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Heart and Vessels

ISSN 0910-8327
Volume 29
Number 2

Heart Vessels (2014) 29:191-197
DOI 10.1007/s00380-013-0347-9

Springer

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ORIGINAL ARTICLE

Elevation of urinary liver-type fatty acid-binding protein as predicting factor for occurrence of contrast-induced acute kidney injury and its reduction by hemodiafiltration with blood suction from right atrium

Hiromasa Katoh · Tsuyoshi Nozue · Yuya Kimura · Sei Nakata · Taku Iwaki · Mitsuhiro Kawano · Masa-aki Kawashiri · Ichiro Michishita · Masakazu Yamagishi

Received: 8 January 2013 / Accepted: 2 April 2013 / Published online: 20 April 2013

Abstract Although contrast-induced acute kidney injury (CI-AKI) has a great impact on patients' prognosis, few data exist regarding predictors of CI-AKI in patients with severe renal dysfunction who have undergone contrast angiography. Therefore, we prospectively studied 25 patients with renal dysfunction, which was defined as the estimated glomerular filtration rate (eGFR) level <45 ml/min/1.73 m^2, undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI). We performed hemodiafiltration with blood suction from the right atrium (RA-HDF). The mean level of urinary liver-type fatty acid-binding protein (L-FABP) at baseline was significantly higher in the CI-AKI group than in the non-CI-AKI group (59.8 ± 45.6 vs 13.4 ± 11.9 μg/gCr, $P = 0.0003$). Multivariate regression analysis demonstrated that baseline urinary L-FABP was an independent significant predictor of CI-AKI ($\beta = 0.741$, $P = 0.013$). Receiver-operating characteristic analysis showed that baseline urinary L-FABP exhibited 100 % sensitivity and 81.8 % specificity for predicting CI-AKI when the cutoff value was defined as 19.0 μg/gCr. Interestingly, the incidence of CI-AKI after CAG or PCI was reduced in the RA-HDF group in a comparison with 41 control patients (12 % vs 27 %) with eGFR level <45 ml/min/1.73 m^2 who underwent PCI before the introduction of RA-HDF. In conclusion, baseline L-FABP levels can be a predictor for occurrence of CI-AKI. We suggest that RA-HDF may prevent the development of CI-AKI in patients with severe renal dysfunction undergoing coronary procedures, although further large-scale prospective study is necessary to confirm our conclusions.

Keywords Contrast-induced acute kidney injury · Coronary procedure · Hemodiafiltration · Liver-type fatty acid-binding protein

Introduction

Contrast-induced acute kidney injury (CI-AKI) is a serious complication of diagnostic coronary angiography (CAG) or percutaneous coronary intervention (PCI). CI-AKI is frequently associated with significant in-hospital and long-term morbidity and mortality, as well as with a prolonged stay in hospital [1–5]. In addition, the clinical outcome of patients who require emergency dialysis after PCI is very poor, with an in-hospital mortality rate as high as 62 % [6, 7]. Although the most important risk factor is pre-existing chronic kidney disease (CKD) [1–3, 7], few data exist regarding the possible predictors for the occurrence of CI-AKI. Furthermore, deterioration of renal function during long-term follow-up after PCI might be associated with adverse cardiac events [8].

Although various strategies, such as the use of acetylcysteine [9], theophylline [10], calcium antagonists [11], or other renoprotective drugs, have been evaluated, hydration

H. Katoh (✉) · T. Nozue · Y. Kimura · S. Nakata · T. Iwaki · I. Michishita
Division of Cardiology, Department of Internal Medicine, Yokohama Sakae Kyosai Hospital, Federation of National Public Service Personnel Mutual Associations, 132 Katsura-cho, Sakae-ku, Yokohama 247-8581, Japan
e-mail: hiromasa_im2_m@yahoo.co.jp

