Cardiac troponin levels in patients with impaired renal function

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Cardiac troponins are important indicators of myocardial damage. Recent studies have shown that serum cardiac troponin levels are raised in at least 50% of patients with renal disease. The mechanisms and implications of these findings are discussed.

Cardiac troponins are increasingly used to aid the diagnosis of myocardial infarction in the UK. They are also gaining popularity as predictors of increased cardiac mortality and morbidity in patients with ischaemic heart disease (IHD).

Cardiac disease is a major cause of death in patients with renal disease, with a reported incidence of between 30 and 50% (US Renal Data Systems, 1997). Unfortunately, the interpretation of serum cardiac troponin levels can be difficult in patients with renal impairment. Several authors have shown that both cardiac troponin T (cTnT) and cardiac troponin I (cTnI) may be raised in patients with renal failure, whether or not they have clinical features of cardiac disease (Ooi and House, 1998; Lowbeer et al, 1999).

This article reviews the recent literature on cardiac troponins in renal patients and examines the implications of raised serum troponin levels for patients with renal impairment.

CARDIAC TROPONINS IN HEALTHY ADULTS

Troponins are a group of proteins involved with muscle contraction via their interaction with the actin–myosin complexes of both cardiac and skeletal muscle. During myocardial ischaemia the permeability of the cell membrane is increased allowing the passage of troponins from the intracellular compartment into the circulation. There are three subtypes, troponin T, troponin I and troponin C. The terminal amino acid sequence on both troponin T and troponin I is different for the cardiac and skeletal muscle isoforms, allowing differentiation of the origin by laboratory assay.

The early tests for cTnT used an autoimmune enzyme-linked immunoadsorbent assay (ELISA) with two antibodies, one cardioselective and one non-cardioselective, and studies reported a cross-reactivity of 3.6% between cardiac and skeletal troponins (Katus et al, 1995). In the second-generation ELISA tests, such as the Enzymun™ test (Boehringer Mannheim UK, Lewes), which use two cardioselective antibodies, this problem has been eliminated (Ishii et al, 1998). There is no cross-reactivity between cTnI and the skeletal isoform in serum assays (Keffer, 1997).

Both cTnT and cTnI are sensitive and specific markers for cardiac damage. They are similar in sensitivity to myocardium-specific creatine kinase-MB (Zaninotto et al, 1999). Troponin T and troponin I are not found in significant levels in the serum of healthy adults.

In patients with normal renal function, cTnT levels are elevated in the first 3–5 hours after a myocardial infarction and remain high for up to 21 days, whereas cTnI levels rise after 3 hours and are raised for up to 7 days. Currently cTnT, using the newer ELISA, appears more sensitive than cTnI (Christensen et al, 1998). Serum cTnT levels significantly greater than 0.1 μg/litre suggest myocardial damage and may provide prognostic information in patients with unstable coronary artery disease (Lindahl et al, 1996). cTnT levels may also be raised in patients with sepsis, probably reflecting myocardial damage (Spies et al, 1998).

CARDIAC TROPONINS IN PATIENTS WITH RENAL DISEASE

In patients with renal failure cardiac troponins may be elevated in the absence of any evidence of myocardial damage. Frankel et al (1996) found cTnT to be elevated in 71% of patients on regular haemodialysis, 57% of patients on peri-

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toneal dialysis and 31% of patients with renal failure but who are not yet on renal replacement therapy. Further studies, using the second-generation assay, have shown that up to 50% of patients with renal failure have a cTnT level >0.1 μg/litre, even though they have no symptoms suggestive of acute myocardial damage (Stolear et al, 1999).

It was initially suggested that the raised serum troponin levels in patients with renal disease were arising from uraemic skeletal muscle (Haller et al, 1996; McLaurin et al, 1997). Serum troponin levels have been found to be elevated in patients with skeletal muscle disorders such as Duchenne's muscular dystrophy, polymyositis, rhabdomyolysis, and myopathies. McLaurin et al (1997) found elevated serum cTnT in 17 out of 24 haemodialysis patients with no evidence of IHD. They took muscle biopsies from the brachioradialis muscle in five patients and demonstrated skeletal muscle expression of cTnT, which they felt might be the result of reexpression of a fetal gene in regenerating uraemic muscle. Their studies, however, used the early ELISA tests for cardiac troponins.

