Enzymes and Protein Markers

Correlation of Antemortem Serum Creatine Kinase, Creatine Kinase-MB, Troponin I, and Troponin T with Cardiac Pathology

DAYLILY S. OOI,[1,3*] PHILLIP A. ISOTALO,[3] and JOHN P. VEINOT[2,3]

Background: Spurious increases in serum troponins, especially troponin T, have been reported in patients with and without acute myocardial syndromes.

Methods: We studied 78 autopsied patients without clinical myocardial infarction (MI) and correlated histologic cardiac findings with antemortem serum creatine kinase (CK), its MB isoenzyme (CK-MB), cardiac troponin I (cTnI), and cardiac troponin T (cTnT).

Results: There was no significant myocardial pathology in 15 patients. Cardiac pathologies were in five groups: scarring from previous MI or patchy ventricular fibrosis (n = 9), recent MI (n = 27), healing MI (n = 7), degenerative myocyte changes consistent with congestive heart failure (CHF; n = 12), and other cardiac pathologies (n = 8). The median concentrations in the five groups were not significantly different for either CK or CK-MB. Compared with the no-pathology group, only the MI group was significantly different for cTnI, and the MI and other pathology groups were significantly different for cTnT. For patients with MI, 22%, 19%, 48%, and 65% had increased CK, CK-MB, cTnI, and cTnT, respectively; for CHF and other cardiac pathologies combined, the percentages were 28%, 17%, 22%, and 50%. For patients with increased cTnI, 72% and 28% had MI and other myocardial pathologies, respectively; patients with increased cTnT had 64% and 36%, respectively. Patients without myocardial pathology had no increases in CK-MB, cTnI, or cTnT.

Conclusions: All patients with increased serum CK-MB, cTnI, and cTnT had significant cardiac histologic changes. The second-generation cTnT assay appears to be a more sensitive indicator of MI and other myocardial pathologies than the cTnI assay used in this study.

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In recent years, serum troponins have been increasingly used in the diagnosis of acute coronary syndromes as studies have shown their greater clinical sensitivity over creatine kinase-MB (CK-MB)[4] *(1, 2)*. In patients with non-Q-wave myocardial infarction (MI) or unstable angina, serum troponins can provide risk stratification for short-term *(3–9)* and long-term *(9, 10)* cardiac events and mortality. This has been attributed mainly to the ability of serum troponins to detect microinfarcts, areas of necrosis too small to produce electrocardiographic changes or increased serum cardiac enzymes. Whereas increased short-term complications and mortality may understandably be explained by these microinfarcts, long-term events have also been attributed to complications of ischemia.

Additionally, a high percentage of end-stage renal failure patients show increased cardiac troponin T (cTnT) in the absence of acute cardiac ischemia *(11, 12)*. There have been suggestions that these represent spurious increases arising from re-expression of the cardiac isoform, the fetal form, in skeletal muscles of these patients *(13)*. We have observed a threefold increase in 1-year mortality in 172 hemodialysis patients with increased cTnT *(14)*, and although increases in cTnT may result from silent MIs that occur frequently in these patients, the temporal pattern of increases was not in keeping with acute ischemic events. This raised the possibility that increased cTnT in this group of patients was indicative of chronic disease processes that compromise survival.

There have been reports of similar increases in mortality associated with increased cTnT in congestive heart

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Divisions of [1] Biochemistry and [2] Anatomical Pathology, Department of Pathology and Laboratory Medicine, Ottawa Hospital-Civic Campus, and [3] Department of Pathology and Laboratory Medicine, University of Ottawa, Ottawa, ON Canada.

*Address correspondence to this author at: Division of Biochemistry, Department of Pathology and Laboratory Medicine, Ottawa Hospital-Civic Campus, 1053 Carling Ave., Ottawa, ON K1Y 4E9 Canada. Fax 613-761-5401; e-mail dsooi@ottawahospital.on.ca.

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[4] Nonstandard abbreviations: CK-MB, creatine kinase-MB isoenzyme; MI, myocardial infarction; cTnI and cTnT, cardiac troponin I and T; and CHF, congestive heart failure.

failure (CHF) patients (15–17) and in patients with sepsis (18). These findings led us to reexamine the basis of increased troponins, especially cTnT, within the context of subclinical myocardial pathology. We used histological examination of the heart at post mortem, which can indicate the extent and type of pathology present, to determine whether increased serum troponin concentrations can be explained by subclinical myocardial pathology.

Materials and Methods

SUBJECTS

Patients were selected from those undergoing postmortem studies at the Ottawa Hospital Civic Campus Department of Pathology and Laboratory Medicine. Patients with a clinical diagnosis of MI or patients in whom no suitable antemortem plasma samples were available were excluded from the study. A total of 78 patients were studied and included 6 from a study of chronic hemodialysis patients (14).

ANTEMORTEM SAMPLES

Samples were routine clinical samples, drawn into evacuated tubes (PST® or SST®; Becton Dickinson) and processed in the routine manner. Sixty-four percent of samples were obtained within 7 days of death; samples from three dialysis patients and one cardiac patient were obtained >6 months before death. Most of the samples (88%) were frozen at −20 °C within 72 h. Twelve patients were studied retrospectively; serum markers were analyzed for clinical reasons in 6, and for a previous study on chronic hemodialysis patients in 6 (14); 11 patients had only cTnT measurements, and one had CK and cTnT.

Creatine kinase was measured on the Boehringer Mannheim/Hitachi 917, using manufacturer's reagents, CK-MB and cardiac troponin I (cTnI) were measured on the AxSYM (Abbott Laboratories), and cTnT was measured on the Elecsys 1010 (Roche Diagnostics). The second-generation cTnT assay was used; this assay has no cross-reactivity with skeletal TnT. The cutoff values used in our laboratory are as follows: CK, 215 U/L for males and 160 U/L for females; CK-MB, 10 μg/L; cTnI, 2.0 μg/L; and cTnT 0.1 μg/L. The interassay imprecision (CV) for each assay is as follows: for CK, 2.3% at 245 U/L; for CK-MB, 12% at 20 μg/L and 8.7% at 124 μg/L; for cTnI, 7.0% at 3.3 μg/L and 7.9% at 34.2 μg/L; and for cTnT, 6.5% at 0.16 μg/L and 6.0% at 1.1 μg/L.

