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A correlation between acute kidney injury and myonecrosis after scheduled percutaneous coronary intervention*

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Abstract: Slight elevations in cardiac troponin I and T are frequently observed after percutaneous coronary intervention (PCI). Contrast-induced acute kidney injury (CI-AKI) is a complex syndrome induced by exposure to intravascular contrast media (CM). Currently, the relationships between the CM, pre-existing kidney insufficiency, CI-AKI, and myonecrosis after elective PCI are unclear. To investigate the relationship between CI-AKI and post-procedural myonecrosis (PMN) after PCI, we analyzed 327 non-ST-segment elevation acute coronary syndrome subjects undertaking elective PCI. The levels of cardiac troponins (cTns), cTnI and cTnT, at baseline and on at least one occasion 18–24 h after PCI were measured. We also recorded serum levels of creatinine (SCr) and the urine albumin:creatinine ratio (ACR) before coronary angiography, and 24–48 h and 48–72 h after contrast administration. A post-procedure increase in cTns was detected in 16.21% (53/327) of subjects with cTns levels >99th to 5×99th percentile upper reference limit (URL). Twenty-seven patients (8.26%) developed CI-AKI. CI-AKI occurred more often in subjects with PMN than in those without PMN (20.8% versus 5.8%, respectively, P=0.001). Multiple logistic regression analysis revealed that pre-existing microalbuminuria (MA) was an important independent predictor of PMN (OR: 3.31; 95% CI: 1.26–8.65, P=0.01). However, there was no correlation between the incidence of CI-AKI and PMN (OR: 2.38; 95% CI: 0.88–6.46, P=0.09). We conclude that pre-existing MA was not only an important independent predictor of CI-AKI but also of PMN.

Key words: Percutaneous coronary intervention, Myonecrosis, Contrast-induced nephropathy, Acute kidney injury, Contrast media

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1 Introduction

Contrast-induced acute kidney injury (CI-AKI), generally defined as an increase in the serum creatinine concentration of >0.5 mg/dl (>44 μmol/L) or >25% above baseline within 48 h after contrast administration (McCullough, 2008), is the third leading cause of hospital-acquired renal insufficiency, accounting for 12% of all cases (Hou *et al.*, 1983). The reported incidence of CI-AKI varies widely (from <1% to >50%), depending on the subject population, the baseline risk factors, and the definition (McCullough, 2008). Although the exact mechanisms of contrast-induced nephropathy (CIN) are uncertain, the incremental presence of predisposing factors including renal impairment, contrast media (CM) load, diabetes, and advancing age seems to contribute (Mehran *et al.*, 2004). Acute renal failure requiring dialysis after coronary intervention is

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associated with poor clinical outcomes, including 22.6% to 35.7% in-hospital mortality and 18.8% two-year survival (McCullough *et al.*, 1997; Gruberg *et al.*, 2000; Li *et al.*, 2012).

According to the universal definition of myocardial infarction, compared with a normal baseline troponin value, the elevation of cardiac biomarkers above the 99th percentile upper reference limit (URL) and <5×99th percentile URL can be assumed to confirm post-procedural myonecrosis (PMN) (Thygesen *et al.*, 2012). Cardiac troponins (cTns; cTnI and cTnT) are particularly sensitive and specific markers of myocardial injury (Hamm *et al.*, 1997; Antman *et al.*, 2000). Post-procedural elevations of cTns levels occur in 5% to 50% of subjects undergoing percutaneous coronary intervention (PCI) (Califf *et al.*, 1998). The association between cTns elevation after elective PCI and cardiac events is conflicted during the follow-up (Fuchs *et al.*, 2000; Nallamothu *et al.*, 2003; Ramírez-Moreno *et al.*, 2004; Prasad *et al.*, 2006; Nienhuis *et al.*, 2007; Milani *et al.*, 2009).

Increased levels of cTnT and cTnI in subjects with renal failure are likely to indicate multifactorial pathology, including cardiac dysfunction, left ventricular hypertrophy, and cardiac microinfarctions. Increases in serum troponins from baseline in subjects with renal disease and with acute coronary syndromes may indicate a poor prognosis. Small studies of subjects with renal failure have suggested that elevation of cTns is associated with an increased risk of major cardiac events.

