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STATE-OF-THE-ART PAPER

Cardiac Troponins in Renal Insufficiency

Review and Clinical Implications

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Patients with renal insufficiency may have increased serum troponins even in the absence of clinically suspected acute myocardial ischemia. While cardiovascular disease is the most common cause of death in patients with renal failure, we are just beginning to understand the clinical meaning of serum troponin elevations. Serum troponin T is increased more frequently than troponin I in patients with renal failure, leading clinicians to question its specificity for the diagnosis of myocardial infarction. Many large-scale trials demonstrating the utility of serum troponins in predicting adverse events and in guiding therapy and intervention in acute coronary syndromes have excluded patients with renal failure. Despite persistent uncertainty about the mechanism of elevated serum troponins in patients with reduced renal function, data from smaller groups of renal failure patients have suggested that troponin elevations are associated with added risk, including an increase in mortality. It is possible that increases in serum troponin from baseline in patients with renal insufficiency admitted to hospital with acute coronary syndrome may signify myocardial necrosis. Further studies are needed to clarify this hypothesis. (J Am Coll Cardiol 2002;40:2065–71) © 2002 by the American College of Cardiology Foundation

The interpretation of elevated serum markers of myocardial necrosis in patients with renal insufficiency is controversial. Traditional serum markers of myocardial necrosis such as creatine kinase, MB-fraction of creatine kinase (CK-MB) and myoglobin are commonly increased in renal failure, even in the absence of clinically suspected myocardial ischemia (1,2). Cardiac troponins are more specific markers of myocardial necrosis. However, cardiac troponins are elevated in some patients with renal failure, even in the absence of clinically suspected ischemia (3–6). Large-scale trials of patients with acute coronary syndromes have documented the importance of troponin elevations in risk stratification, prognosis, and therapeutic utilization (7–9). However, most of these studies excluded patients with elevated serum creatinine.

Cardiovascular disease accounts for roughly 50% of deaths in patients with chronic renal failure (10) and in this cohort the prevalence of coronary artery disease may be as high as 73% (11). Patients with renal failure are at higher risk for silent ischemia and atypical clinical presentation during an acute coronary syndrome (12,13). Angina is often absent in patients with both end-stage renal disease (ESRD) and coronary artery disease, occurring in only 17% in one study (14). The electrocardiogram can be equally unreliable, as ST-segment changes are difficult to interpret secondary to left ventricular hypertrophy, electrolyte disturbances, conduction abnormalities and medications.

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In this paper, we discuss the frequency of cardiac troponin elevations in patients with renal dysfunction, with attention to assay technology and the discordance in the frequency of elevations between cardiac troponin I (TnI) and cardiac troponin T (TnT). In addition, we review the pathophysiology of troponin release, its modification and clearance from the circulation, and possible explanations for troponin elevations in patients with renal insufficiency. Finally, we summarize available evidence pertaining to prognosis and risk stratification using cardiac troponins in renal failure, and make a practical suggestion on how to better interpret elevated serum cardiac troponin levels in patients with impaired renal function and suspected acute coronary syndrome (ACS).

CARDIAC TROPONIN T AND TROPONIN I ELEVATIONS IN RENAL INSUFFICIENCY: PREVALENCE AND CHARACTERISTICS

Troponin biology and assay technology. Three troponin proteins are present in both cardiac and skeletal muscle. Cardiac troponin C is identical to the troponin C expressed in skeletal muscle. However, cardiac TnT and TnI are each derived from genes that are specific to the heart (15). Monoclonal antibody assays can detect cardiac-specific TnT and TnI (16). The original first generation TnT assay consisted of a capture and detection antibody which bound TnT in the sample, forming a sandwich complex. Recognition of TnT requires that each of the two antibodies recognize the same protein in the sample. The capture antibody was cardiac specific, but the detection antibody cross-reacted with skeletal muscle TnT (17). In 1997, a

Abbreviations and Acronyms

ACS	= acute coronary syndrome
CK-MB	= MB-fraction of creatine kinase
ESRD	= end-stage renal disease
TnT	= serum cardiac troponin T
TnI	= serum cardiac troponin I

second-generation assay using cardiac specific capture and detection antibodies was introduced with no cross-reaction with skeletal TnT (18). Data derived from first-generation cardiac TnT assays used after this date are no longer considered "the gold standard" for laboratory testing. A newer third-generation assay with similar specificity is now available using the same cardiac-specific antibodies and substituting recombinant human cardiac TnT as the material standard (19).

