Elevated Serum Cardiac Troponin in Non-acute Coronary Syndrome

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ABSTRACT

Cardiac troponins (CTn) are the most sensitive and specific biochemical markers of myocardial injury and risk stratification. The assay for troponin T (cTnI) is standardized, and results obtained from different institutions are comparable. This is not the case with troponin I (cTnT), and clinicians should be aware that each institution must analyze and standardize its own results. Elevated cTn levels indicate cardiac injury, but do not define the mechanical injury. The differentiation of cTn elevation caused by coronary events from those not related to an acute coronary syndrome (ACS) is tiresome, at times vexing, and often costly. Elevation of cTn in non-ACS is a marker of increased cardiac and all-cause morbidity and mortality. The cause of these elevations may involve serious medical conditions that require meticulous diagnostic evaluation and aggressive therapy. At present, there are no guidelines to treat patients with elevated troponin levels and no coronary disease. The current strategy of treatment of patients with elevated troponin and non-ACS involves treating the underlying causes.

Key words: acute coronary syndrome, non-acute coronary syndrome, troponin I, troponin T, non-acute coronary syndrome troponin elevation

Introduction

Myocardial necrosis signified by troponin is not necessarily due to an acute coronary syndrome (ACS), and many diseases, such as sepsis, pulmonary embolism, heart failure (HF), and renal failure can be associated with an elevated troponin level.[1]

Cardiac troponin (cTn) are highly specific cardiac markers that are extremely valuable and sensitive in the diagnosis of myocardial necrosis[2] and risk stratification.[3] Despite its clear usefulness, some problems still exist with cTn analysis and interpretation, especially at the lower limits of elevation.[4]

Cardiac Troponin Assay

The skeletal and cardiac isoforms of troponin T (cTnI) and troponin I (cTnT) are distinct and detected by monoclonal antibody-based assays currently in use[5] (Table 1). For all intents and purposes cTnI and cTnT provide comparable information, except in patients with renal failure.

However, there are some differences in the biological characteristics of cTnI and cTnT, which are as follows:

A. Variation in commercially available cTn assays: There is only 1 manufacturer for the cTnT assay, since it is patent protected. And there are now 4 generations of cTnT assay; each new generation has improved precision and lower detectable limits. However, there are approximately 20 cTnI assay types employing different reagents, methods of calibration, and clinical performance characteristics.[6,7]
B. Controversy regarding the upper limit of normal: The America College of Cardiology (ACC)/European Society of Cardiology (ESC) committee recommends using the 99th percentile of a reference control group. However, there is no standard in selecting the reference population. Systemic screening via physical examination for cardiovascular disease in this reference population is rare, and screening with echocardiography or stress testing is almost nonexistent.[8]
C. Assay impression: Precision usually is measured by the coefficient of variability (CV: defined as the standard deviation over the sample mean multiplied by 100 and reported as a percentage). The CV is reported by manufacturers and usually obtained by analyzing samples in the same assay run. The ACC/ESC guidelines recommend a CV of $<10\%$ at the 99th percentile of the reference range for the diagnosis of myocardial infarction (MI). It is generally believed that no assay may actually approach this sensitivity.[9]
D. Choice of cut off limits: In 2000, the ACC/ESC recommended use of the 99th percentile of reference control group with an acceptable imprecision (CV defined as $<10\%$) as a cut off limit for diagnosis of MI.[1] Because no assay achieves this precision, some investigators recommend using the lowest value at which a CV of 10% can be achieved.[10,11]

False Positive Results

The term false positive troponin should be restricted to analytical issues. Several reports indicate that cTnI assay components cross-react with rheumatoid factors, heterophile antibodies, fibrin clots, bilirubins, or products of hemolysis[12,13,14] (Table 2).

The Concept of Demand Ischemia

Demand ischemia without significant coronary artery disease refers to a mismatch between myocardial oxygen

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TABLE 1: Differences between cardiac troponin I and T assays

	Cardiac Troponin I	Cardiac Troponin T
False positive due to cross-reactivity with assays	Present in heterophilic antibodies, rheumatoid factor, fibrin clots, microparticles, and hemolysis.	Present with early-generation assays in diseases that involve skeletal muscle regeneration (e.g., Duchenne muscular dystrophy). Clinically significant negative interference with grossly hemolyzed samples.
Available assays	Several manufacturers	1 manufacturer, 4 generations
Standardization of assays	No standardization between assays, results cannot be compared across different assays.	Good standardization, results can be compared among different centers.