In a similar study Haller et al (1998) took skeletal muscle samples from five haemodialysis patients with raised serum cTnT levels and could find no increased expression of cTnT in skeletal muscle. They concluded that the cTnT was of cardiac origin. Ricchiuti et al (1998) took skeletal muscle biopsies from 45 haemodialysis patients and were able to demonstrate cTnT expression in the skeletal muscle but, using the second-generation assay, they were unable to detect raised cTnT levels in the serum. They concluded that the troponin T detectable in the serum of renal patients was of cardiac origin. It appears that when using the second-generation ELISA there are few false-positives and the raised cardiac troponin levels seen in uraemic patients probably arise from cardiac muscle.

There does not appear to be any significant gender difference. Male and female dialysis patients with IHD have similar levels of cardiac troponins (Lowbeer et al, 1999; Stolear et al, 1999). Age may be a factor. Older dialysis patients had significantly higher cTnT levels than younger patients in two studies (Ooi and House, 1998; Stolear et al, 1999), which probably reflects greater myocardial damage in the elderly. Significant differences remained even when diabetic patients and those with known cardiac disease were removed from the analysis (Ooi and House, 1998).

RELATIONSHIP BETWEEN CARDIAC TROPONIN LEVELS AND DEGREE OF RENAL IMPAIRMENT

Several studies have failed to show any relationship between the serum cardiac troponin level and the degree of renal impairment. Collinson et al (1998) studied 198 patients with renal dysfunction, ranging from mild impairment (serum creatinine 120–200 μmol/litre), through to moderate impairment (chronic renal failure (CRF): serum creatinine >200 μmol/litre; glomerular filtration rate (GFR) <40 ml/min) to patients with end-stage renal failure on regular haemodialysis.

Collinson et al (1998) also looked at a group of patients with acute renal failure (serum creatinine >500 μmol/litre). They found no predictive association between cTnT and urea or creatinine levels, but they noted that cTnT was significantly higher as renal dysfunction increased (renal impairment *vs* CRF $P<0.0001$; CRF *vs* haemodialysis $P<0.0039$). Highest levels were found in patients with multiple organ failure. cTnI showed a similar trend which did not reach statistical significance. In the patients with acute renal failure they found that elevated levels of cTnT observed during the acute phase returned to normal on recovery of renal function.

Haemodialysis does not appear to influence levels of cardiac troponins. Several studies have shown no significant difference between pre- and post-dialysis levels (Collinson et al, 1998; Lowbeer et al, 1999; Möckel et al, 1999). There was no correlation between cTnT and duration or adequacy of dialysis (Haller et al, 1998; Ooi and House, 1998).

CAN CARDIAC TROPONINS PREDICT OUTCOME IN RENAL FAILURE PATIENTS?

Several authors have suggested that raised cardiac troponin levels may be a measure of underlying cardiac pathology and thus help to identify those patients with a poor cardiac prognosis (Olatidoye et al, 1998). Van Lente at al (1999) looked at the ability of cardiac troponins to predict adverse cardiac outcomes in patients with renal impairment. They studied patients presenting with renal impairment (serum creatinine >20 mg/litre) and possible acute coronary syndromes, and matched each patient to two patients with normal renal function but similar peak troponin levels (either cTnT or cTnI). They found that, in patients with renal impairment, the ability of cardiac troponins to predict adverse cardiac events within 6 months was reduced,

compared with patients with normal renal function. cTnT and cTnI were no better than creatinine kinase-MB at predicting adverse cardiac outcomes within 6 months. Möckel et al studied 40 patients with chronic renal impairment who had no recent history of acute coronary syndromes and followed them for 9 months. They did not feel that cTnT levels could predict patient outcome.

