Troponin elevations in patients with chronic cardiovascular disease: An analysis of current evidence and significance

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ABSTRACT

Serum troponin elevation above the 99th percentile of the upper reference limit in healthy subjects (<0.01 ng/ml measured using currently available high-sensitivity cardiac troponin laboratory assays) is required to establish the diagnosis of myocardial necrosis in acute cardiovascular syndromes, as well as guide prognosis and therapy. In the perioperative period, for patients with cardiac disease undergoing noncardiac surgery, it is a particularly critical biomarker universally used to assess the myocardial damage. The value of troponin testing and elevation (as well as its significance) in patients with chronic cardiac valvular, vascular, and renal disease is relatively less well understood. This evidence-based review seeks to examine the currently available data assessing the significance of troponin elevation in certain chronic valvular and other disease states.

Key words: Aortic stenosis; Heart failure; Heart transplantation; Troponin

HISTORY, INTRODUCTION, AND EVOLUTION OF CARDIAC BIOMARKERS IN MEDICINE

Cardiac biomarkers, which have played a crucial role in the development of modern cardiology, have evolved significantly since their inception during the 1950s. In the current era, assays of biomarkers are universally performed and indispensable for the diagnosis and therapy of acute cardiovascular syndromes as well as to assist in prognostication of chronic cardiac and vascular disease.

In the late 50s and early 1960s, aspartate aminotransferase was the first laboratory test used in the clinical setting for detection of myocardial damage. Subsequently, the development of creatine kinase (CK) as a marker of muscle damage was introduced via several researchers. Elashi discovered that plasma CK activity was sensitive for skeletal muscle disease, while Dreyfus discovered that increased levels of CK were present in patients with myocardial infarction. While CK was discovered as a biomarker, the laboratory tools to reliably and efficiently measure CK levels were not developed until the mid-1960s by a pathologist Sidney Rosalski. He famously sketched a new enzymatic reaction for CK measurement on the back of a paper dinner napkin, and the future of cardiac biomarkers was born.¹⁻⁴

Various subunits of the CK molecule were discovered in the 60s, but it was not until the
mid-1970s that Roberts created the first quantitative assay for CK-MB, launching a further genesis of the biomarker revolution in cardiac disease. Rosalki et al. subsequently developed rapid immunological assays for the CK-MB molecule, opening a new methodology of cardiac biomarker testing.

In 1978, Katus et al. started to pursue assays for myofibrillar proteins. His team had several reasons for pursuing this novel testing, despite the popularity of CK, and lactate dehydrogenase (LDH) as biomarkers for cardiac disease. First, LDH and CK lacked exact cardiac specificity. Second, rapid immunological assay techniques allowed for detection of small amounts of molecules independent of enzymatic reactions or biological activity. Finally, differences in contractile properties between cardiac and skeletal muscle were discovered to be related to quantifiable differences in their respective isoforms, thus leading to the potential for study in the setting of cardiac disease.

Initially, the work on myofibrillar proteins focused on light myosin chains by Haber at the Massachusetts General Hospital; however, the discovery in 1982 of light myosin chains in skeletal muscle lead to the push for a more specific myofibrillar protein assay for use in cardiac disease. Katus et al. subsequently focused on cardiac troponin T (cTnT), which Western blot analysis research revealed was indeed specific to cardiac muscle. Subsequently, during the early to late 1980s, troponin I assays were developed and published by a team at Washington University, which showed not only cardiac specificity but a sustained increase in value during cardiac damage. This is attributed to not only cytosolic troponin I release during damage, but also myofibrillar release of troponin I during the repair and remodeling period following cardiac insult.

In more recent years, the development of high-sensitivity tests for both troponin T and troponin I have allowed physicians to measure concentrations greater than ten-fold lower than standard assays. This has resulted in capturing measurable troponin levels in patients with the stable or even subclinical disease. Three subunits exist within the troponin-tropomyosin complex, and each has a specific role involved in achieving contraction of the myofibril. Troponin C, which binds to calcium, is found in both skeletal and cardiac muscle; troponin I, which prevents myosin-actin binding; and troponin T, which binds to tropomyosin, both have unique subtypes specific to cardiac muscle.

This development and breadth of clinical testing have led to the application of cardiac biomarkers as diagnostic and prognostic indicators in various disease processes including aortic and mitral valvular disease, advanced congestive heart failure (CHF), heart transplant rejection, cardiomyopathy, and chronic renal failure.

