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Review Article

The Significance of Troponin and Ck-Mb in Association with Q-Wave Myocardial Infarction

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Abstract. Acute myocardial infarction (AMI) is the global main cause of morbidity and mortality. AMI describes the process of cell death due to prolonged ischemia identified by the appearance of pathological Q-wave in electrocardiogram (ECG). Myocardial cell death does not occur directly after the onset of myocardial ischemia, however, it occurs more than 6 hours after the onset. Thus, certain cardiac markers, such as cardiac troponin and creatinine kinase-MB (CK-MB) which formed in myocardial cell damage, play a vital role in diagnosing AMI.

Keywords: Cardiac Biomarker, CK-MB, Diagnosis, Q-wave Myocardial Infarction, Troponin

Abstrak. *Infark miokard akut (IMA) adalah penyebab utama morbiditas dan mortalitas di dunia. IMA menggambarkan proses kematian sel akibat iskemia berkepanjangan yang ditandai dengan adanya gelombang-Q pada elektrokardiogram (EKG). Kematian sel miokard tidak muncul secara langsung setelah terjadinya onset iskemia miokard, melainkan muncul lebih dari 6 jam setelah onset. Oleh karena itu, penanda cedera jantung tertentu seperti troponin jantung dan kreatinin kinase-MB (creatinine kinase-MB / CK-MB) yang terbentuk ketika terjadinya kerusakan sel miokard berperan penting dalam mendiagnosis IMA.*

Kata kunci: *Biomarker Jantung, CK-MB, Diagnosis, Infark Miokard Gelombang-Q, Troponin.*

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1. Introduction

Acute coronary syndrome (ACS) is a spectrum of coronary artery diseases that include unstable 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. ACS symptoms include chest pain, referred pain, nausea, vomiting, dyspnea, diaphoresis, and light-headedness. Diagnosis of AMI includes STEMI and NSTEMI, requires at least two of these criteria: symptoms of ischemia, changes in ECG, and increase in serum cardiac markers [1, 2].

Clinical history and ECG results can diagnose AMI accurately for most AMI patients. However, fews conditions show negative results including the prolonged myocardial injury, age of infarction, location of infarction (high lateral and posterior part of the heart are unable to be detected by ECG), the presence of conduction defects, previous infarction, acute pericarditis or changes in electrolyte concentration [3].

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. However, those biochemistry parameters have poor specificity problem, thus they are not often used and replaced by cardiac troponins which are more specific to myocardial cell injury. 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[3].

2. Myocardial Infarction

Acute myocadial infarction (AMI) remains as the risk factor for the high morbidity and mortality globally. AMI describes the process of myocardial cell death caused by ischemia, or imbalance of perfusion between supply and demand in coronary artery which accounts for acute thrombotic occlusion. Size of infarct mostly depends on the distribution of occluded artery. Treatment with thrombolytic agent can limit the size of infarct. Initial identification and confirmation of AMI are required to make a quick and precise decision, hence, allowing best treatment for the patients with AMI[3, 4].

ECG is used to classify two types of AMI, which are Q-wave MI (transmural) and non Q-wave MI (nontransmural / subendocardial). The presence of Q-wave indicates the continuous necrosis in endocardium to epicardium, while the absence of Q-wave indicates less extensive myocardial damage and possibly an increased potential for recurrent coronary events. Previous MI and AMI

can be differentiated by the pathological Q-wave in ECG or imaging of the loss of myocardial tissues (i.e., a thinned area and failure in contraction) without ischemia. It has been indicated that Q-wave infarction is associated with higher levels of certain enzymes including serum glutamicoxaloacetic transaminase (SGOT), lactate dehydrogenase (LDH), and creatinine phosphokinase. These high enzyme levels are caused by the presence of considerable myocardial necrosis presence [4-6].

3. Diagnosis of Myocardial Infarction

Patients are diagnosed with AMI when there is evidence of the presence of myocardial necrosis consistent with acute myocardial ischemia. Myocardial cell death does not occur directly after myocardial ischemia onset, but occurs more than 6 hours after the onset. Criteria which define the diagnosis of AMI by World Health Organization (WHO) in the early 1970s to the 1990s are the presence of at least two of these characteristics: (1) symptoms of acute ischemia (chest pain), (2) development of Q-wave in ECG, (3) elevation of serum enzyme levels such as: total CK, CK-MB, AST and 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 (MI), emphasizing the significance of sensitive and serological biomarkers for the diagnosis of AMI, and introduced cardiac troponins as the "gold standard" [7-9].

For most patients with STEMI, clinical evaluation and ECG provide accurate diagnosis andrevascularitation could possibly be initiated in minutes. However, STEMI only represents about 5% of patients that come with chest pain complaint. ECG itself is often inadequate to diagnose AMI because ST elevation can also occur in other clinical conditions such as initial repolarisation pattern, acute pericarditis, left ventricle hypertrophy, left bundle branch block (LBBB), hyperkalemia and Brugada syndrome. Therefore, cardiac troponins are becoming more popular in diagnosing AMI. Cardiac troponins are sensitive and specific for the presence of cardiac myocytenecrosis and are very useful in clinical practice to identify patients with high risk ACS [7, 8].

