Impact of chronic kidney disease on the incidence of peri-procedural myocardial injury in patients undergoing elective stent implantation

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Abstract

Background. It is well known that chronic kidney disease is a strong independent predictor of adverse outcomes after percutaneous coronary intervention in patients with ischemic heart disease. Recently, peri-procedural myocardial injury has been associated with adverse cardiac events. The aim of this study was to investigate the relationship between renal function and peri-procedural myocardial injury in patients undergoing elective stent implantation.

Methods. This study comprised 273 consecutive patients who underwent elective stent implantation. They were divided into two groups: estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m² and eGFR ≥ 60 mL/min/1.73m². Peri-procedural TnT levels higher than three times the normal limit were defined as peri-procedural myocardial injury.

Results. Patients with eGFR < 60 mL/min/1.73m² showed a higher incidence of peri-procedural myocardial injury compared to patients with eGFR ≥ 60 mL/min/1.73m² (4.3 versus 20.9%, P < 0.0001). Even after a multivariate adjustment, the eGFR level predicted peri-procedural myocardial injury [odds ratio 0.92, 95% confidence interval (CI): 0.89–0.95, P < 0.0001]. Total stent length was also an independent predictor of peri-procedural myocardial injury (odds ratio 1.09, 95% CI: 1.02–1.16, P = 0.009). Using a receiver-operating curve analysis, eGFR level of 62.1 mL/min/1.73m² (sensitivity 93.3%, specificity 57.2%) was the best value (area under the curve ¼ 0.803) to maximize the power of eGFR levels in predicting peri-procedural myocardial injury.

Conclusions. Patients with eGFR < 60 mL/min/1.73m² were strongly associated with peri-procedural myocardial injury after elective stent implantation. Therefore, eGFR may be a simple and convenient predictor of peri-procedural myocardial injury.

Keywords: chronic kidney disease; coronary heart disease; integrated backscatter intravascular ultrasound; percutaneous coronary intervention; renal function

Introduction

Studies have suggested that chronic kidney disease (CKD) is associated with adverse cardiovascular events [1–4]. Moreover, coronary artery diseases have been also found to be common in patients with CKD [1, 2]. In such situations, percutaneous coronary intervention (PCI) with stent implantation for coronary artery disease has been widely performed in patients with CKD [2, 5, 6]. However, such patients frequently experience adverse cardiac events even after PCI with stent implantation [7, 8].

Factors such as no-reflow, macroscopic embolization and occlusion of the side branch can cause peri-procedural myocardial injury, which is often observed even after apparently successful PCI [9–12]. In addition, an increase in cardiac enzyme after PCI is widely known to be related to negative clinical outcomes [9–12]. Lesion characteristics and procedural factors such as administration of statin, coronary plaque composition are related to peri-procedural myocardial injury [13–17]. It has also been reported that there is a significant positive association between coronary plaque composition and renal function in patients who underwent elective PCI [18]. Thus, we hypothesized that patients with CKD are prone to an increase in the incidence of peri-procedural myocardial injury after elective stent implantation. This study was performed to test whether there was a relationship between patients with CKD and peri-procedural myocardial injury after stent implantation.

Materials and methods

Patients and study design

This study consisted of patients who were treated with successful elective PCI with stent implantation at Chubu Rosai Hospital between September 2005 and December 2008. All had angina pectoris or documented myocardial ischemia. Exclusion criteria included patients with chronic
total occlusion, those receiving hemodialysis, those with elevated pre-procedural cardiac biomarkers, those who needed angioplasty with atherectomy such as directional coronary atherectomy or rotational atherectomy, those in need of multi-vessel stenting in a single procedure, those with exclusion of a major side branch (>1 mm) after PCI and those who displayed plaque areas with a severe calcified lesion that could not be evaluated by intravascular ultrasound. Those found eligible comprised a total of 273 patients, all of whom had received dual anti-platelet therapy with aspirin (100–162 mg/day) and thienopyridine before PCI. In addition, a statin had been administered for at least 1 month. Immediately before PCI procedures, a bolus of 10 000 U heparin was administered.

According to their estimated glomerular filtration rate (eGFR), patients were divided into two groups: eGFR <60 mL/min/1.73m² and eGFR ≥60 mL/min/1.73m². eGFR was calculated using the new Japanese equation: eGFR (mL/min/1.73m²) = 194 × Serum creatinine − 1.094 × Age − 0.287 (in females) [19]. Written informed consent was obtained from all patients before their procedures and study protocols were approved by the institutional ethics committee.

