CLINICS

CLINICAL SCIENCE

The relationship between hyperuricemia and the risk of contrast-induced acute kidney injury after percutaneous coronary intervention in patients with relatively normal serum creatinine

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OBJECTIVES: Hyperuricemia is a risk factor for contrast-induced acute kidney injury in patients with chronic kidney disease. This study evaluated the value of hyperuricemia for predicting the risk of contrast-induced acute kidney injury in patients with relatively normal serum creatinine who were undergoing percutaneous coronary interventions.

METHODS AND RESULTS: A total of 788 patients with relatively normal baseline serum creatinine (<1.5 mg/dL) undergoing percutaneous coronary intervention were prospectively enrolled and divided into a hyperuricemic group (n = 211) and a normouricemic group (n = 577). Hyperuricemia is defined as a serum uric acid level>7 mg/dL in males and >6 mg/dL in females. The incidence of contrast-induced acute kidney injury was significantly higher in the hyperuricemic group than in the normouricemic group (8.1% *vs.* 1.4%, $p<0.001$). In-hospital mortality and the need for renal replacement therapy were significantly higher in the hyperuricemic group. According to a multivariate analysis (adjusting for potential confounding factors) the odds ratio for contrast-induced acute kidney injury in the hyperuricemic group was 5.38 (95% confidence interval, 1.99-14.58; $p = 0.001$) compared with the normouricemic group. The other risk factors for contrast-induced acute kidney injury included age >75 years, emergent percutaneous coronary intervention, diuretic usage and the need for an intra-aortic balloon pump.

CONCLUSION: Hyperuricemia was significantly associated with the risk of contrast-induced acute kidney injury in patients with relatively normal serum creatinine after percutaneous coronary interventions. This observation will help to generate hypotheses for further prospective trials examining the effect of uric acid-lowering therapies for preventing contrast-induced acute kidney injury.

KEYWORDS: Hyperuricemia; Contrast-Induced Acute Kidney Injury; Risk Factors; Percutaneous Coronary Intervention.

Liu Y, Tan N, Chen J, Zhou Y, Chen L, Chen S, et al. The relationship between hyperuricemia and the risk of contrast-induced acute kidney injury after percutaneous coronary intervention in patients with relatively normal serum creatinine. Clinics. 2013;68(1):19-25.

Received for publication on August 19, 2012; **First review completed on** September 23, 2012; **Accepted for publication on** September 23, 2012

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INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) has been recognized as a serious complication of percutaneous coronary intervention (PCI) and may cause an increase in morbidity and mortality (1,2). In addition to prophylactic intravenous volume expansion with isotonic crystalloid solution (3), few prophylactic strategies for CI-AKI are clearly effective. A key step in minimizing the risk of CI-AKI is identifying at-risk patients.

Many risk factors, such as pre-existing renal dysfunction, exposure to a high volume of contrast medium, older age, hypovolemia, congestive heart failure, emergent PCI, and exposure to nephrotoxic drugs, have been associated with developing CI-AKI (4-7). Currently, the most widely recognized risk factor for developing CI-AKI is baseline renal impairment, which is conventionally defined as a serum creatinine (SCr) level≥1.5 mg/dL (132 mmol/dL) (5,8). Few studies have investigated patients with normal renal function, although these patients constitute the majority of those undergoing PCI. CI-AKI prophylaxis, including hydration, is not typically administered to patients with normal baseline SCr (<1.5 mg/dL).

No potential conflict of interest was reported.

DOI: 10.6061/clinics/2013(01)OA04

The relationship between hyperuricemia (HUA) and CI-AKI has not been extensively studied. It has been suggested that tubular obstruction by uric acid plays a role in the pathogenesis of CI-AKI (9,10). HUA is accompanied by enhanced synthesis of reactive oxygen species, activation of the renin–angiotensin–aldosterone system, an increase in endothelin-1, and inhibition of the nitric oxide system; all of these factors play a role in the pathogenesis of CI-AKI (11-13).

