Diagnostic markers of acute myocardial infarction (Review)

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Abstract. Acute myocardial infarction (AMI) is a major cause of morbidity and mortality worldwide. The highest risk of fatality occurs within the initial hours of onset of AMI. Thus, early diagnosis of cardiac ischemia is critical for the effective management of patients with AMI. Improper diagnosis of patients with chest pain often leads to inappropriate admission of patients without AMI and vice versa. In addition to clinical history, physical examination, accurate electrocardiogram findings and assessment of cardiac biomarkers have an important role in the early diagnosis of acute ischemia. The present review discusses in detail the various cardiac biomarkers released during the event of an AMI.

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Abbreviations: AMI, acute myocardial infarction; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; CRP, C-reactive protein; PTX-3, pentraxin 3; MPO, myeloperoxidase; PAPPA, pregnancy-associated plasma protein A; TNF-α, tumor necrosis factor-α; CK-MB, creatine kinase myocardial band; H-FABP, heart fatty acid-binding protein; BNP, B-type natriuretic peptide; IMA, ischemia-modified albumin; GDF-15, growth-differentiation factor-15; ACS, acute coronary syndrome; MYO, myoglobin; MMP-9, matrix metalloproteinase-9

Key words: acute myocardial infarction, electrocardiogram, atherosclerosis, biomarkers

1. Introduction

In the early 1970s, the World Health Organization (WHO) had defined the term myocardial infarction by the presence of 2 of the 3 following characteristics (1,2): i) Symptoms of acute ischemia (chest pain), ii) development of Q waves in electrocardiogram (ECG) and iii) increase of enzymes in the blood [combination of total creatine kinase (CK), CK-myocardial band (MB), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH)]. However, in 1999, the Joint European Society of Cardiology and the American College of Cardiology Committee jointly proposed the new definition for myocardial infarction, emphasizing the importance of sensitive and serological biomarkers for the diagnosis of acute myocardial infarction (AMI), and introduced cardiac troponins (cTn) as the gold standard (3) (Fig. 1).

2. Biomarkers of myocardial infarction

Myocardial infarction is defined as myocardial cell death due to prolonged ischemia (4). Myocardial cell death does not occur immediately following the onset of myocardial ischemia, but occurs ≥6 h. Atherosclerosis is by far the most common cause of myocardial infarction. The major risk factors of atherosclerosis are hyperlipidemia, diabetes, smoking, hypertension, gender and age. Endothelial dysfunction and inflammation have a major role in the initiation of the atherosclerotic plaque formation (5,6). Atherosclerosis is characterized by lipid accumulation in the vessel walls leading to the formation of an atherosclerotic plaque consisting of a central lipid core surrounded by foamy macrophages and smooth muscle cells covered by a fibrous cap (7). Rupture of the fibrous cap leads to communication between the lipid content of the plaque and the blood flowing through the arterial lumen (8). The tissue factor expressed by the macrophages activates the platelets eventually leading to the formation of intraluminal thrombus (9,10). Finally occlusion of the coronary artery by the thrombus reduces the blood supply to the myocardial tissues leading to ischemia and necrosis, eventually causing myocardial infarction (11) (Fig. 2).

Rapid identification of AMI is mandatory to initiate effective treatment for better prognosis. The newer concept of diagnosis of AMI emphasizes the importance of the 12-lead ECG and the assessment of early cardiac biomarkers since ECG by itself is often inadequate to diagnose AMI (Table I).

In the year 1954, AST was the first cardiac biomarker to be used. AST is found in the liver, heart, skeletal muscles, brain

