Universe International Journal of Interdisciplinary Research
(Peer Reviewed Refereed Journal)
© UIJIR | ISSN (O) – 2582-6417
MAY 2022 | Vol. 2 Issue 12
www.uijir.com

AN OVERVIEW ON CARDIAC BIOMARKERS

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DOI No. – **08.2020-25662434**

Abstract

Different cardiac biomarkers or cardiac enzymes have conventionally continued to be utilized for assessment and diagnose of acute myocardial-infarction patient. Cardiac biomarkers are the proteins that are released from the damaged myocardial cells through their injured cell membranes into the circulation. Several cardiac markers have been used in the diagnosis and management of cardiovascular disease. However, a lack of sensitivity and specificity to cardiac muscle necrosis continues to be the need to look for newer specific molecules. Cardiac markers can be classified into those that signify myocardial necrosis (creatine kinase-MB fraction, myoglobin and cardiac troponins), those that indicate myocardial ischemia (ischemia modified albumin), those that suggest myocardial stress (natriuretic peptides), and those markers of inflammation and prognosis (C-reactive protein, soluble CD40 ligand, and homocysteine). The present review highlights different cardiac biomarkers.

Keywords*: Biomarkers, Cardiovascular disease, Myocardial Infarction*

INTRODUCTION

In today's emergency care, determining the cause of heart ischemia is difficult. A blood-borne biomarker is a more appealing option than cardiac imaging or stress testing since it is less expensive and easier to get. Screening, diagnostic tests, and prognosis are all available. Biomarkers that represent prodromal indications enable early diagnosis or the determination of the desired outcome at a more primitive stage of disease. The biological information required for the diagnosis is obtained from blood, urine, and cerebrospinal fluid. Biomarkers are utilised as an indicator of a biological element that indicates a subclinical manifestation, stage of the ailment, or a surrogate manifestation of the disease under these circumstances. Bio-markers used for screening or diagnosis are frequently surrogates for disease symptoms. Biomarkers could be used for a variety of purposes, including: 1) identifying individuals who are likely to be affected or who are in the "preclinical" stages of the illness, 2) reducing disease heterogeneity in clinical trials or epidemiologic studies, 3) reflecting the natural history of disease, including induction, latency, and detection, and 4) serving as a clinical trial target. The benefits of increased validity and precision significantly outweigh the challenges of collecting such tissues from patients.

Individuals who test positive, regardless of whether or not they have the disease, are required to be followed up on by most ethical review boards and healthcare systems. Treatment for people who test positive should also be offered, and it should be both accessible and acceptable. Those who test positive and are sick should be given access to therapy, which must be adequate and readily available. It's important to remember that the major advantage of screening is primary prevention (before the start of symptoms) or secondary prevention (early or prodromal identification). Consider the advantages of conducting a therapy trial in patients prior to the onset of overt symptoms. [1,2]. In clinical research and practise, diagnostic testing for neurological

illnesses is being employed more frequently. The collection of information from multiple sources, some of which include diagnostic test results, aids in the diagnostic effort's ultimate goal of raising the probability of a certain diagnosis. Clinical tests are also used for other purposes, but presumably less frequently, such as measuring disease severity, predicting disease onset, or monitoring the response to a certain treatment. More critically, illness biomarkers lend themselves well to clinical trials. Another benefit of this type of diagnostic test is that it reduces disease heterogeneity in clinical trials or observational epidemiologic research, allowing for a better knowledge of the disease's natural history, including induction, latency, and detection stages.

Until the 1980s, the elevation of enzymes aspartate aminotransferase and lactate dehydrogenase were used to evaluate the myocardial injury. Raise of muscle/brain isoenzyme of creatine kinase, creatine kinase, myocardial-specific troponins I and T, and myoglobin occurs in all patients with myocardial infarction and necrosis. B-type natriuretic peptide which is a biomarker for heart failure is produced mainly by the ventricular myocardium in retort to ventricular wall stress is now used in hazard identification besides prediction of individuals by severe myocardial infarction early next to an acute coronary event. Glycogen phosphorylase isoenzyme BB which is elevated within 1 to 3 hours after myocardial ischemic attack is a new cardiac biomarker which is considered to improve timely diagnosis of an acute coronary event. Another biomarker for detecting ischemia is Ischemia modified albumin which is produced when circulating serum albumin interacts with the ischemic cardiac muscle. A leukocyte enzyme myeloperoxidase is a novel cardiac marker produced from the free radicals generated by oxygen and it has been associated with the reduction of nitrous oxide thereby causing vasoconstriction, formation of soft plaque creations embedded with lipid and instability of atherosclerotic plaques. Myeloperoxidase levels have been associated with the antagonistic events related to coronary artery disease and cardiovascular outcomes. A nonspecific marker of inflammation secreted by macrophages and T cells, C-reactive protein acts as prognostic indicator associated with myocardial atherosclerotic plaques formation. Increased of CRP activity can forecast the adverse cardiovascular outcomes that may occur during primary or secondary management stages. It is a nonspecific indicator but when used in combination with B-type natriuretic peptide, cardiac troponin it may have diagnostic value as cardiac biomarker for acute coronary events in the emergency department.