Toprak et al. observed that HUA was a risk factor for CI-AKI in patients undergoing coronary angiography with chronic kidney disease (SCr≥1.2 mg/dL) (14). We aim to identify the risk predictors in this cohort and evaluate the value of HUA in predicting the risk of CI-AKI in patients with relatively normal SCr who are not receiving sufficient renal prophylaxis.

METHODS

Study population

We conducted a prospective, controlled single-center observational study at Guangdong Cardiovascular Institute, Guangdong General Hospital, Guangdong Academy of Medical Sciences between February 2010 and January 2011. The exclusion criteria were pregnancy, lactation, sepsis, the intravascular administration of a contrast medium within the past seven days, nephroprotective drug treatment (e.g., N-acetylcysteine, theophylline, prostaglandin E1, sodium bicarbonate), nephrotoxic drug intake (e.g., non-steroidal anti-inflammatory drugs, metformin, aminoglycosides, amphotericin B, cisplatin) within the past seven days, a history of serious reactions to contrast media, renal transplantation, end-stage renal disease necessitating dialysis, and severe concomitant disease of other systems. We also excluded the patients who died during PCI or who had hemodynamic instability requiring an intra-aortic balloon pump (IABP) before PCI. The Ethics Committee of the Guangdong General Hospital approved the study. All of the eligible patients provided written informed consent.

Study protocol

We screened 960 patients who underwent PCI. A total of 788 patients met the inclusion criteria. The eligible patients were divided into two groups: hyperuricemic (n = 211) and normouricemic (n = 577). As in previous studies (15,16), HUA was defined as a serum uric acid level>7 mg/dL (417 μmol/L) in males and>6 mg/dL (357 μmol/L) in females. None of the patients in the hyperuricemic group had gout, documented uric acid stones, or any acute HUA complications (i.e., they had asymptomatic HUA).

Left ventricular function was evaluated with echocardiography in all of the patients within 24 h of admission. The patients were hydrated with intravenous isotonic saline (0.9%) at a rate of 1 mL/kg body weight per h for 1-8 h before and 6-8 h after PCI. In the patients with left ventricular ejection fraction (LVEF) <40% or overt heart failure, the hydration rate was reduced to 0.5 mL/kg per h. PCI was performed with a low-osmolar, non-ionic contrast medium (LOCM). The PCI operations and the use of an IABP, inotropic drugs, tirofiban, beta-blockers, angiotensin-converting-enzyme inhibitors, and diuretics were left to the discretion of the cardiologists.

The primary endpoint of the study was the occurrence of CI-AKI, which was defined as an increase in serum creatinine of≥0.5 mg/dL above the baseline value within 48-72 h after PCI (17,18). We obtained the blood samples used to measure preoperative serum uric acid, baseline serum creatinine (SCr) (prior to the pre-procedural hydration), blood urea nitrogen (BUN), random blood glucose, electrolytes before PCI, serum lipids, fasting blood glucose, albumin, hemoglobin, and other standard clinical parameters after an 8-h overnight fast. Follow-up SCr and BUN levels were measured one, two, and three days after the procedure (19% of the patients stayed in the hospital for three days and participated in the sampling on day 3). Baseline creatinine clearance was calculated with the Cock-Croft–Gault formula: (140-age)×weight (kg)/SCr (mg/dL)72×(0.85 for females) (19). The major in-hospital clinical event (e.g., death) was recorded at the same time.

Statistical analysis

SPSS software for Windows (version 13.0, SPSS Inc., Chicago, Illinois, USA) was used for the analyses. The demographics and traditional risk factors were compared between the hyperuricemic and normouricemic groups. All of the values are expressed as the mean ± SD or medians and interquartile ranges. The differences between the means were compared with an unpaired t-test for the variables that were normally distributed and with the Mann-Whitney *U*-test for the variables that were not normally distributed. Categorical variables were analyzed using the χ^2 test. We performed logistic regression analysis with CI-AKI as the dependent variable. The variables that were statistically significant according to the univariate analysis were included in the final multivariate model to identify the CI-AKI predictors. A two-sided 95% confidence interval (CI) was constructed around the point estimate of the odds ratio (OR). All of the tests were two-sided, and a p-value<0.05 was considered statistically significant.