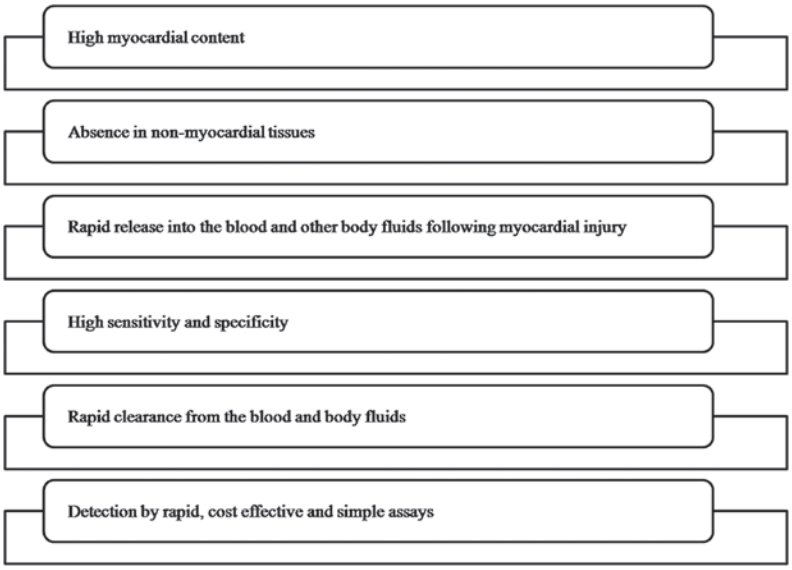

Figure 1. Characteristics of an ideal cardiac biomarker.

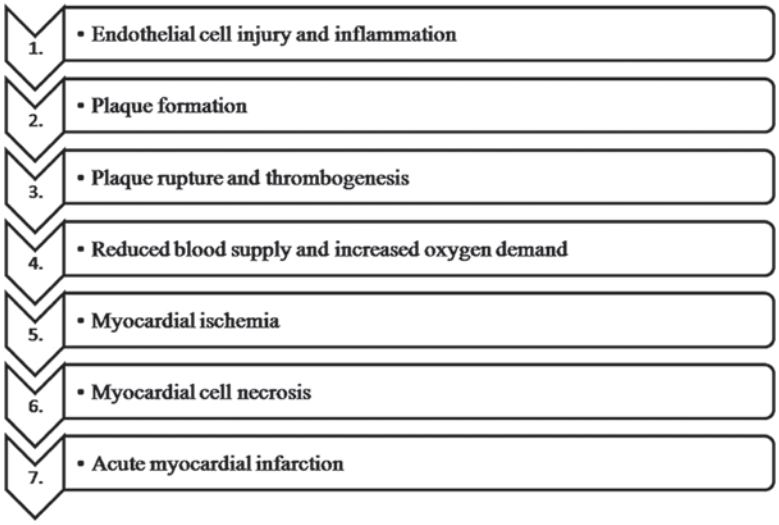

Figure 2. Schematic representation of the pathogenesis of myocardial infarction.

and kidneys. Due to its lack of specificity to the cardiac tissue it is no longer used for the diagnosis of AMI (12,13). In the year 1959, the total CK level was assessed for AMI, as it was a good indicator of skeletal muscle injury (14). Following this, in the year 1960, LDH was used for diagnosis of AMI (15). Finally in the year 1979, WHO recommended the panel of CK, AST and LDH for the diagnosis of AMI (2).

However, the assessment of the cardiac biomarkers was revolutionized in the year 1980 after the development of immunoassays (16).

3. Inflammatory markers

C-reactive protein (CRP). CRP is an acute phase protein secreted by the hepatocytes during an inflammatory stimulus (17). In addition to being an inflammatory marker, CRP has a pro-inflammatory effect causing expression of adhesion molecules and inflammatory cells (18). It has been shown that CRP is increased in patients with unstable angina; however, owing to lack of sensitivity and specificity, it cannot be used as a diagnostic marker (19). As a prognostic indicator, high CRP levels have also been associated with poor outcome (20).

Pentraxin 3 (PTX-3). PTX-3 of the PTX family is a specific marker of vascular inflammation produced by the vascular endothelial cells, vascular smooth muscle cells, macrophages, and neutrophils in response to an inflammatory stimulus (21). The PTX-3 level has been proposed as a prognostic biomarker of adverse outcome in patients with unstable angina pectoris, myocardial infarction and heart failure (22,23). However, as opposed to CRP, PTX-3 predicts advanced atherosclerosis and is more specific for vessel wall inflammation (24).

Interleukin (IL)-6. Another marker of early atherosclerosis is IL-6, which has a major role in the recruitment and activation of inflammatory cells in response to ischemia and further

Table I. Biomarkers of myocardial infarction.

Type	Marker
Obsolete	Aspartate aminotransferase
	Total CK
	Lactate dehydrogenase
Established	Troponin T
	Troponin I
	Myocardial fraction of CK
	Myoglobin
Emerging	Heart fatty acid-binding protein
	B-type natriuretic peptide
	Ischemia-modified albumin
	Pregnancy-associated plasma protein A
	Copeptin
	Growth differentiation factor-15

CK, creatine kinase.

during the reperfusion of the infarcted myocardium (25). In addition, it stimulates the liver to produce the acute phase protein, CRP (26). Thus, an elevated serum level of IL-6 and CRP are associated with the development of atherosclerosis and additionally to the development of type II diabetes in insulin-resistant individuals (27).

