

*Original Article***Cardiac troponin-I accurately predicts myocardial injury in renal failure**Greg S. Martin<sup>1</sup>, Bryan N. Becker<sup>2</sup> and Gerald Schulman<sup>2</sup><sup>1</sup>Department of Internal Medicine, and <sup>2</sup>Division of Nephrology, Vanderbilt University Medical Center, Nashville, Tennessee, USA**Abstract**

**Background.** Non-specific elevations of creatine kinase isoenzymes (CK-MB) and cardiac troponin-T may be seen in renal failure, confusing the diagnosis of myocardial infarction. Cardiac troponin-I (cTn-I) has been shown to be specific for myocardial damage in several disease states, but has not been prospectively evaluated in the setting of renal failure.

**Methods.** This prospective case series evaluated 56 patients with acute or chronic renal failure or end-stage renal disease to assess the sensitivity and specificity of cTn-I for detecting myocardial injury in this patient population. During a 6-month period, patients admitted with suspected myocardial injury by history, physical examination, and electrocardiography were evaluated. Cardiac troponin-I (cTn-I) measurements were assessed between 8 and 48 h after admission. Appropriate medical care and further cardiac testing (echocardiography, stress testing, or arteriography) was performed at the discretion of the primary physician.

**Results.** Myocardial injury was diagnosed in 18/56 (32%) patients by positive cTn-I levels, while only 7/56 (13%) patients had evidence of myocardial damage by CK-MB. Twenty-one of 56 (38%) patients had indeterminate CK-MB levels and 53% of these patients demonstrated myocardial ischaemia on follow-up testing. Sixteen patients had negative cardiac studies; all of these patients had negative cTn-I levels, while seven of these 16 (44%) patients had indeterminate CK-MB measurements. All of the patients with positive cTn-I levels had positive cardiac studies. Positive troponin levels were associated with increased in-hospital mortality. Sensitivity and specificity for CK-MB were 44 and 56% respectively, and 94 and 100% for cTn-I.

**Conclusion.** These data support the use of cTn-I for diagnosing myocardial injury in patients with renal failure. Elevated cTn-I levels are associated with increased short-term mortality in renal failure patients. The accuracy of cTn-I could potentially limit unneces-

sary cardiac testing in renal failure patients, while the enhanced sensitivity contributes to risk stratification and aids in diagnosing true myocardial injury in this population susceptible to non-specific elevations in other muscle enzymes.

**Key words:** end-stage renal disease; myocardial ischaemia; renal failure; troponin-I

**Introduction**

The conventional tools for diagnosing acute myocardial injury have been history and physical examination in conjunction with 12-lead electrocardiography (ECG), serial creatine kinase isoenzyme (CK and CK-MB) measurements, and determination of lactate dehydrogenase (LDH) isoenzyme ratios. Unfortunately, CK-MB assays can be misleading in renal failure due to non-specific enzyme elevations in 5–50% of renal patients [1,2]. Efforts to improve patient triage and cost-effective use of cardiac care facilities have spurred continuing interest in defining rapid assays for accurately ruling out acute myocardial injury.

One set of assays has focused on proteins from the troponin complex. Three troponin subunits regulate muscle contraction by modulating the calcium-dependent interaction of actin and myosin: the tropomyosin-binding subunit T, the calcium-binding subunit C, and the actomyosin-ATPase-inhibiting subunit I. Troponin-I exists in three isoforms: slow-twitch, fast-twitch, and cardiac. Cardiac troponin-I (cTn-I) is the 26.5 kDa isoform of the muscle subunit, and is genetically and structurally distinct from that produced in extracardiac muscle [3,4].

Studies have demonstrated that cTn-I and cardiac troponin-T (cTn-T) correlate with acute myocardial injury in the general population, both turning positive within 6–8 h and remaining so for at least 4–7 days [5,6]. Spurious cTn-T elevations, similar to CK-MB, have been identified in patients with renal failure [7,8]. Cardiac troponin-I has been shown to be specific for myocardial damage in the setting of hypothyroidism, rhabdomyolysis, skeletal muscle injury, burns, cocaine intoxication, and the perioperative period [9–14], but

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has not been prospectively evaluated in the setting of renal failure. Therefore this study investigated whether cTn-I is a more accurate predictor of myocardial injury than CK-MB in patients with renal failure.