M. Kawano
Division of Rheumatology and Nephrology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

M. Kawashiri · M. Yamagishi
Division of Cardiovascular Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

with 0.9 % saline is an only useful method to prevent the onset of CI-AKI [12]. Prophylactic hemodialysis (HD) after the administration of contrast medium does not prevent the development of CI-AKI in patients with renal dysfunction [13, 14]. On the other hand, Marenzi et al. [15] reported the efficacy and safety of periprocedural hemofiltration (HF). We previously reported the efficacy of a contrast removal system from the coronary sinus using an adsorbing column during CAG [16]. This suggests the possibility of blood suction from the right atrium for hemodiafiltration (HDF). Therefore, we attempted to determine the markers associated with development of CI-AKI and the possibility of hemodiafiltration with blood suction from right atrium (RA-HDF) in patients with severe renal dysfunction undergoing diagnostic CAG or PCI.

Patients and methods

Study population

The ethics committee of Yokohama Sakae Kyosai Hospital approved the protocol, and written informed consent was obtained from each patient. This study was registered in the UMIN protocol registration system under identification number UMIN000003145.

We recruited patients with CKD from 2126 patients who were scheduled to undergo CAG or PCI at our institution between February 8, 2010, and December 31, 2011. The inclusion criterion were estimated glomerular filtration rate (eGFR) level <45 ml/min/1.73 m^2, which was calculated using the modified Modification of Diet in Renal Disease (MDRD) equation [17]: eGFR (ml/min/1.73 m^2) = 194 × serum Cr (mg/dl)$^{-1.094}$ × Age (years)$^{-0.287}$ (× 0.739 for female subjects). Exclusion criteria were as follows: acute coronary syndrome, cardiogenic shock, congestive heart failure, pregnancy, dehydration, intravascular administration of contrast medium within the previous 7 days, chronic dialysis, and history of allergy to the contrast medium. A nonionic, low-osmolality contrast medium (Iopamidol 370; Bayer, Berlin, Germany) was used in all patients.

Among the patients who had undergone elective PCI at our hospital from January 2008 to December 2009, those with eGFR level of less than 45 ml/min/1.73 m^2 were selected as the control group. Exclusion criteria for this group were the same as those for the RA-HDF group.

Study protocol

Each patient was admitted to our hospital 1 day before the scheduled coronary procedure, and serum and urinary parameters were measured and echocardiography performed before starting the hydration process. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method.

All patients were continuously administered 0.9 % saline by intravenous infusion at a rate of 1 ml/kg/h for 24 h from 12 h before the coronary procedure. Serum and urinary parameters were measured at 24 and 48 h. Additional measurements of serum markers were performed at 1 week and 1 month. RA-HDF was started 30 min before the scheduled coronary procedure and continued until 30 min after the procedure.

CI-AKI was defined as an absolute increase of serum creatinine (Cr) level at least 0.3 mg/dl, or a relative increase of serum Cr level more than 25 % from the baseline value within 1 week after the administration of contrast medium [13–15, 18]. We calculated the contrast-induced nephropathy (CIN) risk score [19] of all patients after the coronary procedures. These patients were followed up for more than 10 months (median follow-up period: 19 months).

Laboratory determinations

Serum cystatin C (CysC) was measured by particle-enhanced immunonephelometry on a Behring nephrometer system (Dade Behring, Tokyo, Japan) [20]. Urinary liver-type fatty acid-binding protein (L-FABP) was measured by specific enzyme-linked immunosorbent assay [21]. Urinary *N*-acetyl-β-D-glucosaminidase (NAG) was determined by spectrophotometry. Serum β_2-microglobulin (β_2-MG) was measured by latex agglutination turbidimetry. All urinary markers were corrected by the value of urinary Cr.

Periprocedural hemodiafiltration with blood suction from the right atrium

We used an 8-F and 60-cm straight sheath (XEMEX Introducer set Anti-kinking type Long; Zeon Medical, Tokyo, Japan) as a blood-suction catheter with 4 hand-made side holes near the tip of the sheath. This sheath was inserted into the right atrium from the right femoral vein and located near the orifice of the coronary sinus. Blood passed through a continuous hemofilter (EXCELFLO AEF-10; Asahi Kasei Kuraray Medical, Tokyo, Japan) and returned to a superficial vein of a lower limb or left femoral vein. HDF was performed using isotonic replacement fluid (SUBPACK-Bi; Nipro, Osaka, Japan) and its conditions were as follows: quantity of blood flow 100 ml/min, dialysate flow rate 4000 ml/h, filtration flow rate 1500 ml/h.