4. Biomarker of Myocardial Infarction

Biomarker, the short term of biological marker, was first introduced in 1989. Biomarker is defined as"a characteristic that is objectively measured and evaluated as an indicator of normal biological processes or pharmacologic responses to a therapeutic intervention". Specificity of a biomarker depends not only on its ability to avoid cross-reactivity with another associated biological molecules, but also on its biological characteristics which show that the marker is not derived from other tissues, whether in a small amount or pathological condition. Since the organ

target of myocardial injury is the heart, cardiac specificity is the most important biological characteristic of MI biomarker [7].

The first biomarker used in clinical practice to diagnose AMI is AST. Studies demonstrated that AST is elevated in AMI patients. However, AST is not only found in the heart, but also in the liver, skeletal muscle, kidneys and brain. Therefore, AST is not specific in diagnosing AMI since it will be elevated if there is injury in any of those tissues. Besides that, patients with minor MI or non-Q-wave MI might not have elevated AST value. Another biomarker, total CK, is also not cardiac specific because it might be elevated in some conditions includingskeletal muscle injury (distrophy, myopathy and myocitis), brain injury, cardiac cateterisation without myocardial damage, hypothyroidism, stroke, surgery, and convulsive patients without skeletal muscle injury [7, 8].

Due to the low specificity and availability of more specific alternative biomarkers of AMI, the National Academy of Clinical Biochemistry (NACB), together with leading researchers in the field of cardiac biomarkers, have proposed Standards of Laboratory Practices for the use of cardiac markers in coronary artery diseases. NACB suggests the use of two biomarkers for the diagnosis of AMI: an early marker and a definitive marker. Blood levels of the early marker must be consistently elevated within the first 6 hours after the onset of symptoms. Myoglobin, an oxygen storing protein found in skeletal and cardiac muscles, is proposed as the ideal early marker. Myoglobin is released into circulation as early as one hour after myocardial injury andusually rises 2-4 hours after onset of myocardial injury, peaks at 8-12 hours, then returns to normal within 24 hours. Thus, myoglobin is the ideal early marker although it lacks cardiac specificity [8, 10].

The definitive marker should be detectable in the circulation within 6-9 hours after the onset of symptoms, have high sensitivity and specificity for MI, and blood levels must remain elevated for several days. Cardiac troponins are proposed as the ideal definitive markers for AMI diagnosis. When cardiac troponin (cTn) is not available, the next best alternative is CK-MB (measured by mass assay). In addition, studies show that performing three-test panel (myoglobin-CKMB-cTn) is better than performing only two-test panel (myoglobin-cTn). It is demonstrated that CK-MB may provide some additional useful information in patients with ACS since CK-MB also indicates reinfarction and MI extension. The kinetics of myoglobin, cardiac troponins and CK-MB levels versus time after onset of infarction can be seen in Figure 1 [7, 8].

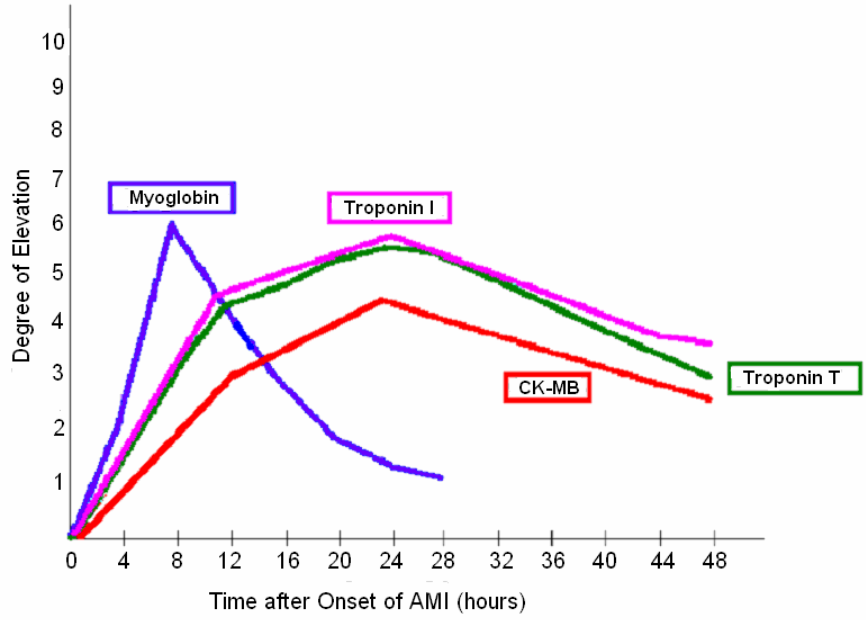

Figure 1. Kinetics of myoglobin, cardiac troponins and CK-MB levels vs time after onset of infarction [8].

