

Cardiac troponin in the intensive care unit

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*Presented 25th September, 2009 at CSCI meeting, Ottawa
Dr. Lim was the 2008 Joe Doupe Lecturer*

Clin Invest Med 2009; 32 (5): E405-E410.

Abstract

Purpose: Cardiac troponin is specific to the myocardium and is a useful biomarker for the diagnosis of myocardial infarction. Detection of elevated blood levels of troponin indicates damage to myocardial cells, but does not indicate the mechanism. Causes other than acute coronary syndromes and myocardial infarction can result in troponin elevation and these conditions frequently occur in critically ill patients in the intensive care unit. The interpretation, clinical significance and appropriate management of an elevated troponin measurement in critically ill patients are uncertain.

Source: Studies evaluating the prevalence of troponin elevation among medical-surgical intensive care unit patients, and its prognostic significance with regards to adverse outcomes will be reviewed.

Conclusions: Cardiac troponin elevation is common and observed in 40 to 50% of critically ill medical and surgical patients. Elevated levels appear to identify patients at increased risk for death in the intensive care unit or hospital setting. This finding, and its relation to myocardial infarction and acute coronary syndromes, requires prospective study to better understand the implications for diagnosis and management.

Myocardial infarction is a major cause of morbidity and mortality worldwide. The ability to diagnose myocardial infarction accurately is, therefore, critical so that treatments aimed at decreasing death and disability can be implemented. Myocardial cell death results in the release of proteins into the blood which can act as biomarkers for myocardial infarction. Car-

diac troponin (cTn) I and T are regulatory proteins that control the interaction of actin and myosin, the proteins involved in myocardial cell contraction. Injury to myocardial cells results in release of cTn into the blood approximately 4 to 6 hr following acute myocardial infarction, with peak levels occurring at 12 to 24 hr and elevated levels remaining for up to 7 to 10 days.¹ Clearance of cTn from the circulation occurs predominantly through the kidneys.^{2,3} Because cTnI and cTnT are specific to the myocardium, they have become the preferred biomarkers for the diagnosis of acute myocardial infarction.

In patients presenting with suspected myocardial infarction, detection of cTn in blood (plasma) samples can be done using commercially available immunoassays. The high sensitivity of these assays for detecting myocardial damage has resulted in the widespread recommendation that clinicians measure cTn in patients suspected of having myocardial ischemia or infarction.⁴ The International Federation of Clinical Chemistry Committee on Standardization of Markers of Cardiac Damage have published quality specifications for cTn to establish uniform criteria to evaluate the analytical qualities and clinical performance of the commercially available assays.⁵

However, the diagnosis of acute myocardial infarction has evolved as more sensitive and specific cardiac biomarkers of myocardial necrosis and in-

creasingly precise imaging techniques capable of detecting very small infarcts have been introduced into clinical practice. These developments resulted in a redefinition of myocardial infarction, published in 2000 following a consensus conference supported by The Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC).⁴ This document was updated to a universal definition of myocardial infarction in 2007, with the support of the American Heart Association (AHA)/World Heart Federation (WHF).⁶

Acute myocardial infarction is defined by a rise and/or fall of cTn and at least one of: ischemic symptoms, development of new ischemic electrocardiogram (ECG) changes or pathologic Q waves on the ECG, or imaging evidence of myocardial infarction (new loss of viable myocardium or a new wall motion abnormality).⁶ Importantly, according to the universal definition, any amount of myocardial necrosis resulting from ischemia is considered an infarct. This has resulted in the classification of many patients as having myocardial infarction who would have previously received a diagnosis of unstable angina, based on evidence from randomized trials demonstrating that patients with increased cTn levels are at risk of ischemic death, and these patients benefit from antiplatelet therapy and invasive strategies (i.e., percutaneous coronary intervention).⁷