POSTMORTEM STUDIES

Gross and histological examinations of the heart were performed by a cardiac pathologist (J.P.V.) without knowledge of the serum marker values. Postmortem examinations were completed within 24 h of death in all patients.

Patients were classified as having recent MI if there was coagulative and contraction band necrosis <5 days old; healing MI if the infarct was >1 week old as evidenced by healed edges but without significant fibrosis; and old infarcts if there was prominent fibrosis. The other cardiac disorders seen were degenerative changes associated with CHF (myocytes characterized by clear cytoplasm and loss of myofilaments, often accompanied by pericellular fibrosis), inflammation, fibrosis, nonbacterial thrombotic endocarditis, sepsis changes, amyloid deposition, and infiltration by tumor.

STATISTICAL ANALYSIS

Means were compared using the Analysis ToolPak of Microsoft Excel, Ver. 7. χ^2 analysis and the Fisher's exact two-tailed test were performed. Odds ratios were calculated to determine the relationship between increased serum markers and the presence of cardiac pathology, using Epi Info, Ver. 6 (Department of Surveillance and Epidemiology, CDC) and InStat, Ver. 2.04 (GraphPad Software). Statistical significance was defined as $P < 0.05$ unless otherwise stated. Clinical sensitivities and specificities were calculated for all cardiac pathologies and for acute MI (recent and healing). For the latter diagnosis, patients with other cardiac pathologies were considered not to have disease.

Results

A summary of 66 patients for whom all cardiac markers were measured is shown in Table 1. A complete listing of the patient characteristics, clinical diagnoses, main cardiac histologic findings, and other significant vascular diseases is available as a supplement through the *Clinical Chemistry* Web site. The file can be accessed by a link from the on-line Table of Contents (http://www.clinchem.org/content/vol46/issue 3/). There was no myocardial pathology in 15 patients; there was old MI or ventricular fibrosis in 9, recent MI in 27 (11 microinfarcts), healing MI in 7, degenerative changes in 12, and miscellaneous pathology in 8 patients.

In the patients with no myocardial pathology, CK was increased in 3 of 15, and cTnI was just below the cutoff concentration (1.9 μg/L) in 1 patient. In patients with myocardial pathology, cTnT was most frequently increased. Although increases in CK were noted without increases in the other markers, increased CK-MB was associated with increased cTnI and cTnT in all patients. Similarly, all but one patient with increased cTnI had increased cTnT. The median concentrations and the percentages of patients with increased CK-MB, cTnI, and cTnT, but not CK, were higher in patients with myocardial pathology than for those with no myocardial pathology (Table 2 and Fig. 1). However, the odds ratio for the presence of acute MI was significant for cTnI and cTnT only, and the odds ratios for the presence of CHF changes and other cardiac pathologies were significant for cTnT alone. There was no significant difference between the groups with recent and healing MIs, nor did the size of the infarct appear to have any effect; hence, they were studied together. When all cardiac pathologies were con-

Table 1. Summary of patient and sample characteristics and pattern of increased serum markers in the 66 patients[a] with all four marker results available.

						No. (%) of patients with increased serum concentrations				
	n	Males, %	DM[b] and/or CRF, %	Sampled >6 days prior to death, %	Stored at 4° C >72 h, %	CK[c]	CK-MB, cTnI, and cTnT	cTnI and cTnT	cTnI only	cTnT only
No myocardial pathologies	14	36	50	14	29	3 (21)	0	0	0	0
Old MI or fibrosis	7	43	29	29	0	2 (29)	0	0	1 (14)	1 (14)
Recent MI	11	82	18	27	36	2 (18)	2 (18)	2(18)	0	2 (18)
Recent microinfarct	10	70	40	40	10	2 (20)	2 (20)	4(40)	0	2 (20)
Healing MI	6	67	50	33	17	2 (33)	1 (17)	2(33)	0	0
CHF	10	40	20	40	20	4 (40)	1 (10)	1(10)	0	1 (10)
Other myocardial pathologies[d]	8	50	50	38	25	1 (13)	2 (25)	0	0	3 (38)

[a] Detailed information on all patients, including significant medical history and cardiac findings at post mortem, is available as a supplement from the *Clinical Chemistry* Web site. The file can be accessed by a link from the on-line Table of Contents (http://www.clinchem.org/content/vol46/issue3/).
[b] DM, diabetes mellitus; CRF, chronic renal failure.
[c] Increase in CK occurred in isolation or in combination with another pattern group.
[d] Includes inflammation, necrosis, nonbacterial thrombotic endocarditis, and amyloid deposition.

sidered, the clinical sensitivities (95% confidence intervals) for CK, CK-MB, cTnI, and cTnT were 38% (25–52%), 26% (15–40%), 44% (31–59%), and 53% (41–65%), respectively. The specificity for CK was 80%, whereas the other markers showed 100% specificity. For acute MI, the specificities for CK, CK-MB, cTnI, and cTnT were 75% (59– 87%), 92% (79–98%), 87% (73–96%), and 73% (57–85%), respectively. The clinical sensitivities for acute MI were 22% (9–42%), 19% (6–38%), 48% (29–68%), and 62% (44–78%), respectively. When we used only the samples collected within 6 days of death, the sensitivities changed marginally to 17% (4–41%), 22% (6–48%), 61%

Table 2. Median and range of serum concentrations in the five histologic groups, odds ratios of having abnormal pathology compared with no myocardial pathology, and the significance based on χ^2 analysis.

