Early Renal-Protective Effects of Remote Ischemic Preconditioning in Elderly Patients with Non-ST-Elevation Myocardial Infarction (NSTEMI)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF Suzhen Guo
CDE Lian Jian
CD Degang Cheng
DE Li Pan
E Shaoying Liu
AEFG Chengzhi Lu

Department of Cardiology, Tianjin First Central Hospital, Tianjin, P.R. China

Corresponding Author: Chengzhi Lu, e-mail: luchzhtj@163.com
Source of support: This work was supported by the Pilot Fund (LHJJ20158630)

Background: With the wide clinical application of angiography, contrast-enhanced nephropathy (CIN) has become the third-leading cause of acute kidney injury (AKI). Remote ischemic preconditioning (RIPC) is a non-fatal ischemia-reperfusion injury that can provide protection against lethal ischemia-reperfusion. This study aimed to assess the effect of RIPC on CIN in elderly patients with non-ST-elevation myocardial infarction (NSTEMI).

Material/Methods: Patients were randomly divided into 2 groups with 119 patients in each group treated with interventional therapy. Patients in the RIPC group received distal ischemic preconditioning 2 h before contrast exposure, while patients in the control group received a sham RIPC procedure. Incidence of CIN was the primary outcome. Changes in creatinine, NGAL, and KIM-1 after contrast administration were secondary outcomes.

Results: CIN occurred in a total of 27 (12.3%) patients, including 12 (10.1%) in the RIPC group and 15 (15.1%) in the control group (P=0.329). RIPC treatment significantly reduced the levels of NGAL (P=0.024) and KIM-1 (P=0.007) at 12 h after contrast administration, suggesting RIPC treatment reduces sub-clinical renal damage. Subgroup analysis revealed that significant reduction of KIM-1 and NGAL by RIPC, mainly occurring in patients with a Mehran risk score of 6–10.

Conclusions: Although RIPC did not significantly reduce CIN incidence in elderly patients with NSTEMI, the application of more sensitive biomarkers – NGAL and KIM-1 – indicated a reduction of sub-clinical renal damage by RIPC, especially in the early stage of injury. As a simple and well-tolerated method, RIPC may be a potentially feasible option to prevent CIN.

MeSH Keywords: Acute Kidney Injury • Biomarkers, Pharmacological • Creatinine • Myocardial Infarction

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/917442

📄 2629   📊 3   📈 2   📚 28

Background

With the wide clinical application of angiography, contrast-enhanced nephropathy (CIN) has become the third-leading cause of acute kidney injury (AKI) [1–3]. The incidence of CIN is relatively high, ranging from 10% to 58%. It has been reported to be associated with approximately 6% in-hospital mortality [1,4]. CIN also increases the length of hospital stay and cost of hospitalization, imposing a heavy medical burden on society. Therefore, it is crucial to develop effective and safe strategies for CIN prevention and treatment.

Currently, the diagnosis of CIN is primarily based on an increase of serum creatinine within 48–72 h after contrast exposure, without other obvious causes [1–3]. However, serum creatinine is not reliable and is always delayed in indicating AKI [5], and more than half of kidney function may have been lost before serum creatinine starts to rise [6]. In the past decade, several new biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1), have been discovered for early detection of AKI [3,7–9]. Human NGAL, also known as lipocalin-2 (LCN2), is a 25-kDa protein covalently bound to neutrophil gelatinase. Several studies reported that NGAL could be a predictive biomarker of CIN during coronary angiography with intra-arterial contrast media administration [10–14]. The overall AUC-ROC of NGAL to predict CIN was 0.894 (95% CI, 0.732-0.892) during coronary angiography within 6 h after contrast media administration [14]. KIM-1, a transmembrane glycoprotein, is not expressed in healthy kidneys, but elevated after kidney injury. Tu et al. found that KIM-1 increased significantly by 6 h after ICU admission in patients with septic AKI, while serum creatinine started to rise after 24 h, indicating its potential clinical application as an early biomarker in the diagnosis of septic AKI [9]. In the present study, we assessed the level of serum creatinine and observed the changing trend of NGAL and KIM-1.