4. Plaque destabilization markers

Myeloperoxidase (MPO). MPO is a metalloproteinase produced by the polymorphonuclear leukocytes and macrophages. It initiates the production of reactive oxygen species that are important for the development of atheroma and plaque rupture (28). Thus, an increased level of MPO is a marker of plaque instability (29). Furthermore, it serves as a predictive marker for future cardiovascular adverse events (30).

Pregnancy-associated plasma protein A (PAPPA). PAPPA is also a metalloproteinase that has an active role during the rupture of an atherosclerotic plaque (31). It is primarily produced by the syncytiotrophoblasts of the placenta, as well as by the fibroblasts, vascular endothelial cells and vascular smooth muscle cells. In atherosclerosis, it has been associated with plaque progression and instability (32).

Soluble cluster of differentiation 40 ligand (sCD40L). sCD40L of the tumor necrosis factor-α (TNF-α) family is upregulated on the platelets located in the intraluminal thrombus. The activation of the inflammatory and coagulant pathways during thrombogenesis causes the release of CD40L into the circulation, thus indicating plaque rupture and subsequent myocardial infarction (33).

TNF-α. TNF-α is a pleiotropic cytokine produced by the endothelial cells, smooth muscle cells and macrophages. TNF-α levels are markedly elevated in advanced heart failure (34). The role of TNF-α in atherosclerosis is the production of tissue inhibitors of metalloproteinases by the fibroblasts. Thus, the production of excess amounts of metalloproteinases causes rupture of the atheromatous plaque (35). Additionally, it can stimulate the synthesis of IL-6 by the smooth muscle cells. This confirms the role of TNF-α in the regulation of the inflammatory cascade. Thus, elevated levels of TNF-α are indicative of recurrent non-fatal myocardial infarction or a fatal cardiovascular event (36).

5. Myocardial necrosis markers

Troponins. The troponins are a complex of 3 protein subunits, namely troponin C, troponin T and troponin I, located on the thin filaments of the skeletal and cardiac muscle fibers. Troponin C is the calcium-binding component, troponin T is the tropomyosin-binding component and troponin I is the inhibitory component. As the isoforms of troponin C is identical in the skeletal and cardiac muscle, troponin C is not extremely specific for myocardial injury (37,38). The isoforms of troponin T and troponin I differ in the skeletal and the cardiac muscle, and thus are extremely specific for cardiac tissue necrosis (39). Troponin T is present chiefly in the bound form to the contractile elements of the myocardial cells; however, it is also present free in the cytoplasm. Troponin T exhibits a dual release initially of the cytoplasmic component and later of the bound component (40). Troponin I is extremely specific for the cardiac muscle and has not been isolated from the skeletal muscle. This absolute specificity makes it an ideal marker of myocardial injury (41). They are released into the circulation 6-8 h after myocardial injury, peak at 12-24 h and remain elevated for 7-10 days (42). The only disadvantage of cTn is the late clearance that makes it difficult to identify a recurrent myocardial infarction.

Myoglobin (MYO). MYO is a small cytoplasmic oxygen-binding protein found in the skeletal as well as the cardiac muscle. It is released extremely early into the serum, 1 h after the onset of myocardial injury, peaks at 4-12 h and returns to baseline values immediately (43,44). The major disadvantage of MYO is the lack of specificity to the cardiac tissue due to the presence of large amounts of MYO in the skeletal muscle (45). The levels of MYO can therefore not be used as a single diagnostic marker, but in conjunction with the troponins or CK-MB. Thus, serum levels of MYO can be used to rule out, rather than diagnose, myocardial infarction (46).

CK and CK-MB. CK was first indicated as a cardiac biomarker in the year 1979. CK is an enzyme that is found primarily in the cardiac muscle and skeletal muscle. This enzyme has 3 isoenzymes: MM, MB and BB. CK-MM is the skeletal muscle fraction, CK-MB is the cardiac muscle fraction and CK-BB is the brain fraction of the total CK (47). Previously, the total CK was assessed for myocardial infarction. However, as the total CK contains 95% of the CK-MM fraction, recent concepts have proposed the use of the relative index score (RI) as follows (48).

$$\text{CK-MB RI} = [\text{CK-MB (ng/ml)}/\text{Total CK (U/l)}] \times 100$$

The CK-MB rises in the serum at 4-9 h after the onset of chest pain, peaks ~24 h and returns to baseline values at

48-72 h. The one advantage of CK-MB over the troponins is the early clearance that helps in the detection of reinfarction. Thus, the serum level of troponin along with the level of the CK-MB fraction is assessed for the diagnosis of myocardial infarction (49).

