A review of troponins in ischemic heart disease and other conditions

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Measuring cardiac troponin (cTn) I and T levels is currently considered to be a cornerstone for making the diagnosis of acute coronary syndrome (ACS).

Based on current literature, cTnI and cTnT are known to be very sensitive and specific for myocardial damage, regardless of the underlying cause. Lately, it has been found that cTns can be elevated and reflect worse prognoses in many situations where ACS is excluded. Such information can affect the validity of cTns as markers for ACS without classic symptoms. This may call for a revision of the troponin cutoff values to make a diagnosis of ACS. Furthermore, it opens a new field of study to determine appropriate management of patients with elevated cTn levels in whom ACS has been excluded.

Key Words: *Coronary artery disease; Management; Nonischemic origin of troponin; Prognosis; Troponin*

The patient who describes chest pain to the primary care physician represents an immediate challenge. Although chest pain can be a sign of a fatal heart attack, it can also stem from many other benign conditions. Creatine kinase (CK) and lactate dehydrogenase have been found to be nonspecific markers for acute coronary syndrome (ACS). In addition, troponins are highly accepted as more specific and sensitive markers that carry serious and fatal prognoses, even at low levels. More attention should be paid when making the diagnosis of ACS based on elevated troponin levels, because they are found to be elevated in many other conditions. The present review discusses the prognostic importance of elevated troponins level in ACS and other conditions, and emphasizes the need for more data to standardize the use of troponins in the diagnosis of ACS and to find appropriate management for many other conditions where ACS is excluded.

REVIEW OF TROPONINS

Pathophysiology of troponins

Troponins are protein complexes that modulate the contraction and relaxation of striated muscle. They are composed of three subunits: troponin I, T and C (TnI, TnT and TnC).

TnT binds to tropomyosin, thereby attaching the troponin complex to the thin filament. TnC binds to calcium ions, thereby exposing myosin-binding sites so that contraction can take place. TnI binds to actin and inhibits actin and myosin interaction (1). Troponins are found in skeletal and cardiac muscle, but not in smooth muscle. Approximately 7% of cardiac TnT (cTnT) and 3.5% of cTnI exist freely in the cardiac myocyte cytoplasm. The rest is bound to the sarcomere. cTnT content per gram of myocardium is roughly twice that of cTnI, and cTnI is smaller than cTnT (23.5 kDa versus 33 kDa) (1-3).

Studies have failed to find any cTnI outside the heart at any neonatal stage; in contrast, cTnT is expressed to a minor extent in skeletal muscle (4-6). These fetal isoforms are not detected by today's techniques of immunohistochemistry and polymerase chain reaction (6,7).

Cardiac and skeletal troponins are encoded by different genes in the two types of muscle, yielding proteins that are immunologically distinct when identified by monoclonal antibodies. Because the amino acid sequence of TnC is the same in the two types of muscle, its detection is not useful (1,8).

Measuring troponin levels and interpretation of their elevation

Although cTnI and cTnT are specific markers for myocardial damage, different assays have different degrees of sensitivity and specificity. First-generation assays can mistakenly detect skeletal muscle troponin. cTnT assays are produced by a single manufacturer, and so tend to have relatively uniform cutoff concentrations. In contrast, cTnI assays, which use different kits to detect different epitopes, have different cutoff concentrations and standardizations (1).

The upper reference limit of cTn level is defined as the 97.5th percentile of the values measured in the normal control population (1). According to the American College of Cardiology (ACC) and the European Society of Cardiology (ESC), acute myocardial infarction (MI) should be diagnosed if cTnI or cTnT levels are higher than the 99th percentile with a coefficient of variation (a measure of how consistently an assay is able to produce the same result for the same sample) of 10% or less (very difficult to achieve), detected within 24 h after the index clinical event (1,9). Values in the intermediate zone suggest minor myocardial damage (1).

Macroinfarction is considered when the cTn level is higher than the 99th percentile and when the CK-MB fraction is elevated in the presence of ischemic symptoms. Microinfarction is considered when the cTn level is higher than the 99th percentile with a normal CK-MB fraction level.

