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Effects of delayed remote ischemic preconditioning on peri-operative myocardial injury in patients undergoing cardiac surgery — A randomized controlled trial☆

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ABSTRACT

Background: Remote ischemic preconditioning (RIPC) has two time windows for organ protection: acute and delayed. Previous studies have mainly focused on the acute time window to evaluate organ protection by RIPC. We evaluated myocardial protection by delayed RIPC in adult patients undergoing cardiac surgery.
Methods: A total of 160 adult patients undergoing cardiac surgery with cardiopulmonary bypass were randomized to receive either delayed RIPC (four cycles of 5 min of ischemia followed by 5 min of reperfusion by inflation to 200 mm Hg and deflation of a blood pressure cuff on the upper arm) or the control treatment 24–48 h before surgery. The primary endpoint was post-operative troponin I levels serially measured for 72 h. Secondary endpoints included post-operative serum creatinine levels, acute kidney injury, and composite complications.
Results: There were no significant differences in post-operative troponin I values. The incidence of acute kidney injury, defined by the Acute Kidney Injury Network staging system, was lower in the delayed RIPC group compared to the control group (30.0% vs. 47.5%; relative risk, 0.768; 95% confidence interval, 0.599–0.985; $p = 0.023$). Moreover, the occurrence of composite complications was lower in the delayed RIPC group compared with the control group (65.0% vs. 81.3%; relative risk, 0.536; 95% confidence interval, 0.311–0.924; $p = 0.020$).
Conclusions: While RIPC did not provide cardioprotective effects in patients undergoing cardiac surgery, it appeared to reduce acute kidney injury, as well as the rate of composite complications.

1. Introduction

Remote ischemic preconditioning (RIPC) by brief episodes of limb ischemia and reperfusion provides protection against acute ischemia–reperfusion injury in distal organs [1]. RIPC is a non-invasive and powerful therapeutic intervention for inducing organ protection and is associated with a reduced risk of peri-operative myocardial injury after cardiac surgery [2–4]. Additionally, it provides a protective effect to other distal organs, such as the kidneys and lungs [4–7].

The protective effect of preconditioning has a biphasic pattern; acute protective effects wane after a few hours, but a delayed second window of protection occurs after 12–24 h [8,9]. The acute effects rely on the activation of existing signaling molecules, whereas the delayed effects are achieved by increased expression of protective proteins [8,9]. Delayed phase preconditioning provides sustained protection from myocardial infarction, as well as protective potential against myocardial stunning, arrhythmia, and endothelial dysfunction [8].

However, unlike acute RIPC, clinical trials investigating the benefits of delayed RIPC are lacking. We hypothesized that delayed RIPC has clinically significant myocardial protective effects. The aim of the study was to investigate whether delayed RIPC decreased myocardial injury in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).

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2. Methods

2.1. Study population

Ethical approval for this study (1211-041-441) was provided by the institutional review board of Seoul National University Hospital. The study protocol was registered at ClinicalTrials.gov (NCT01903161). Written informed consent was obtained from all patients enrolled in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. There were no important changes to the methods or outcomes after trial commencement. Patients aged 18 to 80 years and scheduled for elective cardiac surgery with CPB were included. Exclusion criteria were as follows: left ventricular ejection fraction < 30%, pre-operative administration of vasopressors or inotropes, chronic liver disease with Child-Pugh class C, chronic kidney disease requiring dialysis, diabetes, peripheral vascular disease affecting the upper limbs, descending thoracic aortic surgery, and rare surgeries, such as cardiac transplantation or correction of congenital anomalies. A total of 160 patients were included in the study from May 2013 to January 2015.

2.2. Randomization

This was a double-blind, parallel-group randomized study conducted at the Seoul National University Hospital, a tertiary hospital in Seoul, Korea. Eligible patients were randomly allocated to either the delayed RIPC group or the control group using a computer-generated list. The randomization sequence was created with a 1:1 allocation using a random block size of 4. The random list was generated by a statistician who was not involved in the study and who was blinded to all patients, medical personnel, and investigators.

2.3. Remote ischemic preconditioning

An independent nurse performed RIPC 24 to 48 h prior to surgery. RIPC consisted of four cycles of 5 min of ischemia, which was induced by a blood pressure cuff in the upper arm inflated to 200 mmHg, followed by 5 min of reperfusion, during which the cuff was deflated. In the control group, the same blood pressure cuff was placed around the upper arm, but the cuff was inflated to 10 mm Hg and ischemic preconditioning was not induced.

2.4. Anesthesia and cardiopulmonary bypass techniques

All patients received standard peri-operative care. Routine monitoring included a bispectral index, cerebral oximetry, a pulmonary artery catheter, and transesophageal echocardiography. Anesthesia was induced with intravenous midazolam 0.15 mg/kg, sufentanil 1 μg/kg, and vecuronium 0.15 mg/kg, and was maintained with target controlled infusions of remifentanil 6–12 ng/mL and propofol 1.5–2.5 μg/mL, maintaining bispectral index values between 40 and 60.

