

Biochemical Markers of Myocardial Ischemia in Renal Failure

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Patients with chronic renal failure are a major cardiac risk population. Coronary artery disease is highly prevalent in these patients and accounts for much of their observed morbidity and mortality. The diagnosis of myocardial ischemia in this group can be difficult. These patients have a high prevalence of abnormal baseline electrocardiograms and echocardiograms, atypical cardiac symptoms, and silent myocardial ischemia.¹ They often are not able to undergo exercise stress tests for risk stratification, and the false-negative rate of pharmacologic stress testing in these patients is unacceptably high.

The *sine qua non* of the diagnosis of acute coronary syndromes is the elevation of the cardiac enzymes. However, these biochemical markers of cardiac injury can be falsely elevated in patients with end-stage renal disease (ESRD). These patients tend to show higher-than-normal concentrations of the creatine kinase (CK) isoenzyme MB (CK-MB) and the cardiac isoenzyme of troponin T without evident cardiac disorder.^{2,3} All these factors make the diagnosis of acute coronary syndromes problematic and often challenging in this patient group.

This article considers the use of biochemical markers for the diagnosis of acute coronary syndromes in the setting of renal failure, with a focus on the cardiac troponins T and I. Their diagnostic and prognostic utility is reviewed.

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE IN PATIENTS WITH RENAL FAILURE

The prevalence of ESRD in the United States is growing at the rate of 7% to 9% per year; by the year 2010, an estimated 350,000 patients will be affected. Reports from the US Renal Data System reveal that the 5-year survival rate of all patients commencing dialysis is 29.4%. Of these deaths, nearly half (47.2%) are of cardiac origin.⁴

Acute myocardial infarction is the cause of death in 10.5% of all ESRD patients, and cardiac arrest the cause of death in 20.2%.⁴ In these patients, congestive heart failure is a strong independent predictor of death. In the Canadian Hemodialysis Morbidity Study, the incidence

of myocardial infarction or angina requiring hospitalization in ESRD patients on dialysis was 10% per year.⁵ The cardiovascular mortality rate in ESRD patients on dialysis is approximately 10 to 20 times higher than in the general population. Atherosclerosis is accelerated in patients on long-term hemodialysis. Coronary revascularization carries much greater morbidity and mortality in ESRD patients. Coronary artery bypass grafting has a mortality rate of approximately 10% in dialysis patients,^{6,7} including a high incidence of perioperative morbidity.⁸

Diabetes mellitus is the cause of 35% of new cases of ESRD annually, and hypertension accounts for an additional 30% of new cases.⁴ Sixty percent to 90% of patients with progressive chronic renal failure develop hypertension before beginning dialysis therapy. Risk factors for coronary artery disease in dialysis patients with diabetes or hypertension include dyslipidemia, elevated homocysteine levels, and abnormalities in calcium and phosphate metabolism, which cause hyperparathyroidism with vascular calcification.

The prevalence of asymptomatic coronary artery disease is 20% to 40% among persons with chronic renal failure. Symptomatic myocardial ischemia is usually caused by atherosclerotic obstructive disease of the epicardial coronary arteries. Clinically significant myocardial ischemia and angina pectoris can occur in some dialysis patients who have no evidence of significant narrowing of coronary arteries on angiography. This outcome probably results from small vessel disease which has been described in association with hypertension, left ventricular hypertrophy, and diabetes mellitus—all common in patients with ESRD.

CREATINE KINASE MB

CK-MB, the traditional marker for myocardial injury, loses its specificity in the setting of renal failure because

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Table 1. Common Noncardiac Causes of Elevated Creatine Kinase Isoenzyme MB Levels

Chronic renal failure/end-stage renal disease
Duchenne's muscular dystrophy
Hypothermia
Hypothyroidism
Polymyositis/dermatomyositis

of noncardiac sources of this enzyme (Table 1). In the general population, an elevation of CK-MB (greater than 1.0 U/L or an MB index greater than 2.5) has a sensitivity for diagnosing acute myocardial infarction of 46.4% at 4 hours and 91.5% at 6 hours after onset.⁹ However, in chronic renal failure patients, nonspecific modest elevations of CK-MB can cause false-positive results at rates of 20% to 30% in the absence of myocardial injury. This elevation has been attributed to increased reexpression of fetal CK-MB in myopathic skeletal muscles in renal patients.¹⁰ Injured skeletal muscle, undergoing regeneration, may produce increased amounts of CK-MB to reach the proportion found in myocardium. Total CK and lactate dehydrogenase may be elevated for similar reasons.

CARDIAC TROPONINS

Troponin (Tn) is a complex of 3 proteins that bind to the thin filaments of striated muscle but is absent in smooth muscle. This complex is part of the regulatory and structural backbone of the contractile apparatus of striated muscle (ie, cardiac and skeletal muscle). The proteins of the troponin complex regulate muscle contraction by modulating the calcium-dependent interaction of actin and myosin. The 3-subunit complex consists of subunit T (TnT), which binds tropomyosin; subunit I (TnI), which inhibits actomyosin-ATPase; and subunit C (TnC), which binds calcium (Figure 1). These intracellular and structural sarcomeric proteins are released into the circulation from injured muscle cells following the loss of cell membrane integrity,¹¹ thereby acting as markers of injury.