Remote ischemic preconditioning (RIPC) is a non-fatal ischemia-reperfusion injury that provides protection against lethal ischemia-reperfusion in other organs or tissues [15]. Previous studies showed that RIPC was able to increase myocardial salvage and protect against CIN in patients with ST-elevation myocardial infarction (STEMI) [16,17]. However, the role of RIPC on CIN in patients with non-ST-elevation myocardial infarction (NSTEMI) is still not clear. Here, we evaluated the effect of RIPC on CIN in patients with NSTEMI who underwent interventional therapy.

Material and Methods

Subjects

From March 2015 to October 2017, 260 patients with NSTEMI who underwent interventional therapy in the First Central Hospital of Tianjin were assessed for eligibility in this study. Twenty-two patients refused to participant. Patients aged >65 years with creatinine clearance >30 ml/min/1.73 m^2 were included.

Patients were randomly divided into 2 groups (the RIPC and control group, n=119 in each group) with a computer-generated block randomization stratified according to GRACE classification and creatinine clearance. Two patients (1 from each group) withdrew from the study due to intolerance to the upper-arm pressure. Two patients (1 from each group) were excluded due to contrast agent dose >300 ml, and 9 patients (5 from RIPC group, 4 from control) were excluded due to contrast agent dose <50 ml. Five patients (2 from the RIPC group and 3 from the control group) were lost during follow-up. Therefore, data from 110 patients in each group were reported. The detailed trial profile is shown in Figure 1. The study was approved by the Tianjin First Central Hospital Ethics Committee of Clinical Research Projects. Informed consent was obtained from all patients.

Procedures

In the RIPC group, RIPC was performed with 3 cycles of alternating 5-min inflation/5-min deflation of the upper arm 2 h before contrast agent administration to induce transient and repetitive arm ischemia and reperfusion. The maximum inflation of the blood pressure cuff was 200 mmHg.

In the control group, sham RIPC was performed with an uninflated pressure cuff on the upper arm for 30 min. The hydration procedure was initiated 6 h prior to interventional treatment with intravenous injection of isotonic saline (60 ml/h), and was continued for 6 h after PCI. When there were no contraindications, all patients continued to take their previous medications, such as regular dose of dual anti-platelet drugs (aspirin and clopidogrel), regular statins, receptor blockers, and vascular conversion enzyme inhibitors.

Outcomes

Incidence of CIN was the primary outcome. CIN was defined as a ≥25% relative increase in serum creatinine from baseline or an absolute increase from baseline above 0.5 mg/dl within 48–72 h after contrast medium exposure. Here, we chose 48 h after contrast administration to detect serum creatine, as previously reported [5,18].
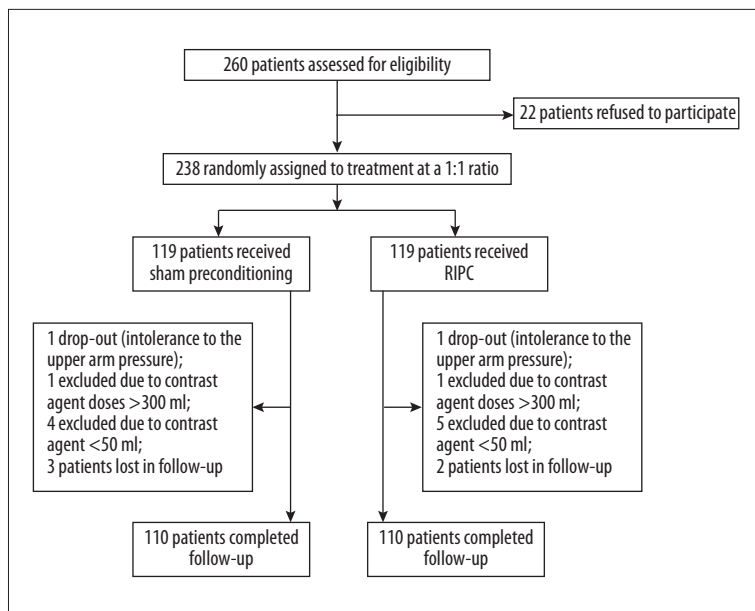
Figure 1. Study flow chart.

