www.cardiologyrounds.ca AUGUST/SEPTEMBER 2003 volume VIII, issue 7

CARDIOLOGY Rounds®

AS PRESENTED IN THE ROUNDS OF THE DIVISION OF CARDIOLOGY, ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Troponin: A window for assessing the high cardiovascular mortality in chronic renal failure

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Cardiovascular disease (CVD) is the leading cause of death in patients with end-stage renal disease (ESRD) and accounts for about 50% of overall mortality.[1] The prevalence of coronary artery disease (CAD) is high in this patient population, likely the result of associated comorbidities such as advanced age, diabetes, hypertension, and dyslipidemia. In addition, ESRD itself may play an important role in cardiovascular pathophysiology through activation of the sympathetic nervous and renin-angiotensin-aldosterone systems, increased oxidative stress and inflammatory response, hyperhomocysteinemia, promotion of endothelial dysfunction, and vascular calcification.[1] It is now recognized that renal dysfunction of any severity is a powerful independent predictor of adverse outcome in acute coronary syndromes (ACS).[2,3,4] In the US Renal Data system, the mortality rate after myocardial infarction (MI) among 34,189 ESRD patients was approximately 60% and 90% at 1 and 3 years, respectively.[5] It is evident that patients with ESRD carry an enormous CVD burden and early accurate diagnosis with aggressive treatment is an important strategy to improve their prognosis.[6,7] However, the diagnosis of ACS is often difficult in patients with renal dysfunction. For example, silent myocardial ischemia is frequent in patients with diabetes, which is the leading cause of renal failure today. In addition, the electrocardiogram (ECG) may be difficult to interpret due to the presence of left ventricular (LV) hypertrophy and conduction abnormalities. Conversely, the clinical presentation may also resemble ACS, with symptoms due to acute pulmonary edema resulting from volume overload and diastolic dysfunction rather than myocardial ischemia. As the overall clinical picture is often unclear, a sensitive and specific cardiac marker would be most helpful in this situation. This issue of *Cardiology Rounds* presents the current knowledge about troponin and its use as such a marker in patients with chronic renal failure.

Troponins

Troponins (Tn) comprise 3 distinct proteins – I, C, and T – that regulate the calcium-dependent interaction of the contractile proteins myosin and actin in the skeletal and cardiac sarcomere.[8] Because the cardiac troponins I (cTnI) and T (cTnT) are structurally different from their skeletal counterparts, over the past decade, sensitive immunosorbent assays have been developed and used as diagnostic tests. Under normal circumstances, neither cTnI, nor cTnT is detectable in the circulation. Consequent to the increased sensitivity and specificity of cTn compared to prior markers of myocardial necrosis (ie, creatine kinase and its isozyme CK-MB), the current ACC/ESC guidelines state that cTnI and cTnT are the preferred biomarkers for the diagnosis of MI,[9] and that an MI is diagnosed in appropriate circumstances when the cTn exceeds the 99th percentile value for a reference control population.

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Multiple studies have established the prognostic value of cTn in ACS.[10,11] In addition, cTn has been shown to be a useful marker for identifying high-risk patients who benefit from potent pharmacological therapies and an early invasive risk stratification.[12,13] Unfortunately, the clinical utility of cTn among patients with renal failure remains unclear and this has created much confusion for physicians caring for these patients.

Prevalence of elevated troponins in patients with renal failure

The prevalence of elevated cTn depends on the patient population, the severity of renal dysfunction (dialysis-dependent or not), the troponin assay used, and the chosen cutoff value. Elevated cTn levels in the ESRD population are associated with advanced age, history of ischemic heart disease, diabetes, and LV hypertrophy.[14,15,16] Older first-generation cardiac cTnT assays exhibited cross-reactivity with skeletal muscle troponin, giving rise to a high rate of apparently false-positive tests. The currently available second- and third-generation assays show minimal cross-reactivity and are more specific. Using these newer assays, studies demonstrate that the prevalence of elevated cTnT ranges from 17% to 53% among asymptomatic patients with ESRD.[14-20,22] The prevalence of elevated cTnI is significantly lower, ranging from 3% to 15%.[14-17,21,22] Abnormal cTn was defined using the manufacturers' recommended upper reference limit in most of these studies. The proportion of patients with abnormal cTn varies greatly when different cutoff levels are chosen (eg, 99th percentile of a normal population).[22]

