Cardiac troponins in the intensive care unit: Common causes of increased levels and interpretation

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**Background and Objectives:** Clinical chemistry is an important component of the diagnosis of many conditions, and advances in laboratory science have brought many new diagnostic tools to the intensive care unit clinician, including new biomarkers of cardiac injury like troponin T and I. Interpretation of these clinical laboratory results requires knowledge of the performance of these tests.

**Setting and Patients:** This article reviews the interpretation and performance of diagnostic markers of myocardial injury in patients with diverse clinical conditions of interest to critical care practitioners.

**Conclusions:** Cardiac troponin I and T, regulatory components of the contractile apparatus, are sensitive indicators of myocardial injury and have become central to the diagnosis of myocardial infarction. The troponins are also released in a number of clinical situations in which thrombotic complications of coronary artery disease and resultant acute myocardial infarction have not occurred. These situations include conditions like pulmonary embolism, sepsis, myocarditis, and acute stroke. Elevated troponins in these conditions are thought to emanate from injured myocardial cells and, in most circumstances, have been associated with adverse outcomes. Practitioners should be mindful of the wide spectrum of diseases that may result in elevated troponin when interpreting these measurements. (Crit Care Med 2007; 35:●●●●)

**Key Words:** diagnostic markers; myocardial injury; critical care; cardiac troponin

The diagnosis of many acute medical conditions relies on diagnostic testing added to the information gained from history and physical examination of the patient. This is certainly true in the assessment of the critically ill, for whom history may be unavailable and the physical examination nondiagnostic. The science of laboratory testing continues to mature, with new markers entering clinical practice and more precise instrumentation reaching the market. The recent introduction and evolution of the cardiac troponins to clinical practice is a case in point.

Excitation-contraction coupling within the cardiac myocytes is triggered by intracellular Ca\(^{++}\) and is thought to occur as interdigitated thick and thin filaments of the sarcomere slide past one another. This process is closely regulated by the troponin complex. Ebashi et al. (1) identified troponins as the Ca\(^{++}\) binding site of the myofibrillar thin filament. Greaser and Gergely (2) demonstrated that the troponin complex varies among three distinct proteins, which were designated troponin T (cTnT), troponin C (cTnC), and troponin I (cTnI). These proteins are phylogenetically quite old, with at least one epitope conserved across the vertebrate phyla (3). The nomenclature for the troponin proteins refer to their functional properties (I for inhibitory, C for calcium binding, and T for tropomyosin binding). All three proteins of the troponin complex interact to varying degrees. Troponin C initiates contraction by binding Ca\(^{++}\) to its N-terminal regulatory site. This binding changes the confirmation of troponin C, signaling troponin I to release its inhibition of actomyosin (4). The vast majority of the cardiac troponins are bound in the contractile apparatus. However, approximately 7% of cTnT and 3–5% of cTnI exist free in the cytosol in cardiac myocytes (5). The cardiac specificity of the troponin C and I proteins has led to their clinical application in the diagnosis of myocardial injury.

Compelling clinical data demonstrating the utility of the troponins in the diagnosis of cardiac ischemia led the European Society of Cardiology and the American College of Cardiology to recommend replacing the traditional myocardial muscle creatine kinase isoenzyme (CK-MB) with cardiac troponins as the preferred diagnostic marker for acute myocardial infarction (MI) (6).

The appropriate application of these diagnostic markers requires an understanding of the basics of interpreting clinical laboratory testing and the clinical conditions associated with elevations of these markers. The knowledge of acute conditions other than acute myocardial infarction that may be associated with troponin release is clinically important.

**Interpreting Clinical Laboratory Tests**

The performance of any laboratory test is described in terms of sensitivity and specificity. Sensitivity in the context of the diagnosis of disease is defined as the percentage of people with the condition in question who test positive (7). Similarly, specificity is defined as the percentage of people free from the disease whose test result is negative. Although high sensitivity and specificity are desirable characteristics for a diagnostic test, these variables do not clearly describe the performance of a test in clinical practice. It is important to realize that sensitivity and specificity are not fixed characteristics of a diagnostic test. Sensitivity and specificity may be affected by the population used to derive the values. If the pop-
Ischemia is required to develop myocardial injury, which leads to myocytes death. Prolonged ischemia of sufficient duration leads to ischemia of the cardiomyocytes. Interventions modifying the value defined as a positive test. Receiver operating characteristic curves are commonly constructed to describe the performance of diagnostic tests through the complete range of positive cut-off values. The area under the receiver operating characteristic curve is an indication of test performance independent of positive cut-off value. Receiver operating characteristic curves for biomarkers of myocardial injury, including the cardiac troponins, have been published for a population of patients evaluated for possible MI.

