Acta Med. Okayama, 2021
Vol. 75, No. 1, pp. 45–53

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Possible Protective Effect of Remote Ischemic Preconditioning on Acute Kidney Injury Following Elective Percutaneous Coronary Intervention: Secondary Analysis of a Multicenter, Randomized Study

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Remote ischemic preconditioning (RIPC) is a promising strategy for protecting against ischemic reperfusion injury. This study is a secondary analysis of a randomized study that aimed to evaluate the effect of RIPC on the early increase in serum creatinine (SCr) following percutaneous coronary intervention (PCI), which is associated with contrast-induced acute kidney injury. Patients with stable angina undergoing elective PCI were assigned to control, RIPC, and continuous infusion of nicorandil (nicorandil) groups. The endpoint of this study was the incidence of the early increase in SCr, a predictor of contrast-induced acute kidney injury, which was defined as either a >20% or absolute increase by 0.3 mg/dl of SCr levels after 24 h of PCI. This study included 220 patients for whom a dataset of SCr values was available. The incidence of the early increase in SCr was significantly lower in the RIPC than in the control (1.3% vs 10.8%, $p=0.03$) group, but was not significantly different between the nicorandil and control groups. In multivariate analysis, RIPC remained a significant factor associated with a reduction in the incidence of early increase in SCr. RIPC reduces the incidence of early increase in SCr in patients with stable angina following elective PCI.

Key words: remote ischemic preconditioning, stable angina, serum creatinine, acute kidney injury

Acute kidney injury (AKI) induced by contrast following percutaneous coronary intervention (PCI) is associated with increased short- and long-term mortality in patients with coronary artery disease [1]. To prevent contrast-induced AKI, infusion of saline has been used in clinical practice since 1980 [2]. Infusion of sodium bicarbonate was expected to be a replacement therapy to prevent contrast-induced AKI. However, multicenter, randomized trials have shown no advantage of this method compared with infusion of saline [3,4]. A variety of pharmacotherapies have been evaluated for prevention of contrast-induced AKI. Infusion or oral administration of nicorandil, which has dual properties of a nitrate and an ATP-sensitive K^+ channel agonist with vasodilatory effects, decreases the incidence of contrast-induced AKI [5,6]. However, the benefit of these therapies remains unclear.

Received May 18, 2020; accepted October 5, 2020.
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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

Contrast-induced AKI is usually defined as an increase in in the serum creatinine (SCr) level from baseline 48 to 72 h after contrast exposure [7-10]. However, with the development of new technology, most patients are discharged in 1 or 2 days after PCI, without the measurement of SCr at 48-72 h after PCI. To stratify patients' risks of contrast-induced AKI prior to PCI, a scoring system is useful. Inohara *et al.* reported that the AKI prediction model derived from the National Cardiovascular Data Registry (NCDR) was well-fitted to analysis of a Japanese PCI cohort [11]. Meanwhile, Ribichini *et al.* evaluated predictors of contrast-induced AKI after angiography and PCI, and found that an increase in SCr of 5% to 10% above baseline at 12 h predicted the development of contrast-induced AKI [12]. Liu *et al.* reported that long-term mortality in patients after coronary angiography was similar for patients with early (within 24 h) and late (24-48 h) increases in SCr ≥0.3 mg/dL or ≥50% [13]. Thus, the early increase in SCr after contrast exposure may be a useful predictor for contrast-induced AKI and its associated long-term mortality.

Remote ischemic preconditioning (RIPC) is defined as transient brief episodes of ischemia at a remote site before a subsequent prolonged ischemia/reperfusion injury of the target organ. RIPC is an adaptational response that protects against an ischemic and reperfusion insult [14]. Several studies have shown the tissue-protective effects of RIPC in various target organs, including the kidneys [8, 15-20]. Therefore, RIPC may offer a novel noninvasive treatment strategy for decreasing the incidence of AKI.

