CARDIOVASCULAR MEDICINE

Cardiac structural and functional abnormalities in end stage renal disease patients with elevated cardiac troponin T

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Objectives: To identify in a prospective observational study the cardiac structural and functional abnormalities and mortality in patients with end stage renal disease (ESRD) with a raised cardiac troponin T (cTnT) concentration.

Methods: 126 renal transplant candidates were studied over a two year period. Clinical, biochemical, echocardiographic, coronary angiographic, and dobutamine stress echocardiographic (DSE) data were examined in comparison with cTnT concentrations dichotomised at cut off concentrations of $< 0.04 \mu\text{g/l}$ and $< 0.10 \mu\text{g/l}$.

Results: Left ventricular (LV) size and filling pressure were significantly raised and LV systolic and diastolic function parameters significantly impaired in patients with raised cTnT, irrespective of the cut off concentration. The proportions of patients with diabetes and on dialysis were higher in both groups with raised cTnT. With a cut off cTnT concentration of $0.04 \mu\text{g/l}$ but not $0.10 \mu\text{g/l}$, significantly more patients had severe coronary artery disease and a positive DSE result. The total ischaemic burden during DSE was similar in cTnT positive and negative patients, irrespective of the cut off concentration used. LV end systolic diameter index and E:Ea ratio were independent predictors of cTnT rises $\geq 0.04 \mu\text{g/l}$ and $\geq 0.10 \mu\text{g/l}$, respectively. Diabetes was independently associated with cTnT at both cut off concentrations. Mortality was higher in all patients with raised cTnT.

Conclusions: Patients with ESRD with raised cTnT concentrations have increased mortality. Raised concentrations are strongly associated with diabetes, LV dilatation, and impaired LV systolic and diastolic function, but not with severe coronary artery disease.

Cardiovascular disease remains the leading cause of death in patients with end stage renal disease (ESRD) and accounts for about 45% of all deaths.¹ Cardiac risk is increased 20-fold for those on dialysis and remains fivefold increased after renal transplantation.² Identifying markers of high risk in this patient group is therefore essential to allow improvements in diagnosis, risk stratification, and treatment. Cardiac troponin T (cTnT) is raised in a proportion of patients with ESRD and is associated with increased mortality.³⁻⁴ The reasons for this remain unclear. Possible mechanisms include coronary artery disease (CAD),⁵ left ventricular (LV) dysfunction, LV hypertrophy, cardiac microinfarctions, and arrhythmia. The objective of this study was to prospectively investigate cardiac structural and functional abnormalities in a group of patients with ESRD and to relate these with cTnT concentration and outcome.

METHODS

Population

This was a prospective observational study of an unselected group of renal transplant candidates. One hundred and twenty nine consecutive patients referred for renal transplantation evaluation were enrolled. Three declined coronary angiography so were not included in the analysis, leaving a sample size of 126 patients. Exclusion criteria were age less than 18 years, severe aortic stenosis, unstable angina, and inability to give consent. All patients had coronary angiography, including young, non-diabetic patients who usually would be considered at low cardiac risk and not referred for

this investigation. Informed consent was required for this. The study had approval from the local ethics committee.

Study entry was at the time of echocardiography. At this stage full demographic data, physical examination, and haematological and biochemical blood tests were acquired. Glomerular filtration rate was estimated according to the Cockcroft-Gault equation as $(140 - \text{age}) \times \text{ideal body weight (kg)}/72 \times \text{stable serum creatinine } (\mu\text{mol/l}) \times (0.85 \text{ for female patients})$.

Transthoracic echocardiography

The General Electric Vingmed (Horton, Norway) System 7 ultrasound machine was used. Studies were performed 16-24 hours after dialysis, when patients were closest to their euvolaemic state.⁶ Two dimensional measurements were performed as recommended by the American Society of Echocardiography.⁷ Values were indexed to body surface area. LV ejection fraction (LVEF) was determined by the modified biplane Simpson's rule. Measurements were averaged over three cardiac cycles. Impaired LV systolic function was defined as $\text{LVEF} < 50\%$.⁸ LV mass was calculated according to Devereux *et al.*⁹ This was corrected for body surface area to give the LV mass index (LVMI). LV

Abbreviations: BNP, brain natriuretic peptide; CAD, coronary artery disease; cTnT, cardiac troponin T; DSE, dobutamine stress echocardiography; ESRD, end stage renal disease; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Vp, propagation velocity

hypertrophy was defined as LVMI ≥ 125 g/m² for men and LVMI ≥ 110 g/m² for women.