	No myocardial pathology	Old MI or patchy fibrosis	Recent/healing MI	CHF	Other myocardial pathologies
CK					
n	15	7	27	10	8
Median, U/L	55	73	49	82	47
Range, U/L	9–270	22–1085	10–478	10–304	23–421
Odds ratio	1.0	1.6	1.1	2.7	0.6
95% CI[a]		0.1–18.8	0.2–8.3	0.3–23.7	0.0–9.1
CK-MB					
n	14	7	27	10	8
Median, μg/L	1.2	2.7	2.5	3.1	2.2
Range, μg/L	0.5–4.0	0.0–5.3	0.9–75.7	0.9–15.9	1.0–18.4
Odds ratio	1.0	Undefined	3.2	4.6	11.2
95% CI			0.1–72.1	0.2–124.7	0.5–266.9
cTnI					
n	14	7	27	10	8
Median, μg/L	0.1	0.3	1.3	0.3	0.3
Range, μg/L	0.0–2.9	0.1–2.9	0.0–139.2	0.0–4.4	0.0–12.7
Odds ratio	1.0	6.7	27.0[b]	8.5	11.2
95% CI		0.2–187.4	1.5–498.5	0.4–199.6	0.5–266.9
cTnT					
n	15	9	34	12	8
Median, μg/L	0.02	0.03	0.13	0.07	0.26
Range, μg/L	0.00–0.07	0.01–0.15	0.00–13.11	0.0–1.41	0.03–0.62
Odds ratio	1.0	10.3	49.4[b]	22.7[b]	48.7[b]
95% CI		0.4–243.5	2.7–895.4	1.1–467.8	2.2–1102.7

[a] CI, confidence interval.
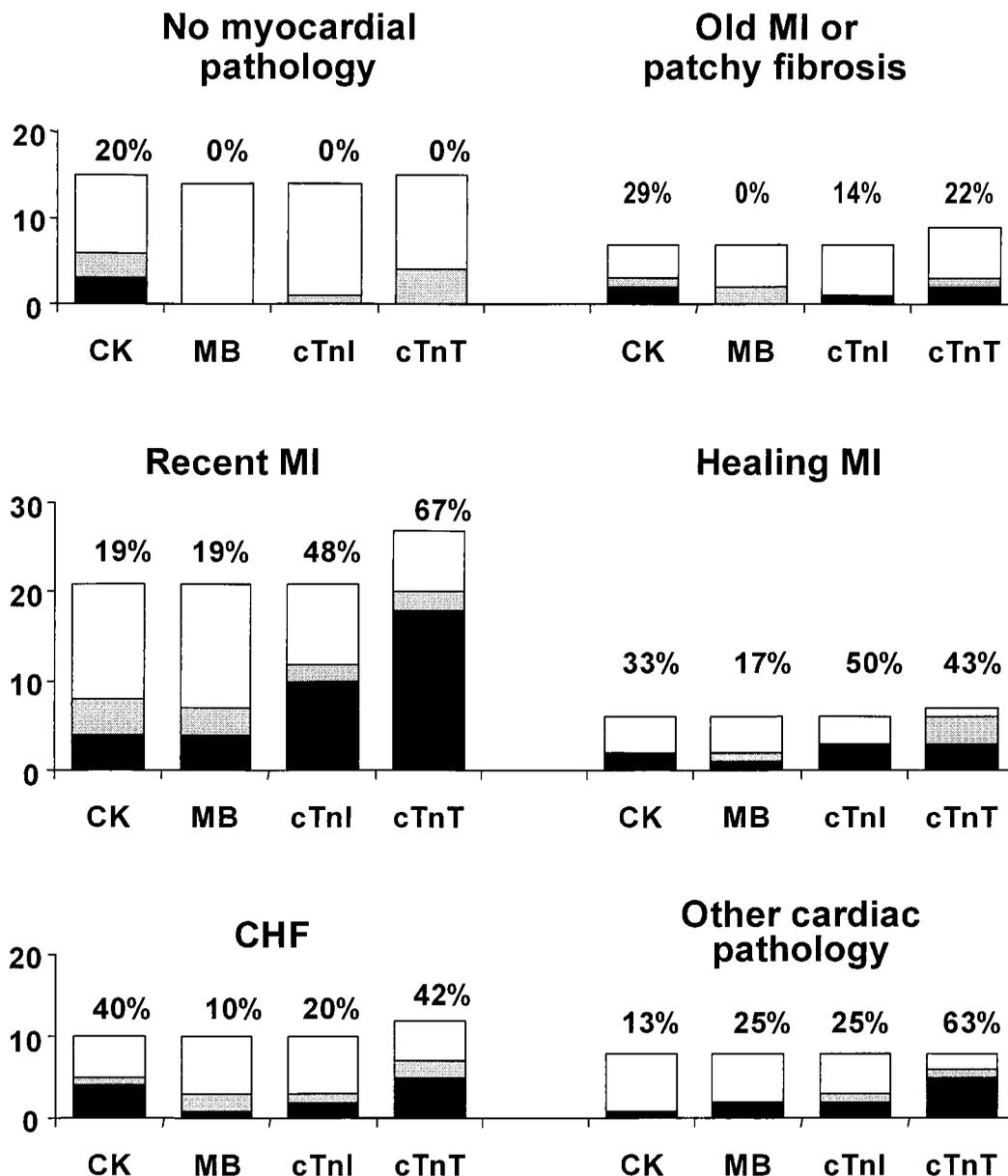[b] Significance based on χ^2 analysis: $P < 0.01$ for two-tailed test.

Fig. 1. Distribution of serum CK, CK-MB (*MB*), cTnI, and cTnT concentrations in the various groups.

Filled portions of the columns and *percentages* shown above the columns represent concentrations above the upper cutoff; *gray portions* represent marginal increases (values between cutoff and one-half the cutoff value); *open portions* represent no significant increases (below one-half the cutoff value).

(36–83%), and 70% (46–88%), respectively, and did not increase further when we restricted samples to within 3 days of death. For acute MI, the sensitivity of cTnT was not significantly different from that of cTnI, but it was significantly different from both CK-MB and CK. For cardiac pathologies other than acute MI, the sensitivity for cTnT over cTnI did not achieve statistical significance, with an observed difference of 21% and a SE of 12%.

