Troponin Elevation in Patients Without ACS

Acute myocardial infarction is an important cause of troponin release and can be classified into one of the five different types described in the Fourth Universal Definition of Myocardial Infarction (2018).**(Ref:1&3)** One new aspect to this document is the

differentiation of MI from myocardial injury. Many processes can lead to myocardial injury and troponin elevation in the absence of AMI.
This is appreciated in cardiology, but less so in general practice, leaving medical trainees with yet another consultation for “troponinitis” or “troponinemia.”

The Fourth Universal Definition of MI task force recommendations for institutions transitioning to high-sensitivity troponin testing is published in Jacc journal **(Ref:2)** The hs-cTn test is critical because correct interpretaion unlocks management.

The challenge is that hs-cTn assays are so sensitive that they can detect a circulating troponin level in an otherwise

healthy individual, some of which may even be above the upper reference limit (URL). This means the concept of a "troponin-positive" patient needs to be retired, since it says nothing about the patient's condition.
Also, it is important to remember that cardiac troponins are not cardiac enzymes. Troponin is 99% cardiac specific coming from cardiomyocytes

that has two cardiac sources. Fully 95% of cardiac troponin is in the cardiac contractile apparatus, where troponin acts as a structural *protein*; and 5% of Troponin is found in cardiac cytosoles. In the setting of myocardial injury what happens is that the cytosolic troponin rapidly effluxes from the cardiac myocytes and this explains why with high sensitivity assays we can detect a

meaningful change in troponin within one hour of the injury onset. Then the sarcomeric troponin falls off over period of hours to days which explains the prolong presence of Troponin in circulation after cardiac injury. Although myocardial injury is a prerequisite for the diagnosis of MI, it is also an entity in itself. Put another way, an abnormal troponin is necessary but absolutely

insufficient in isolation to make the diagnosis of myocardial infarction. Myocardial injury can be detected within 1 hour of injury onset. To accurately confirm an MI, the Fourth Universal Definition calls for the presence of acute myocardial injury (evidenced by a rise and/or fall of troponin), together with at least one of the following: conclusive symptoms or

signs; changes on electrocardiography; evidence of a loss of myocardial function on imaging (such as echocardiography); evidence of obstructive coronary artery disease at coronary angiography; or the unfortunate situation in which there is autopsy evidence of AMI.
Likewise, the diagnosis of acute or chronic myocardial injury requires at least one hs-cTn value above the 99th

percentile URL; it is considered acute if there is a rise or fall of cTn values and chronic if the pattern is unchanging. The diagnosis of MI, including type 2 MI (an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis), requires clinical evidence of myocardial ischemia. If there is no evidence to support the presence of myocardial ischemia, a

diagnosis of myocardial injury should be made.

three keys that are important for the power of troponin testing.

- Serial testing is crucially important to determine whether the injury identified is acute or chronic. Some patients have elevated troponin levels that do not change over time.

An accelerated protocol typically involves retesting in 1 hour. Without evidence of a rise or fall in the concentration of troponin on that second test, the likelihood of an AMI is considerably lower and the injury is more likely chronic in nature.

- The magnitude of elevation is also important for narrowing the

differential diagnosis. Small increases in troponin levels can be related to a wide variety of injury states; some of these may be acute, such as heart failure (HF).

- Clinicians should have a thorough understanding of the states that can lead to myocardial injury (**Table**).

Differential Diagnosis for an Elevated hs-cTn Result

Injury related to primary myocardial ischemia	**Injury not related to myocardial ischemia**
• Plaque rupture • Intraluminal thrombus	• Cardiac contusion, surgery, ablation, pacing, or defibrillation • Rhabdomyolysis with cardiac involvement • Myocarditis • Cardiotoxic agents (e.g., anthracyclines, Herceptin)
Injury related to myocardial oxygen supply/ demand imbalance • Tachy/bradyarrhythmias • Aortic dissection or severe aortic valve disease • Hypertrophic cardiomyopathy • Cardiogenic, hypovolemic, or septic shock • Severe respiratory failure • Severe anemia • Hypertension with or without left ventricular hypertrophy • Coronary endothelial dysfunction, spasm, or dissection	**Multifactorial or indeterminate myocardial injury** • Heart failure • Stress cardiomyopathy • Pulmonary embolism • Pulmonary hypertension • Sepsis • Critical illness • Renal failure • Severe acute neurological disease (e.g., stroke, subarachnoid hemorrhage) • Infiltrative cardiomyopathies (e.g., amyloidosis, sarcoidosis) • Strenuous exercise

While the differential diagnosis for abnormal hs-cTn is broad at lower concentrations, it narrows with higher values, explaining why magnitude of elevation is important. A very low troponin level of 5 ng/L can be detected in healthy individuals, while 10 ng/L may be indicative of stable angina, HF, left ventricular hypertrophy, or subclinical heart disease.

Low (50 ng/L) and moderate (100 ng/L) concentrations of hs-cTn can be detected with MI, stress cardiomyopathy, pulmonary embolism (PE), HF, shock, hypertensive crisis, and subarachnoid hemorrhage. The list narrows with high hs-cTn concentrations (1,000 ng/L) and includes large MI, myocarditis, stress cardiomyopathy, PE, and critical illness. And it narrows even further with very

high hs-cTn concentrations (10,000 ng/L): very large MI or myocarditis. Finally, while high-sensitivity troponin testing has changed the field, unstable angina – when defined as an acute coronary syndrome (ACS) without an abnormal troponin – still exists. A normal troponin does not exclude ACS. Once again, clinical judgment must be a rule when evaluating patients.

Take-home Messages:

- A central tenet of the 2018 Universal Definition of Myocardial Infarction is that high-sensitivity cardiac troponin (hs-cTn) is not a biomarker of acute myocardial infarction (AMI). It merely identifies myocardial *injury*.

- It is the job of the clinician to ascertain the cause of myocardial injury and determine whether it is acute or chronic.
- If unsure whether the patient has AMI, hs-cTn tests can be remeasured as soon as 1 hour after the first measurement. Without evidence of a rise or fall in the concentration of troponin on that second test, the

likelihood of AMI is considerably lower.

References:

1: Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol* 2018;72:2231-64.

2: Januzzi JL Jr, Mahler SA, Christenson RH, et al. Recommendations for Institutions

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3: Valentine CM, Tcheng JE, Waites T. Translating the Translation: What Clinicians Should Know About the Fourth Universal Definition of

Myocardial Infarction. *J Am Coll Cardiol* 2018;72:2668-70. https://www.onlinejacc.org/content/72/21/2668