EDUCATIONAL COMMENTARY – CARDIAC MARKERS

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Learning Outcomes
Upon completion of this exercise, the participant will be able to:

- Discuss the use of CK-MB, troponin I, troponin T, and myoglobin levels in the diagnosis and treatment of cardiac disease, particularly myocardial infarction.
- State the proper sample for analysis of CK-MB, troponin I, troponin T, and myoglobin levels in blood.
- Describe the time sequence for elevation of CK-MB, troponin I, troponin T, and myoglobin levels in blood following myocardial infarction.

The leading cause of death for both men and women in the United States is coronary heart disease. When a patient presents in the emergency department with chest pain, physicians must consider a continuum of acute coronary syndromes: ranging from non-cardiac chest pain to unstable angina, in which oxygen deprivation occurs without permanent damage to heart muscle, on to a heart attack or myocardial infarction (MI) with permanent heart muscle damage. If an MI can be diagnosed within six hours of onset, thrombolytic or other reperfusion therapy can be initiated. Conversely, ruling out an MI within 24 hours avoids critical care unit (CCU) costs. One study concluded that approximately 70% of patients with chest pain admitted to CCU were found to not have MI.

Diagnosis of an MI in the past utilized the World Health Organization (WHO) criteria defining MI as the presence of two out of three characteristics: symptoms of acute ischemia (chest pain), development of Q waves in ECG, and elevation of biochemical markers. Biochemical markers are cellular constituents released from damaged heart muscle and detected in the blood. Initially these markers were the enzymes aspartate transaminase (AST), lactate dehydrogenase (LD), and creatine kinase (CK). These enzymes are found in other tissue and non-cardiac related elevations result from any damage to these tissues.

Of these enzymes, creatine kinase (CK) emerged as the primary indicator of MI. Two subunits, B(brain) and M(muscle) combine to form 3 isoenzymes of CK: CK-MM(CK-1), CK- MB(CK-2), CK-BB(CK-3). Elevations in total CK activity occur in conditions affecting brain, skeletal muscle, and heart muscle. CK-MB(CK-2) is found almost entirely in myocardial tissue and elevations of this isoenzyme became the gold standard marker for MI. As seen in Figure 1 the CK-MB level typically rises 6 to 10 hours after the onset of chest pain in MI patients, peaks at 12 to 24 hours, and returns to baseline levels within 72 hours.

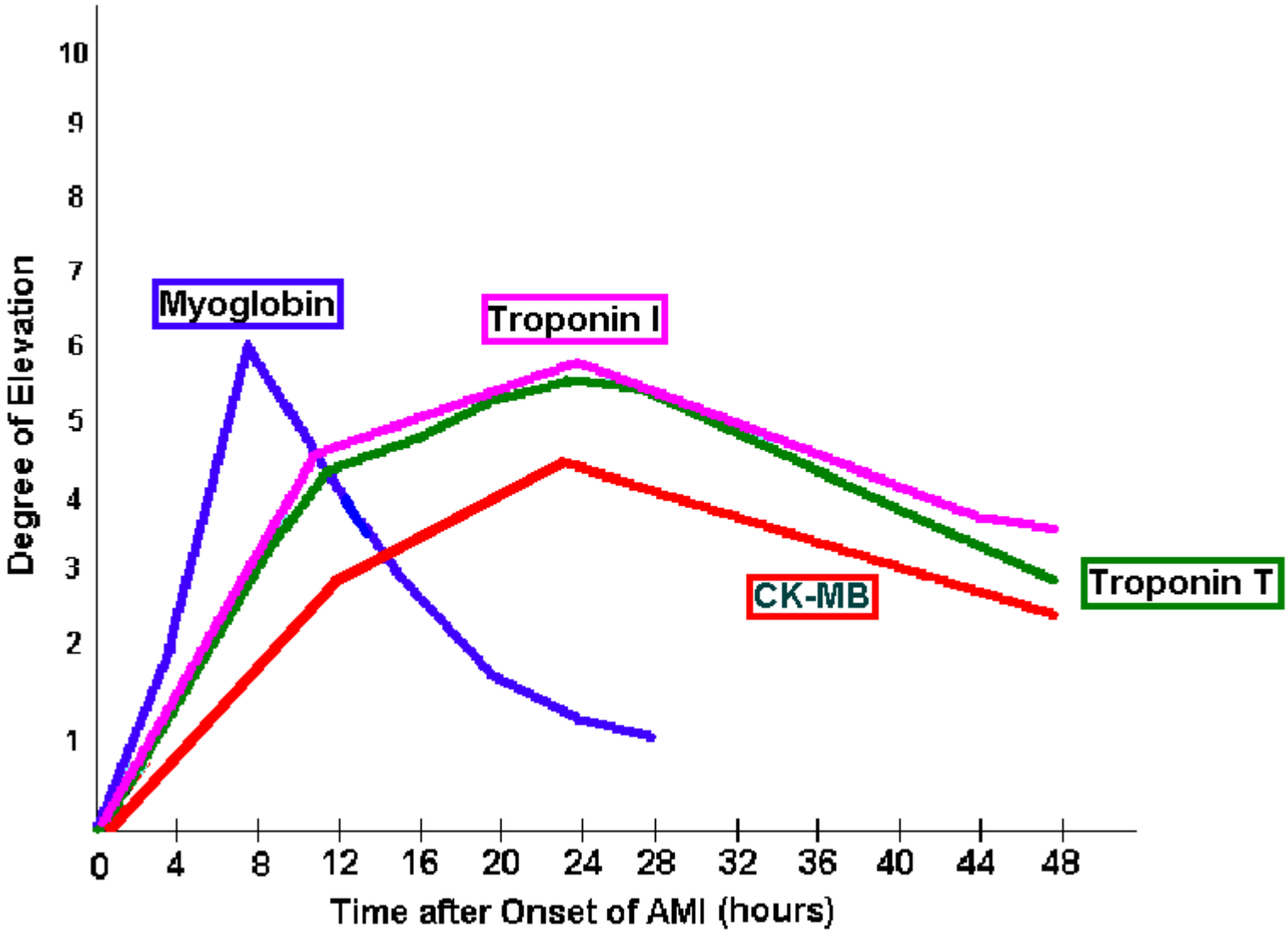
Because of the time lag from onset of chest pain to the rise in CK-MB levels there is a need for an early indicator of MI. Myoglobin has emerged as an ideal early marker. Blood levels of myoglobin become elevated within two hours of an MI (Figure 1), peak within 4-10 hours and return to normal within 24 hours. Myoglobin is a low-molecular weight protein that binds oxygen in muscle and damage to any muscle tissue will result in elevation of myoglobin in blood. Thus, its presence is not diagnostic of MI, but it still has utility in the early triage of chest pain patients.

