

Tobacco smoking protective effect via remote ischemic preconditioning on myocardial damage after elective percutaneous coronary intervention: Subanalysis of a randomized controlled trial

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ABSTRACT

Background: Remote ischemic preconditioning (RIPC) is promising for preventing periprocedural myocardial damage (pMD) in patients undergoing percutaneous coronary intervention (PCI). However, the impact of RIPC on pMD on smokers is not well elucidated. The aim of this study was to investigate an association between tobacco smoking and RIPC on pMD in patients planning to undergo PCI.

Methods: This study used data from a multicenter randomized controlled trial involving patients with stable angina who planned to undergo elective PCI. We analyzed data for 262 patients in the control ($n = 133$) and upper-limb RIPC ($n = 129$) groups, including 166 current or former smokers. The major outcome was the pMD incidence following PCI, with pMD defined as an elevated level of highly sensitive cardiac troponin T or a creatine kinase myocardial band 12 or 24 h after PCI.

Results: The incidence of pMD was significantly lower in the upper-limb RIPC group than in the control group (28/83 patients [33.8%] vs. 43/83 patients [51.8%], respectively; $p = 0.018$). In a multiple logistic regression model, tobacco smoking was an independent predictor of interacting with and enhancing the effect of RIPC on reducing the incidence of pMD after PCI (regression coefficient, -0.4 [95% confidence interval, -0.74 to -0.082]; $p = 0.015$).

Conclusions: Tobacco smoking may have a beneficial effect on RIPC against pMD after PCI.

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1. Introduction

Periprocedural myocardial damage (pMD) leads to adverse cardiac events during long-term follow-up [1]. A promising approach to reduce the incidence of pMD is remote ischemic preconditioning (RIPC), a phenomenon wherein the presence of 1 or more organs with reversible ischemia leads to a protective effect on other remote organs by neurohormonal transduction [2–7]. Our recent multicenter randomized controlled trial [8] showed that RIPC and intravenous nicorandil moderately, but not significantly, reduced myocardial biomarker levels following elective percutaneous coronary intervention (PCI). However, the question of which patients benefit from RIPC remains unanswered.

Therefore, we performed prespecified subgroup analyses to clarify for which patients RIPC more effectively exerts a myocardial protective effect during elective PCI. We hypothesized that tobacco smoking influences the effect of RIPC on pMD. This hypothesis was based on the finding that smokers undergoing thrombolytic therapy for ST-segment elevation myocardial infarction have lower in-hospital mortality than nonsmokers, a phenomenon called the “smoker’s paradox.” [9,10] The aim of this study was to investigate the effect of RIPC on pMD following PCI in smokers using the data from our recent multicenter randomized controlled trial.

2. Methods

2.1. Study design

This study was designed as a subanalysis of the randomized controlled trial “Cardiac Preconditioning Effect of Remote Ischemia

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and Nicorandil in Patients Undergoing Elective Percutaneous Coronary Intervention” (RINC trial) [8]. Briefly, the RINC study was a prospective, open-label, multicenter, randomized controlled trial conducted at 18 hospitals from February 2011 to January 2013 (the study design is described in the trial protocol provided in the Supplementary File).

The current study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and the Okayama University Hospital Ethics Committee as well as ethics committees in each research facility. The current study was registered in the UMIN Clinical Trials Registry, June 2011 (UMIN000005607), available at: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000006626.

2.2. Participants

Patients were randomly assigned in a 1:1:1 ratio to control, intravenous nicorandil, and RIPC groups. Eligible patients were adults >20 years of age who had been diagnosed with silent myocardial ischemia or stable angina and who were awaiting elective PCI. Each patient provided written informed consent. We excluded patients who had acute coronary syndrome, had contraindications to intravenous nicorandil administration, were planning to undergo elective PCI for chronic total occlusion or had undergone PCI performed with a Rotablator™ (Boston Scientific, Boston, MA), were receiving glibenclamide for diabetes, had an aortovenous shunt in the arm, or had a lifetime prognosis of <12 months. This subanalysis was designed to investigate the effect of RIPC on pMD following PCI in smokers. Therefore, this analysis included patients in the control and RIPC groups.

2.3. Interventions

The intervention protocol and PCI procedure are described in detail elsewhere [8]. Briefly, the RIPC group underwent upper-limb compression of 200 mm Hg or decompression (three cycles in total, by 5-min inflations and deflations of a blood pressure cuff) using a newly developed, automated, continuous blood pressure device (FB-270; Fukuda Denshi, Tokyo, Japan) as PCI pretreatment.