RESULTS

A total of 788 patients were enrolled in the study. Based on their serum uric acid concentrations, 211 patients were assigned to the hyperuricemic group and 577 to the normouricemic group (mean serum uric acid 481 ± 72 and 310 ± 66 μmol/L, respectively, $p<0.001$); mean age (65 ± 12 and 62 ± 11, respectively, $p<0.001$); and proportion of males (70% and 82%, respectively, $p<0.001$). The following demographic, clinical, and angiographic characteristics were compared between the hyperuricemic and normouricemic groups (as shown in Tables 1 and 2): older age (21% *vs.* 11%, $p<0.001$), pre-existing renal dysfunction (48% *vs.* 29%, $p<0.001$), serum cholesterol levels (total cholesterol 4.77 ± 1.29 *vs.* 4.56 ± 1.11 mmol/L, $p = 0.024$; low-density lipoprotein cholesterol 3.07 ± 1.06 *vs.* 2.92 ± 0.95, $p = 0.055$), severely reduced LVEF (12% *vs.* 8%, $p = 0.061$), hypertension (70% *vs.* 54%, $p<0.001$), anemia (22% *vs.* 16%, $p = 0.065$), multivessel coronary disease (79% *vs.* 69%, $p<0.001$), the exposure time to contrast agents, the number of coronary lesions, and the ratio of smokers to non-smokers were significantly different between the two groups. There were no significant differences between the two groups in the incidence of diabetes mellitus (20% *vs.* 23%, $p = 0.441$), emergent PCI (23% *vs.* 26%, $p = 0.404$), contrast amount, coronary heart disease type, or other parameters.

We determined the CI-AKI risk scores according to Scheme Model A developed by Mehran et al. (7). The mean and median CI-AKI risk scores in the hyperuricemic group

Table 1 - Baseline demographics and clinical characteristics.

Variables	Hyperuricemic group (n = 211)	Normouricemic group (n = 577)	*p*-value
Age (y)	65 ± 12	62 ± 11	<0.001
Age>75 y (%)	44 (21)	63 (11)	<0.001
Males (%)	147 (70)	472 (82)	<0.001
Weight (kg)	65 ± 11	64 ± 10	0.240
SBP (mmHg)	132 ± 23	131 ± 21	0.940
Smokers (%)	87 (41)	267 (46)	0.208
Hypertension (%)	148 (70)	311 (54)	<0.001
Diabetes (%)	42 (20)	130 (23)	0.430
Unilateral/bilateral RAS≥50 (%)	7 (3)	17 (3)	0.788
Hyperlipidemia (%)	40 (19)	96 (17)	0.445
Total cholesterol (mg/dl)	4.77 ± 1.29	4.56 ± 1.11	0.024
LDL-cholesterol (mg/dl)	3.07 ± 1.06	2.92 ± 0.95	0.055
Serum uric acid (μmol/L)	481 ± 72	310 ± 66	<0.001
Coronary heart disease type			0.347
Acute coronary syndrome (%)	193 (92)	539 (93)	
Stable angina (%)	18 (8)	38 (7)	
Previous MI (%)	24 (11)	73 (13)	0.629
CABG (%)	4 (2)	4 (1)	0.220
LVEF (%)	57 ± 13	58 ± 12	0.469
LVEF <40% (%)	26 (12)	46 (8)	0.061
Emergent PCI (%)	48 (23)	148 (26)	0.404
ACEI/ARB usage (%)	185 (88)	529 (92)	0.088
Diuretic usage	36 (17)	70 (12)	0.073
Baseline SCr (μmol/L)	94 ± 19	85 ± 18	<0.001
CrCl, (mL/min)	65 ± 24	75 ± 24	<0.001
CrCl<60 mL/min, (%)	100 (48)	165 (29)	<0.001
Anemia (%)	46 (22)	93 (16)	0.064
Hypoalbuminemia (%)	28 (13)	67 (12)	0.527
HbAlc (%)	6.5 ± 1.1	6.5 ± 1.3	0.876

SBP, systolic blood pressure; RAS, renal artery stenosis; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker; CrCl, Creatinine clearance; HbAlc, glycated hemoglobin.

were significantly greater than the scores in the normouricemic group (mean 8.1 ± 4.8, median 7.4, interquartile range 5.8–10.8 *vs.* mean 6.2 ± 4.0, median 6.3, interquartile range 1.8–9.2, $p<0.001$) (Table 2).