Frequency of cardiac TnT and TnI elevations. Studies using the original first generation troponin assays on small groups of patients with ESRD without clinical or electrocardiographic evidence of acute ischemia report up to 71% of patients having increased TnT (3,20–22). Troponin I is increased in only about 7% of patients with renal failure (3,20,22,23). In two of these studies the number of TnT-positive patients declined significantly when a more cardiac specific, second generation TnT assay was used (71% to 17% and 54% to 15%) (3,22). However, second generation TnT assays continue to demonstrate increased TnT in up to 53% of patients with renal failure and no clinical evidence of acute myocardial necrosis (3,22,24–31).

Discordance between cardiac TnT and TnI elevations. Using the most current assays, cardiac TnT is elevated more frequently than cardiac TnI in patients with renal failure. The lower incidence of TnI elevations and the lack of expression of cardiac TnI in non-cardiac tissue (3,32,33) has prompted some to suggest that TnI may be a more specific diagnostic and prognostic marker of ischemic heart disease in patients with renal failure (34–36). However, this is not the case in patients without renal failure, where two meta-analyses (37,38) have shown similar ability of TnI and TnT to predict adverse events.

Several important differences in cellular biology, protein chemistry and assay technology between the two troponins make it difficult to conclude that TnI is more cardiac specific than TnT in the setting of renal failure. Approximately 7% and 3.5% of cardiac TnT and TnI exist freely in the cardiac myocyte cytoplasm, respectively (39). The rest is bound within the sarcomere. This cellular distribution determines release kinetics (40), with free cytosolic proteins being released earlier. The TnT content per gram of myocardium is roughly twice that of TnI (41). Additionally, TnI assays may have more imprecision at the lower end of the reference range compared to assays for TnT (24). It is unknown whether these differences impart an advantage favoring TnT over TnI in the detection of smaller amounts of myocardial necrosis.

Dialysis may differentially affect serum levels of TnT and TnI. Regardless of the method of clearance or type of membrane used, TnI levels decreased by up to 86% from pre to post dialysis (24). However, mean TnT increased post dialysis, and the percent of patients with elevated troponins was higher post-dialysis, possibly due to hemoconcentration. Although the membranes used in their study should only clear molecules with a maximal weight less than intact TnT or TnI, the authors speculated that TnI, may adsorb onto the dialysis membrane because of its hydrophobicity. These findings have been confirmed by some groups (42,43), but refuted by others (44).

Troponin T and TnI are released in different forms from damaged myocytes after acute myocardial infarction (Fig. 1) (45). Troponin T is released as intact TnT:I:C complex, free TnT and smaller immunoreactive fragments. However, TnI is only identified in intact TnT:I:C complex and TnI:C. As a result of its hydrophobicity, free TnI may bind to other

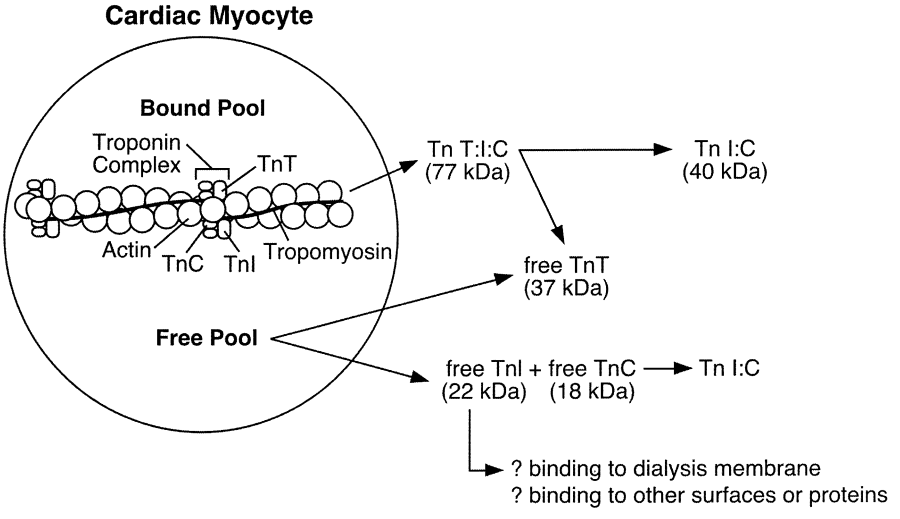

Figure 1. Troponin release profile after myocardial infarction. kDa = molecular weight in kiloDaltons; TnC = cardiac troponin C; TnI = troponin I; Tn T:I:C = intact troponin complex; Tn I:C = binary troponin I:C complex; TnT = troponin T.

surfaces and/or proteins, thus potentially masking its antigenic epitopes (46). Uremia augments the free serum concentration and clearance of highly protein-bound drugs such as fosphenytoin (47). It is unknown if uremia can alter the detection, release or clearance of different troponin subunits in the serum. This may be especially relevant for protein bound cardiac TnI.