PCI was performed in a conventional manner. The details of each procedure depended on the practice of each hospital. The perfusion status of the target-related coronary artery was determined according to the Thrombolysis In Myocardial Infarction study classification [11]. The final Thrombolysis In Myocardial Infarction flow grade was assessed from the final angiography image, and coronary stenosis was assessed by angiography or fractional flow reserve.

Randomization was conducted by the Clinical Trials Unit based at Okayama University via a secure website and was stratified by the center using random permuted blocks to balance for age (<65 or ≥65 years), sex (male or female), renal dysfunction (baseline estimated glomerular filtration rate of <60 or ≥60 mL/min/1.73 m²), and PCI center. All participants provided written informed consent before enrolling.

2.4. Outcomes

The major outcome of this study was a reduced incidence of pMD after PCI, which was defined as an elevated level of high-sensitivity cardiac troponin-T (cTNT) (>0.07 ng/mL) or creatine kinase myocardial band (CK-MB) (>10 ng/mL) and a CK-MB/creatinine kinase ratio of >5% at 12 or 24 h after PCI [8]. This definition is based on the diagnostic

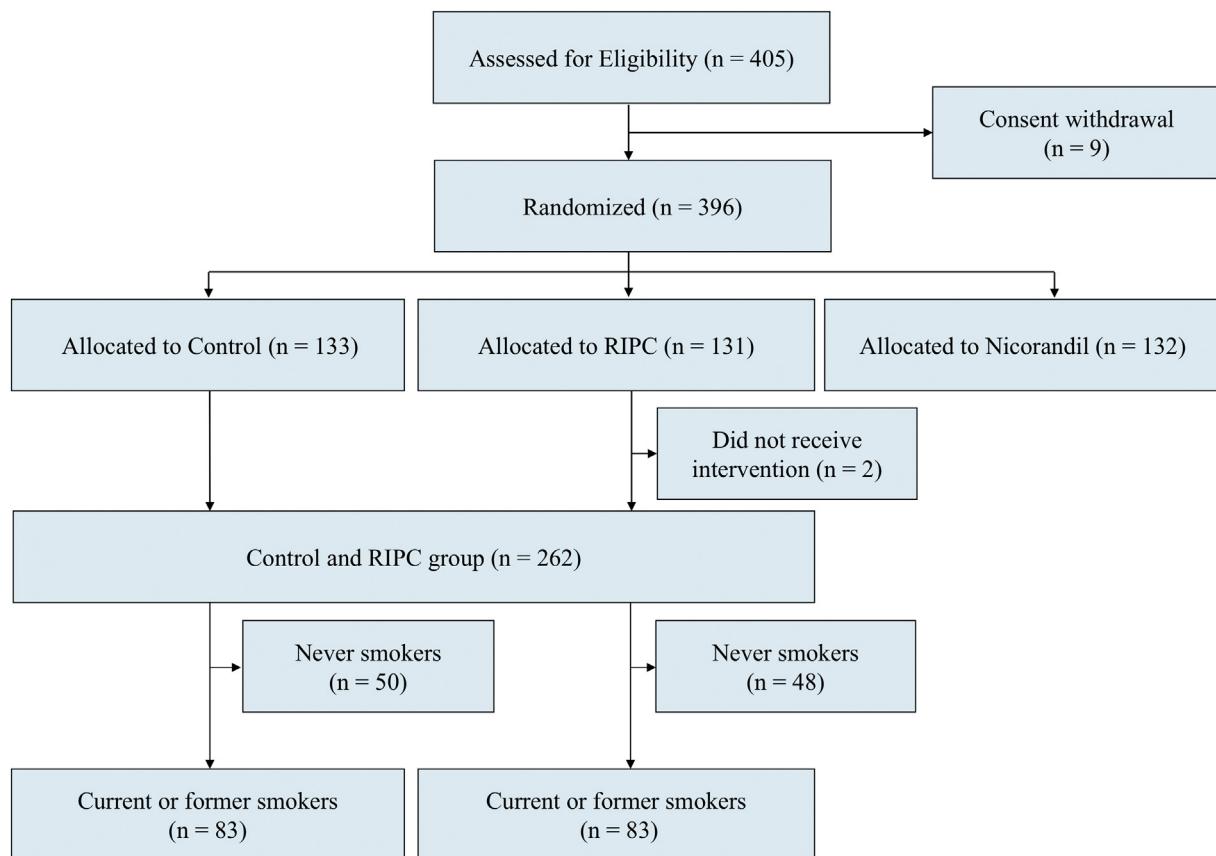


Fig. 1. Study flow diagram. In total, 405 patients were enrolled in this study. Among these, 396 patients underwent randomization. Excluding patients who received no intervention ($n = 2$) and those allocated to the nicorandil group ($n = 132$), we allocated 262 patients to the control and remote ischemic preconditioning groups and included these patients in the subanalysis ($n = 262$).

Table 1
Baseline characteristics of current or former smokers.

	Control n = 83	RIPC n = 83	p Value
Age – yr.	69.3 ± 10.7	70.0 ± 10.2	0.69
Male – no. (%)	77 (93)	79 (95)	0.51
BMI (kg/m ²)	24.1 ± 3.0	24.0 ± 3.4	0.81
Stable angina – no. (%)			
Symptomatic	61 (74)	65 (79)	0.46
Asymptomatic	22 (26)	18 (21)	
Prior diagnoses – no. (%)			
Diabetes	38 (46)	37 (45)	0.88
Use of Insulin	10 (12)	6 (7)	0.29
