EDUCATIONAL COMMENTARY – CARDIAC FUNCTION: BIOCHEMICAL MARKERS UPDATE

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LEARNING OUTCOMES

Upon completion of this exercise the participant should be able to

- list and discuss the recommended biomarkers for diagnosis of myocardial infarction and heart failure.
- discuss the advantages and disadvantage of the high-sensitivity cardiac troponin assays.
- describe the use of biomarkers for risk stratification.

Acute coronary syndrome

According to the 2011 Heart Disease and Stroke Statistics of the American Heart Association, approximately every twenty-five seconds an American has a coronary event and approximately every minute someone dies of one. The report, which analyzed statistics through 2008, found that in 2007, one of every six deaths in the United States was caused by coronary heart disease. Cardiovascular disease costs more than any other diagnosis-related group, with an estimated cost of $286 billion in 2007. It is predicted that this year, 785,000 Americans will have a first coronary attack and 470,000 will have a recurrent attack.

The term acute coronary syndrome (ACS) describes either acute myocardial infarction (MI) or unstable angina (UA). UA is defined as chest pain or discomfort accelerating in frequency or severity that may occur while at rest but does not result in myocardial necrosis. The diagnosis of ACS is based on history, physical examination, symptoms, the 12-lead electrocardiogram (ECG) at presentation, and detection of a biomarker of myocardial injury (see Biochemical Markers of Cardiac Function, API Chemistry Educational Commentary, 2008, 2nd Test Event). According to the 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, ECG results are used to divide ACS patients into three major groups for the evaluation and management of ACS. These groups are: patients with new ST-segment elevation that leads to a diagnosis of acute ST-elevation MI, those who present with ST-segment depression or T-wave inversion that is strongly indicative of ischemia classified as UA or non-ST elevation MI, and those with normal or nondiagnostic changes in ST segment or T wave considered low- to intermediate-risk ACS.
Cardiac marker guidelines

In 2007, the National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for the Utilization of Biochemical Markers in Acute Coronary Syndromes and Heart Failure recommended cardiac troponin T (cTnT) or cardiac troponin I (cTnI), macromolecules that are released from damaged myocytes, be used as the primary marker for the diagnosis of MI.\(^3\) Also in 2007, the European Society of Cardiology, the American College of Cardiology, the American Heart Association, and the World Heart Foundation published guidelines on the universal definition of MI in which detection of cTn is the essential element along with at least one of the following: symptoms or ECG changes indicative of ischemia, development of pathological Q waves in the ECG, or imaging evidence of new loss of viable myocardium or regional wall motion abnormality.

**Diagnosis and follow-up testing of MI**

Diagnosis of MI calls for a cTn concentration above the 99th percentile of a healthy population (a value that only one of one hundred healthy patients will exceed) using an assay with a coefficient of variation (CV) of 10% or less. Measurements should occur at the time of first presentation and six to nine hours later. The guidelines note the importance of monitoring changes to detect rising or falling cTn values. ACS is unlikely if the troponin concentration is normal twelve hours after the onset of chest pain. Reference ranges for cTn are method and population dependent.

**Analytical aspects of troponin measurement: establishing the MI cutoff**

Even though the guidelines for troponin cutoff levels are clear, the implementation of the cutoff at the 99\(^{th}\) percentile is not uniform. When the guidelines were initially established, the first-generation troponin assays did not have the necessary sensitivity and precision to meet the CV of 10\% or less standard at the 99\(^{th}\) percentile. Commercially available assays were not sensitive enough to detect normal values in all subjects of the healthy population used to establish the 99\(^{th}\) percentile; even today, assays can measure cTn values in only 10\% to 20\% of individuals in the healthy population. As a result, diagnostic cutoffs were set at levels higher than the 99\(^{th}\) percentile reference range and some of these cutoffs persist. However troponin assay performance has improved dramatically: current assays are able to reliably detect at the recommended 99\(^{th}\) percentile with a CV of 10\% or less, and many are precise at even lower limits of detection.

Another aspect affecting the cutoff is the choice of the reference healthy population. In one study, an initial 99\(^{th}\) percentile cutoff was lowered from 44 ng/L (0.044 µg/L) to 28 ng/L (0.028 µg/L) when more strict criteria were applied to selection of the elderly reference population. Other studies have indicated
sex and age differences for troponin, but at this time there is no indication that sex- or age-specific cutoffs are warranted. Still another confounding factor is that there is no reference material available to standardize the many assays available. Roche Diagnostics is the only manufacturer of cTnT, so this assay is effectively standardized and a cutoff of 10 ng/L (0.01 µg/L) is typically utilized. Standardization of cTnI is difficult because there are at least eighteen different commercial cTnI assays currently available in the US. Because of the cTnI assay differences, the 99th percentile cutoff has to be established for each method and there is no consistent cutoff between methods. In spite of the difficulty, an international group has begun a cTnI standardization effort.

