20)

Conclusion:

Over past few years the use of biomarkers extensively increased for diagnosis because of their sensitivity, specificity and they are playing an important role in detection of disease, risk stratification, diagnostic based treatment of myocardial infarction. Currently the best biomarkerfor detection of myocardial infraction is cardiac Troponin. However, there are further emerging biomarkers which are in the research stage that have chances of more diagnostic, prognostic characteristics.

Author contributions

All authors are contributed equally.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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