Temporal profile of protein release in myocardial infarction

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Abstract

Acute myocardial infarction (AMI) is one of the most important cardiovascular diseases in developed countries, where it represents the major cause of death and disability. The diagnosis of ''classic'' AMI is based on the triad of typical symptoms and changes in the electrocardiogram and in biomarkers. Biomarkers are proteins that are released into the circulation by the damaged myocardial cells. The rate of appearance of these proteins depends on several factors, mainly the rate of their elimination from the blood. Each protein has a specific time course of release in terms of first detection in the blood at concentrations above the upper reference limit, peak plasma concentration, and normalization. Blood sample for determination of biomarker changes should be taken at the time when the patient presents and later during the course of the disease, according to the kinetics of each marker. Currently, cardiac troponins and creatine kinase MB mass are the biomarkers most used for the diagnosis of AMI. Emerging markers include C-reactive protein, pentraxin-3, and brain natriuretic peptide.
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Keywords: Acute myocardial infarction, biomarkers, protein release

Introduction

Acute myocardial infarction (AMI) is one of the most important diseases in developed countries, where it represents a major cause of death and disability. In the majority of cases, AMI is caused by an abrupt coronary thrombosis as a result of erosion of, or development of a fissure in a ''vulnerable'' non flow-limiting coronary atherosclerotic plaque. The diagnosis of ''classic'' AMI is based on the triad of typical symptoms and changes in the electrocardiogram and in biomarkers. As acute coronary artery occlusion occurs, myocardial cell necrosis develops after 20 min and can be identified by the appearance in the blood of different proteins released into the circulation by the damaged cardiac myocytes [1]. The rate of appearance of biomarkers depends on several factors, mainly the rate of their elimination from the blood (greatly influenced by the patency of the culprit vessel). Release of each marker is characterized by a specific time course, including the first detection in the blood at concentrations above the upper reference limits, the peak concentration, and normalization (*Table I*). The ideal biomarker should have high sensitivity and specificity, appear early during the course of the disease to allow a rapid diagnosis, remain abnormal for several days to allow a late diagnosis, and be easily assessed by user-friendly assay. This ideal marker has not yet been discovered; however, cardiac troponin is an established marker for both diagnosis and prognosis in acute coronary syndromes. Emerging markers – such as high-sensitivity C-reactive protein (CRP) and brain natriuretic peptide (BNP) – are used as inflammatory indexes to evaluate the extent of the necrosis and to determine prognosis [2,3].

Table I. First detection, peak, and normalization of protein plasma concentration during acute myocardial infarction.

Marker	First detection	Peak	Normalization
Myoglobin	2 h	4–12 h	24 h
MB-CK mass	3–12 h	24 h	48–72 h
Troponin	3–6 h	24–48 h	5–10 days (cTnI) 5–14 days (cTnT)
C-reactive protein	4–6 h	50 h	NA
Pentraxin TX3	2–4 h	20–24 h	NA
Brain natriuretic peptide	early	20 h to 5 days	<30 days to NA

NA, not available.

Myoglobin

Myoglobin is a small, nonenzymatic heme protein, rapidly released into the circulation from injured myocardial cells. It is detectable in blood as early as 1 h after myocardial injury. The peak of its concentration is reached earlier (approximately 12 h) than that of any other biomarker and tends to normalize within 1 day (*Figure 1*). Because of its high sensitivity and low specificity for AMI, this marker is particularly suited to excluding AMI at the earliest phase of the disease. As it is not cardiac specific, false-positives may be found in patients with acute or chronic skeletal muscle damage or in patients with chronic renal failure. As for many other biomarkers, a more rapid increase in the plasma concentration of myoglobin is found in patients who achieve a full reperfusion. The early normalization of myoglobin makes this marker particularly indicated for the diagnosis of re-infarction [4,5]; in this event, a ''double-peaked'' curve is usually detected.

Creatine kinase MB isoenzyme

Creatine kinase MB (CK-MB) is a cytosolic carrier protein for high-energy phosphatase. For several years, the isoenzyme MB has been the marker of AMI used most. The plasma concentration of CK-MB mass starts to increase above the cutoff value between 3 and 12 h after the onset of chest pain. It reaches a peak at 24 h and reverts to normal values within 48–72 h (*Figure 1*). Although it is found in the greatest concentration in cardiac tissue, increased concentrations of CK-MB may be found in renal failure, hypertension, skeletal muscle injury, and other conditions. However, a high concentration of CK-MB may be considered diagnostic for myocardial infarction, especially if combined with the typical increase and decrease in values [6,7].

