REVIEW

Elevation of cardiac troponin I indicates more than myocardial ischemia

John P. Higgins, MD, MPhil*
Johanna A. Higgins, MD†

From the Departments of *Cardiovascular Medicine and Surgery, and †Medicine, University of Oklahoma, St. John Medical Center, Tulsa, Okla.

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Abstract

Elevated cardiac troponin I (cTnI) levels in patients hospitalized with chest pain often lead to a diagnosis of acute myocardial infarction (MI) or unstable angina. However, as we describe in this review, this finding may occur in other conditions, leading to an incorrect diagnosis and other, sometimes invasive, tests. We review briefly cTnI, its release and detection. We describe the various conditions that may cause an elevated cTnI level and give possible explanations for these findings, and we offer some guidelines for diagnosis in patients with an elevated cTnI.

Résumé

On diagnostique souvent un infarctus aigu du myocarde (IAM) ou une angine instable à cause de concentrations élevées de troponine cardiaque I (cTnI) chez des patients hospitalisés pour des douleurs à la poitrine. Comme nous le décrivons toutefois dans cette analyse critique, de tels résultats peuvent indiquer d'autres problèmes et risquent d'entraîner un diagnostic erroné et d'autres examens parfois effractifs. Nous passons brièvement en revue la cTnI, son mode de libération et la façon de la détecter. Nous décrivons les diverses conditions qui peuvent faire monter la concentration de cTnI et nous en proposons des explications possibles. Nous offrons des guides de diagnostic pour les patients qui présentent une concentration élevée de cTnI.

Introduction

Physicians often observe elevated cardiac troponin I (cTnI) levels in hospitalized patients, and in most cases make the diagnosis of acute coronary syndrome (ACS), either acute myocardial infarction (MI) or unstable angina. However, this may be a false-positive finding, sometimes a spurious nonsustained elevation leading to an incorrect diagnosis, thus subjecting the patient to additional cardiac evaluation and invasive testing.[1]

The clinical utility of a diagnostic test is directly related to the test's ability to reflect the underlying pathology of the disease in question. Cardiac troponin I is specific for heart-muscle damage. The false-positive findings are related to the accuracy of the test as well as the provisional diagnosis. Unfortunately, multiple assays exist for cTnI with varying sensitivities, specificities and cut-off points for acute MI. There are no uniform standards.

In this paper we provide a brief review of cTnI, its release and detection assays and list the various conditions that may result in elevated cTnI levels and possible explanations for these elevations. Finally, we furnish some guidelines for the probable etiology underlying a patient's elevated cTnI level.

Materials and methods

We reviewed the English-language scientific literature by searching the MEDLINE and EMBASE databases for the period 1976–2003. Key words used

in the search included "troponin I" and "heart diseases." The bibliographies of articles were also searched; in addition, Web sites containing published papers were examined for pertinent information. Original investigations and reviews dealing with elevated cTnI levels in various patient populations were selected. Also included were papers covering the topics of cTnI elevations secondary to myocardial damage or ischemia. Data quality was determined by publication in peer-reviewed literature; data extraction was performed by one author.

Cardiac troponin I

Cardiac troponin I (cTnI), a 24-kDa protein, is the inhibitory subunit of troponin, part of the thin filament cardiac contractile apparatus, troponin–tropomyosin complex.[2,3] The troponin portion of this complex consists of 3 subunits: cardiac troponin T (cTnT), which binds to tropomyosin and facilitates contraction; cTnI, which binds to actin and inhibits actin–myosin interactions; and troponin C (TnC), which binds to calcium ions.[4]

Although troponins are present in skeletal muscle, myocardium contains cTnT and cTnI isoforms that are not present in skeletal muscles (i.e., the amino acid sequences of cardiac TnT and TnI differ from those found in skeletal muscle), allowing separation by immunologic techniques.[5–7] Troponin I has 3 isoforms: cardiac muscle (cTnI), and fast-twitch skeletal muscle and slow-twitch skeletal muscle (both designated skeletal or sTnI); each isoform is encoded by an individual gene. In contrast, TnC has the identical amino acid sequence in cardiac and slow-twitch skeletal muscle, which excludes it from being a meaningful cardiac-specific marker.[8]

