Cardiac Enzymes/Markers

CREATINE KINASE

Creatine kinase is comprised of three cytosolic isoenzyme forms named CK-MM(CK3), CK-MB(CK2), and CK-BB(CK1) and one mitochondrial form. These proteins are dimeric and are comprised of subunits coded for by specific genes for CK-M, CK-B and CK-Mi. Although CK-MM is predominant in both skeletal and heart muscle, CK-MB has been shown to be more specific for myocardium, which contains from 5-30% of total CK activity as CK-MB.

CKMB

CK-MB is an enzyme protein found in all muscle, but found in higher concentration in myocardium than in skeletal muscle; skeletal muscle is generally assumed to contain less than 2% CK-MB. The distribution of CKMB is apparently not homogeneous within the myocardium. Some studies have shown proportions less than 1% from normal left ventricle at autopsy. Others have shown proportions approaching 50% in papillary muscle. An early study showed that infarcted tissue contained a lower percentage of CK and isoenzymes than surrounding unaffected tissue. Other studies have shown that CK-MB rises during regeneration of injured skeletal muscle to the extent that its proportion mirrors that of the myocardium.

Four to six hours following an acute MI, the ordinary kinetics of CK-MB shows a rise above the baseline values. The observation of the rise is more important than the absolute value of the marker. Sensitivity on single test CK-MB results varies considerably due to the variability of time of collection after the event and ranges from 0-62% at 0 hours to 92-100% at 3 hours after the event.

CK-MB may be used to assess reperfusion after thrombolytic therapy. Early reperfusion causes an earlier increase above the reference interval as well as an earlier and greater peak after reperfusion than after un-reperfused AMI. An alternative use for CK-MB would be to assess successful reperfusion early after the therapy is administered. The rate of increase of CK-MB could be used to determine the presence or absence of reperfusion. Studies have demonstrated that (1) two-fold increases in CK-MB occur within 90 minutes of successful reperfusion, (2) the rate of increase of CK-MB in the first 4-6 hours after admission to the ED separate reperfused from non-reperfused patients, and (3) washout of total CK-MB parallels the washout of the tissue CK-MB2 isoform after reperfusion.

CK-MB also rises following surgery. Detection of perioperative myocardial infarction is difficult because of the contribution of skeletal muscle CK-MB. The use of a CK-MB:total CK ratio does not aid in differentiating skeletal muscle injury from myocardial injury.

The upper reference interval for CK-MB in hospitalized patients who have not suffered a myocardial infarction is less than 6.3 ng/mL. In patients who have had coronary artery bypass graft surgery, the peak results following surgery may exceed 80 ng/mL in the absence of perioperative myocardial infarction.

TROPONINS

The troponin complex is a group of three protein subunits located on the thin filament of the contractile apparatus. These three subunits, troponin T (TnT), troponin I (TnI), and troponin C (TnC), differ in genetic and protein structure and act together to regulate muscle contraction. Troponin T is a 37-39 kD tropomyosin-binding protein. Troponin I is a 26.5 kD actomyosin-ATP inhibiting protein. Troponin C is an 18 kD calcium-binding protein. The regulatory troponin complex does not exist in smooth muscle, but has isoforms in fast and slow skeletal muscle and cardiac muscle. While troponin C has the same structure in cardiac and slow skeletal muscle, there are specific cardiac isoforms for the troponins I (cTnI) and T(cTnT). Although most troponin is bound in the complex, there is a small cytoplasmic pool of troponins T and I which are released within the first several hours after cell injury.

Troponin I is a more specific marker for cardiac injury in cases involving skeletal muscle injury and renal failure. The release kinetics of cTnI from cardiac muscle following myocardial ischemia are very similar to those of CK and CK-MB in the early phase of release. The earliest detection of cTnI following an ischemic episode is 4-6 hours after the event. However, following myocardial infarction, cTnI remains elevated in the circulation for 3-9 days, in contrast to CK-MB which normalizes in 2-3 days.

The advantage to using cTnI instead of CK-MB is that in the absence of infarction or ischemia, the circulating cTnI is virtually undetectable. The presence of measurable cTnI is a strong indication of an acute coronary syndrome.

Troponin I values >0.5 ng/mL suggest myocardial injury to an extent that qualifies as an Acute Myocardial Infarction (AMI). The clinical sensitivity is 96% and the clinical specificity is 94% at the 0.5 ng/mL AMI cutoff.

Troponin I can also be elevated in a number of other non-ischemic conditions as follows: congestive heart failure, hypertension with left ventricular hypertrophy, hemodynamic compromise (e.g., shock), viral injury (e.g., myocarditis), secondary to myocardial trauma or toxic injury.

Implementation of 99th Percentile Reference Limits for Cardiac Troponin in the Diagnosis of Myocardial Infarction.

In 2000, the joint commission of the American College of Cardiology and the European Society of Cardiology issues a consensus document on the "redefinition of Myocardial Infarction." (1) This document was updated in conjunction with the American Heart Association and the world Heart Federation in 2007. (2)

In these documents, the definition of myocardial infarction included the following:

- Detection of rise and/or fall of cardiac biomarkers (i.e. troponin) **with at least one value above the 99th percentile of the upper reference limit** (URL) together with evidence of myocardial ischemia with at least one of the following:
    - Symptoms of ischemia
    - EKG changes indicative of new ischemia (i.e. new ST-T wave changes or new left bundle branch block (LBBB)
    - Development of pathological Q waves on the ECG
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

With the introduction of ultra-sensitive cardiac troponin assays, clinical laboratories can detect myocardial cellular necrosis more precisely than ever before. Based on the ACC/ESC/AHA/WHF recommendations, many hospitals have changed their troponin reference range to include the 99th percentile of the upper reference range: a troponin of >0.06 ng/mL for troponin assays used at Gettysburg and York Hospitals. (3) The WellSpan Health Acute Myocardial Infarction Clinical Effectiveness Team (AMI-CET) in conjunction with the WellSpan Clinical Laboratory recommended that York Hospital and Gettysburg Hospital implement this change in the cardiac troponin reference range by moving from the current 95th percentile of the URL to the 99th percentile. The new reference range was implemented on **November 2, 2011**. The troponin values are reported in one of three categories:

<0.06 ng/mL	Negative
0.06-0.5 ng/mL	Troponin I values in this range suggest the possibility of low level myocardial injury – the presence of which may be associated with increased cardiac risk of MI
>0.5 ng/mL	Troponin I values in this range suggest myocardial injury to an extent which qualifies as acute myocardial infarction. (AMI).