Pulsed Doppler was used to record transmitral flow in the apical four chamber view. Flow propagation velocity (Vp) was calculated from colour M mode in the apical four chamber view. Tissue Doppler velocities were acquired at the lateral mitral annulus. LV filling pressure was estimated from E:Ea and E:Vp ratios.¹⁰ LV diastolic dysfunction was defined from the transmitral Doppler pattern as slow relaxation (E:A ratio < 1 , E deceleration time > 220 ms), restrictive filling (E:A > 2.0 , E:A between 1 and 2 with E deceleration time < 150 ms), or pseudonormal (Ea < 0.08 ms, Vp < 0.45 m/s in the context of normal transmitral Doppler).¹¹

Dobutamine stress echocardiography

Images were acquired in standard parasternal long and short axis and apical two, three, and four chamber views at baseline and during stepwise infusion of dobutamine infusion, given according to a protocol based on three minute stages of 5, 10, 20, 30, and 40 μ g/kg/min. Atropine was administered up to a total of 1.0 mg intravenously if the target heart rate was not achieved with dobutamine alone. Blood pressure and 12 lead ECG were recorded at each infusion stage. Baseline, low dose (heart rate 10–15 beats above baseline), peak, and recovery (10 minutes after drug infusion was terminated) stage images were stored and analysed in digital quad screen format. The test was stopped if (1) the target heart rate was achieved ($[220 - \text{age}] \times 0.85$); (2) ST depression > 2 mm occurred; (3) significant tachyarrhythmia (sustained supraventricular tachycardia or a > 3 beat run of ventricular tachycardia) occurred; (4) symptomatic severe hypotension occurred; (5) blood pressure exceeded 240 mm Hg systolic or 140 mm Hg diastolic; or (6) new regional wall motion abnormalities occurred.

Two experienced observers blinded to the rest of the study reported images off line. The LV was divided into a 17 segment model for qualitative analysis.¹² Regional wall motion was described as hyperkinetic, normal, hypokinetic, akinetic, and dyskinetic. Results were classified as a normal response with an overall increase in wall motion or abnormal response. An abnormal response was described by the occurrence under stress of hypokinesia, akinesia, or dyskinesia in one or more resting normal segments or worsening of wall motion in one or more resting hypokinetic segments.¹³ The peak wall motion score index was calculated for each patient. All images were stored in digital format and two experienced observers blinded to the rest of the study made offline measurements. Consensus was obtained in discordant cases.

cTnT and N-terminal pro-B-type natriuretic peptide assays

Blood samples, obtained at the time of echocardiography, were drawn into gel serum separator tubes (SST tubes, Becton-Dickinson, Oxford, UK) and allowed to clot. Serum was separated by centrifugation at 3000 rpm for 10 minutes. Measurement of cTnT was by the third generation Elecsys 2010 STAT electrochemiluminescent immunoassay (Roche Diagnostics, Lewes, UK).¹⁴ The assay detection limit was < 0.01 μ g/l. The total assay coefficient of variation was 5.5% at 0.32 μ g/l and 5.4% at 6.0 μ g/l. The functional sensitivity corresponding to a 10% coefficient of variation was 0.03 μ g/l. The receiver operating characteristic curve medical decision cut off for myocardial infarction is 0.05 μ g/l with an optimised threshold of 0.1 μ g/l recommended by some authors.¹⁵ The 99th centile of 350 healthy subjects was ≤ 0.01 μ g/l.

Patients were divided into two groups according to two cut points: 0.04 μ g/l as the midpoint between the functional sensitivity and receiver operating characteristic curve cut off and a recommended clinical threshold concentration of 0.1 μ g/l. Patients with ESRD with baseline cTnT above either of these concentrations are at increased risk of cardiovascular and all cause mortality.⁴

N-terminal pro-B-type natriuretic peptide (NT-proBNP) was determined by electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics). The assay detection limit is 1 pg/ml and is linear up to 25 000 pg/ml, with no high dose hook effect up to 100 000 pg/ml. The functional sensitivity is 10 pg/ml. At concentrations > 70 pg/ml the intra-assay coefficient of variation is $< 4\%$ and the interassay precision is $< 5\%$. A baseline NT-proBNP concentration ≥ 125 pg/ml was taken as raised.¹⁶