1. Myoglobin: Myoglobin is a cytoplasmic hemoprotein that can be detected in skeletal and cardiac muscle tissue. Because of its low molecular weight, myoglobin is a sensitive marker for muscle injury. When muscle tissue is damaged, it is rapidly released within 2-4 hours, peaks at 6-12 hours, and returns to normal within 24-36 hours. Cell death and changes in the permeability of the skeletal muscle cell membrane release myoglobin from muscle tissue. The sodium potassium ATPase pump maintains a very low intracellular sodium concentration under normal conditions. In return for calcium extrusion from the cell, a second sodium-calcium channel pumps more sodium into the cell. Furthermore, the majority of intracellular calcium is generally stored in organelles. Damage to muscle cells disrupts both pathways, resulting in an increase in cytoplasmic free ionised calcium. The high intracellular calcium stimulates a slew of calcium-dependent enzymes that further degrade the cell membrane, allowing intracellular components like myoglobin and creatine kinase to leak into the bloodstream. The reactive oxygen species generated by damage to both muscle and kidney epithelial cells promote the oxidation of ferrous oxide to ferric oxide (Fe^{+3}), thus generating a hydroxyl radical. Both the heme moieties and the free iron-driven hydroxyl radicals may be

critical mediators of the direct tubule toxicity, which mainly occurs in the proximal tubule. [3]

2. Cardiac Troponins: Troponins are a type of regulatory protein that is essential for muscle contraction. Troponin, often known as the troponin complex, is a group of three regulatory proteins involved in muscle contraction (troponin C, troponin I, and troponin T). Troponin is found in both skeletal and cardiac muscle, however different forms of troponin are found in different muscle types. The key difference is that the TnC subunit of troponin has four calcium ion-binding sites in skeletal muscle but only three in cardiac muscle. Troponin is found in the groove between actin filaments in muscle tissue and is associated to the protein tropomyosin. Tropomyosin prevents contraction by blocking the attachment point for the myosin crossbridge in a relaxed muscle. Calcium channels in the sarcoplasmic membrane open and release calcium into the sarcoplasm when the muscle cell is induced to contract by an action potential. Some of the calcium binds to troponin, causing it to change shape and expose myosin (active sites) binding sites on the actin filaments. When myosin binds to actin, a crossbridge is formed, and muscle contraction occurs. Troponin (together with actin and tropomyosin) is a component of thin filaments and the protein complex to which calcium binds to trigger the creation of muscle force. TnC, TnI, and TnT are the three subunits of troponin, each of which plays a function in force control. Tropomyosin covers the active sites on actin that myosin (a molecular motor arranged in muscle thick filaments) binds to generate force when intracellular calcium levels are low. When calcium binds to certain places in TnC's N-domain, tropomyosin is rolled away from actin's myosin-binding sites, allowing myosin to attach to the thin filament and exert force and/or shorten the sarcomere. [4]