Hypertension	70 (84)	66 (80)	0.42
Dyslipidemia	63 (76)	69 (83)	0.25
Renal dysfunction	35 (42)	30 (36)	0.43
Multiple ASCVD	35 (42)	36 (43)	0.88
Tobacco smoking – no. (%)			
Current	15 (18)	12 (15)	0.53
Former	68 (82)	71 (85)	
Echocardiographic parameters at randomization			
LVEF (%)	62.3 ± 10.2	61.6 ± 11.5	0.67
E/e'	11.9 (9.0–15.2)	11.1 (8.9–15.8)	0.82
Laboratory data at randomization			
Hemoglobin (g/dL)	13.5 ± 1.7	13.7 ± 1.6	0.52
Platelet (10 ⁴ /μL)	20.1 ± 6.3	19.5 ± 5.7	0.52
Total cholesterol (mg/dL)	162 (136–189)	158 (143–178)	0.75
eGFR (mL/min/1.73 cm ²)	66.5 ± 16.8	66.8 ± 17.4	0.93
HgbA1C (%)	5.7 (5.3–6.4)	5.7 (5.3–6.6)	0.99
CRP (mg/dL)	0.095 (0.030–0.180)	0.100 (0.035–0.175)	0.96
BNP (pg/mL)	30.0 (17.2–60.3)	43.6 (16.2–103.5)	0.21
Myocardial biomarker at randomization			
cTNT (ng/mL), *	0.011 (0.007–0.019)	0.011 (0.007–0.017)	0.79
CK-MB (ng/mL), *	3.7 (2.3–5.0)	3.5 (2.8–4.3)	0.71
Medications at randomization – no. (%)			
Antiplatelet	83 (100)	82 (99)	0.32
β-blockers	32 (39)	39 (47)	0.27
ACEI/ARB	53 (64)	46 (55)	0.27
CCB	24 (43)	27 (50)	0.85
Statins	65 (78)	66 (80)	0.44
ACC-AHA coronary classification			
Type B2 and C – no. (%)	39 (47)	42 (51)	0.64
Target vessel – no. (%)			
LAD	32 (39)	36 (43)	0.77
LCX	13 (16)	15 (18)	
RCA	33 (40)	29 (35)	
Multiple	5 (6)	3 (4)	
Amount of contrast medium (mL)	90 (73–130)	95 (76–119)	0.95
PCI operation time (min)	67 (49–90)	65 (50–95)	0.90
Puncture site – no. (%)			
Radial artery	52 (63)	51 (61)	0.74
Brachial artery	10 (12)	8 (10)	
Femoral artery	20 (24)	24 (29)	
Did not undergo PCI	1	0	
Catheter size – no. (%)			
6 Fr.	72 (88)	73 (88)	0.171
7 Fr.	7 (8)	10 (12)	
8 Fr.	3 (4)	0	
Did not undergo PCI	1	0	
Using device information			
No. of stents in procedure	1 (1–2)	1 (1–2)	0.139
DES – no. (%)	67 (88)	71 (89)	0.91
Maximal stent Diameter (mm)	3.0 (2.75–3.5)	3.0 (2.5–3.5)	0.23
Total stent Length (mm)	24 (16–40)	23 (18–33)	0.55
Post dilatation – no. (%)	57 (75)	64 (80)	0.45
Maximal dilatation pressure (atm.)	16.1 ± 4.3	16.8 ± 4.5	0.40

Data are presented as mean ± standard deviation, n (%), or median (interquartile range).

