Elevated cardiac troponin T is associated with increased left ventricular mass index and predicts mortality in continuous ambulatory peritoneal dialysis patients

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Abstract

Background. Patients with end-stage renal disease have a high risk of premature death, which is due mainly to cardiovascular (CV) events. Elevated cardiac troponin T (cTnT) is related to increased left ventricular mass index (LVMI) and predicts poor outcome in chronic haemodialysis patients. We investigated the prognostic value of cTnT and its relationship with left ventricular mass in continuous ambulatory peritoneal dialysis (CAPD) patients.

Methods. Sixty-five CAPD patients (mean age: 56 ± 12 years; 36% males) with no evidence of acute coronary syndrome in 28 days prior to the study were examined prospectively. After 48 months of follow-up, we evaluated total and CV mortality.

Results. During follow-up, 23 patients (35%) died (70% CV causes, 22% infection, 4% tumour, 4% unknown). In univariate analysis, concentrations of cTnT ≥ 0.035 ng/ml, increased LVMI, diabetes, serum albumin and age were all strong predictors of total mortality. In multivariate logistic regression analysis, cTnT ≥ 0.035 ng/ml and age independently predicted total mortality [odds ratio (OR): 4.31; 95% confidence interval (95% CI): 1.16–16.04; \( P = 0.008 \) and OR: 1.08; 95% CI: 1.02–1.15; \( P = 0.002 \), respectively]. cTnT level ≥ 0.035 ng/ml was the only independent predictor of CV mortality in multivariate logistic regression analysis (OR: 8.94; 95% CI: 2.23–35.88; \( P < 0.005 \)). There was a significant positive correlation between serum cTnT level and LVMI (\( \rho = 0.41 \); \( P < 0.002 \)). Neither cTnI, CK nor CK-MB were related to total or CV mortality.

Conclusions. Elevated serum cTnT but not cTnI predicted total and CV mortality in CAPD patients. Elevated cTnT levels were also associated with increased LVMI.

Keywords: continuous ambulatory peritoneal dialysis; left ventricular hypertrophy; survival; troponin

Introduction

Despite recent advances, mortality in patients with end-stage renal disease (ESRD) undergoing peritoneal dialysis or haemodialysis remains high. The main cause of total mortality in these patients is cardiovascular (CV) disease, which accounts for about half of all deaths. The prevalence of ischaemic heart disease in dialysis patients is 10–20 times greater than in the general population. According to the US Renal Data System, ~40% of patients with ESRD have had a myocardial infarction or coronary revascularization [1]. In addition, the rate of survival after myocardial infarction is much lower in dialysis patients than in the general population. In these patients, commonly found CV risk factors include diabetes, hypertension, dyslipidaemia and left ventricular hypertrophy. CV disease mortality is approximately 10–30 times higher in dialysis patients than in patients from the general population and this is independent of gender, race and the presence of diabetes [2].

Cardiac troponins T and I (cTnT and cTnI) are subunits of the cardiac actin–myosin complex, which leak into the circulation during myocardial damage, and their detection has been used as a sensitive and specific marker of myocardial cell necrosis [3–5]. Although elevated serum levels of cTnT have been associated with mortality in haemodialysis patients,
the prognostic value of cTnI is controversial [6–8]. Furthermore, increased left ventricular mass, which is a strong predictor of death, has been associated with elevated cTnT and predicts poor outcome in haemodialysis patients [8]. Despite these findings, the prognostic values of cardiac troponins have not been well established in continuous ambulatory peritoneal dialysis (CAPD) patients.

The aim of the present study was to evaluate the prognostic value of cTnT for total and CV mortality and the relationship between this cardiac protein and left ventricular mass in CAPD patients. In addition, we assessed whether other markers of myocardial injury, such as cTnI, creatine kinase (CK) and CK-MB, are predictors of mortality in these patients.

Subjects and methods

We enrolled ESRD patients that were treated with CAPD for ≥12 weeks. They were prospectively followed for 48 months. Primary outcomes were total and CV mortality at 48 months.

We excluded patients having CV disease within 4 weeks prior to study onset. Demographic and laboratory data as well as medical history cardiac risk factors were evaluated. Blood samples were obtained for analysis of complete blood count, serum albumin, creatinine, CK, CK-MB and cTnI at study entry. Serum samples for the measurement of cTnT were obtained and stored at −70°C for ~6 months. Kt/V was calculated from total loss of urea nitrogen in the spent dialysate using the Watson equation [9]. The study was approved by the local ethics committee and informed consent was obtained from each patient.