In addition to the problems with determining sensitivity and specificity described above, the clinician evaluating a test result in a particular patient is really interested in the probability that a patient has or does not have the condition in question, given his or her test result—the so-called positive predictive value (PPV) of the test. By Bayes rule, the predictive value of a test is dependent on the prevalence of the disease in the population, in addition to the specificity and sensitivity of the test.

Thus, a positive test from a patient with very little chance of the disease will not be a strong indication of disease.

Troponin I and T in Myocardial Ischemia

Acute coronary syndrome (ACS) includes unstable angina, non–ST-segment elevation MI, and ST-segment elevation MI. The most common substrate for ACS is an unstable atherosclerotic plaque in a coronary artery that ruptures and exposes thrombogenic material to the blood stream, leading to acute thrombotic obstruction of the vessel (9). This obstruction leads to ischemia of the cardiomyocytes. Prolonged ischemia of sufficient severity leads to myocytes death and the release of biomarkers of cell injury, including troponin I and T. A finite period of ischemia is required to develop myocardial cell death. In most animal models, this period varies from 10 to 20 mins (10).

The traditional diagnosis of MI required fulfilling at least two of three World Health Organization criteria: 1) typical symptoms, 2) typical electrocardiographic changes, or 3) elevated levels of CK-MB. The application of troponin testing to patients presenting with symptoms of acute myocardial ischemia revealed that approximately half of patients not meeting the WHO criteria for MI test positive for cardiac troponin, indicative of myocardial necrosis (11). This observation led to the revised definition of MI, which uses troponin elevation above the 99th percentile of an apparently healthy population. This redefinition of MI has led to an increase in the proportion of ACS patients assigned the diagnosis of MI. Concern that low-risk patients were being labeled as MI using this new definition has been adequately addressed by studies confirming adverse prognosis among those patients meeting the revised definition of MI (12). More than 15 clinical studies have confirmed the increased risk of death or recurrent ischemia in patients with ACS without ST-segment elevation (13). Even very low-level elevations of troponin have clinical relevance. In the TACTICS-TIMI 18 trial (14), elevations of cTnI just above the 99th percentile for the assay were associated with a tripling of the risk of recurrent MI or death.

Cardiac Troponins in Myocarditis and Pericarditis

Both myocarditis and pericarditis may present with precordial chest pain and mimic much of the clinical presentation of MI (15, 16). Myocarditis is an acute inflammatory process that may produce regional wall motion abnormalities. Damaged myocytes release CK-MB and cardiac troponins. Patients with pericarditis often have involvement of the epicardium with myocyte injury. cTnI is elevated in approximately one third of these patients but does not seem to portend a worse prognosis (17, 18).

Cardiac Troponins in Percutaneous Coronary Interventions

Percutaneous coronary intervention has become the preferred reperfusion strategy for most patients with acute ST-segment elevation MI and is employed in many other patients with coronary artery disease (19). As many as 40% of percutaneous coronary intervention patients will have elevated troponin measurements. There is considerable evidence that large increases in biomarkers of myocardial injury are prognostic in this patient population (20, 21). In a study by Brener et al. (21), a normal CK-MB after the procedure was shown to be associated with a mortality of 7.5%, elevations up to three times the upper limit with a mortality of 8%, elevations three to five times the upper limit with a mortality of 11%, elevations five to ten times the upper limit with a mortality of 10.8%, and elevations of greater than ten times the upper limit with a mortality of 29.3%. Prospective data for cardiac troponin measurements after percutaneous coronary intervention have also indicated prognostic importance (22, 23).