## Subjects and methods

### Patients

A prospective, observational, case-series study was implemented at an academic medical centre (Vanderbilt University Medical Center) and an associated teaching hospital (St Thomas Hospital). During a 6-month period, 56 patients with end-stage renal disease (ESRD), chronic renal failure (CRF), or acute renal failure (ARF) admitted with a primary diagnosis of suspected myocardial injury were evaluated. The study population consisted of equal numbers of males and females, with a mean age of 62 years. There were 24 African-Americans, 31 Caucasians, and one Asian; 50 patients with CRF/ESRD and six patients with ARF. All patients except one had at least two co-morbid illnesses (hypertension, diabetes, coronary artery disease or congestive heart failure, obstructive lung disease, peripheral vascular disease, or cardiac arrhythmias). All patients were evaluated by history, physical examination, ECG, and serial CK with CK-MB measurements. Each patient had one serum cTn-I determination between 8 and 48 h after admission. A positive cTn-I level was defined as  $>0.8$  ng/ml. CK-MB levels were considered positive when the total CK was elevated with an MB fraction  $>5\%$  while levels were negative when the MB fraction was  $<5\%$  (regardless of total). CK-MB assays were considered indeterminate when total CK levels were within normal limits but MB fractions were  $>5\%$ . Both laboratory assays were fluorometric enzyme immunoassays (Stratus, Dade International, Miami, Florida, USA). A marker was considered elevated if it was above the established normal range at any time during the suspected myocardial event, and each suspected myocardial event within the study period was considered independently. Further cardiac testing was performed at the discretion of the patient's primary physician, and a positive test was defined as demonstrating a new cardiac abnormality (by echocardiography or nuclear imaging) or severe occlusive coronary artery disease (by arteriography).

### Statistical methods

Test characteristics were calculated from data gathered on patients with available follow-up cardiac testing. Data are reported as percentages with 95% confidence intervals. Statistical comparisons between groups were performed with a two-tailed *t* test or Chi square analysis where indicated. A *P* value less than 0.05 was considered statistically significant.

## Results

The study cohort was contrasted by CK-MB or cTn-I and stratified according to diagnostic testing as shown in Figure 1. Myocardial injury was diagnosed in seven of 56 (13%) patients by standard CK-MB determination, while 18/56 (32%) were positive by cTn-I testing. All patients with negative CK-MB were also cTn-I negative. One patient each in the CK-MB negative

group and cTn-I negative group had evidence of myocardial ischaemia on follow-up testing. However, a positive cTn-I was highly predictive of a positive diagnostic cardiac test in follow-up (Table 1).

Twenty-one of 56 (38%) patients enrolled had indeterminate CK-MB results. Nine of these 21 had positive cTn-I values. Of those with indeterminate CK-MB values, 53% (8/15) demonstrated myocardial ischaemia on follow-up testing, while six patients did not undergo further cardiac evaluation. Of patients with indeterminate CK-MB and positive cTn-I values, all had positive cardiac studies. Likewise, seven of eight (88%) with indeterminate CK-MB and negative cTn-I values had negative studies.

Elevated cTn-I levels were associated with a significantly worse in-hospital prognosis, particularly among patients with CRF/ESRD. The mortality rate for patients with elevated cTn-I levels was 29% (4/14), while only five of 33 (15%) of patients with normal cTn-I levels died during hospitalization ( $P < 0.001$ ).

Sensitivity and specificity for CK-MB in this study were respectively 44% (95% confidence interval, 20–68%) and 56% (95% confidence interval, 32–80%). Values for cTn-I were much higher at 94% sensitivity (95% confidence interval, 82–106%) and 100% specificity. Positive and negative predictive values were excellent for both CK-MB (100 and 90% respectively) and for cTn-I (100 and 94%), though CK-MB calculations were confounded by the inclusion of the large 'indeterminate' category.

