Cardiac Biomarkers in Emergency Care

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KEYWORDS

• Acute coronary syndromes • Biomarkers • Sensitivity and specificity • Troponin

KEY POINTS

- Cardiac troponin is the reference standard biomarker for diagnosing acute myocardial infarction and has replaced creatine kinase-MB.
- High-sensitivity assays can rule in and rule out acute myocardial infarction for many patients with just 1 blood test; with a second sample just 1 hour later, most patients can have the diagnosis either ruled in or ruled out.
- Biomarkers such as copeptin and heart-type fatty acid-binding protein have shown great promise as early markers of myocardial injury, although their use has yet to become established in widespread clinical practice.

BACKGROUND

Cardiac biomarkers have been used for the diagnosis of acute myocardial infarction (AMI) since the 1950s. Identifying a characteristic release pattern of creatine kinase (CK), alanine aminotransferase, and lactate dehydrogenase could take as long as several days but was neither sensitive nor specific. Matters improved through the subsequent use of CK-MB, a cardiac-specific isoform of CK. However, the subsequent development of assays for cardiac troponin (cTn) types cTnI and cTnT yielded substantial improvements in diagnostic performance. In the year 2000, the European Society of Cardiology and American College of Cardiology jointly recommended that cTn should be considered the preferred biomarker for diagnosis of AMI.[1] Since then, assays for cTn have improved greatly. The third universal definition of myocardial infarction (**Box 1**) now defines AMI as an increase and/or decrease of cTn with at least 1 concentration above the 99th percentile of values in a healthy reference population, in conjunction with at least 1 supporting feature from the patient's history, electrocardiogram (ECG), cardiac imaging, and coronary angiography.[2] The use of CK-MB is only recommended when cTn assays are not available.

ANALYTICAL CONSIDERATIONS

Troponin is a structural protein contained within the contractile apparatus of myofibrils. There are 3 troponins: I, T, and C. Commercially available

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Box 1
A summary of the requirements for a diagnosis of acute myocardial infarction as specified in the third universal definition of myocardial infarction

This requires

- Detection of an increase and/or decrease of cTn with at least 1 value above the 99th percentile of a healthy reference population

Plus at least 1 of

- History compatible with myocardial ischemia
- New compatible ECG changes (eg, ST-segment deviation, left bundle branch block, pathologic Q waves)
- Imaging evidence of new loss of viable myocardium
- Intracoronary thrombus on coronary angiography

AMI, evidence of myocardial necrosis plus evidence of myocardial ischemia.

Data from Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60(16):1581–98.

automated immunoassays are available for highly cardiac-specific isoforms of cTnI and cTnT. To comprehend recent advances in cTn assays and their practical application, it is important for clinicians to have a basic understanding of important analytical issues relating to the measurement of cTn. This includes an understanding of some key terminology, summarized in **Box 2**.

Importantly, clinicians must understand the concept of precision. No cTn assay will return exactly the same result when the same sample is repeatedly measured. The precision of the assay relates to the degree of scatter that is likely to be obtained, and this is measured by the coefficient of variation (CV). When measuring a sample with a concentration equal to the 99th percentile upper reference limit, the optimal CV for a cTn assay is less than or equal to 10%. A CV greater than 20% has been described as unacceptable for clinical use.[3] As precision improves, it is possible to have greater confidence that an observed increase or decrease of cTn concentrations on serial sampling is in fact genuine, rather than being a consequence of assay imprecision.

Until recently, cTn assays have been limited by the inability to detect cTn concentrations in apparently healthy individuals. Thus, the 99th percentile upper reference limit has been equal to the limit of detection (LoD) of the assay. This may explain why cTn remains an insensitive tool for diagnosis of AMI in the first hours after the onset of AMI. Because of this, with contemporary cTn assays patients must usually remain in the hospital for serial sampling over 6 to 9 hours before the diagnosis of AMI can be confidently ruled out.

HIGH-SENSITIVITY TROPONIN ASSAYS

The clinical utility of the first high-sensitivity cTn (hs-cTn) assay was first reported in 2009.[4,5] There

Box 2
Key definitions relating to analytical performance of cardiac troponin T assays

99th percentile

Refers to the 99th percentile of cTn concentrations in a sample of apparently healthy individuals

By convention, this is used to define the upper reference limit of cTn assays

Limit of blank (LoB)

When analyzing a sample containing no cTn, assays will not always return a result of zero

The LoB is derived by repeatedly testing a sample that is known to contain no cTn and is equal to the mean plus 1.645 multiplied by the standard deviation of the results obtained

Limit of detection (LoD)

The lowest concentration of analyte that can be distinguished from the LoB; the LoD will, therefore, be higher than the LoB

Coefficient of variation (CV)

Measures the precision of an assay and expressed as a percentage

Equal to the standard deviation divided by the mean of repeated measurements on any given sample

Data from Armbruster D, Pry T. Limit of blank, limit of detection and limit of quantitation. Clin Biochem Rev 2008;29(Supplement 1):S49–52.