Located specifically in the mammalian heart, cTnI is never expressed in skeletal muscle.[8] In the heart, sTnI is the dominant isoform during fetal development and in the neonatal period. During the first 9 months of life, a transition from sTnI to cTnI occurs; thus, cTnI measurement may be unreliable for assessment of neonatal and perinatal cardiac damage.[9] However, cTnI has been detected in a subgroup of small-for-gestational-age newborns, probably reflecting myocardial injury before birth.[10]

Although most of the cTnI is incorporated in the troponin complex, 3%–8% is dissolved in the myocyte cytosol.[11–14] There is a 13-fold greater concentration of cTnI than creatine kinase-MB isoenzyme (CK-MB) in the heart.[15]

Release and degradation

Many factors determine the rate of appearance in the blood of a marker such as troponin I, including molecular weight, charge, binding to intra- or extracellular components, intra- or extracellular degradation and clearance by way of the kidney, liver or reticuloendothelial system.[16]

Myocytes that undergo insult (ischemic or other) recover, succumb or hibernate.[16] Apoptosis (cell death) and necrosis of myocytes both occur in every case of acute MI.[17] Interestingly, one group studying the release and detection of troponin I found that only 15 minutes of mild ischemia was enough to cause the release of cTnI degradation products, an interval too brief to induce cell death.[18]

Following an acute MI, the dominant form of cTnI released is the binary complex form, cTnI–TnC, with smaller amounts of the ternary cTnT–cTnI–TnC complex.[19] Approximately 3%–10% is released as the free molecule.[20] Because most troponin I released is in the form of a complex with troponin T or troponin C, or both, as well as undergoing proteolytic degradation, very little of what is identified in the blood by conventional immunoassays comprises free, unaltered protein.[16,18,20]

The N-terminal and C-terminal ends have the strongest antigenic regions;[21–23] the 31-amino-acid sequence on the N-terminal region is specific for cTnI.[21,24,25] Following release, the N-terminal and C-terminal ends are rapidly degraded. The most stable region of the molecule is the central region, which is protected by bound TnC. This makes epitopes in the central region "invisible" to antibodies early on, yet better detected in late samples (5–7 d after release). Many degradation products exist; one study, using Western blot-direct serum analysis, was able to detect intact cTnI and a spectrum of up to 11 modified products in the serum of patients with acute MI.[26]

After acute MI, approximately 50% of patients have a rise in their cTnI within 3–4 hours, with a peak at 10–24 hours.[6,27–33] Levels remain elevated for

4–10 d because of a gradual degradation of myofibrils and release of the troponin complex.[32,34] This results in troponin I having a wider diagnostic window than CK-MB.[35] Sensitivity and specificity of cTnI for CK-MB measured acute MI in the current generation assays are 90%–98% and 94%–100% respectively.[11,35–39] Further, in skeletal muscle injury, neither cTnI nor the messenger RNA for cTnI is detectable or expressed (i.e., there is no "return to ontogeny").[15,40,41]

Not much is known about the clearance of cTnI. Significantly shorter half-life has been noted in non-Q-wave infarcts (mean [and SD] 6.8 [5.6] h) versus Q-wave infarcts (20.4 [10.7] h) ($p < 0.01$), which may reflect differentials in the extent of myocardial necrosis as well as release kinetics.[42] Another study suggested that sustained elevations of cTnI may be related to continuous release from myofibrils in the troponin complex rather than prolonged serum half-life.[43] Thus, determination of clearance rates may be difficult since the duration of elevation is related to the size of the infarct as well as extent of reperfusion, with larger infarcts being associated with more sustained elevations.

