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The trouble with troponin

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Diagnostic tests are double-edged swords. They typically have good sensitivity when illness is likely but can contribute to misdiagnosis when disease prevalence is low. In cardiology, troponin has become an essential tool to diagnose or exclude acute myocardial infarction (AMI). However, discovery of elevated serum troponin in patients without AMI can confuse physicians and lead to poor decision making.

An example is an 85-year-old woman with a urinary tract infection and an elevated serum troponin level defined as >99th percentile. Is the patient having a heart attack? Should heparin and dual antiplatelet therapy be started? Should she be taken to the cardiac catheterization lab for urgent coronary angiography? Should treatment of her urinary tract infection be modified? Does she have a poor prognosis? All too often this patient is admitted to a cardiac intensive care unit, is anticoagulated, and undergoes cardiac catheterization followed by percutaneous coronary intervention of coronary stenoses that are identified.

Troponin testing to diagnose AMI developed in the early 1990s as an alternative to the creatinine kinase (CK) assays then in use.[1,2] Interpretation of CK results required evaluating both the quantity and percentage of the cardiac-specific isoform (MB-CK). MB-CK can be produced by injured skeletal muscle, making AMI diagnosis difficult in patients with trauma or rhabdomyolysis. Troponins are proteins that exist in both skeletal and cardiac muscle as a ternary complex of I, T, and C subunits. They function to mediate the calcium-regulated interaction between actin and myosin. Cardiac-specific isoforms of the I and T isoforms exist that can be differentiated from skeletal muscle isoforms using monoclonal antibodies.[3] These antibodies have been incorporated into assays for cardiac troponin testing that are now in widespread clinical use and are integral to the current third international universal definition of MI.[4] Only ST-elevation MI can be diagnosed acutely in the absence of a myocardial biomarker elevation.

However, research has shown that troponin is not a specific marker for AMI or ischemia and frequently accompanies noncardiac diseases including stroke, sepsis, and renal failure. The exact pathophysiology is unclear. Though some patients with ischemic heart disease suffer ischemic injury driven by increased cardiac performance, ischemic heart disease is not required for troponin elevation.[5] Troponin elevation in hospitalized pediatric populations without ischemic heart disease has been documented, and development of high-sensitivity troponin assays has led to recognition that serum cardiac troponin can be detected in populations without acute disease.[6] There is even evidence that troponin can be released from cardiac myocytes in the absence of cell death.[5] In addition, recent studies suggest that a small amount of circulating troponin may be normal. When blood samples from over 150,000 individuals were tested using new very high-sensitivity assays, 80% had detectable troponin.[7]

Troponin elevation in the absence of AMI can create cognitive dissonance for physicians on the front lines of patient care. Under current guidelines, detecting troponin elevation provides half of the information needed to make a diagnosis of AMI. All that is then needed is a clinical setting consistent with acute myocardial ischemia and symptoms of ischemia.[4] Patients with sepsis, pneumonia, cholecystitis, and acute gastrointestinal diseases often have nausea, shortness of breath, and pain. Many have known coronary artery disease or risk factors for ischemic heart disease. Many patients, including diabetic patients and women, have atypical symptoms when experiencing myocardial ischemia and infarction. To make matters worse, patients with elevated troponin are known to have worsened clinical outcomes in many non-AMI disease states.[7,8] Physicians detecting troponin elevation in their patients have reason for concern.

Data from our health care system indicate that 30% of hospitalized patients have troponin testing as part of their inpatient management.[9] Fewer than 3% of hospitalized patients are diagnosed with AMI, many with ST elevation allowing diagnosis by electrocardiographic criteria alone. More than 70% of elevated troponin values identified in our health care

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system are found in patients without AMI.[10] The positive predictive value of testing in our system is <30%. When utilization was reviewed, most testing occurred in patients unlikely to have AMI or in whom the diagnosis would not be expected.[9]

A pregnancy test is a good example of a test with high predictive value. A patient with a positive urine pregnancy test has a high likelihood of pregnancy. The diagnosis is confirmed with a second serum test. D-dimer testing for pulmonary embolism is an example of a test that, like troponin testing for AMI, has a low positive predictive value. A diagnosis of pulmonary embolism is not made based on D-dimer testing alone. Diagnosis requires a confirmatory test, usually computed tomography imaging. Current guidelines for AMI diagnosis do not discuss or recommend confirmatory testing when troponin elevation is detected, and there is no consensus on what testing might be used. The diagnosis depends on clinical judgment. As a result, patients diagnosed with non–ST-elevation MI appear to represent a heterogeneous group of whom an unknown portion have classic coronary plaque rupture and thrombosis.

A desire to exclude, rather than to diagnose, AMI may drive much of the troponin testing in our health care system. Symptoms of AMI can be atypical, and large numbers of patients with such symptoms seek care each day. Missing AMI can be catastrophic for treating physicians. "Failure to diagnose" AMI is a major tort, with judgments that can exceed $1 million in states without tort reform. Limiting testing to individuals thought likely to have AMI would significantly reduce testing and improve positive predictive value. But to achieve this goal will likely require tort reform to protect physicians choosing not to test patients unlikely to have AMI.

The trouble with troponin is an 85-year-old woman with a urinary tract infection who spends extra days in the hospital undergoing cardiac testing and who leaves with a drug-eluting stent in an obtuse marginal branch with instructions to take dual antiplatelet therapy for 12 months. The diagnosis of MI itself, once attached to the patient's chart, may haunt the patient, leading to unnecessary worry, treatment, and follow-up. For the hospital, a patient discharged with AMI who is readmitted (or, worse, passes away) ends up incorporated into metrics that affect hospital rankings and reimbursement.

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