



Title: Troponin Testing

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One of the major challenges in cardiovascular laboratory medicine revolves around acute coronary syndromes. Although acute coronary syndrome constitutes a continuum, it is usually divided into non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) based upon electrocardiogram changes at presentation.

Patients with unstable angina are also classified into the acute coronary syndrome definition and present with chest pain or other symptoms without electrocardiogram changes or evidence of myocardial necrosis. Annual statistics estimate there are 610,000 new and 325,000 recurrent acute myocardial infarctions with 6 million visits to emergency rooms across the United States. A smaller percentage (approximately 2% to 5%) of myocardial infarctions are missed in the emergency room. Mortality rates for patients over 40 years of age are high; 20% within the first year following an MI and 30% to 40% within the next 5 years. Notably, the mortality rate is also higher for females than males. The diagnostic challenge relies on clearly differentiating patients who do have an acute myocardial infarction from those who have not and can be sent home. Furthermore, situations are often not black and white and decisions are often needed about what to do with patients who have slightly elevated troponins but aren't changing.

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The cardiac troponin complex consists of three regulatory proteins (troponin C, I, and T) that control the calcium-mediated interaction of actin and myosin. Troponin C exhibits no cardiac specificity and therefore cannot be used as a biomarker of necrosis. Both troponin I and T have cytosolic and structural pools, with most existing in the structural pool. Troponin I and T are both structural biomarkers of cardiac necrosis and exhibit exquisite myocardial specificity. Presently most laboratories run a troponin assay, either troponin T or troponin I, and may also offer testing for CK-MB and/or myoglobin. Troponin demonstrates improved myocardial specificity and sensitivity over both CK-MB and myoglobin and essentially obsoletes the utility of either marker.

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Cardiac troponin is the best marker for definitive diagnosis of AMI. Troponins appear in the serum relatively early after the onset of symptoms and remain abnormal for 4-10 days. Elevations of troponin T persist longer than troponin I because it is larger (at 37 kDa versus 24 kDa). An increase in troponin may also be seen following unstable angina or a small myocardial infarction, and in both situations the troponin concentration would be above the 99th percentile.

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In 2007, a universal definition of MI was established to improve the accuracy of MI diagnosis. Updates to this definition maintained cardiac troponin as the preferred biomarker of myocardial necrosis, which it has been for the past decade. However, at that time it was recognized that more sensitive troponin assays were detecting other etiologies of both acute and chronic troponin elevations and therefore additional emphasis was placed on observing a rise and/or fall of cardiac troponin above the 99th percentile. At least 1 of those troponin concentrations should be above the 99th percentile of the assay and there also needs to be evidence of myocardial ischemia (being symptoms, ECG changes, pathological Q waves, or imaging evidence). The timing of samples remains critical and serial testing is recommended for interpretation. Based on evidence that even small amounts of troponin reflect incremental risk and indicate myocardial injury, consensus documents recommend that the normal range of troponin be set at the 99th percentile of a normal healthy population. Furthermore, recommendations from the IFCC working group on standardization of cardiac markers state the total imprecision should be < 10% at the 99th percentile. The logic being that failure of this goal could increase the risk of reporting misleading results that may prompt unnecessary confirmatory testing or lead to clinical inaction when inappropriately low concentrations are reported.

Because of this last recommendation, manufacturers must now provide precision information on the package insert and it has become clear that many commercial troponin assays are unable to achieve this acceptable level of precision. The precision also varies by specimen type and platform within the same manufacturer, as the larger instruments generally have better analytical characteristics. Most healthy normal individuals are then below the limit of quantitation and the lack of precision limits the ability to detect and define significant elevations in troponin at the low end of the range. Clinical laboratories should carefully consider the effect of imprecision on clinical decision making when implementing or choosing a new troponin assay.