Renal dysfunction is defined as a baseline estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m².

RIPC indicates remote ischemic preconditioning; BMI, body mass index; DM, diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; LVEF, left ventricular ejection fraction; E, peak velocity of early diastolic filling wave; e', mitral annulus velocity; sCRN, serum creatinine; HgbA1C, hemoglobin A1C; CRP, C-reactive protein; BNP, brain natriuretic peptide; cTNT, cardiac troponin T; CK, creatine kinase; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blockers; AHA, American Heart Association; ACC, American College of Cardiology; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; DES, drug-eluting stent; atm., atmospheres.

criteria for myocardial injury associated with PCI from the third universal definition of myocardial infarction [12]. Blood samples to test for cTNT (99th percentile upper reference limit: 0.014 ng/mL) and

CK-MB were collected at 12 and 24 h after PCI. To avoid interhospital variations in the cTNT and CK-MB levels, these markers were evaluated at a single institution (SRL Inc., Hachioji Laboratory, Tokyo, Japan). The

study investigators collecting and analyzing the data were blinded to the treatment assignments.

The secondary outcomes were the incidence of pMD and the elevation of cardiac biomarker levels after PCI between the control and RIPC groups in a subgroup with an interaction effect reducing the incidence of pMD after PCI.

2.5. Statistics

Data were analyzed according to a predefined statistical analysis plan, and an independent statistician verified and replicated the analyses. Continuous variables are presented as mean \pm standard deviation or as median with interquartile range, depending on the Shapiro-Wilks test for normality. Categorical variables are presented as absolute value and proportion (%).

In the subgroup analysis, we used Student's *t*-test or the Mann-Whitney *U* test to compare continuous variables between the control and RIPC groups. The χ^2 test was used to compare categorical variables between the groups. We also used a repeated-measures linear mixed-effects model to assess cTNT and CK-MB as continuous variables. Independent variables in this model were the log-transformed baseline cTNT or CK-MB level and treatment arm, scheduled visit as a class variable (12 h, 24 h), and the interaction between the arm and the visit using a complex symmetrical matrix. We used the Bonferroni method as the post hoc test.

We used a multiple logistic regression model to calculate the odds ratio between study groups while adjusting for the following stratification factors: age (<65 or \geq 65 years), sex (male or female), renal dysfunction (baseline estimated glomerular filtration rate of <60 or \geq 60 mL/min/1.73 m²), and American College of Cardiology/American Heart Association coronary classification type B2 and C [8].

All analyses were performed with R software, version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria, <https://www.r-project.org/foundation/>) and SAS software, version 9.3 (SAS Institute Inc., Cary, NC). A value of $p < 0.05$ was considered statistically significant.

3. Results

Fig. 1 shows the flow diagram for the study. The RIPC study originally comprised 396 patients who were randomized to receive interventions. The current study included 262 patients (133 patients in the control group, 129 patients in the RIPC group), and the baseline characteristics between these groups were well balanced (Table S1, Supplementary File). Of the 166 current or former smokers, 83 served as the control group, and 83 from the RIPC group were included in the subgroup analysis. The patients' baseline characteristics are shown in Table 1. All patients received optimal medical therapy and maintenance dose of clopidogrel before PCI. We found no significant difference between groups. Table 1 also shows the information of PCI. No significant difference was observed in the proportion of ACC-AHA coronary classification type B2/C 47% vs. 51%; radial artery access 63% vs. 61%; drug-eluting stent use 88% vs. 89%; median of maximal stent diameter 3.0 mm vs. 3.0 mm; total stent length 24 mm vs. 23 mm between control and RIPC groups.

