Cardiac troponin T predicts occult coronary artery stenosis in patients with chronic kidney disease at the start of renal replacement therapy

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Abstract

Background. The high prevalence of asymptomatic coronary artery stenosis (CAS) in chronic kidney disease (CKD) has emerged as an important predictor of outcome. However, diagnostic tools that can identify asymptomatic CAS have not yet been established. We investigated whether asymptomatic patients at the initiation of renal replacement therapy (RRT) could be screened using cardiac troponin T (cTnT) and atherosclerotic surrogate markers such as ankle-brachial blood pressure index (ABPI) and intima-media thickness (IMT).

Methods and results. Among 142 patients who were about to start RRT, 60 who were asymptomatic underwent coronary evaluation by multi-slice computed tomography (MSCT) and/or coronary angiography (CAG). CAG diagnosed 35 patients (43.8%) as CAS positive and 27 of them had multi-vessel disease. Factors associated with CAS were smoking, elevated cTnT, low ABPI and high IMT. Moreover, the severity of CAS was associated with smoking, cTnT and ABPI. Stepwise logistic regression analyses revealed that cTnT was a powerful predictor of asymptomatic multi-vessel CAS. Receiver operating characteristic analyses documented the usefulness of cTnT as a screening tool with a cut-off point 0.05 ng/ml. The optimal screening tool for multi-vessel CAS was cTnT (sensitivity, 92.6%; 95% CI, 82.7–99.9; specificity, 63.6%; 95% CI, 47.2–80.0).

Conclusion. We concluded that cTnT should be measured as part of a strategy for detecting asymptomatic CAS, especially multi-vessel disease in patients with CKD at the start of RRT.

Keywords: asymptomatic coronary artery stenosis; cardiac troponin T; cardiovascular risk stratification; chronic kidney disease; myocardial biomarkers

Introduction

Cardiovascular mortality in dialysis patients with chronic kidney disease (CKD) is 10- to 30-fold higher than that of the general population [1]. In fact, ~50% of patients on dialysis therapy die due to cardiovascular disease (CVD) [2]. Coronary artery stenosis (CAS) might play a particularly important role in the pathogenesis of CVD [3] and CAS progresses during the early stages of CKD [4–6]. However, scant symptoms and the absence of effective screening tests result in delayed diagnosis, which leads to a poor prognosis. Therefore, establishing a diagnostic tool that can identify asymptomatic patients at high risk for CAS is a key issue in the clinical management of such patients during the pre-dialysis stages of CKD.

Elevated levels of cardiac biomarkers, namely brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP) and cardiac troponin T (cTnT), might predict the prognosis of asymptomatic CKD patients undergoing dialysis [7–12]. A potent stimulus for the release or production of natriuretic peptides is mechanical stretching [13], whereas plasma cTnT specifically and sensitively reflects myocardial injury and is considered to be an index of irreversible myocardial change [14]. In addition, cTnT levels can predict multi-vessel CAS in dialysis patients [15]. However, the significance of screening CKD patients for CAS using these cardiac biomarkers at the pre-dialysis stages remains unknown. If asymptomatic CAS can be diagnosed in CKD patients at pre-dialysis, then subsequent cardiovascular risk stratification should improve the prognosis of dialysis patients.

Thus, we investigated the applicability of measuring these cardiac biomarkers for early screening of asymptomatic CAS among CKD patients without a history of cardiac disease at the initiation of renal replacement therapy (RRT). Moreover, surrogate markers of atherosclerosis such as ankle-brachial blood pressure index (ABPI) and intima-media thickness of carotid artery (IMT) were also estimated as predictors of asymptomatic CAS at the start of RRT.
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Methods

Study design and patients

The institutional review board at our hospital approved the study and each patient provided written and informed consent to participate. We initially considered 142 consecutive patients with CKD who started dialysis therapy between January 2005 and December 2006. Figure 1 shows that we excluded 62 patients because of a history of ischaemic heart disease, heart failure, valvular disease and arrhythmia and because of pulmonary oedema or heart failure at the start of dialysis. Other exclusion criteria included age ≥ 85 years, malignancy, cachexia and severely reduced activities of daily life (ADL, Barthel index ≤ 20 [16]). Eighty asymptomatic patients were eligible for primary screening (diabetes mellitus or smoking or elevated cTnT > 0.01). Finally, CAS was evaluated by multi-slice computed tomography (MSCT) and/or coronary angiography (CAG) in 60 patients whose results were positive at a primary screening.