We recently reported a multicenter, randomized trial that examined whether pre-procedural RIPC or intravenous nicorandil reduces periprocedural myocardial injury in patients who undergo elective PCI for stable coronary artery disease. This study showed that RIPC or intravenous nicorandil moderately reduced biomarker release and periprocedural myocardial injury, but these results were not significant [21]. Therefore, an exploratory analysis to identify a population in whom RIPC or intravenous nicorandil is effective was planned. Considering the tissue-protective effects of RIPC in various organs, RIPC could have a protective effect on contrast-induced AKI. In our previous randomized study [21], we collected serum creatinine value at baseline and 24 h after PCI. We hypothesized that RIPC reduced the incidence of the early increase in creatinine, which is associated with the development of contrast-induced AKI. Thus, this study aimed to evaluate the effect of RIPC or nicorandil on the early increase in SCr as a substudy of our previous multicenter, randomized study.

Materials and Methods

The main study (Cardiac Preconditioning Effect of Remote Ischemia and Nicorandil in Patients Undergoing Elective Percutaneous Coronary Intervention: RINC) was a prospective, open-label, multicenter, randomized, controlled trial, which was conducted between February 2011 and January 2013 [21]. The current study was a post-hoc analysis of the RINC study. The study was approved by the ethics committees of all participating hospitals. All participants provided written informed consent before enrolling. This study was conducted in accordance with the principles expressed in the Declaration of Helsinki. The study is registered at the UMIN Clinical Trials Registry (UMIN000005607).

Patient population. Figure 1 shows a flow diagram of the study. Eligible patients were adults (>20 years old) who were diagnosed with silent myocardial ischemia or stable angina and planned to have elective PCI. Patients were excluded for the following reasons: they had acute coronary syndrome, they had contraindications for intravenous nicorandil administration, they planned elective PCI for a chronic total occlusion lesion or PCI with a rotablator, they were using sulfonylurea drugs, they had an aorta-venous shunt in one or both arms, and their prognosis was regarded as <12 months [21, 22]. In the main study, 396 patients underwent randomization. In this post-hoc analysis, patients were included if blood samples for measuring SCr levels before PCI and 24 h after PCI were available. Finally, 220 patients were included in this post-hoc analysis (n=74 in the control group, n=77 in the RIPC group, and n=69 in the nicorandil group).

Study protocol. The intervention protocol and PCI procedure have been described previously [21]. Patients were randomly assigned to control, RIPC, or 6 mg/h intravenous nicorandil (nicorandil) groups. In patients who were assigned to the RIPC group, 5-min inflation of a blood pressure cuff to 200 mmHg around the upper arm, followed by 5-min deflation of a cuff to 0 mmHg was performed three times for at least 1 h each time before PCI. This procedure was automatically per-