A comparison of cTnI and CK-MB results shows a closer relationship than that observed with cTnT.[15,16] There appears to be an important discordance between cTnT and cTnI measurements in the ESRD population, with a correlation coefficient of 0.14 and a kappa value of 0.19, suggesting poor agreement.[16,17] Hemodialysis may differentially alter the serum levels of cTnI and cTnT, resulting in a rise of cTnT and a decrease of cTnI.[17,18] The reason for this observation remains unclear, but it has been speculated that cTnI, is more hydrophobic and may be more readily adsorbed onto the dialysis membrane. In contrast, hemoconcentration may cause the increase in cTnT level after dialysis.[17]

The greater prevalence of elevated cTnT compared to cTnI is unlikely to be explained by the effect of dialysis, since pre-dialysis levels were measured in most studies. Differences between cTnI and cTnT release kinetics, cellular concentrations and distributions, precision of assays at lower detection thresholds, are more likely to account for the discrepancy of abnormal results.[23] Furthermore, because cTnI is more susceptible to biochemical modifications and binding to serum proteins that mask the antigenic epitope, cTnI and its metabolites may be less stable and more difficult to detect in the uremic milieu.[23] The prevalence of abnormal cTn is significantly less among patients with renal failure not requiring dialysis. In one study, only 4% of 83 moderate to severe renal failure patients (mean creatinine level 218 µmol/L) had elevated cTn levels.[14] However, no precise relationship exists between serum creatinine and cTn concentrations.[24,25]

Mechanisms of troponin elevation in patients with renal failure

It has been suggested that isoforms of cTnT are expressed in injured and regenerating skeletal myocytes from patients with renal failure.[23] An isoform of TnT that closely resembles cTnT is described in the skeletal muscle of patients with ESRD.[23] The cross-reactivity between this isoform and the antibodies used in first generation cTnT assays results in a high false-positive rate. However, despite the use of more specific antibodies in the second- and third-generation assays, a high prevalence of abnormal cTnT levels continues to be observed amongst the ESRD population. Moreover, the hypothesis fails to explain the abnormal cTnI levels since a similar skeletal muscle isoform of cTnI has not been identified.

Decreased renal clearance of cTn has been proposed as a possible mechanism. Yet, several lines of evidence argue against this supposition. First, cTnT and cTnI often form complexes with other proteins, resulting in molecular weights similar to that of albumin, which is not cleared by the kidney.[24] In a small study of 35 patients with acute MI, the apparent half-lives of cTnI were similar among patients with ESRD and those with normal renal function.[26] Furthermore, there is no significant correlation between serum creatinine and Tn levels.[24,25] More importantly, even if the kidney played an important role in cTn clearance, it would not account for the origin of circulating cTn detected by the specific assays.

A more plausible mechanism for the persistent elevation of serum cTn levels is from an as yet unexplained myocardial source. Abnormal cTn levels should not be regarded merely as the result of a lack of specificity since there is no true "gold standard" for myocardial necrosis. Furthermore, it is quite possible that patients with renal failure have ongoing silent or otherwise subclinical cardiomyocyte damage.[23] For example, uremic pericarditis can occur in this patient population despite dialysis and

can lead to epicardial myocyte injury. Cardiomyopathy may result from toxins that are not removed by the failing kidney. Hypertension and left ventricular hypertrophy are common among ESRD patients, and chronic pressure and volume overload may result in myocyte stretch and loss of membrane integrity. While some studies have demonstrated a correlation between Tn level and degree of hypertrophy or systolic dysfunction,[15,27] this is not a consistent finding.[28] Most importantly, because atherosclerosis is so prevalent in this patient population, an elevated cTn level may result from myocardial necrosis secondary to epicardial or microvascular CAD. However, all these hypotheses (Table 1) remain unproven and it is likely that several mechanisms are responsible.

