Elevated Cardiac Troponins: the Ultimate Marker for Myocardial Necrosis, but Not Without a Differential Diagnosis

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ABSTRACT: Cardiac troponins are released from myocytes following myocardial damage and loss of membrane integrity. Their significance when diagnosing acute myocardial infarction is immense, e.g., their high sensitivity and specificity for myocardial tissue, the prognostic information they bear, and their role in risk stratification and therapeutic decisions. However, one cannot fully and blindly rely on cTn testing in diagnosing acute MI since many other conditions are associated with elevation of troponin. A review of the literature demonstrates a myriad of such examples including non-thrombotic cardiac injury, systemic diseases and laboratory interferences. Failure to acknowledge the differential diagnosis of elevated troponin may lead to over-diagnosis of MI and, accordingly, misdiagnosis of the real cause. It is of utmost importance that all physicians who measure troponin recognize the possibility of falsely diagnosing MI and are familiar with the main alternative causes for cardiac troponin elevation. IMAJ 2009;11:50–53

KEY WORDS: cardiac troponin, myocardial infarction, troponin elevation

cTn = cardiac troponin
MI = myocardial infarction

The value of cardiac troponins in the setting of diagnosing myocardial ischemia is well known and recognized by all medical practitioners. Their irreplaceable role was recently validated by the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction [1] who, like their predecessors, singled out cardiac troponins as the ideal biomarkers for the detection of recent myocardial damage [1-9]. Following loss of myocyte-membrane integrity, cardiac troponins find their way into the systemic circulation and can be detected in the serum 4–6 hours after the initial event, peaking at 24 hours [9-11]. They have numerous advantages that make them a most valuable entity. Most importantly, they are highly sensitive and nearly absolutely specific for myocardial tissue, as their composition differs from skeletal muscle troponins [1-3,6,9-11]. Using these enzymes enables us to detect even the smallest myocardial cell injury and micro-infarction at a far greater sensitivity than previously possible using creatinine kinase testing. Moreover, laboratory essays for cardiac troponins are a readily available convenient and inexpensive bedside method to rule out acute MI in an emergency setting. Another bonus is their prognostic value, having proved to be a strong and independent risk factor for adverse outcomes and cardiac events and thus an important player in risk stratification and therapeutic decisions [3-9,11]. Their pivotal role in all aspects of acute coronary syndrome management is well established, and they have long been incorporated in the international definitions and guidelines for acute coronary syndromes and MI [1,2].

In view of the above advantages, clinicians should keep in mind that several conditions other than acute MI, although generally undervalued, are associated with elevations of these enzymes [7-34]. Non-MI reasons for elevated cTn can be largely divided into two categories: non-thrombotic causes and cTn false positive testing.

NON-THROMBOTIC CARDIAC TISSUE DAMAGE

Attention should be drawn to the unequivocal notion that although cTns reflect cardiac cell damage, they do not specify its mechanism. In a recent 2007 publication, the Joint Task Force specifically states that high levels of cTn in the absence of clinical evidence of ischemia should prompt a search for other causes of myocardial necrosis [1]. Review of the literature demonstrates a variety of non-thrombotic cardiac conditions associated with cTn elevation:

- **Congestive heart failure** [7,9,10-13]: an increase in cTn is seen in patients with severe but stable congestive heart failure as well as in patients with an acute presentation. The mechanism of troponin release is not entirely clear, but it is probably multifactorial and includes ongoing destruction of contractile proteins due to release of cytokines and oxidative stress, left ventricular hypertrophy, global wall stretch, impaired hemodynamic function, and concomitant renal disease. Extent of troponin positivity was found to correlate with worse outcomes.
- **Coronary vasospasm** [11,13,14]: cardiac troponins are released from myocytes in reversible as well as irreversible tissue damage. Temporary vasospasm of the coronary arteries is sufficient to alter membrane permeability and cause spillage of cTns from their cytosolic pool.

- **Cardiac trauma** [7,9,11,13]: any mechanical trauma is capable of damaging cardiac myocyte integrity and causing troponin release. Additionally, trauma to coronary arteries can occur, leading to ischemia.
- **Myocarditis/perimyocarditis** [7-11,13,15]: in patients with myocarditis, the inflammation itself causes myocardial cell necrosis and troponin spillage. Patients with pericarditis pose a serious challenge to examiners because they present with symptoms similar to acute MI and their electrocardiograms demonstrate ST segment changes. Troponin elevation in the setting of perimyocarditis is thought to be caused by damage to the outermost layer of the myocardium.
- **Pulmonary embolism** [7,9-11,13,16]: chest pain and dyspnea are commonly seen in both pulmonary embolism and acute MI. In the case of massive PE, myocardial damage from right ventricular dilation and strain seems to be a reasonable explanation for cTn elevation. Surprisingly, however, submassive PE was also found by some authors to cause such elevations. Elevated cTn in PE patients is associated with the development of right ventricular dysfunction and recurrent PE, cardiogenic shock, and death.
- **Post-cardiac surgery and cardiac ablation** [7,9,11]: minor elevations of cTn are often observed after elective percutaneous coronary intervention and are almost inevitably present after open heart surgery.
- **Cardioversion and cardiopulmonary resuscitation** [7,9,11,13]: prolonged hypotension and hypoxemia during resuscitation can account for myocardial ischemia. Chest compressions and defibrillation add mechanical and electrical trauma. A direct correlation between amounts of defibrillation energy delivered and cTn release has been noted.
- **Sepsis** [7,9,10,17]: in septic patients there are a number of mechanisms that can cause myocardial damage, such as release of cytokines and reactive oxygen species, direct effect of bacterial endotoxins, concomitant myocarditis, prolonged hypotension, and dysfunction of the coronary autoregulation. In these patients as well, troponin holds valuable prognostic information.
- **Critically ill patients** [7,9,10,17]: elevated cTns are a common finding in intensive care units. Concomitant sepsis often occurs. Troponin values correlate with the severity of the disease and increased risk of death.
- **End-stage renal disease** [7,9-11,18-20]: both cTn-T and cTn-I are elevated in ESRD patients, accounted for by their decreased renal elimination, uremic myo/pericarditis, congestive heart failure, left ventricular hypertrophy, and hemoconcentration following dialysis. Increased troponin levels in ESRD patients are associated with a substantial risk of death and morbidity.
- **Arrhythmias** [7-9,13,14,21]: especially tachycardias, which warrant hospital admission, but also bradyarrythmias and heart block, are able to raise cTn level, apparently by causing hemodynamic compromise and reversible myocyte injury.
- **Stroke** [22,23]: acute cerebrovascular events can produce neurally mediated myocyte damage, possibly by creating an imbalance of the autonomic nervous system with sympathetic activity excess and catecholamine release.
- **Epileptic seizures** [23-25]: although cases of acute MI following generalized tonic-clonic seizures have been described, there are reports of cTn elevation in the face of GTC seizures lacking any clinical evidence of acute MI. There are a couple of culprit mechanisms for this phenomenon. First, given that GCT seizures constitute a highly strenuous physical exertion, with a concomitant augmentation of afterload by tonic skeletal muscle contraction, a transient supply and demand mismatch at the myocardial level is elicited. Second, neurally mediated cardiac myocyte damage similar to the pathology seen in stroke and cerebral hemorrhage is possible.

