The Role of Cardiac Troponin in the Recent Redefinition of Acute Myocardial Infarction

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ABBREVIATIONS: AMI = acute myocardial infarction; cTnI = cardiac troponin I; cTnT = cardiac troponin T.

INDEX TERMS: AMI; cardiac marker; troponin.

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Troponin is a complex of three proteins (troponins T, I, and C) that bind to the thin filament (actin) of striated muscle. Its major regulatory function is to bind calcium and regulate muscle contraction. Following injury to muscle cells (heart or skeletal muscles) the intact troponin complex along with free troponin subunits are released into blood. Although troponin is found in both skeletal muscles and the myocardium, the amino acid sequences for *cardiac* troponin T (cTnT) and I (cTnI) isoforms are significantly different from their *skeletal muscle* counterparts. This is not the case for troponin C, where the subunits from these tissues are identical. Commercial assays have been constructed for measurement of cTnT and cTnI in blood that have been shown to have high specificity for cardiac disease. These assays also have high sensitivity, because the tissue concentrations of cardiac troponin T and I are higher than for other cardiac markers such as myoglobin and creatine kinase. Moreover, the normal concentrations of these cardiac proteins are much lower than for myoglobin and CK, as these proteins are also released from normal skeletal muscle turnover.[1]

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LEARNING OBJECTIVES

1. Describe the structure and function of the three troponin proteins.
2. Explain the release of cardiac troponins following an acute myocardial infarction.
3. Discuss the clinical utility of troponin T versus troponin I.
4. Describe the impact of troponin assays on the redefinition of acute myocardial infarction.
5. Explain the issues surrounding lower cutoff concentrations for troponin assays.

Following acute myocardial infarction (AMI), cardiac troponins are released into blood from two subcellular pools. The initial rise within the first six hours after disease onset is due to the free cytosolic pool, estimated to be about 6% to 8% for cTnT and 3% to 4% for cTnI.[2] There is a second, continual increase of cardiac troponin that is due to the gradual breakdown of myofibrils themselves. Therefore, the troponins are increased for much longer time than myoglobin or CK.

CARDIAC TROPONIN T VS. CARDIAC TROPONIN I

Although both proteins are simultaneously released after the onset of irreversible injury, there are some differences in the clinical utility of troponin T vs. I. After AMI, cTnT remains increased for seven to ten days while cTnI remains abnormal for only five to seven days. However, when blood is collected during the optimum time intervals, the clinical sensitivity and specificity for diagnosis of AMI are high for both assays (95% to 99%). In addition, either test can be used for risk stratification, i.e., the identification of cardiac patients who are most likely to suffer AMI or death in the short term.

The major clinical difference between these two markers is in the detection of non-ischemic cardiac injury in patients

with renal failure. Clinical trials have shown that cTnT identifies more renal patients at high cardiovascular risk than cTnI.[4] One explanation may be related to the size and clearance of these proteins. Cardiac troponin T at 37 kDa, is a slightly larger protein than cTnI at 24 kDa. Troponin I binds to other serum proteins that may obscure the antibody epitope necessary for recognition by an immunoassay. The therapeutic significance of these findings in renal failure patients remains to be determined.

REDEFINITION OF AMI

The original definition of AMI was established in 1979 by the World Health Organization (WHO).[5] The diagnosis required the presence of two of the following three criteria: 1) clinical history including the presence of chest pain, 2) unequivocal electrocardiographic (ECG) changes, and 3) unequivocal changes in enzyme activities such as creatine kinase. Cardiac troponin as a biomarker was not available at the time these criteria were written. With the discovery that troponin was useful not only for diagnosis of myocardial infarction, but also for risk stratification, new definitions of AMI were necessary. In 2000, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) proposed new definitions for the diagnosis of AMI.[6] Unlike the WHO criteria where the presence and levels of serum biomarkers was only one of three equally applied criteria, the ESC/ACC redefinition *requires* the presence of an abnormal concentration of serum biomarkers in the context of cardiac ischemia (history, ECG, and/or pathologic changes). The ESC/ACC further suggested that the cutoff concentrations for cardiac markers be lowered to maximize the number of cardiac cases that can be detected by troponin. Given that about one third of patients with unstable angina have detectable concentrations of cardiac troponin in blood, this has resulted in the diagnosis of higher numbers of patients. At the same time, this redefinition has led to confusion amongst clinicians and laboratorians regarding the appropriate assay cutoff concentrations that should be used. The various methods for assigning cutoff concentrations are discussed below.