Changes in creatinine from baseline to 48 h and changes in NGAL and KIM-1 from baseline to 12 and 48 h after contrast administration were used as secondary outcomes.

Data collection

Baseline characteristics were recorded at admission for all patients, including sex, age, BMI (body mass index), medical history (hypertension, diabetes, dyslipidemia, and smoking), family history, blood glucose, medication, and baseline cardiac function grade. BMI was calculated as follows: BMI=body weight (kg)/height (m)^2. In addition, contrast agent dosage, laboratory biochemical indicators, preoperative creatinine clearance, perioperative blood pressure, and the duration of PCI procedure were also recorded.

Elbow venous blood was routinely collected preoperatively and 12 and 48 h postoperatively from each patient. Blood samples were centrifuged at 3000 rpm for 10 mins and stored at −18°C. Conventional coronary angiography or PCI was performed. The intraoperative medication and surgical options were performed according to medical routines. No intraoperative or postoperative complications were observed. The characteristics of coronary artery lesions were recorded, including the number of lesion vessels, the target vessel site, and the number of stents implanted. All patients were treated with isotonic contrast agent (Whistler Parker, General Electric Pharmaceutical Shanghai Co.) to record the amount of contrast agent. Contrast agent doses <50 ml or >300 ml were excluded from the study. Renal function was measured. All patients were followed up for 1 month after intervention therapy. The levels of NGAL and KIM-1 were detected.

Measurement of NGAL and KIM-1

All patients were assessed for NGAL and KIM-1. The levels of NGAL and KIM-1 were detected in Tianjin First Central Hospital using enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Inc., Minneapolis, USA). The tests were performed in strict accordance with the instructions of the reagents and equipment suppliers.

Statistical analysis

Currently, limited clinical data are available for estimation of the incidence rate of CIN in elderly patients with NSTMI. As previously reported, the incidence of CIN is between estimated to be 15–30% [15,18] . We calculated the sample size based on this estimate, and assumed a minimum difference of 10% as a clinically important difference between groups regarding the incidence rate of the primary endpoint [5,18]. Therefore, at least 68 patients were needed in each group to ensure such a reduction to be detected (power 90%, α=0.05).

The data were stored and analyzed using SPSS 24.0 (SPSS, Chicago, IL). *P* values <0.05 were considered to be statistically significant. The distribution of continuous variables was assessed using Q-Q plots, histogram analysis, and standard deviation tests. The Kolmogorov-Smirnov test was used to test whether a variable was normally distributed. The *t* test was used for normally distributed continuous variables and the non-parametric Mann-Whitney-Wilcoxon test was used for non-normally distributed continuous variables. The chi-square test was used for categorical variables. Paired tests were used to determine intra-group differences of parameters before and after treatment (or parameters at different timepoints)

Table 1. Baseline characteristics of patients.