High-sensitivity cTn assays

Manufacturers have steadily improved cTn assays to the point that a number of high-sensitivity assays have been used in clinical settings in Europe for several years and are now available in the US for research purposes. These assays have limits of detection ten- to one hundred-fold lower than the current assays. The manufacturers are in the process of or plan to apply for Food and Drug Administration clearance. When the assays are approved and implemented, clinicians and laboratorians will be faced with several challenges. Measurement of lower levels of cTn should allow an earlier diagnosis of MI, but results will be more difficult to interpret. High-sensitivity cTn (hs-cTn) assays allow measurement of previously undetectable levels in the healthy population, which means a lowering of the 99th percentile will occur.

With a lower cutoff, there will be more instances of an elevated troponin in acute and chronic conditions other than ACS and heart failure. Some of these acute conditions include cardiac, vascular, respiratory, and infectious disease processes. Chronic conditions in which elevated troponin levels occur include end-stage renal disease, hypertension, and diabetes. A complete list and discussion of these conditions may be found in a review article by Kelley et al.4 Findings of exercise-induced cTn will likely increase with the use of hs-cTn. One study determined that 86% of marathon runners had cTnT concentrations greater than the 99th percentile with the hs-cTnT assay compared to 45% using the conventional assay.5

One consequence of hs-cTn implementation will be that cardiologists will encounter more “troponin referrals,” in which an elevated troponin level occurs in the absence of any evidence of ACS. Some investigators have suggested that clinicians should not order troponin level testing in patients with extremely low likelihood of having ACS. Another approach currently utilized in some settings is performance of a delta check to determine a δ change in cTn between samples collected at presentation and at fixed intervals thereafter. Some institutions set a minimum increase, measured either in ng/L or in percent change, in order to diagnose an MI. Elevated cTn levels due to chronic conditions should not
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exhibit a significant δ change between samples. This approach will probably be adopted more frequently when the hs-cTn assays are placed into service.

Risk stratification in ACS

cTn levels have also been used for prediction of future risk (risk stratification) of cardiac events including death. Typically, the times for blood sampling for risk stratification are the same as for diagnosis of ACS, at hospital presentation and at six to nine hours. Based on the results of two large studies published in December 2010, the introduction of hs-cTn assays may enhance the value of troponin measurement for risk stratification.6,7 In one study, it was demonstrated that individuals with detectable hs-cTn levels initially were at greater risk of heart failure and cardiovascular death compared with patients with undetectable levels. In patients with detectable levels, an increase of more than 50% was associated with a greater risk for heart failure and cardiovascular death; if levels decreased by 50% or more, risk also decreased.6 In another study, researchers found a rising prevalence of cardiovascular disease, chronic kidney disease, diabetes or hypertension and a rising incidence of all-cause mortality associated with rising cTn levels.7

Heart failure

Nearly five million Americans are currently living with congestive heart failure, a complex clinical syndrome characterized by an impaired ability of the ventricles to fill with or eject blood. In 2011, approximately 550,000 people will be newly diagnosed as having congestive heart failure, also known simply as heart failure (HF). Myocardial ventricular wall stress stimulates release and cleavage of proBNP into B-type natriuretic peptide (BNP) and the biologically inactive fragment NT-proBNP. BNP, an antagonist to the renin-angiotensin-aldosterone system, helps to decrease blood pressure. The use of the hemodynamic stress biomarkers BNP and NT-proBNP for the diagnosis and monitoring of HF has been discussed in a previous commentary (Update on BNP and NT-proBNP, API Chemistry Educational Commentary, 2006, 3rd Test Event).

Diagnosis and risk stratification of heart failure

Recommendations for the use of biochemical markers to diagnose and stratify risk of HF are similar to those for ACS if BNP or NT-proBNP testing is substituted for troponin testing. Thus, BNP or NT-proBNP testing is recommended for diagnosis of HF in both the acute and non-acute setting and serial measurement of these analytes is also useful for clinical assessment when additional risk stratification is required. Studies of the correlation between BNP/NT-proBNP levels and prediction of mortality have yielded conflicting results but there does appear to be a role for these markers in risk stratification of
patients suffering from HF.\(^5\)

In 2009, a meta-analysis of forty studies addressing the use of BNP or NT-proBNP for risk prediction of cardiovascular diseases other than HF concluded that there is a strong association between circulating BNP/NT-proBNP levels and CVD risk.\(^5\) Further investigation in large general population studies is warranted.

**Summary and conclusions**

The recommended biomarkers for the diagnosis of ACS and HF are cTn and BNP/NT-proBNP respectively. The universal definition of MI includes the detection of cTn at a concentration above the 99th percentile of a healthy population using an assay with a CV \(\leq 10\%\). Since their introduction, cTn assays have improved their sensitivity and precision and can now achieve measurements required for the detection of MI using the universal definition. The expected introduction of high-sensitivity troponin assays in the near future will provide clinicians and laboratorians with a more powerful tool but will also require education concerning the implications of the detection of lower levels of this marker.

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REFERENCES