Overall, the incidence of CI-AKI was significantly different ($p<0.001$) between the two groups; CI-AKI occurred in 17 (8.1%) members of the hyperuricemic group and 8 (1.4%) members of the normouricemic group. The levels of uric acid were significantly higher in the CI-AKI group than in the group without CI-AKI (448 ± 131 *vs.* 353 ± 99 μmol/L, $p=0.001$). In-hospital mortality was significantly higher in the hyperuricemic group than in the normouricemic group (2.4% *vs.* 0.3%, $p=0.007$) (Table 3). Hyperuricemia increased the rates of CI-AKI requiring renal replacement therapy (1.4% *vs.* 0%, $p=0.004$), IABP therapy (6.2% *vs.* 2.8%, $p=0.025$), and post-procedural hypotension (5.3% *vs.* 1.9%, $p=0.011$).

A multivariate analysis (adjusted for other potential confounding factors, gender, age>75 y, CrCl<60 ml/min, multivessel coronary disease, emergent PCI, LVEF<40%, hypertension, diabetes, ACEI/ARB, IABP, exceeding maximum contrast dose, anemia, diuretic usage) revealed that the odds ratio (OR) for CI-AKI in the hyperuricemic group compared to the normouricemic group was 5.38 (95% confidence interval [CI], 1.99-14.58, $p=0.001$) (Table 4). Notably, age>75 years (OR: 3.55, 95% CI: 1.21-10.42,

Table 2 - Angiographic and procedural characteristics.

Characteristic	Hyperuricemic group (n = 211)	Normouricemic group (n = 577)	*p*-value
Number of diseased vessels	2.3 ± 0.8	2.1 ± 0.9	<0.001
Multivessel coronary disease (%)	167 (79)	398 (69)	0.005
Number of stents used	2.1 ± 1.3	2.0 ± 1.2	0.163
Total stent length (mm)	52 ± 34	47 ± 32	0.070
Type of LOCM			0.963
Iopamiron (%)	109 (52)	297 (52)	
Ultravist (%)	102 (48)	280 (48)	
Contrast amount (mL)	156 ± 69	150 ± 60	0.256
Exceeding MCD (%)	13 (6)	22 (4)	0.157
Procedure duration of (min)	88 ± 37	83 ± 37	0.087
CIN score mean (SD) ‡	8.1 ± 4.8	6.2 ± 4.0	<0.001
CIN score median (IQR) ‡	7.4 (5.8-10.8)	6.3 (1.8-9.2)	<0.001

Abbreviations: LOCM, low-osmolar contrast media.
MCD: maximum contrast dose (mL) = (5 × body weight [kg]) divided by serum creatinine (mg/dL);
‡: Scheme (Model A) to define contrast-induced nephropathy (CIN) risk score by Mehran et al. (J Am Coll Cardiol Vol. 44, No. 7, 2004).

Table 3 - Hyperuricemia and in-hospital clinical complications.

Complication	Hyperuricemic group (n = 211)	Normouricemic group (n = 577)	*p*-value
CI-AKI (%)	17 (8.1)	8 (1.4)	<0.001
Death (%)	5 (2.4)	2 (0.3)	0.007
Cause of death			0.001
Cardiogenic shock (%)	0	1 (0.2)	
Cardiac rupture (%)	1 (0.5)	1 (0.2)	
Arrhythmia (VT/VF) (%)	2 (0.9)	0	
Non-cardiac cause (%)	2 (0.9)	0	
Renal replacement therapy (%)	3 (1.4)	0	0.004
2nd myocardial infarction (%)	1 (0.5)	0	0.098
Target revascularization (%)	1 (0.5)	2 (0.3)	0.797
Acute heart failure (%)	6 (2.8)	1 (1.0)	0.095
IABP (%)	13 (6.2)	16 (2.8)	0.025
Mechanical ventilation (%)	6 (2.8)	5 (0.9)	0.078
2nd angina (%)	7 (3.3)	37 (6.4)	0.094
Tachyarrhythmia (%)	7 (3.3)	12 (2.1)	0.316
Hypotension (%)	11 (5.3)	11 (1.9)	0.011
Cerebrovascular accident (%)	1 (0.5)	1 (0.2)	0.458

VT/VF, ventricular tachycardia/ventricular fibrillation; IABP, intra-aortic balloon pump.