Patients with diabetes mellitus had significantly lower CK-MB, cTnI, and cTnT; the median values for patients without and with diabetes were 2.5 vs 1.5 μg/L for CK-MB; 0.3 vs 0.2 μg/L for cTnI; and 0.08 vs 0.03 μg/L for cTnT. However, excluding the 11 diabetic patients from the analysis did not influence the findings. The medians for cTnI and cTnT were higher in patients with chronic renal failure than for those with normal renal function (1.6 vs 0.2 μg/L for cTnI and 0.20 vs 0.05 μg/L for cTnT), but the differences did not achieve statistical significance. Eliminating the 12 retrospective patients and studying only the 66 patients with results available for all markers yielded similar results.

The presence of acute myocardial ischemia was the most common cause of increased serum concentrations of

CK-MB, cTnI, and cTnT, contributing to >60% of increased values. Interestingly, patients with microinfarcts were just as likely to have increased values as patients with larger infarcts.

Discussion

The findings of this study confirm the increased clinical sensitivity of serum troponins over CK and CK-MB in acute coronary syndromes. Many of the patients with borderline increases in serum troponins had small MIs at postmortem. Because of the nature of this study, where a single plasma sample was used, the longer period of increased concentrations seen with serum troponins following an acute ischemic event (19, 20) may have contributed to the higher percentage of increased concentrations observed.

The important finding of this study was the presence of histologic changes in the hearts of almost all of the patients with increased serum CK-MB, cTnI, and cTnT. What had been considered as spurious increases, because of a lack of symptoms and clinical signs when currently available diagnostic modalities were used, is explained by diseased cardiomyocytes. Furthermore, there appears to be a difference between patients with acute ischemia and those with other myocardial disorders. In the former, the percentage of patients with increased cTnI is very similar to that for cTnT (50% vs 63%). The slightly higher positivity for cTnT can be explained by its longer half-life, which makes it more likely that a single random sample would have increased values. In patients with other myocardial pathologies, cTnT is increased more than twice as frequently as cTnI. This may explain the discordance seen between the troponins in end-stage renal failure patients but not seen in acute coronary syndromes. To explain this discrepancy, one could hypothesize that cTnT is more likely than the other markers to leak into circulation with minor pathologic changes. Approximately 6% of cTnT is present in the cytoplasm of cardiomyocytes (21) in contrast to 3% of cTnI (22). Additionally, cTnT in serum exists mainly as free subunits, whereas cTnI exists complexed as a binary structure with troponin C, or as a ternary structure with both troponins C and T (23), indicating that cTnI is released as a larger complex. Loss of cell membrane integrity could possibly allow selective leakage of cytosolic components into the circulation, with preferential leakage of cTnT when membrane damage is minor. With increasing destruction of the membrane architecture, larger cytosolic components may be leaked into circulation, leading to increases for both troponins.

Myocytes may die from several different processes, including necrosis (oncosis) and apoptosis, and it is recognized that these processes may be interrelated (24, 25). Unlike necrosis, apoptosis proceeds through a genetically programmed series of biochemical and morphological steps designed to avoid the indiscriminate release of cytosolic contents and the ensuing inflammatory response. In apoptosis, the cell membrane remains intact, at least for some time. This would lead one to hypothesize that various myocyte cellular components appear in circulation at the different times of apoptotic and necrotic cell death.

The increased mortality seen with increased troponins, especially cTnT, in nonischemic settings supports our findings. We had been perplexed previously by the increased mortality associated with unexplained increases in cTnT in chronic hemodialysis patients (14). Two recent studies (26, 27) in dialysis patients have shown similar associated mortality. In our study (14), we were surprised to find that increased cTnT is a better predictor of mortality in patients without coronary artery or peripheral vascular disease and in non-diabetics, the groups traditionally considered at lower mortality risk for atherosclerosis. This now can be explained by cTnT reflecting subclinical myocardial pathology rather than acute coronary ischemia. Furthermore, we found a higher mortality risk associated with increased cTnT in the nonhypertensive group. Whereas systemic arterial hypertension is associated with atherosclerosis and mortality in most other diseases, in this group of patients, where hypertension occurs frequently either as the cause or the effect, the fall in blood pressure often denotes cardiac decompensation (28). Increased cTnT in this group of patients therefore indicates the presence of cardiac disease and hence, not surprisingly, the poorer outcome.

Both patients with sepsis affecting the myocardium had increased cTnT, consistent with previous studies showing it to be a prognostic marker in sepsis (18). Similar prognostic values in CHF patients have also been reported recently (15–17) and support our postulation that cTnT may be a useful prognosticator even in non-infarct-related cardiac disease. Such increases in cTnT may be indicative of non-infarct-related myocyte pathologies, as noted in our study.

With the use of serum troponins in acute coronary syndromes, there may be a need to reexamine the interpretation of the many risk-stratification studies of unstable angina and non-Q-wave MI patients (3–10). These studies used mainly cardiac end-points, and an increased mortality generally was attributed to underlying ischemic disease. In light of our findings, one should consider the presence of other myocardial pathologies, in addition to the presence of microinfarcts, as contributing factors for mortality. Interestingly, a study of patients with low-grade or atypical angina showed a greater than twofold difference in event-free survival at 6 months between cTnT-positive and -negative groups despite very similar incidences of positive angiographic abnormalities (64% vs 47%) (8). Increased troponins, especially cTnT, even in the absence of acute ischemia are indicative of compromised myocardium and carry a poor prognosis.

This study had several limitations. The nature of the study was such that samples could not be obtained from patients at a standard time before death. There also is the

issue of the quality of the samples, both plasma and histologic. Because of the retrospective nature of the study, the plasma samples used were those that had been stored following routine analysis. Most of the samples were frozen within the recommended 72 h for the cTnI assay *(29)*, and only 42% were frozen within the 24 h recommended for the cTnT assay *(30)*. The effect, if significant, would have produced even greater discrepancy between the two troponins. In addition, recent studies have shown that degradation of cTnI complexes, which is the predominant form in serum, and oxidation or phosphorylation of the cTnI molecule can produce changes in immunoreactivity, leading to increasing or decreasing concentrations with storage *(31)*. However, because only two patients with MI and one patient with sepsis were cTnT positive and cTnI negative, we do not think this had a major impact on our findings. Another limitation was that postmortem samples almost invariably show some autolysis, and more detailed studies, such as electron microscopy, were not possible. However, it would be ethically unacceptable at present to perform endomyocardial biopsies in patients to clarify the basis for increased serum troponins.