Causes of elevated cardiac troponin levels

Although elevated levels of cTn indicate that myocardial necrosis has occurred, this does not indicate the mechanism resulting in necrosis. In the absence of ischemic symptoms, other etiologies of myocardial necrosis need to be sought (Table 1). In addition to acute coronary syndromes/myocardial infarction, conditions resulting in an imbalance between myocardial supply and demand ('demand ischemia'), direct damage to the myocardium, or myocardial strain are all recognized to result in increased cTn levels.^{8,9} The mechanism in these conditions is variable. For exam-

ple, right heart strain and myocardial necrosis in the right ventricle is believed to account for the cTn elevation observed in patients with pulmonary embolism. In sepsis, systemic hypotension resulting in suboptimal coronary artery blood flow and cytokine release are hypothesized to result in cTn leakage from myocardial cells.^{10,11}

Recognition of these different causes for cTn elevation led to the classification of different types of myocardial infarction: type 1 (spontaneous myocardial infarction related to ischemia due to a primary coronary event); type 2 (myocardial infarction secondary to supply-demand imbalance); type 3 (sudden unexpected cardiac death); type 4a (myocardial infarction associated with percutaneous coronary interven-

TABLE 1. Conditions associated with increased cardiac troponin other than acute coronary syndromes (Adapted from Jeremias⁹ and Ammann²³)

Demand ischemia
Sepsis / systemic inflammatory response syndrome
Hypotension
Hypovolemia
Supraventricular tachycardia / atrial fibrillation
Left ventricular hypertrophy
Coronary vasospasm
Intracranial hemorrhage or stroke
Ingestion of sympathomimetic agents
Severe anemia
Direct myocardial damage
Cardiac contusion
Direct current cardioversion, defibrillator shocks
Cardiac infiltrative disorders (amyloidosis)
Chemotherapy
Myocarditis
Pericarditis
Cardiac transplantation
Cardiac surgery
Cardiac procedures (closure of atrial septal defect, percutaneous coronary intervention, radiofrequency ablation)
Myocardial strain
Congestive heart failure
Cardiomyopathy (dilated, hypertrophic)
Pulmonary embolism
Pulmonary hypertension
Chronic obstructive pulmonary disease
Strenuous exercise
Other
Chronic renal insufficiency

tion); type 4b (myocardial infarction associated with stent thrombosis) and type 5 (myocardial infarction associated with coronary artery bypass grafting).⁶

The prognostic significance of elevated cardiac troponin levels

Myocardial infarction was redefined to include cTn, not only because elevated cTn levels are useful in the diagnosis of myocardial infarction, but because elevated cTn levels have predictive value in identifying patients who are at risk of adverse outcomes. Patients with acute coronary syndromes (ST-elevation and non ST-elevation myocardial infarction and unstable angina) and elevated cTn have an increased risk of death and recurrent ischemic events compared with patients with cTn levels below the detection limit. Furthermore, increasing cTn levels are associated with proportionate increases in mortality.¹²⁻¹⁴ Consequently, cTn measurement in patients with an acute coronary syndrome is a useful marker for risk stratification.

Elevated cardiac troponin in the intensive care unit

Although much is understood about the epidemiology, diagnosis and management of acute coronary syndromes and myocardial infarction, the occurrence of this syndrome in critically ill patients in the intensive care unit (ICU) remains uncertain. The ease with which cTn can be measured has resulted in its frequent use as a screening test; cTn is often measured as a routine laboratory test on ICU admission or following an episode of hypotension or arrhythmia to assess for myocardial infarction as a possible cause of, or to assess for damage resulting from, these clinical events.