Coronary angiography

All patients underwent coronary angiography. Two experienced observers interpreted the angiograms blindly and reached a consensus in case of disagreement. Stenosis severity of each epicardial artery was assessed visually and graded as follows: no stenosis, mild ($< 50\%$ luminal

Table 1 Baseline characteristics of renal transplant candidates

Age (years)	52 (12)
Sex (men/women)	80/46
Ethnicity	
White	63 (50%)
Asian	24 (19%)
Afro-Caribbean	31 (25%)
Chinese	4 (3%)
Other	4 (3%)
Serum creatinine (μ mol/l)	608 (272)
Serum haemoglobin (g/l)	10.2 (1.6)
Cholesterol (mmol/l)	4.9 (1.8)
cTnT (μ g/l)	0.02 (0–0.11)
NT-proBNP (pg/ml)	304.2 (49.8–1156.8)
End stage renal disease cause	
Diabetes	48 (39%)
Glomerulonephritis	29 (23%)
Hypertension	18 (14%)
Adult polycystic kidney disease	9 (7%)
Obstructive uropathy	9 (7%)
Other	13 (10%)
Dialysis modality	
Predialysis	57 (45%)
Haemodialysis	41 (33%)
Peritoneal dialysis	28 (22%)
Dialysis duration (months)	2.73 (2.19)
Previous transplantation	16 (13%)
Cardiac symptoms	53 (42%)
Diabetes	50 (39%)
IDDM	20 (40%)
NIDDM	30 (60%)
Hypertension	115 (91%)
Raised cholesterol	71 (56%)
Smoker	18 (14%)
Pre-existing cardiac disease	
IHD	17 (13%)
HF	17 (13%)
Severe CAD at angiography	36 (29%)
Positive DSE result	37 (30%)
Mean LVEF (%)	66 (14)
Raised cTnT (μ g/l)	
> 0.01	75 (59%)
0.01–0.03	23 (18%)
0.04–0.09	14 (11%)
≥ 0.1	38 (30%)

Data are mean (SD), number (%), or median (interquartile range). CAD, coronary artery disease; cTnT, cardiac troponin T; DSE, dobutamine stress echocardiography; HF, heart failure; IDDM, insulin dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 2 Baseline differences between patients with and without raised cTnT