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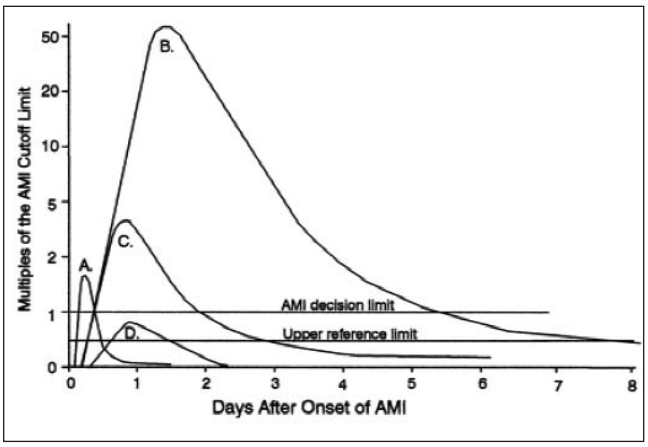

Figure 1) *Time course of blood levels of cardiac markers after acute coronary syndromes.* **A** *Myoglobulin or creatine kinase (CK)-MB isoforms.* **B** *Troponin.* **C** *Total CK-MB after acute myocardial infarction (AMI).* **D** *Troponin after unstable angina pectoris (the cutoff for AMI is at 1)*

According to the ACC/ESC definition of an acute MI, virtually all patients with unstable angina pectoris who have elevated cTns meet the criteria for an acute non-ST elevation MI (30% of previously diagnosed unstable angina pectoris cases are now considered to be non-ST elevation MI) (1).

The ACC/ECC joint committee disagreed with the suggestion of using two cutoff values, one for MI and one for unstable angina with myocardial necrosis. The committee believed it lacked a scientific basis and would lead to increased heterogeneity of diagnoses due to the different cutoff values used by different laboratory kits. In addition, patients with elevated cTn levels have similar risk profiles and coronary artery pathophysiology to patients who fit the diagnosis of non-Q wave MI (10).

After acute MI, cTnI and cTnT levels increase (first, by the release of the free cytosol fraction) after 6 h, are detected in the blood after 12 h, peak after one to two days, and reach the pre-MI normal levels after 10 days.

CK-MB isoforms (MB1 and MB2) are the most sensitive and specific markers for early (within 6 h) diagnosis of acute MI (11) (Figure 1). Their use is only indicated if positive results would change therapy. Their role has become less clear after the improvement of troponin assays (12).

Prognostic values of elevated troponin levels

Any elevation of cTn levels in patients with ST elevation MI, non-ST elevation MI, unstable angina, congestive heart failure and chronic kidney insufficiency portends a worse outcome (13-17).

Patients with elevated cTns have a higher cardiac mortality rate, are more likely to have coronary thrombi, showers of emboli in the coronary microvasculature, and depressed ventricular function (1).

Recently, it has been found that elevations in cTn levels from causes other than ischemic heart disease (Table 1) are associated with worse prognoses (17,18).

Prognostic value in unstable angina pectoris and non-ST elevation MI

According to the Fast Revascularization during InStability in CAD (FRISC) II trial (19), any elevation of cTnT in the noninvasive arm of the study increased the likelihood of severe three-vessel disease, an unstable plaque with thrombus and downstream microembolization, and impairment of coronary flow, all of which were associated with an increased risk for reinfarction and death. Higher serum troponin levels were associated with a greater likelihood of persistent occlusion of the culprit vessel, a reduced left ventricle ejection fraction and increased mortality (19).

In a meta-analysis of seven clinical trials and 19 cohort studies of patients with non-ST elevation MI (20), the mortality rate was found to be higher for patients with either a positive cTnT test at 28 weeks or a positive cTnI test at 10 weeks.

In another meta-analysis of 21 studies (21), patients with a non-ST elevation MI and a positive cTnT or cTnI level had a higher cardiac mortality rate in both short-term (30 days) and long-term (five months to three years) follow-up.

Similar results were observed in the Thrombolysis in Myocardial Infarction (TIMI) IIIB (22) and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) IIa trials (23).