TABLE 2: Analytical causes of false positive troponins

–Rhabdomyolysis in the first and second generation
–Heterophilic antibodies
–Rheumatoid factor
–Fibrin clot
–Microparticles
–Analyzer or analyte malfunction

demand and supply in the absence of flow limiting epicardial stenosis. Myocardial oxygen demand and serum troponins are increased in a number of clinical settings: sepsis, septic shock, and systemic inflammatory response syndrome (SIRS)[15,16,17] (Table 3), hypotension or hypovolemia,[18] noncardiac critically ill patients presenting to the emergency department,[19] and atrial fibrillation or other tachyarrhythmias.[20,21]

Simultaneously, myocardial oxygen delivery may be reduced from a reduced coronary perfusion due to tachycardia and decreased oxygen delivery to the heart.

Non-ACS Related Elevation of Cardiac Troponin

1. Acute Pulmonary Embolism (PE): The acute right ventricular strains secondary to increase in pulmonary artery resistance is the cause for troponin elevation in PE.[22] Studies investigating the release of kinetics of cTnT in patients with PE showed that the peak cTnT was lower and persisted for a shorter period of time compared with cTnT values in acute myocardial infarction (AMI).[23]

   Cardiac troponins T (cTn) have emerged as important prognostic tools for risk stratification of patients with PE. Giannitsis et al. showed that troponin positive patients ($\geq$0.1 ng/ml) were at increased risk for a complicated in-hospital course, including death, prolonged hypotension, cardiogenic shock, and need for resuscitation.[24]

   In patients with moderate PE, defined by hemodynamic stability and right ventricular dysfunction, elevated cTn may help in guiding therapeutic management. It has been shown that patients with right ventricular dysfunction determined by echocardiography are at an increased risk of adverse clinical outcome.[25]

   This risk is 10-fold higher in the presence of elevated cTn (>0.04 ng/ml), justifying a more aggressive treatment approach such as thrombolysis or embolectomy.[26]
2. Acute and Chronic HF: Elevated cTn in HF is associated with decreases in left ventricular ejection fraction, and correlates with the severity of heart failure and prognosis. The aggravation of HF, ischemic or nonischemic, results from progressive myocyte loss caused by necrosis and apoptosis.[27] In chronic stage HF, elevated cTnI values were found in 15%–23% of cases (>0.1 ng/ml).[28,29] The presence of cTn in HF predicts poorer short-term and long-term outcomes. Patients with increased troponin values have significantly lower ejection fraction, higher clinical grading of HF (New York Heart Association [NYHA] functional class), and greater mortality.[30]
3. Cardioversion, Ablation, and Cardiac Arrest: Elective electrical cardioversion in most patients does not result in troponin elevation.[31,32] When present, elevations are mild.[33,34] Elevations are common in patients with cardiac arrest who undergo direct-current shock (often multiple) or prolonged resuscitation, or both.[34,35] Substantial elevation should suggest the presence of myocardial injury.
4. Sepsis/Septic Shock and SIRS: Troponin elevations in patients with sepsis are common.[17,36] The mechanism of elevation of troponin in septic patients is unclear. One reason for the release of cTn from damaged myocardial cells might be an oxygen supply-demand mismatch of the myocardium. In addition, local and circulating inflammatory markers, including tumor necrosis factor, interleukin-6, and bacterial

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TABLE 3: Examples of reported elevations of cardiac troponin