Once released into the circulation, TnI is susceptible to various biochemical modifications including phosphorylation, oxidation and proteolysis (46,48,49). Proteolysis of TnT has been described to a lesser extent (48). These modifications affect the interaction of TnI with other troponin molecules and alter recognition by monoclonal antibodies, thus affecting assay performance (46,48,49). Furthermore, pathological states such as ischemia and myocardial stunning result in altered proteolytic profiles of TnI (50). The specific effects of renal failure on TnI chemistry are unknown and studies characterizing the biochemical profile of troponin degradation products in these patients may provide helpful information. Perhaps TnI is more susceptible to chemical modification and less stable than TnT in the circulation of patients with renal insufficiency.

ORIGIN OF CARDIAC TROPONIN ELEVATIONS IN PATIENTS WITH RENAL INSUFFICIENCY

"Uremic skeletal myopathy": A source of cardiac troponin T? Many investigators hypothesize that uremic-induced skeletal myopathy may be responsible for increased troponins in renal failure. The hypothesis centers on the notion that uremia may promote re-expression of cardiac TnT from injured or regenerating skeletal muscle fibers. Indeed, the skeletal muscle from patients on maintenance hemodialysis has significant morphological changes by both electron and light microscopy (51). Early reports describe elevated serum TnT levels in patients with skeletal muscle injury or inflammatory myopathies in the absence of any obvious history of myocardial ischemia (52,53). Serum levels of cardiac TnT are also increased at the end of a marathon in male runners without known coronary artery disease (54). These reports used first generation TnT assays that have known cross-reactivity to skeletal TnT.

Several isoforms of cardiac TnT have been described in developing and adult myocardial tissues (16,55,56). A TnT species closely resembling cardiac TnT isoforms has been found in human fetal skeletal muscle (57) and in skeletal muscle of other developing animals (56). These cardiac-like TnT isoforms decrease during maturation, resulting in their absence in non-diseased adult human and rat skeletal muscle (16,32,56,57). On the contrary, neither cardiac TnI nor any of its isoforms have been demonstrated in skeletal muscle (3,32,33).

Could the metabolic perturbations of renal failure stimulate re-expression of cardiac TnT isoforms in skeletal muscle? Perhaps more importantly, if re-expression of cardiac TnT isoforms takes place in skeletal muscle, can these isoforms be detected in the serum of patients with renal failure by the current TnT serum assays? Using polymerase chain reaction or western blot techniques, some groups have identified cardiac-like TnT isoforms and messenger ribonucleic acid in skeletal muscle from patients with ESRD (3,16,18,32). However, the monoclonal antibodies in the second-generation TnT would not detect the cardiac TnT isoforms in these samples (16,32) or in skeletal muscle biopsies from Duchenne muscular dystrophy patients with increased serum cardiac TnT and no clinical or echocardiographic evidence of cardiac disease (58). There is no close association between increased serum cardiac TnT and clinical or electromyographic changes of skeletal myopathy in patients with ESRD (59). In summary, there are insufficient data to support a skeletal muscle source for serum cardiac TnT elevations in patients with ESRD.

Other potential contributions to serum troponin elevations. Serum troponin elevation may be the result of small areas of clinically silent myocardial necrosis. Pathological evidence exists documenting the presence of such micro-infarctions in patients with elevated troponins (60,61). These infarctions may be unrecognized clinically and may not be associated with increased serum CK-MB. It is possible that patients with ESRD are more likely to sustain repeated episodes of clinically silent micro-infarctions secondary to their high incidence of coronary artery disease.