The incidence of pMD after PCI in the RIPC group was significantly lower than that in the control group in current or former smokers (28/83 patients [33.8%] vs. 43/83 patients [51.8%], respectively; $p = 0.018$) (Fig. 2). We also found a similar effect of RIPC in the reduction of pMD after PCI between current and former smokers (7/15 patients [47%] to 3/12 patients [25%], 46% relative risk reduction, $p = 0.42$ and 36/68 [53%] to 25/71 [35%], 33% relative risk reduction, $p = 0.041$, respectively) (Fig. 2). We also analyzed sequential changes in cardiac biomarker levels after PCI from baseline using a repeated-measures linear mixed-effects model (Fig. 3). Sequential changes in both cTNT and CK-

MB at 12 and 24 h after PCI in the RIPC group were significantly lower than those in the control group ($p = 0.009$ and $p = 0.030$, respectively). In a multiple logistic regression model adjusted for our stratification factors, RIPC in current or former smokers was also effective in reducing the incidence of pMD compared with the control group [adjusted odds ratio (95% confidence interval): 0.45 (0.24–0.86); $p = 0.016$] (Table 2).

In the overall patients, the logistic regression model showed that the subgroup including current or former smokers had a lower incidence of pMD after PCI (regression coefficient, -0.4 ; 95% confidence interval, -0.74 to -0.082 ; $p = 0.015$) (Fig. S1 and Table S2, Supplementary File). Because this model was adjusted for age, sex, renal dysfunction, and American College of Cardiology/American Heart Association coronary classification, tobacco smoking was an independent predictor of interacting with and enhancing the effect of RIPC on reducing the incidence of pMD after PCI.

4. Discussion

The results of this substudy suggest that RIPC might be appropriate for current or former smokers to improve pMD after elective PCI for stable coronary artery disease. The existence of a "smoker's paradox" implies that the outcomes of acute myocardial infarction may be more favorable in smokers than in nonsmokers [9,10]. Previous studies have suggested that the mechanism of the "smoker's paradox" is associated

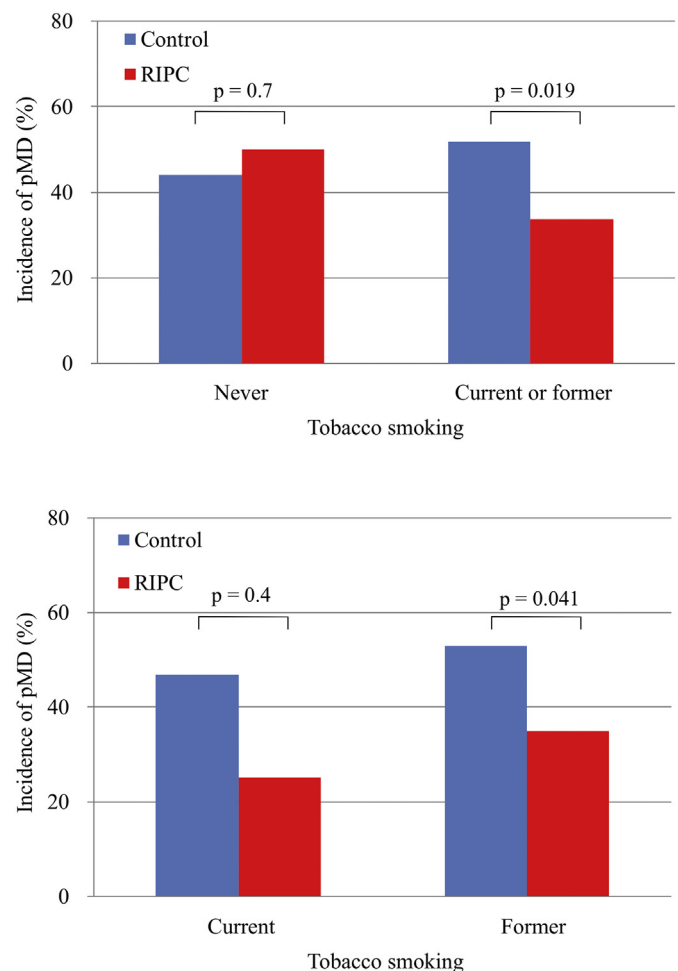


Fig. 2. Incidence of myocardial damage after percutaneous coronary intervention in current or former smokers. This figure shows the incidence of periprocedural myocardial damage (pMD) after percutaneous coronary intervention for the controls versus the remote ischemic preconditioning (RIPC) group among never, current, and former smokers.