Heart fatty acid-binding protein (H-FABP). H-FABP is a small cytosolic low molecular weight protein found in the cardiac tissues that are responsible for the transport of fatty acids from the plasma membrane to sites of β-oxidation in mitochondria and peroxisomes, and to the endoplasmic reticulum for lipid synthesis (50). It is chiefly present in the myocardium and, to a lesser extent, in the brain, kidney and skeletal muscle. H-FABP is released extremely early into the serum following myocyte rupture (51). An increased concentration of H-FABP appears as early as 30 min after myocardial injury, peaks at 6-8 h and returns to baseline levels at ~24 h (52). Additionally, H-FABP can be used as a predictive biomarker of mortality following acute coronary syndrome (ACS) (53).

B-type natriuretic peptide (BNP). BNP is a neurohormone released from the cardiac cells. Studies have shown that elevated BNP is a predictive marker of death and heart failure. However, they are not useful for the diagnosis of AMI (54).

Ischemia-modified albumin (IMA). Under ischemic conditions, the level of IMA in the blood is significantly increased, thus aiding in the diagnosis of acute ischemia prior to the onset of myocardial necrosis (55). The measurement of IMA is enabled by the binding of the cobalt to the damaged N-terminus of the albumin. The increase in IMA levels occurs immediately after the onset of ischemia and returns to baseline values within 6-12 h, thus enabling early identification of ischemia (56).

Growth-differentiation factor-15 (GDF-15). GDF-15 is a member of the transforming growth factor-β family of cytokines that is primarily expressed by the placenta; however, under abnormal conditions, it can be expressed by various tissues (57). During cardiac ischemia, the level of GDF-15 is increased favoring diagnosis of ACS (58). However, owing to its lack of specificity, it can be used as a predictive marker of mortality rather than a diagnostic marker following ACS (59).

Copeptin. Copeptin, the C-terminal portion of provasopressin is cosecreted with vasopressin. Copeptin is secreted extremely early in the course of an AMI from the pituitary (60). Copeptin levels are significantly increased within minutes in patients with AMI. Thus, copeptin can be used as a diagnostic and prognostic marker of myocardial injury (61).

F2 isoprostanes. F2 isoprostanes are products of arachidonic acid metabolism. During atherosclerosis, the F2 isoprostanes are secreted by a variety of cells including the monocytes. Studies have shown that the F2 isoprostane level is increased in the urine of patients with unstable angina. Additionally, it can be used as a predictive marker of complications in non-fatal myocardial infarction, development of heart failure and fatality (62).

6. Salivary biomarkers associated with myocardial necrosis

Saliva offers an easy, simple and non-invasive screening procedure for various systemic diseases. Whole saliva contains constituents from serum, gingival crevicular fluid and oral mucosal transudate making it a valuable diagnostic tool. Salivary markers of acute myocardial infarction include MYO, CRP, MPO, CK-MB and cTn, which when used in combination with an ECG, shows a positive correlation in patients when compared to healthy controls (63). The salivary MYO levels were found to be significantly higher within 48 h of onset of chest pain in AMI patients and correlated positively with its serum concentration (64). In a study performed by Miller *et al* (65), the salivary concentrations of CRP, TNF-α, matrix metalloproteinase-9 (MMP-9) and MPO were significantly higher in patients with AMI and correlated positively with the serum concentrations. Studies reveal that salivary soluble intracellular adhesion molecule 1 is significantly elevated in AMI patients; however, levels of salivary sCD40L were significantly lowered in AMI patients. In a study performed by Foley *et al* (66), salivary levels of troponin I and CRP correlated with the serum levels in patients with myocardial injury. Additionally, levels of MMP-9 and MPO in saliva correlated with its serum levels (67). Thus, these studies suggest that saliva can be used as an alternative to serum in the diagnosis of myocardial infarction (68).

7. Conclusion

The analysis of cardiac biomarkers has become the frontline diagnostic tools for AMI, and has greatly enabled the clinicians in the rapid diagnosis and prompt treatment planning, thereby reducing the mortality rate to a great extent. However, the future of cardiac biomarkers will follow the analysis of a panel of markers for the diagnosis and prognosis of myocardial infarction.

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