As data accumulate from clinical and laboratory studies, we need to reexamine the basis of increased troponins, especially cTnT, in patients without acute ischemia. The debate continues as to which troponin is superior. An important part of this debate is the poor specificity of cTnT in end-stage renal disease patients. Our findings imply that these increases, rather than being spurious, are indicative of underlying cardiac pathology. Although cTnI and cTnT are equal in the management of patients with acute coronary syndromes, cTnT is superior in detecting minimal cardiac disease and may be a better predictor of risk in certain groups of patients.

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Nephrology Dialysis Transplantation

Original Article

Cardiac troponin I (2nd generation assay) in chronic haemodialysis patients: prevalence and prognostic value

Marta Beciani[1], Angela Tedesco[1], Anneo Violante[1], Silvia Cipriani[2], Michele Azzarito[3], Antonio Sturniolo[2] and Giorgio Splendiani[2]

[1]Chemical Laboratory, Aurelia Hospital, Rome, [2]Chair of Nephrology, 'Tor Vergata' University, Rome and [3]CICU, Aurelia Hospital, Rome, Italy

Abstract

Background. Elevated serum cardiac troponin T (cTnT) levels are frequently observed in chronic dialysis patients and have been shown to be associated with increased morbidity and mortality. The aim of this study was to determine whether cardiac troponin I (cTnI), which is less frequently elevated, has similar clinical significance.

Methods. We studied 101 asymptomatic patients with no clinical evidence of coronary artery disease who were undergoing chronic dialytic treatment. We measured their serum cTnI levels immediately before the start of their dialysis sessions by a second-generation assay (OPUS-DADE). Our study included a year-long follow-up with trimestral cTnI assays as well as clinical, X-ray and echocardiographic surveillance. We considered patients with serum cTnI $\geqslant 0.15$ ng/ml as positive and those with levels < 0.15 ng/ml as negative.

Results. Among the 14 patients with high serum cTnI levels, nine (64%) suffered acute cardiac events during the 12-month follow-up. In contrast, among the 72 patients with low cTnI levels only seven (9.7%) had acute events. In another group of 15 patients with variable cTnI levels, three patients (20%) had cardiac events.

Conclusion. Based on these results, serum cTnI appears to be a valuable predictive marker of cardiovascular events in asymptomatic dialysis patients. For those patients who might benefit from thorough cardiac investigation and treatment, information on cTnI could be useful in preventing cardiac events.

Keywords: cardiac troponin I; myocardial injury; renal disease

Correspondence and offprint requests to: Dr Silvia Cipriani, Via Olivella 120, 00041 Albano Laziale, Rome, Italy. Email: silvia.cipriani@tiscalinet.it

Introduction

Cardiac disease is the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD). The incidence and prevalence of coronary artery disease (CAD) is 16 times higher in these patients than in a normal population of the same age, sex and risk factors. In the USA, CAD is responsible for 22% of all deaths in dialysed patients [1]. Myocardial ischaemia in dialysis patients may be asymptomatic (especially in diabetic patients), and may occur in the absence of critical stenoses of coronary arteries [2].

CK-MB, a serological marker of myocardial injury, is not of significance in this population. In fact, it appears increased in 5–50% of chronic dialysis patients in the absence of cardiac symptoms or evidence of myocardial injury. Abnormal protein metabolism and muscle wasting are possible causes of this increase [2].

In recent years, new markers of myocardial injury have been introduced into clinical practice. Among these, cardiac troponins (cTn) have proven to be specific markers of myocardial damage [3,4].

The Joint European Society of Cardiology/American College of Cardiology (ESC/ACC) Expert Committee considered the cardiac troponin (I or T) measurement as the gold standard biochemical test for diagnosis of myocardial damage, because 'cTn has nearly absolute myocardial tissue specificity, as well as high sensitivity, thereby reflecting even microscopic zones of myocardial necrosis' [5]. Furthermore, increasing evidence indicates that abnormal troponin measurements identify a subgroup of patients who have an increased risk of major cardiac events [3,6].

The troponin complex consists of three regulatory subunits that mediate the contractile function of striated muscle. These are troponin C (cTnC), which binds calcium, troponin I (cTnI), which binds actin and inhibits actin–myosin interactions, and troponin T (cTnT), which binds tropomyosin and thus attaches

and sometimes negative during the year). The incidence of cardiac events in this group was 20% (three patients).

The third group included 14 patients (mean age 67 years) with positive cTnI values in each of the five measurements. The incidence of cardiac events in this group was 64% (nine patients), a highly significant difference compared to the first group ($P < 0.0001$).

The diagnostic criteria for cardiac events were based on the Consensus Document of the Joint ESC/ACC Committee for Redefinition of Myocardial Infarction.

CAD was diagnosed by biochemical, electrocardiographic and X-ray examinations: increased value for cardiac troponin (> 2 ng/ml), ST-segment elevation, presence of Q waves or left bundle branch block in two or more contiguous leads, evidence of new left ventricular dysfunction on echocardiogram.

With respect to the aetiology of chronic renal disease, there were no statistically significant differences between the three groups. The majority of patients suffered from vascular renal disease (36.5% of the total population), in 26% of patients we could discover no pathology underlying the chronic renal failure, and the remaining subject were affected by primary renal disease (19.8%), diabetic nephropathy (8.9%) and polycystic kidney disease (8.9%). Cardiac findings are summarized in Table 2.

Among those patients with a history of CAD, 28% were in the third group (cTnI-positive patients), while among the 72 patients in the first group (cTnI-negative patients) 15.2% had a positive case history.