Statistical analysis

Statistical analyses were performed using StatView 5.0 for Windows (SAS Institute, Cary, NC, USA) and Statistical

Package for the Social Sciences version 19.0 (SPSS, Chicago, IL, USA). Results are expressed as the mean ± standard deviation (SD). Differences in continuous variables between the two groups were compared by unpaired *t* test when the variable showed a normal distribution or by the Mann–Whitney *U* test when it did not. Categorical variables between the two groups were compared by the Chi-square test or Fisher exact test. Univariate analysis was performed to determine the factors that correlated with the occurrence of CI-AKI. Univariate predictors whose level of significance was $P < 0.1$ were entered into the multivariate regression model. The receiver-operating characteristic (ROC) was analyzed to determine the cutoff value of baseline urinary L-FABP for predicting CI-AKI. A probability value of $P < 0.05$ was considered statistically significant.

Results

Marker for the development of CI-AKI under RA-HDF

A total of 25 patients (23 men, mean age 80 years) who met the criterion were entered. Among them, CI-AKI was observed in 3 patients. There were no significant differences in baseline clinical characteristics between patients with or without CI-AKI (Table 1).

Regarding serum and urinary markers, there were no significant changes in serum markers at any time point in the CI-AKI group, although the level of serum β_2-MG at baseline was higher (7.50 ± 4.34 vs 4.75 ± 1.78 mg/l, $P = 0.047$) and that of serum CysC tended to be higher in the CI-AKI group than in the non-CI-AKI group (Table 2). Interestingly, the levels of urinary L-FABP and NAG in the CI-AKI group were significantly higher both at baseline (59.8 ± 45.6 vs 13.4 ± 11.9 μg/gCr, $P = 0.0003$ and 17.5 ± 11.4 vs 9.6 ± 5.4 U/gCr, $P = 0.049$, respectively) and at 24 h (82.0 ± 107.8 vs 17.5 ± 18.3 μg/gCr, $P = 0.008$ and 25.4 ± 23.2 vs 8.7 ± 4.7 U/gCr, $P = 0.003$, respectively) than those in the non-CI-AKI group.

The univariate analysis revealed that six markers, namely blood urea nitrogen, hemoglobin, serum CysC, serum β_2-MG, urinary L-FABP, and urinary NAG at the baseline, were associated with predicting CI-AKI. Among them, multivariate regression analysis demonstrated that baseline urinary L-FABP was an independent significant predictor of CI-AKI ($\beta = 0.741$, $P = 0.013$) (Table 3). When we performed ROC analysis to determine the optimal cutoff value of baseline urinary L-FABP as a predictor of CI-AKI, urinary L-FABP level exhibited 100 % sensitivity and 81.8 % specificity for predicting CI-AKI at a cutoff value of 19.0 μg/gCr, with the area under the curve of 0.92 (Fig. 1).

Table 1 Baseline clinical characteristics of patients with and without CI-AKI in the RA-HDF Group