Blood sampling and analyses

We collected blood samples from each patient once at 1–2 weeks before starting dialysis. The samples were separated by centrifugation; sera then were frozen and stored at −80°C. We measured serum cTnT using a commercially available, second-generation electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany) with a detection limit of 0.01 ng/ml. In symptomatic patients, values >0.1 ng/ml indicate myocardial ischaemia. cTnT was measured sequentially 3–6 months and 1–2 weeks before the start of RRT. Plasma BNP and ANP were determined using a specific immunoradiometric assay kit (Shiono RIA; Shionogi Co. Ltd, Osaka, Japan), as described in [17]. Serum creatinine, lipid, albumin, inorganic phosphate, creatine kinase (CPK) and its isozyme, lactate dehydrogenase (LDH), ferritin, intact-PTH (iPTH) and haemoglobin were measured using routine methods. Creatinine clearance (Ccr) was estimated based on 24-h urine collection and calculated from the Cockcroft–Gault formula [18] in some (n = 20) patients with reduced ADL.

Measurement of ABPI

We simultaneously measured bilateral arm and ankle blood pressure by an oscillometric method using a VaSera VS-1000 (Fukuda Denshi, Co. Ltd, Tokyo, Japan) once, at 1–2 weeks before starting RRT.

Measurement of IMT

The bilateral carotid arteries were examined at the common carotid artery, the internal carotid artery and the carotid bifurcation by high-resolution B-mode ultrasound (Accuson, Mountain View, CA, USA) using an 8.0-MHz liner array transducer. The IMT was defined as the distance between the leading edges of the lumen-intima echo and of the media-adventitia echo. The IMT was measured in a blinded manner by two experienced sonographers and the maximal thickness was recorded.

Echocardiography

Echocardiography was performed by an experienced physician who was unaware of the myocardial biomarker levels. All measurements proceeded according to the recommendations of the American Society of Echocardiography [19]. Left ventricular mass was calculated from two-dimensional guided M-mode images according to the formula of Devereux and Reichek [20], and the left ventricular mass
index (LVMI) was derived from the measured left ventricular mass/body surface area. Left ventricular hypertrophy (LVH) was defined as a LVMI \( \geq 134 \text{ g/m}^2 \text{ for men and } \geq 110 \text{ g/m}^2 \text{ for women} \) [21]. Systolic dysfunction was defined as an ejection fraction of <55%.

**Coronary evaluation**

To study the potential association between the presence of asymptomatic CAS and myocardial biomarker concentrations, we evaluated the coronary arteries by MSCT and/or CAG in 60 asymptomatic patients whose primary screens were positive. Although we encouraged all 60 patients to undergo CAG evaluation, only 18 of them agreed and 42 initially underwent MSCT. After the results of MSCT were clear, 30 patients with suspected CAS underwent CAG (Figure 1).

Angiograms were evaluated by two expert angiographers who were blinded to the levels of myocardial biomarkers. Coronary arteries were interpreted (QCA-CMS \( \geq 5.3 \)) and CAS was defined as a \( \geq 50\% \) lumen narrowing of the major coronary arteries or their branches. Left main stenosis was regarded as equivalent to two-vessel disease.

**Statistical analysis**

Continuous values are expressed as means ± SDs or medians and interquartile ranges. Variables with a skewed distribution were log transformed (ln). We replaced numerical cTnT values of \( \leq 0.01 \) with 0.01. We assessed between-group differences for continuous and categorical data using the Mann–Whitney U-test and the \( \chi^2 \)-test or the Fisher exact test, respectively. The difference of the sequential measurement of cTnT was tested by means of the paired t-test. We also performed logistic regression analysis (forward selection method) to identify the predictors for asymptomatic CAS. Receiver operating characteristic (ROC) curves were drawn and the areas under the curves were calculated. The optimal cut-off values were selected when the product of sensitivity and specificity was maximized. Data were statistically analysed using SPSS version II. P values <0.05 were considered statistically significant.

**Results**

**Patient characteristics**

Table 1 shows the main demographic and clinical characteristics, echocardiographic parameters and concentrations of biomarkers in 142 patients (69 men) with a median age of 68.0 years at the start of dialysis. The prevalence of DM was 33.8%, and 27.5% of the total number of patients were smokers. Blood pressure was controlled by an average of 146.9 \( \pm 27.8/77.1 \pm 14.9 \text{ mmHg} \) and their median urinary protein excretion was 2.4 g/day. Echocardiography revealed asynergy or reduced ejection fraction (<55%) in 32 patients (22.5%). The median ANP concentration was 97.5 pg/ml, indicating volume overload. The BNP levels ranged from 36.1 to 1240.0 pg/ml (median 322.0). We could not detect cTnT in 72 patients (≤0.01 ng/ml), whereas the remainder had increased cTnT levels (>0.01 ng/ml), of which 23 were >0.1 ng/ml, the diagnostic threshold of acute myocardial infarction. The median values of ABPI and IMT were 1.09 and 1.80, respectively.