All troponin I values >0.06 ng/mL will be reported as "high". Clinicians are reminded that the definition of myocardial infarction includes a peaking pattern in cardiac biomarkers as well as the presence of clinical evidence of myocardial ischemia. An increase in falsely elevated troponin I levels is expected. Falsely abnormal cardiac troponin may be due to non-ischemic causes such as congestive heart failure, renal failure, myocarditis and myocardial trauma, among others. As always, emphasis in diagnosis of AMI should be placed on the clinical presentation of each patient.

Additionally, in our constant effort to remain compliant with evidence-based guidelines, the AMI CET has recommended that blood samples for measurement of cardiac enzyme be drawn ***every 6 hours rather than every 8 hours*** to optimize clinical sensitivity for ***ruling out*** an AMI. (4). These changes (from Q8 to Q6) became effective in the relevant CPOE power plans on **November 2, 2011**.

Changing the URL for cardiac troponin and the interval between blood samples will bring WellSpan Health into the current standard of care regarding the diagnosis and treatment of myocardial infarction. The AMI CET appreciates your consideration in this matter. For clinically or laboratory related questions or comments about the changes, please contact Dr. James Mills, Co-Chairman WSH AMI CET (jmills@wellspan.org) for the former or Dr. Stephen Manzella (smanzella@wellspan.org) for the latter.

1) The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial Infarction redefined – A consensus document of the Joint ESC/ACC Committee for the Redefinition of Myocardial Infarction. Eur Heart J; 2000:21:1502-13; J Am Coll Cardiol; 2000:36:959-69
2) Thygesen, K, et. Al.; Universal Definition of Myocardial Infarction; Eur Heart J; 2007:28:2525-38
3) Melanson, S., Tanasijevic, M. and Jarolin, P, Cardiac Troponin Assays: A View from the Clinical Chemistry Laboratory, circulation; 2007:116:e501-e504
4) Thygesen, K, et.al.; Universal Definition of Myocardial Infarction; Eur Heart J; 2007:28:2525-38

C-REACTIVE PROTEIN

Acute Phase Reactant

Assay to order:

- CRP Quantitative [CRP QUANT]

Acute phase reactants (APRs) are a group of proteins whose concentration changes in response to a variety of inflammatory states including infection, post-surgery, trauma, post-myocardial infarction, malignancy, and any condition associated with tissue necrosis. C-reactive protein (CRP), which was the first APR to be discovered, is also the one exhibiting the most dramatic increases in concentration. The increase occurs rapidly (within 24-48 hours) from the normal baseline level of <0.8 mg/dL, and the level may be as high as 2000 times normal in the presence of bacterial infections. More moderate elevations in CRP are found in chronic inflammatory conditions such as systemic lupus erythematous (SLE), malignancies, congestive heart failure, and pregnancy. However, changes in CRP levels in these conditions are nonspecific and provide no information on the cause or source of the inflammation [1]. Serial measurements may provide an index of disease activity and are useful to assess the response to therapy.

Risk Factor for Development of Atherosclerosis

Assay to order:

- CRP High sensitivity [CRP HS]

Atherosclerosis is now widely accepted as a chronic inflammatory disorder that is initiated by vascular injury. Despite its lack of specificity, measurement of relatively low levels of CRP (< 5 mg/L) by the high sensitivity CRP (hsCRP) assay has now emerged as one of the most powerful predictors of cardiovascular risk, independent of age, smoking, LDL cholesterol, blood pressure, and diabetes[2].

Many interventions known to reduce cardiovascular risk have been linked to lower CRP levels. In particular, weight loss, diet, exercise, and smoking cessation all lead to reduced CRP levels and reduced vascular risk.

Several pharmacological agents are proven to reduce vascular risk influence CRP levels. Of these, the statin drugs are the most important. However, where as all subjects taking statins achieve a beneficial reduction in LDL levels, there seems to be responders and non-responders in terms of CRP reduction.

Clinical Recommendations

Recently the American Heart Association and the Center for Disease Control provided guidelines for the use of inflammatory markers [3]. The following recommendations were given:

- Results for hsCRP should be expressed in mg/L.
- Measurement of hsCRP should be done twice (averaging results), optimally two weeks apart, in metabolically stable patients without obvious inflammatory or infectious conditions.
- If the hsCRP level is > 10 mg/L, the test should be repeated and the patient examined for non-cardiovascular sources of inflammation or infection.
- The relative risk categories for average hsCRP levels are:

<1.0 mg/L	Low risk of developing cardiovascular disease (CVD)
1.0-3.0 mg/L	Average risk of developing CVD
>3.0 mg/L	High risk of developing CVD

- Screening of the active adult population is not recommended, but as an adjunct to the other major risk factors for cardiovascular disease.

References:

- McClatchey: Clinical Laboratory Medicine. 1994, p.1555.
- Ridker: Circulation.2003;107:363-369.
- Pearson, et.al.: Circulation.2003;107:499-511.