CUTOFF CONCENTRATIONS FOR CARDIAC MARKERS AND TROPONIN

Cutoff concentrations for cardiac markers have undergone evolutionary changes as assays have improved and new biomarkers have been developed. Originally, cutoff concentrations were established using receiver-operating curve (ROC) analysis, a statistical technique that plots clinical sensitivity versus specificity at different biomarker cutoff concentrations. For the diagnosis of AMI, the cutoff was set to differentiate between unstable angina and myocardial infarction. Although both unstable angina and myocardial infarction are characterized by plaque rupture resulting in thrombus formation within the coronary artery, substantial irreversible myocardial damage only occurs in AMI where there is a totally occlusive clot. Unstable angina was thought to be associated with normal levels of serum biomarkers.

Risk stratification studies using cardiac troponin have altered the view of the optimum cutoff concentrations that should be used. As early as 1992, it was recognized that unstable angina patients who had a minor increase in cardiac troponin suffered a higher frequency of cardiac death and myocardial infarction in 30 days than other unstable angina patients who had normal troponin concentrations.[7] In the ensuing years, these observations have been confirmed in dozens of clinical trials on tens of thousands of patients for both cTnT and cTnI. In order to identify as many patients who are at high risk as possible, the ESC/ACC has recommended lowering the cutoff concentrations for troponin to the 99th percentile value of the normal range.[8] Recent trials have shown that use of very low cutoff concentrations for troponin results in the identification of extra cardiac patients at risk for future untoward events.[9] Use of low cutoff concentrations, however, increases the incidence of false positive results due to assay imprecision. None of the existing commercial assays for cTnT and cTnI have the sensitivity to measure troponin in blood of healthy subjects with sufficient assay precision necessary to eliminate false positive results. As a compromise, the ESC/ACC has recommended that the cutoff concentration have a minimum assay imprecision of 10% or less. This results in a cutoff value that is higher than the 99th concentration.[10] Manufacturers of commercial troponin assays are in the process of improving the sensitivity and precision of their assays so that even lower diagnostic cutoff concentrations can be used.

CONCLUSIONS

Table 1 summarizes the continuing issues for use of cardiac troponin in acute coronary issues. Cardiac troponin has become the gold standard for the diagnosis of AMI. This marker is gradually replacing the need for creatine kinase and the MB isoenzyme. Qualitative and quantitative assays for cTnT and cTnI are now available on point-of-care testing (POCT) platforms. Despite its widespread use, improvements in commercial assays are warranted to take full advantage of troponin's capabilities, particularly in risk stratification. A major continuing issue is the lack of assay standardization across commercial cTnI assays. This problem is being addressed by a subcommittee of the American Association for Clinical Chemistry.

Table 1. Continuing issues for use of cardiac troponin in acute coronary syndromes

Issue	Resolution/commentary
Renal disease	cTnT detects more cases of cardiac disease than cTnI; the impact on clinical practice remains to be determined.
New definition of AMI	Will result in more AMI cases worldwide
Confusion on cutoffs	Use lowest troponin value that produces a 10% CV. New high sensitivity assays being developed.
No cTnI standardization	AACC cTnI Subcommittee addressing this issue
No POCT standardization to central lab assays	Has inhibited implementation of quantitative POCT.

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