Table 1: Possible mechanisms of troponin elevation in renal failure

- Uremic skeletal myopathy*
- Decreased renal clearance*
- Uremic perimyocarditis
- Toxic cardiomyopathy
- Marked changes in ventricular volume or afterload, leading to myocardial injury
- Epicardial coronary artery stenosis causing silent micro-infarctions
- Microvascular coronary artery disease

* Unlikely mechanisms

Prognostic value of elevated troponins in patients with renal failure and ACS

In a case-matched study, Van Lente et al suggested that the prognostic value of cTn was reduced in the setting of renal failure.[25] In a much larger study, Aviles et al determined the prognostic value of cTnT in relation to renal function among 7033 patients enrolled in the Global Use of Strategies to Open Occluded Coronary Arteries IV (GUSTO IV).[29] In a multivariate analysis adjusting for other potential confounders, abnormal cTnT was associated with a significantly higher risk of death or MI at 30 days, regardless of the calculated creatinine clearance rate (adjusted odds ratios ranged from 2.4 to 4.8). In the Canadian ACS Registry, a prospective multicentre observational study, creatinine clearance rates were determined in 3531 patients with ACS. Similar to other studies, renal impairment was a powerful independent predictor of mortality at 1-year follow-up. During initial hospitalization, cTnT or cTnI was measured at the local site using the available assay and its upper reference limit. No significant trend was observed for an increasing prevalence of abnormal cTn across the strata of patients with worsening renal function. In the group with the lowest quartile of creatinine clearance (<54 mL/min), abnormal cTn level was associated with higher one-year mortality (25.2% vs 16.7%, P<0.01) (unpublished data; Dr. S. Goodman). These findings are consistent with those from GUSTO-IV and suggest that cTn remains a useful marker of adverse outcome in the setting of ACS, even in the presence of renal impairment.

Prognostic value of elevated troponin in asymptomatic patients with renal failure

If chronically elevated circulating cTn levels have a myocardial origin, it would not be surprising if they were associated with adverse outcomes. Several studies have evaluated the prognostic value of cTn in ambulatory ESRD patients with no symptoms or ECG abnormalities suggestive of recent ACS and found conflicting results. In a study of 128 consecutive patients undergoing long-term hemodialysis with no history of CAD, an elevated cTn was not associated with any increase in all-cause or cardiovascular mortality over 2 years.[21] However, patients with known ischemic heart disease were excluded and it is possible that patients with abnormal cTnI underwent more aggressive investigations and treatment that altered their natural history. Moreover, there was significant variability with an overlap between "normal" and "elevated" values with the first-generation assay used in this study. A 6-month pilot study showed that both cTnI and cTnT predicted adverse cardiovascular events among 49 asymptomatic ESRD patients, but not among the 83 patients with renal failure not undergoing dialysis.[14] A prospective cohort study of 113 ESRD patients also reported a significant association between elevated cTnI and cTnT levels and 6-month mortality, although the causes of most deaths were noncardiac.[16] Dierkes et al followed 102 ESRD patients for 2 years and found that cTnT (measured using a second-generation assay) was the strongest independent predictor of all-cause mortality.[20] This association did not change significantly after adjusting for other known confounders (adjusted hazard ratio 3.68, 95% CI, 1.62-8.35). A graded relationship between cTnT level and mortality was also evident. Ooi and colleagues observed 224 ESRD patients on hemodialysis for up to 34 months and confirmed the independent association between cTnT level and mortality. In addition, patients with cTnT levels that increased over a 1-year period had a higher mortality rate, lending support to the notion that Tn reflects the underlying disease process.[19]

Table 2: Practical recommendations regarding the use of troponins in renal failure

- A baseline troponin level may be helpful for future reference.
- Although there are no accepted cutoff values, rapidly rising or very high troponin levels are unlikely due to renal failure alone.
- In suspected acute coronary syndromes, repeat measurements during the early phase may clarify the clinical picture.
- Whenever possible, troponin results should be integrated into the overall clinical assessment.
- In confirmed acute coronary syndromes, elevated troponins carry the same prognostic significance as for patients with normal renal function.