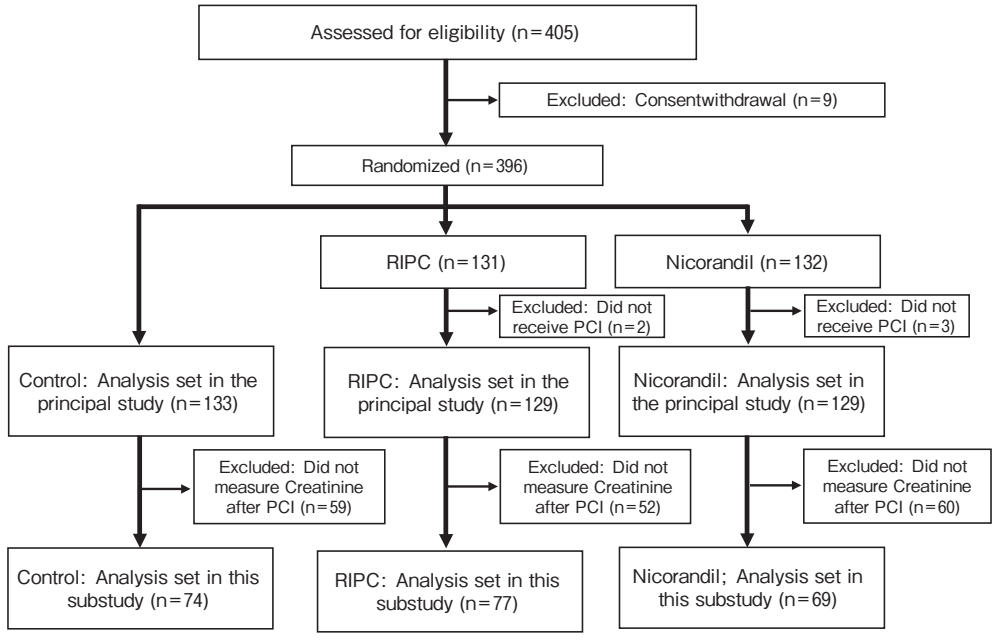

Fig. 1 Flow diagram of the study. A total of 405 patients were enrolled in this study. Among them, 396 patients underwent randomization, and 220 were included in the per-protocol set as the complete study population.
RIPC, remote ichemic preconditioning; PCI, percutaneous coronary intervention.

formed by a newly developed automated continuous blood pressure device (FB-270; Fukuda Denshi, Tokyo). In patients who were assigned to the nicorandil group, 4 mg of nicorandil was intravenously administered for 5 min at least 1 h before PCI, followed by continuous infusion of nicorandil (6 mg/h) for at least 8 h during PCI. The infusion was stopped at the direction of the attending doctor. Patients in the control group did not receive any additional pre-treatment before PCI. Blood samples were collected before PCI (until 2 days before the planned PCI) and at 24 h after PCI. The total volume of drip infusion associated with PCI (> 1,500 ml or < 1,500 ml) was collected.

End points. The primary end point of this subanalysis was the incidence of the early increase in SCr following PCI.

Early increase in SCr was defined as either a > 20% increase or an absolute increase by 0.3 mg/dl of SCr 24 h after PCI. The definition of early increase in SCr was based on a previous study of the definition of AKI following angiography with use of contrast [23, 10].

The incidence of early increase in SCr was also evaluated according to the Mehran Score and the tertile of contrast medium (first: 9-80 ml; second: 83-118 ml; third: 120-232 ml). The Mehran score is used to predict the risk of developing contrast-induced AKI [24], and accounts for such factors as hypotension, use of an intra-aortic balloon pump, congestive heart failure, age, anemia, diabetes mellitus, contrast media volume, and estimated glomerular filtration rate (eGFR). Mehran scores of < 5, 6-10, 11-15, and > 15 were categorized as low, moderate, high, and very high risk.

Statistical analysis. Continuous variables are presented as the mean ± standard deviation or as the median (25-75 th percentile), as appropriate. Categorical variables are presented as numbers and ratios (%). Continuous variables were compared using analysis of variance or the Kruskal-Wallis test, as appropriate. Categorical variables were compared using Pearson's chi-square test. For multiple comparison, the Bonferroni post-hoc test was applied.

We assumed that occurrence of renal failure event would be 20% in the control group, and 4% in the RIPC group or nicorandil group as in previous studies [5, 6, 8, 18, 25, 26]. To ensure that the two-sided significance level was 5% and the power was 90%, 77 patients in each group were required.

Odds ratios (ORs) between groups and their 95% exact confidence intervals (CIs) were calculated. In addition, a multivariate logistic regression model was

used to calculate the OR between study groups with adjustment for factors having p values < 0.10 in univariate analysis (*i.e.*, smoking), as well as duration of blood sampling and total fluid volume. All analyses were performed with IBM SPSS version 25. A p value < 0.05 was considered statistically significant.

Results

Study population. Table 1 shows the baseline patient characteristics in the control, RIPC, and nicorandil groups. Among all patients, the mean age, eGFR at baseline, and volume of contrast medium used for PCI were 70.7 ± 8.8 years, 64.3 ± 16.5 ml/min/1.73 m^2, and 103.2 ± 39.5 ml, respectively. These parameters were not significantly different among the three groups. Other baseline patient characteristics and medications were also not significantly different among the groups.