There are data indicating that serum TnT and TnI are increased in patients with heart failure in the absence of acute ischemia (62,63). Such troponin elevations associate with prognosis and severity of heart failure (62), although a recent study has demonstrated that only serum elevations of cardiac TnT but not TnI were predictive of all cause and cardiovascular mortality in patients with dialysis-dependent renal failure (64). Patients with renal failure have a high incidence and prevalence of heart failure, and epidemiological data suggest that the prevalence of heart failure increases during the transition from mild renal insufficiency to ESRD (65). There is a possibility that apoptosis might explain modest elevation of serum troponin, but this concept has been understudied. If increased serum troponins in patients with decreased renal function indicate myocardial damage, could these markers identify patients at risk to develop heart failure? Such patients might benefit from further testing with echocardiography. In one small study, all patients with chronic renal failure, elevated antemortem cardiac TnT and no clinical evidence of acute myocardial infarction, had cardiac pathology consisting of either recent acute myocardial infarction/microinfarct, healing microinfarct, heart failure/degenerative changes or other myocardial pathology (60).

Patients with renal failure frequently have left ventricular hypertrophy. The presence of left ventricular hypertrophy is significantly correlated with increased TnT in patients with ESRD without acute myocardial ischemia (66). The relative amount of individual troponin isoforms changes in hyper-

trophied myocardium (67). It is possible that failing or hypertrophied hearts have a different mechanism of release of troponin into the serum, reflecting overall changes in myocardial protein turnover (68).

It is unlikely that elevated serum troponin is the result of decreased clearance by the failing kidney. Free TnT and bound TnT are relatively large molecules (37 and 77 kDa, respectively), similar in molecular weight to albumin (60 kDa), making it improbable that the kidney would be responsible for their clearance. Creatine kinase and its isoforms are of similar size and are mainly cleared by the reticulo-endothelial system (69), whereas myoglobin is smaller (18 kDa) and cleared by the kidney (70). It is possible that smaller immunoreactive troponin fragments are cleared by the kidney, but this remains to be clarified. Improvement in renal function after renal transplant does not appear to alter the occurrence of elevated serum troponin (71). Even if the kidney were partially responsible for troponin clearance, it does not explain why troponin is released from the heart. Furthermore, the majority of studies have failed to show a relationship between serum creatinine concentrations and overall frequency or degree of troponin elevation (3,6,44,72). During myocardial necrosis the elimination rate and apparent half-life of serum cardiac TnI is not significantly different in patients with normal renal function or ESRD (73). Additionally, preliminary results from western blot analysis fail to implicate renal tissue as the source of serum cardiac TnT in patients with renal failure (74).

CARDIAC TROPONIN ELEVATION IN RENAL INSUFFICIENCY: WHAT DOES IT MEAN?

Reports of positive serum troponin in patients with renal failure have relied upon historical, clinical, electrocardiographic and rarely, echocardiographic data to exclude ischemic myocardial injury. Other studies have incorporated traditional markers such as CK-MB as the diagnostic benchmark to "diagnose" acute myocardial infarction. The resting electrocardiogram and risk factors taken from the medical history are neither sensitive nor specific in diagnosing acute myocardial ischemia (75). Furthermore, the use of traditional cardiac markers as the diagnostic standard for acute ischemic injury assumes that troponins have an inferior or equal sensitivity.

The decreased sensitivity of functional stress testing in patients with ESRD (76) and the lack of information on plaque morphology provided by angiography, may leave us without a true laboratory or radiological gold standard to diagnose myocardial ischemia/infarction. Rather, we may have to rely on cardiovascular and overall clinical outcomes to determine if troponin elevations in patients with renal failure are reflective of cardiovascular disease and/or increased risk of death.

Patients with renal insufficiency and no suspicion for myocardial ischemia. Multiple studies have been published regarding the prognostic power of serum troponin in the setting of renal insufficiency (24–27,31,35,44,72). Recently, several studies using second-generation cardiac troponin assays in larger populations studied over a longer period of time have been published. A significant difference in overall one year survival was noted for patients with ESRD and serum TnT $>$ 0.1 ng/ml by laboratory and bedside second-generation assays (28). Another group studied 102 patients with ESRD without any clinical evidence of acute ischemic heart disease (29). Troponin T $>$ 0.1 ng/ml was strongly associated with all cause mortality and TnT $>$ 0.05 ng/ml was associated with fatal cardiovascular disease events. This association was independent of baseline presence of heart disease. All patients with non-detectable TnT were alive at follow up. The largest population studied to date was recently published, consisting of 244 patients on chronic hemodialysis for up to 34 months (30). Troponin T was significantly associated with death from all causes, with the strongest association for TnT values above the clinical event threshold of 0.1 ng/ml. A trend of increasing TnT measurements during longitudinal follow up was also predictive of progression of cardiac disease and all-cause mortality. Taken together, the three largest prospective studies of patients with renal failure strongly suggest an association between troponin elevation and risk of death. We believe that TnT may prove to be a marker of subclinical myocyte damage in patients with renal failure. This may be secondary to clinically silent myocardial necrosis or perhaps, unrecognized heart failure.