## Discussion

The use of CK-MB alone for diagnosing myocardial infarction can be misleading in patients with renal failure given the significant number of false positive or indeterminate results [1,2]. In this study we evaluated cTn-I as a marker for myocardial injury in patients with renal failure, and found it to be more sensitive and specific than CK-MB in this patient population. Moreover, the group of patients with indeterminate CK-MB values had a high incidence of cardiac abnormalities on follow-up cardiac testing, which were correctly predicted by cTn-I levels.

Positive and negative CK-MB assays correlated well with positive and negative cTn-I assays. Positive and negative cTn-I levels demonstrated little or no correlation with CK-MB measurement due to the large number of indeterminate CK-MB values. Despite the high prevalence of ischaemic heart disease in the renal failure population, sensitivity and specificity for CK-MB are of limited value due to the large number of 'indeterminate' patients. Indeed, by designating a 'CK-MB indeterminate' category we have artificially enhanced the predictive values of positive and negative CK-MB categories.

Elevated cTn-I levels were highly predictive of positive cardiac testing. In addition, elevated cTn-I measurements distinguished a group of patients with worse short-term prognosis, similar to that reported by Apple

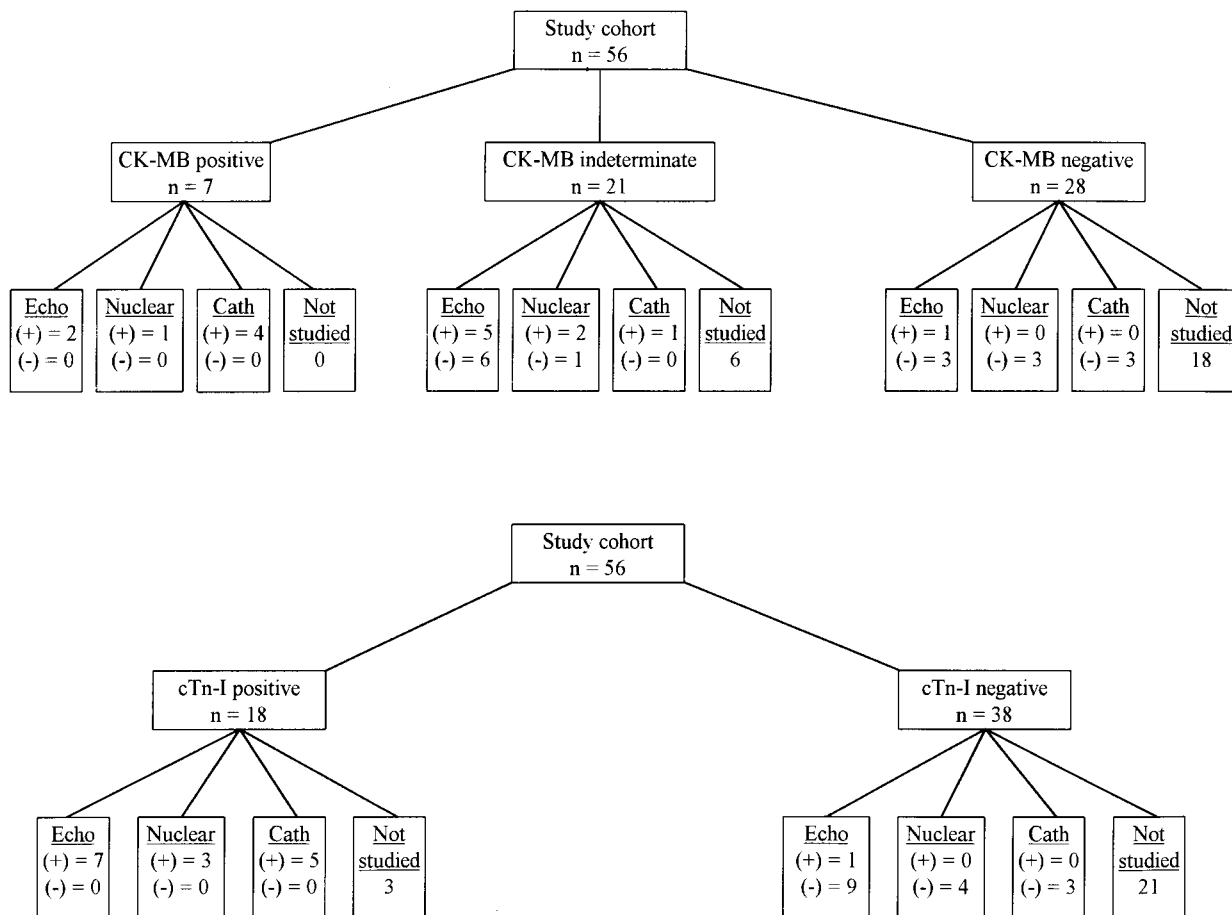


Figure 1.

and Antman [15,16]. It has been suggested that cTn-I is significantly more sensitive than other muscle enzyme assays in distinguishing cardiac muscle damage of any aetiology, i.e. ischaemia, inflammation, or trauma [17–19]. It is possible that cTn-I elevations in the face of normal CK-MB concentrations represented patients in an unstable phase of cardiac disease, and may have identified patients who had sustained significant cardiac injury several days prior or in whom cardiac injury was an ongoing phenomenon. The release kinetics of cTn-I have led to the proposal that current cTn-I assays replace LDH isoenzymes in evaluating subacute myocardial injury [20]. Given the calculated sensitivity of cTn-I in this study and the known false positive or indeterminate rate inherent to CK-MB assays, it may

be reasonable to consider cTn-I the rapid assay of choice for evaluating myocardial injury in the renal failure population.