	cTnT cut off (µg/l)		p Value			p Value
	≥0.04 (n = 52)	<0.04 (n = 74)		≥0.10 (n = 38)	<0.10 (n = 88)	
Age (years)	54 (12)	51 (13)	NS	54 (14)	51 (11)	NS
Dead	10 (19%)	2 (3%)	0.003	8 (21%)	4 (5%)	0.003
Creatinine (µmol/l)	712 (293)	514 (246)	0.02	736 (324)	586 (253)	0.033
Dialysis	34 (65%)	35 (47%)	0.011	28 (73%)	41 (47%)	0.025
Diabetes	34 (65%)	16 (22%)	<0.001	24 (63%)	26 (30%)	0.014
History of HF	10 (19%)	1 (1%)	<0.001	8 (21%)	3 (3%)	<0.003
History of IHD	15 (28%)	2 (3%)	0.009	9 (24%)	8 (9%)	0.012
No of abnormal ECGs	35 (67%)	14 (19%)	0.022	14 (37%)	35 (40%)	NS
Positive DSE	21 (40%)	16 (22%)	0.007	11 (29%)	26 (30%)	NS
PWMSI	1.23 (0.34)	1.19 (0.23)	NS	1.21 (0.22)	1.18 (0.44)	NS
Number of ischaemic segments	1.87 (0.79)	1.68 (0.85)	NS	1.79 (0.92)	1.64 (0.63)	NS
Severe CAD	20 (38%)	16 (22%)	0.04	12 (32%)	24 (27%)	NS
No of severely diseased arteries	1.24 (1.02)	0.83 (0.63)	0.05	1.14 (1.11)	1.08 (0.92)	NS
NT-ProBNP (pg/ml)	2921 (698)	542 (132)	0.02	3941 (683)	602 (447)	0.002
Cholesterol (mmol/l)	4.4 (1.3)	5.1 (1.3)	0.05	4.4 (1.3)	5.8 (1.9)	0.003
Haemoglobin (g/l)	11.4 (1.4)	10.8 (1.4)	NS	11.5 (1.4)	11.0 (1.5)	NS
Statin treatment	25 (48%)	38 (51%)	NS	20 (53%)	43 (49%)	NS
LVEDDI (cm/m ²)	2.1 (0.4)	1.4 (0.5)	<0.001	2.2 (0.5)	1.6 (0.3)	<0.001
LVEDDI (cm/m ²)	3.3 (1.1)	2.5 (0.4)	<0.001	3.4 (0.6)	2.6 (0.5)	<0.001
LVESVI (ml/m ²)	33 (12)	18 (7)	<0.001	35 (17)	17 (8)	<0.001
LVEDVI (ml/m ²)	82 (23)	56 (20)	<0.001	85 (22)	58 (25)	<0.001
LVFS (%)	29.7 (10.1)	41.1 (7.6)	<0.001	28.1 (9.2)	40.1 (9.2)	<0.001
LVEF (%)	55.8 (14.6)	71.6 (18.6)	<0.001	54.1 (13.2)	71.8 (12.2)	<0.001
Smax (m/s)	0.07 (0.02)	0.10 (0.04)	<0.001	0.06 (0.02)	0.10 (0.02)	<0.001
LVMI (g/m ²)	171.4 (92.7)	136.8 (63)	0.03	179.4 (85.7)	132.8 (63)	0.03
E:Ea	16.9 (6.5)	10.4 (4.5)	<0.001	16.7 (6.9)	10.9 (4.7)	<0.001
E:VP	2.54 (0.81)	1.89 (0.64)	<0.001	2.60 (0.80)	2.02 (0.71)	0.001
LA (cm)	3.9 (0.6)	3.4 (0.7)	<0.001	4.0 (0.6)	3.3 (0.4)	<0.001

Data are mean (SD) or number (%).

LA, left atrium; LVEDDI, left ventricular end diastolic diameter index; LVEDVI, left ventricular end diastolic volume index; LVESDI, left ventricular end systolic diameter index; LVESVI, left ventricular end systolic volume index; LVFS, left ventricular fractional shortening; LVMI, left ventricular mass index; NS, not significant; PWMSI, peak wall motion score index; Smax, peak systolic velocity; Vp, propagation velocity.

narrowing), moderate (50–70% luminal narrowing), or severe (> 70% luminal narrowing). Severe CAD was defined as luminal stenosis > 70% in one or more epicardial arteries.

Statistical analysis

Continuous variables were expressed as mean (SD). Variables with skewed distribution were expressed as median with interquartile range. Differences between groups were determined with the unpaired *t* test. Categorical variables were compared by χ^2 analysis or Fisher's exact test. Linear regression analysis was used to assess the correlation of cTnT, as a continuous variable, with various parameters. Stepwise multiple logistic regression analysis by forward selection was used to determine independent predictors of a raised cTnT concentration at different cut off concentrations. Long term survival related to troponin concentration was analysed in a Kaplan-Meier model. The log rank test was used to evaluate the differences between Kaplan-Meier curves. All statistical tests were two tailed with *p* < 0.05 to indicate significance. The level of agreement between two observers was analysed with κ statistics. The SPSS statistics package (SPSS Inc, version 12, Chicago, Illinois, USA) was used.

Follow up

Follow up was obtained by review of inpatient and outpatient medical records and telephone calls to the transplant unit. The primary end point was total mortality.

RESULTS

Baseline characteristics

Table 1 shows the clinical characteristics of the patients studied. Sixty nine (55%) patients were on dialysis. The mean

time on dialysis was 2.73 (2.19) months. For those not on dialysis, mean creatinine clearance was 16 (9) ml/min. Fifty three (42%) patients had cardiac symptoms (chest pain in 62% and shortness of breath in 38%). Medication used was aspirin by 58 patients (46%), β blockers by 44 patients (35%), angiotensin converting enzyme inhibitors by 54 patients (43%), statins by 63 patients (50%), erythropoietin by 53 patients (42%), and loop diuretic by 56 patients (43%).