Study patients underwent cardiac surgery using a non-pulsatile CPB technique with a membrane oxygenator and cardiotomy suction. Cardiac protection was achieved using antegrade or retrograde cold-blood cardioplegia. Heparin was administered before CPB and was reversed by protamine after discontinuing CPB. The target activated clotting times during surgery were more than 500 s. At the end of surgery, patients were transferred to the intensive care unit. Intensive care unit management was provided by attending physicians and standardized for all patients according to the routine protocol of our institution.

2.5. Study outcomes

The primary endpoint was serum troponin I, measured at 1, 6, 12, 24, 48, and 72 h post-operatively. Serum troponin I has previously been used as a marker of perioperative myocardial injury after cardiac surgery [4,10]. The secondary endpoints included post-operative serum creatinine levels, acute kidney injury (AKI), defined by the Acute Kidney Injury Network (AKIN) staging system [11], and composite complications. In the AKIN criteria, the pre-operative creatinine levels were used as baseline levels. Composite complications included in-hospital death, myocardial infarction, new onset atrial fibrillation, stroke, AKI, respiratory failure, persistent cardiogenic shock, and gastrointestinal complications [12]. Myocardial infarction was defined as an elevation of cardiac biomarker values (>10× 99th percentile upper reference limit) in patients with normal baseline troponin values (<99th percentile upper reference limit). Additionally, new pathological Q waves or new left bundle branch block, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, was required [13]. Respiratory failure was defined as the need for post-operative mechanical ventilation for >72 h. Persistent cardiogenic shock was defined as use of inotropic agents, vasopressors, or a mechanical assist device for more than 72 h. Gastrointestinal complications were defined as gastrointestinal bleeding requiring transfusion, pancreatitis requiring nasogastric suction, cholecystitis requiring drainage, or mesenteric ischemia requiring exploration.

2.6. Statistical analysis

In the study by Hong et al. [10], the area under the curve (AUC) of post-operative troponin I was 69.4 ± 74.5 h·ng/mL. Presuming that the difference of 50% in troponin I AUC was clinically significant, 74 patients were required in each group to detect a difference, with a type I error of 0.05 and a power of 0.8. To allow for dropouts, 80 patients were recruited for each group. Continuous variables of patient demographics and group characteristics were compared using the Student's *t*-test or the Mann–Whitney U test after testing for normality. Categorical variables were analyzed using the χ^2 test or Fisher's exact test, where appropriate. Changes in serum troponin I and creatinine over time were analyzed using repeated measures analysis of variance (ANOVA) or the generalized estimating equations method. Student's *t*-test was used to compare these data at each time point. A p value < 0.05 was regarded as statistically significant. The AUC was determined using the standard trapezoidal method. Data were analyzed using SPSS ver. 21.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patients

Of the 232 patients screened, 72 were excluded; 16 for left ventricular ejection fraction < 30%, 18 for renal impairment requiring renal replacement therapy, 19 for diabetes, 9 for pre-operative administration of vasopressors or inotropes, 8 for peripheral vascular disease, and 2 for declining to participate (Fig. 1). One hundred sixty randomized patients received the allocated interventions and were included in the final analysis. Demographic data for the patients are shown in Table 1. Time from RIPC or sham to aorta cross clamp and reperfusion, aortic cross-clamp time, duration of CPB, and surgery were comparable between groups (Table 2).

3.2. Serum troponin I

Serum troponin I levels significantly increased after surgery and peaked 1 h post-operatively (Fig. 2). Changes in serum troponin I were not significantly different between groups (p = 0.662). Moreover, the total 72 h AUC of troponin I did not differ between the delayed RIPC and control groups (median, interquartile range [IQR], 743.45, 276.36–1464.06 h·ng/mL vs. 530.78, 264.58–1232.61 h·ng/mL, p = 0.414).

3.3. Acute kidney injury

The incidence of post-operative AKI based on the AKIN staging system was decreased in the delayed RIPC group compared to the control group (30.0% vs. 47.5%; RR, 0.768; 95% CI, 0.599–0.985; p = 0.023, Table 3). In both groups, most AKIs were categorized as AKIN class 1. The number of patients categorized as AKIN class 3, which includes individuals who received renal replacement therapy, was comparable between groups (5.0% vs. 5.0%). Changes in serum creatinine were not significantly different between groups (p = 0.615, Fig. 3).

3.4. Composite complications

The rate of composite complications was lower in the delayed RIPC group compared to the control group (65.0% vs. 81.3%; RR, 0.536; 95% CI, 0.311–0.924; p = 0.020). Causes of death included cardiogenic shock (four patients in the control group and one patient in the delayed RIPC group), diffuse bleeding of unknown etiology (one patient in the control group), and septic shock (one patient in the delayed RIPC group). Incidence of post-operative new onset atrial fibrillation was lower in the delayed RIPC group with a marginal statistical significance (33.8% vs. 48.8%; RR, 0.774; 95% CI, 0.594–1.008; p = 0.054, Table 3). Individual risks of stroke, respiratory failure, persistent cardiogenic shock, and gastrointestinal complications were lower in the delayed RIPC group, but the difference did not reach statistical significance.