Variables	CI-AKI ($n = 3$)	Non-CI-AKI ($n = 22$)	*P* value
Age (years)	83 ± 7	79 ± 8	0.39
Gender (male/female)	2/1	21/1	0.23
BMI (kg/m^2)	23.0 ± 1.6	23.8 ± 3.3	0.70
LVEF (%)	46 ± 6	55 ± 12	0.27
BNP (pg/ml)	420 ± 494	188 ± 206	0.14
Hb (g/dl)	9.9 ± 2.3	11.8 ± 1.6	0.09
BUN (mg/dl)	47.3 ± 21.6	31.2 ± 12.0	0.059
Cr (mg/dl)	2.5 ± 1.2	1.9 ± 0.7	0.19
eGFR (ml/min/1.73 m^2)	22 ± 12	29 ± 9	0.25
CKD stage (Stage 3/4/5)	1/1/1	10/10/2	0.48
CIN risk score[a]	15.3 ± 5.1	12.8 ± 2.8	0.20
Volume of contrast media (ml)	78 ± 3	98 ± 33	0.31
Contrast media volume/eGFR	4.7 ± 3.4	3.9 ± 2.3	0.57
Volume used for hydration (ml)	1368 ± 168	1497 ± 225	0.35
Running time of RA-HDF (min)	87 ± 16	97 ± 28	0.57
Diabetes mellitus (%)	2 (67)	15 (68)	0.99
Hypertension (%)	3 (100)	22 (100)	–
Anemia (%)	3 (100)	18 (82)	0.99
ACE inhibitors or ARBs (%)	3 (100)	19 (86)	0.99
Diuretics (%)	3 (100)	11 (50)	0.23

Data are expressed as the mean ± SD or number (%)

RA-HDF hemodiafiltration with blood suction from the right atrium, *CI-AKI* contrast-induced acute kidney injury, *BMI* body mass index, *LVEF* left ventricular ejection fraction, *BNP* brain natriuretic peptide, *Hb* hemoglobin, *BUN* blood urea nitrogen, *Cr* creatinine, *eGFR* estimated glomerular filtration rate, *CIN* contrast-induced nephropathy, *ACE* angiotensin-converting enzyme, *ARB* angiotensin-receptor blocker

[a] Ref. [19]

Application of RA-HDF and its long-term results

In addition to the original 25 patients, 41 other patients with eGFR level <45 ml/min/1.73 m^2 (33 men, mean age 75 years) were selected as the control group in the study with RA-HDF.

The hemodynamics of the patients did not change throughout the procedure, and no complications associated with RA-HDF occurred. Baseline clinical, biochemical, and procedural characteristics of the subjects are shown in Table 4. In the RA-HDF group, the mean age of the patients was higher (80 ± 8 vs 75 ± 7 years, $P = 0.008$) and baseline renal function was worse (serum Cr 2.0 ± 0.8 vs 1.7 ± 0.9 mg/dl, $P = 0.002$; eGFR 28 ± 9 vs 36 ± 7 ml/min/1.73 m^2, $P = 0.0004$) than those of the controls.

Table 2 Serial changes of serum and urinary markers

Variables	All patients (n = 25)	CI-AKI (n = 3)	Non-CI-AKI (n = 22)	P value
Serum CysC (mg/l)				
Baseline	2.20 ± 0.70	2.85 ± 1.27	2.12 ± 0.58	0.09
At 24 h	2.03 ± 0.65‡	2.65 ± 0.94	1.94 ± 0.58§	0.08
At 48 h	2.05 ± 0.67‡	2.75 ± 1.05	1.96 ± 0.57‡	0.051
Serum β_2-MG (mg/l)				
Baseline	5.08 ± 2.28	7.50 ± 4.34	4.75 ± 1.78	0.047
At 24 h	4.92 ± 2.37	7.20 ± 3.84	4.61 ± 2.04	0.08
At 48 h	5.07 ± 2.52	7.87 ± 4.63	4.69 ± 1.99	0.04
Urinary L-FABP (μg/gCr)				
Baseline	19.0 ± 23.1	59.8 ± 45.6	13.4 ± 11.9	0.0003
At 24 h	25.3 ± 41.5	82.0 ± 107.8	17.5 ± 18.3	0.008
At 48 h	13.7 ± 13.4	15.4 ± 8.8	13.5 ± 14.0	0.82
Urinary NAG (U/gCr)				
Baseline	10.6 ± 6.6	17.5 ± 11.4	9.6 ± 5.4	0.049
At 24 h	10.7 ± 9.8	25.4 ± 23.2	8.7 ± 4.7	0.003
At 48 h	8.7 ± 4.4*	11.7 ± 5.3	8.3 ± 4.2	0.21

Data are expressed as the mean ± SD

CI-AKI contrast-induced acute kidney injury, *Cr* creatinine, *CysC* cystatin C, *β_2-MG* β_2-microglobulin, *L-FABP* liver-type fatty acid-binding protein, *NAG* *N*-acetyl-β-D-glucosaminidase