ECGs did not show significant differences between the three groups, and within a single group, ischaemic alterations were uniformly distributed among patients with or without cardiac pathology. Echographic evaluation gave the same results (Table 1).

An increased myocardial mass and wall thickness was observed in 35% of patients, irrespective of the group they belonged to.

Table 3 shows the results obtained from patients with positive cTnI.

Discussion

Several previous papers have referred to the significance and importance of cardiac troponins in cardiac risk stratification, although contradictory results are reported.

In fact, poor cardiac outcome or mortality have been associated with elevation of serum cTnI and cTnT levels by some authors [12], while other studies have failed to detect prognostic values in uraemic patients. Cardiac troponin T was found to be predictive of myocardial injury by Martin [13], and associated with increased risks of morbidity and death in renal failure by Ooi and Zimmerman [14]. Tun *et al.* [15] hypothesized that cTnI may be a marker of ischaemic myocardial micro-injury, and Collison [8] defined as 'minimal myocardial damage' the pathology of those patients with positive cTnI without an ECG abnormality. Roppolo *et al.* [16] found that three dialysed patients without cardiac symptoms and with elevated serum cTnI at the beginning of their studies suffered adverse complications within 6 months, thus concluding that a positive cTnI was virtually 100% specific and 100% predictive for future cardiac events. Elsewhere in the literature, specificities of cTnI from 100 to 82% are reported [17]. On the other hand, Khan *et al.* [18] found that cTnI had a limited role in predicting cardiac events.

According to Apple *et al.* [19], our results confirm that a single measurement of cTnI in dialysed patients provides important information for the stratification of the risk of acute cardiac disease. In our population, nearly all those patients who died in the course of the study had pathological cTnI values. These findings are in agreement with those of Porter *et al.* [20].

After analysing our results, we came to several conclusions. Investigated patients did not show any signs or symptoms of intercurrent acute CAD; therefore elevated cTnI levels singled out microscopic necrotic lesions and allowed us to stratify the population for the short-term risk of major cardiac events.

It is well known that dialysed patients show more important alterations of coronary arteries than do control subjects of the same age with identical risk factors. In 'normal' patients, the release of troponin by myocardial cells is considered to be a consequence of hypoxic injury due to coronary plaque instability. We can state that in dialysed patients with important coronary damages, the dialytic procedure could lead to haemodynamic alterations and subsequent myocardial injury, even in the absence of clinical symptoms. Myocytic injury causes the release of minimal quantities of cTnI into the blood stream, and as a result, its blood levels can fluctuate if only the myocyte

Table 2. Incidence of cardiovascular pathology at starting time

Cardiovascular pathology	Total (incidence) (%)	Group I (incidence) (%)	Group II (incidence) (%)	Group III (incidence) (%)
Arterial hypertension	41.5	43.0	46.6	28.5
Coronary heart disease	17.8	15.2	20.0	28.5
Dilated cardiomyopathy	7.9	6.9	13.3	7.1
Peripheral arterial disease	6.9	5.5	13.3	7.1
Others	25.9	29.4	6.8	28.8

Table 3. Outcome in cTnI-positive patients

Patients	Aetiology of ESRD	troponin (ng/ml)					Events
		T0	T3	T6	T9	T12	
BD	Polycystic kidney	0.18	0.21	0.24	0.25	0.18	–
LT VD	NDD	0.71	0.24	0.38	0.37	0.20	–
MA	NDD	0.19	0.18	0.15	0.16	0.16	–
PC	Glomerulonephritis	0.20	0.17	0.15	0.21	0.22	–
CC	Nephrosclerosis	0.30	0.25	0.26	0.45[b]	0.25	CAD
SS	Polycystic kidney	0.22[b]	0.18	0.15	0.15	0.16	CAD
SF	Glomerulonephritis	0.24	0.17	0.18[b]	0.16	0.19	CAD
SF	Diabetes	0.18	0.16	0.19[b]			AMI[c]
LS	Nephrosclerosis	0.30	0.25	0.26	0.20[b]		AMI[c]
RM	Nephrosclerosis	0.32[b]					AMI[c]
AG	Nephrosclerosis	0.33	0.27	0.16[b]			AMI[c]
BB	NDD	0.16	0.60[b]				SD[c]
RV	Nephrosclerosis	0.15	0.41[b]				SD[c]
GR[a]	Polycystic kidney	0.54[b]	<0.1	<0.1	<0.1	<0.1	PTCA

[a]Patient GR changed cTnI value after PTCA treatment, which was performed after a positive cTnI test. [b]Cardiac event. [c]Death. AMI, acute myocardial infarction; SD, sudden death; CAD, coronary artery disease; PTCA, percutaneous transluminal coronary angioplasty.

membrane has been damaged (second group of patients), while they are constantly elevated if a continuous hypoxic injury and deeper myocardial damage occur (third group of patients).

The cTnI level is independent of the ECG or ECHO findings. As observed for cTnT by Deegan *et al.* [21] and Stolear *et al.* [22], the prognostic value of cTnI in our uraemic patients is independent of co-morbidity.

Minimal quantities of cTnI released into the blood stream of a 'normal' subject are easily extracted and eliminated by the kidney, while in uraemic patients they tend to accumulate, reaching significant plasma levels. We think that this is one of the reasons that cTnI levels are so significant in nephropathic patients. The background level of cTnI is effectively zero or so low as to be undetectable.

Cardiac troponins have emerged as sensitive and specific markers for detecting myocardial injury and infarction, thus facilitating rapid bedside diagnosis and early risk stratification. The use of these markers could potentially increase our ability to reserve the most expensive and aggressive therapies for those patients who have the highest risks [23].

Patients positive for cTnI may benefit from PTCA (Table 3) or from anti-platelet and anti-thrombotic therapies, neurohormonal antagonists with BB or ACE inhibitor, while in patients negative for cTnI a less intensive management approach may be appropriate so as to avoid the cost and risks associated with potentially unnecessary therapies. The cost effectiveness of including cTnI assays in strategies for the cardiovascular care of patients with renal dysfunction has recently been shown by Polaczyk *et al.* [24].

