

Causes of Cardiac Troponin Elevation

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Introduction

The thin filament of both skeletal and cardiac muscle is made up of the proteins actin, troponin and tropomyosin respectively. Troponin in both skeletal and cardiac muscle is a complex made up of three individual proteins, each with specific roles, denoted as troponin I, troponin C, and troponin T (Al-Otaiby et al. 2011). The troponin I (TnI) protein of the complex serves as an inhibitor of the ATPase activity required for cross-bridge formation. Troponin C (TnC) binds calcium ions to allow access of the myosin heads to their binding sites on the actin filament by removing the overlaying regulatory protein tropomyosin. The troponin T protein attaches the troponin regulatory complex to the actin filament and also binds to the tropomyosin protein (Al-Otaiby et al. 2011). While both skeletal and cardiac muscle have gene expression of the troponin complex with all three individual proteins, the troponin I and T proteins have tissue-specific isoforms. A troponin C isoform is shared between cardiac tissue and slow-skeletal tissue known by the finding of cardiac troponin C in slow muscle fibers, making it undesirable for diagnostic use (Kobayashi et al. 2008). Because of the high specificity of troponin I and T found in cardiac tissue, regarded as cardiac troponin I (cTnI) and cardiac troponin T (cTnT), they each can be used as a biomarker for cardiac injury (Babuín and Jaffe 2005). Myocyte necrosis is an accepted cause of cardiac troponin release; yet the cardiac damage responsible for the troponin release may include cell injury without necrosis (Jaffe 2012). Whether the elevated cardiac troponin levels are from myocyte necrosis or a more reversible form of cardiac damage, it is agreed that the presence is due to myocardial injury. Elevated cTn levels from myocardial injury can be due to a wide variety of diagnoses, including acute coronary syndrome, other cardiovascular diseases or non-cardiac diseases. Acute coronary syndrome (ACS) refers to symptoms caused by coronary artery obstruction that varies from unstable angina pectoris (chest

pain due to reduced heart blood flow) and myocardial infarction (Tanindi and Cemri 2011). Cardiovascular causes apart from ACS include conditions such as acute pericarditis, acute inflammatory myocarditis, atrial fibrillation, tachycardia and heart failure (Tanindi and Cemri 2011). But non-cardiac conditions are frequently responsible for elevated cTnT levels, including pulmonary embolism, renal failure, stroke, sepsis, diabetic ketoacidosis, respiratory failure, and intense exercise (Jaffe 2012).

Acute Coronary Syndrome and Cardiac Troponins

Acute coronary syndrome (ACS) is a collection of symptoms caused by reduced or blocked blood flow to the heart. The main symptom of ACS is chest pain, known as angina pectoris (Meune et al. 2011). Acute coronary syndrome includes the diagnosis of unstable angina pectoris and acute myocardial infarction (Tanindi and Cemri 2011). Elevated levels of cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are regarded as the biochemical markers of myocyte necrosis for the diagnosis of myocardial infarction (Chan and Ng 2010; Sharma et al. 2004).

In a study by Wong et al. of the 1021 patients hospitalized during an 8-week period that required a cardiac troponin T test, 195 patients with elevated cTnT were diagnosed with ACS and 80 of the patients with normal cTnT were also diagnosed with ACS (2006). In the study ACS accounted for more patients that had raised cTnT compared to non-ACS, yet the non-ACS patients of this distinction had the higher mortality (Wong et al. 2006). However those with ACS and elevated cTnT still had a significantly higher mortality than their counterparts with normal cTnT (Wong et al. 2006). A study by Meune et al. (2011) had similar findings regarding acute coronary syndrome, where almost a third of ACS patients had normal cTnT. Meune et al. (2011) also found that those with ACS with normal levels of cTnT compared to those with non-cardiac

disease and normal cTnT levels, the ACS patients had an increased incidence of acute myocardial infarction within 30, 90, and 360 day and death from acute myocardial infarction.