TROPONIN AS A PROGNOSTIC INDICATOR IN AORTIC VALVE DISEASE

There is a significant body of literature that documents elevated troponin T and troponin I levels in patients with aortic stenosis (AS).

Saito et al. described preoperative levels of high-sensitivity troponin T as a prognostic marker for patients with AS after valve replacement surgery. His group investigated major adverse cardiac events (MACE) in patients with AS and found that increased levels of high-sensitivity troponin T are a significant factor to predict MACE in this patient population. Sixty patients were studied from 2003 to 2010 who had aortic valve replacement (AVR) for severe AS. Exclusion criteria included patients who had concomitant coronary artery disease (CAD), acute coronary syndrome, severe aortic regurgitation, combined mitral valvular disease, and inoperable patients. The study concluded that levels of high-sensitivity troponin T were predictors for the occurrence of a fatal arrhythmia and cardiac death in the postoperative period.

The physiological mechanisms for the release of troponin T in the population were hypothesized as multifactorial and include the following: Transient, clinically silent ischemic episodes, small vessel occlusions, inflammatory processes, cardiomyocyte apoptosis, and increased myocardial strain due to pressure or volume overload. Due to increased afterload secondary to AS, left ventricular hypertrophy can result in ischemia due to supply/demand mismatch as well as myocardial fibrosis that can serve as an arrhythmogenic substrate in this patient population.

Røsjø et al. studied 57 patients with AS in which echocardiographic data and prognosis were correlated with high-sensitivity troponin T levels. His group found that while troponin T levels were universally detected in patients with moderate and severe AS, left ventricular mass and systolic function were independent determinants of elevated troponin T levels.
levels in patients with AS. High levels of troponin T were noted to be associated with poor prognosis in AS patients.\[8\] Solberg et al. also showed high-sensitivity troponin T as individually correlated with prognosis in a study of 136 patients and suggested high-sensitivity troponin T as a possible biomarker for risk stratification in AS patients.\[9\]

Troponin I has also been studied as a prognostic marker in the setting of AS.\[10-12\] Nahar et al. compared troponin I levels in twenty healthy patients versus twenty AS patients with intact ejection fractions. While healthy subjects had undetectable levels of troponin I in their samples, it was noted that AS patients had elevated levels of troponin I despite the absence of depressed ejection fractions or heart failure symptoms.\[12\] Kupari et al. studied 131 patients undergoing echocardiograms and cardiac catheterizations for AS. Their findings showed leakage of troponin I into the coronary sinus were associated with impairment of left ventricular systolic function in AS patients.\[11\]

The largest study of troponin I as a prognostic indicator in AS patients to date was performed by Chin et al. in which they measured cardiac troponin I (cTnI) levels in two patient cohorts. The first cohort, or mechanism cohort, consisted of 122 patients who underwent cardiac magnetic resonance imaging and echocardiography to measure left ventricular mass, function, and levels of fibrosis. The second cohort, or outcome cohort, consisted of 131 patients who had a long-term follow-up for the occurrence of AVR and cardiovascular deaths. The combined cohorts consisted of 253 patients, 98% of who showed detectable and increased troponin I concentrations as compared to healthy volunteers.\[10\]

The mechanism cohort showed that increased plasma cTnI concentrations were associated with left ventricular mass and replacement myocardial fibrosis, independent of sex, age, CAD, or AS severity. The outcome cohort, over a median follow-up of 10.6 years, showed that plasma cTnI concentrations were associated with the need for AVR or cardiovascular death. The study concluded that high-sensitivity troponin I concentrations hold potential to serve as an objective marker for early identification of left ventricular decompensation in patients with AS, as well as the timing of AVR earlier in a patient’s disease course than would be otherwise pursued.\[10\]

**TROPTONIN AS A PROGNOSTIC INDICATOR IN MITRAL VALVE DISEASE**

There exists a paucity of literature describing troponin as a prognostic indicator in nonsurgical mitral disease. The largest set studies to date, consisting of 81 and 15 test subjects, respectively, show that increased levels of cTn serve as an indicator of mitral valve disease severity and prognosis in dogs.\[13,14\] A study of sixty patients with the cardiac disease compared to thirty healthy patients by Nahar et al. describes a lack of elevation of cTnI in mitral stenosis and combined mitral/AS patients as compared to AS patients.\[15\]

The vast majority of the literature describing troponin as a prognostic indicator in mitral disease focuses on the perioperative period.\[16-23\] Troponin I levels were studied retrospectively by Oshima et al. in a set of 24 patients undergoing mitral valve surgery. The length of cardiopulmonary bypass time as well as aortic cross clamp time influenced troponin I levels in these patients, with higher troponin I levels on postoperative days 1 and 2 significantly correlating with increased intensive care unit and postoperative hospital length of stays. The study concludes by suggesting that postoperative cTnI levels are potentially useful in predicting postoperative course in mitral valve surgical patients.\[20\]