**Primary screening test**

Patients whose primary screens were positive were likely to be older, excrete more urinary protein, have higher cardiac biomarker levels and abnormal UCG findings compared with those who were negative. Moreover, ABPI was lower and IMT was higher in the former group rather than the latter group (data not shown).

**Prevalence of CAS**

Figure 1 shows that 35 of the 60 patients who were positive at the primary screening were CAS (+) and 25 were CAS (−) according to the CAG/MSCT assessment. Among 30 patients suspected CAS by MSCT, 26 patients were diagnosed as CAS by CAG. The prevalence of multi-vessel disease (≥2-vessels or left main) was 77% and comprised 1-, 2- and 3-vessel disease in 8 (22.9%), 10 (28.6%) and 17 (48.5%) patients, respectively. Percutaneous coronary intervention (\( N = 26 \)) or coronary artery bypass graft (\( N = 2 \)) was performed to prevent myocardial ischaemia from worsening. The intervention was successful in all patients.

**Predictor of asymptomatic CAS**

Smoking, lower ABI, greater IMT and elevated cTnT were associated with CAS (+), whereas we could not identify a difference in systolic and diastolic blood pressure, fibrinogen, proteinuria and total cholesterol, LDH and CPK levels between the two groups (Table 2). The findings were similar between groups with multi-vessel CAS (−) and multi-vessel CAS (+) (Table 3). The use of renin-angiotensin system (RAS) inhibitors or statin was
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Table 2. Comparison of variables between occult CAS (−) and occult CAS (+)

<table>
<thead>
<tr>
<th></th>
<th>Occult CAS (−) N = 25</th>
<th>Occult CAS (+) N = 35</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, number (%)</td>
<td>11 (44)</td>
<td>21 (60)</td>
<td>0.221</td>
</tr>
<tr>
<td>Age</td>
<td>60.5 (56–73)</td>
<td>64.0 (57.3–73)</td>
<td>0.835</td>
</tr>
<tr>
<td>Diabetes mellitus, number (%)</td>
<td>14 (56)</td>
<td>23 (66)</td>
<td>0.445</td>
</tr>
<tr>
<td>Smoking, number (%)</td>
<td>5 (20)</td>
<td>20 (57)</td>
<td>0.009</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>150.6 ± 17.9</td>
<td>146.9 ± 26.7</td>
<td>0.669</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77.7 ± 13.9</td>
<td>78.0 ± 14.7</td>
<td>0.774</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>71.0 ± 7.7</td>
<td>76.8 ± 16.6</td>
<td>0.448</td>
</tr>
<tr>
<td>Abnormal ultrasound cardiogram, number (%)</td>
<td>7 (28)</td>
<td>8 (23)</td>
<td>0.879</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>149.3 ± 49.1</td>
<td>163.0 ± 33.8</td>
<td>0.431</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>373.9 ± 90.7</td>
<td>461.2 ± 129.3</td>
<td>0.071</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>3.3 (1.3–7.6)</td>
<td>4.3 (2.4–6.4)</td>
<td>0.272</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>173.0 (159.0–188.0)</td>
<td>162.0 (148.3–219.3)</td>
<td>0.373</td>
</tr>
<tr>
<td>Creatine kinase (IU/l)</td>
<td>94.0 (55.0–147.5)</td>
<td>70.0 (55.0–91.0)</td>
<td>0.572</td>
</tr>
<tr>
<td>Lactate dehydrogenase (IU/l)</td>
<td>441.0 (395.5–530.0)</td>
<td>421.0 (371.0–450.0)</td>
<td>0.953</td>
</tr>
<tr>
<td>Atrial natriuretic peptide (pg/ml)</td>
<td>63.0 (45.0–130.0)</td>
<td>98.0 (75.8–147.5)</td>
<td>0.671</td>
</tr>
<tr>
<td>Brain natriuretic peptide (pg/ml)</td>
<td>193.5 (83.4–338.0)</td>
<td>305.0 (217.8–506.5)</td>
<td>0.468</td>
</tr>
<tr>
<td>Cardiac troponin T (ng/ml)</td>
<td>0.05 (0.02–0.08)</td>
<td>0.07 (0.05–0.11)</td>
<td>0.006</td>
</tr>
<tr>
<td>Ankle-brachial blood pressure index</td>
<td>1.13 (1.05–1.21)</td>
<td>1.04 (0.96–1.12)</td>
<td>0.002</td>
</tr>
<tr>
<td>Intima-media thickness (mm)</td>
<td>1.40 (0.80–1.90)</td>
<td>2.00 (0.95–2.58)</td>
<td>0.022</td>
</tr>
<tr>
<td>Statin use, number (%)</td>
<td>6 (24)</td>
<td>12 (34)</td>
<td>0.568</td>
</tr>
<tr>
<td>Renin–angiotensin system inhibitor use, number (%)</td>
<td>12 (48)</td>
<td>17 (49)</td>
<td>0.965</td>
</tr>
</tbody>
</table>