Patients with coronary artery disease (CAD) at baseline were those who had experienced a myocardial infarction, unstable angina pectoris, angiographically proven significant stenosis (>50% of the luminal diameter) or had undergone bypass surgery or angioplasty. Diabetes was diagnosed according to World Health Organization criteria [10]. Hypercholesterolaemia was defined as low-density lipoprotein (LDL)-cholesterol >130 mg/dl or patients having normal LDL-cholesterol while undergoing hypolipidaemic drug therapies. Participants were classified as hypertensive if resting systolic blood pressure (BP) was ≥140 mmHg and/or diastolic BP was ≥90 mmHg or if they took antihypertensive medications.

Two-dimensionally guided M-mode echocardiograms (GE Vingmed System V Ultrasound; Horten, Norway) of the left ventricle were obtained from patients in the left decubitus position. The left ventricular mass was calculated according to the formula of Devereux and Reichek [11] and this was indexed for body surface area to obtain the left ventricular mass index (LVMI). All echocardiographic measurements were performed according to recommendations of the American Society of Echocardiography by an observer unaware of the biochemical findings, including cTnT and cTnI.

Analytical methods

Venous blood was collected at baseline and centrifuged (relative centrifugal force = 18,381 g). Serum was analysed for total CK, CK-MB, cTnI, creatinine and albumin. Routine chemical variables were measured by standardized methods using autoanalyser. The remaining serum was stored at −70°C. Serum cTnT was measured using a commercially available third-generation immunoassay (Elecsys troponin T STAT; Roche Diagnostics, Mannheim, Germany). Serum cTnI was measured by a standard immunoassay (Immulite; Diagnostic Product Corporation, Los Angeles).

According to the manufacturers, the lower limit of detection and the concentration with ≤10% precision were 0.01 and 0.035 ng/ml for cTnT and 0.2 and 0.6 ng/ml for cTnI, respectively. We adopted the recommendations of the Joint Committee of the American College of Cardiology and the European Society of Cardiology [12] to establish the upper limit of normal cut-off values of 0.035 and 0.6 ng/ml for cTnT and cTnI, respectively.

The laboratory staff was unaware of the baseline clinical status of the patients until the study was completed. The clinical data, including baseline and outcome status of the CAPD patients, were recorded by the clinicians, who were unaware of the laboratory results, the echocardiographic parameters and of cTnT and cTnI. The blinding was carried out by keeping patient clinical and echocardiographic data files apart from the laboratory-result files until the study was completed.

Statistical methods

Mean values were calculated for continuous variables and absolute and relative frequencies for discrete variables. Univariate comparisons of continuous data were performed with the use of unpaired Student’s t-tests. For comparison of discrete variables, χ² tests or Fisher’s exact tests were used. Multivariate logistic regression analysis using the backward selection procedure was used to identify independent predictors of total and CV mortality. Only the variables with significant univariate association were included in multivariate analysis. Cumulative survival curves were constructed by using the Kaplan–Meier method for total or CV mortality end-points. Correlation between serum cTnT level and LVMI was tested with the Spearman rank correlation (ρ = correlation coefficient). All comparisons were two-sided and P < 0.05 was considered to be significant. Statistical analysis was performed with a commercially available statistical package (SPSS for Windows Version 10.0; SPSS, Inc., Chicago, IL, USA).

Results

Sixty-five CAPD patients (36 males, 29 females; mean age: 56 ± 12 years) who had been receiving CAPD for ≥3 months (mean: 33 ± 10 months; median: 30 months; range: 3–96 months) were included in the study. The baseline characteristics of the 65 CAPD patients are presented in Table 1.

Causes of ESRD included hypertensive nephrosclerosis in 26 patients, diabetic nephropathy in 11, chronic glomerulonephritis in nine, obstructive uropathy in three, polycystic kidney disease in five, tubulointerstitial nephritis in one and unknown conditions in 10. Five patients had undergone renal
transplantation, two patients had switched from CAPD to haemodialysis and three patients had also been treated with haemodialysis for a certain period during the 48 months.

Predictors of total and CV mortality

During 48 months of follow-up, 23 patients (35%) died. CV events were the main cause of death (n = 16, 70%), followed by infection (n = 5, 22%), tumour (n = 1, 4%) and unknown aetiology (n = 1, 4%).