Each of the troponin subunits has 3 different isoforms: one for slow-twitch skeletal muscle, one for fast-twitch skeletal muscle, and one for cardiac muscle. Cardiac troponin C is of little value for the specific diagnosis of myocardial ischemia because of extracardiac expression in slow skeletal muscle fibers and the fact that TnC is identical in both cardiac and skeletal muscle. In contrast, cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are ideally suited as serodiagnostic markers for myocardial injury because the heart

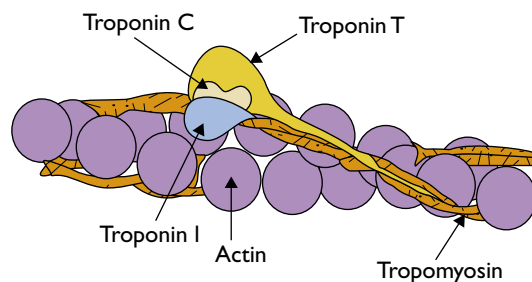


Figure 1. Components of the troponin-tropomyosin complex in cardiac muscle. Troponin T binds the troponin complex to the tropomyosin strand. Troponin C binds calcium and initiates contraction. Troponin I inhibits contraction in the resting state. (Adapted with permission from Collinson PO. Troponin T or troponin I or CK-MB [or none?]. Eur Heart J 1998;19 Suppl N:N17.)

and extracardiac muscles express distinct isoforms.¹¹ No specific immunoassay is presently available to measure cTnC for clinical use.

The different isoforms of the troponin subunits are encoded by different genes. As compared to the skeletal muscle isoforms of troponin I, cTnI has an additional 31 amino acid residues at the N-terminus, and its amino acid sequence shows 40% dissimilarity from the other 2 isoforms. The recognition site of the antibody used in the assay for cTnI is in the cardiac-specific region, which makes the test very specific as a marker for myocardial injury. cTnI is not upregulated in skeletal muscle with hypertrophy or injury, and also the skeletal form is not upregulated in the heart with hypertrophy or injury. cTnT and cTnI, which are expressed in cardiac muscle and not in healthy adult skeletal muscle or other tissue types, possess high cardiac specificity.

The early increase in troponin levels after acute myocardial infarction is largely explained by the presence of cytosolic cTnT and cTnI—pools of soluble unbound enzyme in the sarcoplasm—that may be rapidly released after myocardial damage. These reservoirs account for approximately 5% of total cTnT and 3% of total cTnI¹² and are roughly equivalent to the amount of CK-MB present in the cytosol. However, a substantial amount of troponin is complexed to the contractile apparatus, and the amount of total troponin ranges from 13 to 15 times the amount of CK-MB per gram of myocardium.

Unexplained elevated cTnT, without elevation of other cardiac enzymes or with no evidence of an acute coronary syndrome, is a common reason to seek cardiology consultation.¹³ The interpretation of elevated cTnT in clinical setting other than an acute coronary syndrome should be made with awareness of the multiple

confounding factors that interfere with the correct interpretation of this test.^{13–17} cTnT mRNA has been isolated in diseased human skeletal muscle that expresses cTnT isoforms. cTnT expression is suppressed in skeletal muscle during ontogenic development, but cTnT, like CK-MB, is reexpressed in myopathic skeletal muscle in chronic renal failure patients. This reexpression has been shown in various studies,^{18–21} but a study by Haller et al²² found no evidence of the expression of either cTnT mRNA or protein in the skeletal muscle of ESRD patients. Additional studies are required to provide more definitive data on the issue of whether damaged skeletal muscle in patients with chronic renal disease expresses cTnT.

cTnT levels may also be elevated in nonrenal conditions that cause skeletal muscle regeneration (eg, polymyositis/dermatomyositis, Duchenne’s muscular dystrophy)¹³ (Table 2). cTnT level is often elevated in asymptomatic patients with left ventricular hypertrophy, coronary artery disease, and diabetes mellitus—all of which are common in patients with chronic renal failure. In the setting of left ventricular hypertrophy, elevation of cTnT has been attributed to myocardial remodeling.²³ Renal failure and dialysis contribute to cTnT elevation isolated from coronary artery disease. Younger patients on hemodialysis or peritoneal dialysis without cardiac problems show a high prevalence of elevated cTnT. This elevated troponin level is at least partly the result of decreased renal clearance. In one study, diabetic patients with normal serum creatinine levels had normal cTnT levels, and those with increasing serum creatinine levels had elevated cTnT levels.²⁴

cTnT is more likely to be elevated in dialysis patients than in those patients with renal failure not on dialysis. It is thought that cTnT is so sensitive a marker that it detects subclinical myocardial injury (“microinfarctions”) during repetitive cardiac stress provoked by hemodialysis sessions as well as by fluid overload. In a prospective study on a diverse group of renal disease patients, cTnT was increased in the following groups, although measurements of CK-MB and lactate dehydrogenase taken simultaneously were nondiagnostic for cardiac ischemia: patients with chronic renal failure on hemodialysis (71%), patients with chronic renal failure on peritoneal dialysis (57%), patients with chronic renal failure without hemodialysis (30%), adolescent patients with chronic renal failure on hemodialysis (20%), and patients with a known cardiomyopathy (18%).²⁵

