Managing Troponin Testing

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Editor's Note: *The Expert Clinical Management series consists of shorter, practical review articles focused on the optimal approach to a specific sign, symptom, disease, procedure, technology, or other emergency department challenge. These articles—typically solicited from recognized experts in the subject area—will summarize the best available evidence relating to the topic while including practical recommendations where the evidence is incomplete or conflicting.*

INTRODUCTION

Troponin is released in myocardial injury whether or not the injury is caused by acute myocardial infarction (Figure 1). There are 4 main categories of disease that might result in acute myocardial injury. Acute myocardial infarction can occur because of obstruction to flow through the coronary vessels (type I acute myocardial infarction) or through supply-demand mismatch, as might occur in profound anemia with decreased oxygen-carrying capacity (type II acute myocardial infarction). Nonischemic cardiac conditions, as well as noncardiac disorders, also cause myocardial injury.

There are no "false-positive" troponin elevations; all reflect myocardial injury and all portend a worse prognosis than for otherwise similar patients without a troponin elevation. This has been shown for patients with heart failure,[1] renal failure,[2] gastrointestinal bleeding,[3] sepsis,[4] respiratory disease,[5] pulmonary embolism,[6] subarachnoid hemorrhagic, or stroke.[7,8] An elevated troponin level even indicates a worse prognosis in asymptomatic people without known cardiovascular disease.[9-11] The higher the troponin, the worse the prognosis, regardless of the cause of the elevation[1,12]; thus, the mantra that "any troponin is worse than no troponin and more troponin is worse than less troponin."

LABORATORY MEDICINE 101 FOR EMERGENCY PHYSICIANS

Troponin levels generally begin to increase within 2 to 4 hours; most acute myocardial infarction patients can be identified within 6 to 9 hours after the onset of pain. Troponin assays, used in the United States, are becoming increasingly sensitive, with measurable troponin values (those within the normal range but above the lower limit of detection) now detectable in 20% to 50% of patients with the standard contemporary assays (also known as sensitive or moderately sensitive assays). Troponin assays currently used in Europe and pending approval in the United States measure troponin levels above the lower limit of detection in 50% or more of patients (these are referred to as high-sensitivity assays).

It is important to verify that your laboratory defines abnormal values by the 99th percentile of a normal population, rather than the former 95% threshold, and that your assay demonstrates no greater than a 10% to 20% coefficient of variation at this upper limit of normal. The strategies discussed in this article assume compliance with these important benchmarks. Although all troponin I and T assays differ, their interpretation is similar; therefore, in this article I will simply refer to them all as troponins.

APPROACH TO INTERPRETING TROPONIN VALUES

A general approach to troponin interpretation is outlined in Figure 2. Emergency physicians are faced with interpretation of troponin results in 3 different scenarios: the test was ordered specifically to exclude an acute coronary syndrome, as part of a panel for some other condition, or through standing orders, and after clinical evaluation the clinician would not have ordered the test.

When Acute Coronary Syndrome Is the Primary Concern

A troponin elevation in the presence of a compatible history or ECG evidence of ischemia indicates an acute myocardial infarction. The third universal definition of myocardial infarction requires a combination of an increase or decrease in cardiac biomarkers, with at least 1 value above the 99% percentile of the upper reference limit and a

Cardiac

Ablation

Apical ballooning

Cardiac contusion

Cardiomyopathy: hypertrophic, infiltrative

Cocaine

Defibrillator shocks

Dysrhythmias

Endothelial dysfunction

Heart failure

Myocardial contusion

Myocardial toxicity (chemotherapy agents, snake venoms)

Myocarditis

Pulmonary embolism

Structural heart disease

Noncardiac

Burns

Hyperthyroidism

Hypo- or hypertension

Renal dysfunction

Sepsis

Shock

Stroke and subarachnoid hemorrhage

Vasculitis

Figure 1. Some cardiac and noncardiac causes of troponin elevation in the absence of thrombotic occlusion.

history concerning for acute ischemia, new significant ECG changes, including ST- or T-wave changes, left bundle branch block, pathologic Q waves, evidence of regional wall motion abnormality, loss of viable myocardium, or detection of thrombus.[13]

In a patient with an acute coronary syndrome, verification of a troponin elevation will prompt specific therapies such as enoxaparin, glycoprotein IIb and IIIa receptor antagonists, and percutaneous coronary intervention.[12,14] When it is not clear whether a troponin elevation reflects acute or chronic myocardial injury, a repeated value 1 to 3 hours later (Δ value) can be helpful because it will increase with acute injury.

The exclusion of acute myocardial infarction such that a patient can be discharged requires reducing the likelihood of a serious cause to an acceptable threshold, typically considered to be less than a 1% to 2% likelihood of adverse events.[15] Traditionally, this required serial troponin values during 12 or more hours. Multiple studies now show that myocardial infarction can be ruled out within a shorter timeframe, using Δ values (the absolute change in troponin values taken 1 to 3 hours apart).

The European Society for Cardiology (ESC)[14] recommends a rapid rule-out protocol at 0 and 3 hours, using high-sensitivity cardiac troponin tests. They endorse an even more rapid rule-out and rule-in protocol at 0 and 1 hours with a few selected high-sensitivity assays.[14] The International Federation of Clinical Chemistry recommends Δ values 3 hours apart.[16] This strategy works with some of the contemporary moderate-sensitivity assays used currently in the United States and the high-sensitivity assays used in Europe. The use of an absolute rather than relative difference between values appears superior.[17,18] The optimal absolute difference required to identify acute myocardial infarction depends on the specific assay being used and the interval between values.

Several large clinical studies support this approach.[19-26] Using several different assays, Reichlin et al[19] and Keller et al[20] found very high sensitivities (>90%) at presentation that approached 100% by 3 hours. Performance characteristics at 3 hours were similar between standard contemporary and high-sensitivity troponins.[21] Point-of-care assays currently do not share these performance characteristics.[22]

Contemporary troponin assays (those with moderate sensitivity) alone do not reduce the miss rate to less than 1%, but combining troponin testing with some features of the clinical presentation achieves that goal. Two large trials, ASPECT and ADAPT,[23,24] found that a combination of a nonischemic ECG, 2 troponins 2 hours apart, and a TIMI score of 0 had a 0.3% to 0.9% prevalence of 30-day adverse events rates (including acute myocardial infarction). The TRAPID trial, using high-sensitivity troponins 1 hour apart, had a 0.9% misdiagnosis rate in the 63% of patients without acute myocardial infarction.[25] These studies have limitations because they did not use the test results to discharge the patients and few patients presented shortly after symptom onset, when the performance of the assays is less well defined.[27]

An additional useful feature is the duration of chest pain. Although not well defined, there is some duration of chest pain that is long enough that the patient either has had an