Learning Objectives

On completion of this exercise, the participant should be able to

- understand the biomarkers that can be used to measure cardiac events;
- differentiate between conventional and high-sensitivity troponin assays;
- review the history of the use of high-sensitivity troponin assays in acute-care settings outside of the United States;
- define the value of using high-sensitivity troponin assays for early detection and intervention in acute myocardial infarction; and
- understand the challenges high-sensitivity troponin assays pose for health care clinicians and pathology laboratory professionals.

Introduction and Background

The heart has three main arteries, two of which supply it with oxygenated blood, which is necessary for the muscle of the heart to properly function and sustain life. When the heart is deprived of oxygen due to cardiovascular blockage or dysfunction, myocardial infarction, or heart attack, can occur. The longer oxygen deprivation lasts, the more damage to the heart tissue. Depending on the severity of the cardiac event, a variety of symptoms may be present for the affected patient; most commonly, these include chest pain, shortness of breath, dizziness, and nausea. Most myocardial infarctions occur over several hours, so warning signs should not be ignored.\(^1\)

Each year about 610,000 people die of heart disease in the United States, accounting for roughly 1 in 4 of all American deaths.\(^2\) About 25% of heart attacks occur without the patient experiencing any previous warning, and about 25% of heart attack patients die before making it to a hospital.\(^1\) Typically, those who survive can return to normal life; however, those with severe damage may experience further complications such as stroke, shock causing damage to the liver or kidneys, decreased heart function, or sudden death following myocardial infarction. Common risk factors for heart attack include coronary artery disease, obesity, high blood pressure, smoking, stress, and sedentary lifestyle.\(^1\)

Myocardial infarction is defined as necrosis of the myocardial tissue of the heart in conjunction with the clinical evidence of myocardial ischemia due to an imbalance between supply and demand of blood within the coronary arteries. The myocardium, the cardiac muscle tissue, is regulated by proteins called cardiac
troponins, which are responsible for the contraction and relaxation of the heart muscle. When the heart muscle is damaged these cardiac proteins are released into the blood circulation, varying with the degree of impact or damage to the myocytes (cells of the myocardium). To diagnose myocardial infarction, troponin levels are measured in the patient’s circulating blood, as troponin is a sensitive marker of the degree of protein release by the myocardium. In the event of a myocardial infarction, the earlier the identification, the better the outcome for the patient, because antithrombotic drugs can be administered to prevent further heart muscle damage and preserve heart function. Immunoassays for troponin T and troponin I have become the gold standard laboratory tests for diagnostic and prognostic determination of cardiac function.3

Clinical and Laboratory Diagnosis of Myocardial Infarction

In angina, blood flow is diminished and is then restored with no permanent damage to the heart tissue, whereas in myocardial infarction, the blood flow is diminished but is not restored quickly, and permanent damage to the heart muscle occurs. Laboratory testing, echocardiograms, and clinical presentation are all assessed in the evaluation of a patient presenting with myocardial infarction–like symptoms.

When diagnosing an acute myocardial infarction (AMI), there are many biomarkers that can be measured from a patient’s blood. However, many are not specific to cardiac tissue and therefore are not definitive for pathologic diagnosis. These markers include aminotransferase, lactate dehydrogenase, troponin C, and CKMB. In contrast, troponin I and troponin T have nearly absolute myocardial tissue specificity and therefore have become the gold standard for pathology/laboratory diagnosis of heart attack.3

Cardiac Troponins

Cardiac troponins are proteins that are responsible for the contraction and relaxation of the heart muscle through the regulation and control of calcium and the interaction of actin and myosin. Troponins are broken down into three subproteins: C, I, and T. Troponin C binds calcium; troponin I inhibits actin-myosin interactions, responsible for relaxation; and T binds tyrosine, responsible for the contraction of the muscle. All three subproteins are released into the blood stream when the heart muscle is stressed. Troponin C is expressed in both skeletal and heart muscle and is not routinely measured, whereas troponins T and I are unique to the heart and therefore routinely measured. Normal range for a healthy individual is hypothesized to be between 0.1 and 0.2 ng/L; this small value is associated with the normal microscopic loss of cardiomyocytes as a part of normal cell death.3

Because the initial release of troponin can be detected in the first hours of a heart attack, usually 2 to 4 hours after onset, it is currently recommended that three specimens be collected: at presentation in the
emergency department, 6 hours after presentation, and 9 hours after presentation. With a myocardial infarction, gradual dispersion of these proteins will continue, and concentrations can remain elevated in the blood for 4 to 7 days.4-6 According to Daubert and Jeremias,3