Primary end point. Of the 220 patients, the early increase in SCr occurred in 11 patients. First, the incidence of early increase in SCr was evaluated according to the Mehran score. The incidence of the early increase in SCr in the low risk (n = 92), moderate risk (n = 74), and high and very high risk (n = 54) groups was 1.1%, 8.1%, and 7.4%, respectively (p = 0.08). In addition, the incidence of early increase in SCr was evaluated according to the tertile of contrast medium. The incidence of AKI in the first (n = 78), second (n = 73), and third (n = 68) tertiles was 3.9%, 4.1%, and 0%, respectively.

The incidence of the early increase in SCr (primary endpoint) was significantly lower in the RIPC group than in the control group (1 [1.3%] vs 8 [10.8%] patients, p = 0.03), but it was not significantly different between the nicorandil (2 [2.8%] patients) and control groups (p = 0.18) (Fig. 2). A further analysis in patients with eGFR < 60 mL/min per 1.73 m^2 was performed (control: n = 34; nicorandil: n = 28; RIPC: n = 34). The incidence of early increase in SCr was 9% (n = 3) in the control, 2% (n = 2) in the nicorandil, and 0% in the RIPC group, respectively, and there was no significant difference between the control and nicorandil (p = 0.81) or between the control and the RIPC (p = 0.08) groups.

Independent association between the early increase in SCr and RIPC. To examine the association between

Table 1 Patients' characteristics among the control, RIPC, and nicorandil groups

	Control group (n = 74)	RIPC group (n = 69)	Nicorandil group (n = 77)	p value
Age, years	72 ± 9	70 ± 10	70 ± 8	0.15
Male sex	51 (71)	53 (84)	59 (76)	0.46
Body mass index, kg/m^2	23.8 ± 3.2	24.1 ± 3.6	25.0 ± 3.4	0.10
Diabetes mellitus	37 (50)	32 (46)	38 (49)	0.90
Hypertension	65 (88)	59 (86)	64 (83)	0.71
Smoking	45 (61)	49 (51)	52 (66)	0.42
Previous ASCVD	34 (49)	35 (51)	35 (45)	0.78
LDL-cholesterol, mg/dl	90 ± 29	91 ± 31	89 ± 24	0.92
Serum creatinine, mg/dl	0.87 ± 0.22	0.90 ± 0.21	0.93 ± 0.37	0.35
eGFR, ml/min/1.73 m^2	64 ± 17	63 ± 15	64 ± 19	0.84
Hemoglobin A1c, %	6.1 ± 1.1	6.1 ± 1.2	6.1 ± 1.1	0.94
Contrast medium, ml	100 [80–130]	105 [80–121]	102 [70–130]	0.89
Total volume of drip infusion (> 1,500 ml)	34 (50)	41 (53)	28 (41)	0.29
Duration from baseline blood sampling to PCI (days)	5 [4–7]	6 [4–8]	6 [4–7]	0.80
Left ventricular ejection fraction, %	61 ± 11	61 ± 11	64 ± 9	0.20
Mehran score	7 [4–11]	6 [3–10]	6 [3–10]	0.98
Medications				
ACEI/ARB	52 (70)	42 (55)	45 (65)	0.12
Statin	58 (78)	62 (81)	55 (80)	0.95
Insulin	10 (14)	6 (7.8)	12 (17)	0.21
Oral hypoglycemic agent	26 (35)	31 (40)	19 (28)	0.27

Data are presented as mean ± standard deviation, n (%), or median [25–75 th percentile].
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; RIPC, remote ischemic preconditioning.

the early increase in SCr and RIPC, 151 patients in the control (n = 74) and the RIPC (n = 77) groups were analyzed. Table 2 compares the patient characteristics between patients with and without the early increase in SCr. There were no significant differences in characteristics between the 2 groups. Finally, logistic regression analysis was performed (Table 3). Multivariate analysis using factors that showed p values < 0.10 in univariate analysis, the total volume of drip infusion, and the duration from baseline blood sampling to PCI showed that RIPC remained a significant factor associated with a reduction in the early increase in SCr (odds ratio, 0.12; 95% confidence interval, 0.01-0.96; $p = 0.04$).