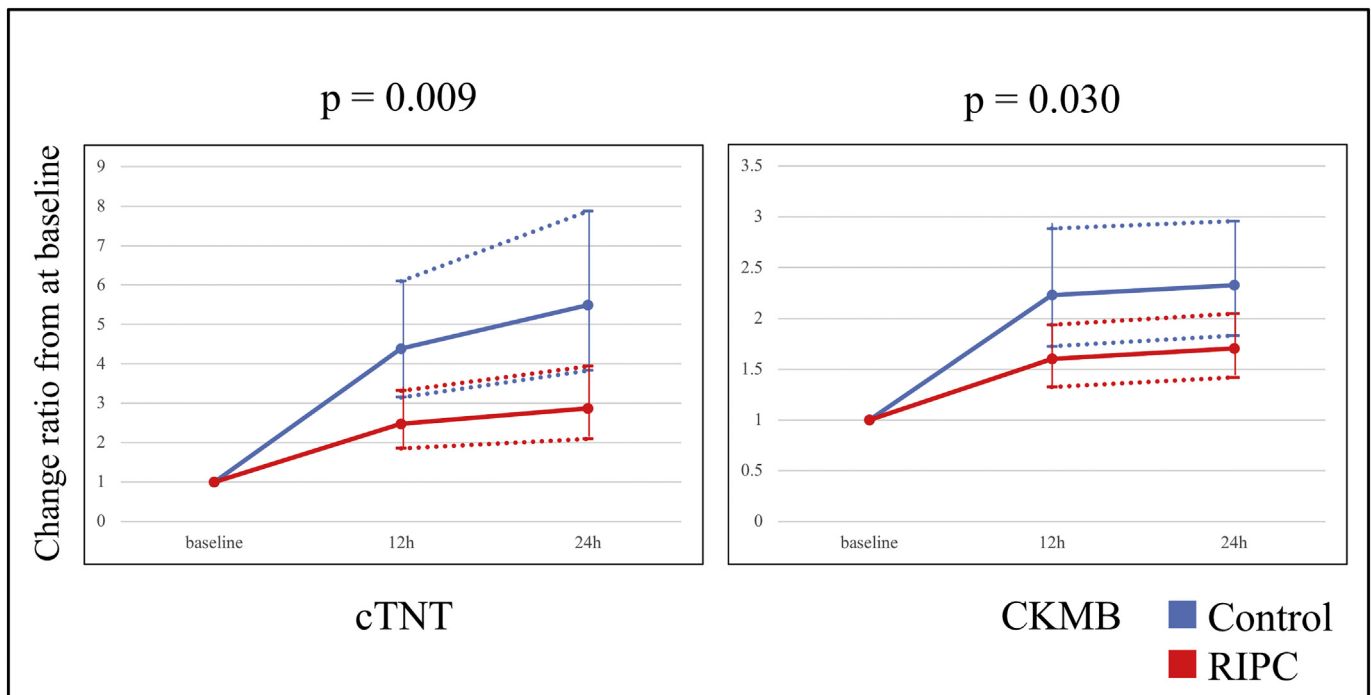


Fig. 3. Sequential changes in cardiac biomarker release after percutaneous coronary intervention in smokers. This figure shows the sequential changes from baseline in the release of cardiac biomarkers after percutaneous coronary intervention for the control group (blue line) versus the RIPC group (red line) in current or former smokers. (A) Sequential change ratios (mean 95% confidence interval) of cardiac troponin T (cTNT) from baseline. (B) Sequential change ratios in creatine kinase myocardial band (CK-MB) from baseline. The estimated change ratios of cTNT (12 or 24 h from baseline) for the RIPC group versus the controls were 2.48 [95% confidence interval (CI): 1.86–3.32] or 2.87 (95% CI: 2.09–3.94) vs. 4.38 (95% CI: 3.15–6.09) or 5.49 (95% CI: 3.83–7.87), respectively ($p = 0.009$). The estimated change ratios of CK-MB (12 or 24 h from baseline) for the RIPC group versus the controls were 1.62 (95% CI: 1.32–1.94, $p = 0.23$) or 1.70 (95% CI: 1.42–2.05) vs. 2.23 (95% CI: 1.73–2.89) or 2.33 (95% CI: 1.83–2.96), respectively ($p = 0.030$). RIPC, remote ischemic preconditioning.

with a procoagulant state with effects on endothelial dysfunction, increased platelet activation and aggregation, increased circulating levels of fibrinogen, and increased thrombin generation [13,14]. Conversely, RIPC offers an organ-protective effect partly due to endothelial nitric oxide synthase by stimulating the neurohumoral pathway [2,15]. These findings suggest that smoking could enhance the myocardial preconditioning effect to relieve endothelial dysfunction by RIPC, which may explain our study results.