However there is ongoing uncertainty regarding the epidemiology, interpretation and management of an elevated cTn measurement in critically ill patients for several reasons. First, there is a general tendency in the ICU to prioritize other aspects in the care of the critically ill patient and to attend to the issues that precipitated the ICU admission. Consequently, in many

cases, the cause of the cTn elevation is not investigated, making both the frequency with which these conditions occur and the etiology of cTn elevation in the ICU uncertain. Second, conditions other than acute coronary syndromes may result in elevated cTn levels, and these conditions are commonly observed in the ICU setting. It is likely that these conditions represent many of the observed cTn elevations, yet distinguishing these conditions from myocardial infarction is difficult. This is due to the challenge of diagnosing myocardial infarction in the ICU setting where patients are frequently intubated, sedated, and receiving analgesic medications making it unlikely for these patients to experience or communicate ischemic symptoms. Lastly, it is unclear if an elevated cTn measurement in critically ill patients carries prognostic significance as in the acute coronary syndrome population. Whether cTn can be used to identify high risk patients who may warrant increased monitoring or benefit from therapies that may improve outcomes in the ICU requires investigation.

The epidemiology of elevated cardiac troponin in the intensive care unit

Previous studies have demonstrated that elevated cTn levels are observed in up to 50% of critically ill patients in the ICU^{15,16}, and many patients do not have evidence of clinically important atherosclerotic coronary artery disease.^{17,18} In our single centre medical-surgical ICU, a retrospective chart review of 198 consecutive patients admitted for at least 72 hr found that 72 patients (42%) had elevated cTnI levels.¹⁹ In patients who had 12-lead ECGs performed, 38 patients (22%) met criteria for myocardial infarction based on an elevated cTnI and at least one ECG having ischemic changes and 34 patients (20%) had elevated cTnI without ischemic ECG changes (elevated cTn only).

Subsequently, cTn elevation was studied prospectively in our ICU.²⁰ Among 115 consecutive critically ill patients admitted to the ICU, 93 (81%) of these

patients had at least one cTn measurement and one 12-lead ECG recording. Forty-four (47%) of these patients had at least one elevated cTn measurement and 24 (26%) met criteria for myocardial infarction, based on duplicate adjudication of ECGs.

Although the majority of the patients in the prospective study described above underwent ECG recording and cTn measurements, a more precise estimate of the frequency of cTn elevation can only be done using screening investigations. Hence, a prospective screening study was performed where all consecutive patients admitted to our ICU were enrolled in the study and underwent screening.²¹ Screening cTnT and 12-lead ECGs were completed daily for the first week in ICU, then on alternate days for one month, followed by weekly for a maximum of 2 months or until ICU death or discharge. Among 103 consecutive critically ill patients, we found that 52 (51%) had an elevated cTn measurement; 37 (36%) of these patients had ischemic ECG changes meeting diagnostic criteria for myocardial infarction and 15 (15%) patients had an elevated cTn in the absence of ischemic ECG changes.

A systematic review which included a total of 20 observational studies of 3,278 patients found that an elevated cTn measurement was found in 12 – 85% of critically ill patients with the median frequency of 43% (interquartile range [IQR] 21 – 59%).²² The median frequency of an elevated cTn measurement was 53% (IQR 16 – 63%) among medical ICU patients, 43% (IQR 29 – 64%) in mixed medical-surgical ICU patients, and 32% (IQR 16 – 61%) in surgical-trauma ICU patients. Elevated cTn levels were most frequently found among patients admitted with sepsis or septic shock, with a median frequency of 60% (IQR 50 – 80%).

In summary, based on retrospective, prospective and screening studies evaluating the prevalence of cTn elevation in medical-surgical critically ill patients, cTn elevation is common and observed in approximately 40 to 50% of patients. Using an elevated cTn level and ischemic ECG changes as criteria for myo-

cardial infarction, approximately 20 to 25% of patients appear to have myocardial infarction complicating their ICU admission.

The prognostic significance of elevated cardiac troponin in the intensive care unit

We also evaluated whether cTn elevation was predictive of adverse outcomes in the above-listed studies. In the retrospective study, elevated cTnI was associated with ICU, but not hospital, mortality based on univariable analysis (19). There was no significant difference in hospital or ICU length of stay in patients meeting criteria for myocardial infarction compared to patients with cTn elevation alone. However, this study was not powered to detect differences between groups.