LV dimensions and systolic function were within normal limits for the population as a whole. Twenty three patients had impaired LV function but none of these had severe impairment (LVEF < 30%). Seventy eight patients (62%) had LV hypertrophy by echocardiographic criteria. Diastolic dysfunction was seen in 81%: 47 (37%) with a slow relaxation pattern; 36 (29%) a pseudonormal pattern; 19 (15%) a restrictive filling pattern.

A third of the patients had severe CAD or a positive dobutamine stress echocardiography (DSE) result. The level of agreement between the two observers was κ = 0.82 for DSE and κ = 0.85 for coronary angiography. Thirty eight (30%) patients had cTnT $\geq$ 0.1 µg/l and 52 (41%) had cTnT > 0.04 µg/l. Seventy four (59%) patients had a baseline NT-proBNP concentration $\geq$ 125 pg/ml. The proportion with raised NT-proBNP was significantly higher in those on dialysis than in predialysis patients (68% v 29% respectively, *p* = 0.001).

Differences between patients with and without raised cTnT

cTnT positive and negative patients were compared at cut off concentrations of 0.04 µg/l and 0.10 µg/l. Table 2 shows the results. Among patients with a raised cTnT concentration, a

Table 3 Univariate linear regression analysis of echocardiographic parameters and cTnT in the whole population and in diabetic patients only

	Whole population					Diabetic patients				
	Mean (SD)	β	p Value	95% CI	R ²	Mean (SD)	β	p Value	95% CI	R ²
LVESDI (cm/m ²)	1.6 (0.6)	2.2 (0.5)	<0.001	1.2 to 3.2	0.38	1.8 (0.5)	0.003 (0.18)	NS	-0.3 to 0.4	0.33
LVFS (%)	37 (10)	-23 (6)	<0.001	-11 to -36	0.35	35 (8)	-0.9 (2)	NS	-2.3 to 4.8	0.39
LVEF (%)	67 (14)	-34 (9)	<0.001	-17 to -50	0.39	64 (12)	-1.1 (3)	NS	-7.1 to 4.9	0.38
E:Ea	12.6 (5.5)	12.4 (3.5)	0.001	5.4 to 19.4	0.34	14.7 (6.3)	4.1 (1.2)	0.01	1.7 to 6.4	0.46
E:VP	2.06 (0.72)	1.47 (0.5)	0.02	0.56 to 2.38	0.31	2.35 (0.81)	0.4 (0.2)	0.01	0.1 to 0.7	0.42

CI, confidence interval.

higher proportion were diabetic and on dialysis and they had greater LV dilatation, higher LVMI, more impaired LV systolic function, higher estimated LV filling pressures, higher NT-proBNP concentrations, and lower cholesterol concentrations than did patients with negative cTnT. Age, sex, medication, parathyroid hormone concentrations, and calcium-phosphate product were similar in the groups with and without raised cTnT. With a cut off troponin concentration of 0.04 $\mu\text{g/l}$ but not 0.10 $\mu\text{g/l}$, more of the patients in the troponin positive group had severe CAD and inducible ischaemia during DSE. The total ischaemic burden, assessed by the peak wall motion score index and total number of ischaemic segments during DSE, was similar in the troponin positive and negative patients, irrespective of the cut off concentration.

Association of NT-proBNP and cTnT

NT-proBNP concentrations were significantly higher in patients with raised cTnT at both cut off concentrations (table 2). When compared as continuous variables, cTnT and NT-proBNP were found to have a significant positive correlation ($r = 0.55$, $p < 0.001$).

Relation between echocardiographic parameters and cTnT concentration

Linear regression techniques showed that raised cTnT concentrations were associated with increased LV dimensions and filling pressure but reduced systolic function. When this was analysed in the diabetic subgroup, only markers of LV filling pressure were associated with cTnT concentrations. Table 3 shows these results.

Parameters independently associated with raised cTnT

Stepwise logistic regression analysis by forward selection was performed on all the significant parameters identified by univariate analysis. Table 4 shows the results. Diabetes was independently associated with cTnT rise at both cut off concentrations chosen. LVESDI and E:Ea ratio were independently associated with a cTnT rise of $\geq 0.04 \mu\text{g/l}$ and $\geq 0.10 \mu\text{g/l}$, respectively. Stepwise regression analysis showed that NT-proBNP concentrations ($\beta = 3.2 \times 10^{-7} \pm 10^{-6}$, $p = 0.03$) and E:Ea ratio

($\beta = 0.003 \pm 0.001$, $p = 0.04$) best predicted cTnT concentration.