In patients with end-stage renal disease suffering an acute MI, there was a nonsignificant trend toward a longer half-life (1.48 [0.77] d) than in patients with normal renal function (1.08 [0.63] d).[44] Dialysis reduces cTnI levels, probably owing to adherence of the cTnI molecule to the dialysis membrane; therefore samples should be drawn before dialysis.[45,46]

Commercial assays

There are at least 18 different assays for cTnI, which vary in assay type, reagents used, clinical performance characteristics, monoclonal antibodies, epitope recognition used and cut-off level for acute MI.[19,47] Thus, a comparison of absolute values is limited, as there is no standardized cTnI measuring system.[48] In addition, the National Academy of Clinical Biochemists suggests 2 cut-off levels: a low abnormal value (minor myocardial injury or unstable angina) and a higher value (acute MI by World Health Organization criteria).[49] The American College of Cardiology and European Society of Cardiology (ACC/ESC) in a joint position paper recommended an increased value for cTnI defined as a measurement exceeding the 99th percentile of a reference control group, with an acceptable imprecision (coefficient of variation) at the 99th percentile defined as ≤ 10%.[50]

Early generation assays were based on polyclonal antibodies to TnI, and lacked specificity.[32,51] For instance, ultraendurance exercise often led to elevations in cTnI in these assays; 20% of marathoners in the 1995 Boston Marathon, had an increased levels of antibodies in assays for cTnI or cTnT.[52] Current monoclonal assays target more than one antigenic epitope and are more specific.[23,28–30] In current assays, cTnI levels are still increased in ultraendurance exercise, although generally not with as high a percentage as the earlier assays.[53,54] For instance, in a study of 23 athletes participating in an Ironman Triathlon, 2 subjects (9%) had marked increases in both cTnT (0.15 and 0.33 ng/mL) and cTnI (2.09 and 4.44 ng/mL); 4 additional subjects (17%) had moderate increases in cTnT (0.04–0.05 ng/mL) but no detectable cTnI.[55] In addition, wall motion abnormalities and decreases in ejection fraction (EF) were detected in these subjects (echocardiograms done before and after the race). Another study of 19 marathon runners found statistically different median prerace, postrace and 24- to 48-hour concentrations of cTnI, which were 0.0, 0.4 and 0.0 ng/mL, respectively ($p = 0.01$).[56] Of note, cTnI values returned to normal in 24–48 hours. A further study of 38 well-trained cyclists doing an Alpine bicycle ultramarathon echoed these findings: levels of cTnI, negative in all athletes before competition, increased to greater than 0.05 ng/mL in 13 cyclists (34%) immediately after, and were significantly decreased the following day.[57]

Thus, ultraendurance exercise may result in subclinical myocardial damage as indicated by biochemical cardiac-specific markers and echocardiography. One hypothesis for elevated cTnI with ultraendurance exercise is that high concentrations of catecholamines may induce coronary vasospasm and endothelial injury resulting in myocyte injury after exercise.[58] However, the cellular events underlying this troponin release or damage, its prognostic importance and whether it reflects temporary or permanent dysfunction or damage are currently unknown.

Diagnostic assays for cTnI have resulted in up to

20-fold differences in measured values; these discrepancies may result from the release of the numerous cTnI modification products that are present and released from ischemic myocardium.[26,59] Various cut-off levels as well as the differing specificities of antibodies used to detect free or complexed cTnI may explain some of the interassay variability.[4,60] To maximize specificity, Falahati and associates[61] suggested defining the normal range as the mean and 2 standard deviations and adding to this the coefficient of variation. The ACC/ESC guideline[50] recommends a 99th percentile with a maximum of 10% coefficient of variation cut-off, which is somewhat different from the definition of the National Academy of Clinical Biochemists.

Conditions associated with elevated cardiac troponin I

A number of conditions have been associated with elevated cTnI levels (Table 1[4,40,55–57,62–134]).

Reasons for elevated cardiac troponin I

Current or recent acute coronary syndrome

Because of the greater ability of cTnI to detect smaller areas of myocardial damage, micronecrosis or "microinfarcts," patients may have elevated cTnI levels yet normal CK-MB levels.[135,136] Studies have confirmed that damage need only occur to a small number of cardiomyocytes to elevate the cTnI.[49,137–139] Further, new contrast-enhanced magnetic resonance imaging techniques allow direct visualization of myonecrosis and thus provide an anatomical correlate to biochemical evidence of myocardial injury.[140] It has been estimated that in about 30% of patients with a previous diagnosis of unstable angina according to normal CK-MB levels, non-ST-elevation MI is now being diagnosed.[141]

Patients with ACS secondary to coronary vasospasm (positive ergonovine provocation test) may also have elevated cTnI levels;[77] this is probably secondary to myonecrosis from prolonged ischemia.