In contrast, in the prospective study, patients who met criteria for myocardial infarction (elevated cTnT and ischemic ECG changes) had a higher mortality in the ICU compared to patients who did not meet such criteria (38% vs. 18%, $P = 0.050$) as well as higher hospital mortality (50% vs. 22%, $P = 0.010$).²⁰ After adjusting for factors that are known to influence mortality including the Acute Physiology and Chronic Health Evaluation (APACHE) II score (a measure of illness severity) and the need for inotropes or vaso-pressors, myocardial infarction was an independent predictor of hospital mortality with an odds ratio (OR) of 3.2, 95% confidence interval (CI) 1.0 – 10.0). In this study, the presence of an elevated cTn level without ischemic ECG changes was not independently predictive of ICU or hospital mortality.

Last, based on screening cTn measurements and 12-lead ECG recordings, critically ill patients with at least one measurement of an elevated cTn had increased hospital mortality (OR 27.3, 95% CI 1.7 – 449.4), after adjusting for illness severity and advanced life support.²¹ Myocardial infarction was not associated with ICU or hospital mortality in multivariable analysis.

In the systematic review addressing the issue of prognostic significance of cTn elevation, an adjusted analysis of 1,706 patients from 6 observational studies found that an elevated cTn was associated with increased mortality (OR 2.5, 95% CI 1.9 – 3.4; $P < 0.0001$). In the unadjusted analysis of 1,019 patients from 8 studies, an elevated cTn was associated with an increased length of ICU stay of 3.0 days (95% CI 1.0 – 5.1; $P = 0.004$), and an increased length of hospital stay of 2.2 days (95% CI -0.6 – 4.9; $P = 0.12$).

In summary, an elevated cTn level with or without ischemic ECG changes was variably found to be predictive of adverse outcomes. It is notable that these studies were relatively small and were not powered to demonstrate differences between groups. Consequently, it remains uncertain whether an elevated cTn measurement confers prognostic importance in critically ill patients regardless of the presence of myocardial infarction or acute coronary syndromes. A large prospective study is needed to definitively address this question.

Screening for myocardial infarction in the intensive care unit

The utility of screening for myocardial infarction in the ICU remains uncertain. Our prospective screening study found that 37 patients (36%) met diagnostic criteria for myocardial infarction.²⁰ The ICU team diagnosed only 18 (18%) of these patients as having myocardial infarction based on clinical grounds. Screening with cTn measurements and ECG recordings detected an additional 23 patients as having myocardial infarction, reflecting 62% of the infarctions ultimately diagnosed. However, patients with myocardial infarction diagnosed by the ICU team had similar outcomes when compared to patients with myocardial infarction detected by screening alone. Although intriguing, a large prospective study is required to address the issue of the utility of screening in the intensive care unit.

Conclusion

Cardiac troponin has proved to be a useful biomarker for detecting myocardial necrosis and thus improved the ability to diagnose, and risk-stratify, patients with myocardial infarction. Unique aspects in the ICU setting have made the interpretation of an elevated cTn and the diagnosis of myocardial infarction challenging, yet it is apparent that cTn elevation is not only common, but appears to carry prognostic significance. Prospective studies are required to better understand the interpretation and the management implications in the ICU.

Acknowledgements

I would like to acknowledge Dr. Deborah Cook for her mentorship and supervision of this work, Dr. PJ Devereaux and Dr. Mark Crowther for their contributions, the St. Joseph's Hospital Critical Care Research Team for their hard work (Andrea Tkaczyk, Ellen McDonald, France Clarke) and Diane Heels-Ansdell for her statistical expertise. This work was funded by the Canadian Institutes for Health Research, Regional Medical Associates (Hamilton), Thrombosis Interest Group of Canada and the Ontario Association of Medical Laboratories.

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