In the largest published series, 733 ESRD patients had cTnI and cTnT measurements at baseline and were followed for a median of 1.6 years.[22] The utility of different assay cutoff criteria (99th percentile, <10% coefficient of variation, and receiver-operating characteristic curve analysis) was also compared. In multivariate analysis, an elevated cTnT level was an independent predictor of all-cause mortality, regardless of the decision threshold (hazard ratios ranged from 1.8 to 4.7; all $P<0.01$). In contrast, cTnI was only predictive of mortality above the 99th percentile cutoff value (hazard ratio 2.1; $P<0.01$). This unique study suggests that the chosen upper reference limit may affect the prognostic value of cTnI in the setting of renal failure. A recent study demonstrated the incremental and additive prognostic values of cTnT and C-reactive protein (CRP), a marker of inflammation that is often elevated in the ESRD population.[28] In the angiographic substudy, elevated cTnT, but not CRP, was associated with the presence of extensive CAD.

In summary, the literature to date suggests that increased cTn is an independent predictor of overall mortality among stable patients with ESRD who have no clinical evidence for myocardial necrosis. However, it is noteworthy that the association between cTn and cardiovascular mortality or morbidity is generally weaker. This may be due to the limited sample size of the studies or imprecision in classifying the cause of death.

Clinical and therapeutic implications of elevated troponins in patients with renal failure

Given the current state of knowledge about cTn in the setting of renal failure, how can clinicians utilize this cardiac marker to improve patient care? We believe that a baseline cTn measurement may be helpful as a reference for future comparison (Table 2). At present, no definitive recommendations can be made regarding the preferential use of either cTnI or cTnT: the former is often considered more "specific" and less "sensitive," but this partly depends on the assay and the cutoff criteria used. For patients presenting with ACS, the interpretation of cTn should not be influenced by the presence of renal impairment since the prognostic value of the test is similar in the "renal" and "non-renal" populations. In cases where ACS is suspected, but the clinical assessment is otherwise limited, serial cTn measurements can guide management. For asymptomatic ESRD patients, it is important to realize that there is no absolute threshold that is diagnostic for ACS in this population; cTn levels can be 20- to 30-fold higher than the manufacturers' recommended reference level. Therefore, both the trend and degree of cTn elevation should be considered in its interpretation. A rise in cTn, especially to a high level over several hours, strongly indicates recent myocardial injury. On the other hand, a slightly elevated, but invariant cTn level, is less consistent with new myocardial injury.

Patients with renal failure and ACS are a high-risk population. Although these patients are usually excluded from clinical trials, they may still benefit from potent pharmacological and early interventional therapies to the same, or perhaps an even greater, extent as lower risk patients.[4,6,7] Among asymptomatic renal failure patients, elevated cTn appears to be an independent predictor of mortality. Whether cTn has the same therapeutic implications in the non-renal population remains unclear and future studies should determine whether targeted treatment will improve outcome. Meanwhile, clinicians should adhere to current consensus guidelines on risk factor modification.[30,31]

Conclusion

Increased cTn levels are frequently encountered among patients with ESRD and likely reflect ongoing subclinical myocardial injury, although the precise pathophysiology remains to be elucidated. In the setting of ACS, elevated cTnT and cTnI levels are independent predictors of adverse outcome, as in patients with normal renal function. Accumulating evidence suggests that abnormal cTn levels independently predict higher mortality even among asymptomatic ESRD patients. It must be emphasized that cTn, like any other diagnostic test, is a valuable clinical tool that should supplement, but not replace clinical judgment. When used wisely, cTn has the potential to improve patient care.

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Abstracts of Interest

Do cardiac troponins provide prognostic insight in hemodialysis patients?

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BACKGROUND: The diagnosis of myocardial necrosis in patients with chronic renal failure is often difficult because biochemical markers of cardiac damage such as creatine kinase MB (CKMB) and cardiac troponin T (cTnT) may be

spuriously elevated. Recent small studies also report unexplained elevations in cardiac troponin I (cTnI) in chronic renal failure patients undergoing hemodialysis. The relative incidence of elevated cardiac troponins in this population and their relationship to clinical events remain unknown.