Ischemic cardiac injury	
Sympathomimetics	–Cocaine
	–Catecholamine storm — head injury, stroke, intracerebral bleed
Pulmonary embolus	–Presumed right heart strain or hypoxia
Coronary artery spasm	–Small percentage of patients only
Coronary artery embolism	–Clot
	–Air
	–CABG
Coronary artery inflammation with microvascular occlusion	–Vasculitides
	–Connective tissue disease
	–SLE
End-stage renal failure	–More severe CAD but 50% have normal coronaries
Rhythm disturbances	–Prolonged tachyarrhythmia or bradyarrhythmia with IHD
	–Supraventricular tachycardia
Acute heart failure	–Only if caused by IHD
Direct coronary artery trauma	
Extreme endurance exercise	–Extreme marathons — wall motion abnormalities
	–Extreme training — cTn+re deaths presumed to be caused by extreme oxygen debt producing ischemia
Nonischemic cardiac injury	
Known causes of myocarditis	–Infection–Bacterial
	Viral
	–Inflammation
	–Autoimmune polymyositis
	Scleroderma
	Sarcoid
	–Drugs/alcohol
	Chemotherapy
Cardiac trauma	–Direct road traffic accident
	Stabbing
	–Cardiac surgery
	–Cardiac contusion
	–Cardiac transplant-inflammatory/immune-mediated

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TABLE 3: (*Continued*)

Metabolic/toxic/drugs	–Renal failure
	–Hypothyroidism
	–Multiple organ failure
	–Adriamycin, 5 fluorouracil, herceptin, snake venoms

Abbreviations: AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CAD = coronary artery disease; cTn = cardiac troponin; IHD = ischemic heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SLE = systematic lupus erythematosus.

endotoxins, may lead to direct myocardial injury by cytotoxic effects.

5. Acute Stroke: Both elevated cTn levels and electrocardiogram (ECG) changes have been described in the setting of acute stroke or intracranial hemorrhage. The most likely explanation of troponin elevation and myocardial damage in the setting of intracranial hemorrhage is an imbalance of the autonomic nervous system, with the resulting excess of sympathetic activity and increased catecholamine effect on the myocardial cells.[37,38]
6. Troponin and Renal Failure: Persistently elevated cTn is frequently observed among patients with end-stage renal disease (ESRD).[39–41] The prevalence of increased troponin values among patients with chronic renal failure in the absence of clinically suspected ischemia may be as high as 53%.[41] In symptomatic patients with suspected ACS, elevation of cTn is associated with adverse outcomes regardless of renal insufficiency.[42]
   However, in patients with advanced renal failure, cTn concentration develops higher peaks and troponin remains detectable for longer periods. Patients with ESRD already have elevated troponin values before the acute cardiac event. Repeated early measurements are needed to detect a pronounced rise indicating an acute ischemia. Unfortunately, there are no approved protocols on the frequency and interval of blood sampling. Both cTnT and cTnI are commonly increased in asymptomatic patients with ESRD, even when there is no suspected myocardial ischemia. Using a third generation assay for cTnT, up 53% (10% CV; >0.03 ng/ml) of hemodialysis patients had elevated cTnT,[43,44,45] while elevation of cTnI was less frequently observed (up to 19%).[46,47,48] In addition, increased cTn values can be caused by concomitant diseases known to be associated with cTn release, such as severe left ventricular hypertrophy leading to subendocardial ischemia.[49]
7. Pericarditis: In acute pericarditis, troponin elevations are common, especially when ST-segment elevation is present.[50] Troponin release probably represents inflammatory involvement of the epicardium.[51]

Potential Treatment Strategies

Troponin is a highly sensitive biomarker that aids in the detection of myocardial cell damage, which is often but not always, due to the thrombotic obstruction of a coronary artery. Therefore, while troponin may be useful to rule out a non-ST-segment elevation MI (NSTEMI), it is less vital to rule in this event because it is not specific for an ACS. Troponin elevation in the absence of an ACS has significant prognostic value, both short-term and long-term. Hence, given the increased risk for adverse outcomes, patients with troponin elevation require appropriate diagnostic evaluation and therapy aimed at the underlying disorder. The assessment of whether troponin elevation is thrombolic or nonthrombolic may be difficult. Factors suggest coronary heart disease (CHD) include ischemic ECG changes, chest pain, wall-motion abnormalities on echocardiography, and the presence of atherosclerotic risk factors. If present, these should guide further cardiovascular evaluation, including early risk stratification.[5] There are no data available for randomized controlled trials regarding the efficacy of antiplatelets, β-blockers, and revascularizing procedures in non-ACS patients with elevated troponin. Acetylsalicylic acid, being relatively safe in most clinical circumstances, is recommended for use.[52] In such patients, the main goal of treatment strategy is to identify the underlying cause of troponin elevation.

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