In conclusion, our results show that cTnI is essential for identifying those patients with a higher risk of cardiac pathology. In fact, not only does it single out patients who have already shown clinical signs of CAD, but it also selects those who would subsequently be affected by acute cardiac events during the follow-up period.

On this basis it is fair to say that cTnI is a sensitive and specific marker of myocardial injury even in dialysis patients. The second-generation test that we used did not show any of the interferences due to muscular isoforms or therapeutic interventions that have been reported in the literature.

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Predictive Value of Cardiac Troponin I and T for Subsequent Death in End-Stage Renal Disease

Fred S. Apple, PhD; MaryAnn M. Murakami, BA; Lesly A. Pearce, MS; Charles A. Herzog, MD

Background—This study determined the prevalence of increased cardiac troponin I (cTnI) and T (cTnT) in end-stage renal disease (ESRD) patients and whether an increased troponin was predictive of death.

Methods and Results—Serum was obtained from 733 ESRD patients and measured for cTnI and cTnT. Relative risks were estimated using Cox proportional hazards regressions univariately and adjusted for age, time on dialysis, and coronary artery disease. Kaplan-Meier curves compared time to event data between groups. Greater percentages of patients had an increased cTnT versus cTnI at each cutoff, as follows: 99th percentile, 82% versus 6%; 10% coefficient of variation, 53% versus 1.0%; and receiver operator characteristic, 20% versus 0.4%. Increased versus normal cTnT was predictive of increased mortality using all cutoffs and only above the 99th percentile for cTnI. Two-year cumulative mortality rates increased ($P<0.001$) with changes in cTnT from normal (<0.01 μg/L, 8.4%) to small (≥0.01 to <0.04 μg/L, 26%), moderate (≥0.04 to <0.1 μg/L, 39%), and large (≥0.1 μg/L, 47%) increases. Two-year mortalities were 30% for cTnI <0.1 μg/L and 52% if ≥0.1 μg/L. Univariate and adjusted relative risks of death associated with elevated (>99th percentile) cTnT were 5.0 (CI, 2.5 to 10; $P<0.001$) and 3.9 (CI, 1.9 to 7.9; $P<0.001$) and cTnI were 2.0 (CI, 1.3 to 3.3; $P=0.008$) and 2.1 (CI, 1.3 to 3.3; $P=0.007$). Age, coronary artery disease, and time on dialysis were also independent predictors of mortality.

Conclusions—Increases in cTnT and cTnI in ESRD patients show a 2- to 5-fold increase in mortality, with a greater number of patients having an increased cTnT. (***Circulation***. 2002;106:2941-2945.)

Key Words: mortality ■ cardiovascular diseases ■ myocardial infarction ■ kidney

Cardiac disease is the major cause of death in patients with end-stage renal disease (ESRD), accounting for ≈45% of all deaths.[1–3] In dialysis patients, ≈20% of cardiac deaths are attributed to acute myocardial infarction (AMI).[1–3] AMI is a catastrophic clinical event in ESRD patients, with a 2-year mortality of 73%.[3] Increased cardiac death rates in ESRD patients occur more frequently on Mondays and Tuesdays (20%) compared with other days of the week (14%).[4] One challenge confronting the nephrology community is to explore more aggressive treatment modalities for cardiovascular disease in these patients. Recent evidence demonstrates that serum or plasma cardiac troponin T (cTnT) is an important predictor of long-term, all-cause mortality and cardiovascular mortality in patients with ESRD.[5,6]

Over the last 10 years, increases in cTnT and cardiac troponin I (cTnI) have been observed in ESRD patients,[5–13] and the prevalence of increased troponins is correlated with increased risk of coronary artery disease.[7] Recent guidelines endorsed by the European Society of Cardiology (ESC), the American College of Cardiology (ACC), and the American Heart Association (AHA) state that cTnI and cTnT are the preferred biomarkers for the detection of myocardial injury and diagnosis of myocardial infarction (MI).[14–16] In the clinical setting of ischemia, evidence of increased cardiac troponins has been defined as the cornerstone of the redefinition of MI. In addition to the role of cardiac troponin as a diagnostic tool, a strong prognostic value for increased troponins exists, irrespective of the mechanism of injury, in acute coronary syndrome (ACS) patients with or without renal insufficiency.[17–19] Furthermore, early pharmacological intervention trials with low molecular weight heparin as well as with glycoprotein IIb/IIIa inhibitors have demonstrated a significant decrease in risk of death and nonfatal MI in cardiac troponin–positive ACS patients.[20,21] Whether aggressive interventional management in ESRD patients results in improved clinical outcomes has not been studied. Furthermore, no large studies have investigated the prognostic value of cTnT compared with cTnI in ESRD patients. In the present

A

Number of Patients at Risk:	Baseline	1 yr	2 yrs	2.5 yrs
cTnT<0.01 µg/L	132	106	25	12
cTnT≥0.01 to <0.04 µg/L	214	166	41	15
cTnT≥0.04 to <0.10 µg/L	239	180	63	18
cTnT≥0.10 µg/L	148	93	20	8

B

Number of Patients at Risk:	Baseline	1 yr	2 yrs	2.5 yrs
cTnI<0.1 µg/L	688	514	120	51
cTnI≥0.1 µg/L	45	31	6	2

Kaplan-Meier survival curves by baseline troponin cutoffs. A, cTnT using the 99th percentile 0.01 µg/L, 10% CV 0.03 µg/L, and the ROC 0.1 µg/L. B, cTnI using the 99th percentile 0.1 µg/L. The number of patients at risk at baseline, 1 year, 2 years, and 2.5 years for each cutoff is shown at the bottom of the graphs. The 99th percentile refers to the normal reference limit. The 10% CV refers to the lowest concentration that demonstrates a 10% total precision. The ROC cutoff refers to concentrations optimized for the sensitive and specific detection of MI.

troponin elevation detected in outpatient dialysis patients was a powerful predictor of all-cause mortality. It is quite plausible that other mechanisms beside ACS are responsible for the troponin elevation and adverse outcome. Several studies have now demonstrated that significant angiographic findings are linked to cTnT and cTnI elevations, identifying patients with ACS who will benefit from antithrombotic therapy.[33,34] However, no similar data are presently available in the ESRD population relating cardiac troponin status and angiography findings. Paradoxically, the same patient's tests in a hospital setting could be dismissed as false-positives, particularly given the proportion of patients in our study above the cTnT 0.1 cutoff. The clinical duality of cardiac troponin testing in dialysis patients must be acknowledged to avoid incorrect clinical judgments, ie, defining acute coronary syndromes and prediction of mortality (complementary but discrete tasks).