PCI has recently become a common therapy for coronary artery disease (CAD) in the drug-eluting stent era. A large volume CM is sometimes administered in PCI for complicated lesions, including chronic total occlusions.

There have been more studies on CM leading to AKI, including its incidence, mechanisms and prognosis than on the effects of CM on periprocedural myonecrosis. There have been no reports about the relationship between the functions of the kidney, the effects of the CM and myonecrosis.

This study is the first investigation of the incidence of CI-AKI in subjects suffering from periprocedural myonecrosis. Using a population-based prospective cohort, we have evaluated the relationships between pre-existing microalbuminuria (MA), CI-AKI, and myocardial injury.

2 Materials and methods

2.1 Subjects

The present trial was a prospective, observational, single-center clinical study. We reviewed hospital charts of individual subjects to verify the data. From January 2010 to November 2012, the subjects, who undergone elective PCI for the treatment of stable angina pectoris (SAP) or unstable angina pectoris (UAP) or of non-ST-segment elevation myocardial infarction (NSTEMI) at the Cardiology Center of our institution, were selected. We retrospectively enrolled 327 subjects in the study. The clinical characteristics of the subjects in two groups (PMN and non-PMN), such as their age, gender, blood glucose level, blood pressure, baseline cTnI or cTnT, baseline urine albumin:creatinine ratio (ACR), baseline creatinine (SCr), baseline estimated glomerular filtration rate (eGFR), and concomitant medications, were recorded. All data management was performed using dedicated data software (Lauritsen JM & Bruus M. EpiData, Version 3.1).

Inclusion criteria were that subjects had: selected PCI; baseline troponins (cTnT or cTnI) below the 99th percentile URL; eGFR levels of ≥60 ml/min. Exclusion criteria were MA (defined as ACR >300 mg/g); eGFR <60 ml/min; subjects who suffered myocardial infarction up to one week before PCI or who had elevated pre-procedure cTns; cTns of >5×99th percentile URL after PCI; and subjects with conditions (including branch vessel occlusion, dissection, and embolization) known to cause elevated troponin levels.

2.2 Procedures and outcomes

Coronary angiography was performed by the radial or femoral approach. Iohexol (Omnipaque, GE Healthcare Europe, 350 mg iodine/ml) was used in this study. CM was administered by intra-arterial injection as necessary for each subject, and the total CM volume administered was recorded. Stent implantation was successful in all patients. Procedural success was defined as residual stenosis of <20% and thrombolysis in myocardial infarction (TIMI) flow grade 3. The main outcome measured in this study was the occurrence of CI-AKI and PMN. If a subject underwent more than one coronary angiography procedure, the first procedure was considered for this analysis.

2.3 cTnI and cTnT assays

Blood samples for testing cardiac biomarkers were drawn from each subject before and between 18–24 h after PCI. Further measurements were taken from subjects with post-procedural symptoms suggestive of myocardial ischemia. The peak values of cTns were used for analysis. The samples were inserted into tubes with a heparin anticoagulant agent, centrifuged at 3000×*g* for 10 min, and then stored at −40 °C until analyzed. Plasma levels of cTnT were analyzed using the Access 2 Immunochemiluminometric assay (Roche Diagnostics GmbH, Mannheim, Germany). The upper limit of normal for the assay is <0.1 ng/ml. Plasma levels of cTnI were measured by enzyme-linked immunosorbent assay (ELISA; Institute of Cardiovascular Disease, the First Affiliated Hospital of Nanjing Medical University, China), and the upper limit of normal for the assay is <0.5 ng/ml.