Item	RIPC group (n=110)	Control group (n=110)	P
Age (years)	71.69±6.69	70.81±6.27	0.433
Male, n (%)	68 (61.8)	62 (56.4)	0.250
BMI	23.6±3.5	23.8±4.2	0.254
Diabetes, n (%)	42 (38.2)	46 (41.8)	0.510
Systolic blood pressure, mmHg	145.5±26.2	149.5±25.8	0.413
Diastolic blood pressure, mmHg	72.2±12.5	70.6±11.4	0.648
LDL (mmol/L)	2.90±1.007	2.98±0.92	0.721
Hemoglobin (g/L)	131±23.2	133±15.6	0.428
Troponin-I peak (u/L)	8.04±15.7	7.7±17.3	0.660
hsCRP (mg/L)	7.11±2.11	7.26±2.91	0.590
BNP (pg/ml)	468±431	365±615	0.708
GRACE score	108±23	107±22	0.384
Creatinine (mg/dl)	0.82±0.20	0.85±0.25	0.437
eGFR (ml/min/1.73 m^2)	80.95±25.38	79.53±27.00	0.798
NGAL (ng/ml)	104.8±24.47	112.42±29.61	0.104
KIM-1 (ng/ml)	45.26±11.43	46.42±14.76	0.612
Lesion location			
Single-vessel disease, n (%)	31 (28.2)	27 (24.5)	0.646
Two-vessel disease, n (%)	42 (38.2)	43 (39.1)	0.980
Three-vessel disease, n (%)	37 (33.6)	40 (36.4)	0.778
Left main coronary artery disease, n (%)	17 (15.5)	15 (13.6)	0.849
Medications in use			
ACEI/ARB, n (%)	98 (89.1)	94 (85.5)	0.545
Beta blocker, n (%)	85 (77.3)	82 (74.5)	0.753
Diuretics, n (%)	27 (24.5)	21 (19.1)	0.415
Statin, n (%)	102 (92.7)	106 (96.4)	0.374
Sulfonylureas hypoglycemic agents, n (%)	25 (22.7)	22 (20.0)	0.742
Contrast dosage (ml)	141±59.5	143±58.7	0.814
Duration of PCI procedure (min)	57±25	62±22	0.117

within each group, and unpaired tests were used to evaluate inter-group differences of specific parameters between the RIPC and control group.

A subgroup analysis was carried out based on the Mehran risk score, as previously reported in a trail protocol [12]. The Mehran risk score system is a well-validated system including both clinical and procedural variables. It consists of 3 risk classes of developing CIN: low (risk score ≤5), moderate (score 6–10), and high (score ≥11). In the present study, a subgroup analysis

was performed in which all patients were classified based on Mehran risk score.

Results

Baseline characteristics of all patients are shown in Table 1. No significant differences were observed regarding patients' age, sex, and BMI between the RIPC group and control group. Baseline levels of creatinine and eGFR were not significantly different

Table 2. Comparison of changes in biomarkers of renal injury between the 2 groups.