OBJECTIVE: To determine the incidence and prognostic significance of asymptomatic elevations of cTnT and cTnI in patients undergoing hemodialysis for chronic renal failure.

DESIGN: Prospective cohort study.

SETTING: University tertiary care teaching hospital.

PATIENTS: One hundred thirteen patients over 21 years of age undergoing onsite hemodialysis were enrolled between December 1997 and February 1998.

MEASUREMENTS: All-cause and cardiovascular mortality, hospitalization for acute myocardial infarction, unstable angina or congestive heart failure, new onset sustained arrhythmia or need for unscheduled emergency hemodialysis due to volume overload at 30 days and six months.

RESULTS: The incidence of abnormal results for cTnT, cTnI and CKMB were 42%, 15% and 4%, respectively. Independent predictors of mortality at six months were median age greater than 63 years (odds ratio 14.3, 95% CI 1.5 to 130.3, P=0.019) and positive cTnT (odds ratio 13.6, 95% CI 2.5 to 73.2, P=0.002). Diabetics were more likely to have positive cTnI and cTnT results than nondiabetics (P<0.001 and P=0.023, respectively).

CONCLUSIONS: cTnT is commonly elevated in patients with chronic renal failure even in the absence of acute coronary syndromes. cTnT may be an important independent prognostic marker in patients on hemodialysis for chronic renal failure. While less common, elevations of cTnI are more frequent than CKMB elevations. The basis of these cardiac troponin elevations is unclear. These findings may represent, in part, a subclinical myocardial injury, an inflammatory response to chronic renal failure or a chronically volume overloaded state.

Can J Cardiol 2003 Jul;19(8):907-11.

Cardiac troponins have no prognostic value for acute and chronic cardiac events in asymptomatic patients with end-stage renal failure.

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BACKGROUND: Cardiovascular diseases determine overall mortality in patients with end-stage renal failure. Therefore, testing for myocardial ischemia is important. Elevation of cardio-specific troponins have been frequently measured in patients with end-stage renal failure. Thus, we studied systematically whether patients on chronic intermittent hemodialysis without overt coronary heart disease have increased serum levels of cardiac troponin T and cardiac troponin I. After 2 years, the patients were screened again for cardiac events.

METHODS AND RESULTS: The patients had no history of angina during the previous 3 months or myocardial infarction (MI) within the previous 2 years. For analysis we used two cardio-specific assays for troponin T as well as for troponin I and compared the results with the CK-MB concentration. In a number of patients serum concentrations were elevated above the reference range as follows: troponin T rapid bedside assay: 41 of 100 patients, troponin I rapid bedside assay: 27 of 100 patients, quantitative measurement of troponin T: 22 of 100 patients, quantitative measurement of troponin I: 7 of 100 patients, CK-MB: 2 of 100 patients. The increased serum levels of cardiac troponins were neither the result of uremic perimyocarditis (pericardial effusion), changes in the hemodialysis regimen, pulmonary congestion nor were they consistent with the etiology of renal failure. None of the patients with an elevated troponin level in either of the test suffered from any acute cardiac event initially. Within 2 years 18 of 100 patients died, 13 out of them because of cardiac events. Fourteen patients had a myocardial infarction and 19 patients developed angina pectoris. Sensitivity and specificity (0.75 and 0.67) of troponin T rapid bedside assay for MACE (angina pectoris, MI, cardiac death) was lower compared to studies in patients with normal renal function. Correlation between troponin elevation and late outcome was low or absent.

CONCLUSION: Patients on chronic intermittent hemodialysis frequently present with elevated TnT and TnI levels which cannot be used as predictors of acute and chronic cardiac events. Rapid bedside assays have a lower specificity than quantitative assays.

Clin Nephrol 2001;56(1):44-51.

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This publication is made possible by an educational grant from

Novartis Pharmaceuticals Canada Inc.