Original Article

Newer cardiac troponin I assays have similar performance to troponin T in patients with end-stage renal disease

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Abstract

Background Troponin T is present in the blood of a majority of patients with end-stage renal disease (ESRD) undergoing regular dialysis and presence of troponin T is a predictor of adverse outcome in these patients. With several new formulations of troponin I assays available, this study was performed to see whether these newer assays were able to detect troponin I in these patients more effectively than the older assays.

Methods One hundred and forty-three patients undergoing regular haemodialysis or peritoneal dialysis had plasma collected and troponin T and troponin I measured by a variety of assays.

Results The newer troponin I assays (Abbott Architect, Bayer Centaur and Beckman Accu-TnI) were able to detect troponin I (>75% of samples) as effectively as the Roche assay was able to detect troponin T, while other troponin I assays had a much lower rate of detection of troponin – DPC Immulite 2000 16% and Abbott AxSYM 35%. However, the troponin T assay had more samples detected at concentrations corresponding to an assay CV of 10% (59% of samples) than did the newer troponin I assays (highest on the Bayer Centaur at 37%).

Conclusions Newer assays demonstrate that troponin I is present in a similar number of samples as is troponin T, in the blood of patients with dialysis-dependent renal failure, and these newer troponin I assays identify patients at risk of experiencing a cardiac event.

Ann Clin Biochem 2007; **44:** 285–289

Introduction

There is a high morbidity and mortality among patients on dialysis. For example, in Australia in 2004, there were 7952 patients on dialysis and 1205 deaths, equating to 15.4% of the dialysis population (similar rates for both haemodialysis and peritoneal dialysis).[1] These are comparable rates of mortality to those in the developed world generally.

Measurement of the cardiac troponins to aid in the assessment of myocardial injury has been available through service pathology laboratories since the mid-1990s. It was noted very early that cardiac troponin T (*c*TnT) was often detectable in the blood of patients with renal failure[2–4] and in the first instance it was thought this was an artefact.[5] However, subsequent analysis showed that the presence of *c*TnT had a strong association with poor outcomes,[6,7] and that prognosis is related to *c*TnT concentration.[8] While cardiac troponin I (*c*TnI) may also be increased in the blood of dialysis patients, hitherto a relatively smaller proportion of dialysis patients have demonstrated detectable *c*TnI in their blood and it has not been as reliable an index of outcome as *c*TnT.[9]

It has been suggested that the circulating forms of cardiac troponin may be different in acute coronary syndromes and in renal failure. For example, with *c*TnT, there is evidence that this molecule is fragmented into pieces of 8–25 kDa size that are normally released into the circulation and are sufficiently small enough to be cleared by the healthy kidney.[10] In patients with end-stage renal disease (ESRD) there is reduced renal

clearance of these fragments resulting in elevated cTnT values. This is supported by finding a rapid decrease in cTnT concentrations after renal transplantation.[11]

We have been following the clinical progress of a cohort of dialysis patients in whom measurement of cTnT and cTnI by several different assays has been performed and we report our experience in this paper.

Materials and methods

This study was approved by the ACT Community Health Ethics Committee.

Patients

All haemodialysis and peritoneal dialysis patients managed through the Canberra Hospital who could be contacted in a period of a fortnight in March 2005 were asked to donate blood for the measurement of cardiac troponins. A total of 143 patients gave blood for the study. The age range of the patients was 15–82 with a median age of 64 years. Thirty-two patients (22.4%) had diabetes mellitus. Thirty-one patients were undergoing peritoneal dialysis, and 112 haemodialysis. For haemodialysis patients, blood samples were collected pre-dialysis. Peritoneal dialysis patients are on continual dialysis so time of sampling was considered unimportant. At follow-up in September 2006, all cause mortality, cardiac mortality and cardiac events (myocardial infarction, angioplasty, coronary angiography and coronary artery bypass grafting) were noted.

Assays

Patient samples were collected into Vacuette lithium-heparin tubes with separator gel (Greiner Bio-One) and were processed within 2 h of collection. These samples were centrifuged at 3000 *g* for 10 min and the aliquots for each assay stored at −70°C. Prior to assay, each aliquot was thawed and re-centrifuged at 3000 *g* for 10 min.