Troponin kinetics dictate that the sensitivity of troponin improves with time. *Using conventional assays* [emphasis added], the sensitivity of troponin T at the time of hospital admission ranges from 25%–65%, and increases to 59%–90% at 2 to 6 hours after presentation. The sensitivity approaches 100% by 6 to 12 hours after admission. The sensitivity of troponin I upon admission is less than 45%, which improves to 69%–82% when measured 2 to 6 hours later and, similar to troponin T, achieves 100% sensitivity between 6 and 12 hours after admission. Thus, the maximal sensitivity of *standard troponin assays* [emphasis added] is not achieved until 6 or more hours after the initiation of myocardial necrosis. … The positive predictive value of troponin also increases with serial testing, improving from 25% for troponin I and 35% for troponin T at presentation to 89% for troponin I and 57% for troponin T after 12 hours. Specificity does not vary significantly over time. The specificity of troponin I is on the order of 83 to 98 percent with serial testing. Troponin T has specificities ranging from 86%–98%.

**Laboratory Assays**

In 2007, there was a defined consensus effort to standardize the diagnosis of myocardial infarction along with troponin assay measurements. This would require a concentration of cardiac troponin exceeding the 99th percentile of the upper reference limit in a healthy population. However, it was not until the past 7 to 9 years that assays capable of accounting for the 99th percentile have existed: high-sensitivity troponin assays.7,8 These assays can measure concentrations of troponin approximately 10 times smaller than the conventional troponin T and troponin I assays that are considered the standard of care in the United States for testing of patients presenting to the emergency department with symptoms of myocardial infarction.

Traditional assays are not sensitive enough to detect very early onset of myocardial infarctions (less than 2 hours of onset) with sensitivity greater than 60%, but high-sensitivity troponin immunoassays are able to overcome this limitation. High-sensitivity troponin T assays have been available in Canada, Asia, Australia, and Europe for 7 years and are used in clinical settings as a rapid method for ruling in and ruling out acute myocardial infarctions.9 It was not until January 19, 2017, that the US Food and Drug Administration (FDA) announced the clearance of the Roche Diagnostics fifth-generation STAT cardiac troponin T assay (Elecsys Troponin T Gen 5 STAT) in the United States for emergency department patients.9
Benefits of High-Sensitivity Troponin Assays

High-sensitivity troponin assays not only increase the ability to rapidly detect myocardial infarction but could also detect structural cardiac morbidities, as these assays can measure smaller concentrations of troponins. Increased sensitivity in detecting troponin in the very early onset of a heart attack should improve patient outcomes by allowing for clinical intervention in the very early phase of a heart attack.

Analytically, the reporting of results will change, as all high-sensitivity troponin results will be reported in whole numbers rather than decimal values, and the unit of measure will change from ng/mL to ng/L. Also, there will be changes to reference ranges based on sex; as Wu and Christenson state, “the 99th percentile cutoff limit has been changed from <0.010 ng/mL (10 ng/L) for the 4th generation cardiac troponin T (cTnT) assay to sex-specific cutoffs of 14 ng/L (0.014 ng/mL) for women, 22 ng/L (0.022 ng/mL) for men, and 19 ng/L (0.019 ng/mL) for both sexes for the 5th generation.”

High-sensitivity troponin assays will be able to measure cardiac injury and could possibly be used as a predictive measure in the future, which broadens their use. It will still be important to investigate clinical symptoms with electrocardiography, along with serial high-sensitivity troponin assays to measure the rise and fall in cardiac biomarkers. The most significant enhancement seen with these assays is the ability to perform early rule-in and rule-out for myocardial infarction, as high-sensitivity troponin assays have a 99% negative predictive value. In fact, in one study, 60% of patients could be ruled out as early as 1 hour after symptom onset, using a change of less than 3 ng/L of cTnT within the first hour as the cutoff.

Although a 1-hour rule-out has not yet been cleared by the FDA in the United States, in Europe a 1-hour rule-out is used as recommended by the European Society of Cardiology. It is important to note that although this 1-hour rule-out algorithm is used in Europe, such recommendations are not included in product literature from assay manufacturers.