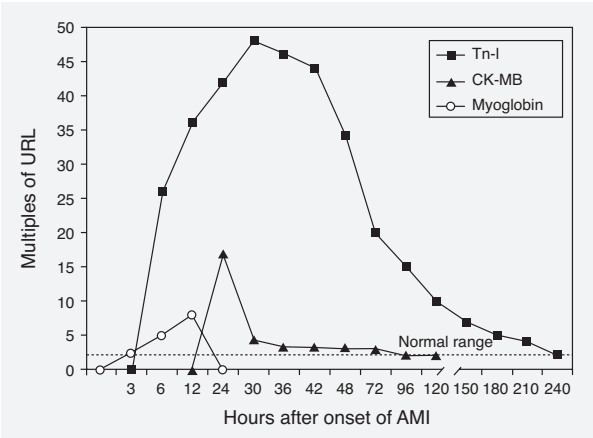

Figure 1. Profile of release of troponin I (TnI), creatinine kinase MB (CK-MB) and myoglobin in acute myocardial infarction (AMI), upper reference limit (URL), data from De Groot et al [5] and Larue et al [8].

Troponin

Cardiac troponin (cTn) is one of the biomarkers that have been found to have both diagnostic and prognostic importance in AMI. It is a protein complex that regulates the calcium-modulated interaction between actin and myosin in striated muscle, and is constituted of three subunits: T, C, and I. Troponins I (cTnI) and T (cTnT) are highly specific and sensitive for cardiac injury [8]. A significant increase in cardiac troponin value is defined as a plasma concentration exceeding the 99th percentile of that of a normal reference population [1].

Generally, in AMI the plasma concentration of troponin begins to increase above the cutoff value by 2–4 h after the onset of symptoms, reaching a peak after 24–48 h; concentrations may remain increased for up to 5–10 days (cTnI) or 5–14 days (cTnT) (*Figure 1*). This long-lasting increase, probably resulting from the continuous release of troponin from the degenerating contractile apparatus of necrotic myocytes, helps in the correct diagnosis of AMI late in the course of the disease. Detection of the typical increase and decrease in concentrations is essential to the diagnosis of AMI, especially if there are coexisting extracardiac conditions that may be associated with high plasma concentrations of troponin (eg, chronic renal failure, trauma, extreme exertion) [9–11].

Measurement of troponins in AMI should be made when the patient is first seen and again 6–9 h later. If AMI is highly suspected but the first measurement does not reveal increased concentrations of troponin, a third

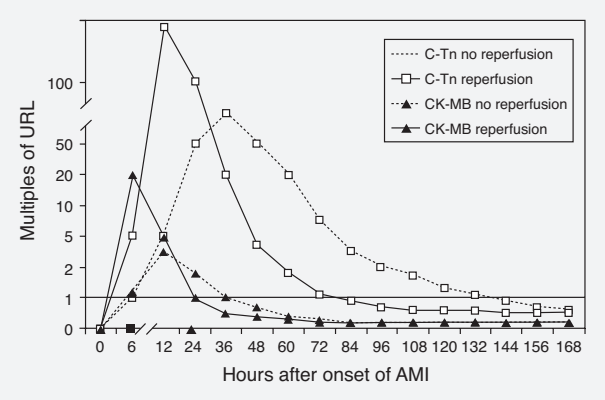

Figure 2. Kinetics of cardiac troponin (cTn) and creatinine kinase MB (CK-MB) in patients who did and did not achieve reperfusion [12,13].

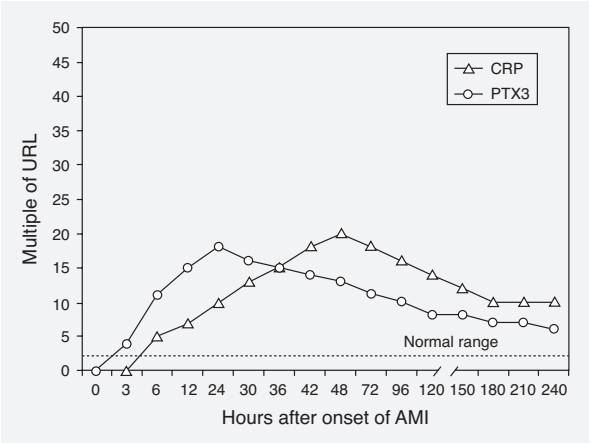

Figure 3. Profile of release of C-reactive protein (CRP) and pentraxin TX3 (PTX-3) [14,18].

blood sample for measurement of troponin should be drawn after an interval of 12–24 h. Myocardial re-infarction may alter the standard time course of release of troponin, accounting for a renewed increase in, or a progressively increasing, plasma concentration. In such an event, two additional blood sample measurements, 3–6 h apart, are recommended. Recurrent myocardial infarction is diagnosed if there is an increase of at least 20% in the second measurement.

Myocardial reperfusion, whether spontaneous, or achieved pharmacologically with lytic agents or mechanically with percutaneous coronary intervention, may affect the kinetics of release of biomarkers in AMI, including troponin. Patients with ST-segment elevation myocardial infarction who achieve an effective reperfusion have a greater and earlier peak plasma concentration of troponin, followed by a faster return to normal – the so-called ''wash-out phenomenon'' – compared with those patients having no significant reperfusion (*Figure 2*) [12,13]. In this event, two blood samples should be collected – at the time of the patient's admission to hospital, and 90 min later – and the enzyme plasma concentrations compared. The ratio between the concentrations at these two points can be used to discriminate between successful and unsuccessful reperfusion. In general, the greater the ratio (at least 5), the more likely it is that reperfusion has occurred. If reperfusion has indeed occurred, estimation of infarct size using peak biomarker concentration may be not reliable.