Analysis for troponin T was performed on the Roche Elecsys 1010™ (Roche Diagnostics Australia, Sydney, Australia), with assay coefficients of variation (CV) being 6.0% at 0.11 μg/L and 2.5% at 2.5 μg/L. Troponin I assays were performed on the DPC Immulite 2000™ (Bio-Mediq DPC Ltd, Melbourne, Australia) (assay CVs 16.0% at 0.39 μg/L and 4.8% at 0.95 μg/L), Abbott AxSYM™ (Abbott Diagnostics, Sydney, Australia) (assay CVs 6.8% at 0.29 μg/L and 5.0% at 1.1 μg/L), Abbott Architect ci8200™ (Abbott Diagnostics, Sydney, Australia) (assay CVs 8.3% at 0.12 μg/L and 7.5% at 0.53 μg/L), Beckman Coulter Access II™ (Beckman Coulter Australia, Sydney, Australia) (assay CVs 13.4% at 0.06 μg/L and 5.1% at 0.54 μg/L) and Bayer Advia Centaur™ TnI-Ultra (Bayer HealthCare Diagnostics Division Australia, Melbourne, Australia) (assay CVs 7.1% at 0.14 μg/L and 5.2% at 1.3 μg/L). Each method was performed according to the manufacturer's guidelines. All of the above precision data were generated as part of routine internal quality control procedures and were similar to manufacturer-quoted data.

All assays were current product generation (October 2006) except for the DPC Immulite that was recently superseded prior to the completion of this study. Troponin T and troponin I analysis on the Immulite, AxSYM and Architect were performed at ACT Pathology, Canberra. Troponin I assays performed on the Access II and Centaur were performed at QHPS, Brisbane. Where necessary, samples were transported on dry ice prior to analysis. Technical information regarding the troponin assays under investigation is detailed in Table 1.

Statistics

Concordance between assays was calculated as κ values using MedCalc™ version 9.2.0.1 software. A κ value of 0.21–0.40 is considered to be fair agreement, 0.41–0.60 moderate agreement and 0.61–0.80 good agreement.

Table 1 *Technical information as provided by manufacturers for cardiac troponin assays*

Cardiac troponin assay	Detection limit (μg/L)	20% CV (μg/L)	10% CV (μg/L)	Reported 99th population percentile (μg/L)
Roche Elecsys 1010 TnT	0.010	0.014	0.030	<0.01
Bayer Advia Centaur TnI-Ultra	0.006	0.017	0.030	0.04
Abbott AxSYM TnI-ADV	0.020	0.040	0.16	0.04
Abbott Architect STAT TnI	0.009	0.015	0.032	0.012
Beckman Coulter Accu-TnI	0.010	0.030	0.06	0.04
DPC Immulite 2000 TnI	0.200	0.300	0.700	0.20

Some of these values were obtained by extrapolation from the precision profile. CV: coefficient of variation

Table 2 *Ability of different assays to detect troponin in plasma of patients with dialysis-dependent renal failure*

	Assay detection limit				
Assay	ND	LOD	20% CV	10% CV	Number of samples
(A) All patients					
Roche Elecsys cTnT	34 (23.8%)	109 (76.2%)	108 (75.5%)	85 (59.4%)	143
Abbott Architect cTnI	23 (16.2%)	119 (83.8%)	73 (51.4%)	45 (31.7%)	142
Abbott AxSYM cTnI	87 (65.4%)	46 (34.6%)	29 (21.8%)	6 (4.5%)	133
DPC Immulite cTnI	120 (83.9%)	23 (16.1%)	12 (8.4%)	5 (3.5%)	143
Beckman Accu-TnI	31 (23.0%)	104 (77.0%)	47 (34.8%)	14 (10.4%)	135
Bayer Centaur cTnI	20 (14.2%)	121 (85.8%)	85 (60.3%)	52 (36.9%)	141
(B) Patients with cardiac event. There were 18 cardiac events – nine non-fatal (acute myocardial infarction, angioplasty, coronary artery bypass graft) and nine fatal					
Roche Elecsys cTnT (18)	2 (11.1%)	16 (88.9%)	16 (88.9%)	15 (83.3%)	18
Abbott Architect cTnI (18)	0 (0%)	18 (100%)	15 (83.3%)	10 (55.5%)	18
Abbott AxSYM cTnI (17)	8 (47.1%)	9 (52.9%)	5 (29.4%)	3 (17.6%)	17
DPC Immulite cTnI (18)	13 (72.2%)	5 (27.8%)	4 (22.2%)	1 (5.6%)	18
Beckman Accu-TnI (17)	0 (0%)	17 (100%)	9 (52.9%)	4 (23.5%)	17
Bayer Centaur cTnI (18)	0 (0%)	18 (100%)	15 (83.3%)	11 (61.1%)	18
(C) Patients with any event. There were 28 events in total – 10 non-cardiac deaths and 18 cardiac events					
Roche Elecsys cTnT	2 (7.1%)	26 (92.9%)	25 (89.3%)	21 (75%)	28
Abbott Architect cTnI	1 (3.6%)	27 (96.4%)	23 (82.1%)	15 (53.6%)	28
Abbott AxSYM cTnI	12 (44.4%)	15 (55.6%)	9 (33.3%)	4 (14.8%)	27
DPC Immulite cTnI	21 (75%)	7 (25%)	6 (21.4%)	2 (7.1%)	28
Beckman Accu-TnI	1 (4%)	24 (96%)	12 (48%)	5 (20%)	25
Bayer Centaur cTnI	0 (0%)	27 (100%)	23 (85.2%)	16 (59.3%)	27

