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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Are serum troponin levels elevated in conditions other than acute coronary syndrome?

A: Yes. Sepsis, stroke, chronic kidney disease, pulmonary disease, chemotherapy, heart failure, and stress cardiomyopathy can all raise serum troponin concentrations, and in some cases the elevations are prognostically important. Careful clinical assessment, serial monitoring of troponin levels, and other supportive tests are usually necessary to tell whether troponin elevations are due to acute coronary syndrome or to these other causes.

NOT ONLY A MARKER OF MYOCARDIAL DAMAGE

Troponin, an intracellular protein found in skeletal and cardiac muscle cells, is essential for muscle contraction. Troponin T and troponin I are clinically equivalent, and both are biomarkers of myocardial damage.

A troponin assay is ordered when patients present with sudden onset of symptoms of acute coronary syndrome such as chest pain, dyspnea, diaphoresis, and electrocardiographic abnormalities. The assay is positive when the manufacturer-specified threshold corresponding to a concentration above the 99th percentile is detected.

Serial testing of serum biomarkers of acute myocardial damage is essential to confirm the diagnosis of myocardial infarction. Because of their higher sensitivity and specificity compared with creatine kinase-MB and other markers, troponins are the preferred biomarker in diagnosing acute coronary syndrome.

In 1984, Piper et al[1] reported that free cytosolic pools of cardiac enzymes could be released after reversible myocardial injury as a result of temporary disruption of the cell membrane. This upended the previous assumption that troponin was released only after irreversible myocardial necrosis, and it provided an explanation for troponin elevations observed in conditions with no evidence of epicardial coronary artery disease or permanent myocardial damage.[1]

A troponin elevation at the time of sepsis diagnosis may double the risk of death

SEPSIS

Studies of patients with sepsis, severe sepsis, and septic shock have shown troponin elevations with no evidence of acute coronary syndrome.[2] In sepsis, troponin elevations are presumed to be caused by a combination of events. Renal dysfunction leads to decreased clearance of troponin fragments by the kidneys. The massive inflammatory response in septic shock results in cytokine-induced cardiac damage, and increased levels of endogenous and exogenous catecholamines damage cardiac myocytes.[3]

Studies of the prognostic value of these elevations have produced mixed and contradictory results. But a 2013 meta-analysis[4] showed that patients with a troponin elevation at the time of diagnosis of sepsis had a risk of death almost twice that of patients without a troponin elevation (relative risk 1.91, 95% confidence interval [CI] 1.63–2.24).

STROKE

Acute ischemic stroke can trigger troponin elevations in several ways. Since the risk factors for acute ischemic stroke and coronary stenosis are similar, patients who have an ischemic stroke have a higher risk of coronary athero-

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sclerosis and coronary stenosis than the general population.[5]

Stroke can cause a variety of cardiovascular and respiratory responses (eg, tachyarrhythmia, hypertensive crisis, respiratory failure) that increase the stress on the myocardium. In patients with stroke and concurrent coronary artery stenosis, the increased metabolic demand can exceed the oxygen supply capacity, resulting in myocardial ischemia, which can manifest as increased levels of serum troponin.[5]

Stroke can also cause troponin elevation through neurogenic myocardial damage. Ischemic stroke and intracranial hemorrhage can trigger alterations in autonomic control. Sometimes this results in increased sympathetic activity with concomitant catecholamine surge, leading to contraction band necrosis and other forms of myocardial damage and, as a result, troponin elevation.[5,6] This may explain troponin elevation in patients with acute ischemic stroke in the absence of concomitant coronary artery disease. Recent evidence suggests that patients with acute ischemic stroke and elevated troponin had significantly less angiographic evidence of coronary artery disease than matched patients with non-ST-elevation myocardial infarction.[7]

CHRONIC KIDNEY DISEASE

Cardiac troponins may be elevated in chronic kidney disease. Explanations for this include the theory that troponin is broken down into fragments that are cleared by the kidney.[8] Therefore, decreased renal function leads to an increase in troponin fragments measured with troponin assays. Other explanations are chronic volume overload, chronic elevation of proinflammatory cytokines, and associated comorbidities such as hypertension.

Troponin elevations can have prognostic significance in chronic kidney disease. In a meta-analysis of 98 studies of patients with chronic kidney disease and no symptoms of acute coronary syndrome, troponin elevation was associated with 2- to 4-fold higher rates of all-cause mortality, cardiovascular mortality, and major acute coronary events in both dialysis-dependent and nondialysis patients.[8] Thus, troponin is a unique factor in risk-stratification in patients with chronic kidney disease and could affect how it is managed in the future.

To determine if an acute coronary syndrome is taking place when evaluating patients with chronic kidney disease and elevated troponins, physicians must use other evidence—for example, serial measurements of troponin levels showing continued troponin elevation, elevations in troponin from the patient's baseline, elevated creatine kinase-MB levels, electrocardiographic changes, and clinical symptoms.

PULMONARY DISEASE

Troponin elevation can signify right heart strain in a variety of pulmonary diseases.

Pulmonary embolism. Troponin elevation is a marker of right ventricular dysfunction in patients with moderate to large pulmonary embolism.

In a study of normotensive patients with acute pulmonary embolism, 52% had elevated serum troponin, and they had a higher risk of an adverse outcome (death, recurrent pulmonary embolism, or major bleeding) within 30 days (odds ratio 4.97, 95% CI 1.71–14.43) and a lower probability of 6-month survival.[9] Troponin elevation in pulmonary embolism is not helpful in confirming the diagnosis but is primarily useful in prognosis.

