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

Marta Beciani¹, Angela Tedesco¹, Anneo Violante¹, Silvia Cipriani², Michele Azzarito³, Antonio Sturniolo² and Giorgio Splendiani²

¹Chemical Laboratory, Aurelia Hospital, Rome, ²Chair of Nephrology, ‘Tor Vergata’ University, Rome and ³CICU, 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 trimestrial cTnI assays as well as clinical, X-ray and echocardiographic surveillance. We considered patients with serum cTnI ≥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

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
the troponin complex to the thin filament. The majority of troponins are incorporated into the troponin complex, although ~6% of cTnT and 2–3% of cTnl may be free in the cytoplasm.

Although all troponins are present in cardiac and skeletal muscle, they are encoded by different genes with different amino acid sequences. In particular, cTnT is expressed on fetal skeletal muscle cells and may be expressed again in the adult following trauma or muscular pathology [7]. Increased plasma levels of cTnT in uraemic patients undergoing dialysis do not correlate with acute CAD, but they can be affected by muscular isoforms and therapeutic procedures [3]. However, cTnI seems to be less influenced by these factors, and therefore a more predictive marker in such patients [8,9]. Nevertheless, until now the prognostic value of cTnI is unclear [10].

The aim of our study was to evaluate whether low values of cTnI could identify patients with cardiac injury, including microscopic lesions, even if they had no symptoms, and to classify investigated patients at risk of acute cardiac events.

**Subjects and methods**

We studied 101 haemodialysis patients who had no clinical evidence of acute myocardial ischaemia. The patients had no history of angina during the previous 3 months or acute myocardial infarction (AMI) during the previous year. Exclusion criteria were recent (3 month) acute CAD, chest pain and recent major cardiovascular surgery. The mean age of the subjects was 64 ± 24 years (mean dialytic age 5 ± 2.3 years), and 68% were male.

At the beginning of the study, the aetiologies of the renal diseases was ascertained using chart reviews, hospital information systems and patient interviews. The major aetiologies were vascular renal disease (36.5%), primary renal disease including glomerulonephritis (19.8%), diabetic nephropathy (8.9%) and polycystic kidney disease (8.9%).

Cardiac status was determined by clinical examination, electrocardiography and two-dimensional echocardiography. The diagnostic criteria used were based on the Consensus Document of the Joint ESC/ACC Expert Committee for the Redefinition of Myocardial Infarction. Most of our patients had a history of cardiovascular disease: arterial hypertension (41.5%), coronary artery disease (17.8%), dilated cardiomyopathy (7.9%), peripheral arterial disease (6.9%) and others.

The length of dialysis sessions and the dialysis filters used (polysulphone biocompatible membranes) were not modified during the study.

We only used predialysis blood samples because Wayand et al. [11] found certain discrepancies between cTnT and cTnl attributable to the dialysis procedure. Pre-dialysis blood samples were drawn from each patient after a long interval (3 days) after the last dialytic session. Subsequently, samples were taken from each patient every 3 months for a year (for a total of five tests) and analysed to measure blood cTnI. The same samples were also used to measure urea nitrogen, creatinine, glucose, protein, and cholesterol levels and electrolyte concentrations, using an IL 900 analyser.

**Analytical methods**

The cTnI was measured on OPUS PLUS (Dade–Behring) using a second-generation immunoassay with mouse Mab anti-cTnI denderimer-linked and Mab anti-cTnl joined to ALP. The detection limit of the assay was 0.1 ng/ml. The reference value, determined in our laboratory according to direction of Dade–Behring (99th percentile of normal reference population) was ≤0.1 ng/ml.

The percent CV of our assay was 8.9 (0.13 ng/ml), 6.0 (0.5 ng/ml) and 5.8 (2.0 ng/ml).

We decided to use a cut-off value of 0.15 ng/ml so that patients showing serum cTnI levels of 0.15 ng/ml or greater were considered positive while those showing levels cTnl serum lower than 0.15 ng/ml were considered negative. We chose the cut-off of 0.15 ng/ml recognizing the analytical imprecision at the lower ranges of sensitivity. This value is higher than 0.10 ng/ml (99th percentile of the normal reference population), but far from 2 ng/ml (threshold value for AMI).

The end-points of our study were CAD/AMI, urgent revascularization (PTCA, by-pass AC), or sudden cardiac death.

**Statistical methods**

The cTnI values of the three groups were analysed by the Student’s t-test. A Kaplan–Meier survival analysis was performed. Differences in survival between groups were analysed using the Cox–Mantel log-rank test.

**Results**

On the basis of their plasma cTnI levels, patients were divided into three groups (Table 1).