The findings of our present study substantiate the cTnT, cTnI difference observed in smaller studies.[4–12] Using the

99th percentile cutoff, 82% (n=601) of cTnT versus only 6% (n=45) of cTnI concentrations were increased. For comparison, using the ROC curve cutoff, 20% (n=148) of cTnT versus only 0.4% (n=3) of cTnI concentrations were increased. We speculate as to the possible causes for the difference in increases in cTnT compared with cTnI. First, increased cTnT but not cTnI reflects increased left ventricular mass in the ESRD population,[26,27] with a different release pattern of cTnT compared with cTnI. Second, cTnT release from injured myocardium may have a longer circulating half-life compared with cTnI because of advanced glycation end products known to accumulate in diabetic patients with renal disease.[28] However, future studies need to evaluate this concept. Third, two small studies have suggested that cTnI decreases after dialysis, either directly attributable to removal by dialysis or indirectly by degradation of the labile cTnI molecule.[29,30] In contrast, cTnT concentrations trend toward increasing after dialysis. This would result in lower circulating cTnI levels compared with cTnT. Future studies need to evaluate this observation using a large patient database. In theory, the release of the troponin ternary CIT complex from injured myocardium should show equal molar increases of cTnI and cTnT. Additional studies are needed to elucidate the mechanism responsible for the cTnI/cTnT differences found in ESRD patients.

Regardless of the mechanisms of myocardial injury in ESRD patients, our present findings continue to substantiate and add to the growing literature demonstrating the prognostic power of cardiac troponin testing for predicting mortality in ESRD patients. In one study involving 102 ESRD patients, an increased cTnT (0.1 µg/L) resulted in a 3.6-fold greater hazard ratio.[5] Furthermore, in a study involving 244 ESRD patients, an increasing cTnT over a 6-month period showed an increasing death rate with a risk ratio of 2.0.[6] Furthermore, increasing cTnT has now been shown to predict an increase in death and MI in ACS patients regardless of their level of creatinine clearance.[19] Future research will need to address whether frequent blood sampling (days, weeks, months) for troponin monitoring will identify or exclude patients with clinically inapparent ACS with or without renal insufficiency. In our present study, we reveal prognostic value for elevated cTnT and cTnI using several cutoff values. It should be noted, however, that a normal cardiac troponin does not preclude risk. Patients below the 99th percentile cutoff had a 2-year mortality rate of 8.4% (cTnT) and 30% (cTnI).

The ultimate role of cardiac troponin testing for risk stratification in chronic hemodialysis patients is speculative but attractive. There are a host of conceivable strategies for the identification of the highest-risk dialysis patients after initiation of renal replacement therapy. Our evidence-based findings suggest that one plausible, cost-effective scenario is the developing role of outpatient cardiac troponin testing. Incorporation of quarterly or semiannual cardiac troponin monitoring in ESRD patients may assist in initiating more aggressive treatment of underlying CAD and detection of subclinical myocardial injury and assist in treatment therapies before renal transplantation. As revealed in our study, not all cardiac troponin assays are equivalent regarding risk assessment in ESRD, and appropriate analytical cutoff values need

STATE-OF-THE-ART PAPER

Cardiac Troponins in Renal Insufficiency
Review and Clinical Implications

Benjamin J. Freda, DO,* W. H. Wilson Tang, MD,† Frederick Van Lente, PHD,‡
W. Franklin Peacock, MD,§ Gary S. Francis, MD FACC†
Cleveland, Ohio

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.

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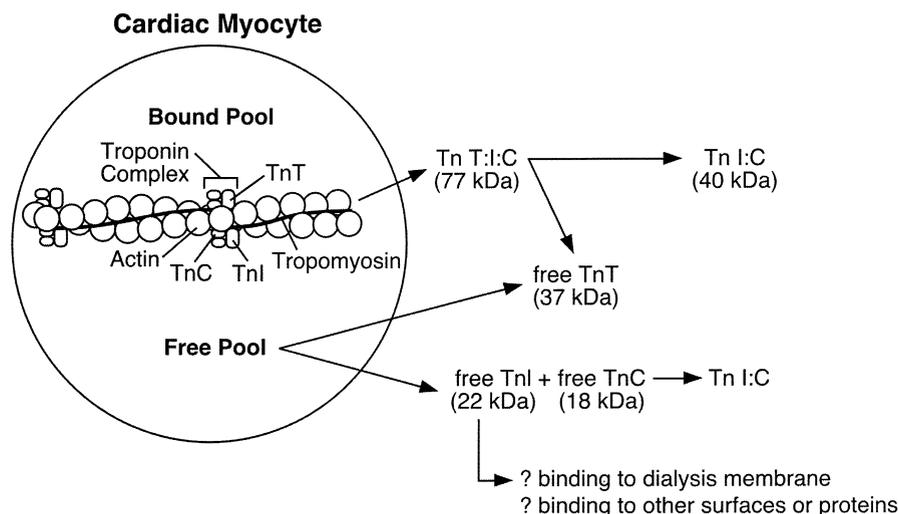
Figure 1. Troponin release profile after myocardial infarction. kDa = molecular weight in kiloDaltons; TnC = cardiac troponin C; TnI = troponin I; Tn T:I:C = intact troponin complex; Tn I:C = binary troponin I:C complex; TnT = troponin T.

surfaces and/or proteins, thus potentially masking its anti-genic 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-