Monaco et al. prospectively studied 185 patients undergoing mitral valve surgery who underwent measurements of cTnI, 24 h after surgery. The study notes that the values of cTn as a prognostic risk factor seem to be independent, yet additive, to the Society of Thoracic Surgery postoperative outcome risk score. When cTnI concentrations were markedly increased, they were strongly associated with risk of impending postoperative complications and were noted to be higher after mitral valve replacement as compared to mitral valve repair. It was hypothesized this differential may exist due to increased myocardial manipulation by the surgeon during a replacement as opposed to repair. The need for intraoperative inotropic support and the length of cardiopulmonary bypass time were shown to be independent predictors of troponin I release significantly related to adverse outcome.\[19\]

Wöhrle et al. recently studied high-sensitivity troponin T as a predictor of adverse outcomes in a group of 34 patients undergoing percutaneous mitral valve repair. Preoperative measures of high-sensitivity
troponin T were measured, and a median follow-up of 211 days ensued. Higher baseline concentrations of high-sensitivity troponin T strongly predicted cardiovascular death as well as rehospitalization for heart failure in this patient population. The authors concluded that troponin T might be a useful addition to prognostic models of mortality and morbidity in this mitral valve disease population.

**TROTONINS AND RENAL FAILURE**

Patients with chronic kidney disease (estimated glomerular filtration rate [GFR] <60 ml/min/1.73 m²) and end-stage renal disease requiring renal replacement therapy are at elevated risk of cardiovascular events and their resulting complications. cTnT has been shown to be chronically elevated in dialysis patients as well as those with reduced GFR. Accurate and timely diagnosis of potential cardiovascular events is critical, as elevations of cTnT in asymptomatic patients are associated with increased mortality. As the technology of assays has evolved over time, the newer, more sensitive cTnT assays have demonstrated greatly improved detection rates for cardiac events; however, controversy exists regarding the diagnostic value of these highly sensitive assays in patients with preexisting renal dysfunction. One contributing factor to this controversy is that changes in the cTnT concentrations have been shown with variations in serum creatinine. Specifically, rises in troponin T occur with acute rises in serum creatinine and falls with decreases in serum creatinine.

In contrast, a recent multicenter study by Twerenbold et al. demonstrated that cTnT assays maintain diagnostic accuracy in patients with renal dysfunction if optimal cutoff levels were used. It should be noted that these optimal cutoff levels were generally higher than those used for patients without renal dysfunction, and at the usual 99th percentile cutoff to diagnose acute myocardial infarction, patients with renal dysfunction had higher sensitivity but lower specificity, which is expected given the elevated baseline in renal patients.

The etiology of persistently elevated troponins in patients with renal dysfunction is currently unknown. Theories include myocyte damage from uremia, ischemia, inflammation, and decreased renal clearance. In contrast, levels of amino-terminal pro-B-type natriuretic peptide (BNP) in patients with low GFR are not simply reflective of decreased renal clearance but are indicative of cardiovascular disease and portend a worse prognosis.

**B-TYPE NATRIURETIC PEPTIDE AND TROPONIN IN CHRONIC DISEASE**

B-type natriuretic peptide or BNP has been well studied as both a prognostic cardiac biomarker as well as for risk stratification in chronic disease. In a recent study examining a low-risk outpatient population, Biener et al. obtained cTnT levels on nearly seven hundred stable patients with CAD in the ambulatory setting. Measurements were obtained during initial presentation to the clinic, with a follow-up level drawn 26 months later. The results noted that those with chronic elevations in cTnT had higher all-cause mortality as well as elevated BNP levels.

In chronic heart failure, BNP is a well-established biomarker primarily used to assist in medical management. In the Trial of Intensified versus Standard Medical Therapy in Elderly Patients with CHF trial, the authors sought to discern whether BNP-guided therapy for heart failure was superior to standard medical therapy in older patients (>75 years of age). Their results demonstrated a positive effect in the younger patient group receiving BNP-guided therapy including reduced mortality and heart failure-related adverse events. Similarly, in the PROTECT trial, in which 151 patients were enrolled, BNP-guided therapy was compared with standard medical therapy. Patients whose therapy was guided by BNP levels demonstrated improvements in quality of life, improved left ventricular ejection fraction, and reduced event rates. Troponin is not as well-established in the treatment of chronic heart failure but is gaining acceptance for use in prognostication and risk assessment. Elevated levels are found even in normal healthy patients and patients with stable coronary disease, and these are associated with risk factors for heart failure.