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Use of a serial sampling strategy allows for differentiation of an acute infarction versus a chronic troponin elevation. There is no absolute agreement about the timing of serial samples; cardiology guidelines recommend baseline and 6 hour samples, with a 12 hour sample drawn in patients with a high suspicion or risk of MI. The International Federation of Clinical Chemistry recommends 0, 4, 8, and 12 hour samples, although it is widely recognized that baseline and either 4 or 6 hour samples will be sufficient for rule in/rule out purposes depending upon the assay and cutoffs used. Biological variation, both short-term and long-term variation, may influence serial sampling as well. There is currently a lack of clear definition of the criteria which defines what a significant change really is.

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It is also important to remember that an elevated concentration of troponin in the blood only signals myocardial damage has occurred and does not indicate the cause of the damage. A variety of conditions may induce myocardial damage besides ischemia and are listed in this table.

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In the past there has been controversy over which biomarker is preferable, troponin I or T. There is no scientific evidence that either of these markers is superior to the other. Therefore, focus should be placed more on the analytic and clinical performance of the assay, rather than which troponin is being tested. There is no way to correlate results from a troponin I assay to troponin T assay and often even between troponin I assays themselves.

A major issue for troponin I assays is the lack of standardization among commercial assays and harmonization of troponin I is an ongoing area of effort. In terms of risk stratification, troponin T or I may be utilized but it is clear that it is predominantly the use of a high-sensitive assay that has benefit over contemporary assays. There is an increased prevalence of troponin T elevations in the setting of renal failure and these are not to be considered false positives but related to overall dysfunction in the cardiorenal system. Patients with a chronic "low level" elevation of troponin have a worse prognosis and increased mortality.

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Another question which often arises is if CK-MB is even needed anymore. It is well recognized and accepted that it does not provide any additional information over troponin even in the setting of suspected re-infarction (which is increasingly rare today), assessing infarct size, before or after percutaneous coronary intervention, or in end stage renal disease patients. The only time CK-MB needs to be ordered is if there are suspicious false-positive troponin T or I results (although these can usually be resolved with heterophile blocking tubes or dilution studies) or if troponin testing is simply unavailable. In the United States, Medicare does not reimburse troponin and CK-MB testing which is performed simultaneously.

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Point-of-care cardiac marker testing is also an area that is commonly debated. The National Academy of Clinical Biochemistry guidelines recommend the turnaround time for troponin should be less than 1 hour over 90% of the time. Ideally, the turnaround time would be less than 30 minutes and timing is defined from collection to reporting. If point of care testing is used the results should be quantitative and the analytical characteristics of the POC test should be identical to the central lab's troponin assay. Currently there are no POC methods that have acceptable analytical sensitivity and it is often argued that the turnaround time is essentially sacrificed for a lower quality result.

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At the forefront of discussion is development of high-sensitivity troponin assays. The definition of a high-sensitive assay would be one that had a total imprecision of less than 10% at the 99th percentile and some would propose also being able to quantitate over 50% of normal values below that 99th percentile.

Although in the United States there are no FDA-approved high-sensitive assays, there are many in development and being used for research use only; several other high-sensitive troponin assays are already in use worldwide. Their use has been shown to diagnose MI earlier, provide greater prediction of death or future MI, and yield an improvement in risk stratification. It should be noted that the improvement in sensitivity is at the expense of specificity.

How sensitive does troponin testing really need to be today? Essentially troponin assays need to diagnose patients with AMI as early as possible and identify patients who are at risk of premature death from cardiovascular disease. To do this as accurately as possible the assays require an acceptable precision within the normal range.

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There are several key points to remember about troponin. First, a single troponin result does not equal a diagnosis. Acute changes in troponin are essential for interpretation and diagnosis of acute myocardial infarction, particularly with use of high-sensitive troponin assays. Point of care testing for troponin has not achieved the same level of precision or sensitivity as highly automated methods and remains an area for improvement. Finally, the precision of troponin assays will continue to improve and introduction of high-sensitivity assays may allow for earlier diagnosis of acute myocardial infarction and better risk stratification for our patients.

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References