Patients with renal insufficiency and suspected acute coronary syndrome. In the setting of suspected ACS and renal failure, the interpretation of serum troponin is problematic. Martin studied 56 patients with renal failure suspected of having acute myocardial ischemia (34). Patients with elevated TnI subsequently underwent echocardiography, nuclear stress testing or angiography. Each patient had a study positive for myocardial ischemia. Troponin I was more sensitive (94% vs. 44%) and specific (100% vs. 56%) than CK-MB for predicting myocardial ischemia. This was subsequently confirmed in another study (36). A recent report showed that elevated TnT or TnI was less predictive of adverse outcomes (in hospital and at six months) in patients with suspected ACS and renal failure (72). The authors suggested using a higher threshold for TnT (0.5 μg/l) to optimize accuracy in predicting adverse outcomes. No significant difference in predictive value was found comparing the two troponins directly. However, a recent analysis of 7,033 patients from the Global Use of Strategies To Open occluded coronary arteries (GUSTO)-IV ACS trial found that the prognostic value of cardiac TnT was not diminished in patients presenting with renal insufficiency and suspected ACS (77). In fact, patients who presented with positive TnT and concomitant renal insufficiency had the highest overall risk of death or acute myocardial infarction. In a retrospective analysis comparing with standard biomarkers such as myoglobin or CK-MB, cardiac TnI was also found to be the most consistent marker

across the spectrum of patients with renal dysfunction (including dialysis-dependent patients) in the setting of acute evaluation for suspected myocardial infarction (78).

From a practical standpoint, sequential serum troponin levels should be measured in patients with renal failure and suspected ACS. A sequential rise in serum troponin is consistent with new myocardial damage in patients with renal insufficiency. This can be measured in multiple time-points during the early hours of presentation. An elevated but invariant troponin level may be more consistent with no new myocardial injury. The clinical status of the patient must also guide the clinician in interpreting the significance of troponin elevations in patients with renal failure and suspected ACS.

Treatment of patients with renal insufficiency and elevated serum troponins. There are no specific guidelines regarding therapy for patients with renal insufficiency, suspected ACS and elevated serum troponins. All patients with ACS and renal insufficiency should be risk stratified according to their clinical stability, serum markers and 12-lead electrocardiogram. It is reasonable to administer antiplatelet therapy, beta-blockers, oxygen and nitroglycerin. The use of antithrombin inhibitors and glycoprotein IIb/IIIa antagonists is unclear at this time, since patients with renal insufficiency have been excluded from most clinical trials. Recent data have shown effectiveness and safety of tirofiban in patients with mild to moderate renal insufficiency (79). The decision to use early coronary angiography must be individualized.

Patients with clinically stable ESRD and elevated serum TnT should be treated with aggressive risk factor modification (HMG-CoA reductase inhibitors, aspirin, and antihypertensive therapy). If echocardiography reveals LV dysfunction, appropriate therapies should be instituted at doses commensurate with renal function. Coronary angiography is the gold standard for establishing the diagnosis of coronary disease and should be considered, especially in patients being evaluated for renal transplantation. The decision to use percutaneous and surgical revascularization in this patient population is complex, as these patients generally have more severe coronary lesions, higher rates of re-stenosis and higher peri-procedure morbidity and mortality (80).

Conclusions. Measurement of serum cardiac troponin has revolutionized the management of ACS. It is a reliable biomarker, useful to guide therapy and to predict outcomes. However, increased serum cardiac troponin levels are frequently observed in patients with renal insufficiency even when the suspicion of active ischemia is relatively low. Although the underlying pathophysiology of this abnormality is still not clearly understood, it may reflect ongoing, often subclinical, myocardial damage (or micro-infarctions) that is partially independent of acute ischemic injury. Whatever the mechanisms involved, sequential serum cardiac TnT or TnI elevation is indicative of acute myocardial damage and denotes increased risk of morbidity and mortality in patients with renal insufficiency regardless of the presence of symptoms. In contrast, the negative predictive value of troponins is still highly useful in this population. Further studies are necessary to determine the disease mechanism behind persistently elevated serum troponin levels in asymptomatic patients with chronic renal failure.

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