Studies (14,24) also showed a reduction in both mortality and recurrent MI in patients with elevated troponin levels who were treated with delteparin or enoxaparin. No benefit was observed in patients without elevated troponin levels when treated with either drug. Only clopidogrel seems to be beneficial in patients regardless of troponin level elevations (25).

Prognostic value in ST elevation MI

The GUSTO-III trial studied patients with ST elevation MI who received thrombolytic therapy. Patients with elevated cTnT (greater than 0.2 ng/mL) at admission had a significantly higher 30-day mortality (26).

A pooled analysis (21) of 21 studies involving 18,982 patients with ACS found that elevated levels of cTnI or cTnT were associated with increased risk of cardiac death or reinfarction (at 30 days and at five months to three years) in both ST elevation MI and non-ST elevation MI.

A study (27) of 140 patients with ST elevation MI who underwent percutaneous coronary intervention (PCI) found that admission cTnT levels of more than 0.1 ng/mL were associated with persistent reduced blood flow (TIMI flow less than 3), higher incidence of no-reflow and higher mortality at 30 days and nine months.

Troponin and infarct size

Infarct size correlates with the troponin level measured at 72 h (more with cTnT than with cTnI) (28,29).

Troponin and reinfarction

Substantial re-elevation of cTnI level was found to occur after reinfarction (30), supporting the conclusion that changes in troponin levels are adequate to diagnose reinfarction (31,32).

Prognostic value after PCI

Troponin level elevation above the 99th percentile after PCI is indicative of cardiac cell injury and MI (33,34). The mechanism of this elevation is unknown (35,36). Some have suggested that increases of more than 25% are caused by the procedure itself, but the primary ACS that necessitated the PCI could still cause such an increase (12).

TABLE 1
Causes of cardiac troponin elevation other than ischemic heart disease

Presumed mechanisms	Diagnoses
Myocardial stress	Congestive heart failure, hypertension with left ventricular hypertrophy, aortic valve disease, hypertrophic obstructive cardiomyopathy with significant left ventricular hypertrophy, strenuous exercise, pulmonary embolism, emphysema and asthma
Direct myocardial damage	Cardiac contusion, direct current cardioversion, ablation and toxins (adriamycin, 5-fluorouracil and transtuzumab)
Demand ischemia	Sepsis, systemic inflammatory response syndrome, burn, hypotension, hypovolemia, left ventricular hypertrophy, sympathomimetic agents and supraventricular tachycardia
Inflammation	Myocarditis, pericarditis, Kawasaki disease and parvovirus B19 infection
Infiltrative diseases	Amyloidosis, hemochromatosis, sarcoidosis and scleroderma
Immunological (autoantibodies, cytokines) causes	Cardiac transplantation, systemic lupus erythematosus, burn and sepsis
Unknown mechanism	Chronic renal insufficiency, neurological diseases (cerebrovascular accident, subarachnoid bleed)

Prognostic value after open-heart surgery
In patients with coronary artery bypass surgery, cTnT was a highly sensitive and specific marker for perioperative MI (37). Elevated troponin levels were associated with increased short- and long-term mortality in patients who had undergone vascular surgery. Even small rises in serum troponin concentration after vascular surgery were associated with increased risk (38). Irrespective of the mechanism, the higher the value after surgery, the worse the prognosis (39,40).

Causes of cTn elevation other than ischemic heart disease
It has been found that troponin release can be caused not only by irreversible cell damage, but also by reversible damage (41).

Among 1000 consecutive patients presenting to the emergency department of a large urban hospital, cTnI level was elevated on admission in 112 patients, 45% of whom had a final diagnosis other than ACS (42).

Another study (43) of 102 patients with a cTnI level of more than 0.6 ng/mL, 66% of patients had a final diagnosis of ACS. Of the 34% of patients who did not have ACS, the elevation in troponin level was secondary to a variety of causes including electrical cardioversion, muscular disorders, chronic renal insufficiency, sepsis, lung disease, hypothyroidism, systemic lupus erythematosus and gynecomastia. The study also indicated that the higher the cTnI level, the higher the positive predictive value was for the diagnosis of ACS (43).