Cardiac Troponins in Heart Failure

In a study published by Horwich et al. (24), the prevalence of elevated cTnI was determined for a cohort of heart failure patients without acute MI or myocarditis. A total of 238 patients with advanced heart failure referred for transplant evaluation had cTnI drawn at the time of initial evaluation and were subsequently followed. Baseline cTnI elevations were found in 49.1% of the population, with a mean value of 0.24 ± 1.08 ng/mL. BNP levels were higher among those patient with an elevated cTnI, and pulmonary artery occlusion pressures were higher in this group. cTnI did not discriminate ischemic vs. nonischemic causes for heart failure in this study but did predict declining systolic performance during the follow-up period and doubled mortality. The cause for elevated cTnI in this study remains uncertain. It is intellectually satisfying to assume that progressive loss of myocytes is responsible for the worsening systolic function and mortality and for the detectable cTnI levels; however, reversible injury releasing cytosolic pool troponin may be responsible. Given the association with elevated BNP and pulmonary artery occlusion pressures, it is also tempting to implicate increased wall stress in the pathogenesis. No matter the mechanism of its release, troponin seems to have prognostic implications. The proper clinical use of cTnI measurements in this population, if any, remains to be determined.
Cardiac Troponins in Pulmonary Embolism

Submassive and massive pulmonary embolism lead to right ventricular dysfunction secondary to increased right ventricular wall stress and right ventricular micro-injury, and has been linked to troponin release (25). A dilated right ventricle under increased wall stress will increase right ventricular oxygen demand and may result in right ventricular hypoperfusion and ischemia. The level of troponin leak seems to correlate with right ventricular dysfunction (26, 27). These troponin elevations are typically small, presumably reflective of the volume of myocardium injured. Nonetheless, has troponin release has prognostic implications. Pruszczyn et al. (28) reported on a cohort of 64 patients with proven pulmonary embolism who presented with normal systemic arterial pressures. Half of the population had elevated troponin levels, and all eight in-hospital deaths came from this population. Another six patients with positive troponin required institution of thrombolysis. Positive troponin was the only significant predictor of an adverse hospital course in a multivariate analysis. In an associated editorial, Goldhaber (29) notes that although similar prognostic information may be obtained from echocardiography, the ease and general availability of troponin measurement may be a significant advantage. Kucher et al. (30) reported the incremental value of cTnT measurement and echocardiographic assessment. Multivariate regression techniques were used. The authors concluded that echocardiography and cTnT had incremental value in assessing prognosis for pulmonary embolism patients.

Cardiac Troponins in Renal Insufficiency

Patients with end stage renal disease have a high prevalence of coronary artery disease (as high as 73%) (31) and a high annual mortality from cardiovascular disease (32). For many years, it has been known that CK and CK-MB may be increased in some patients with chronic renal insufficiency (33, 34). Serum troponins have been demonstrated to be elevated in patients with chronic renal disease not thought to have clinical myocardial ischemia (35, 36). This is particularly true for cTnT. Although some would describe these laboratory anormalities as false–positive results, elevated troponin levels predict short-term prognosis even in patients without ACS (37). The mechanism of elevated troponins in renal insufficiency is not clear. However, it seems that reduced clearance is not a likely explanation. The primary troponins are large macromolecules with extra-renal clearance mechanisms. cTnT fragments of smaller size (8–25 kD) have been demonstrated in patients with end-stage renal disease. These fragments are small enough to be cleared by the kidney of patients with normal renal function (38) and may be measured by immunoassays. Decreased clearance of these fragments might raise serum levels of cTnT or prolong the time it remains measurable but does not explain its release in the first place. Some authors have proposed that elevated troponins in this population is the result of ongoing myocyte damage (39). Pathologic data do support the presence of micro-MI, which might elevate troponin and be clinically silent (40, 41). No matter the cause, elevated troponin levels are strongly associated with the long-term risk of death (42, 43).

Cardiac Troponin Elevation in Sepsis

Myocardial contractility depression is a common finding in patients who present with sepsis (44). The cause of myocardial dysfunction in sepsis is not entirely clear, but cytokine production and release of intracellular mediators likely play a role. Serum troponin elevation has been reported in patients with sepsis. Spies et al. (45), in a population of surgical intensive care unit patients, reported on cTnT levels in a group of 26 patients admitted with sepsis. The investigators a priori selected a cut-off cTnT value as abnormal and dichotomized the population above and below this value. Of septic patients in their study, 69% were positive for cTnT. Although the sample is small, no significant differences in baseline characteristics or cause of sepsis between the cTnT-positive and cTnT-negative patients was evident. However the risk of mortality was twice as great in the cTnT-positive patients. cTnI has also been measured. Ammann et al. (46) reported on cTnI measurements in a small group of septic patients (n = 20), 40% of whom were in septic shock. Furthermore, 85% were found to have elevated levels of troponin, with the highest cTnI reported at 15.4 ng/mL.