$p = 0.021$), emergent PCI (OR: 3.66, 95% CI: 1.40-9.55, $p = 0.008$), diuretic usage (OR: 4.87, 95% CI: 1.87-12.69, $p = 0.001$) and IABP (OR: 7.29, 95% CI: 2.29-23.15, $p = 0.001$) were retained in the final model.

DISCUSSION

The main finding of this study, which was the first to evaluate the value of HUA in predicting CI-AKI development in patients with normal baseline SCr after PCI, was that HUA was a significant and independent predictor of CI-AKI after PCI and resulted in significantly greater in-hospital mortality and incidence of CI-AKI requiring renal replacement therapy after PCI.

Pre-existing renal dysfunction has been known to be the most important risk factor for CI-AKI. At our institution, the patients with elevated baseline SCr received sufficient perioperative CI-AKI prophylaxis following the recent guidelines by the American College of Cardiology (20) and the European Society of Cardiology (21). The patients with normal SCr values, however, did not receive any prophylaxis, as they are typically thought to be at low risk. Chong et al. (22) observed that subgroups of patients with normal baseline SCr who were undergoing PCI were at risk of developing CI-AKI, which results in higher mortality. Therefore, despite normal baseline SCr values, the subgroups of patients undergoing PCI may be at higher risk of developing CI-AKI. In our study, we identified several independent risk predictors of CI-AKI in addition to baseline renal impairment. These risk predictors include older age (>75 years), emergent PCI, and IABP therapy. This is the first study in which HUA has been identified as an independent risk predictor of CI-AKI. Hence, the patients with normal baseline SCr values who have the risk factors discussed above should be considered for additional renal prophylaxis treatment.

Table 4 - Multivariate analysis of CI-AKI risk indicators.

Variable	Odds ratio	95% confidence interval	*p*-value
HUA	5.38	1.99-15.58	0.001
Gender (female)	0.96	0.33-2.81	0.942
Age>75 y	3.55	1.21-10.42	0.021
CrCl<60 ml/min	0.21	0.15-1.50	0.207
Multivessel coronary disease	1.10	0.34-3.54	0.875
Emergent PCI	3.66	1.40-9.55	0.008
LVEF<40%	1.86	0.50-6.87	0.351
Hypertension	1.89	0.64-5.59	0.250
Diabetes	0.61	0.18-2.02	0.416
ACEI/ARB	0.34	1.00-1.20	0.094
IABP	7.29	2.29-23.15	0.001
Exceeding MCD	1.84	0.31-11.10	0.504
Anemia	1.16	0.36-3.72	0.800
Diuretic usage	4.87	1.87-12.69	0.001

CrCl, Creatinine clearance; LVEF, left ventricular ejection fraction; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker; IABP, intra-aortic balloon pump; MCD, maximum contrast dose (mL) = (5×body weight [kg]) divided by serum creatinine (mg/dL).

A few studies have shown an association between HUA and the progression of kidney disease (23,24). Only two small studies, which investigated the relationship between the use of contrast agents and uric acid, have observed that contrast agents had a uricosuric effect that appeared to be caused by an increase in the renal tubular secretion of uric acid (25,26). Little information, however, is available in the literature about the relationship between HUA and the progression of CI-AKI (9,27).

Toprak et al. (14) conducted the most rigorous observational study of the value of HUA for predicting the risk of CI-AKI in patients. The subjects were patients with chronic kidney disease (SCr≥1.2 mg/dL) who were considered at high risk of developing CI-AKI. They received daily prophylaxis using a different definition for CI-AKI (an increase of 25% in creatinine) than the definition that used in the present study. The patients presented with relatively normal baseline SCr levels. Our study could be regarded as an extension of the study by Toprak et al. The results of the present study were consistent with those obtained by Toprak and colleagues; the HUA patients were at risk of developing CI-AKI. Recently, Park et al. (28) also concluded that HUA was independently associated with an increased risk of in-hospital mortality and CI-AKI in patients treated with PCI, although they performed a retrospective analysis that used a different definition of CI-AKI (an increase in SCr≥0.5 mg/dL or≥50% over baseline within seven days of

PCI). Consequently, the incidence of CI-AKI in the present study was lower than the incidence in previous studies (14,28).