4.1. Troponin

The most widely used biomarker in the diagnosis of AMI is troponin. Troponin is a constituent of cardiac and skeletal muscles. Troponin occurs as a complex of three proteins in thin filaments of the muscles which regulates interaction between thick and thin filaments during muscle interaction. Troponin complex consists of three subunits which are troponin T (TnT; the tropomyosin-binding subunit), troponin I (TnI; the inhibitory subunit) and troponin C (TnC; the calcium-binding subunit). This complex controls the calcium mediated interaction between actin and myosin causing the contraction and relaxation of striated muscles. Myocardium transmural necrosis happens at least 2 to 4 hours or more in somecases includingpre-conditioned, collateral circulation or subsequent coronary artery occlusion. Although troponin is unable to provide early detection (first 1-2 hours) ofmyocardial necrosis, troponin can be detected approximately 2-4 hours after the onset of MI [7, 8, 11].

Although TnC is identical in skeletal and cardiac muscles, amino acid sequence of TnT and TnI found in cardiac muscle are different from the ones found in skeletal muscle. Troponin T and I isoforms in cardiac muscle have additional residues in the N-amino terminal, hence, could be identified directly as cardiac troponins (cTn). Cardiac troponin T and I (cTnT and cTnI) are only expressed in cardiac muscle which cause these biomarkers to have a high specificity for myocardial damage. TnT is a cardiac-specific polypeptide which is mainly bound to contractile component of myocyte, but a small amount of TnT is also found in cytoplasm. Cytostolic cTnT is released in the first several hours after infarction. The release of cTnT from myofibril is slower than cytostolic cTnT, which is in the period of several days. The two-phase releases of cTnT cause an early in the circulation (3-4 hours after infarction) which lasts for 10 days or

more, hence, making it useful as a cardiac biomarker. On the other hand, three different TnI isoforms based on tissue specificity have been identified: two in the skeletal muscle and one in the cardiac muscle. While the molecular mass of the two skeletal isoforms are approximately the same (19.8 kDa), the cardiac isoform (cTnI) has additional 31 amino acid sequences in N-terminal which result in the greater molecular mass (24 kDa). In the heart, cTnI is distributed equally in atrium and ventricular. The absolute specificity of cTnI for cardiac tissue also makes it become the ideal biomarker for MI [4, 7, 8].

The cTn subunits occur in the peripheral circulation when damage to the cardiac myocyte first leads to the release of cytostolic cTn, which accounts for 3% to 5%of cTnI and 7% of cTnT levels. Then, the release of bound cTn subunits contributes to the continued rise in the circulation which remains detectable for days (4-7 days for cTnI and 10-14 days for cTnT). The cTn subunits are cleared from the circulation primarily by the reticuloendothelial system, and fragmented into molecules that are cleared renally. Although cTn elevation persists for days, initial detection after the onset of MI is delayed because necrosis typically requires 2-4 hours to occur in the setting of ischemia. Consequently, cTnT and cTnI are detectable only after this latency period following the onset of MI.It is recommended to doserial measurements after the latency period and again after 6-9 hours from the onset of MI. It has to be remembered that cardiac troponins indicate myocardial damage, but not the mechanisms[7, 8].

4.2. Creatinine Kinase-MB

Due to the development in electrophoresis, identification of cardiospecific CK isoenzymes has been increasing. There are three CK isoenzymes which found in the circulation such as CK-MM (CK-1) which derived from skeletal muscle, CK-MB (CK-2) which derived from cardiac muscle and CK-BB (CK-3) which derived from the brain. Cardiac muscle has CK-MB level (25-30%) higher than skeletal muscle (1%). CK-MB level usually elevated significantly 4 to 9 hours after the onset of MI, peaks at 12 to 24 hours, and back to baseline at 48 to 72 hours. Measurement of CK-MB, CK-MB fraction or CK-MB/CK-MM ratio is a more specific biomarker for AMI. Measurement of relative index (RI) is also used to distinguish between the damage in cardiac and skeletal muscle. The RI ratio is (CK-MB/ total CK) x 100. If RI value $\geq$ 5%, then the value corresponds to myocardial damage [7-9].

The detection and measurement of biomarkers are improved as the development of technical advances in automation and immunoassays. Immunoassays were initially configured with polyclonal antibodies before with monoclonal antibodies in 1980s. Monoclonal antibodies allowed measurement of CK-MB by mass which enabled earlier and quicker detection on myocardial damage and was also more sensitive and specific than the original CK-MB activity assay. However, as the research went on, it was realized that even CK-MB mass was elevated in some situations like in skeletal muscle injury, non-ischemic cardiac disease, and certain malignancies. The one advantage of CK-MB over the troponins is the early clearance of CK-

MB that gives additional information of reinfarction. Thus, the serum level of cardiac troponins along with the level of the CK-MB fraction is assessed for the diagnosis of MI[7, 9].

5. Conclusions

Cardiac biomarkers such as cardiac troponins and CK-MB play crucial roles in diagnosing Q-wave MI. MI cell death occurs 6 hours after the onset of MI which can be seen by the presence of Q-wave in ECG for most patients. Myocardial cell death causes elevation in the expression of cardiac troponins and CK-MB. Therefore, in addition to ECG, cardiac troponins and CK-MB are usually assessed when diagnosing AMI.

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