C-reactive protein

Inflammation is a factor in all stages of the atherosclerotic disease process, and represents a pathophysiologic link between the formation of plaque and its rupture, which are responsible for AMI. To date, CRP (an acute-phase reactant protein made in the liver) has been the preferred marker for the detection of inflammation and to define prognosis during acute coronary syndromes [14,15]. When AMI occurs, an exponential increase in CRP is observed, starting 4–6 h after the onset of symptoms and reaching a peak about 50 h later (*Figure 3*). The increase in plasma concentrations of CRP is strictly related to the degree of cardiac damage [14]. High concentrations of CRP, in patients with persistent ST-segment elevation after AMI, is an important negative prognostic factor, in both the short and the long term [16,17].

The specificity of CRP as a marker is very low, because increased concentrations of CRP are detected in several conditions, such as diabetes, obesity, estrogen therapy, hypertension, and smoking.

Pentraxin-3

Pentraxin-3 (PTX3) is related to classic pentraxins (like C-reactive protein CRP or serum amyloid P SAP) but is structurally different. It is made in the liver in response to inflammatory mediators, mainly interleukin-6. It is also produced in large amounts by the heart. PTX3 is detected inside both normal and hypertrophic cardiomyocytes, and is increased in AMI. Its plasma concentration increases rapidly after the onset of symptoms, preceding the increase in CRP concentration, and reaching a peak at 20–24 h after onset of symptoms (*Figure 3*) [18,19]. In patients with unstable angina, the PTX3 concentration increases to a lower value than in AMI. Accumulating evidence suggests that PTX3, binding with C1q in the same way that CRP and SAP bind to C1q, contributes to the mechanism of increase in tissue damage [20].

Brain natriuretic peptide

Brain natriuretic peptide is 32-amino-acid peptide released in response to ventricular stretch. Its functions

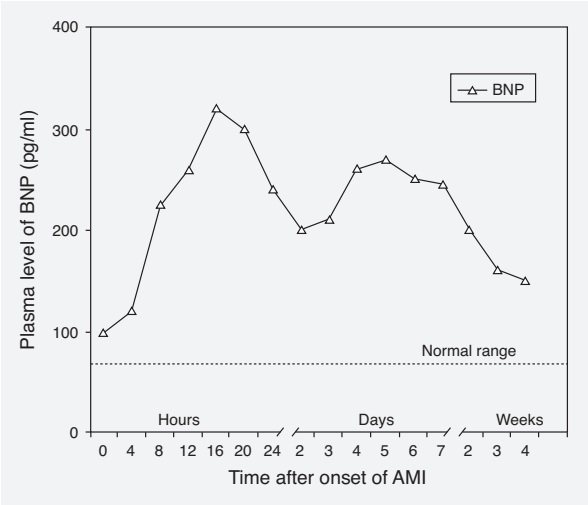

Figure 4. Profile of release of brain natriuretic peptide (BNP) [21].

are similar to those of atrial natriuretic peptide: mainly, reducing systemic vascular resistances and central venous pressure, and increasing natriuresis. Two types of time course of change in BNP concentrations have been reported in association with AMI. The first is a single-peak curve reaching a maximal plasma concentration approximately 20 h after symptom onset and returning slowly to normal within 4 weeks. The second type of curve is characterized by a late peak at 5 days, with values remaining increased at 4 weeks (*Figure 4*). Reasons for the increase in BNP concentrations during AMI are not easily understood. In a study by Morita et al [21], BNP concentration did not correlate significantly with hemodynamic parameters in the early phase of AMI, suggesting that the increased concentration may be the result of myocardial necrosis or local mechanical stress, or both. Interestingly, the biphasic curve was observed more frequently in patients with anterior AMI, signs or symptoms of heart failure, lower ejection fraction, and higher plasma concentrations of CK-MB than was the single-peak curve. These data suggest that increased concentrations of BNP in the late phase of AMI may be related to infarct expansion and ventricular remodeling [21,22]. Kaya et al [22] reported greater plasma concentrations of BNP (single sample) in inferior AMI with right ventricular involvement, compared with those in isolated inferior AMI. This finding reinforces the concept that increased ventricular stretch and filling pressure are potential stimuli for the secretion of BNP during the early phase of AMI in certain patient populations.

Conclusions

Proteins released during acute myocardial infarction can provide important diagnostic and prognostic information. Each possesses a specific time course of release. Because of the rapid increase and decrease in its concentration, and its negative predictive value, myoglobin has a role in the exclusion of AMI. Troponin, with its high cardiac specificity, is the preferred marker for myocardial injury and AMI; several blood sample should be obtained at different times along the course of the disease, to enable diagnosis of cases of late AMI. CRP, PTX3 and BNP are emerging biomarkers that have specific indications in the setting of AMI. ■

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