In the case of an ACS 3–10 days previously, there has already been myocyte necrosis with release of cTnI or CK-MB into the circulation. However, CK-

Table 1: Reasons for and conditions associated with elevated cardiac troponin I levels

Condition/reason	References
Related to myocardial damage	
Acute coronary syndromes — myocardial infarction and unstable angina	4, 62, 63
Acute graft failure in cardiac transplant patients	64–66
Cardiac amyloidosis	67
Cardiac contusion	68, 69
Cardioversion	70, 71
Cerebrovascular accident	72, 73
Chemotherapy	74–76
Coronary vasospasm	77
Heart failure, acute	78, 79
Heart failure, chronic, ischemic, nonischemic	80–85
Human immunodeficiency virus disease	86
Implantable cardioverter defibrillator shocks	87
Interventional closure of atrial septal defects	88
Left ventricular hypertrophy	89
Myocarditis	90, 91
Pericardial effusion	69, 92
Pericarditis	79
Percutaneous coronary intervention	93, 94
Pulmonary embolism	95, 96
Postoperative, cardiac and noncardiac surgery	97, 98
Radiofrequency ablation	99
Scorpion envenomation	100, 101
Sepsis and septic shock	102–106
Subarachnoid hemorrhage	107–109
Tachycardia	110
Ultraendurance exercise (marathon, triathlon)	55–57, 111
Potential analytical causes	
Assay cross-reactivity	
Alkaline phosphatase, elevated	112
Antibody crossreactivity	113, 114
Bilirubin, elevated	115
Cirrhosis of liver	116
Hemolysis	115, 117
Heterophile antibody	113, 118–121
Rheumatoid arthritis, rheumatoid factor	119, 121–123
Decreased clearance	40, 119–121,
Renal failure, acute and chronic	124–133
Miscellaneous	
Central nervous system disorders	86
Hematologic malignant disease	75
Labour and delivery	134
Pre-eclampsia	89

MB levels may have already peaked and returned to reference levels.[35] Due to its longer window of elevation, cTnI may be detectable for up to 10 days following ACS.[34] In this situation, a steadily declining cTnI level would occur.

Patients with unstable angina without infarction may have normal CK-MB levels yet troponins exceeding the upper limits of normal; this possibly reflects low-level or smoldering necrosis, which does increase the likelihood of a subsequent acute coronary event.[16,141] Of practical value, patients who are troponin-positive benefit more from intravenous glycoprotein IIb/IIIa inhibitors, the low-molecular-weight heparin enoxaparin, and an early invasive strategy than those who are troponin-negative.[4,79,142]

Possible explanations for false-negative results in patients with ultimately proven infarction include the possibility that dead (apoptotic) myocytes do not release intracellular enzymes; also, complete lack of washout due to total occlusion of an infarct-related artery and absence of collateral flow can occur.[16]

Sepsis and septic shock

In sepsis and septic shock, various loading conditions on the heart as well as systemic inflammation may lead to myocardial dysfunction and cTnI release.[104,143] In various series, 31%–80% of patients in sepsis or septic shock have documented elevations of cTnI.[102–106]

In a study comparing 20 patients with sepsis, septic shock or systemic inflammatory response syndrome and controls, 85% of those with sepsis showed elevated cTnI levels (median 0.57 ng/mL, ranging from 0.17–15.4 ng/mL), whereas no patient in the control group (no coronary artery disease or myocarditis) showed elevation.[106] In addition, in 5 patients with elevated cTnI levels who died, 4 had normal coronary arteries; further coronary angiography and stress echocardiography ruled out significant coronary artery disease in 5 other patients. Thus, 59% of cTnI patients had no evidence of significant coronary artery disease. Interestingly, 41% of cTnI-positive patients had evidence of infection due to *Streptococcus pneumoniae*; no cTnI-negative or control patient showed evidence of this infection. This study suggests that at least in some patients, serum cTnI values might be an indicator for toxic and inflammatory damage rather than ischemic injury to the heart. Possibilities for such damage include direct effects of bacterial microorganisms, such as bacterial myocarditis, and indirect effects, such as cytokine-mediated inflammatory response (e.g., tumour necrosis factor-α, interleukin-1) affecting myocyte cell permeability to macromolecules, endotoxin effects, myocardial depressant substance and ischemic damage due to elevated oxygen consumption, prolonged hypotension or inotropic agents.[106,144–146]