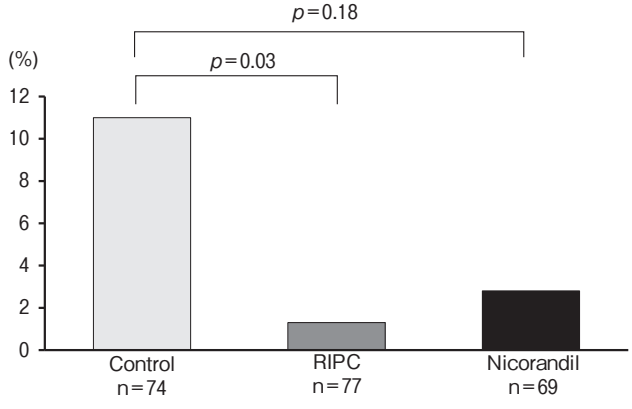

Fig. 2 Incidence of the early increase in serum creatinine post-PCI. The incidence of the early increase in serum creatinine following PCI in the control, RIPC, and nicorandil groups is shown. Fisher's exact test was applied to compare the incidence of the early increase in serum creatinine following PCI between the RIPC and control groups or the nicorandil and control groups.
RIPC, remote ischemic preconditioning.

Discussion

In this post-hoc analysis of a multicenter, randomized, controlled trial, we showed that the incidence of the early increase in SCr in the RIPC group was significantly lower than that in the control group. However, the nicorandil group did not show a significantly lower incidence of the early increase in SCr compared with the control group. This is the first multicenter trial to show the potential benefit of RIPC for preventing contrast-induced AKI following elective PCI in patients with stable coronary artery disease.

Several clinical studies have reported the effect of RIPC on renal outcomes [8, 18-20]. A randomized trial by Zarbock *et al.* reported that performing RIPC before open thoracic cardiac surgery prevented patients from having renal failure 72 h after surgery [20]. Similar studies have reported the protective effect of RIPC in the perioperative period, which suggests that there is a renal protective effect of RIPC in highly invasive sur-

Table 2 Characteristics of patients with and without the early increase in serum creatinine in the control and RIPC groups

	Early increase in serum creatinine		
	Presence (n = 9)	Absence (n = 142)	p value
Male	5 (55)	105 (74)	0.25
Age, years	71 ± 9	76 ± 5	0.08
Diabetes mellitus	6 (66)	69 (49)	0.33
Hypertension	8 (88)	121 (85)	1.00
Dyslipidemia	7 (77)	116 (82)	0.67
eGFR < 60 ml/min/1.73 m^2	2 (22)	65 (46)	0.30
Previous ASCVD	5 (55)	64 (45)	0.73
Smoking	3 (33)	94 (66)	0.07
Contrast medium (ml)	100 [80–121]	100 [75–131]	0.82
ACEI/ARB	8 (89)	86 (61)	0.15
Statin	6 (66)	114 (80)	0.39
Oral hypoglycemic agent	3 (33)	54 (35)	1.00
RIPC	1 (11)	76 (54)	0.01
Total volume of drip infusion (> 1,500 ml)	4 (44)	74 (52)	0.66
Duration from baseline blood sampling to PCI (days)	7 [4–9]	6 [4–8]	0.28

Data are presented as mean ± standard deviation, n (%), or median [25–75th percentile].
RIPC, remote ischemic preconditioning; eGFR, estimated glomerular filtration rate; ASCVD, atherosclerotic cardiovascular disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; PCI, percutaneous coronary intervention.