The etiology for elevated cardiac troponin levels seems to impact the mortality associated with the levels in the studies considered above. Elevated cardiac troponin levels, specifically cTnI levels, were found to be predictors of higher mortality in ACS patients as found by Antman et al. in 1996, at a time when only cardiac troponin T had been studied in terms of prognosis in unstable angina in 1992 and 1993. While cardiac troponins are standard biochemical markers for the diagnosis and prognosis of acute coronary syndrome, elevated levels are not necessary for the diagnosis of ACS and should not hinge on its presence, as shown by its frequency without elevated cardiac troponins in study sample characteristics (Wong et al. 2006; Meune et al. 2011). Their presence due to ACS compared to non-ACS cardiac causes does not seem to predict as high of a mortality risk as when attributed to non-ACS conditions, yet their absence in ACS patients does not imply the lack of risk of an occurrence of a later myocardial infarction or mortality (Wong et al. 2006; Meune et al. 2011). The higher mortality rate for those with elevated cardiac troponin levels and non-ACS conditions suggest that troponin tests are very useful in casual settings outside of angina and myocardial infarction, including other cardiovascular causes and non-cardiac causes.

Non-ACS Cardiac Conditions and Cardiac Troponins

While elevated cardiac troponin level tests have an established role in the diagnosis of acute coronary syndrome of unstable angina pectoris and myocardial infarction, cardiac troponin assays are also utilized in other clinical cardiac cases such as atrial fibrillation (AF), cardiac inflammation, and heart failure to name only a few. As cardiac troponin assays become increasingly sensitive as technology improves, detectable levels of cardiac troponin T and

cardiac troponin I impact an increasing number of diagnosis situations outside of acute coronary syndrome. The challenge in cardiac troponin assays is that the presence of cardiac troponin in the blood stream only shows myocardial damage and does not distinguish clearly between numerous possible mechanisms behind it (Tanindi and Cemri 2011).

With respect to critically ill patients, Lim et al. (2010) found that the largest cause (53.1%) of elevated cardiac troponin levels was myocardial infarction, consistent with the biomarker's use in MI diagnosis. Yet mortality in the ICU was highest not for those with elevated cTnI and cTnT from myocardial infarction but for those without MI, similar to the findings of Wong et al. (2006) regarding non-ACS patients. Normann et al. (2012) had similar conclusions to Lim et al. when considering the presence of cTnT in the elderly. Of those with elevated cardiac troponin levels, a non-ACS diagnosis was the majority in the elderly group at 60.5% and 39.5% due to ACS, while the opposite was found in those younger than 75 years (Normann et al. 2012).

Research in atrial fibrillation includes using cardiac troponin level tests to assess atrial fibrillation (AF) recurrence, newly present atrial fibrillation, and adverse outcomes caused by AF. Atrial fibrillation commonly reoccurs in many patients even after an episode is corrected by electroshock therapy, thus clinicians should acknowledge the common risk of another episode of AF and have a biomarker that is prognostic of its occurrence, which was the suggestion from a study that found cTnT baseline levels could independently predict the first recurrence of AF (Latini, Masson, Pirelli et al. 2010). Identifying atrial fibrillation is important for patients at risk of stroke or those diagnosed with stroke as well. Detection of AF impacts patients in the early stages of ischaemic stroke by providing a more accurate risk assessment due to findings that AF is a predictive of a more severe stroke with larger neurological deficits and early death (Kimura

et al. 2005). A study by Bugnicourt et al. (2010) found that moderately elevated troponin I levels were independently associated with new-onset atrial fibrillation in ischaemic stroke patients, and thus the study suggests that ischaemic stroke patients with moderately elevated cTnI levels be monitored for atrial fibrillation. A study by Hijazi et al. (2012) found results similar to those of Kimura et al. (2005) regarding the role of AF to a more severe stroke and death, finding that elevated cTnI that occur commonly in atrial fibrillation patients are independently related to increased risk of stroke and mortality. The frequency of elevated cardiac troponin I levels in atrial fibrillation patients shown in a study by Parwani et al. (2013) was considered by the researchers to show a need for clinical guidelines for AF-induced raised cTnI levels to avoid confusion and misdiagnosis of myocardial infarction or acute coronary syndrome as sharp increases in cTn levels are the diagnostic biomarker for such events. The study also sought to explain the finding that the AF patients with elevated cTnI levels had a higher mean heart rate by demand ischemia, put forth by other researchers, in which myocardial injury may be due to insufficient oxygen supply for the large demand due to shortened diastole period in tachycardia, not due to coronary artery abnormalities or disease (Parwani et al. 2013; Redfearn et al. 2005). cTnI is not the only cardiac troponin level found in conjunction with atrial fibrillation. Elevated cardiac troponin T levels are also found in patients with atrial fibrillation as found in the study by Wong et al. (2006), where 41 percent of the non-ACS patients and 11% of the ACS patients were found to have AF or flutter on ECG. Atrial fibrillation patients often have elevated cardiac troponin levels, and thus the diagnosis can be muddled with acute coronary syndrome. Additional research and clarification of cTn elevations due to atrial fibrillation supported with a proven mechanism is needed to help clinicians distinguish between AF patients and those with other related conditions, such as ACS. Atrial fibrillation's impact on the risk for stroke, increased