Certain subtypes of troponin (cardiac I and T) are sensitive and specific indicators of damage to myocardium. They are measured in the blood to differentiate between unstable angina and myocardial infarction (heart attack) in people with chest pain or acute coronary syndrome. A person who recently had a myocardial infarction would have an area of damaged heart muscle and elevated cardiac troponin levels in the blood. This can also occur in people with coronary vasospasm, a type of myocardial infarction involving severe constriction of the cardiac blood vessels. After a myocardial infarction troponin may remain high for up to 2 weeks. Cardiac troponins are a marker of all heart muscle damage, not just myocardial infarction, which is the most severe form of heart disorder. However, diagnostic criteria for raised troponin indicating myocardial infarction is currently set by the WHO at a threshold of 2 μg or higher. Other conditions that directly or indirectly lead to heart muscle damage and death can also increase troponin levels, such as kidney failure. Severe tachycardia (for example due to supraventricular tachycardia) in an individual with normal coronary arteries can also lead to increased troponins for example, it is presumed due to increased oxygen demand and inadequate supply to the heart muscle. Troponins are also increased in patients with heart failure, where they also predict mortality and ventricular rhythm abnormalities. They can rise in inflammatory conditions such as myocarditis and pericarditis with heart muscle involvement (which is then termed myopericarditis). Troponins can also indicate several forms of cardiomyopathy, such as dilated cardiomyopathy, hypertrophic cardiomyopathy or (left) ventricular hypertrophy, peripartum cardiomyopathy, Takotsubo cardiomyopathy, or infiltrative disorders such as cardiac amyloidosis. Heart injury with increased troponins also occurs in cardiac contusion, defibrillation and internal or external cardioversion. Troponins are commonly increased in several procedures such as cardiac surgery and heart transplantation, closure of atrial septal defects, percutaneous coronary intervention, or

radiofrequency ablation. [5]

3. Creatine Kinase–MB: Creatine kinase which is also known as creatine phosphokinase (CPK) or phospho-creatine kinase is an enzyme expressed by various tissues and cell types. Creatine kinase catalyses the conversion of Creatine and utilizes adenosine triphosphate to create phosphocreatine and adenosine diphosphate. This Creatine kinase enzyme reaction is reversible and thus adenosine triphosphate can be generated from phosphocreatine and adenosine diphosphate. The mitochondrial creatine kinase (CKm) is found in the intermembrane gap of mitochondria, where it regenerates phosphocreatine (PCr) from mitochondrial ATP and cytosolic creatine (Cr). Aside from the two mitochondrial CK isoenzyme forms, ubiquitous mtCK (found in non-muscle tissues) and sarcomeric mtCK (found in sarcomeric muscle), the cytosol contains three different CK isoforms, depending on the tissue. MM-CK is found in sarcomeric muscle, which includes skeletal and cardiac muscle, while MB-CK is found in cardiac muscle and BB-CK is found in smooth muscle and most non-muscle tissues. A so-called PCr/Cr-shuttle or circuit connects mitochondrial mtCK and cytosolic CK. PCr produced by mtCK in mitochondria is shuttled to cytosolic CK, which is linked to ATP-dependent activities, such as ATPases involved in muscle contraction, such as acto-myosin ATPase and calcium ATPase, and sodium/potassium ATPase involved in sodium retention in the kidney. The attached cytosolic CK receives the PCr shuttled across the cell and regenerates ATP using ADP, which the ATPases can then use as an energy source (CK is associated intimately with the ATPases, forming a functionally coupled microcompartment). PCr is an energy buffer as well as a cellular energy transit form between subcellular energy (ATP) production sites (mitochondria and glycolysis) and energy utilisation sites (ATPases). As a result, CK improves the contractility of skeletal, cardiac, and smooth muscle and is involved in the generation of blood pressure. [6,7]

4. Lactate dehydrogenase: LDH (or LD) is a lactate dehydrogenase enzyme found in practically all living cells (animals, plants, and prokaryotes). LDH transforms lactate to pyruvic acid and back, much as it converts NAD+ to NADH and again. A dehydrogenase is a molecule-to-molecule hydride transfer enzyme. The accumulation of lactic acid is usually blamed for the onset of acidosis during times of severe activity. The assumption that lactate generation is the major source of muscular tiredness during exercise has gained widespread acceptance as a result of this argument. A more detailed, mechanistic examination of lactate synthesis in anaerobic settings reveals that there is no biochemical evidence that lactate production via LDH contributes to acidosis. Despite the fact that LDH activity is linked to muscular fatigue, the production of lactate by means of the LDH complex works as a system to delay the onset of muscle fatigue. LDH prevents muscle failure and exhaustion in a variety of ways. The lactate-forming reaction produces cytosolic NAD+, which is used by the glyceraldehyde 3-phosphate dehydrogenase enzyme to assist maintain cytosolic redox potential and enhance substrate flux through the second phase of glycolysis, resulting in ATP production. Under strong workloads, this effectively gives extra energy to contracting muscles. The synthesis and removal of lactate from the cell also ejects a proton that was consumed in the LDH reaction; the elimination of surplus protons created in the aftermath of this fermentation reaction acts as a buffer for muscular acidosis. Muscle acidosis occurs when proton accumulation exceeds the rate of uptake in lactate synthesis and elimination through the LDH symport. Because LDH is prevalent in red blood cells and can serve as a signal for hemolysis, it is frequently employed in medicine as a marker of tissue breakdown. Due to erythrocyte damage, a blood sample treated wrongly can display false-positively high levels of LDH. It can also be utilized as a myocardial infarction