* $P < 0.05$, ‡ $P < 0.001$, § $P < 0.0001$ compared with the baseline value

Table 3 Predictors of CI-AKI

Variables	β	P value
BUN (mg/dl)	0.266	0.35
Hb (g/dl)	0.096	0.70
Serum CysC (mg/l)	0.065	0.91
Serum β_2-MG (mg/l)	0.356	0.58
Urinary L-FABP (μg/gCr)	0.741	0.013
Urinary NAG (U/gCr)	0.219	0.25

For abbreviations, see Tables 1 and 2

All variables were measured at baseline

Although there was no difference in the ratio of contrast medium volume to eGFR (4.0 ± 2.4 vs 4.7 ± 2.3, P = 0.21) between the two groups, the frequency of CI-AKI was lower (12 vs 27 %, P = 0.26) in the RA-HDF group. In the CI-AKI group, the level of serum Cr returned to its baseline value at 1 month and that of CysC did not increase throughout the follow-up period (Fig. 2). None of the patients who developed CI-AKI required emergency or continuous dialysis. Only one patient who developed CI-AKI died due to sepsis 19 months after the procedure.

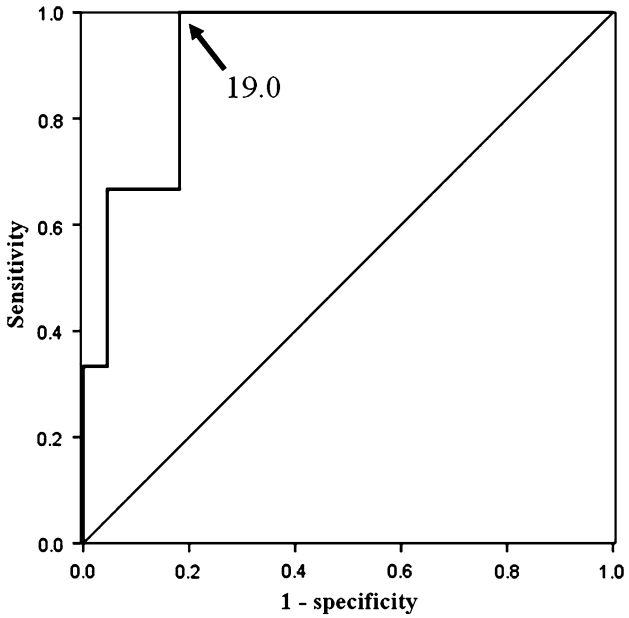

Fig. 1 Receiver-operating characteristic analysis. At a cutoff value of >19.0 μg/gCr, baseline urinary liver-type fatty acid-binding protein exhibited 100 % sensitivity and 81.8 % specificity for detecting contrast-induced acute kidney injury in patients treated with the periprocedural hemodiafiltration with blood-suction from the right atrium

Discussion

The present study demonstrates that the levels of urinary and serum markers such as L-FABP, NAG, CysC, and β_2-MG at baseline were all higher in patients who developed CI-AKI than in those without CI-AKI. Among these markers, urinary L-FABP level at the baseline was the only independent predictor of CI-AKI after multivariate regression analysis when its cutoff value was 19.0 μg/gCr.

The pathogenesis of increased urinary L-FABP in patients who develop CI-AKI is not well understood. Nevertheless, Kamijo et al. [22, 23] reported that urinary excretion of L-FABP might reflect various kinds of stresses that cause tubulointerstitial damage, and may be a useful clinical marker of progression of chronic renal disease. Nakamura et al. [24] reported that baseline urinary L-FABP was significantly higher in the CI-AKI group than in the non-CI-AKI group, suggesting a predictive marker for CI-AKI in patients with moderate CKD. Consistent with these reports, the present study suggests that baseline urinary L-FABP may be useful in predicting the development of CI-AKI in patients with moderate to severe renal dysfunction.