stroke severity and mortality are important reasons to further investigate AF's role in cardiac troponin elevations to allow better risk assessment for possible AF patients.

Myocarditis, myopericarditis and pericarditis are three types of cardiac inflammation that vary in the location of the inflammation usually due to bacterial or viral infection. Each of the three cardiac inflammation types have been studied in relation to elevated cardiac troponin I in patients with diagnosis of myocarditis, myopericarditis or pericarditis. A study by Ilva et al. (2010) showed that roughly 20% of the final diagnoses for non-myocardial infarction patients with elevated cTnI levels were myocarditis. A less recent study by Blich et al. (2008) found a smaller prevalence of myocarditis diagnosis at 4% of the non-ACS patients with elevated cTnI levels. These studies do not address myocarditis specifically but included conclusions regarding patients with cardiac causes of elevated cTnI patients other than myocardial infarction (MI) that led in both studies to an increased mortality compared to myocardial infarction caused cTnI elevation. In a large study with a group of 134 non-MI and non-CAD patients with elevated cTnI levels, 16% of these patients (the second largest division) had elevated cTnI due to myocarditis and 5% due to pericarditis (Mahajan et al. 2005). A study by Imazio et al. (2003) found that cTnI elevation in viral or idiopathic acute pericarditis was associated with younger age, male gender, ST-segment elevation and pericardial effusion, and that cTnI increase was not a negative prognostic marker for complications as those with normal and elevated cTnI levels and acute pericarditis had non-significant differences in complication occurrence. A similar study by Machado et al. (2010) showed that acute pericarditis patients with elevated cTnI divided into pericarditis and myopericarditis groups had a non-significant difference in complication occurrence, but the myopericarditis patients with elevated cTnI had a higher cardiac mortality. While Imazio et al. (2003) found certain patient characteristics of viral or idiopathic acute

pericarditis patients, Machado et al. (2010) found similar results of younger age and ST-segment elevation, with novel characteristics of higher troponin I levels and longer hospitalization stays. The recognition or perhaps purposeful inclusion of myopericarditis patients in the study by Machado et al. (2010) show an uncertainty in the similar characteristics found with the patients in the study by Imazio et al. (2003), which does not describe any myopericarditis patients. Further studies are needed to clarify if distinctions between myocarditis, myopericarditis and pericarditis impacts cardiac troponin I levels to predict patient outcome or complications of cardiac inflammation given the relative common link between cardiac inflammation and elevated cardiac troponin levels shows by the studies mentioned.

Within the elevated cardiac troponin levels and non-ACS group, patients with congestive heart failure (also known as chronic heart failure) have been found to account for large sample proportions for elevated cardiac troponin levels (McFalls et al. 2011; Ilva et al. 2010). Notably stable chronic heart failure has been associated with relatively low levels of cTnT in the blood that in some cases are undetectable completely, in contrast to the common higher levels of cTnT found in severe heart failure or worsening heart failure (Latini, Masson, Anand et al. 2007). The study by Latini, Masson, Anand et al. (2007) speculated that the occurrence of cardiac troponin release from possible myocyte apoptosis in chronic HF might have meant that a distinction between HF patients with normal or elevated cTnT levels impacted prognosis regarding hospitalization and mortality, which has been positively associated for in patients with detected cTn levels. The recommendation for serial cardiac troponin T measurements in the study by Latini, Masson, Anand et al. (2007) was the focus of a later investigation by several of the same researchers, in which similar results were reproduced that patients with chronic HF have very low cTnT concentrations yet they can be used in a serial fashion as independent predictors of

future cardiovascular events in these patients (Masson et al. 2012) In a related study regarding acute decompensated heart failure (ADHF) like results were found, Perna et al. (2005) reported that cTnT was an independent predictor of morbidity and mortality in ADHF patients.