In earlier enzyme-linked immunosorbent assays for cTnT, elevated levels occurred due to low level immunoassay cross-reactivity (1%–2%) errors from skeletal muscle troponin T. The present second-generation

Table 2. Common Noncardiac Causes of Elevated Cardiac Troponin T Levels

Chronic renal failure/end-stage renal disease
Cirrhosis
Duchenne’s muscular dystrophy
Hypothyroidism
Malignancy
Polymyositis/dermatomyositis
Rhabdomyolysis
Sepsis
Ultraendurance exercise

immunoassay does not exhibit cross-reactivity, however, thus eliminating a source of false positive results.²⁶ This suggests that the specificity of the cTnT assay presently available should be as high as that of the cTnI assays. Despite this improvement in specificity of the cTnT assay, false elevation of cTnT in the absence of myocardial injury was reported in up to 18% to 56% of asymptomatic patients with ESRD or chronic renal failure.^{15,27}

cTnI, unlike cTnT, is not expressed in skeletal muscle either in embryonic development or during the repair state. Increase in cTnI only occurs after myocardial damage and is highly sensitive and specific for detection of myocardial injury.^{28–30} A sensitivity of greater than 90% is reached by 12 to 16 hours after onset, and maximal activity is reached by 24 to 36 hours after onset.⁹

PROGNOSTIC VALUE OF TROPONIN ASSAYS IN THE SETTING OF RENAL FAILURE

In the general population, elevated cTnT and cTnI levels predict a poor cardiac outcome even in the absence of myocardial infarction.^{31,32} Patients with low level of troponins have favorable outcomes, whereas elevated levels identify patients at increased risk of adverse outcomes.^{33,34} Studies have shown that patients in the high risk group (ie, those with higher elevations of cTnT) benefit more from treatment than patients in the low risk group (ie, those with lower elevations of cTnT).^{35–37} Both cTnI and cTnT are important prognostic indicators in patients presenting with chest pain, even when the CK-MB fraction is not elevated.^{38,39}

Despite of the reduced specificity of troponin assays in patients with renal disease, it is important to recognize that an elevated troponin level reflects more than a false-positive laboratory finding in these patients. A rapid and significant increase in troponin levels clearly points to an acute coronary syndrome irrespective of the baseline troponin levels, and a sequential assessment is

mandated. Increases in either serum cTnI or cTnT indicate an increasing risk of cardiac events over a 30-day to 1-year period.^{14,38,40}

Troponin levels are important prognostic indicators in asymptomatic, otherwise stable patients on chronic dialysis, especially those with concomitant diabetes mellitus.³⁸ The combination of cTnI and cTnT can be very effective in elucidating cardiac risks of renal patients undergoing chronic dialysis and selecting patients who would benefit from more invasive cardiac investigation.

One study evaluating the relative value of cTnT and cTnI in acute coronary syndromes demonstrated that cTnT provided more information than cTnI for predicting mortality.⁴¹ Another, more recent study showed that the role of cTnI in predicting future mortality and hospital admissions in asymptomatic, ambulatory patients with ESRD on long-term hemodialysis is limited.⁴² Although cTnI is a more specific marker of myocardial injury than cTnT, cTnT remains the better predictor of cardiovascular mortality as well as all-cause mortality.^{43,44}

As cardiac troponins are not normally detected in the blood of healthy people, the cut-off values for elevated troponin levels are set slightly above the noise level of the assays, permitting the tests to be more sensitive to lesser degrees of myocardial injury. The ability of both cTnT and cTnI at the usual diagnostic thresholds to predict risk for subsequent adverse cardiac events is reduced in patients with renal insufficiency.³⁴

In renal failure patients, the use of cardiac troponin levels in diagnosis has not yet been standardized, and the diagnostic and prognostic cutoffs applied to these patients may not be the same as for patients who are not renally impaired. In acute coronary syndromes, cTnI concentrations are comparable in patients with and without renal failure. Mildly elevated cTnT concentrations are relatively common in patients with chronic renal failure, but when measured using a second-generation immunoassay, they are normally below the concentrations observed in the setting of acute myocardial infarction.¹⁷

CONCLUSION

To establish the diagnosis of an acute coronary syndrome in chronic renal failure patients, serial measurement of cTnT or cTnI is required to demonstrate temporal changes. Neither a single negative nor a single positive troponin measurement can be used to diagnose myocardial infarction. Elevations of serum cTnI are highly tissue-specific for myocardial injury and can help to distinguish whether elevations of serum CK-MB or cTnT are due to myocardial or skeletal muscle injury.⁴⁰ cTnT, like cTnI, remains a useful diagnostic and

prognostic test in the management of acute coronary syndrome in renal patients. Prospective study of the use of troponins in renally impaired patients and standardization of assays are warranted to fully elucidate the best marker for detection of myocardial injury and prognosis in this patient population. **HP**

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