**TROPONIN ELEVATION IN HEART FAILURE EXACERBATIONS**

Highly sensitive troponin assays in patients with heart failure exacerbations can reach laboratory threshold significance, and there have been over 26 studies from 1996 to 2012 that have demonstrated this. The mechanism of troponin release from cardiac myocytes in patients with acute heart failure exacerbations is unknown. Troponin elevations exist despite the unlikely event of a type 1 myocardial infarction in...
patients with acute heart failure exacerbations. In a large meta-analysis of two clinical trials, patients with heart failure that had low-level troponin elevations had more heart failure exacerbation events when compared to patients without troponin elevations. Those patients with troponin increases over the 3–4 months follow-up period had increased all-cause mortality; however, when compared to other diagnostic techniques it was inconclusive whether the additional monitoring of troponin levels added much to existing prognostic markers.

There is more research needed to understand the mechanism and significance of troponin release in patients with acute heart failure exacerbations. Further research should also attempt to figure out if triage and treatment of patients with heart failure exacerbations with troponin elevations should be customized.

**TROPONIN ELEVATION IN HEART TRANSPLANT RECIPIENTS-ASSESSING SIGNIFICANCE**

Troponin elevations in patients with heart transplants have been described as both an epiphenomenon and as a poor prognostic sign. Similar to troponin elevations in heart failure exacerbations, troponin elevations in heart transplant patients rarely lead to a definitive diagnosis and a successful intervention. Regardless, detecting troponin elevations in the early perioperative period is distinctly different from troponin elevations in the chronic outpatient setting. Heart transplantation troponin release can be divided up into three distinct time intervals: The initial organ evaluation process, the early postoperative period, and the chronic posttransplant period.

Troponin levels are followed as a prognostic sign to judge the viability of the donor organ. As previously discussed, troponin elevation is nonspecific and should be correlated with the clinical situation and usually with other diagnostic tests. The mechanism of troponin release is difficult to determine and is a topic of controversy. Troponin elevation in the donor heart could represent thoracic trauma, intracranial pathology, or result from cardiopulmonary resuscitation. A troponin elevation could delay organ selection and can lead to further invasive testing. Depending on the age of the donor, a troponin elevation could lead to coronary angiography and serial echocardiography; however, low-level troponin elevations in donor hearts do not seem to predict survival after transplant. In one study, elevated troponin levels in the pretransplant period correlated with reduced left ventricular ejection fraction and regional wall motion abnormalities in the donor heart; however, this did not seem to correlate with early or late posttransplant outcomes.

In the early postoperative period, troponin elevation is typically followed to assess for primary graft dysfunction. Primary graft dysfunction is often multifactorial. Making the proper diagnosis can be crucial to improving outcomes. Primary graft dysfunction can be due to isolated right heart failure, isolated left heart failure, the effects of cumulative ischemic time, reperfusion injury, and possibly acute rejection. Troponin elevation in the early postoperative period is associated with early graft failure. In a retrospective analysis of early graft failure, cumulative ischemic time, donor age, and peak troponins were variables that correlated with postoperative primary graft failure. In addition to total ischemic time, postoperative troponin elevation >10 µg/L is a marker for increased perioperative morbidity and mortality.

After the perioperative period, troponin elevations suggest different pathology. Cardiac allograft vasculopathy (CAV) results in intimal thickening of coronary arteries in the donor's heart and is a sign of chronic rejection, viral infection, and metabolic disorders that lead to graft failure. CAV can present as global graft dysfunction and is a major cause of morbidity and mortality in patients with heart transplants. Persistent troponin elevations lasting up to 1 year are associated with increased morbidity and mortality. These later troponin elevations are related to CAD from CAV and graft failure.

Troponin levels are an important biomarker in patients following heart transplantation. Troponin elevations can be indicative of myocardial damage in the donor's heart prior to transplant, they can be used to assess early graft dysfunction, and they can be helpful in assessing a patient for a later complication of CAV.

**CONCLUSION**

The role and importance of troponin testing in patients with acute cardiovascular syndromes is well-established. It is becoming increasingly apparent also that chronic valve disease in addition to vasculopathies and cardiac allograft disease can affect these biomarkers with varying effects on prognosis and treatment. Future prospective studies will delineate more information will guide the management of these complex patients.
Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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