Non-thrombotic cardiac tissue damage by various mechanisms as well as false positive laboratory results are capable of raising cardiac troponins

A myriad of other conditions was found to be associated with cTn elevation as well [1,7-9,11,13,18,19,23,26,27], including left ventricular hypertrophy, diabetes mellitus, heart transplantation, acute rheumatic fever, chronic obstructive pulmonary disease exacerbations, hypertensive emergency and hypertension (including gestational), aortic dissection, infiltrative diseases (amyloidosis, hemosiderosis, pompe and sarcoidosis), cardiotoxic agents such as adriamycin and cyclophosphamide, intracranial hemorrhage, high endurance physical exercise, postoperative non-cardiac surgery, lobar pneumonia, extensive burns, Chung-Strauss eosinophilia, animal bites (jellyfish, scorpion), and rhabdomyolysis.

FALSE POSITIVE cTn TESTING

Analytical interference by many non-specific causes is a common problem in almost all immunoassays, and cTn assays are no different. Most available troponin essays utilize two-site immunoassays, which render them susceptible to positive interference by other substances – a condition referred to

PE = pulmonary embolism
ESRD = end-stage renal disease

GTC = generalized tonic clonic

as false positive troponin. The most frequently described interfering mechanisms are listed below:

- **Heterophile antibodies [13,28,29]:** these immunoglobulin G antibodies recognize epitopes on the Fc portion of the foreign immunoglobulin. Their appearance in human serum results from exposure to monoclonal mouse antibodies (tumor imaging, immunization with animal-derived serum) or other foreign proteins. This kind of exposure can be occupational or related to living with domestic animals. Their presence in high titers can lead to analytical errors in two-site immunoassays.
- **Rheumatoid factor [13,30,31]:** this antibody, present in the sera of many patients with rheumatoid arthritis, other immune diseases and in normal individuals, can be regarded as part of the heterophile antibodies group. Rheumatoid factor is well known for causing such interferences with several immunoassays, cTn included.
- **Macroenzymes [32]:** these are high molecular mass complexes formed by polymerization of enzymes in the serum and multiple other components. Their formation is associated with several autoimmune and liver diseases. They frequently interfere with the interpretation of serum enzyme results and are the source for diagnostic errors.

Several additional examples of interfering substances are found in the literature [13,33,34]; among them are circulating antibodies from immunotherapies, vaccinations or blood transfusions, fibrin clots, immunocomplexes, and malfunction of the analyzers.

CONCLUSIONS

Current use of troponins in the place of formally used CPK-MB has allowed us to detect even subtle cardiac damage and micro-MI. New assays show positive values when as little as 1 g of myocardial tissue becomes necrotic, while CPK values are still within normal ranges, resulting in a substantial increase in the frequency of MI diagnosis. Measuring troponin considerably augments sensitivity, but at the same time increases false positive results and MI diagnoses. Clinicians must be aware that troponin elevation can be seen in a variety of conditions other than acute MI, including non-thrombotic cardiac injury, systemic diseases and laboratory interferences, and therefore must be interpreted in the clinical and electrocardiographic context in which this enzyme is measured. There is no absolute or accurate control for defining an erroneous elevated troponin result. However, serial measurements can assist in minimizing false positive results by showing the typical rise and fall pattern in acute MI as compared to other causes of cTn elevation. In addition, CPK-MB can be measured when a high index of suspicion for a false positive finding occurs. Recently, a practical algorithm was proposed for the management of patients with indistinct clinical presentation, elevated troponin and several predictors of MI diagnosis in this setting [35], which may further aid in dealing with this perplexing issue.

Troponin elevation should be interpreted in the clinical and ECG context in which it is measured, and existence of its differential diagnosis must be acknowledged

We therefore recommend that all physicians measuring troponin in any hospital ward or ambulatory practice recognize the possibility of falsely diagnosing MI and are familiar with the main alternative causes of cTn elevation.

CPK = creatine phosphokinase

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