indicator. LDH levels peak 3–4 days after a myocardial infarction and stay elevated for up to 10 days. Elevated levels of LDH (where LDH1 is higher than LDH2, i.e. the LDH Flip, as LDH2 is generally higher than LDH1 in serum) can be used to determine whether a patient has had a myocardial infarction if they come to doctors several days after an episode of chest pain. [8]

5. Aspartate transaminase: AST is an important enzyme in amino acid metabolism because it catalyses the reversible transfer of a -amino group from aspartate to glutamate. The liver, heart, skeletal muscle, kidneys, brain, and red blood cells all contain AST. When some organs or tissues, particularly the liver and heart, are harmed, ST, an enzyme found in both mitochondria and cytoplasm, is released into the bloodstream. Acute myocardial infarction was diagnosed using the AST measurement. The amount of AST produced is proportional to the number of cells damaged by disease or injury, while the degree of increase is determined by the duration of myocardial infarction. After 538 hours after cardiac cell damage, serum AST levels rise, peak at 24348 hours, and then recover to normal after 436 days. In acute myocardial infarction, serum AST levels are considerably high, around 103100 times the upper adult reference limit, but there is a modest increase in circulatory failure (shock), acute hepatitis, and a mild rise in severe haemolytic anaemia, post-surgery/trauma, and skeletal muscle disorders. Angina or pericarditis are two other myocardial lesions that do not raise AST levels. An elevated AST level not occurring in the setting of inflammatory liver disease may signify an increased cardiovascular risk related to nonalcoholic fatty liver disease (NAFLD), cardiometabolic risk factors (metabolic syndrome, abdominal obesity, insulin resistance and diabetes), chronic alcoholism and structural heart disease (myocardial infarction or congestive heart failure). A positive association between AST and CVD is more common in epidemiological studies in Asian population. Low AST levels may reflect increased cardiovascular risk related to vitamin B6 deficiency, advanced chronic kidney or liver diseases and inflammatory diseases. High and low AST levels have clinical meaning and both of them should be analysed. [9]

6. Myeloperoxidase: Myeloperoxidase is an enzyme found in the azurophilic granules of polymorphonuclear neutrophils and macrophages, which is released into the extracellular fluid during an inflammatory response. The etiology of instability of coronary artery disease leading to acute coronary syndromes is complicated by oxidative stress and inflammation. The transition of stable coronary artery plaques to unstable lesions is aided by infiltrating macrophages and neutrophils. Myeloperoxidase, a proinflammatory enzyme that is prevalent in ruptured plaque and can be detected in peripheral blood, has recently reawakened attention Myeloperoxidase been secreted during inflammatory conditions and catalyzes the conversion of chloride and hydrogen peroxide to hypochlorite. It is thought to be involved in the oxidation of lipids found in low density cholesterol. Myeloperoxidase also consumes endothelial-derived nitric oxide, lowering nitric oxide bioavailability and limiting its vasodilating and anti-inflammatory effects. Spectrophotometric assays using hydrogen peroxide and o-dianisidine dihydrochloride as substrates can be used to assess Myeloperoxidase activity in blood and tissues. In addition, the Coulter counter and flow cytometry can be used to quantify Myeloperoxidase content in neutrophils as an indication of degranulation. Myeloperoxidase could become a new and helpful cardiac biomarker as a result of the development of various measurement technologies. Leucocytes have a critical function in the rupture of atherosclerotic plaques. In leucocytes, myeloperoxidase can activate metalloproteinases while inactivating the plasminogen activator inhibitor. Nitric oxide is catalytically consumed by leucocytes, resulting in vasoconstriction and endothelial dysfunction.