2.4 Biomarkers of renal function

We measured SCr and ACR levels during hospitalization that occurred before and closest to the time of coronary angiography, and again at 24–48 h and at 48–72 h post-dose. The highest SCr at 24–48 h or 48–72 h post-contrast was used to calculate the peak increases in SCr. The modification of diet in renal disease (MDRD) formula was used to calculate eGFR (Macunluoğlu *et al.*, 2011). CI-AKI was defined as a relative increase in the SCr concentration of at least 25% or an absolute increase in SCr of 0.5 mg/dl (44.2 μmol/L) within 72 h after the procedure, in the absence of other etiologies (Kim *et al.*, 2011). MA was defined as ACR in the range of 30–300 mg/g. All SCr and MA levels were determined by laboratory personnel using an autoanalyzer in our clinical laboratory. In both groups, no CI-AKI prophylaxis measures were used because the subjects were usually considered as a low risk population for CI-AKI.

2.5 Statistical analysis

Continuous variables between groups were compared by one-way analysis of variance (ANOVA) for normally distributed values; otherwise the Mann-Whitney *U* test was used. Proportions were compared using the Fisher exact test when the expected frequency was <5; otherwise the χ^2 test was applied. Continuous variables were summarized by the mean±standard deviation (SD), unless otherwise specified, and categorical data were presented as frequencies. Odds ratios (ORs) and 95% confidence intervals (CIs), for assessing the risk of the incidence of PMN in the overall population according to potential confounding variables, were assessed by logistic regression. All the parameters in Tables 1, 2, and 3 were evaluated first in a univariate model. Variables with a *P* value of <0.05 on univariate testing were subjected to multivariate logistic regression analysis. Although this may have led to an overfitted multivariable model, all these variables were entered in order not to miss potential confounders. All calculations were performed using SPSS version 13.0 (SPSS Inc., Chicago, Illinois, USA), and *P* values of <0.05 (2-tailed) were considered significant.

3 Results

A total of 386 subjects undergoing scheduled PCI and who had been diagnosed with myocardial and kidney injury, were enrolled in the study. Of these, 59 subjects were excluded for a variety of reasons (17 subjects with eGFR levels of <60 ml/min, 16 with MA, 14 with acute myocardial infarction or cardiac death during hospitalization, 12 with cTns levels of >5×99th percentile URL after PCI and accompanied by side effects about dissection and major branch vessel occlusion). Three hundred and twenty-seven subjects with eGFR levels of ≥60 ml/min and without MA or baseline cTns elevation were included in this study. An elevation in post-PCI cTns was detected in 53 (16.21%) subjects with cTns levels >99th to 5×99th percentile URL. The incidence of CI-AKI was 8.26% (27/327). Eleven subjects (3.36%) had elevated cTns and CI-AKI. Patients were divided into two groups based on post-PCI troponin levels: a PMN group (53 subjects, cTns >99th to 5×99th percentile URL) and a non-PMN group (274 subjects, cTns <99th percentile URL).

3.1 Baseline and procedural characteristics

Clinical characteristics were compared between subjects who developed PMN and those who remained free of PMN (Table 1). Pre-procedure SCr levels were (87.5±34.2) mmol/L in subjects with

PMN and (77.7±18.8) mmol/L in subjects without PMN (P=0.12). The pre-procedure eGFR level was (85.0±25.1) ml/min in subjects with PMN and (91.8±20.2) ml/min in subjects without PMN (P=0.032). Subjects suffering PMN had higher pre-procedural ACR levels than those without PMN, P<0.001 (Table 2).

Table 1 A comparison of the clinical characteristics of subjects with or without PMN