Blood samples were obtained immediately before and 18 h after PCI. Serum troponin-T (TnT) levels were measured using an enzyme immunoassay kit (Roche Diagnostics, Tokyo, Japan). The detection limit of serum TnT in the measurement was 0.03 ng/mL, and linearity is achieved from 0.1 to 2 ng/mL. In the case of TnT >0.03 ng/mL, it was considered a negative result. Any reading from 0.03 up to 0.1 ng/mL was considered as 0.1 ng/mL. In the case of TnT >2 ng/mL, it was considered as >2 ng/mL. The primary end point was the rate of the incidence of peri-procedural myocardial injury at 18 h after elective PCI with stent implantation. In the study, a peri-procedural TnT level >0.3 ng/mL, which was three times the normal limit (0.1 ng/mL), was defined as a peri-procedural myocardial injury.

Coronary lesion types were classified by angiographic findings according to the classification of the American Heart Association/American College of Cardiology (AHA/ACC) [20]. Diabetes mellitus was defined as including a history of diabetes, a fasting plasma glucose concentration >126 mg/dL, a randomized plasma glucose concentration of >200 mg/dL and/or anti-hyperglycemic treatment. Hypertension was defined as a history or presence of hypertension with systolic blood pressure of >160 mmHg and/or diastolic blood pressure of >90 mmHg or anti-hypertensive treatment. Smoking status was defined as current or having quit within 6 months before PCI.

**Analysis of angiographical and intravascular ultrasound**

An intracoronary infusion of 2.5–5 mg isosorbide dinitrate was used prior to angiography for quantitative coronary angiography and intravascular ultrasound so as to achieve maximal vasodilatation.

As for quantitative coronary angiography, image calibration with the use of contrast-filled guide catheters was used as the reference standard. Matched end-diastolic frames of angiograms before and after PCI were obtained and then analyzed using a contour detection minimum cost algorithm (QCA-CMS Version 3.0; MEDIS, Leiden, The Netherlands).

Our analysis of intravascular ultrasound was conducted with commercially available imaging systems (Clear View; Boston Scientific, Natick, MA for imaging and SCITIME; Freemont, CA) for a motorized pull-back device and a commercial scanner). The external elastic membrane (EEM) and lumen were traced using manual planimetry in accordance with the guidelines [21]. The cross-sectional area of EEM was measured by tracing the leading edge of the adventitia, while the cross-sectional area of plaque plus media was calculated as (EEM − lumen CSA). Percent plaque area was defined as: [(EEM area − lumen area)/EEM area] × 100. Lesion length was also determined by intravascular ultrasound (IVUS) measurements.

An independent investigator blind to our patients’ characteristics and treatments evaluated the quantitative coronary angiography intravascular ultrasound.

**Statistical analysis**

Statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL). Continuous variables were presented as mean (SD) values. In the QCA parameters, the reference diameter and percentage of diameter stenosis were compared between the two groups by the Mann–Whitney U-test and other parameters by an unpaired Student t-test. Univariate and multivariable logistic regression models were constructed to identify independent predictors of peri-procedural myocardial injury. Various factors that might be related to lesion characteristics (age, gender, eGFR levels, total stent length, direct stenting, prevalence of hypertension and diabetes, low-density lipoprotein cholesterol levels, high-density lipoprotein cholesterol levels, triglyceride levels and AHA/ACC type B2 or C) were included into the multivariable logistic models. The cutoff value of eGFR levels was determined by a receiver-operating curve to maximize the power of eGFR in predicting peri-procedural myocardial injury. A value of P < 0.05 was considered significant.

**Results**

Among all the patients, no angiographically residual stenosis defined as >30% was achieved nor was any occlusion of the large branch or slow phenomenon seen. In addition, no deaths occurred during the PCI procedure. In all patients of both groups, negative results of TnT values were obtained immediately before PCI.

**Clinical variables for the total study population are given in Table 1, with lesion and procedural variables given in Table 2.** The mean age of enrolled subjects was 68.8 ± 8.9 years, 191 were males, 195 had hypertension and 68 were current smokers. The mean body mass index was 24.1 ± 3.1 kg/m² and the mean eGFR was 62.9 ± 19.1 mL/min/1.73m² (range of eGFR: 20.6–130.4 mL/min/1.73m²). Age and the prevalence of hypertension and proteinuria were significantly higher in the lower eGFR group than in the higher group. However, other variables such as the prevalence of diabetes were comparable between the two groups. As for QCA data, there were no significant differences between the two groups in reference diameter (2.7 ± 0.6 versus 2.7 ± 0.6 mm, P = 0.53) and percentage of diameter stenosis (24 ± 9 versus 22 ± 7%, P = 0.43).