Ammann and colleagues (44) evaluated 58 patients who were admitted to the intensive care unit for diagnoses other than ACS. Among the 55% of patients with elevated troponin levels, tumour necrosis factore, interleukin-6 and C-reactive protein levels were significantly higher than among patients with undetectable troponin. Mortality was fourfold higher in the troponin-positive group. Coronary artery disease (CAD) was excluded in 72% of troponin-positive patients. Thus, troponin elevation among intensive care unit patients with sepsis or systemic inflammatory response syndrome and with or without shock is often seen without significant CAD, and carries a worse prognosis (41).

Mechanisms of cTn elevation in situations other than ACS
Any myocardial stress can lead to troponin release (10,45,46) (Table 1). Other factors causing troponin release include sympathetic discharge; cytokine release such as heat shock protein and tumour necrosis factor-alpha; and infections and autoantibodies such as in immune disease after cardiac transplantation and systemic lupus erythematosus (10,45,47).

Prognosis of cTn elevation in situations other than ischemic heart disease
Short- and/or long-term survival is impaired among patients with troponin elevation in many different clinical settings, including congestive heart failure, sepsis, pulmonary disease, acute pulmonary embolism, pericarditis, myocarditis, immune response after heart transplantation and renal insufficiency (18,41,48).

Management of cTns elevation in situations other than ischemic heart disease
Management is still unknown, but one has to exclude any possible underlying ischemic heart disease by clinical evaluation, electrocardiography, echocardiography, cardiac stress testing and, if necessary, coronary angiography.

Treatment should target underlying disorders. All patients should be on acetylsalicylic acid if there is no apparent contraindication. In addition, angiotensin-converting enzyme inhibitors, beta-blockers and statins should be used as indicated. There are no current data to support the use of antithrombotic or antiplatelet agents, or an early PCI in this group (41).

False-positive and false-negative results
Fibrin can confound the assay for cTnI, so heparinized plasma for this assay is preferred (27). Heterophilic antibodies and cross-reacting human antimouse antibodies in patients who make or receive antibodies can lead to false-positive results. Heparin can bind to troponin and lead to lower levels (dose-dependent) (49).

Autoantibodies against the central portion of cTnI can delay the diagnosis and/or result in false-negative results (50).

Elevation of cTns in renal insufficiency
Cardiovascular disease accounts for roughly 50% of deaths in patients with chronic renal failure. Patients with renal failure are at higher risk for silent ischemia (17%) and atypical clinical presentation. Electrocardiogram results are not reliable, because ST segment changes are difficult to interpret secondary to electrolyte imbalances, left ventricular hypertrophy and medications.

TABLE 2
Hypothesized causes of cardiac troponin (cTn) elevation and possible underlying mechanisms in patients with renal insufficiency

Cause	Possible underlying mechanism
Uremic skeletal myopathy and/or re-expression of cTnT	Skeletal muscle injury caused by toxic uremic effect
Silent myocardial necrosis, recurrent silent microinfarctions, congestive heart failure, and left ventricular hypertrophy (more common in end-stage renal disease)	Perfusion defects, abnormal coronary vasomotor activity, and endothelial dysfunction due to oxidative stress and inflammation
Cardiac injury	Calcium and oxalate deposition
Episodes of hypotension	Fluid problems during hemodialysis
Decreased clearance of cTns	Defect of excretion process in renal failure

Using a second-generation assay, cTnT was found to be elevated in up to 53% of patients with renal failure with no clinical evidence of acute myocardial necrosis (51).

Despite using the latest generation assays and higher cutoff values (higher than the 99th percentile) cTnT and cTnI were positive in 82% and 6% of dialysis patients, respectively (results changed according to the cutoff values) (15).

Reasons for discordance between cTnI and cTnT elevation in chronic renal failure

Free cTnT (7%) is more abundant than free cTnI (3.5%) for each given myocyte cytoplasm. Furthermore, the cTnT content per gram is roughly twice that of cTnI. cTnI level decreased by up to 86% from pre- to postdialysis, possibly because it may adsorb to the dialysis membrane; however, cTnT levels tend to increase after dialysis, possibly due to hemoconcentration. Finally, cTnI undergoes more postrelease modifications (phosphorylation, proteolysis and oxidation) than cTnT (51).