In a study of 209 critically ill patients in medical and respiratory intensive care units who underwent daily cTnI measurements, cTnI was elevated in 15% of measurements, most of which represented clinically unrecognized cardiac injury.[102] This finding was more common in young patients and in black people. Mortality in patients with myocardial injury that was recognized (42%) or unrecognized (40%) was higher than in those without myocardial injury (15%, $p < 0.001$). Patients with cardiac injury were more frequently hypotensive (75% v. 50%; $p = 0.007$) and in need of mechanical ventilation (66% v. 27%; $p < 0.001$) and had longer stays in the intensive care unit (5.3 v. 3.1 d; $p < 0.007$) than patients without cardiac injury in this study.

Further evidence that reversible myocardial injury or depression may occur in sepsis includes patients with elevated cTnI levels who survived having normalization of left ventricular function.[147,148] Wu[149] has hypothesized that irreversible damage to the myocyte cell membrane causes an initial release of cytosol troponin followed by the gradual release of myofibril-bound troponin complexes; in contrast, in reversible damage, as seen in sepsis, oxygen deficits cause degradation of free troponin, and release of various factors that might lead to increased permeability of the membrane to macromolecules and leakage of degraded troponin without myocyte necrosis. In addition, no bound troponin complex should be released in the latter situation. Thus, the troponin peak is smaller and short lived, possibly representing detection by the serum assay of troponin I cytoplasmic degradation products released into the circulation.

Other nonischemic diagnoses

Several studies have now suggested that cTnI or cTnI fragments may be released from myocardial cells under circumstances other than cell necrosis, that is, without disruption of myocardial cell membranes.[1] In this manner, cTnI may act as a marker of myocardial stretch or strain, either acutely, such as in pulmonary embolism, septic shock and acute heart failure, or chronically, as in chronic cardiac, renal and hepatic failure.[150] Evidence supporting this hypothesis comes from a number of studies.

In a study of patients with nonischemic heart failure, New York Heart Association class II–IV, with normal coronary angiograms and after exclusion of myocardiopathies, cTnI level correlated with levels of a left ventricular wall strain biologic marker, B-type natriuretic peptide.[84] It should be noted that this was a supersensitive experimental assay that differs from most currently available assays. These authors suggested that cTnI assay may be a promising biochemical method for detecting cardiac myolysis in heart failure, independent of the presence of coronary artery disease, and that elevations of cTnI could be in part related to severely increased left ventricular wall strain and remodelling. Others have found that troponin levels coupled with B-type natriuretic peptide levels appear to be prognostic markers in congestive heart failure.[151]

In a study of 27 patients with moderate heart failure, New York Heart Association class II–III, mean EF 0.31, and controls, patients with symptomatic heart failure had an increased cTnI level (> 0.10 ng/mL) after symptom-limited bicycle exercise.[48] This suggests that minor exercise-induced myocardial damage may be occurring. The only parameter significantly related to the peak exercise cTnI level was the baseline cTnI level, which could imply different levels of apoptosis or protein turnover in moderate heart failure.[48] However, others have found that stress testing does not induce the release of troponin I.[152]

Myocardial strain or excessive wall tension and the inability of the myocardium to adapt, with its attendant myofibrillary damage or myolysis in viable cells, may lead to release of cTnI or antigenic portions of the cTnI protein.[16,150] Increased preload or afterload, without ischemia, may lead to the release of cTnI degradation products, which would be detected by some assays.[153] Interestingly, the increased calcium responsiveness of the contractile apparatus in end-stage failing human hearts appears to result from the complex interplay between changes in the phosphorylation status of myosin light chain 2 and cTnI.[154]