An understanding of the potential pathogenic role of uric acid in acute renal failure (ARF) may be helpful for understanding the relationship between HUA and the progression of CI-AKI. Renal vasoconstriction is thought to play a pathogenic role in ARF. The mechanism for the uric acid–dependent decrease in renal blood flow seems to be the loss of nitric oxide (NO) because the vasoconstriction can be reversed with L-arginine (29). Furthermore, uric acid strongly inhibits the release of NO from endothelial cells (30,31). Uric acid increases the production of the chemotactic factor monocyte chemoattractant protein-1 (MCP-1) in vascular smooth muscle cells and enhances C-reactive protein (CRP) synthesis in human vascular endothelial and smooth muscle cells (31,32). Uric acid also inhibits endothelial cell proliferation and migration (28) and causes endothelial cell apoptosis (33).

When HUA was identified as a potentially modifiable risk factor, we became interested in evaluating its connection with CI-AKI and in-hospital adverse outcomes. Pakfetrat et al. (34) found that serum uric acid levels did not differ significantly between those patients with and without CI-AKI (34). The authors explained that they failed to find a difference because their study included a significant number of patients with normal kidney function. Chen et al. (35) found that HUA was an independent risk factor for mortality from all causes, total cardiovascular disease, and ischemic stroke in the general Taiwanese population, in high-risk groups and potentially in low-risk groups (35). In that study, HUA was significantly associated with increased in-hospital mortality, and both CI-AKI and the need for IABP therapy were significantly correlated with death. However, HUA was not a significant and independent predictor of in-hospital death. There were key differences between our study and these other studies; for example, we only recorded short-term outcomes (in-hospital *vs*. mean follow-up of 8.2 years), and we used a relatively small number of patients (788 *vs*. 146,900).

In another study of stage 3–4 CKD, HUA appeared to be an independent risk factor for all-cause and cardiovascular disease-induced mortality but not for kidney failure (36). Kowalczyk et al. (37) evaluated the impact of HUA on outcomes in patients undergoing invasive treatment for impaired renal function and acute myocardial infarction (AMI). They found that HUA was an independent risk factor for death associated with an adjusted HR of 1.38 (95% CI, 1.23–1.53) in patients with baseline kidney dysfunction ($p = 0.027$), but there was no significant increase in risk for patients with contrast-induced nephropathy ($p = 0.08$). The exact pathophysiological mechanisms behind the relationship are unknown. Uric acid, a marker of xanthine oxidase (XO) activity, reflects the generation of reactive oxygen species. In experimental studies, increased XO activity leads to oxidative stress, which is associated with heart failure after AMI (38). Published data show that both elevated and decreased serum uric acid levels negatively impacted patient outcomes, most likely because of the loss of the plasma antioxidant properties of uric acid (39). In our study, although most of the subjects had not experienced AMI and had relatively normal renal function while undergoing PCI (and thus had a relatively low risk of CI-AKI or death), we also found a significant relationship between higher serum uric acid levels and in-hospital death. However, the proportion of HUA among the patients was higher than the proportion in the study conducted by Kowalczyk et al. (37) (68% [17/25] *vs*. 35.1% [343/693]).

In the multivariate analysis, after adjusting for potential confounding factors (baseline creatinine clearance, LVEF, contrast medium volume), age>75 years, emergent PCI, and IABP therapy were retained in the final model. Because acute kidney injury may result from hemodynamic instability rather than from CI-AKI, performing elective PCI of non-infarct-related arteries in patients with multivessel disease, especially in older patients with multivessel coronary disease, may be beneficial in protecting renal function.