Insufficient sample meant not all samples could be analysed by all assays. Column headed 'Number of samples' refers to number assayed for a particular assay; ND: not detected; LOD: limit of detection; CV: coefficient of variation

Results

Over an average period of follow up of 18 months, in the whole group of 143 patients, there were a total of 28 significant clinical events, including nine cardiac deaths, 10 other deaths and nine cardiac non-fatal events including myocardial infarction and cardiac symptoms and signs requiring either angioplasty or coronary artery bypass grafting. In the subgroup of 74 asymptomatic haemodialysis patients, there were five deaths and five non-fatal cardiac events.

For each analyser, all results were assessed as to whether they were undetectable (below the limit of detection [LOD] for that assay), were above the limit of detection, were above the concentration corresponding to a 20% CV or above the concentration corresponding to a 10% CV. In addition, we performed a similar analysis for the cases where a clinical event had occurred. These data are shown in Table 2.

More than 75% of patients' samples had detectable cTnT present. There were very disparate results for the different cTnI assays. All of the Abbott Architect, Beckman Accu-TnI and Bayer Centaur cTnI-Ultra assays also had detectable cTnI present in more than 75% of samples, while the Abbott AxSYM cTnI assay detected troponin I in only 35% of the samples and the DPC Immulite cTnI in 16% of samples.

At higher concentrations, corresponding to a CV of 10%, the cTnT assay was still positive in nearly 60% of samples, while for the cTnI assays the proportion positive was substantially lower (Table 2). If the 20% CV was used as the detection limit, then the Abbott Architect and Bayer Centaur cTnI assays had nearly identical ability to identify those persons at risk of having a cardiac event, as the cTnT assay.

Table 3 shows a detailed comparison between the three newer cTnI assays and the cTnT assay, using the four discriminators of not detected (ND), LOD, 20% CV and 10% CV. Concordance is high between the cTnI assays, for example, between the Bayer and the Abbott assays, the κ value was 0.742 indicating good agreement. Between the cTnI assays there were no markedly

Table 3 *Concordance between different assays for troponin T and troponin I*

Comparator assays	Concordance				κ
	ND	LOD	20% CV	10% CV	
Architect cTnI/Roche cTnT					
ND	16	1	2	4	κ=0.447
LOD	17	0	11	18	
20% CV	0	0	8	20	
10% CV	1	0	2	42	
Beckman cTnI/Roche cTnT					
ND	16	1	4	10	κ=0.230
LOD	17	0	16	24	
20% CV	0	0	1	32	
10% CV	1	0	1	12	
Bayer cTnI/Roche cTnT					
ND	13	0	2	5	κ=0.450
LOD	17	1	7	11	
20% CV	3	0	10	22	
10% CV	1	0	4	45	
Bayer cTnI/Architect cTnI					
ND	14	5	1	0	κ=0.742
LOD	9	25	2	0	
20% CV	0	15	17	1	
10% CV	0	1	8	43	
Beckman cTnI/Architect cTnI					
ND	12	17	2	0	κ=0.419
LOD	10	24	18	5	
20% CV	1	2	3	27	
10% CV	0	1	1	12	
Beckman cTnI/Bayer cTnI					
ND	13	15	3	0	κ=0.406
LOD	7	19	21	10	
20% CV	0	1	3	29	
10% CV	0	0	1	13	

ND: not detected; LOD: limit of detection; CV: coefficient of variation; CTn: cardiac troponin

discrepant results, i.e. not detected by one assay but present at a concentration corresponding to a 10% CV by the other assay. Even between the cTnT and cTnI assays, there was generally good concordance, with only a small number of markedly discrepant results.