Follow up

Mean follow up time was 1.61 (0.56) years (range 0.19–2.52 years). Over this period 35 patients received a renal transplant, eight were removed from the transplant list, and 12 died, seven of cardiac causes. Mean time to death was 0.71 (0.59) years (range 0.19–2.02 years). Figure 1 shows Kaplan-Meier estimates of all cause mortality according to the cTnT concentration. Survival rates were significantly poorer in those patients with raised cTnT irrespective of the cut off concentration.

DISCUSSION

This study investigated clinical, biochemical, angiographic, and echocardiographic parameters in the same group of patients with ESRD with and without raised cTnT. These parameters were assessed at cut off cTnT concentrations of 0.1 $\mu\text{g/l}$ and 0.04 $\mu\text{g/l}$. These respectively correspond to the suggested cut off for acute myocardial infarction and the 10% coefficient variation cut off, which is suggested to optimise laboratory precision.¹⁷ We found that patients with raised cTnT have increased mortality, as previously described.^{3, 18} These patients were more likely to have diabetes, LV dilatation, impaired LV systolic function, and higher LV filling pressures. There was a less clear association with severe CAD.

The population studied, namely an unselected group of potential renal transplant candidates, was undoubtedly healthier than previously studied patients with ESRD on long term dialysis. This referral bias meant that none of the patients had poor LV systolic function, the vast majority had normal LVEF, a large proportion were not on dialysis, and duration on dialysis was short. Thus, our results apply to patients with ESRD with normal LVEF and may not extend to those with systolic dysfunction. However, the use of biomarkers to assess risk in ESRD is probably most relevant in patients being referred for renal transplantation.

A significantly higher proportion of troponin positive patients were on dialysis. The mechanism for this remains unclear but recent evidence suggests an accumulation of cTnT fragments in the serum of dialysed patients.¹⁹

Irrespective of the cut off concentration used, cTnT positive patients had significantly more dilated left ventricles, more significantly impaired LV systolic function, and higher estimated LV filling pressures. This is in keeping with previous studies and supports the argument that “false positive” cTnT concentrations in renal failure represent clinically significant myocardial damage.^{20–21} LV dysfunction and dilatation are independent predictors of mortality in ESRD.^{22–23} These echocardiographic findings may therefore at least partly explain the observed higher mortality seen in renal failure patients with raised cTnT. LA size was significantly higher in patients with raised troponin. This parameter is an independent marker of outcome in

Table 4 Independent predictors of raised cTnT by stepwise multivariate logistic regression analysis

	OR (95% CI)	p Value
cTnT $\geq 0.04 \mu\text{g/l}$		
Diabetes	18.8 (3.6 to 97.3)	<0.001
LVESDI	6.9 (2.5 to 15.1)	<0.001
cTnT $\geq 0.10 \mu\text{g/l}$		
Diabetes	10.2 (3.0 to 34.5)	<0.001
E:Ea	1.2 (1.1 to 1.4)	0.003

OR, odds ratio.

Figure 1 Kaplan-Meier survival curves according to cardiac troponin T (cTnT) concentration.

cardiovascular disease and undoubtedly relates to increased LV filling pressures.²⁴ LVMI was also higher in the cTnT positive group, another parameter known to be associated with increased mortality in ESRD.²⁵ It is important to note that the cardiac structural differences in the troponin positive and negative groups could not be explained by differences in medication, blood pressure, body mass index, or haemoglobin or parathyroid hormone concentrations.

In this study, 59% of patients had raised NT-proBNP concentrations, as defined by the threshold concentration for heart failure diagnosis in non-uraemic patients. NT-proBNP is predominantly excreted by the kidneys, in contrast to clearance of brain natriuretic peptide (BNP) by receptor internalisation and plasma neuropeptidase degradation. NT-proBNP may therefore be inferior to BNP in ESRD for risk stratification. Indeed, a BNP cut off concentration of 390 ng/l has been shown to predict mortality in haemodialysis patients.²⁶ Apple *et al*²⁷ concluded that NT-proBNP has poor prognostic ability at the threshold derived from the 99th centile of the reference interval. However, tertile analysis from the same data suggested significant prognostic value of NT-proBNP if a higher cut off concentration is used. This suggests that raised NT-proBNP concentrations in renal failure are not simply a reflection of impaired excretion. Further studies are required to clarify this. Recently, DeFilippi *et al*²⁸ showed that NT-proBNP concentration rise in asymptomatic patients with chronic kidney disease who are not on dialysis reflects CAD and LV hypertrophy independent of renal function. In our study, the positive correlation between NT-proBNP and cTnT reflects, in part, the raised LV filling pressure and impaired systolic function of the cTnT positive patients. However, the strong association of NT-proBNP with dialysis, as previously reported,²⁹ suggests that dialysis may be a factor in the cardiac structural differences seen between troponin positive and negative patients because of greater cardiac injury, higher LV filling pressure, reduced clearance, or all three.