Previously, several studies demonstrated the usefulness of baseline serum CysC as a predictor of CI-AKI [25, 26]. Kato et al. [25] reported a cutoff value of serum CysC for detecting CI-AKI was 1.2 mg/l, and Artunc et al. [26]

Table 4 Baseline clinical, biochemical, and procedural characteristics of the subjects

Variables	RA-HDF group (n = 25)	Control group (n = 41)	P value
Age (years)	80 ± 8	75 ± 7	0.008
Gender (male/female)	23/2	33/8	0.30
Height (cm)	161.4 ± 7.3	162.7 ± 7.6	0.48
Body weight (kg)	61.7 ± 9.2	64.6 ± 11.6	0.29
BMI (kg/m^2)	23.7 ± 3.1	24.3 ± 3.3	0.47
Cr (mg/dl)	2.0 ± 0.8	1.7 ± 0.9	0.002
eGFR (ml/min/1.73 m^2)	28 ± 9	36 ± 7	0.0004
CKD stage (Stage 3/4/5)	11/11/3	34/6/1	0.004
CIN risk score[a]	13.1 ± 3.1	12.9 ± 4.0	0.78
Volume of contrast media (ml)	96 ± 31	159 ± 55	0.0001
Contrast media volume/eGFR	4.0 ± 2.4	4.7 ± 2.3	0.21
Procedure type (CAG/PCI)	14/11	0/41	0.0001
Volume used for hydration (ml)	1482 ± 220	1671 ± 326	0.01
Diabetes mellitus (%)	17 (68)	31 (76)	0.50
Hypertension (%)	25 (100)	30 (73)	0.005
Anemia (%)	21 (84)	28 (68)	0.25
Medication			
ACE inhibitors or ARBs (%)	22 (88)	19 (46)	0.0007
Statins (%)	17 (68)	20 (49)	0.13

Data are expressed as the mean ± SD or number (%)

RA-HDF hemodiafiltration with blood suction from the right atrium, *BMI* body mass index, *Cr* creatinine, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease, *CIN* contrast-induced nephropathy, *CAG* coronary angiography, *PCI* percutaneous coronary intervention, *ACE* angiotensin-converting enzyme, *ARB* angiotensin-receptor blocker

[a] Ref. [19]

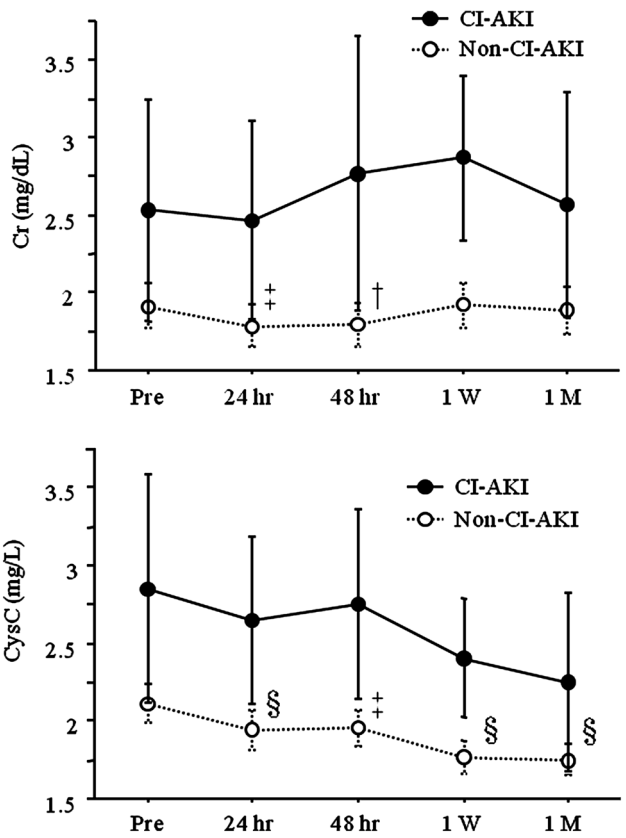

Fig. 2 Serial changes in levels of serum creatinine (*Cr*) and cystatin C (*CysC*). In the contrast-induced acute kidney injury group (*CI-AKI*), the level of serum creatinine returned to its baseline value at 1 month and that of cystatin C did not increase throughout the follow-up period. Data are expressed as the mean ± SE. † $P < 0.01$, ‡ $P < 0.001$, § $P < 0.0001$ compared with the baseline value