Variable	Non-PMN group (n=274)	PMN group (n=53)	P value
Mean age (year)	61.2±9.4	65.5±10.7	0.003
Female	71 (25.9%)	12 (22.6%)	0.731
UA	207 (75.5%)	41 (77.4%)	0.862
NSTEMI	4 (1.5%)	0 (0%)	0.616
Hypertension	175 (63.9%)	45 (84.9%)	0.004
Diabetes	63 (23.0%)	14 (26.4%)	0.598
Hyperlipidemia	18 (6.6%)	5 (9.4%)	0.555
Smoking	124 (45.3%)	19 (35.8%)	0.229
Prior MI	20 (7.3%)	2 (3.8%)	0.549
Prior PCI	26 (9.5%)	4 (7.5%)	0.799
Prior CABG	3 (1.1%)	2 (3.8%)	0.186
SBP (mmHg)	131.9±13.8	134.1±17.1	0.32
Heart rate (beat/min)	69.8±11.4	69.8±11.8	0.99
LDL-C (mmol/L)	2.5±0.7	2.5±0.7	0.89
GLU (mmol/L)	5.5±1.5	5.9±1.8	0.07
LVEF (%)	64.4±6.4	65.1±4.8	0.49
Medication at discharge			
Aspirin	272 (99.3%)	53 (100%)	1.000
β-blockers	203 (74.1%)	40 (75.5%)	0.866
Statins	272 (99.3%)	52 (98.1%)	0.413
ACEI/ARB	198 (72.3%)	38 (71.7%)	1.000

Values are given as number of patients (percent) or mean±SD. UA: unstable angina; NSTEMI: non-ST-segment elevation myocardial infarction; MI: myocardial infarction; CABG: coronary artery bypass graft; SBP: systolic blood pressure; LDL-C: low-density lipoprotein cholesterol; GLU: glucose; LVEF: left ventricular ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker

Table 2 Biomarkers of renal function

Variable	Non-PMN group	PMN group	P value
Pre-Scr (mmol/L)	77.7±18.8	87.5±34.2	0.12
Pre-eGFR (ml/min)	91.8±20.2	85.0±25.1	0.032
Post-Scr (mmol/L)	80.7±18.9	94.2±43.6	0.015
Post-eGFR (ml/min)	87.8±19.3	79.0±24.2	0.004
ACR (mg/g)	7 (5, 12)	13 (7, 31)	<0.001
MA	19/240 (7.9%)	13/51 (25.5%)	0.001
CI-AKI	16/274 (5.8%)	11/53 (20.8%)	0.001

Values are given as mean±SD, median (interquartile range), or number of patients with MA or CI-AKI/total patient number (percent)

Angiographic and procedural characteristics are listed in Table 3. All subjects accepted several seconds of balloon pre-dilation after coronarography and before stent implantation. For each subject, the procedure was successful and they each achieved post-procedure TIMI grade 3 flows. Subjects with PMN had more extensive CAD with a greater incidence of 3-vessel (P=0.012) and multivessel (P=0.045) CAD than non-PMN subjects. Gensini scores were significantly higher in the PMN group compared with the non-PMN group (112.7±65.0 vs. 88.9±71.2, respectively, P=0.024). There was a prominent difference between the groups in the number of target coronary lesions (4.2±1.5 and 3.1±1.7, respectively; P<0.001). Contrast volume was significantly greater in patients presenting with PMN ((212.7±62.4) ml) than in those without PMN ((176.2±59.0) ml), P<0.001. In concert with having more extensive coronary disease, subjects with increased cTns ≥99th percentile URL underwent more 2-vessel (P=0.014) and 3-vessel (P=0.020), and left

Table 3 A comparison of periprocedural characteristics between PMN and non-PMN groups

Variable	Non-PMN group (n=274)	PMN group (n=53)	P value
No. of diseased arteries			
LM or LM+single	4 (1.5%)	0 (0%)	1.000
LM+double or three	4 (1.5%)	2 (3.8%)	0.251
Single	86 (31.4%)	3 (5.7%)	<0.001
Double	89 (32.5%)	14 (26.4%)	0.423
Three	69 (25.2%)	23 (43.4%)	0.012
Multiple	24 (8.8%)	10 (18.9%)	0.045
Lesions	3.1±1.7	4.2±1.5	<0.001
Gensini score	88.9±71.2	112.7±65.0	0.024
Contrast used (ml)	176.2±59.0	212.7±62.4	<0.001
No. of treated arteries			
Single	170 (62.0%)	17 (32.1%)	<0.001
Double	76 (27.7%)	24 (45.3%)	0.014
Three	28 (10.2%)	12 (22.6%)	0.020
LM	3 (1.1%)	0 (0%)	1.000
LAD	207 (75.5%)	44 (83.0%)	0.288
LCX	94 (34.3%)	26 (49.1%)	0.045
RCA	101 (36.9%)	31 (58.5%)	0.006
No. of stent	2.3±1.3	3.2±1.3	<0.001
Stent length (mm)	54.3±35.6	73.6±33.9	<0.001

