Use of cardiac troponin T in diagnosis and prognosis of cardiac events in patients on chronic haemodialysis

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Abstract

Background. Patients undergoing chronic haemodialysis frequently have elevated serum cardiac troponin T (cTnT) levels resulting in difficulty in diagnosing acute coronary syndromes (ACS) in these patients. We sought to determine whether: (i) cTnT concentrations were consistent over time; (ii) intradialytic changes in cTnT levels were due to haemoconcentration; (iii) baseline cTnT levels predicted subsequent mortality or ACS.

Methods. We measured serial pre- and post-dialysis cTnT concentrations in 75 asymptomatic patients undergoing chronic haemodialysis at baseline, and at 48 h, 8 months and 15 months. At 15 months, we also measured pre- and post-dialysis haematocrit levels in order to adjust the post-dialysis cTnT concentration for the effect of ultrafiltration. Kaplan–Meier survival curves, log-rank tests and Cox models were employed to determine whether baseline cTnT levels predicted death or ACS within 18 months.

Results. Thirty-five (47%) patients had a baseline pre-dialysis cTnT concentration in the diagnostic range for an ACS (cTnT ≥ 0.03 μg/l). There was a strong correlation between serial cTnT concentrations in individual patients (P < 0.0001 for each time point). The median cTnT concentration was significantly greater post- than pre-dialysis (P < 0.01 for each serial analysis); however, there was no significant difference following correction of post-dialysis cTnT levels for the effect of haemoconcentration (P = 0.48). Elevated baseline cTnT levels were associated with an increased risk of mortality or ACS at 18 months (P = 0.0015).

Conclusion. In asymptomatic patients on haemodialysis, serum cTnT concentrations are frequently elevated, and they rise during dialysis due to haemoconcentration. cTnT levels fluctuate minimally in individual patients in the medium term, therefore annual measurements may be useful reference points in the diagnosis of chest pain and in the prediction of ACS and mortality.

Keywords: acute coronary syndrome; cardiac troponin T; diagnosis; haemodialysis; prognosis

Introduction

Major studies have shown that sensitive and specific markers of myocardial necrosis such as cardiac troponin T (cTnT) are useful both diagnostically and prognostically in acute coronary syndromes (ACS); however, in the majority of these studies, patients with renal failure were excluded [1–3]. Elevated serum cTnT levels are commonly observed in patients with renal failure, even in the absence of an acute coronary syndrome [4–8]. Initially, this was considered to represent a false-positive result, but subsequently it has been shown that elevations in cTnT remain prognostically significant in asymptomatic patients on chronic haemodialysis [4–8]. The cause of the elevation in cTnT in dialysis patients is unclear, but may reflect increased cTnT release due to ongoing minor myocardial necrosis or greater left ventricular mass [6], or reduced renal clearance of immunoreactive cTnT fragments [9].

Elevations in serum cTnT concentration are now used routinely in the diagnosis of ACS in non-uraemic patients [10]. This strategy cannot, however, be readily applied to patients with renal failure who present with chest pain, as more than 50% of asymptomatic haemodialysis patients have serum cTnT levels in the diagnostic range for ACS [7,11]. One option could be to compare the cTnT concentration to previous results, in a manner analogous to comparing current and historical electrocardiograms (ECGs). However, this strategy requires that serial cTnT measurements within
individuals are consistent over time and few studies have addressed this question [11,12]. An additional concern is that some [11,12], but not all [13,14], studies have detected a rise in cTnT during haemodialysis. While this may be explained by haemoconcentration alone, it does raise the possibility that the haemodynamic stress of dialysis induces minor myocardial necrosis.

We sought, therefore, to determine the degree of fluctuation in serum cTnT levels within individual patients that occurs both during haemodialysis and over the course of a 15-month period, by measuring serial pre- and post-dialysis cTnT concentrations in a cohort of patients undergoing chronic haemodialysis. Furthermore, we compared the variation in pre- and post-dialysis cTnT levels with changes in serum haematocrit (Ht) to determine if haemoconcentration due to ultrafiltration during dialysis could account for any increase in cTnT detected. Finally, we followed the patients for 18 months to determine if the baseline cTnT level correlated with patient outcome, as assessed by all-cause mortality or hospital admission due to an ACS.

Subjects and methods

Patients and protocol

The study population consisted of a cohort of 75 patients who had been undergoing chronic intermittent haemodialysis at Daisy Hill Hospital for at least 6 weeks prior to initial blood letting in July 2003. Blood samples were obtained from each patient immediately prior to and at the end of dialysis. Serum cTnT concentration was measured using the ‘third generation’ ECLIA assay on an E170 analyser (Roche Diagnostics) according to the manufacturer’s protocol. This assay has a limit of detection of 0.01 µg/l and above this gives a quantitative reading. Our laboratory reference ranges for minimal myocardial necrosis and myocardial infarction are 0.03–0.1 and >0.1 µg/l respectively. Pre- and post-dialysis serum cTnT levels were measured at the start of the study and at 48 h, 8 months and 15 months later in those patients continuing on haemodialysis.