	RIPC group (n=110)	Control group (n=110)	P
Change in creatinine from baseline to 48 h, mg/dl	0.02±0.14	0.06±0.09	0.053
Change in NGAL from baseline to 12 h, ng/ml	11.58±18.01	18.34±15.35	0.02
Change in NGAL from baseline to 48 h, ng/ml	7.81±14.93	9.74±9.74	0.377
Change in KIM-1 from baseline to 12 h, ng/ml	5.04±8.76	10.88±14.71	0.01
Change in KIM-1 from baseline to 48 h, ng/ml	3.39±9.69	5.26±8.19	0.23
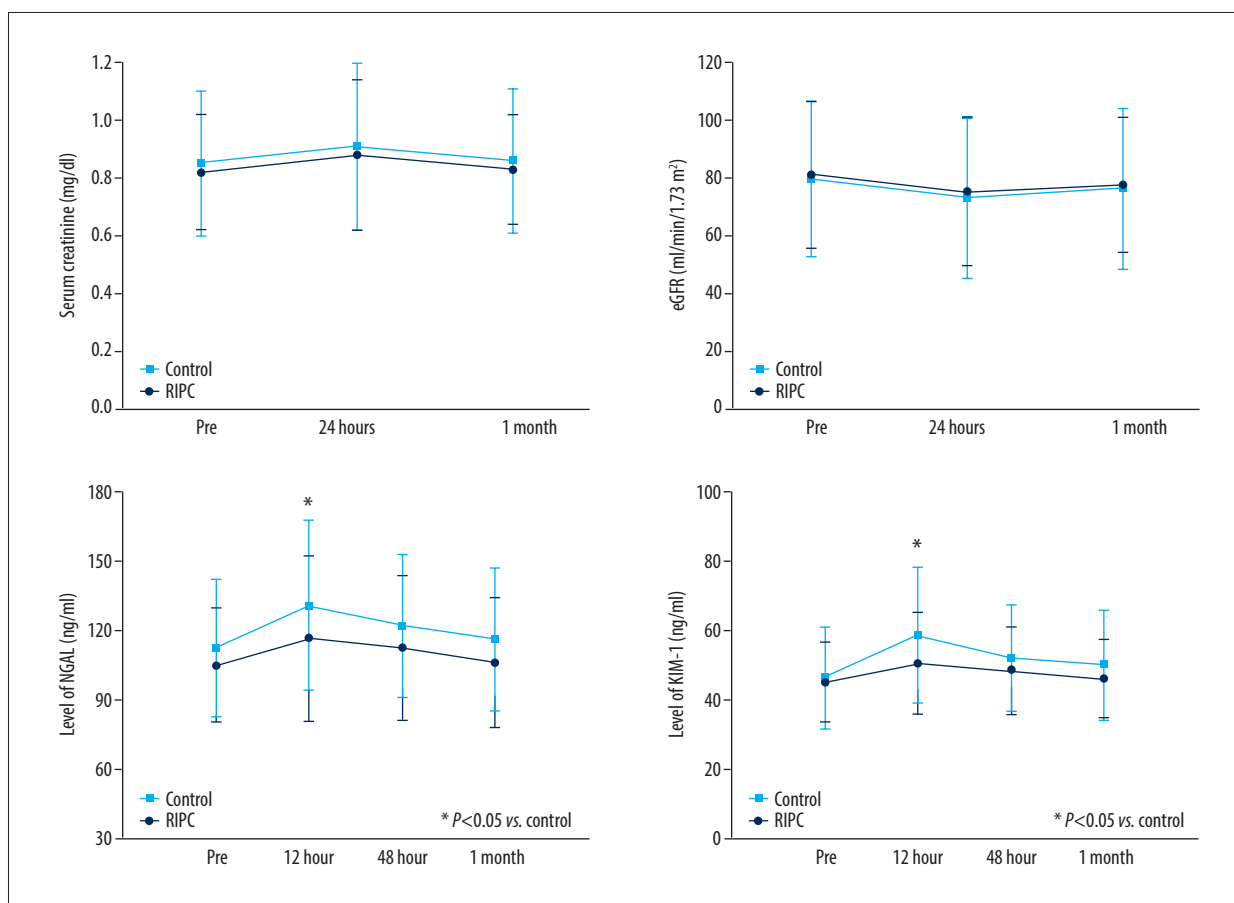
Figure 2. Levels of creatinine, eGFR, NGAL, and KIM-1 at different timepoints after surgery. * $P<0.05$ *vs.* control group.

between the 2 groups (for control and RIPC, respectively: serum creatinine, 0.85±0.25 *versus* 0.82±0.20 mg/dl; creatine clearance, 79.53±27.00 versus 80.95±25.38 ml/min/1.73 m²). Similar contrast dosages were used in both groups, with 143±58.7 versus 141±59.5 ml for the control and RIPC group, respectively. The duration of the PCI procedure was 62±22 min in the control group and 57±25 min in the RIPC group.

CIN occurred in 12 (10.1%) patients in the RIPC group and in 18 (15.1%) in the control group. RIPC did not significantly change the incidence of CIN (P=0.329). No significant effect

of RIPC was observed with regard to the change in creatinine from baseline to 48 h after contrast administration (Table 2). None of the patients required hospitalization or dialysis treatment due to CIN. One patient with left main coronary artery disease combined with three-vessel disease developed CIN and died of heart failure 2 weeks after partial revascularization.

The changes in NGAL and KIM-1 levels after RIPC were quite interesting. NGAL and KIM-1 levels peaked at 12 h after contrast administration (Figure 2). Although both NGAL and KIM-1 were elevated in both groups with or without RIPC, the levels

Table 3. Changes in serum creatinine, KIM-1, and NGAL per group stratified by Mehran risk score.

