Cardiac troponin I: the gold standard in acute myocardial infarction diagnosis

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Abstract

Cardiovascular diseases are leading cause of morbidity in the world. Measurement of the level of biochemical markers in the serum is one of World Health Organisation (WHO) criteria in diagnosing acute myocardial infarction (AMI). Non-specific clinical state of patients and insufficiently sensitive electrocardiographic (ECG) diagnostics, at patient's hospital admission time, point out the importance of biochemical markers in acute myocardial infarction diagnosis. Technology development and new diagnostic methods lead to the invention of highly sensitive and specific marker as myocardial damage evidence. Cardiac Troponin I (cTnI) is specific marker for myocardial damage1. Its elevation in the serum within myocardial ischemia symptomatology is important in diagnosis of myocardial infarction.

Keywords: acute myocardial infarction; cardiac troponin I.

Abbreviations: AMI - acute myocardial infarction, ECG - electrocardiogram, WHO - World Health Organisation, cTnI - cardiac troponin I, CK-MB - creatine kinase muscle band isoenzyme, CK-MM - creatine kinase muscle isoenzyme, ACS - acute coronary syndrome, ATP-ase - adenosine triphosphatase.

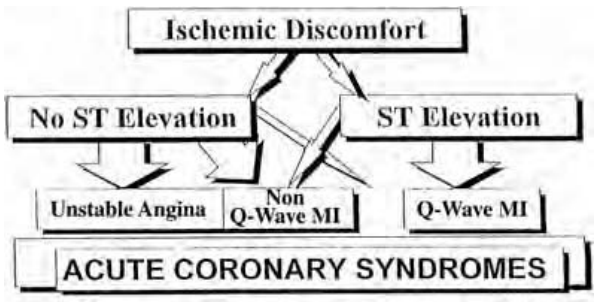
Introduction

Biochemical markers of myocardial damage are essential for diagnosis, risk stratification and selection of the ACS patients' treatment. Testing of the patient for AMI diagnosis has been rapidly changed in comparison to the traditional enzymatic assay and mass measurement of the specific and sensitive protein markers. The measurement of troponin I or troponin T in the blood has been accepted by the Joint Committee of the ESC/ACC as a standard biomarker for the diagnosis of acute myocardial infarction.
Due ESC/ACC recommendations, patients with ischemic symptoms are diagnosed as a non-stable angina when cardiac troponin is normal or as an AMI when cardiac troponin is increased. Today, improved diagnostic methods allow earlier detection of myocardial necrosis. Due to that, clinicians can initiate proper treatment as quickly as possible after the correct MI diagnosis.

Acute coronary syndrome - pathogenesis

Myocardial infarct is a terminal event of syndrome called acute coronary syndrome. Long duration of coronary ischemia is a cause of the myocardial infarction with following tissue necrosis.
ACS starts with asymptomatic coronary artery diseases, progresses to stable and non-stable angina, ECG non-Q-wave MI, transmural infarction, cardiac arrhythmia and death. All forms of the syndrome (Figure 1), including non-stable angina, ECG non-Q-wave MI, and Q-wave MI, share a common pathogenic substrate: atherosclerotic lesion of coronary arteries. When atherosclerotic plaque ruptures or erodes, pathophysiologal processes are triggered resulting in thrombus formation2. Inflammatory and thrombotic mechanism are involved in pathogenesis of the syndrome. Inflammatory reactions result in he plaque rupture and give possibilities of the onset of coagulation process that finishes with thrombus formation. When thrombus formation results in reduction or cessation of the blood flow within the affected coronary vessel, the resulting imbalance between oxygen require and supply produces the clinical manifestation of ischemia.