The mechanisms causing the observed cardiac abnormalities in patients with ESRD with raised troponin remain unclear. In experimental models of renal failure, cardiac function is impaired with microvascular changes and LV hypertrophy associated with reduced capillary density.³⁰ These functional and anatomical changes may contribute to susceptibility to ischaemic injury. In postmortem examination of patients with ESRD, raised cTnT was associated with recent acute myocardial infarction or microinfarcts, heart failure, or other myocardial damage.³¹ Some have suggested an association with CAD.³² In our study, only with a cut off concentration of 0.04 µg/l was there a significant difference between cTnT positive and negative patients for severe CAD

and inducible ischaemia. At a concentration of 0.10 µg/l this difference was lost. Moreover, the total ischaemic burden during DSE was similar in patients with and without raised troponin, irrespective of the cut off concentration used. CAD or a positive DSE result was not independently associated with raised cTnT. This suggests that the structural cardiac differences and subsequent increased mortality seen in patients with ESRD with raised troponin are not explained by the presence of severe CAD alone. This is in keeping with the results of Obialo *et al*.³² DeFilippi *et al*³³ noted an association with cTnT concentration and diffuse CAD in 67 patients with ESRD. However, the cTnT concentration was below the threshold for myocardial necrosis. In our study, serum cholesterol was significantly lower in the troponin positive patients despite similar use of statins in each group. The reasons for this are unclear but may be related to poorer nutritional status of those with raised troponin. Other potential mechanisms for cardiac injury in ESRD are microinfarction and myocarditis, but these have yet to be substantiated by clinical studies.

Diabetes remained independently associated with raised cTnT, irrespective of the cut off concentration. This was found in two previous studies^{3 20} but contrasts with the findings of Apple *et al*.⁴ Diabetic patients with ESRD have a high prevalence of CAD. Moreover, this coronary risk factor results in functional, biochemical, and morphological cardiac abnormalities independent of ischaemia.³⁴ Microvascular disease and diabetes are also strongly associated.³⁵ These factors may contribute to the increased mortality and observed cardiac damage in patients with ESRD with raised troponin.

A role for troponin in the risk stratification of patients with ESRD, particularly those referred for renal transplantation, is attractive. A multibiomarker risk stratification model, including troponin, has recently been proposed.²⁷ Given the poorer prognosis associated with raised troponin in renal failure, tighter control of fluid shifts during dialysis and greater use of angiotensin converting enzyme inhibitors may be advocated in this patient group. However, further prospective studies are required to determine whether any intervention will improve long term mortality in troponin positive patients with ESRD.

Study limitations

This was a small, observational study so conclusions regarding mortality must be made with caution. The population selected was heterogeneous and comprised dialysis and non-dialysis patients. Nevertheless, this study population is representative of renal transplant candidates in whom cardiac risk assessment is important. Given the

changes that occur in hydration status between dialysis sessions, echocardiographic parameters and biochemical markers should be measured at similar times after dialysis if comparisons are to be made. In this study, all measurements were made 16–24 hours after dialysis.⁶ Lastly, as discussed earlier, BNP, being a smaller molecule than NT-proBNP and not reliant on renal clearance, may have been better for examining the relation between troponin and natriuretic peptides.

Conclusions

In an unselected group of renal transplant candidates, patients with raised cTnT had clear evidence of myocardial dysfunction as evidenced by LV dilatation, impaired LV systolic function, and raised LV filling pressure. Severe CAD did not appear to be centrally involved in the cTnT rise but this rise was strongly associated with diabetes.

These findings may, at least in part, explain the observed higher mortality of patients with ESRD with raised troponin.

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