Values are given as number of patients (percent) or mean±SD. LM: left main; LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery; Single, double, three: number of diseased and treated arteries vessel

circumflex artery (P=0.045) and right coronary artery (P=0.006) PCI, compared with subjects without cTns elevation. These subjects also had a greater total length of implanted stent ((73.6±33.9) mm, P<0.001) and a greater number of stents implanted ((3.2±1.3), P<0.001).

3.2 Adjusted multivariate risk factor logistic analysis

In the univariate analyses, cardiovascular risk factors such as advanced age, the prevalence of hypertension, pre-procedural MA, amount of contrast used, number of lesions, and Gensini score were positively correlated with the incidence of PMN. After adjustment for those confounders, advanced age, the prevalence of hypertension, amount of contrast used, number of lesions, and Gensini score were not isolated risk factors of PMN, but, pre-procedural MA was still independently associated with a higher incidence of PMN in subjects with eGFR levels of ≥60 ml/min, without MA, and undergoing scheduled coronary angiography, P=0.01 (OR: 3.31; 95% CI: 1.26–8.65) (Table 4). However, the incidence of CI-AKI was not correlated with PMN, P=0.09 (OR: 2.38; 95% CI: 0.88–6.46).

Table 4 Adjusted multivariate risk factors in relation to PMN determined by logistic analysis

Variable	Correlation coefficient	P value	OR (95% CI)
Age			
≤56 years	Reference		
57–69 years	−0.68	0.14	0.51 (0.21–1.25)
≥70 years	0.84	0.07	2.32 (0.95–5.70)
Hypertension	0.53	0.24	1.70 (0.70–4.11)
MA	1.20	0.01	3.31 (1.26–8.65)
CI-AKI	0.87	0.09	2.38 (0.88–6.46)
Contrast used			
≤140 ml	Reference		
141–215 ml	0.68	0.24	1.97 (0.64–6.02)
≥216 ml	0.78	0.20	2.19 (0.67–7.19)
Number of lesions			
≤2	Reference		
3–4	1.32	0.04	3.73 (1.04–13.43)
≥5	1.14	0.11	3.12 (0.77–12.59)
Gensini score			
≤44	Reference		
45–120	1.25	0.16	3.49 (0.61–19.88)
≥121	1.35	0.15	3.85 (0.60–24.62)

4 Discussion

Our study showed that the rate of CI-AKI in patients with post procedural myocardial injury and undergoing elective PCI was higher than that in patients free of injury. Another major finding of the present study was that subjects who subsequently developed PMN had higher preoperative levels of ACR than those who did not. According to the redefinition of PMN as a cTns elevation of >1×99th and <5×99th percentile URL, 16.21% (53/327) of subjects suffered from PMN. Twenty-seven (8.26%) subjects suffered from CI-AKI after PCI, and PMN and CI-AKI occurred simultaneously in 11 subjects (11/327, 3.36%).

With the expansion of the use of iodinated CM in both diagnostic and interventional cardiovascular procedures, in combination with an increasingly elderly and infirm patient population, the incidence of CI-AKI is likely to grow rapidly. CI-AKI is a serious complication of radio-contrast vascular examination, especially in high-risk subjects with decreased renal function.

Zhao *et al.* (2011) assessed the toxic effects of non-ionic CM (iopromide and iodixanol) on glomerular and aortic endothelial cells (ECs) in an in vivo study. The results showed that endothelial nitric oxide synthase (eNOS) expression in the glomerular endothelium decreased 12 h after CM injection. Furthermore, plasma creatinine and endothelin-1 levels increased and were significantly and negatively correlated with plasma nitric oxide (NO) concentration after CM administration. We conclude that the decreased expression of eNOS and increased plasma endothelin-1 may be involved in non-ionic iodinated CM-induced endothelial dysfunction and kidney injury. A study by Ma *et al.* (2010) implicated female sex as an independent risk factor for the development of CI-AKI following PCI.