Table 1. Baseline clinical characteristics of the CAPD patients

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Gender (male/female)</th>
<th>Age (years)</th>
<th>Duration of dialysis (months)</th>
<th>Baseline CAD</th>
<th>Risk factors</th>
<th>Current smoker</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>Hypercholesterolaemia</th>
<th>Hyperglycaemia</th>
<th>Albumin (g/dl)</th>
<th>Calcium (mg/dl)</th>
<th>Phosphorus (mg/dl)</th>
<th>Alkaline phosphatase (IU/l)</th>
<th>Kt/V (units)</th>
<th>LVMI (g/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>36/29</td>
<td>56 ± 12</td>
<td>33 ± 10</td>
<td>10 (15%)</td>
<td>16 (26%)</td>
<td>14 (22%)</td>
<td>46 (71%)</td>
<td>35 (54%)</td>
<td>14 (22%)</td>
<td>9.5 ± 0.1</td>
<td>31.0 ± 0.8</td>
<td>2.16 ± 0.08</td>
<td>3.16 ± 0.8</td>
<td>4.8 ± 1.7</td>
<td>2.19 ± 0.08</td>
<td>197 ± 66</td>
</tr>
</tbody>
</table>

Values are given as means±SD or n (%).
This prospective study investigated the value of cardiac troponins as predictors of total and CV mortality in patients with CAPD. We found that elevated serum concentrations of cTnT were significantly associated with poor long-term outcome in CAPD patients. In addition, we revealed a significant positive correlation between cTnT and LVMI.

Elevated serum levels of cTnT have been shown to be related to mortality in haemodialysis patients [6–8]. Although there was initial controversy regarding the prognostic value of cTnI in haemodialysis patients, Apple et al. [7] recently showed that cTnI was highly predictive of mortality in a cohort of 733 patients with ESRD. For patients with CAPD, only one study with a limited sample size \((n=26)\) had investigated the prognostic value of cardiac troponins as a predictor of death [13]. In this study, Löwebeer et al. [13] used prospective data to show that elevated cTnT but not cTnI predicts poor outcome in CAPD patients. Moreover, they found an association between serum cTnT and the inflammatory marker C-reactive protein. The present study, which enrolled a larger patient group, confirmed that elevated cTnT strongly predicts long-term total and CV mortality. This relationship was independent of baseline diabetes and CAD. Additionally, in agreement with Löwebeer et al. [13], we showed that elevated levels of cTnI were not associated with mortality.

cTnT is a serum marker of myocardial injury that is elevated in 30–75% of haemodialysis patients [7,8]. Initial reports of elevated serum cTnT levels in haemodialysis patients may have been attributable to features of the first-generation cTnT assays, which exhibited low cardio-specificity due to cross-reactivity with skeletal muscle troponin T [14]. The expression of cTnT isoforms in skeletal muscle of patients with ESRD has been investigated widely, but divergent results have been reported [5,14,15]. Although Diris et al. [16] recently reported that impaired renal function leads to accumulation of cTnT fragments and that this probably causes elevation of serum cTnT in haemodialysis patients, there are no data in CAPD patients [16]. However, newly developed second- and third-generation cTnT assays are highly cardio-specific and do not show cross-reactivity with skeletal muscle troponin isoforms in patients with ESRD [4]. Therefore, it is well accepted that elevated serum cTnT concentrations in ESRD patients, measured by

**Table 4.** Comparison of variables with respect to different cut-off levels of cTnT

<table>
<thead>
<tr>
<th>Variable</th>
<th>cTnT &lt; 0.035 ng/ml ((n=36))</th>
<th>cTnT (\geq 0.035) ng/ml ((n=29))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI (g/m²)</td>
<td>139.7±5.0</td>
<td>180.6±7.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.8±0.4</td>
<td>3.7±0.6</td>
<td>0.48</td>
</tr>
<tr>
<td>Duration of dialysis (months)</td>
<td>31.6±23.0</td>
<td>36.6±26.8</td>
<td>0.43</td>
</tr>
<tr>
<td>Total CK (U/l)</td>
<td>94±73</td>
<td>75±42</td>
<td>0.33</td>
</tr>
<tr>
<td>CK-MB (ng/ml)</td>
<td>10.0±3.6</td>
<td>10.0±3.6</td>
<td>0.83</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>9±3</td>
<td>9±3</td>
<td>0.71</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>32±4</td>
<td>32±5</td>
<td>0.98</td>
</tr>
<tr>
<td>CAD</td>
<td>3 (8%)</td>
<td>7 (24%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (17%)</td>
<td>8 (28%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (64%)</td>
<td>23 (79%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>18 (50%)</td>
<td>17 (59%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>8 (22%)</td>
<td>6 (21%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Current smoker</td>
<td>9 (25%)</td>
<td>7 (24%)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Values are expressed as means±SD or \(n\) (%).