Collectively the shared findings in heart failure suggest that cardiac troponin levels, specifically cTnT levels, allow prognosis of the events of hospitalization for worsening heart failure (as in the case of ADHF occurrence) or mortality from heart failure. Studies support the use of serial cTnT measurements to allow accurate risk assessment for heart failure patients.

Non-Cardiovascular Conditions and Cardiac Troponins

Elevated cardiac troponins are well-established biomarker for acute coronary syndrome and have been reported in the context of many non-ACS conditions involving the cardiac system such as atrial fibrillation, inflammatory conditions of the heart and heart failure. In all the studies referenced in ACS and non-ACS cardiac causes, cardiac troponins not only indicated cardiac injury but also a worsened prognosis of mortality. There are numerous non-cardiac conditions that present with or cause elevated cardiac troponin levels, such as sepsis, diabetic ketoacidosis, renal insufficiency and failure, pulmonary embolism and exercise.

Sepsis is the presence of an infection with systemic infectious manifestations. Sepsis can be further classified into severe sepsis where defined sepsis is present as well as induced organ dysfunction or tissue hypoperfusion (decreased blood flow). Septic shock occurs when sepsis-induced hypotension continues even with adequate fluid resuscitation (Dellinger et al. 2013). In a study by Ilva et al. (2010), over 10% of patients with non-cardiac cTnI elevations in the study were due to sepsis or septic shock diagnoses, and the highest in-hospital mortality occurred in the non-cardiac cTn positive patients, specifically the highest in the subgroup with sepsis. Similarly in a study by Blich et al. (2008), the largest division in non-ACS patients with elevated cTnI was

those with sepsis, and the patients with elevated cTnI not related to ACS defined a “high-risk group with poor short- and long-term outcomes.” Sepsis was the etiology of elevated cTnT in 18.4% of critically ill patients in a study by Lim et al. (2010), the second highest only below myocardial infarction. Of the sepsis patients, the median stay in the ICU was 9 days, 20 days total in the hospital, and with a 55.6% mortality incidence (Lim et al. 2010). In a study focused on severe sepsis patients by John et al. (2010), cTnI was found as an independent prognosticator of mortality outcome, and the sepsis patients with elevated cTnI levels also had a significantly lengthened stay in the ICU and hospital compared to the sepsis patients with normal cTnI levels. Sepsis is a common non-cardiac cause of elevated cardiac troponin levels, specifically cTnI, as shown by sample characteristics in several studies (Wong et al. 2006; Ilva et al. 2010; Blich et al. 2008; Lim et al. 2010). Elevated cTnI levels in sepsis patients are independently prognostic of mortality and longer hospital stays, including in the ICU. (Ilva et al. 2010; Blich et al. 2008; Lim et al. 2010; John et al. 2010).

Diabetic ketoacidosis (DKA) is defined as the presence of three features in diabetic patients, uncontrolled hyperglycemia, metabolic acidosis, and elevated ketone concentration in the body (Kitabchi et al. 2009). In a study by Carlson et al. (2008) the final diagnosis of the 4.3% of group with no chest pain and increased troponin was hyperglycemia or ketoacidosis. Mahajan et al. (2006) found similar prevalence of elevated troponin levels caused by diabetic ketoacidosis at 2% in the group with elevated cardiac troponin levels not caused by myocardial infarction (MI) or coronary artery disease. A study by Moller et al. (2005) focused on 2 patients with Type 1 diabetes whose elevated cTnT levels and at first ECG changes similar to myocardial infarction, posed a confusing situation for whether the patients were experiencing MI or cTnT leak due to severe ketoacidosis. Yet the absence of any chest pain, normal coronary angiogram, and ECG