Cardiac Troponin in Mixed Critical Care Patients

Mortality of adult patients admitted to the intensive care unit is related to organ dysfunction (47). Cardiac dysfunction is present in a significant fraction of these patients. These patients are at increased risk for cardiac ischemia because of underlying coronary artery disease, increased tissue oxygen demands, tachycardia, and other factors (48). In a cohort of 260 patients admitted to an adult intensive care unit (49), 21% had recognized cardiac dysfunction, including MI, unstable angina, and congestive heart failure. These patients had higher Acute Physiology and Chronic Health Evaluation II scores and were significantly older. All patient had cTnI determination. These patients had a greater rate of multiple organ dysfunction and longer hospital lengths of stay. Their hospital mortality rate could not be linked to cTnI levels. The authors performed a multivariate analysis to determine independent predictors of hospital mortality. In this analysis, the development of multiple organ dysfunction, clinically recognized cardiac dysfunction, pulmonary dysfunction, vascular thrombosis, and severe sepsis or septic shock were independently associated with hospital mortality. Cardiac troponin I was not a significant predictor in their models.

Arlati et al. (50) examined a group of patients with sepsis, septic shock, and hypovolemic shock. cTnI was elevated in 74.2% of the patients and was found to correlate with the degree of hypotension in the cohort. In another cohort of 58 critically ill patients without ACS, 55% were positive for cardiac troponin, and positive troponin increased the risk of mortality (51). Those patients admitted with systemic inflammatory response syndrome, sepsis, or septic shock were even more likely to test positive (63%).

Cardiac Troponins in Acute Stroke

Acute stroke is a leading cause of death in Western civilization and is associated with significant disability (52). CK-MB elevations have been previously reported after acute stroke and identified as a prognostic determinant (53). In an observational study from New Zealand, 181 consecutive stroke patients admitted to the medical service of Auckland Hospital during a 9-month period had serum
cTnT measurements determined. cTnT levels were elevated in 17% of acute stroke patients, 40% of whom died. cTnT-negative patients had an in-hospital mortality of only 13% (relative risk, 3.2). Using multivariable modeling, the authors looked at several variables that might predict death. These variables include historical factors, such as the presence of ischemic heart disease and diabetes mellitus, smoking, and impaired renal function, and measures of stroke severity. Only altered level of consciousness at presentation and elevated cTnT were predictive of mortality. Interestingly, severity of stroke by clinical assessment or computed tomography was not clearly associated with increased cTnT. This finding differs from that reported by Chalela et al. (54), who noted an association between National Institutes of Health Stroke Scale and increased cTnI in a retrospective study of 160 patients with acute stroke in whom cTnI was measured. cTnI elevations occurred in ten patients, including two who had electrocardiograms suspicious of ischemia.

The pathogenesis of myocyte damage in stroke is thought to be neurally mediated through abnormal autonomic activity. However, co-existent ACS must also be considered.

Conclusions

Cardiac-specific troponins are sensitive biomarkers of myocardial injury. They are elevated in many clinical syndromes associated with direct myocardial injury, myocardial ischemia, or ventricular strain. In some settings, the assessment of whether an elevated cardiac troponin is the result of a thrombotic complication of coronary artery disease or some other condition can be challenging. Examined from this perspective, one might consider cardiac troponins to be plagued by false-positive results. In each of these clinical conditions, the preponderance of the data support myocardial injury as the source of the elevated troponin, and in most circumstances, elevated cardiac troponins portend a worse prognosis. If one examines elevated cardiac troponins as a marker of myocardial injury, the false-positive rate declines substantially. The clinician using clinical troponin measurements should be mindful of the basic principles of laboratory test interpretation and the conditions that lead to troponin release.

REFERENCES

20. Colombo A, Stankovic G: Nothing is lower than 0, and 3 is closer to 0 than to 5: Medicine is not arithmetic. Eur Heart J 2002; 23:840–842