Patients with eGFR <60 mL/min/1.73m² exhibited a higher incidence of peri-procedural myocardial injury

**Table 1. Baseline characteristics**

| Characteristic | Male, n (%) | Age, years | Ejection fraction, n (%) | Clinical history, n (%) | Hypertension | Diabetes mellitus | Current smoker | Old myocardial infarction | Previous PCI | Previous coronary artery bypass graft | Prevalence of proteinuria | Waist circumference, cm | Blood lipid levels, mg/dL | Triglycerides | High-density lipoprotein | Low-density lipoprotein | C-reactive protein, g/dL | Creatine kinase MB (IUL) | Medication | Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, n (%) | Calcium channel blockers, n (%) | Beta-blockers, n (%) | Insulin, n (%) |
|---------------|-------------|------------|-------------------------|------------------------|--------------|------------------|---------------|--------------------------|-------------|-------------------------------|------------------------|------------------------|--------------------------|--------------|--------------------------|--------------------------|------------------------|---------------------|-----------------|----------------------|-------------------------|------------------------|---------------------|----------------------|
defined as TnT levels higher than three times the normal limit compared to patients with eGFR \( \geq 60 \) mL/min/1.73m\(^2\) (20.9 versus 4.3\%, \( P < 0.0001 \)) (Figure 1). Creatine kinase MB levels at 18 h after PCI were significantly higher in the lower eGFR group than in the higher group (15.3 ± 7.0 versus 19.7 ± ± 14.4 IU/L, \( P = 0.002 \)).

Even after multivariate adjustment, an eGFR level contributed to predict peri-procedural myocardial injury (odds ratio 0.92, 95% confidence interval (CI): 0.89–0.95, \( P < 0.0001 \)) (Table 3). In addition, total stent length was an independent predictor of peri-procedural myocardial injury (odds ratio 1.09, 95% CI: 1.02–1.16, \( P = 0.009 \)). In contrast, diabetes, hypertension and lipid profiles such as high-density lipoprotein, low-density lipoprotein and triglyceride levels were not predictors of peri-procedural myocardial injury.

To further clarify the importance of eGFR, we determined a cutoff value using a receiver-operating curve analysis. The result showed a 62.1 mL/min/1.73m\(^2\) (sensitivity 93.3\%, specificity 57.2\%) to be the best value (area under the curve = 0.803) to maximize the power of eGFR levels in predicting peri-procedural myocardial injury (Figure 2).

**Discussion**

The main findings of the present study were that patients with CKD who underwent elective stent implantation were more prone to peri-procedural myocardial injury and that eGFR showed a significant negative correlation with the incidence of peri-procedural myocardial injury. Interestingly, we showed that the optimal cutoff values of eGFR for the prediction of peri-procedural myocardial injury were 62.1 mL/min/1.73m\(^2\), which approximated the cutoff level of CKD Stages 2 and 3. From the viewpoint of risk stratification in PCI procedure, our findings might be of considerable significance since it is well known that peri-procedural myocardial injury is more likely to worsen clinical outcomes [9–12].

The relationship between renal function and adverse cardiac events after PCI has been well known, but its underlying mechanisms have not been fully understood and some mechanisms can be explained. Contrast-induced nephropathy after PCI is frequently seen in patients with CKD and contributes to worsening clinical outcomes [5, 7]. Additionally, a progressive increase in neointimal growth after PCI has been observed as renal function deteriorated, a finding related to a higher restenosis rate after PCI in patients with CKD [6, 8]. However, limited data are available to date regarding peri-procedural myocardial injury. Our findings might also provide an additional explanation of severe clinical outcomes in patients with CKD who undergo PCI for ischemic heart disease.

Recent studies have reported that there is an association between renal function and coronary plaque characteristics. Nakano et al. [22] clearly showed that CKD is significantly associated with the severity of coronary atherosclerosis in autopsy samples from a general population. Lower eGFR has a relationship with advanced atherosclerosis and calcified lesions, which may be complex for PCI treatment. In addition, it has been reported that a lower eGFR is strongly predictable of lipid-rich composition in coronary plaque, using integrated backscatter intravascular ultrasound [18]. PCI for coronary complex lesions and a high-lipid core area in elective stent implantation induces procedural-related complications such as peri-procedural myocardial injury [13, 23]. Thus, unique coronary plaque characteristics in patients with CKD can explain the mechanisms in our findings. Moreover, increased levels of inflammation and oxidative stress are frequently seen in patients with CKD [24–26]. Since microvascular thrombosis, platelet activation, inflammation and oxidative stress cause peri-procedural myocardial injury [27, 28], these factors were also important in patients with CKD. Taken together, renal CKD may be strongly related to peri-procedural myocardial injury after PCI.