Mehran risk score	Group	n	Change in serum creatine (mean±SD)	P	Change in KIM-1 (mean±SD)	P	Change in NGAL (mean±SD)	P
≤5	Control	30	0.0486±0.0581	0.834	4.23±5.64	0.815	24.6±20.9	0.004
	RIPC	34	0.0538±0.0939		3.62±10.1		5.42±17.3	
6–10	Control	50	0.102±0.112	0.149	9.33±10.0	<0.001	27.5±20.5	<0.001
	RIPC	47	0.0564±0.120		−1.43±9.90		2.26±18.8	
≥11	Control	30	0.000±0.193	0.251	1.15±6.32	0.584	21.9±28.5	0.012
	RIPC	29	0.0624±0.122		2.50±8.06		1.17±16.8	

of NGAL and KIM-1 were significantly lower in the RIPC group as compared with the control group (NGAL: *P*=0.024; KIM-1: *P*=0.007) (Figure 2). The changes in NGAL and KIM-1 from baseline to 12 h after contrast exposure were significantly reduced in patients with RIPC (Table 2). Our results suggest that RIPC treatment may reduce sub-clinical renal damage, especially early in the injury. At 48 h after the operation, the increased levels of NGAL and KIM-1 in the RIPC group started to decrease, and no significant difference was observed as compared with the control group (NGAL: *P*=0.083, KIM-1: *P*=0.147). All patients were followed up at 1 month after procedures. NGAL and KIM-1 levels almost returned to the baseline level, and no significant difference was observed between the 2 groups (NGAL: *P*=0.059, KIM-1: *P*=0.098) (Figure 2).

A subgroup analysis was performed in which all patients were classified based on Mehran risk score. Our results revealed no significant change in serum creatine levels after contrast medium injection in all subgroups. Significantly reduced serum KIM-1 and NGAL levels were simultaneously observed in patients with a Mehran risk score 6–10 in the RIPC group as compared with the control group (Table 3).

Discussion

We found that RIPC did not significantly reduce the incidence of CIN in elderly patients with NSTEMI who received PCI. However, we observed significantly lower levels of 2 early renal injury biomarkers (KIM-1 and NGAL) in patients with RIPC. Our results suggest that RIPC causes a reduction of sub-clinical renal damage.

RIPC may reduce renal reperfusion injury through a variety of complex enzymatic reactions, anti-inflammatory effects, signal transduction pathways, and neural and humoral pathways [13,18–21]. The effect of RIPC on CIN has been widely studied. Whittaker and Przyklenk [22] retrospectively showed the prospects for the application of RIPC in the prevention

and treatment of CIN. Er et al. [5] revealed that intermittent arm ischemia could reduce CIN incidence from 40% to 12%. Zhou et al. [20] reported that the incidence of CIN was dramatically reduced, from 26.3% (without RIPC) to 10.0% (with RIPC), in patients with acute coronary syndrome.

However, reduction of CIN incidence is not always observed in clinical settings. A multicenter trial reported that upper-limb RIPC did not show a relevant benefit among patients undergoing elective cardiac surgery [16]. Menting et al. [7] reported that RIPC could not reduce CIN occurrence in a multicenter, single-blinded, randomized controlled trial enrolling 76 patients. Singh et al. [18] found that RIPC prior to elective PCI was not effective in preventing CIN in patients with diabetes who had pre-existing CKD. Here, we found that RIPC did not significantly reduce CIN incidence in elderly patients with NSTEMI.

Zaugg et al. [23] attributed the poor effectiveness of preconditioning to the specific group of patients, such as patients with diabetes or older age. In the present study, we only enrolled elderly patients aged >65 years, and the poor effectiveness may be related to the relatively large group of older patients, as proposed by Zaugg et al. [23].

It is unclear how long in advance RIPC should be performed before contrast infusion. Er et al. performed RIPC out 45 min before contrast administration [5]. Other time intervals between RIPC in advance and contrast infusion have also been reported, such as 1 h [22] and 2 h [24] before contrast administration. Here, we chose to perform RIPC 2 h before contrast infusion. This choice took into account the clinical feasibility in our hospital, to allow sufficient time to complete RIPC before patients entered the interventional catheter room. To date, few studies have evaluated whether use of different time intervals between RIPC and contrast infusion influence the effect of RIPC on CIN. Well-designed studies should be carried out to study this.