Our results suggested that HUA was an independent, modifiable risk factor for CI-AKI and that it significantly increased the in-hospital adverse outcomes among the patients who were undergoing coronary angiography. Measuring serum uric acid levels before PCI seems to be a useful method for assessing the risk of developing CI-AKI and short-term clinical outcomes. In addition, an increase in the serum uric acid level may serve as a disease biomarker during the perioperative period. Physicians should be encouraged to identify males whose uric acid levels approached or exceeded 7 mg/dL and females whose levels approached or exceeded 6 mg/dL, as they are the patients at high risk for CI-AKI, and prophylactic measures should be considered to preserve renal function. Another implication of this result is that uricosuric agents may be useful in treating CI-AKI in patients who have undergone PCI or other procedures. Setting a new marker for CI-AKI may motivate large-scale future studies, which may find that reducing the level of serum uric acid is an effective prophylactic strategy for treating CI-AKI.

A recent study prospectively randomized 159 patients with SCr>1.1 mg/dL undergoing cardiac catheterization and interventions to receive allopurinol (300 mg, p.o.) 24 h before the administration of a radiocontrast agent and routine hydration (40). They found that CIN occurred in 6 of 80 patients (7.5%), and the median uric acid concentration decreased from 6.8 mg/dL [3.5-13.5 mg/dL] to 6.3 mg/dL [3.1-10.4 mg/dL] 48 h after administering contrast ($p<0.0001$) in the control group, but none of the subjects developed CIN in the allopurinol patients ($p = 0.013$), whose mean uric acid concentration decreased from 6.8 mg/dL [3.3-17.2] to 5.48 mg/dL [2.1-14.6 mg/dL]. Although the authors concluded that the reduction in the prevalence of CIN after administering allopurinol might have been caused by the antioxidant capacity of allopurinol, the results clearly showed a reduction in the uric acid concentration.

Study limitations

The current study has four limitations. First, it was a prospective, observational study with a small sample size, and it was conducted in a single center over a short observation period. PCI operations and the decision to use IABP, inotropic dugs, tirofiban, beta-blockers, ACE-inhibitors, and diuretics were left to the discretion of cardiologists; therefore, the results were influenced by operator bias. In addition, to avoid introducing potential selection bias, we used serum creatinine<1.5 mg/dl as our inclusion criteria instead of creatinine clearance <60 ml/min (using the Cock-Croft-Gault formula to better assess kidney function). Second, because of the variation in the measurement times, we may have missed the peak levels of creatinine

post-procedure. The variation and the failure to carry out systematic measurements at the optimal times for determining the peak creatinine concentrations post-procedure may have led us to underestimate the true incidence of nephropathy in the current study population. Third, information about the repeated measurements of serum uric acid levels and body mass index were not available in the original data set. Fourth, although some patients had relatively normal SCr levels and did not receive the same hydration strategy (i.e., the same duration and rate of hydration) as those with elevated SCr values, these patients may have actually exhibited some degree of renal damage, and thus, the incidence of CI-AKI may be underestimated.

Our study found that CI-AKI might still develop even in patients with normal SCr levels. HUA is a significant and independent predictor of CI-AKI after PCI and results in a significant increase in in-hospital mortality and the incidence of CI-AKI requiring renal replacement therapy after PCI. Thus, despite having normal baseline SCr levels, patients with HUA, IABP, emergent PCI or older age should receive more comprehensive renal prophylaxis to reduce the occurrence of CI-AKI. The serum uric acid measurements that are taken before PCI seem to be a useful method for assessing the risk of developing CI-AKI and short-term clinical outcomes. This observation may generate hypotheses for future prospective trials that examine the effectiveness of uric acid-lowering therapies for preventing CI-AKI.

■ ACKNOWLEDGMENTS

Grants were received from the Guangdong Cardiovascular Institute and Science and Technology Planning Project of Guangdong Province (Number: 2008A030201002), China.

■ AUTHOR CONTRIBUTIONS

Liu Y, Tan N, Chen J, Zhou Y, Chen Z, Li L conceived and designed the study, analyzed and interpreted the data. Chen S drafted the manuscript and critically revised the manuscript for intellectual content. Chen L inspected and approved the final version of the manuscript. All of the authors were involved in the manuscript preparation.

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