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**Table 2. Lesion and procedural characteristics**

<table>
<thead>
<tr>
<th>Lesion location, n (%)</th>
<th>eGFR ( \geq 60 ) (mL/min/1.73m(^2)) (n=163)</th>
<th>eGFR &lt; 60 (mL/min/1.73m(^2)) (n=110)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left anterior descending artery</td>
<td>83 (50.9)</td>
<td>46 (41.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>63 (38.7)</td>
<td>40 (36.3)</td>
<td>0.81</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>17 (10.4)</td>
<td>24 (21.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>AHA/ACC type</td>
<td></td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>A</td>
<td>36(22.1)</td>
<td>23(20.9)</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>24(14.7)</td>
<td>24(21.8)</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>33(20.2)</td>
<td>20(18.2)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>70(42.9)</td>
<td>43(39.1)</td>
<td></td>
</tr>
<tr>
<td>Target EEM, mm(^3)/m(^2)</td>
<td>232.7 ± 162.5</td>
<td>273.6 ± 208.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Plaque volume, mm(^3)</td>
<td>142.8 ± 109.1</td>
<td>165.5 ± 125.7</td>
<td>0.11</td>
</tr>
<tr>
<td>% Plaque volume</td>
<td>59.6 ± 9.0</td>
<td>61.5 ± 9.5</td>
<td>0.10</td>
</tr>
<tr>
<td>Stent procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of stents, n</td>
<td>1.39 ± 0.68</td>
<td>1.53 ± 0.80</td>
<td>0.12</td>
</tr>
<tr>
<td>Direct stenting, n (%)</td>
<td>71 (45.4)</td>
<td>32 (29.1)</td>
<td>0.60</td>
</tr>
<tr>
<td>Total stent length, mm</td>
<td>27.2 ± 15.8</td>
<td>29.0 ± 17.2</td>
<td>0.38</td>
</tr>
<tr>
<td>Maximum pressure inflation, atm</td>
<td>16.8 ± 3.7</td>
<td>16.9 ± 3.6</td>
<td>0.91</td>
</tr>
<tr>
<td>Total inflation time, s</td>
<td>123.8 ± 91.5</td>
<td>129.1 ± 84.3</td>
<td>0.63</td>
</tr>
</tbody>
</table>

**Fig. 1. Incidence of peri-procedural myocardial injury.** Patients with CKD had a significantly higher incidence of peri-procedural myocardial injury compared to those without (4.3 versus 20.9\%, \( P < 0.0001 \)).
Pharmacological intervention and/or a distal protection device may be considered to decrease complications in patients with CKD who undergo PCI. Previous studies have reported that treatment with statins reduces both coronary plaque and lipid volumes [30–32]. Even in patients with CKD Stage 3, administration of statins has a beneficial effect on coronary plaque composition [18]. Although statins were administered to all our patients based on the findings of previous researchers [14, 15], their treatment varied from a month to several years. Thus, further investigations are warranted in this regard.

Several limitations of the study should be discussed. First, the study was conducted in a single center and consisted of a relatively small sample size. The techniques used for the PCI procedure might also affect the results. Second, the debulking of the surface of a coronary artery that may induce myocardial injury often occurs during a simple passage of an IVUS catheter. Third, patients who underwent rotational atherectomy during PCI were excluded because such debulking devices are considered to be associated with increased levels of cardiac enzyme elevation [33]. Fourth, peri-procedural samples were collected only once 18 h after PCI in the study. Finally, data on longer follow-ups were unknown. Such study limitations need to be carefully considered.

In conclusion, patients with CKD experienced significantly greater peri-procedural myocardial injury compared to those without it and lower eGFR levels were a simple and convenient predictor of peri-procedural myocardial injury after elective stenting. The findings emphasize that patients with CKD are considered a high-risk population in PCI with stent implantation.

Table 3. Multivariate logistic regression analysis with peri-procedural myocardial injury

<table>
<thead>
<tr>
<th>Variables</th>
<th>Multivariate OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99 (0.93–1.05)</td>
<td>0.65</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.70 (0.24–2.04)</td>
<td>0.51</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>0.92 (0.89–0.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total stent length (mm)</td>
<td>1.09 (1.02–1.16)</td>
<td>0.03</td>
</tr>
<tr>
<td>Direct stenting</td>
<td>0.75 (0.21–2.68)</td>
<td>0.65</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.74 (0.59–5.16)</td>
<td>0.32</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.11 (0.40–3.10)</td>
<td>0.84</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (mg/dL)</td>
<td>1.01 (0.99–1.02)</td>
<td>0.65</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mg/dL)</td>
<td>0.99 (0.95–1.05)</td>
<td>0.83</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>0.99 (0.98–1.01)</td>
<td>0.30</td>
</tr>
<tr>
<td>Total inflation time (s)</td>
<td>1.01 (0.99–1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>AHA/ACC type B2 or C</td>
<td>1.12 (0.42–3.01)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Fig. 2. Receiver-operating characteristics analysis of the ability of an eGFR to identify peri-procedural myocardial injury.
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Conflict of interest statement. None declared.

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