This study is limited by its observational nature and the moderate amount of follow-up data used to calculate test characteristics. Additionally, because of the small population size, this study is subject to beta error. Yet it is important to recognize that ultimately there is no 'gold standard' for determining the accuracy of positive and negative cardiac serodiagnostic markers. We included three forms of cardiac evaluation, each with strengths, weaknesses, and the possibility of false positives and negatives. The method of cardiac evaluation was determined by the primary physician or consulting cardiologist, recognizing the

Table 1. Correlation of serum cTn-I concentrations and positive cardiac testing

Diagnostic test	Total number of tests	New myocardial injury with normal cTn-I	New myocardial injury with elevated cTn-I	P value of elevated vs normal cTn-I
Echocardiogram*	26	1	12	<0.0001
Nuclear study	9	0	3	<0.02
Cardiac catheterization	8	0	5	<0.005

\*Includes two-dimensional and stress echocardiography.

need for various imaging modalities between patients. Despite these factors, the calculated sensitivity and specificity were similar to those reported previously for CK-MB in this patient population, and these test characteristics strongly favor the use of cTn-I.

This study supports a change in the current methods utilized for assessing myocardial injury in renal failure patients. Large scale trials are required to confirm the accuracy of cTn-I in the renal failure population. Implementation of cTn-I assays could result in substantial health care savings. At our institution, CK-MB and cTn-I assays are comparable in cost at \$33 and \$35 respectively. Single cTn-I sampling vs serial CK-MB could save \$64 per admitted patient in laboratory expense alone. Larger reductions in cost could be achieved with diminished pharmacy administration, reduced utilization of telemetry and cardiac care services, and more appropriate usage of equipment and nursing in patients with negative cTn-I values. Emergency department usage of cTn-I over an observation period of 6–8 h would permit early and accurate characterization of chest pain in renal-failure patients. Patients could be subsequently admitted or discharged for further evaluation in the outpatient setting, resulting in additional savings from fewer unnecessary cardiac procedures and hospitalizations. Moreover, use of cTn-I may allow for a more precise determination of those patients at increased risk for short-term mortality. Ultimately, the benefits of utilizing cTn-I in the renal failure population lie in the improved patient care delivered as a result of more refined diagnostic standards.

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Received for publication: 31.10.97

Accepted in revised form: 5.3.98