The mechanism of preconditioning remains unclear. Some data [2,15] support a role of nitrate oxide, stromal cell-derived factor, interleukin, and micro-RNA; however, these factors alone insufficiently explain the protection seen with RIPC. Additionally, which patients benefit most from the effect of RIPC remains unclear. Only a small number of single-center studies with small sample sizes have evaluated RIPC in patients with elective PCI, and the subgroup or exploratory analysis was insufficient. A previous post hoc subgroup analysis of a single-center randomized controlled trial to investigate the efficacy of RIPC in patients with ST-elevated myocardial infarction treated with primary

PCI [16] showed that smoking might reduce the myocardial protective effect of RIPC because smoking disrupts the transduction pathways involved in RIPC. The present study, however, was subanalysis of the largest multicenter clinical trial to date of patients undergoing elective PCI and included a post hoc analysis to investigate the effect of RIPC for pMD after PCI in smokers. RIPC is a favorable, low-cost, and safe treatment providing myocardial protection; however, patient stress and complications are concerns. Our results showed that RIPC was more effective in smokers, and we promote RIPC specifically for these patients. However, our post hoc finding was obtained from a limited sample size, and the result requires further investigation in large-scale multicenter trials.

This study has certain limitations. First, the study was a subanalysis of a randomized controlled trial. Although the RINC study is the largest randomized controlled trial to date of RIPC in patients undergoing elective PCI, our study sample size was comparatively small because of the subgroup analysis. Second, we defined pMD in this study by the high-sensitivity cTNT and CK-MB levels. However, myocardial infarction with PCI (type 4a) is defined by the cTNT level, but not the CK-MB level, in the third universal definition of myocardial infarction [12]. High-sensitivity cTNT is a more sensitive and specific marker of myocardial injury than is CK-MB. A previous study showed that CK-MB elevation was more strongly associated with myonecrosis and adverse events following PCI than was cTNT elevation. Therefore, the definition of pMD in this study could reflect a clinically meaningful surrogate marker [17].

In conclusion, our subanalysis of the RINC study, which was a multicenter randomized controlled trial, showed that tobacco smoking had a myocardial protective effect following upper-limb RIPC on pMD after PCI and significantly reduced the incidence of pMD after PCI in current or former smokers. These results suggest that RIPC might improve pMD after PCI in smokers. To confirm the favorable effect of RIPC on

Table 2

Odds ratios of remote ischemic preconditioning for periprocedural myocardial damage after percutaneous coronary intervention in current or former smokers.

	Odds ratio (95% CI)		p Value
Model 1	0.47	(0.25–0.89)	0.019
Model 2	0.46	(0.25–0.87)	0.017
Model 3	0.45	(0.24–0.86)	0.016

Model 1: Crude model.

Model 2: Adjusted for age and sex.

Model 3: Adjusted for age, sex, renal dysfunction, diabetes, and ACC-AHA coronary classification type B2 and C.

CI indicates confidence interval; ACC, American College of Cardiology; AHA, American Heart Association.

pMD after PCI in smokers, further investigation in a multicenter prospective study is required.

Disclosures

Declaration of interest statement

KE, TM, KK, MN, MD, AT, and KN declare that they have no financial or personal competing interests. MM declares that he receives honoraria from Abbott Vascular Japan Co., Ltd. (Aichi, Japan) and lecture fees from Medtronic Japan Co., Ltd. (Tokyo, Japan), Daiichi Sankyo Co., Ltd. (Tokyo, Japan), and Bayer Yakuhin, Ltd. (Osaka, Japan). HI declares that he receives lecture fees from Chugai Pharmaceutical Co., Ltd. (Tokyo, Japan).

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Previous presentation

The findings of this study were presented in part at the European Society of Cardiology congress 2016, Rome, Italy, on August 28, 2016, and at the 26th Annual Scientific Meeting of the Japanese Association of Cardiovascular Intervention and Therapeutics, Kyoto, Japan, on July 8, 2017.

Author contributions

KE, TM, and KK contributed to the study design. KE, TM, KK, TH, KN, and HI contributed to the data interpretation and drafting of the manuscript. All authors have read the final manuscript and confirm that they meet the ICMJE criteria for authorship.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2018.12.005>.

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