CAS: coronary artery stenosis.
Data are shown as numbers (%), medians (interquartile range) or means ± SD.

not found to be related to the prevalence or severity of CAS (Tables 2 and 3).

We examined the independent determinants of asymptomatic CAS at the start of RRT using stepwise logistic regression analyses. We found that ln-cTnT and ABPI were significantly independent predictors of asymptomatic multi-vessel CAS (Table 4). Thus, we applied ROC analyses to estimate the value of cTnT in screening for asymptomatic CAS. We also compared the diagnostic power of both ABPI and IMT with that of cTnT by ROC analysis (Figure 2). The best cut-off points were determined to maximize the sensitivity and specificity of predicting CAS. The best cut-off points for screening overall and multi-vessel CAS were the same, being 0.05 for cTnT, 1.12 for ABPI and 1.95 for IMT. Among the three markers, cTnT was the best screening tool for asymptomatic, especially multi-vessel CAS (sensitivity, 92.6%; 95% CI, 82.7–99.9; specificity, 63.6%; 95% CI, 47.2–80.0) (Table 5).
Table 4. Predictors of coronary artery stenosis in asymptomatic patients at start of RRT by stepwise logistic regression analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABPI</td>
<td>0.000</td>
<td>0.000–0.697</td>
<td>0.041</td>
</tr>
<tr>
<td>Multi-vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABPI</td>
<td>0.001</td>
<td>0.000–1.057</td>
<td>0.052</td>
</tr>
<tr>
<td>Ln-cTnT</td>
<td>6.502</td>
<td>1.517–27.863</td>
<td>0.012</td>
</tr>
</tbody>
</table>

RRT: renal replacement therapy; CAS: coronary artery stenosis; cTnT: cardiac troponin T; ABPI: ankle-brachial pressure index; BNP: brain natriuretic peptide; CI: confidence interval.

Variables entered in model were DM, smoking, ln cTnT, fibrinogen, proteinuria, left ventricular mass index, ankle-brachial pressure index and intima-media thickness.

Serial measurement of cTnT

Finally, we measured cTnT sequentially to examine how the cTnT levels were fluctuating. We could see the intra-subject fluctuations; however, cTnT levels were likely to remain higher in multi-vessel CAS (+) patients compared with multi-vessel (-) patients (Figure 3).
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Table 5. Sensitivity and specificity of cTnT, ABPI and IMT for diagnosing CAS

<table>
<thead>
<tr>
<th>Cutoff value</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall CAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cTnT</td>
<td>0.05</td>
<td>74.3 (59.8–88.8)</td>
</tr>
<tr>
<td>ABPI</td>
<td>1.12</td>
<td>77.1 (63.2–91.1)</td>
</tr>
<tr>
<td>IMT</td>
<td>1.95</td>
<td>57.1 (40.7–73.5)</td>
</tr>
<tr>
<td>Multi-vessel CAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cTnT</td>
<td>0.05</td>
<td>92.6 (82.7–99.9)</td>
</tr>
<tr>
<td>ABPI</td>
<td>1.12</td>
<td>77.8 (62.1–93.5)</td>
</tr>
<tr>
<td>IMT</td>
<td>1.95</td>
<td>63.0 (44.7–81.2)</td>
</tr>
</tbody>
</table>

cTnT: cardiac troponin T; ABPI: ankle-brachial pressure index; IMT: intima-media thickness; CAS: coronary artery stenosis; CI: confidence interval.

Discussion

The present study provides evidence of a high prevalence of asymptomatic CAS at the start of RRT (43.8%, 35/80), especially among diabetic patients (62.2%, 23/37). The prevalence of asymptomatic CAS in our study was similar to that of others [4,5], but we examined more patients. Recent findings indicate that CVD at the early stages of CKD adversely affects prognosis [1,6,22]. Our results confirmed the need for aggressive pre-dialysis coronary evaluation. At present, diagnostic flow chart to identify asymptomatic CAS in CKD patients has not been established.