Myocardial stunning, a form of ischemic injury that occurs with transient ischemia followed by reestablishment of flow and results in reversible cardiac dysfunction, may be secondary to proteolysis of the myofilament protein cTnI.[155,156] Cardiomyocyte apoptosis is present in many cardiac disease states, including heart failure and ischemic heart disease. Apoptosis (preserved membrane integrity) in addition to necrosis (loss of membrane integrity) may lead to the release of cTnI.[157] Apoptosis is associated with the activation of caspases that mediate the cleavage of vital structural proteins. Furthermore, in cardiac myocytes, apoptosis may not be complete, allowing the cells to persist for a prolonged period within the myocardium. Therefore, activation of apoptotic pathways may lead to contractile dysfunction prior to cell death.[158] Other animal studies suggest that release of troponin I can occur in the absence of irreversible ischemia;[159] it should be noted that these are in-vitro studies and this phenomenon has not been documented in vivo.

Infiltrative disorders and their depositions in and around the myocytes may lead to cTnI release. In a case report of a patient with amyloidosis, electron microscopy revealed myocyte compression injury from amyloid infiltration, probably precipitating the cTnI release.[67]

Heart transplant recipients can have chronically elevated cTnI levels, suggesting ongoing myocardial stress or damage, some of which may be immunologic. In a study of 110 consecutive patients who received a heart transplant and survived at least 1 year after transplantation, cTnI levels remained persistently elevated during the first 12 months in 56 patients (51%). Persistently elevated cTnI levels were associated with increasing fibrin deposits in microvasculature and cardiomyocytes ($p < 0.001$), subsequent development of coronary artery disease (odds ratio, 4.3; 95% confidence interval [CI],

1.8–10.1; $p < 0.001$), and graft failure (odds ratio, 3.4; 95% CI, 1.2–9.7; $p = 0.02$).[66]

In a study of 204 patients (mean [and SD] age 45 [10] yr) with aggressive malignant disease, the cTnI plasma concentration was measured after every single cycle of high-dose chemotherapy.[76] According to the cTnI value (≤ 0.4 ng/mL or > 0.4 ng/mL), patients were divided into a troponin-positive (cTnI+, $n = 65$) and a troponin-negative (cTnI–, $n = 139$) group. In the cTnI– group, echocardiographic left ventricular EF progressively decreased after high-dose chemotherapy, reaching a maximal reduction after 3 months; however, myocardial depression was transient and no longer detectable at later follow-up. By contrast, in the cTnI+ group EF reduction was more marked and still evident at the end of the follow-up. In cTnI+ patients, a close relationship between the short-term cTnI increment and the greatest EF reduction was found ($r = –0.87$, $p < 0.001$). Thus, the elevation of cTnI in patients who received high-dose chemotherapy for aggressive malignant tumours accurately predicts the development of future EF depression. In this setting, cTnI can be considered a sensitive and reliable marker of acute minor myocardial damage with relevant clinical and prognostic implications.

Assay cross-reactivity

Several reports of assay components cross-reacting with rheumatoid factor, heterophile antibody, bilirubin or hemolysis have been published.[113,118–123,159] This problem appears to occur more often with the microparticle enzyme immunoassay technique used in several assays. When suspected, taking several simultaneous samples and testing them at laboratories using different assays may help to differentiate a true elevation from a cross-reaction.

Acute and chronic renal failure

Elevations in cTnI levels occur in 4%–17% of patients with renal failure; acute renal failure and chronic renal failure, especially patients on hemodialysis, can affect cTnI levels.[40,119–121,125–131,133] Not all cTnI assays are elevated in asymptomatic hemodialysis patients.[124] Even though elevations of troponin I in this patient population (especially asymptomatic patients) are not always related to ACS, the elevation may reflect ongoing myositis. Also, these elevations still are predictive of outcome; and cTnI is more sensitive and specific than CK-MB. In end-stage renal disease patients admitted with suspected myocardial injury according to their history, and physical examination or electrocardiography, or both, the sensitivity and specificity for ACS were 44% and 56% for CK-MB and 94% and 100% for cTnI respectively.[160]

Patterns of elevation

In an individual subject, measurement of enzyme or marker released from the heart must be related to the subject's baseline value over time. Such diagnosis based on serial determinations rather than a single "normal" or "abnormal" value will reflect the dynamic nature of the changes in marker concentration and better capture the evolving event.[16]