**Discussion**

This prospective study investigated the value of cardiac troponins as predictors of total and CV mortality in patients with CAPD. We found that elevated serum concentrations of cTnT were significantly associated with poor long-term outcome in CAPD patients. In addition, we revealed a significant positive correlation between cTnT and LVMI.

Elevated serum levels of cTnT have been shown to be related to mortality in haemodialysis patients [6–8]. Although there was initial controversy regarding the prognostic value of cTnI in haemodialysis patients, Apple et al. [7] recently showed that cTnI was highly
second- or third-generation cTnT assays, originate from the heart and not from the skeletal muscle. In the current study, we used a third-generation cTnT assay and concluded that the cTnT elevations observed in 45% of the CAPD patients reflected minor myocardial damage regardless of whether ischaemic heart disease had been detected at baseline. High levels of troponins may be secondary not only to epicardial coronary artery stenosis [17], but also to microvascular lesions or direct injury to myocardial cells (toxins, stretching, hypoxia and apoptosis) and, most importantly, to left ventricular hypertrophy, which is observed during the development of cardiomyopathy in haemodialysis patients [18].

The present study showed that elevated cTnT levels were associated with increased LVMl, but not with coronary heart disease, diabetes or other CV risk factors. To our knowledge, this is the first demonstration of this relationship in CAPD patients; although associations between cTnT and LVMl have been reported in haemodialysis patients [8]. Accordingly, the strong link between left ventricular mass and cTnT levels may also help to explain the high prognostic power of this cardiac protein in dialysis patients. However, elevated cTnT remained an independent predictor of total and CV mortality in logistic regression analysis and this was apart from its association with left ventricular mass. Although previous trials in haemodialysis patients have shown similar results, the present study is the largest to date in CAPD patients.

The Joint Committee of the American College of Cardiology and the European Society of Cardiology recommend that the lowest concentration of cTnT at which 10% imprecision is achieved should be used as the cut-off for diagnosis of cardiac injury [12]. In the current study, only four of 65 patients had cTnT values above the cut-off value of 0.6 ng/ml and these patients did not have higher mortality. Similarly, Löwbeer et al. [13] found that only one of 26 patients had detectable cTnI concentrations and that elevated cTnI was not associated with mortality in CAPD patients.

In our study, a greater proportion of CAPD patients had elevated cTnT [≥0.035 ng/ml; 29 (45%)] than had elevated cTnI [≥0.6 ng/ml; 4 (6%)]. This disparity in the number of patients having elevated cTnT vs cTnI may be due to several factors, including differences in half-life, differences in detection or release of complex forms or alterations in catabolism pathways [5]. While cTnT accounts for 8% of the cytosolic pool [19], cTnI accounts for only 4% [3]. Cytosolic cTnT and cTnI are bound differently. Also, the transient membrane permeability changes that occur during myocardial cell injury may differentially affect their release. Further investigations will be necessary to elucidate the mechanisms responsible for the different release patterns of cTnT and cTnI.

In several prospective studies, pre-term and stable CAD was a highly predictive marker of mortality in patients on haemodialysis [7,20]. However, the present study did not support these findings. Although coronary angiography is considered to be the gold standard for CAD diagnosis, it is an invasive procedure that produces potentially serious complications in ESRD patients. Thus, we did not routinely perform this procedure for the diagnosis of CAD and an independent cardiologist, who evaluated the indications of the coronary angiography, indicated angiography in only 10 of 65 CAPD patients at baseline. From this analysis, CAD was diagnosed in 10 out of 65 CAPD patients, with documented myocardial infarction in three of the 10 patients and unstable angina pectoris and angiographically proven significant stenosis in seven of the patients. Nevertheless, CAD may have been underestimated in the present study. A second limitation of this study was the smaller sample size compared with the previous haemodialysis studies.

In conclusion, we found that elevated baseline serum cTnT but not cTnI significantly predicted total and CV mortality in clinically stable CAPD patients. Furthermore, elevated cTnT levels were also associated with increased LVMl. These data support the hypothesis that this marker may be useful for developing risk stratification in clinically stable CAPD patients.

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Conflict of interest statement. None declared.

References

Cardiac troponins, LVMI and mortality in CAPD patients


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