The current diagnosis and monitoring of CIN mainly depend on changes in serum creatinine levels (SCr), but SCr takes 48–72 h

or more to increase. Renal tubular function may have been significantly impaired within a few hours after contrast infusion. Contrast agents have direct tubulotoxicity to renal tubular cells, causing cellular membrane damage, cell necrosis and apoptosis, epithelial vacuolization, and interstitial inflammation [25,26]. NGAL is a protein released from kidney tubular cells after harmful stimuli, which has been used for early and sensitive detection of CIN [13,27]. The tubular biomarker KIM-1 is an early marker of tubular damage that is closely related to contrast-induced long-term clinical outcomes, such as adverse renal events, dialysis, longer hospitalization, and even death [28]. Considering the hysteresis of SCr, NGAL and KIM-1 were used as observational indicators in this study. Our results suggested that, although RIPC treatment did not reduce the incidence of CIN, it may have early renal-protective effects against CIN, as indicated by the significantly reduced KIM-1 and NGAL levels.

Igarashi et al. employed a new CIN definition based on liver-type fatty acid binding protein (L-FABP). They defined CIN as a >25% relative increase from baseline when baseline L-FABP is >17.4 µg/g Cr [6]. As reported by Menting et al., this provides interesting proof of concept evidence, but its clinical relevance remains to be established [7]. Similar to their findings, we also found that RIPC treatment significantly reduced the incidence of KIM-1 or NGAL based CIN (defined as an increase of >25% from baseline) (data not shown). Because none of these early biomarkers have been reported in the definition of CIN, we did

not report these results in our study. More studies should be carried out in the future to better define CIN, and these early biomarkers for CIN would be promising candidates.

Er et al. found that 60% of the participants were at high risk of CIN, and they found that performing RIPC before contrast medium administration could prevent CIN in high-risk patients [5]. Our results showed significantly reduced levels of serum KIM-1 and NGAL were simultaneously observed in patients at moderate risk of CIN.

Conclusions

In conclusion, we found that RIPC did not reduce CIN in elderly patients with NSTEMI. However, the application of more sensitive biomarkers, NGAL and KIM-1, indicated a reduction of sub-clinical renal damage by RIPC, especially in the early stage of injury. As a simple and well-tolerated method, RIPC may be a potentially feasible therapeutic option, and its impact on prognosis needs to be assessed by longer follow-up or in a larger group of patients. Further large-scale clinical trials are required to confirm the efficacy of this approach.

Conflict of interest

None.

References:

1. Pannu N, Wiebe N, Tonelli M: Prophylaxis strategies for contrast-induced nephropathy. JAMA, 2006; 295: 2765–79

2. Nash K, Hafeez A, Hou S: Hospital-acquired renal insufficiency. Am J Kidney Dis, 2002; 39: 930–36

3. Solomon R: Contrast media nephropathy – how to diagnose and how to prevent? Nephrol Dial Transplant, 2007; 22: 1812–15

4. Gleeson TG, Bulugahapitiya S: Contrast-induced nephropathy. Am J Roentgenol, 2004; 183: 1673–89

5. Er F, Nia AM, Dopp H et al: Ischemic preconditioning for prevention of contrast medium-induced nephropathy: Randomized pilot RenPro Trial (Renal Protection Trial). Circulation, 2012; 126: 296–303

6. Igarashi G, Iino K, Watanabe H, Ito H: Remote ischemic pre-conditioning alleviates contrast-induced acute kidney injury in patients with moderate chronic kidney disease. Circ J, 2013; 77: 3037–44

7. Menting TP, Sterenborg TB, de Waal Y et al: Remote ischemic preconditioning to reduce contrast-induced nephropathy: A randomized controlled trial. Eur J Vasc Endovasc Surg, 2015; 50: 527–32

8. Harjai KJ, Raizada A, Shenoy C et al: A comparison of contemporary definitions of contrast nephropathy in patients undergoing percutaneous coronary intervention and a proposal for a novel nephropathy grading system. Am J Cardiol, 2008; 101: 812–19