changes that could have been otherwise attributed, suggested that MI was not the causes of elevated cTnT. The researchers concluded that while the exact mechanism of myocardial damage could not be proven, severe DKA can lead to myocardial injury not due to any abnormal vessel changes, perhaps due to the role of acidosis during hypoxia causing myocyte death or elevated free fatty acids in the blood could lead to myocyte membrane abnormalities (Moller et al. 2005). A study by Al-Mallah et al. (2008) with 96 diabetic ketoacidosis patients, 26 of whom had positive troponin levels, had no significant differences in baseline characteristics yet the DKA group with elevated cardiac troponin levels had significantly increased mortality at 2 year follow-up and significantly increased major adverse coronary event rate compared to DKA patients with normal cTn levels. Al-Mallah et al. (2008) suggest that further studies with DKA patients and assessing future cardiac event risk and mortality risk are needed to clarify if patients with DKA impacts the risk assessment of cardiac events and future cardiac care. More research is needed to investigate the mechanism by which cardiac troponins are released when the etiology is diabetic ketoacidosis.

Chronic kidney disease (CKD) has ranges from mild disease that reduces kidney function minimally to renal insufficiency, which is characterized by reduced glomerular filtration rate (GFR) in the kidneys that can progress over time in severity from moderate chronic to severe chronic renal insufficiency, and then to the stage of renal failure where dialysis is necessary. McGill et al. (2010) found that in a study sample of dialysis-dependent chronic renal failure patients, high-sensitive cTnT assays are better predictors of mortality on a longer time frame than the cardiac biomarker NT-proBNP and is more able to discriminate between low and high risk patients for mortality. A study by Dubin et al. (2013) of patients with chronic kidney disease found that cTnT by high-sensitivity assays were found in large majority of the patients and that

there was an association between the lower the estimated GFR the higher the cTnT levels. The study also found other independent associations between variables of older age, male gender, black race, left ventricular mass, diabetes and higher blood pressure and higher cTnT levels, suggesting further research given the other associations to be able to implement further risk classifications to subgroups in patients with CKD and elevated cTnT. Pfortmueller et al. (2013) found comparable results to Dubin et al. that high-sensitive cTnT levels correlated inversely with estimated GFR in patients with renal insufficiency. The research by Pfortmueller et al. (2013) also included the accuracy of myocardial infarction diagnosis given the presence of cTnT levels due to renal insufficiency with the symptoms of chest pain and shortness of breath and found that diagnostic accuracy was about 50/50 (correlation coefficient of 0.535). Cardiac troponin T, especially with high-sensitivity assays, is a strong predictor of mortality in patients with chronic kidney disease over that of other cardiac biomarkers (McGill et al. 2010). cTn levels not only predict mortality but also have a strong inverse correlation with estimated GFR in patients with renal insufficiency (Dubin et al. 2013; Pfortmueller et al. 2013). While cardiac troponins have a use in risk assessment for patients with chronic kidney disease, their presence poses a challenge to these patients that may also be experiencing other cardiovascular events that rely on a diagnostic biomarker like cTnT.

Pulmonary embolism is the blockage of an artery (and thus blood flow) in a lung due to the dislodging of a formed thrombus in another location that traveled to the lungs. Pulmonary embolism has been found as the etiology of elevated cTn levels at an incidence equal to that of diabetic ketoacidosis induced cTn elevation (Mahajan et al. 2006). Mahajan et al. (2006) proposed that a large pulmonary embolism could cause increased oxygen demand by the right ventricle, due to insufficient pulmonary blood flow and oxygenation, leading to right ventricle

dilation and ischemia causing the release of cardiac troponins into the blood. A study focusing on acute pulmonary embolism in the elderly population by Ng et al. (2013) found that elevated cTnT levels in these patients were significantly and independently associated with mortality during hospital stay or long-term. Arram et al. (2013) found that cTnI and myoglobin levels were significantly associated with cardiac side-effects of acute pulmonary embolism, assessed by ECG right ventricular strain and dysfunction. Pulmonary embolism can directly affect heart function by impairing oxygen supply to the heart. This heart ischemia leads to released cardiac troponins. Perhaps cardiac troponin level associations with heart function impairment from pulmonary embolism can lead to better management of these patients to help prevent and look out for cardiac complications and death.