Table 3 Odds ratios for the early increase in serum creatinine

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
RIPC	0.11	0.01–0.89	0.04	0.12	0.01–0.96	0.04
Male sex	0.44	0.11–1.73	0.23			
Age	1.08	0.98–1.19	0.11			
Diabetes mellitus	2.11	0.51–8.79	0.30			
Dyslipidemia	0.78	0.15–3.99	0.78			
Hypertension	1.39	0.17–11.68	0.76			
eGFR <60 ml/min/1.73 m^2	0.34	0.07–1.69	0.19			
Previous ASCVD	1.52	0.39–5.91	0.54			
Smoking	0.26	0.06–1.07	0.06	0.24	0.05–1.09	0.07
Contrast medium	0.98	0.96–1.01	0.19			
ACEI/ARB	5.21	0.63–42.79	0.13			
Statin	0.49	0.12–2.09	0.34			
Oral hypoglycemic agent	0.82	0.19–3.39	0.78			
Total volume of drip infusion (>1,500 ml)	0.66	0.16–2.76	0.57	0.75	0.18–3.10	0.69
Duration from baseline blood sampling to PCI (days)	1.06	0.87–1.30	0.57	1.09	0.88–1.34	0.44

Multivariate analysis included factors with $p<0.1$ in univariate analysis.
CI, confidence interval; RIPC, remote ischemic preconditioning; eGFR, estimated glomerular filtration rate; ASCVD, atherosclerotic cardiovascular disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; PCI, percutaneous coronary intervention.

gery. However, there are a limited number of studies in patients after angiography or PCI. In a previous, single-center randomized trial, the incidence of AKI in the control group was 40% [8], higher than that in our RINC study (11%) in patients after elective angiography. Another multicenter randomized trial reported that the incidence of contrast-induced nephropathy in the RIPC group was not significantly lower than that in the control group (3.8% and 5.1%, $p=0.74$) [27]. There are some differences between these previous trials and our RINC study. First, patients in the previous trials had an eGFR <60 ml/min/1.73 m^2, while patients in our RINC study had a mean eGFR of 64 ml/min/1.73 m^2. Therefore, the RINC study included patients with mild renal insufficiency. Second, in the previous trial, measurement of SCr levels was performed until 48 h after the procedure to define contrast-induced AKI. However, in our study, SCr levels were checked once in 24 h after PCI. The incidence of the early increase in SCr is associated with contrast-induced AKI, but is not generally used to define contrast-induced AKI. Thus, this study did not evaluate the incidence of contrast-induced AKI directly. Third, the use of contrast, the PCI procedures and the prior infusion of saline or other fluids were controlled according to the patient's baseline kidney function by physicians within the protocol of the main study to prevent large myocardial injury, which may be associated with AKI. However, there are also several strengths of our study. First, this study is the first multicenter trial to show the potential benefit of RIPC on contrast-induced renal injury in patients after PCI. Second, the occurrence of early increase in SCr has clinical relevance and importance for the development of contrast-induced AKI [12,13]. Therefore, any reduction in the incidence of the early increase in SCr would provide practical benefit for patients following PCI.

The actual mechanism of RIPC remains controversial, but neuronal and hormonal pathways have been proposed to account for the protection against ischemic reperfusion injury. [14,28]. We previously reported that three cycles of ischemia-reperfusion in an upper limb enhanced parasympathetic nerve activity in healthy subjects, which might induce vasodilation [29]. RIPC induces nitric oxide synthase, which produces nitric oxide, which is a humoral factor that exhibits vasodilatory activity in the manner of adenosine and bradykinin [30]. A clinical randomized trial showed that the significantly higher circulating nitric oxide level in an RIPC group compared to the control group was maintained until 24 h after cardiac surgery [31]. Another study showed that RIPC induced a significant

decrease in the renal resistivity index through increased intra-renal perfusion in healthy volunteers [32]. In the target organ, RIPC activates the phosphoinositide 3 kinase/Akt/cyclic guanosine monophosphate/protein kinase G pathway, which modulates mitochondrial ATP-sensitive K^+ channels [28]. This pathway may prevent cell damage. With regard to the mechanism of RIPC in renal protection, the following possibility should be considered. Nephrons with a microvascular network are vulnerable to injury. When contrast medium is used, there is sustained (hours to days) intrarenal vasoconstriction and ischemic injury [33]. This ischemic disorder triggers a cascade of oxidative injury causing death of renal tubular cells. RIPC might provide the kidney with resistance to ischemic injury by reducing vessel resistance and increasing renal perfusion. Because the main study of this subanalysis was not designed to investigate the mechanisms of RIPC, change in neuronal and hormonal factors was not examined. Further studies will be needed to elucidate the underlying mechanisms of RIPC.