9. Balemans CE, Reichert LJ, van Schelven BI et al: Epidemiology of contrast material-induced nephropathy in the era of hydration. Radiology, 2012; 263: 706–13

10. Evola S, Lunetta M, Macaione F et al: Risk factors for contrast induced nephropathy: A study among Italian patients. Indian Heart J, 2012; 64: 484–91

11. McManus DD, Gore J, Yarzebski J et al: Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. Am J Med, 2011; 124: 40–47

12. Ali ZA, Callaghan CJ, Lim E et al: Remote ischemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair: A randomized controlled trial. Circulation, 2007; 116(11 Suppl.): I98–105

13. Nusca A, Miglionico M, Proscia C et al: Early prediction of contrast-induced acute kidney injury by a "bedside" assessment of Neutrophil Gelatinase-Associated Lipocalin during elective percutaneous coronary interventions. PLoS One, 2018; 13: e0197833

14. Haase M, Bellomo R, Devarajan P et al., NGAL Meta-Analysis Investigator Group: Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: A systematic review and meta-analysis. Am J Kidney Dis, 2009; 54: 1012–24

15. Fu N, Li X, Yang S et al: Risk score for the prediction of contrast-induced nephropathy in elderly patients undergoing percutaneous coronary intervention. Angiology, 2013; 64: 188–94

16. Meybohm P, Bein B, Brosteanu O et al: A multicenter trial of remote ischemic preconditioning for heart surgery. N Engl J Med, 2015; 373: 1397–407

17. Hu J, Liu S, Jia P et al: Protection of remote ischemic preconditioning against acute kidney injury: A systematic review and meta-analysis. Critical Care, 2016; 20: 111

18. Balbir Singh G, Ann SH, Park J et al: Remote ischemic preconditioning for the prevention of contrast-induced acute kidney injury in diabetics receiving elective percutaneous coronary intervention. PLoS One, 2016; 11(10): e0164256

19. Yang Y, Lang XB, Zhang P et al: Remote ischemic preconditioning for prevention of acute kidney injury: A meta-analysis of randomized controlled trials. Am J Kidney, Dis, 2014; 64: 574–83

20. Tu Y, Wang H, Sun R et al: Urinary netrin-1 and KIM-1 as early biomarkers for septic acute kidney injury. Ren Fail, 2014; 36: 1559–63

21. Maisel AS, Wettersten N, van Veldhuisen DJ et al: Neutrophil gelatinase-associated lipocalin for acute kidney injury during acute heart failure hospitalizations: The AKINESIS Study. J Am Coll Cardiol, 2016; 68: 1420–31

22. Zhou F, Song W, Wang Z et al: Effects of remote ischemic preconditioning on contrast induced nephropathy after percutaneous coronary intervention in patients with acute coronary syndrome. Medicine (Baltimore), 2018; 97: e9579

23. Zaugg M, Lucchinetti E: Remote ischemic preconditioning in cardiac surgery – ineffective and risky? N Engl J Med, 2015; 373: 1470–72

24. Igarashi G, Iino K, Watanabe H, Ito H: Remote ischemic pre-conditioning alleviates contrastinduced acute kidney injury in patients with moderate chronic kidney disease. Circ J, 2013; 77: 3037–44

25. McCullough PA: Contrast-induced acute kidney injury. J Am Coll Cardiol, 2008; 51: 1419–28

26. Panchapakesan U, Pollock C, Saad S: Renal epidermal growth factor receptor: Its role in sodium and water homeostasis in diabetic nephropathy. Clin Exp Pharmacol Physiol, 2011; 38: 84–88

27. Devarajan P: Review: Neutrophil gelatinase-associated lipocalin: A troponin-like biomarker for human acute kidney injury. Nephrology (Carlton), 2010; 15: 419–28

28. Chaykovska L, Heunisch F, von Einem G et al: Urinary vitamin D binding protein and KIM-1 are potent new biomarkers of major adverse renal events in patients undergoing coronary angiography. PLoS One, 2016; 11: e0145723