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EDITORIAL COMMENT

Cardiac Troponin and the True False Positive*

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Over the past 50 years, biomarkers have evolved to diagnose acute myocardial infarction (MI). In the 1960s, the enzyme aspartate transaminase (AST), now most commonly associated with liver parenchymal injury, was the preferred biomarker to diagnose acute MI (1). This was subsequently replaced by lactate dehydrogenase (LDH) and creatine kinase (CK). In recent decades, biomarkers for MI detection became more sensitive and specific for myocardial injury. In the 1980s, testing for the MB fraction of CK advanced the field substantially; CK-MB was more sensitive and clearly more specific than total CK; however, compared with what today's clinician expects from a blood test for MI detection, even CK-MB had substantial limitations.

In the 1990s, cardiac troponin, a more specific and sensitive biomarker for myocardial injury entered clinical practice (1). Unlike CK or CK-MB, which are enzymes, troponin is a component of the contractile apparatus in both skeletal and cardiac myocytes that regulates and facilitates the interaction between actin and myosin filaments. The cardiac troponin complex is composed of 3 isoforms: troponin T, troponin C, and troponin I. In cardiac myocytes, approximately 4% to 5% of troponin is found in the cytosol, and this troponin is responsible for the initial surge of troponin in the setting of myocardial injury. The remainder of troponin is found in the sarcomere, and when cell injury occurs, it provides a slow, continuous troponin release over several days (2). Because troponin I and T are more specific to cardiac myocytes than troponin C, they were developed as the preferred biomarkers of myocardial injury.

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Cardiac troponin assays were developed for the purpose of diagnosing acute MI, and they have since become the preferred diagnostic biomarkers supported by the Universal Definition of MI (3). To diagnose acute MI, there must be a rise and/or fall in cardiac troponin above the 99th percentile combined with evidence of myocardial ischemia as suggested by 1 of the following: 1) symptoms of myocardial ischemia; 2) new ischemic electrocardiographic changes; 3) new pathological Q waves; 4) new ischemic regional wall motion abnormalities on cardiac imaging; or 5) acute coronary thrombus on coronary angiography (3).

To facilitate earlier detection of myocardial injury and diagnosis of MI, troponin assays have become increasingly sensitive. Assays are now classified as high sensitivity if the troponin concentration can be detected above the limit of detection but below the 99th percentile in 50% of healthy individuals and the coefficient of variation (a measure of imprecision) at the 99th percentile value is 10% or less.

As anyone with experience in laboratory testing may know, with their greater sensitivity for detection of myocardial injury, high-sensitivity troponin assays are clearly less specific for the diagnosis of acute MI.

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TABLE 1 Causes of False Negative and Positive Troponin Values

False Negative Troponin	False Positive Troponin
Hyperbilirubinemia	Heterophile antibodies
Lipemia	Myopathies
Biotin (vitamin B_7)	Rheumatoid factor
Cardiac troponin autoantibodies	Fibrin interference
Hemolysis	Hemolysis
Analyzer malfunction	Elevated alkaline phosphatase
	Analyzer malfunction

Indeed, although not previously recognized, elevated cardiac troponin (representing true myocardial injury) is present in several cardiac and noncardiac conditions in the absence of acute MI. Cardiac causes of troponin elevation include heart failure, pulmonary embolism, Takotsubo cardiomyopathy, myocarditis, cardiomyopathies, arrhythmias, valvular heart disease, and cardiac contusions, among others (4). Noncardiac causes include renal failure, sepsis, anemia, hypotension, hypoxia, and noncardiac surgery (4). Although clinicians sometimes refer to troponin detection in these scenarios as "false positives," this is *not* accurate because the detection of troponin reflects true cardiac myocyte injury and release. These are *true* positives, in the sense that the assay is doing what it is supposed to do—detect myocardial injury.

More rarely, however, true "false" troponin results may occur (**Table 1**). In this issue of *JACC: Case Reports*, Santos et al. (5) present a case of a false positive troponin result caused by circulating heterophile antibodies. This is not the first time this circumstance has been encountered; indeed, heterophile antibodies are widely understood to be risk factors for true false positive troponin results in the absolute absence of myocardial injury. Heterophile antibodies are induced by both endogenous (e.g., autoimmune) and external (e.g., human antimouse) antigens, and these antibodies may interfere with troponin immunoassay execution. The exact prevalence of heterophile antibodies in the population is uncertain, but it is estimated to be between 0.2% and 3.7% (6). Heterophile antibodies can arise from exposure to pets, ingestion of animal products, and vaccinations. However, they are also produced in infectious mononucleosis and atypical respiratory infections, and they may be seen in Burkitt lymphoma and rheumatoid arthritis. In addition to interfering with troponin assays, heterophile antibodies can also interfere with thyroid function tests, hormones, and tumor markers; in some cases, the presence of heterophile antibodies may have serious implications for patient care (7).

In addition to heterophile antibodies, troponin concentrations may also be falsely affected by hemolysis causing false elevations and reductions, depending on the assay (**Table 1**) (8). Similarly, hyperbilirubinemia, cardiac troponin autoantibodies and lipemia can decrease troponin concentration results (8). Biotin (vitamin B_7) is found in multivitamins, hair, and skin supplements, and it can also cause falsely low troponin concentrations (9). Conversely, myopathies can have been associated with skeletal expression of the fetal troponin T gene program, leading to true elevation of cardiac troponin T concentrations in the absence of myocardial injury (10). In addition, rheumatoid factor, elevated alkaline phosphatase, and fibrin interference have been associated with falsely elevated troponin values (8).

When approaching any patient with a suspected false troponin result (after ruling out ischemia and other cardiac and noncardiac causes of troponin elevation), physicians should again probe the history for any history of dietary supplement use, autoimmune phenomena, or other hints of potential heterophile presence. Then, the troponin assay should be repeated. If results are still abnormal, consider sending an alternative troponin assay; usually this suffices, but occasionally one may need to measure a third troponin and/or CK-MB. If uncertainty persists, further testing with blocking antibodies, as pursued by Santos et al. (5) in this case, frequently clarifies the diagnosis.

Finally, it is necessary to emphasize that with increasing sensitivity of troponin assays, clinicians are faced with the rise in frequency of *true* positives related to cardiac injury that may not be related to an acute MI. Clinicians should remember that these "true positive" cases of myocardial injury may not equal MI. However, this prevalent injury should not be ignored in the absence of an MI: these patients are higher risk and should be regarded as such (4,11). In contrast, the frequency of heterophile-based assay interference is very low and is more of a clinical curiosity. The report by Santos et al. (5) shines an interesting light on the phenomenon of "true false positives" in this setting.

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