Collinson et al (1998) suggested that in patients with renal impairment and possible IHD serial cardiac troponin levels were more helpful than single readings in evaluating cardiac disease.

Several recent studies suggest that cTnT can predict cardiac outcome in dialysis patients. Haller et al (1998) studied 97 dialysis patients and found significantly lower ($P<0.01$) cTnT levels in those with a low cardiac risk compared with those with positive indicators of cardiac disease.

Stolear et al (1999) studied 94 patients on regular haemodialysis and measured cTnT on three occasions at monthly intervals. Levels were greater than 0.1 μg/litre in 47 (50%) patients. They followed the patients for 12 months, by which time 24 of the patients had died, mostly from cardiovascular disease. A total of 14 patients with a history of IHD died during the study. There appeared to be a significant difference in the survival of patients with high and low cTnT levels ($P = 0.0031$). Of the 24 patients who died within 12 months, 22 had had a raised cTnT (>0.1 μg/litre), whereas only 2 of the patients with a cTnT of less than 0.1 μg/litre had died over the same period ($P = 0.0001$). Two further patients died of acute myocardial infarction after the 12-month period and both had raised cTnT levels in the initial tests.

Lowbeer et al (1999) also found that haemodialysis patients with a history of IHD, but no symptoms suggestive of acute ischaemia, had higher levels of cTnT than those without known IHD ($P = 0.004$). Ooi and House (1998) showed a similar trend which did not reach statistical significance.

Lowbeer et al (1999) also found an association between left ventricular hypertrophy and raised cTnT levels in dialysis patients in the absence of symptoms of the acute coronary syndrome. They noted a correlation between cTnT and left ventricular mass index.

CARDIAC TROPONINS IN PATIENTS WITH RENAL DISEASE AND DIABETES

Patients with diabetes and renal impairment might be expected to have a higher incidence of cardiac disease. Lowbeer et al (1999) showed that in patients on dialysis (either peritoneal dialysis or haemodialysis) those with diabetes but no history of IHD were more likely to have raised levels of cTnT than those without diabetes or IHD ($P<0.003$). Ooi and House (1998) showed a similar trend in their study. These results reflect the high level of cardiac disease in patients with both diabetes and renal impairment.

CONCLUSIONS

Patients with renal disease may have increased levels of serum cardiac troponins in the absence of acute cardiac syndromes. It is now felt that this results from clinically undetectable myocardial damage. Raised cardiac troponin levels in renal patients are commoner in those with diabetes, IHD and left ventricular hypertrophy. The presence of a raised serum cardiac troponin level in patients with renal impairment should alert clinicians to the likelihood of underlying and potentially life-threatening cardiac disease. Renal patients with raised cardiac troponin levels are at greater risk of both cardiac and non-cardiac mortality in the coming months.

In patients with renal impairment or renal failure presenting with an acute coronary syndrome, the cTnT is best measured by second-generation assays. The authors would advise doing serial measurements and looking for a rise of more than 50% over the few days immediately following the onset of cardiac symptoms.

Since raised cardiac troponin levels in dialysis patients appear to predict a poor cardiac outcome, the authors would advise full cardiological work-up, including coronary angiography, in patients waiting for a kidney transplant, and on dialysis, who have raised cTnT levels, even in the absence of symptoms of cardiac disease and in the presence of a normal routine electrocardiogram. **HM**

Conflict of interest: none.

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KEY POINTS

- Serum cardiac troponin levels are raised in at least 50% of patients with advanced renal disease.
- Raised cardiac troponin levels in renal patients reflect cardiac damage which may not be clinically apparent.
- Second-generation assays of cardiac troponin-T (cTnT) appear to be more reliable than earlier assays or cardiac troponin-I (cTnI).
- Serial measurements of cTnT are helpful in evaluating acute coronary syndromes in renal patients.
- Renal patients with persistently raised cTnT levels are at increased risk of acute cardiac events.
- Dialysis patients with raised cTnT levels should undergo full cardiological work-up before renal transplantation.