Our study showed that nicorandil moderately reduced the incidence of the early increase in SCr, but this effect was not statistically significant. This finding is in line with previous studies showing the efficacy of nicorandil for avoiding AKI [6]. In that protocol, nicorandil was administered by injection of 4 mg followed by infusion at 6 mg/h for 24 h and by oral administration, based on our previous study showing that intravenous nicorandil in conjunction with coronary angioplasty is associated with better functional and clinical outcomes in patients with an anterior acute myocardial infarction [34]. Therefore, in this study, 4 mg of nicorandil was intravenously administered for 5 min at least 1 h before PCI, followed by continuous infusion of nicorandil (6 mg/h) for at least 8 h [21]. Nawa *et al.* reported that creatinine values at 24 h after PCI in the continuous nicorandil infusion group were significantly lower than those in the control group [5]. However, our study failed to show significant reduction of the incidence of the early increase in SCr, despite a longer duration of nicorandil administration than that in our study. To achieve the maximum effect of nicorandil for preventing AKI, the optimal dose and administration duration need to be clarified.

In this study, we evaluated the effects of RIPC and nicorandil on renal function. RIPC is probably mediated by neural and hormonal factors [14, 28] and can be applied to all patients with renal dysfunction undergoing PCI. Meanwhile, nicorandil is a synthetic K-ATP channel activator and increases vascular nitric oxide content by activating endothelial nitric oxide synthase [35]. Nicorandil is also used widely in patients with renal dysfunction. The combination of RIPC and nicorandil might have additive effects on renal function, although further studies will be needed to confirm this.

Limitations. This study had several limitations. First, this study was a post-hoc analysis of a randomized, controlled trial. A small number of early increases in SCr occurred after PCI in the RIPC group and the nicorandil group. Second, the infusion volume, such as for saline around PCI, was not available in this subanalysis. We cannot deny the possibility that some patients received additional infusion or other protective pretreatments for kidney function because the renal function of patients before PCI was not blind. Third, almost half of the patients were excluded due to the lack of SCr after PCI, although the number of patients satisfied our sample-size calculation. When we examined the homogeneity of patient characteristics between this study and the main study in each group, no significant differences were found (data not shown). Fourth, the early increase in SCr used in our study was different from the definition commonly used for contrast-induced AKI [24]. Contrast-induced AKI is usually defined as an increase in the SCr level from baseline at 48 to 72 h after contrast exposure [7-10]. In this study, blood sampling was performed only once, at 24 h after PCI. However, early increases in SCr have been associated with the development of contrast-induced AKI and prognosis [12, 13], and are thus of clinical importance. Fifth, a sham RIPC group was not set in this study. Therefore, we cannot completely rule out that this nonblinded intervention affected the outcomes.

In conclusion this secondary analysis of the RINC study shows that RIPC significantly reduces the incidence of the early increase in SCr following elective PCI in patients with stable angina. Our study suggests that RIPC was beneficial for renal protection in these patients. Further investigation using a multicenter, prospective study is required to evaluate the effect of RIPC on contrast-induced AKI following PCI in patients with stable angina.

Acknowledgments. In addition to the authors named above, the RINC study collaborators were as follows: Atsushi Takaishi, MD, PhD;

Yusuke Kawai, MD, PhD; Tetsuya Satoh, MD, PhD; Katsumasa Satoh, MD, PhD; Takefumi Oka, MD, PhD; Natsuki Takahashi, MD, PhD; Satoru Sakuragi, MD, PhD; Atsushi Mima, MD, PhD; Kenki Enko, MD, PhD; Shingo Hosogi, MD, PhD; Seiji Nanba, MD, PhD; Ryoichi Hirami, MD, PhD; Yasukazu Fujiwara, MD; Yoshimasa Morimoto, MD; Shunji Suemaru, MD; and Toshiaki Yamanaka, MD.

Funding. This research was supported by a grant from the Okayama Medical Foundation.

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