Mechanism of cTn elevation in patients with renal insufficiency

The exact mechanism is still unknown (51-57) (Table 2). It is less likely due to decreased clearance of cTns, because patients with renal disease have the same clearance rate of troponin levels as patients without renal disease after ACS. Troponin levels remain elevated even after kidney transplantation (51).

Prognostic values of cTns in asymptomatic patients with end-stage renal disease

Serum elevation of cTn levels is highly prognostic for both short- and long-term outcomes in symptomatic and asymptomatic patients.

There is increasing evidence that elevation in serum cTnI and cTnT levels in stable asymptomatic patients with end-stage renal disease is predictive of worse long-term cardiovascular outcomes (15). The reason for this correlation is unknown, although a correlation between increased troponin levels and diffuse CAD in those patients has been reported (58,59).

A prospective study of 733 asymptomatic patients with end-stage renal disease showed that increased levels of both cTnT and cTnI were associated with increased risk of mortality at two years. Adjusted relative risks of death were two- to fivefold higher among those with increases in cTnT and cTnI values (as defined by the 99th percentile values of 0.01 μg/L and 0.1 μg/L for cTnT and cTnI, respectively) (15).

A study (16) of 107 hemodialysis patients found that elevation in cTnT was associated with an almost sevenfold increase in risk of death after two years.

Similar association has been reported in asymptomatic patients with chronic kidney disease who are not dialysis-dependent (60).

Prognostic values of cTns in symptomatic patients with end-stage renal disease

Elevation in cTnT levels may also be highly prognostic for both short- and long-term outcomes among patients with renal insufficiency who present with ACS.

Studying cTnT levels in the GUSTO-IV trial showed that increased cTnT levels are associated with a small but significant increased risk of MI or death in both patient groups of normal and low creatinine clearance (most patients had mild to moderate renal dysfunction and only 2% had creatinine clearance of less than 10%, so it is uncertain for patients with end-stage renal disease) (61).

Those patients had more severe coronary atherosclerosis, higher rates of restenosis and higher periprocedural morbidity and mortality (51).

Accuracy of elevated cTnT and cTnI levels in patients with end-stage renal disease

A number of studies have reported a large percentage of false-positive elevations of serum cTnT in patients with end-stage renal disease (15,62,63) up to 14 times above normal in one patient (64). cTnI is less likely to be associated with false-positive results in patients with end-stage renal disease (62,65). A higher troponin threshold was proposed as diagnostic of myocardial ischemia in patients with chronic renal insufficiency (66). Serial measurements, preferably of cTnI, and if not available, of cTnT and CK-MB, are suggested to diagnose ACS.

Management of patients with renal insufficiency and high cTn levels

There are no specific guidelines to date for managing such patients. A sequential rise in serum troponin is consistent with new myocardial damage in patients with renal insufficiency. Coronary angiography is still the gold standard for diagnosis of ACS in patients with end-stage renal disease.

It is reasonable to use acetylsalicylic acid, beta-blockers and angiotensin-converting enzyme inhibitors if not contraindicated (51). Recent data have shown effectiveness and safety of tirofiban in patients with mild to moderate renal insufficiency (51).

CONCLUSIONS

One should not make the diagnosis of ACS based solely on the presence of increased levels of cTns, because they can be increased by other factors.

The use of pretest probability when measuring cTns is helpful in making the diagnosis of ACS.

Mild elevation of cTnT or cTnI levels, even in patients without evidence of ischemic heart disease, carries important prognostic value, and should be managed appropriately.

Subsequent cTn level measurement in patients with renal failure and elevated cTn levels is important to differentiate acute from chronic events. In both symptomatic and asymptomatic patients, elevated cTn levels imply worse prognoses and should be managed appropriately.

More effort should be given to standardizing the use of both cTnI and cTnT in the diagnosis of ACS, taking into consideration the other causes of troponin elevation.

More studies are needed to establish the management of patients with elevated cTns in the absence of ischemic heart disease and in asymptomatic patients with renal failure.

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