Discussion

It was noted at the time that troponin assays were introduced into routine pathology practice, that patients with ESRD, undergoing haemodialysis, often had detectable cTnT in their blood.[2–4] Many studies have since been published showing that there is a strong relationship between cTnT concentration and mortality.[6,7] This relationship holds whether the patient is symptomatic or asymptomatic, and is most apparent when the assay LOD is used as the cut point.[9]

To date, published data have shown that cTnI is positive in a much smaller proportion of dialysis patients than is cTnT, and is less predictive of outcome.[9] The studies using cTnI are hard to compare because of the poor standardization of cTnI assays with quite different numbers being generated between different assays, and the different epitopes that antibodies used in different assays are raised against. In addition, there is the added problem of different studies reporting to different reporting criteria, e.g. 10% CV, 99th population percentile, LOD, etc. Thus, different studies are hard to compare.[12]

A recent paper has shown that the antibody configuration of cTnI assays is of critical importance in their ability to predict risk of death in patients with coronary artery disease.[13] Looking at clinical outcomes in patients with acute coronary syndromes, they found that the Beckman Accu-TnI and Abbott Architect cTnI assays were superior in performance to the Roche Elecsys cTnT and Immulite 2500 cTnI assays. In the current study, the Architect and Centaur cTnI assays detected cTnI in more samples than did the other cTnI assays studied. These two assays have similar antibody specificity but slightly different assay architecture. The Architect cTnI method is a chemiluminescent microparticle immunoassay with two monoclonal capture antibodies directed to amino acids 24–40 and 87–91 on cTnI, and a monoclonal detection antibody to amino acids 41–49 that is labelled with an acridinium derivative. The Centaur cTnI method is a direct chemiluminescent immunoassay that uses two biotinylated monoclonal antibodies directed to amino acids 41–49 and 87–91, and a polyclonal detection antibody to amino acids 27–40 that is labelled with acridinium ester. This reaction is enhanced by use of solid phase latex particles conjugated with streptavidin. In contrast, the AccuTnI method uses two monoclonal troponin I antibodies directed to amino acids 24–40 (capture antibody labelled with ALP), and 41–49 (detection antibody attached to paramagnetic particles).

Although the current study is primarily an assay comparison study, we have also assessed the relationship of the different assays to clinical outcomes in our patient population. We found that comparing three newer cTnI assays (Beckman Accu-TnI, Abbott Architect and Bayer Centaur) to the Roche troponin T assay, cTnI and cTnT were present in a similar number of samples from patients with dialysis-dependent ESRD.

The data generated in Table 2 use manufacturer-supplied data on assay precision. The strong concordance between assays supports the validity of their quoted numbers.

We have demonstrated that cTnI and cTnT are present in a similar number of samples from dialysis patients. While it has been suggested that cTnI is cleared by a predominantly non-renal mechanism,[14] and that cTnT is cleared through the kidney,[15] the data we present in this paper indicate that this interpretation may need to be reassessed.

It is worth noting that two of the cTnI assays had identical performance to the cTnT assay at the concentration corresponding to a 20% CV, in identifying those persons at risk of experiencing a cardiac event (Table 2B). Our numbers are small and this relationship may not be borne out as the period of follow up extends. However, there is now a large literature indicating that both cTnT and cTnI at concentrations down to the LOD are informative for worse outcomes, both in the renal dialysis populations[9] and in investigation of persons experiencing acute coronary syndromes.[16]

In summary, we have measured cTnT and cTnI in the blood of patients with dialysis-dependent ESRD. We have found that the newer cTnI assays are capable of detecting troponin I in as many samples as have detectable TnT, and both the cTnI and cTnT assays identify persons at a higher risk of experiencing an adverse event.

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Accepted for publication 8 January 2007