reported that this value was 1.3 mg/l. However, these studies involved subjects with mild to moderate renal dysfunction, and we enrolled patients with severe renal dysfunction. In addition, the mean baseline serum CysC level was quite higher than previously reported cutoff levels. Thus, we speculate that serum CysC might not work as a useful predictor for CI-AKI, because the patients enrolled in this study had a high risk profile.

In the present study, the incidence of CI-AKI was reduced by introducing periprocedural RA-HDF. In patients with severe CKD whose baseline urinary-L-FABP is less than 19.0 μg/gCr, periprocedural RA-HDF may be useful in preventing the development of CI-AKI. Mehran et al. [19] reported that the frequency of the CI-AKI in patients with a high risk profile (CIN risk score 11–15) was 26.1 %. In our control group, the mean CIN risk score was 12.9 ± 4.0, and the frequency of CI-AKI in this group was 27 %. However, despite the high risk profile, CI-AKI developed only in 3 of 25 patients (12 %) treated with periprocedural RA-HDF.

Regarding long-term results, the renal function of patients who developed CI-AKI improved within 1 month after the administration of contrast medium, and the increase in serum Cr level did not last during the follow-up period. Moreover, during a follow-up period of 1–2 years, none of these patients required the continuous HD.

Prophylactic HD has been demonstrated to be of no benefit even when being started just after coronary procedures [13, 14, 27]. One of the possible reasons for the lack of efficacy of the previous studies may be explained by the rapid onset of renal injury following administration of contrast medium. Renal hypoperfusion has been noted within 20 min after the injection of contrast medium, suggesting that renal injury may occur at its first renal hemodynamic passage [27, 28]. In the present study, we

started RA-HDF 30 min before the administration of the contrast medium. Moreover, blood was drawn from the right atrium near the orifice of the coronary sinus. For these reasons, contrast medium injected into a coronary artery could be effectively removed by this method in comparison with the postprocedural HD previously reported.

Study limitations

The present study has several limitations. With respect to RA-HDF, there were no data on predictive markers in the control group. However, the incidence of CI-AKI in the RA-HDF group was reduced by the present procedure, although patients of both groups had the same high risk profiles and ratios of contrast medium volume to eGFR. This suggests the possibility of RA-HDF for the prevention of CI-AKI. The removal ratio of contrast medium by RA-HDF remains an unknown quantity. The previous study showed that HDF removed contrast medium more effectively than conventional low-flux HD and HF [29]. Because the extraction ratio of contrast medium was reported to be higher in HDF than that in low-flux HD and HF, this effect can explain why RA-HDF worked favorably in preventing CI-AKI. Klarenbach et al. [30] reported that prophylactic hemofiltration might be potentially cost-effective in patients at high risk for CI-AKI. The cost-effectiveness of RA-HDF was not evaluated in this study, but we believe that RA-HDF would be more cost-effective. Because RA-HDF can be carried out in the catheterization laboratory and did not require the intensive care unit setting, it is possible to save time by performing contrast removal, which is a shorter procedure than prophylactic hemofiltration [15]. Finally, the small number of patients at a single center with a nonrandomized, single-arm design might result in insufficient statistical power to evaluate the usefulness of RA-HDF in preventing the development of CI-AKI. Therefore a large-scale prospective study is necessary to confirm our conclusions.

Conclusions

The present study demonstrates that baseline urinary L-FABP levels can be a predictor for the occurrence of CI-AKI after coronary procedures with contrast agents. We suggest that periprocedural RA-HDF may prevent the development of CI-AKI in patients with severe renal dysfunction undergoing coronary procedures, although further large-scale prospective study is necessary to confirm our conclusions.

Conflict of interest The authors have no conflict of interest to disclose.

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