EDUCATIONAL COMMENTARY – UPDATE ON CARDIAC MARKERS

Educational commentary is provided through our affiliation with the American Society for Clinical Pathology (ASCP). To obtain FREE CME/CMLE credits click on Continuing Education on the left side of the screen.

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

- Discuss the clinical uses of troponin measurements in addition to diagnosis of a myocardial infarction (MI).
- List potential markers of cardiac ischemia.
- Describe the principle of the assay to measure ischemia modified albumin (IMA).

The prevalence of heart disease is increasing, and by 2020 it is expected to be the leading cause of death worldwide. The acute coronary syndrome (ACS), a continuum of disease that encompasses unstable angina, reversible myocardial injury, and myocardial infarction (MI), results from the process of plaque accumulation progressing to thrombus formation, which leads to ischemia, and subsequent myocardial infarction. Historically, laboratory testing for cardiac disease has focused on the measurable risk factors of coronary artery disease (lipids, homocysteine, etc.) and on biomarkers of the necrosis resulting from an MI (myoglobin, CK-MB, troponin, etc.).

More recent research has focused on discovery and development of markers capable of detecting the early stages of heart disease. Many potential markers have been identified and most of these are focused on myocardial ischemia, the reversible process preceding myocardial necrosis. Myocyte cell death and subsequent infarction occurs if oxygen is not restored to the tissue within 10-15 minutes of ischemia (local deficiency of blood supply). Detection of ischemia could allow early intervention, prevention of an MI, and reversal of the effects of ischemia. Potential markers of ischemia include indicators of pro-inflammation (interleukin-6, tumor necrosis factor alpha), plaque destabilization (matrix metalloproteinase 9, myeloperoxidase, intercellular and vascular adhesion molecules), plaque rupture (soluble CD40 ligand, placenta growth factor), acute phase reactants (high sensitivity C-reactive protein [hs-CRP]), and ischemia itself (ischemia modified albumin [IMA], free fatty acids, and choline). Of these tests, hs-CRP is now accepted as a risk indicator for cardiovascular disease (see “The Use of High Sensitivity CRP in Cardiovascular Disease”, API Immunology Educational Commentary, 2005 3rd Test Event, for a detailed discussion).

IMA was the first ischemia marker approved by the FDA for clinical use. Acute ischemia causes alteration of the N-terminus of albumin, resulting in reduced capacity to bind transition metal ions such as cobalt. This altered binding forms the basis of the spectrophotometric test for IMA. The clinical utility of IMA is still undetermined. IMA is positive within 6-10 minutes of an ischemic event and returns to baseline levels approximately 6 hours after the event. Noncardiac events causing elevated IMA levels include endurance exercise, cancer, infections, end-stage renal disease, liver disease, and brain ischemia. The interpretation of positive IMA results is not fully clarified, but its primary use may
be in the risk stratification of patients presenting with chest pain. The combination of negative IMA and troponin with a nondiagnostic ECG has a negative predictive value of 99%. In one study, the combined use of these 3 tests identified 95% of patients whose chest pain was due to ischemic heart disease. IMA may also be a predictor of subsequent elevated troponin levels.

CardioMPO™, an ELISA test that measures the level of myeloperoxidase (MPO) in lithium heparin plasma, has received FDA approval for use in the evaluation of patients presenting with chest pain. In a study of over 600 patients presenting with chest pain in the emergency department, MPO was identified as a strong predictor of major adverse cardiac events over the following 1 to 6 month period. Further clinical studies of MPO measurement in conjunction with clinical history, ECG, and other cardiac markers will help to establish MPO’s eventual role as a cardiac risk marker.