Our study suggests that cTnT can help screening asymptomatic CAS, especially the multi-vessel type due to the high sensitivity and specificity for CAS. Recently, de Filippi et al. [15] reported that high levels of cTnT are powerful predictors of severe CAS in haemodialysis patients. They found a significant relationship between cTnT and the prevalence of multi-vessel CAS; in fact 50% of patients with cTnT ≥0.065 had multi-vessel disease. The cut-off value of cTnT derived from our study was similar to theirs.

Which factors cause an elevation of cTnT remains unclear, although subclinical myocardial ischaemia might be an important pathogenic factor [23]. We found here that even a slight elevation of cTnT, that is, to a level below that used to define acute coronary syndrome, was associated with asymptomatic, especially multi-vessel CAS. Therefore, subclinical ischaemic myocardial injury might constitute a significant factor underlying elevated cTnT. In addition, volume overload and/or anaemia at the start of RRT in the presence of occult CAS might enhance cardiac load, resulting in myocardial hypoxia and induce cTnT release. Elevated cTnT is also associated with increased cardiac mortality and all-cause mortality in patients with CKD [9–12,15]. Our results indicated that asymptomatic CAS could explain the association between elevated cTnT and mortality.

That some patients with elevated cTnT had no significant CAS might be explained by LVH status. Several investigators have reported that elevated cTnT is closely associated with left ventricular hypertrophy [24,25]. Transient alterations in sarcolemmal-membrane permeability in hypertrophic response or microvascular disease commonly associated with LVH are the assumed mechanisms that contribute to elevated cTnT [26,27]. However, we could not find any association between LVMi and CAS severity or cTnT levels in either the univariate or the multivariate analyses (data not shown), possibly because most (75%) patients had LVH.

Moreover, some patients without CAS as well as LVH had elevated cTnT levels, which might be explained by microvascular disease. In this study, 9 and 12 patients showed false positive in overall and multi-vessel CAS analysis, respectively. Among them, 5 and 7 patients were diabetic patients, respectively. A recent study showed marked coronary microvascular dysfunction in diabetic uncomplicated patients [28]. In short, it is likely that cTnT elevation might be caused by microvascular dysfunction, especially in diabetic patients.

We also evaluated the difference of power between cTnT, ABPI and IMT to screen asymptomatic CAS. Other studies have shown that ABPI is a strong predictor of CVD and mortality both in the general population and in dialysis patients [29–31]. Our results confirmed that cTnT, ABPI and IMT are predictive for asymptomatic CAS. In particular, cTnT was an excellent marker for screening asymptomatic multi-vessel CAS in patients starting RRT.

Clinical screening for CAS in all patients starting RRT has not historically been indicated from a cost-effectiveness viewpoint. Excluding the patients, for example those who were elderly (≥85 years), with poor ADL, or had a malignancy, was consistent with our current practice. Moreover, performing CAG in asymptomatic patients at early CKD stages cannot yet be recommended, because a positive impact of early intervention on prognosis has not been proven. Therefore, aggressive CAS screening at the initiation of RRT should alert physicians, especially nephrologists, to high-risk asymptomatic patients who might benefit from early intervention.

Study limitations

We did not perform coronary evaluations (MSCT/CAG) in all patients, because 20 of the 80 patients were negative in the primary screen and had some residual renal function. Therefore, coronary evaluation was limited to the patients (60/80) with diabetes, elevated cTnT (>0.01 ng/ml) or who smoked. Consequently, of the patients whose primary screen was negative, and in whom the assumed risk of CAS was low, we could not prove that coronary artery stenosis was infrequent. Although the gold standard tool for diagnosing CAS is CAG, 42 patients of our patients selected MSCT instead of CAG. Twelve of these 42 patients were negative on MSCT. We considered these 12 patients as CAS negative, since the reported negative predictive value of MSCT is 96% [32,33].

Another limitation of this study is that we did not consider the influence of medication such as erythropoietin and iron, which might influence the level of cardiac biomarkers [34,35].

In conclusion, our findings suggest that asymptomatic multi-vessel CAS is frequently present at the start of RRT in cTnT positive patients. However, whether more intensive evaluation, such as identifying more patients with CAS...
and treating asymptomatic CKD patients, will improve outcomes remains unknown. Although large-scale studies will be necessary to clarify the significance of measuring cTnT, we suggest that this tool be included in the overall strategy for CVD management in patients with CKD.

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