Figure 1. Spectrum of acute coronary syndromes



Am Heart J 2000; 139: 461-75

Acute myocardial infarction diagnosis

According to WHO recommendations, a traditional approach to patients with suspected acute myocardial infarction is based on three criteria:

- clinical symptoms that points on ischemia (chest discomfort that lasts about 30 minutes)
- electrocardiographic changes (depression or elevation of ST segment or T wave inversion)
- biochemical markers detection

According to WHO recommendations, myocardial infarction is defined as a presence of two out of three mentioned criteria.
The leading cardinal symptom of patients with acute coronary syndrome is chest pain that demands further clinical evaluation. Pain is a result of the imbalance between myocardial oxygen supply and need[3].
Electrocardiography is a method that enables the further risk stratification of patients with chest pain. If thrombus formation completely occludes coronary artery, ECG pattern involves development of the typical Q-wave. In case of transitory or non-complete occlusion, ECG changes have less prognostic importance. Unstable angina is diagnosed by the conventional enzyme markers being in referential values or minimally elevated. Biochemical markers in AMI diagnosis are very important in cases of nonspecific clinical symptomatology and untypical electrocardiographic changes.
A need for the redefinition of MI comes from the presence of advanced technology and highly sensitive cardiac markers which could detect small infarcts of less than 1.0 g of necrosis that do not cause diagnostic ECG changes or functional abnormalities [4].
About 30% of patients with previously diagnosed nonstable angina pectoris have elevated cTnI level in the blood[5]. In such patients there is no evidence of elevated CK or CK-MB isoenzyme activity.

Recommendations of the Joint European Society of Cardiology (ESC) and American College of Cardiology (ACC) Committee in consensus document advice to reexamine the definition and diagnosis of MI. MI is a minimal myocardial necrosis followed by the elevation of cardiac troponin I in the blood.

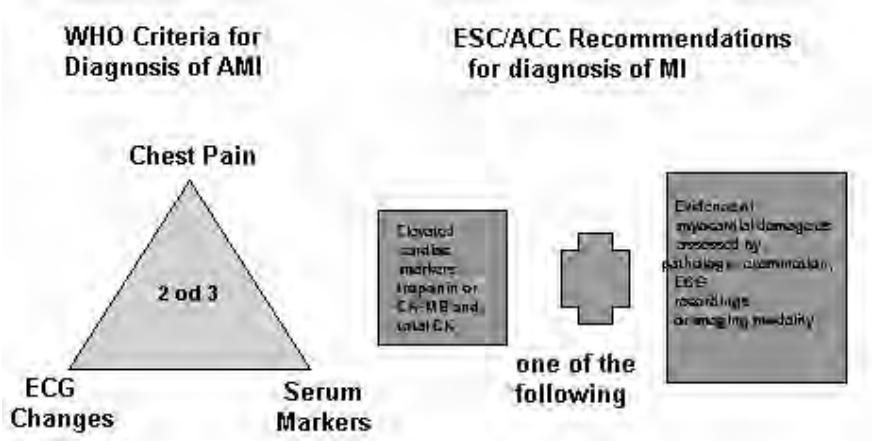
New definition of myocardial necrosis is "**maximal concentration of troponin T or troponin I that exceeds the 99% of the value for the referent control group, on at last one occasion during the first 24 hours following the evidence of clinical event**." [6]

Importance of the new definition is that the previously diagnosed severe stable and non-stable angina is now rediagnosed as myocardial infarction. Suggested ESC/ACC criteria differ from WHO criteria in the presence of two parameters in MI diagnosis: elevated cardiac markers with another changes, whether it is ECG changes or typical ischemic chest pain (Figure 2.)

Biochemical markers in diagnosis of acute myocardial infarction

Biochemical markers usage in the acute myocardial infarction diagnosis began after the year 1954 when La Due and his associates reported their investigation results about aspartate aminotransferase elevation in MI patients[7].
In last twenty years, the gold standard in laboratory diagnosisa of MI has been measurement of CK-MB activity. Increase or decrease in its activity has been used in diagnosis and monitoring of the treating course of patients with MI. This isoenzyme is not completely specific for the myocardial muscle. Its share in total myocardial muscle mass is just 3% from the total creatine kinase quantity.
CK-MB isoenzyme increases in myocardium as a response to ischemia. It has been considered for a long time that CK-MB is not detectable in skeletal muscles containing the majority of the CK-MM isoenzyme. Now we know that under the control of regulation genes, CK-MB content in skeletal muscle increases after injuries or during the regeneration process[8]. Due to this fact, there is