Atheromatous plaques have been discovered to contain myeloperoxidase. Patients with chronic angina have considerable amounts of Myeloperoxidase in their circulating neutrophils, which decrease significantly after an acute coronary syndrome. [10]

7. C-terminal-provasopressin (Copeptin): Copeptin is a more stable arginine vasopressin (AVP) substitute with well-known osmoregulation and cardiovascular homeostasis effects. Vasopressin is considered to promote peripheral vasoconstrictor activity after an AMI, increasing afterload and ventricular stress, increase protein synthesis in myocytes, leading to hypertrophy, and increase coronary artery vasoconstriction. These effects are mediated by the V1 receptor, whereas water retention in the renal tubules is mediated by the V2 receptor. Pharmacological therapy is now being developed for these receptors. Copeptin is produced in a stoichiometric ratio with vasopressin, and it is stable and easy to measure. It was recently demonstrated that copeptin was a strong prognostic marker for prognosis in patients after an acute myocardial infarction, in patients with chronic heart failure, and in patients with acute destabilized heart failure. Copeptin is a good marker of neurohormonal stress, making it useful in risk stratification in sepsis and other disorders. It is not, therefore, limited to the cardiovascular system. [11]

8. Heart-Type Fatty Acid Binding Protein (H-FABP): Heart-type fatty acid-binding protein (H-FABP), is a small (15 kDa) cytoplasmic protein involved in lipid homeostasis, found to be released earlier into the blood stream and rises as early as 30 minutes after the onset of acute. It's also found in modest amounts in the brain, kidneys, and skeletal tissue, and levels can rise as a result of acute ischemic strokes and strenuous activity. Early in myocardial infarction and necrosis, it is quickly released into the cytosol. H-FABP has been established in studies to be an early marker of ischemia (before morphological signs of myocardial necrosis) and can thus aid in earlier MI diagnosis. However, investigations seeking to diagnose AMI using H-FABP alone have had poor results. H-FABP levels were clearly related with the composite end point of mortality, myocardial infarction, and heart failure after 10 months in several more recent trials. After controlling for hsCRP and Troponin, the top quartile of H-FABP levels was linked with 6.59 times higher all-cause mortality than the bottom quartile. [12]

9. B-type natriuretic peptide: B-type natriuretic peptide (BNP) is a 32–amino acid polypeptide secreted by ventricular myocytes during periods of increased ventricular stretch and wall tension. This peptide is believed to play an important role in the regulation of blood pressure, blood volume, and sodium balance. On secretion, the BNP precursor is split into the biologically active peptide and the more stable N-terminal fragment (NT-proBNP). Measurement of circulating levels of BNP or NT-proBNP has been recommended in the diagnosis and prognosis of patients with symptoms of left ventricular dysfunction and for stratification of risk in patients with acute coronary syndromes. Because in vitro studies have reported that natriuretic peptides are directly released from cardiomyocytes in response to myocardial ischemia, it has been proposed that their circulating levels are relevant to subsequent risk of cardiovascular diseases (CVDs) other than heart failure. [13]

10. C-reactive protein: C-reactive protein (CRP) is a non-specific biomarker of inflammation. Recent research has shown that inflammation is an important step in the genesis of atherosclerosis, and is involved in the development of unstable plaques. Measurement of serum levels of CRP using a high sensitivity assay (hsCRP) can demonstrate subclinical inflammatory states, which may reflect vascular inflammation. Clinical studies have shown that elevated hsCRP

levels in healthy populations predict vascular events such as myocardial infarction and stroke as well as the development of diabetes. In patients with acute coronary syndromes, higher hsCRP levels are associated with adverse outcomes and subsequent vascular events. CRP has been found in human atherosclerotic plaque and CRP has been shown to cause endothelial cell dysfunction, oxidant stress and intimal hypertrophy in experimental models. [14]

11. Ischemia modified albumin: Ischemia-modified albumin (IMA) is a form of human serum albumin in which its N-terminal amino acids are modified because of ischemia. IMA is produced when ischemic stressors released from hypoxic heart tissue modify circulating albumin, thereby reducing its binding affinity to heavy metal ions such as cobalt. The ability of albumin to bind to cobalt is reduced in patients with myocardial ischemia, providing the basis for the albumin cobalt-binding test for detecting IMA. IMA is currently approved by the US Food and Drug Administration as a biomarker able to detect myocardial ischemia within minutes, while the levels of IMA continue to increase for 6-12 h. [15]

CONCLUSION

A cardiac biomarker is a detectable sign of heart disease severity or presence. A biomarker, in a broader sense, is anything that can be utilized as a predictor of a specific disease condition or physiological state. A multi-indicator approach, comprising of two or more pathologically diverse markers are used for the determination of myocardial toxicity.

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