Surprisingly, patients with PMN had higher ACR (13 mg/g vs. 7 mg/g, P<0.001) and pre-existing MA (25.5% vs. 7.9%, P=0.001), and decreased eGFR levels (85.0±25.1 vs. 91.8±20.2, P<0.032) at baseline compared with patients without PMN (Table 2). However, after adjustment for confounders, pre-procedural MA was still independently associated with a higher incidence of PMN in subjects with eGFR ≥60 ml/min, without MA, and undergoing

scheduled coronary angiography, P=0.01 (OR: 3.31; 95% CI: 1.26–8.65) (Table 4). Similarly, Song *et al.* (2012) found that 32% of subjects (6/19) had troponin I and T concentrations above the 99th percentile of a reference population, without known confounders, resulting in elevated troponin levels. This suggests that impaired renal function disease influences plasma cardiac troponin levels in AKI as well as in chronic kidney failure. Aksoy *et al.* (2009) and Tsutamoto *et al.* (2009) postulated that it is the impaired renal function that causes the accumulation of troponin. In our study, factors described in the literature as being associated with elevated cardiac troponins in chronic kidney failure were excluded.

In this study, patient factors such as advanced age, prevalence of hypertension, the presence of many diseased coronary arteries and lesions, a high total number of vessels treated, a high total number of stents placed and a high total stent length, and high Gensini scores were significantly associated with elevated troponin levels in PMN patients, compared with patients without PMN (Table 3). We speculate that cardiac troponin levels become elevated owing to these unfavorable factors, coupled with intraoperative effects of the guiding wire, balloon dilatation, stent implantation, and the contrast agent inducing damage to the coronary arterial ECs, causing the accumulation of fibrin and platelets on vessel surfaces, leading to microthrombosis. This theory is supported by the results of a previous in vitro study (Aliev *et al.*, 2003), in which a single injection of CM (verographin, iodamid and iodolipol) induced damage to arterial ECs, forming microthrombosis and fibrin accumulation on vessel surfaces. The common features of EC damage induced by different types of CM appeared to be a non-specific reaction to injury stimuli. These changes were visible mostly during the first 72 h and then decreased. After 7 d, the ECs partially restored their previous intact morphology. Thus, CM is not only involved in formation of AKI but also induces myonecrosis after PCI.

The significance of these changes in the absence of ongoing acute cardiac pathology is unknown. However, prevention of CI-AKI and PMN continues to elude clinicians and is a major concern during PCI, as subjects undergoing these procedures often have multiple co-morbidities. The future determination of the mechanisms that underlie the damaging effect of the CM on vascular wall cells, especially the vascular endothelium, and the possible prevention of this damage by vasoprotectors, will result in greater application of diagnostic procedures. Better preventive strategies are needed to improve clinical outcomes in subjects at a high risk of developing CI-AKI and PMN.

A limitation of this study was the limited number of subjects because of the short time period and the use of a single medical center. Therefore, caution is needed in extrapolating these results to all patients. Multiple centers and large sample numbers will be needed for further studies.

5 Conclusions

We conclude that pre-existing MA was not only an important independent predictor of CI-AKI but also of PMN. CI-AKI occurred more often in subjects with PMN than in those without PMN. However, the incidence of CI-AKI was not correlated with the incidence of myonecrosis. Patients with pre-existing MA and reduced eGFR were loaded with small amounts of contrast agent in the process of coronary angioplasty, which prevented CIN and PMN.

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Compliance with ethics guidelines

Min ZHANG, Hao-yu MENG, Ying-ming ZHAO, Zhi-wen TAO, Xiao-xuan GONG, Ze-mu WANG, Bo CHEN, Zheng-xian TAO, Chun-jian LI, Tie-bing ZHU, Lian-sheng WANG, and Zhi-jian YANG declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000(5). Informed consent was obtained from all patients for being included in the study.

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