As previously stated, the European Society of Cardiology recommends a 1-hour rule-in or rule-out using a high-sensitivity troponin assay to determine myocardial infarction in patients presenting to the emergency department with acute myocardial symptoms. In a study in the *European Heart Journal*, Twerenbold et al discussed the ability to determine a safe algorithm for patients presenting to the emergency department with symptoms of acute myocardial infarction within 1 hour of presentation. Using a high-sensitivity troponin I assay, rule-out was determined to be less than 3 ng/L at presentation, or less than 6 ng/L at presentation and less than 3 ng/L delta at 1 hour. Rule-in was greater than 120 ng/L at presentation or delta of 12 ng/L or greater at 1 hour. Patients whose values were between 3 and 120 ng/L on arrival to the emergency department were observed.
A single center in the United States verified a European Society of Cardiology study on high sensitivity cTnT (hs-cTnT). This rule-out algorithm was less than 12 ng/L at arrival and less than 3 ng/L delta at 1 hour, and rule-in was 52 ng/L or greater at arrival and a delta of 5 ng/L or greater at 1 hour. Patients with values between 12 and 52 ng/L at arrival to the ED were observed. The study concluded:

0/1-hour hs-cTnT algorithm to rule-in/rule-out AMI had a high negative predictive value (99.4%) for AMI but did miss 2 (0.6%) AMIs. However, the sensitivity of the rule-out algorithm for type 1 AMI at presentation was 100%. The algorithm may not be as sensitive for type 2 AMIs. The specificity for the rule-in of AMI was reasonable at 92.0% but the positive predictive value was modest at 42.0%. Further multicenter studies in the US are needed to verify these results.

Challenges With High-Sensitivity Troponin Assays

High-sensitivity troponin assays reinforce that not all troponin increases are associated with myocardial infarction and that there are patients with other cardiac disease who will have to be treated accordingly. High-sensitivity troponin assays have different sensitivities and specificities than those for the conventional troponin assays with which many laboratorians and clinicians are currently familiar (see Figure). There are significant changes to the reference ranges used, which will require much education and communication to all involved in the care of the patient both clinically and in the laboratory. This change will affect the appropriateness and triaging of patients as they are admitted to an emergency department or inpatient unit. The clearance of these tests could lead to the testing of asymptomatic patients for risk assessment in addition to those presenting to the emergency department with chest pain.
It could be argued that, used appropriately, a 1-hour rule-in or rule-out algorithm would reduce the length of stay in the emergency department. However, patients will most likely be further evaluated for their presenting symptoms and will need some form of further workup, which will continue to occupy time in the emergency department although the patient’s acuity level may be downgraded. The true benefit will be seen in patients who are ruled in faster for myocardial infarction and can be treated sooner. In addition, clinicians may be faced with additional challenges, as the range of patients who present with acute elevation of troponin T may broaden. Based on the patient, it is estimated that approximately 0.7% of the population will have modest elevations unrelated to cardiac events.

In addition to clinician interpretation and treatment challenges, there are challenges and limitations to the assay itself. Many European studies have focused on the superiority of troponin T assays to troponin I assays, as the sensitivity, specificity, and precision of the troponin T assays are more standard than those of troponin I.

Historically, strategies have been put in place to reduce the overall impact of interferences to the conventional troponin assays. These include blocking reagents and antibody fragments to adjust for specimen-type interferences, and interference such as hemolysis. Hemolysis is always a challenge with critically ill patients, because blood is commonly collected from a line draw. These strategies will be challenged with more sensitive assays: minor interferences could have a significant impact on result interpretation, increasing the risk for false-positive and false-negative results when ruling in or out acute myocardial infarction. Sample types can also have an impact on the analytic variation of both conventional and high-sensitivity troponin assays.

In addition to possible assay interferences, difficulties have been reported with assay calibrators for high-sensitivity troponin T assays. Depending on the calibration lots, a drop of 25-50% in detectable values has been reported, requiring additional quality assurance monitoring of values near the 99th percentile of the upper reference limit.

Conclusion

High-sensitivity troponin testing is beneficial in many ways, especially for patients presenting to the emergency department in the very early phases of myocardial infarction, approximately 1 hour after onset vs approximately 2 to 4 hours after onset. It is hypothesized that there is a potential for early release from the emergency department, faster emergency department to inpatient bed time, and earlier intervention for those with acute myocardial infarction, but more data will have to be measured to definitively confirm
these predictions. Results from this assay will allow further differentiation of cardiac injury and myocardial infarction and can possibly be used to predict risk and prognosis.

Since the first hs-cTn assay was approved by the US FDA on January 19, 2017, the United States will most likely begin to see a shift from conventional to high-sensitivity troponin assays. Standard practices will need to be developed and studied in the clinical setting. Because these assays have different sensitivity, specificity, reference ranges, and units of measure, there will be a need for education and communication to all involved in the care of the patient, both clinically and in the laboratory. These new assays could bring significant change to management of myocardial infarction in the out-patient, emergency department, and inpatient unit settings.

References

1. Understanding heart attack: the basics. Web MD. 


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