Therefore, serial cTnI measurements may help to clarify the reason for elevation, and reflect the kinetics of the injury stimulus; spurious elevations are often isolated. Following acute MI, there is a characteristic, time-dependent, typical rise and gradual fall in cTnI levels over a period of days, often associated with a more rapid rise and fall in CK-MB levels or myoglobin levels.[1,31,119,161,162] In addition, ischemic symptoms, electrocardiographic changes or recent coronary intervention should be present to establish an acute, evolving or recent acute MI.[50] A rapid rise and fall over a period of hours is not consistent with a hypothesis of irreversible myonecrosis.[149]

Clinical and prognostic value

Like most tests, cTnI levels lose their positive predictive value when used in a broad population, many of whom do not have the underlying disorder for which the test is designed (i.e., myocardial cell necrosis). Several studies confirm this.

In one study involving 1000 consecutive patients presenting to an urban hospital emergency room, 112 patients had elevated cTnI levels (> 0.6 ng/mL); 50 (45%) of the 112 had a noncardiac cause for the elevation of cTnI.[1] In another study of 102 consecu-

tive hospital patients with elevated cTnI levels (> 0.6 ng/mL), 35 (34%) did not have an ACS. Their diagnoses included nonischemic dilated cardiomyopathy, muscular disorders, central nervous system disorders, human immunodeficiency virus disease, chronic renal failure, sepsis, lung diseases and endocrine disorders.[86] The mean (and SD) value of serum cTnI in patients with diseases other than ACS was significantly lower than in those with ACS (2.0 [1.9] ng/mL v. 24.7 [28.2] ng/mL; $p < 0.001$). Those with a history of chest pain or previous acute MI were more likely to have an ACS ($p < 0.001$ for both). However, given the high coefficient of variation, cTnI elevations in a large number of the patients who had noncardiac causes may in fact have represented analytical variation rather than being truly representative of cardiac damage. In both these studies, the cut-off point for an elevated cTnI level appears to be low, which may have increased sensitivity at the expense of specificity.

In a heterogeneous group of patients with chest pain, 1929 consecutive patients admitted from the emergency department for possible acute MI underwent serial myocardial marker sampling of cTnI and creatine kinase, CK-MB, over an 8-hour period.[163] Patients with ST-segment elevation were excluded. End points included acute MI, death, significant complications (e.g., cardiac or respiratory arrest, intra-aortic balloon pump, pulmonary artery catheter or pacemaker placement, revascularization or inotropic infusion) and significant disease. Events occurred in 513 (27%) of the 1929 patients evaluated: acute MI in 175 (9.1%) and death in 34 (1.8%); an additional 248 patients (13%) without acute MI had complications, and 323 (17%) without acute MI had significant disease. Sensitivity of cTnI for acute MI was high (96%). Patients without acute MI who were cTnI-positive were more likely to have complications (43% v. 12%) or significant disease (41% v. 17%) than those who were cTnI-negative; however, the sensitivity of cTnI for these 2 end points was low (14% and 21% respectively). Predictive values were unchanged after excluding patients with ischemia indicated on the electrocardiogram. Thus, troponin I had a high sensitivity for CK-MB acute MI when used as part of a rapid rule-in protocol; however, the sensitivity for other end points was low. Use of cTnI alone failed to identify the majority of patients who had either significant disease or complications.

In patients presenting with a history or electrocardiogram consistent with ischemia, the test has a higher positive predictive value. In addition, it furnishes prognostic information. In the Thrombolysis in Myocardial Infarction 11B study, 681 patients were admitted with electrocardiographic evidence of ischemia or biochemical evidence of infarction without ST-segment elevation. Patients with cTnI of 0.10 ng/mL or more on admission or at any time in the first 24 hours were at increased risk for death or acute MI by 43 days (relative risk, 2.2–3.0; $p < 0.001$), even among those with CK-MB concentrations within the reference interval.[164]