Figure 2 New and old criteria for the myocardial infarction dyagnosis

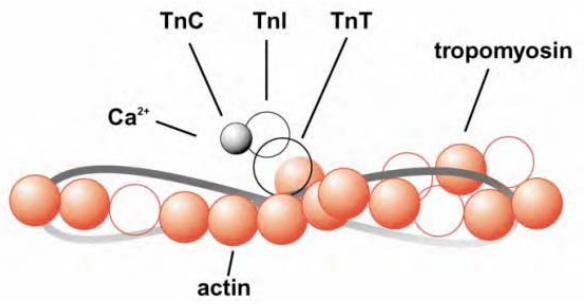


possibility of the masking of CK-MB release from the myocardium in the case of simultaneously damaged skeletal and hart muscles. Another problem is a small sensitivity in the first couple of hours following the infarction onset. Reviewing these acknowledgements raises a need of finding a marker with high sensitivity and specificity for the hart muscle.

Troponin complex

While searching for the sensitive and specific laboratory test in urgent MI diagnosis a troponin complex has been found
Troponin complex consists of three subunits: troponin I (TnI), troponin C (TnC), and troponin T (TnT). This complex (Figure 3)

Figure 3 Troponin complex components



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Different function, molecular weight and the origin of protein subunits are associated with the distinct aminoacid sequences encoded by separate genes.
Troponin I is an inhibitory unit that regulates contraction of skeletal and heart muscle. It inhibits Mg^{2+} activated actinomyosin ATP-ase activity. Its molecular weight is 23 000 Dalton.

Troponin I have three isoforms: two for skeletal muscles (slow and fast ones) and one for the heart muscle. Aminoacid sequence of the cardiac isoform makes troponin specific for the heart muscle. The N-terminus of the cTnI has 31 additional amino acid residues that are not present in skeletal troponin isoforms, allowing the development of specific antibodies as a condition for the development of a new diagnostic test. The majority of cTnI is bound to contractile apparatus (97%) and about 3% of it is a free cytosolic component. After cell necrosis, cTnI releases into the circulation with other troponin complex subunits[11].

Concentration of cTnI elevates almost at the same time as CK-MB concentration after the onset of symptoms, but its increase is higher and persists 5-7 days. This could be explained by the higher content of cTnI in myocardium (4-6 mg/g wet weight of tissue) in comparison to the CK-MB content. The initial cTnI rise is seen during the first couple of hours, with the peak level achieved between 12 and 24 hours after the estimated time of myocardial necrosis[12].

Half-life of cTnI in the serum is about 90 minutes. The possible time of the cardiac troponin I detection is related to the extent of myocardial damage. Long duration of the elevated values points out the prolonged protein release from the infracted area. Decreased concentration of cTnI points out the reparation of myocardial damage.
Cardiac specificity is proved in several clinical conditions without the detection of cTnI elevation in the blood:

- muscular dystrophy patients
- marathon and exercise sport activities
- muscle injuries
- renal diseases

Suitability of cTnI to "The Gold standard" for the Diagnosis Acute Myocardial Infarction[13]:

- cTnI is only found in cardiac muscle during adult life and embriogenesis
- cTnI is not synthesised in response to skeletal muscle injury
- The antibodies used in the assay for cTnI do not cross-react with the skeletal muscle troponin I
- cTnI is not elevated in patients suffering from the variety of clinical conditions
- Elevation of cTnI closely correlates with the evidence of myocardial injury demonstrated by echocardiography
- There is 13-fold greater concentration of the cTnI in the heart in comparison to the CK-MB concentration
- Elevation of the cTnI is at least as sensitive in the clinical detection of cardiac injury as CK-MB elevation
- Risk of the 24-hour and 30-day death or MI with detected positive CK-MB results is lower than with the detected positive troponin I results[14].

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