While exercise is known to be beneficial to cardiovascular health, prolonged endurance exercise has been found to result in cardiac impairments, such as left ventricular functional impairment and atrial fibrillation/flutter, and the release of cardiac biomarkers such as cardiac troponins into the bloodstream (Shave and Oxborough 2012; Heidüchel et al. 2006). A study by Mehta et al. (2012) found that previous exercise training (defined as the average number of miles run per week) was significantly negatively associated with the amount of cTnI in the bloodstream after a marathon, implying that exercise training history is related to cTnI release. An earlier study by Sahlén et al. (2009) found comparable results to the later results by Mehta et al. when focused on a sample of endurance runners ages greater than or equal to 55 years looking at cTnT, where those with elevated troponin levels were independently predicted by less previous long distance running training experience, older age and a greater increase in creatinine levels. High sensitivity assays of cardiac troponin I were found to show a significant increase in cTnI in athletes competing in a half marathon run compared to insignificant or undetectable

levels of cTnI in the athletes using the conventional immunoassay (Lippi et al. 2012). While Lippi et al. (2012) did not find significant results with the conventional assay, the methodology used by Mehta et al. (2012) does not include the use of high sensitivity cTnI assays yet produced significant results. A study by Tian et al. (2012) comparing adolescent and adult athletes response to treadmill exercise by changes in cTnT levels using high-sensitivity assays found that in both adolescents and adults cTnT levels significantly increased by the completion of the exercise and peaked at 3 to 4 hours post-exercise. However the adolescent group had a significantly higher peak high-sensitivity cTnT level after the same exercise, even when the participants had been matched, and the study could not conclude why the adolescent group showed such results for more research is needed (Tian et al. 2012). On a longer time frame reported by Tian et al. (2012), cTnI was found to peak around 9 hours after walking exercise of moderate-intensity, yet even at a delayed peak time, the study still showed that even in less intense cardiovascular exercise than marathon-like events in other studies led to a comparable increase in circulating biomarker levels (Eijsvogels et al. 2010). Eijsvogels et al. (2010) also found that higher post-exercise cTnI levels were related to walking speed, increased age and presence of cardiovascular pathologies. It is important to note again that the methodology differences between using high-sensitivity assays and conventional assays seems to impact the results of studies regarding endurance exercise-induced cardiac troponin release, as shown when comparing the study results of Lippi et al. (2012) and Mehta et al. (2012) for example, for the scale of the troponin release may be much smaller than that of diagnostic use for other etiologies discussed. Thus it may be unrealistic to draw a conclusion that prolonged endurance exercise causes cardiac troponin release comparable to other etiologies or that it implies cardiac damage that is significant (and if so, to a point that it is more harmful than beneficial). Much more

research is needed to elucidate an accurate view of possible cardiac damage due to endurance exercise and if biomarkers such as cTnT or cTnI can be used with the same prognostic strength as in other etiologies.

Conclusion

Elevated cardiac troponin I and T levels have an established role in the diagnosis of acute coronary syndrome, yet the lack of elevated troponins does not discount the presence of ACS. The presence of elevated cardiac troponin levels does correlate as a prognostic marker for higher mortality in patients with ACS, the mortality predicted by elevated cTn levels is much higher in those with non-ACS or even non-cardiac etiologies. Thus elevated cardiac troponin levels are useful in predicting high risk patients with causes ranging from myocarditis to heart failure to renal failure. While the mechanisms of elevated cardiac troponin levels are quite unknown in most situations outside of myocardial infarction, where the direct ischemia has a logical consequence of myocyte death proposed as either apoptosis or membrane disruption, other etiologies linked to elevated cardiac troponin levels do not have a clear mechanism. Future research should focus on the mechanism of release in etiologies well documented to be prone to cardiac troponin elevation, so that clinicians may better assess risk of future cardiac events and even death based on the degree of cardiac injury. There is a potential that cardiac troponin assays could, with more research into mechanisms of cardiac damage, enhance care in many different diagnostic categories, whether the etiology itself is cardiac related or not.

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