In patients with unstable angina or non-Q-wave MI, cTnI can help to predict which patients have a high probability of failing medical therapy and thus may aid in identifying patients for early cardiac catheterization.[165] Patterns of cTnI enzyme changes may also have a prognostic value in patients with unstable angina even with cTnI levels below the acute MI cut-off level.[161] Patients with unstable angina who have significant release of cTnI have evidence of more complex lesions on coronary angiography.[166] If cTnI is positive in such ACS patients, the risk of death or acute MI is significantly higher by a factor of 2–5.[167–169] Furthermore, left ventricular EF is significantly and inversely correlated to peak cTnI, reflecting infarct size.[42,170]

If the peak cTnI at least 6 hours after the onset of chest pain is in the normal range and the electrocardiogram is normal or unchanged, it is very unlikely that the patient will die or have a nonfatal MI in the next 30 days.[39,171,172]

In those with elevated cTnI levels but no CK-MB acute MI who were originally considered to have unstable angina, does the positive cTnI test still provide prognostic information? In most cases, yes. In one study of patients presenting with chest pain, baseline troponin elevation without CK-MB elevation was associated with increased risk for early and short-term adverse outcomes.[173] In another study of patients with sepsis or septic shock, those with elevated cTnI levels had worse left ventricular function, and higher rates of morbidity and mortality.[149] In patients having acute pulmonary embolism, those with high troponin

concentrations (cTnI > 1.5 ng/mL) compared with those with only moderately elevated levels (cTnI 0.07–1.5 ng/mL) had a higher overall mortality and complicated in-hospital course.[174]

In a study of 78 patients with heart failure (45 inpatients, 33 outpatients) who were followed up prospectively for 12 months, plasma cTnI of 0.3 ng/mL or greater was detected in 46%.[85] Levels of cTnI were strongly associated with other clinical indicators of heart failure severity and remained independent predictors of prognosis after adjustment for these factors, suggesting a potential role for cTnI in the clinical management of such patients.

The use of markers of vascular inflammation and ventricular failure together with cTnI measurement may aid in diagnosis and therapeutic decision-making.[4] Such a multimarker approach measuring cTnI, C-reactive protein, B-type natriuretic peptide, tumour necrosis factor-α and interleukin-6 in patients with suspected ACS may best reflect the underlying ischemic disease, in addition to guiding therapy and furnishing prognostic information.[175,176]

Conclusions

Variations in assays for cTnI measurement are myriad, and cut-off points for determination of acute MI are also variable. "Blanket" screening of all patients or an elevated cTnI level in a patient with low clinical suspicion may not indicate acute MI or other ACS, and careful examination is warranted. Although elevated cTnI levels are highly sensitive and specific for myocardial damage, they do not always reflect underlying ischemic heart disease.[73,110]

Leakage of cTnI from the myocardium may represent reversible or irreversible injury to the contractile apparatus of the myocyte.[25,149] Causes of such injury may include ischemia, inflammation, infection, the presence of toxins, excessive myocyte tension and infiltrative diseases.[90] Such conditions either place extra biochemical stress (such as elevated inflammatory cytokines or sepsis) or mechanical stress (such as decompensated heart failure or acute pulmonary embolism) on the myocardium. Because of this, patterns of elevation as well as other concomitant laboratory tests may help differentiate between the etiologies of elevated cTnI.

Irrespective of the nature of the cause, release of cTnI reflects a myocardial leak and has prognostic value in terms of associated risk of death regardless of the mechanism of myocardial damage such as ACS, pulmonary embolism, heart failure, sepsis or trauma.[3,85,173] Additionally, elevations of cTnI in patients with renal disease, although less specific, does provide prognostic information. In asymptomatic patients with end-stage renal disease, cTnI is less helpful in diagnosis and prognosis, although it is still superior in sensitivity and specificity to CK-MB assays.[46,127,160,177]

Thus, the proper interpretation of cTnI for assessing myocardial damage needs to consider the clinical context of the individual patient for whom it was ordered.

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Medical subject headings: biological markers; coronary vasospasm; heart diseases; heart injuries; kidney failure, chronic; myocardial infarction; myocardial ischemia; review; troponin I

Correspondence to: Dr. John P. Higgins, Associate Professor of Medicine, University of Oklahoma, c/o Muskogee Heart Center, Inc., 3340 West Okmulgee St., Muskogee, OK 74401, USA; fax 918 772-1233; jphboston@hotmail.com