Within the last decade the cardiac isoforms of troponin T and troponin I have been recommended as a replacement for CK-MB as the primary cardiac marker. Troponin is a complex of three proteins on the thin filaments of skeletal and cardiac muscle fibers. During muscle contraction the troponin complex regulates the interaction between the thick and thin filaments. This complex consists of troponin T (TnT), troponin I (TnI) and troponin C (TnC). Troponin C is identical in skeletal and cardiac muscle, but the amino acid sequences of troponin T and troponin I found in cardiac muscle is different from that of the troponins in skeletal muscle. These isoforms of cardiac troponins, cTnT and cTnI, are very specific to cardiac muscle and their presence in blood indicates cardiac tissue necrosis. Because of this specificity, cardiac troponin T or I is now the preferred cardiac marker. There is some evidence that cTnI is more cardiacspecific than cTnT, but both troponins are considered to be acceptable. Cardiac troponins T and I begin to rise 4-8 hours after an MI, peak at approximately 12 - 24 hours, and remain elevated for up to 10 days (Figure 1). Current consensus guidelines recommend specimen collection at admission, 2-4 hours, 6-9 hours, and an optional collection at 12-24 hours. Diagnosis is based on use of an early marker, such as myoglobin, and a more definitive marker that increases later, troponin.

In 2000 a joint committee of the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) redefined MI as any amount of myocardial necrosis, as indicated by an elevation of troponin, in the setting of clinical ischemia. Of importance to the laboratory, the recommended decision limit (lower limit of normal) is the 99^{th} percentile of the values for a reference control group. An acceptable coefficient of variation at that cutoff should be defined as $\leq$10%. Current troponin assays cannot meet these guidelines because of lack of sensitivity and poor precision at the low end. Laboratories in conjunction with clinicians must decide whether to use the recommended lower decision limit or continue to use their current cutoff. Some laboratories have chosen to use two cutoffs: one to identify MI (usually their current cutoff) and a lower cutoff (any measurable troponin) to identify patients at high risk for subsequent adverse clinical events such as MI or death. When choosing troponin decision levels, the assay capabilities, particularly the sensitivity and precision at very low levels, must be considered. Probable future uses of troponin levels include risk stratification and therapeutic monitoring of cardiac drugs.

The specimen of choice for all of these cardiac markers is serum. Specimen type and handling and test methodology affect measurements of cardiac markers. Extended storage (days) at room temperature causes a deterioration of CK-MB, but the greater deterioration is seen with electrophoretic methods than with immunoassays. Heparinized plasma is generally acceptable for CK and CK-MB analysis but other anticoagulants may interfere with CK activity. Initially, heparinized plasma was an acceptable specimen for troponin analysis, but subsequent studies have shown decreased troponin levels in plasma and poor correlation between serum and plasma troponin levels. Manufacturers of both troponin T and I assays no longer recommend the use of heparin plasma tubes.

Figure 1 Plot of cardiac marker levels vs time after onset of symptoms



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