The first group included 72 patients (mean age 60 years) with negative cTnI values in each of the five measurements of the year. The incidence of cardiac events in this group was 9.7% (seven patients).

The second group included 15 patients (mean age 64 years) with variable cTnI levels, (sometimes positive

<table>
<thead>
<tr>
<th>Group (n = patients)</th>
<th>Mean age (years) (± SD)</th>
<th>Troponin value (ng/ml)</th>
<th>Cardiac events (incidence) (%)</th>
<th>ECHO positive at starting time (%)</th>
<th>ECG positive at starting time (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (72)</td>
<td>60 ± 5.2</td>
<td>Negative &lt;0.15</td>
<td>7 (9.7)</td>
<td>35</td>
<td>18</td>
</tr>
<tr>
<td>II (15)</td>
<td>64 ± 7.0</td>
<td>Variable &lt;/&gt;0.15</td>
<td>3 (20)</td>
<td>38</td>
<td>32</td>
</tr>
<tr>
<td>III (14)</td>
<td>67 ± 8.3</td>
<td>Positive &gt;0.15</td>
<td>9 (64)</td>
<td>40</td>
<td>36</td>
</tr>
</tbody>
</table>

Table 1. cTnI blood levels, incidence of cardiac events and cardiac status assessment
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 \((>2 \text{ ng/ml})\), 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 \((36.5\% \text{ of the total population})\), 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

<table>
<thead>
<tr>
<th>Cardiovascular pathology</th>
<th>Total (incidence) (%)</th>
<th>Group I (incidence) (%)</th>
<th>Group II (incidence) (%)</th>
<th>Group III (incidence) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypertension</td>
<td>41.5</td>
<td>43.0</td>
<td>46.6</td>
<td>28.5</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>17.8</td>
<td>15.2</td>
<td>20.0</td>
<td>28.5</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>7.9</td>
<td>6.9</td>
<td>13.3</td>
<td>7.1</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>6.9</td>
<td>5.5</td>
<td>13.3</td>
<td>7.1</td>
</tr>
<tr>
<td>Others</td>
<td>23.9</td>
<td>29.4</td>
<td>6.8</td>
<td>28.8</td>
</tr>
</tbody>
</table>
Cardiac troponin I in chronic haemodialysis patients

Table 3. Outcome in cTnI-positive patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Aetiology of ESRD</th>
<th>troponin (ng/ml)</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>T0</td>
<td>T3</td>
</tr>
<tr>
<td>BD</td>
<td>Polycystic kidney</td>
<td>0.18</td>
<td>0.21</td>
</tr>
<tr>
<td>LTVD</td>
<td>NDD</td>
<td>0.71</td>
<td>0.24</td>
</tr>
<tr>
<td>MA</td>
<td>NDD</td>
<td>0.19</td>
<td>0.18</td>
</tr>
<tr>
<td>PC</td>
<td>Glomerulonephritis</td>
<td>0.20</td>
<td>0.17</td>
</tr>
<tr>
<td>CC</td>
<td>Nephrosclerosis</td>
<td>0.30</td>
<td>0.25</td>
</tr>
<tr>
<td>SS</td>
<td>Polycystic kidney</td>
<td>0.23</td>
<td>0.27</td>
</tr>
<tr>
<td>SF</td>
<td>Glomerulonephritis</td>
<td>0.24</td>
<td>0.27</td>
</tr>
<tr>
<td>SF</td>
<td>Diabetes</td>
<td>0.18</td>
<td>0.16</td>
</tr>
<tr>
<td>LS</td>
<td>Nephrosclerosis</td>
<td>0.30</td>
<td>0.25</td>
</tr>
<tr>
<td>RM</td>
<td>Nephrosclerosis</td>
<td>0.33</td>
<td>0.27</td>
</tr>
<tr>
<td>AG</td>
<td>Nephrosclerosis</td>
<td>0.33</td>
<td>0.27</td>
</tr>
<tr>
<td>BB</td>
<td>NDD</td>
<td>0.16</td>
<td>0.60</td>
</tr>
<tr>
<td>RV</td>
<td>Nephrosclerosis</td>
<td>0.15</td>
<td>0.41</td>
</tr>
<tr>
<td>GRa</td>
<td>Polycystic kidney</td>
<td>0.54</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

*aPatient GR changed cTnI value after PTCA treatment, which was performed after a positive cTnI test. bCardiac event. cDeath. AMI, acute myocardial infarction; SD, sudden death; CAD, coronary artery disease; PTCA, percutaneous transluminal coronary angioplasty.

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.

Acknowledgements. We would like to thank Mrs Marisa Argento for proof reading and checking the English language for us.

Conflict of interest statement. None declared.

References


Received for publication: 27.11.01
Accepted in revised form: 7.11.02