For the past 50 years the primary cardiac markers have been biomarkers of necrosis (see “Cardiac Markers”, API Chemistry Educational Commentary, 2001 3rd Test Event, for further information). Cardiac troponin (cTnT and cTnI) has been designated the “gold standard” for MI diagnosis by a joint committee of the European Society of Cardiology (ESC) and the American College of Cardiology (ACC), but troponin is not an early marker of myocardial necrosis. For patients presenting with chest pain, multiple samples (admission, 6-9 hours, and 12-24 hours, if early samples are negative) should be tested. MI cannot be excluded until the second negative troponin result is obtained after 6 hours. Troponin may be used for diagnosis days after the acute event because elevated levels persist after levels of other markers (myoglobin, CK-MB) return to normal. The cutoff troponin concentration for designating a positive result is controversial. The ESC/ACC group recommended a diagnostic cutoff of the 99th percentile of a reference control population, which is a much lower value than levels established based on comparison to previous CK-MB levels. The group also recommended that assays have a coefficient of variation of 10% or less at this cutoff, a goal that few current troponin assays can achieve. Some researchers have recommended choosing a decision point at a value based on correlation to prediction of risk. Another complicating factor is the different results obtained with different troponin assays, even when the same cutoff decision point is used. Because manufacturers use different calibrators and antibodies targeting different sites, cTnI results for the same sample measured with different assays may vary as much as 30-fold. There are current efforts worldwide to standardize assays and develop reference calibrators.

Myoglobin, the earliest appearing biomarker, and/or CK-MB are recommended for patients in need of an early diagnosis, but subsequent confirmation of diagnosis usually requires detection of cardiac troponin. The rise and fall of CK-MB is more predictable than that of troponin, and CK-MB measurements are beneficial for determining a timeline of the MI or for detection of reinfarction. Assays that measure CK-MB protein directly, known as mass assays, are preferred for clinical applications because they are typically more sensitive than activity assays measuring enzymatic activity. The diagnostic sensitivity of CK-MB was less than that of troponin when 6 cohort studies totaling 18,500 patients were compared. One reason for the increased sensitivity of troponin over
CK-MB is that troponin has a baseline level of almost zero, while most people have a measurable amount of CK-MB which must be substantially exceeded in order to detect myocardial damage.

Troponin levels are used for purposes other than the diagnosis of infarction. Elevated troponin levels are predictors of an adverse outcome in ACS patients. Also, in patients with chest pain, a positive troponin indicates a 3- to 8- fold greater risk of death or reinfarction than a negative result. The American Heart Association and the ACC have incorporated cardiac troponin measurements into the treatment algorithms of their guidelines. Cardiac troponin measurements have also been used to predict which patients benefit most from different treatments.

Table: Markers of Cardiac Event Progression

<table>
<thead>
<tr>
<th>Cardiac Event Progression</th>
<th>Test(s)</th>
<th>(Potential) Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque Destabilization</td>
<td>CardioMPO™</td>
<td>Potential predictor of adverse cardiac event</td>
</tr>
<tr>
<td>Acute Phase Reactant</td>
<td>hs-CRP</td>
<td>Recognized risk indicator for CV disease</td>
</tr>
<tr>
<td>Ischemia</td>
<td>IMA</td>
<td>Ischemia marker positive within 6-10 minutes</td>
</tr>
<tr>
<td>Necrosis (MI)</td>
<td>Troponins T &amp; I</td>
<td>“Gold standard” for diagnosis of MI</td>
</tr>
</tbody>
</table>

Abbreviations:
- MPO = myeloperoxidase
- hs-CRP = high sensitivity C-reactive protein
- CV = cardiovascular
- IMA = ischemia modified albumin
- MI = myocardial infarction

In summary, today there are several uses for markers of cardiac necrosis, particularly troponin, including risk stratification and treatment guidance, as well as diagnosis of myocardial infarction. There are several potential markers of cardiac ischemia, including one (IMA) in use and another (MPO) approved for use by the FDA, but their eventual utility has not been completely determined. The use of the hemodynamic stress biomarkers BNP and NT-proBNP for the diagnosis and monitoring of heart failure has been discussed in a previous commentary (“B-type Natriuretic Peptide (BNP)”, API Chemistry Educational Commentary, 2002 3rd Test Event) and will be updated in a future commentary in 2006.

© ASCP 2006

Editor’s note: The library of ASCP Educational Commentaries from past testing events may be found by clicking on ASCP Commentaries under Education on the left side of the home page of API’s website (www.api-pt.com). Commentaries are organized by specialty (Blood Bank, Chemistry, Coagulation, Hematology, Immunology, Laboratory Medicine/Management, Microbiology, or Microscopy).