At the time of the 15-month measurement, pre- and post-dialysis Ht levels were also determined. The post-dialysis cTnT level was adjusted for haemoconcentration due to ultrafiltration during dialysis using the formula: adjusted post-dialysis cTnT = unadjusted post-dialysis cTnT × (pre-dialysis Ht/post-dialysis Ht).

Follow-up data were obtained 18 months after initial sampling using the patients’ haemodialysis unit records and inpatient notes. The primary end-points were all-cause death or hospital admission with a diagnosis of ACS (either myocardial infarct or unstable angina).

Statistical analysis

As the assay had a limit of detection of cTnT of 0.01 µg/l, all results <0.01 µg/l were designated as 0.009 µg/l for statistical analysis. The cTnT levels were not normally distributed, therefore medians are reported and non-parametric analysis was employed. Baseline pre-dialysis cTnT levels were compared between patients grouped according to sex, age, length of time on dialysis and presence of co-morbidity using the Mann–Whitney U-test. The Kruskal–Wallis test was employed to compare cTnT levels according to renal diagnosis. Pre- and post-dialysis measurements were compared using the Wilcoxon matched-pairs signed-rank test, and the degree of correlation between measurements was assessed using the Spearman’s rank correlation coefficient. Kaplan–Meier survival analysis was performed, and the log rank test was employed to assess differences in event-free survival according to stratified serum cTnT levels. Cox proportional models were used to estimate hazard ratios for death or ACS.

Results

The baseline characteristics of the patient population are described in Table 1. At baseline, the median (interquartile range) pre-dialysis cTnT level in the study population was 0.023 (0.009–0.073). Baseline pre-dialysis cTnT levels were undetectable in 29 (39%) of the patients, while 35 (47%) had levels consistent with minimal myocardial necrosis or myocardial infarction (Table 1). There were significant differences in baseline pre-dialysis cTnT levels between patients when grouped according to sex, age, renal diagnosis and presence of co-morbidity (Table 2).

Four complete serial cTnT measurements were unavailable for 29 of the 75 patients: 17 patients died; six patients were transplanted; two patients had recently suffered myocardial infarcts; a further three patients were in a tertiary centre at the time of one of the measurements; and one patient was transferred to another haemodialysis unit.

In the 46 patients for whom four serial cTnT measurements were available, there were no significant differences between the median pre-dialysis cTnT levels at baseline (0.014 µg/l) and at 48 h (0.009 µg/l, P = 0.39) or 8 months later (0.011 µg/l, P = 0.72).
However, the median pre-dialysis cTnT level at 15 months was significantly greater than at baseline (0.029 vs 0.014 mg/l, \( P = 0.003 \)). The increase in cTnT at 15 months could not be accounted for by a reduction in dialysis adequacy [median Kt/V was significantly greater at 15 months compared to baseline (1.7 vs 1.6, \( P = 0.02 \)]. However, there was a strong correlation between baseline cTnT and CRP levels (\( r = 0.42, \ P = 0.005 \)) and there was a trend towards an increase in median CRP at 15 months compared to baseline (8 vs 7 mg/l, \( P = 0.13 \)).

For these 46 patients, the baseline pre-dialysis cTnT concentration correlated strongly with the corresponding levels at 48 h, 8 months and 15 months (\( P < 0.0001 \) for each analysis). The number of patients with an increase in cTnT level from baseline that resulted in a change of diagnostic category (from normal to minor myocardial necrosis or from minor myocardial necrosis to myocardial infarct) was three (7%), three (7%) and 11 (24%) at 48 h, 8 months and 15 months, respectively (Figure 1). While small increases in cTnT levels at 15 months were common, 24 (52%) patients had levels more than 25% greater than baseline only four (9%) patients had levels more than double the baseline level. In contrast, all four patients who were hospitalized with an ACS exhibited a more than 3-fold rise in cTnT (range 3.5–16.8 times baseline).