Pulmonary arterial hypertension. Cardiac troponin elevations can also indicate severe disease and poor outcomes in patients with pulmonary arterial hypertension. A study by Heresi et al[10] confirmed this, even in patients with only slight elevations in troponin levels. Troponin was detected in 17 (25%) of 68 patients with pulmonary arterial hypertension diagnostic category 1. Further, patients with detectable troponin had more advanced functional class symptoms, a shorter 6-minute walk distance, more pericardial effusions, larger right atrial area, and higher B-type natriuretic peptide and C-reactive protein levels.[10]

Measuring troponins in the setting of pulmonary hypertension allows clinicians to identify high-risk patients and may help guide the management of these patients.

Cardiac troponin elevations with pulmonary arterial hypertension can indicate severe disease and poor outcomes

Chronic obstructive pulmonary disease. Elevation of serum troponins is also reported in patients with acute exacerbation of chronic obstructive pulmonary disease and has been correlated with increased all-cause mortality rates in these patients.[11]

CHEMOTHERAPY

Chemotherapy-induced cardiotoxicity may result in troponin elevations. Chemotherapy causes cardiac toxicity by several mechanisms, including production of oxygen free radicals, disturbance of mitochondrial energy metabolism, intracellular calcium overload, and increased lipid peroxidation. Chemotherapeutic agents associated with cardiotoxicity include anthracyclines, trastuzumab, chlormethine, and mitomycin.

Chemotherapy-induced left ventricular deterioration is often irreversible. Monitoring troponin levels can help identify problems before cardiac dysfunction becomes clinically evident during the weeks and months after the start of high-dose chemotherapy.

Cardinale et al[12] found marked myocardial depression 7 months after the start of high-dose chemotherapy. They reported a close relationship between short-term troponin elevation and the greatest reduction in left-ventricular ejection fraction ($r = -0.87$; $P < .0001$). Normal troponin values after high-dose chemotherapy also seemed to identify patients at lower risk, with either no cardiac damage or only transient subclinical left-ventricular dysfunction.[12]

Monitoring troponin levels during chemotherapy can identify problems before cardiac dysfunction is clinically evident

HEART FAILURE

Heart failure leads to release of cardiac troponins through myocardial strain and myocardial death. Volume and pressure overload of the ventricles causes excessive wall tension, resulting in myofibrillar damage. Measuring troponins is an effective way to detect cardiac myolysis in heart failure, independent of the presence of coronary artery disease.

In heart failure, elevated troponins correlate with adverse outcome in both hospitalized and stable patients. In addition, elevation of both troponins and B-type natriuretic peptide is associated with worse heart failure outcomes than elevation of either marker alone.

A prospective study[13] of patients with New York Heart Association class III or IV heart failure showed that an increase in troponin concentration from normal baseline was associated with a risk of death, cardiac transplant, or hospitalization that was 3.4 to 5.09 times higher. Further elevations in B-type natriuretic peptide during the study period were associated with a poor outcome (hazard ratio 5.09; $P < .001$). Combined elevations of troponin and B-type natriuretic peptide defined the group at highest risk (hazard ratio 8.58; $P < .001$).

Increased myocardial wall stress may lead to decreased subendocardial perfusion, with resulting troponin elevation and decline in left ventricular systolic function. Further, in vitro experiments with myocytes established a link between myocardial wall stretch and programmed cell death, which may contribute to troponin elevations.[14]

STRESS CARDIOMYOPATHY

Profound reversible myocardial depression and troponin elevation are seen after sudden emotional stress, a condition called stress-induced or takotsubo cardiomyopathy. While the exact mechanism of stress-induced cardiomyopathy remains unclear, it is thought to be due to sudden supraphysiologic elevation of catecholamines and related neuropeptides. Although vasospasm in the epicardial and microvascular circulation has been suggested as the possible mechanism of left ventricular systolic dysfunction and troponin elevation, cardiac myocyte injury from catecholamine-induced cyclic AMP-mediated calcium overload and oxygen-derived free radicals appears to be a more likely mechanism.[15]

PSEUDOELEVATIONS OF TROPONIN

In rare cases, endogenous antibodies (eg, heterophilic antibodies) in the blood specimen can interfere with the processing of the troponin immunoassay in the laboratory, causing a false-positive assay. This can occur with samples from patients with a viral infection or autoimmune condition as well as with samples from patients treated with intravenous immunoglobulin (Ig). Heterophilic antibodies can bind to the Fc region of the test antibodies in certain troponin assays, leading to false-posi-

tive elevations.[16] Macrotroponin, a molecule found in patients with autoantibodies against troponin I, is composed of troponin I fragments and IgG antibodies and can also cause a false-positive troponin immunoassay.[16]

In patients with seropositive rheumatoid arthritis, a false-positive troponin I assay was associated with a high concentration of IgM rheumatoid factor with the use of certain immunoassay techniques.[17] In patients with acute skeletal muscle injury, the first-generation troponin T assay was found to be falsely positive due to the nonspecific binding of skeletal muscle troponin T to the walls of the test tube used for the assay. When the second-generation troponin T assay was used, troponin T levels were found to be slightly more positive than troponin I levels (1.7 vs 1.5 times the upper limit of normal), especially in patients with renal failure.[18]

Troponin may also be falsely elevated in hemolyzed blood samples. This has to be taken into consideration in interpreting the results of troponin testing in severely hemolyzed blood samples. However, Puelacher et al[19] suggested that the presence of hemolysis did not appear to interfere with clinical value of the test.

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