### Table 2. Baseline pre-dialysis median cTnT levels according to patient demographics, renal diagnosis and presence of comorbidity

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients (%)</th>
<th>Median cTnT/μg/l (interquartile range)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 45 (60)</td>
<td>0.048 (0.009–0.093)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Female 30 (40)</td>
<td>0.009 (0.009–0.023)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>≥65 yrs 37 (49)</td>
<td>0.048 (0.014–0.084)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>&lt;65 yrs 38 (51)</td>
<td>0.009 (0.009–0.042)</td>
<td></td>
</tr>
<tr>
<td>Length of time on dialysis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>≥24 mths 42 (56)</td>
<td>0.037 (0.009–0.077)</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>&lt;24 mths 33 (44)</td>
<td>0.018 (0.009–0.063)</td>
<td></td>
</tr>
<tr>
<td>Renal diagnosis</td>
<td>Diabetic 12 (16)</td>
<td>0.083 (0.038–0.254)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Glomerulonephritis 12 (16)</td>
<td>0.009 (0.009–0.014)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ischaemic 10 (13)</td>
<td>0.069 (0.04–0.092)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obstructive/CPN 10 (13)</td>
<td>0.032 (0.018–0.094)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>APKD 7 (9)</td>
<td>0.009 (0.009–0.049)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertensive 3 (4)</td>
<td>0.009 (0.009–0.009)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown 17 (23)</td>
<td>0.014 (0.009–0.056)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other 4 (5)</td>
<td>0.014 (0.009–0.066)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td>IHD Y 25 (33)</td>
<td>0.064 (0.041–0.107)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>N 50 (67)</td>
<td>0.009 (0.009–0.032)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVD Y 13 (17)</td>
<td>0.073 (0.045–0.094)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>N 62 (83)</td>
<td>0.014 (0.009–0.057)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes Y 18 (24)</td>
<td>0.083 (0.009–0.151)</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>N 57 (76)</td>
<td>0.018 (0.009–0.055)</td>
<td></td>
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</tbody>
</table>

![Fig. 1. Percentage of patients changing diagnostic criteria from baseline or with pre-dialysis cTnT double or >25% above baseline at 48 hours and at 8 or 15 months.](image-url)
In each of the serial measurements, the median serum cTnT level was significantly greater post-dialysis than pre-dialysis (Figure 2). In the final measurement, following adjustment for haemoconcentration due to the effect of ultrafiltration during dialysis, there was no significant difference between the median pre- and post-dialysis cTnT levels (0.032 vs 0.038 μg/l, \( P = 0.48 \)). Furthermore, there was a positive correlation between the relative change in the cTnT levels and in the relative change in haematocrit (\( P = 0.04 \)) that occurred in each individual during dialysis. There was no correlation between the pre- or post-dialysis cTnT levels and the ultrafiltration volume or reduction in blood pressure during dialysis (data not shown).

After 18 months of follow-up, 17 (23%) patients had died: four due to ischaemic heart disease; four due to infection; one acute abdomen; one ischaemic stroke and the remaining patients withdrew from dialysis due to general debility. In addition, four patients were hospitalized with an ACS. Fatal and non-fatal cardiac events occurred exclusively in those patients with an elevation in baseline cTnT concentration \( \geq 0.03 \mu g/l \). The risk of death or ACS was significantly greater in patients with an elevated baseline pre-dialysis cTnT (\( P = 0.0015 \)) and the degree of risk was dependent on the magnitude of the elevation in baseline cTnT (Figure 3). In a multivariate analysis including age, sex, length of time on dialysis, baseline CRP and Kt/V, and associated co-morbidity such as diabetes, ischaemic heart disease and peripheral vascular disease, independent risk factors for death or ACS were: baseline pre-dialysis cTnT (hazard ratio 1.06 [95% CI 1.02–1.10] per 0.01 μg/l rise in cTnT); length of time on dialysis (hazard ratio 1.30 [95% CI 1.08–1.56] per year on dialysis); age (hazard ratio 1.06 [95% CI 1.01–1.10] per year increase); and dialysis adequacy (hazard ratio 0.74 [95% CI 0.58–0.94] per 0.1 increase in Kt/V).

Discussion

In our cohort of 75 asymptomatic patients undergoing chronic haemodialysis, almost half had serum cTnT levels that would be consistent with a diagnosis of an ACS in patients with normal renal function. This finding is in agreement with previous studies [4,8] and illustrates the difficulty in utilizing cTnT levels to diagnose ACS in patients on haemodialysis who present with chest pain. This problem is compounded by the fact that patients with renal failure often have silent ischaemia and abnormal baseline ECGs.

One solution would be to raise the threshold of serum cTnT concentration required for the diagnosis of an ACS in uraemic patients. However, patients on haemodialysis have widely varying baseline cTnT levels; therefore small rises in cTnT below the new threshold may be clinically significant in patients with negligible baseline values and, conversely, levels above the new threshold may not be indicative of an ACS in patients with high baseline levels. Observing serial measurements for an acute rise in cTnT may be helpful, but would result in diagnostic delay. In addition,
a patient presenting more than 12h after the onset of chest pain may not exhibit further rises in cTnT as levels may already have peaked. A further option would be to compare the cTnT at the time of chest pain with the historical samples from the patient, analogous to the comparison of ECGs during pain with previous ECGs.

Our study demonstrates the potential validity of the latter approach by showing that, in the absence of an acute coronary event, pre-dialysis serum cTnT levels are relatively consistent in the medium term in individuals on haemodialysis. As in other studies, less than 10% of the patients exhibited a more than doubling of baseline values at 15 months [11], although small increases (>25%) occurred in the majority of patients [12]. These small increases may reflect progression of coronary atherosclerosis or left ventricular hypertrophy or a reduction in residual renal function with cumulative time spent on dialysis. In the presence of an ACS, however, serum cTnT levels were substantially increased relative to baseline. Therefore, we suggest that all patients on chronic haemodialysis have an annual measurement of serum cTnT, which could be used as a reference point should they present with chest pain. A small increase over time is common, but levels more than double the baseline are uncommon and may indicate an ACS. This could be confirmed by dynamic cTnT changes on subsequent measurements, dependent on the timing of sampling with respect to the onset of chest pain.

In each of the serial measurements, we found that serum cTnT levels were significantly greater post- than pre-dialysis. This is in keeping with a previous study of 59 haemodialysis patients, which detected a significant rise in cTnT during dialysis in each of five serial measurements [13], but it is in contrast to two smaller studies, comprising 26 and 16 patients, respectively, in which no rise was observed [14,15].

In the diagnosis of ACS it is, therefore, imperative to consider the timing of the sample with respect to dialysis when comparing current and historical cTnT concentrations.

It has been speculated that intradialytic rises in cTnT levels may occur as a result of haemoconcentration due to ultrafiltration [11]. However, it is also possible that they may reflect coronary insufficiency induced by hypotension during dialysis in patients with fixed coronary artery stenoses. In keeping with this concept, Jung et al. [16] have recently reported an association between elevated cTnT levels and severe coronary artery calcification in patients on haemodialysis. Reassuringly, our study is the first to show that there is no significant rise in cTnT during dialysis following correction for haemoconcentration and, indeed, the changes in cTnT levels were positively correlated with changes in Ht. Furthermore, there is a 2–6h delay between myocardial necrosis and a rise in serum cTnT levels, and a large component of the fall in blood pressure tends to occur in the last hour of dialysis. Therefore the rise in cTnT immediately post-dialysis is unlikely to be due to intradialytic ischaemia. In addition, there was no correlation between the pre- or post-dialysis cTnT levels and either the ultrafiltration volume during dialysis or the fall in blood pressure during dialysis, indicating that chronic elevations in cTnT levels are unrelated to hypotension during dialysis.

By demonstrating that the cTnT concentration remains an independent risk factor for ACS or mortality in the medium term, the current study reaffirms the prognostic value of cTnT in asymptomatic patients on haemodialysis. Further research is required to determine whether elevations in cTnT levels can be used to identify haemodialysis patients, with or without symptoms, who would benefit from cardiac intervention, as has been demonstrated in non-uraemic populations with ACS [17]. In addition, the role of cTnT in identification of patients who require cardiac assessment prior to transplantation warrants investigation.

We acknowledge that the current study has several limitations. We have not sought to examine the pathophysiology underlying the elevation in cTnT levels in haemodialysis patients, and therefore we do not have complete echocardiographic or angiographic information on the patients. Furthermore, while the small increase in pre-dialysis cTnT observed at 15 months compared to baseline was not related to changes in dialysis adequacy, we cannot exclude the possibility that it may be due to reduced renal clearance resulting from a fall in residual renal function. The outcome data was based on the review of patient notes: a diagnosis of angina was based on the clinical evaluation of the physician treating the patient, and the cause of death was not determined by post-mortem examination. It is possible that some of the sudden cardiac deaths were due to hyperkalaemia rather than an ACS. Blood sampling immediately post-dialysis may precede a rise in cTnT induced by intradialytic ischaemia, therefore further sampling at 6h post-dialysis may be useful. Finally, we have examined a single biochemical marker. Additional biomarkers, such as pro-B-type natriuretic peptide and cardiac troponin I may individually or in combination prove more sensitive and specific in the diagnosis and prognosis of cardiac events in patients on haemodialysis [18].

In conclusion, the current study supports the accumulating evidence that cTnT is a useful prognostic marker in asymptomatic patients on haemodialysis. In addition, we have determined that the rise in cTnT levels during dialysis is probably due to haemoconcentration, and that in the medium term there are only moderate fluctuations in the pre-dialysis cTnT levels. Annual measurements of cTnT concentrations in patients on chronic haemodialysis may be useful both in identifying those at risk of coronary events, and as a diagnostic reference level for patients presenting with chest pain and an elevation in cTnT.

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Conflict of interest statement. None declared.

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