4. Discussion

In patients undergoing cardiac surgery with CPB, we did not detect cardioprotective effects of delayed RIPC, as assessed by troponin I levels. However, delayed RIPC appeared to reduce both AKI and composite complications compared with controls.

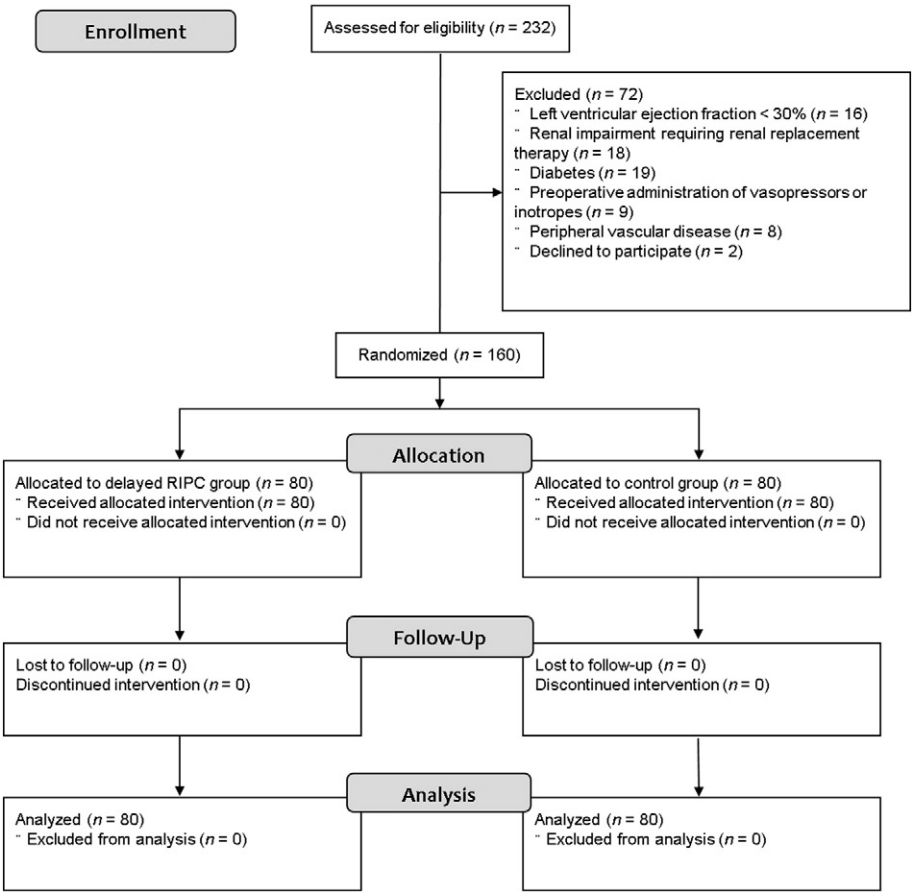

Fig. 1. Consort diagram.

Table 1
Baseline characteristics.

	Delayed RIPC (n = 80)	Control (n = 80)	p value
Age (year)	61.8 (11.1)	62.8 (13.2)	0.618
Male gender	39 (48.8%)	46 (57.5%)	0.267
Weight (kg)	58.0 (10.4)	59.3 (8.9)	0.393
Height (cm)	160.0 (9.7)	162.6 (10.0)	0.102
Body mass index (kg/cm^2)	22.5 (3.0)	22.4 (2.8)	0.789
Hypertension	24 (30.0%)	31 (38.8%)	0.244
Previous stroke	6 (7.5%)	8 (10.0%)	0.576
Current smoker	13 (16.3%)	15 (18.8%)	0.677
Left ventricle ejection fraction (%)	59.2 (8.9)	57.7 (9.8)	0.335
Congestive heart failure	13 (16.3%)	11 (13.8%)	0.658
Previous cardiac surgery	21 (26.3%)	15 (18.8%)	0.256
EuroSCORE II	2.7 (2.6)	2.4 (1.9)	0.458
Serum troponin I (ng/mL)	0.0 (0.0)	0.8 (6.1)	0.316
Serum creatinine (mg/dL)	0.9 (0.2)	0.9 (0.3)	0.684
Serum lactate (mmol/L)	1.1 (0.4)	1.1 (0.5)	0.490
Platelet count ($\times 10^9$/L)	197.9 (57.9)	200.0 (65.5)	0.886
Fibrinogen (mg/dL)	279.0 (69.5)	296.4 (56.1)	0.056
Type of procedures			
Mitral valve (alone)	21 (26.3%)	14 (17.5%)	0.181
Aortic valve (alone)	22 (27.5%)	22 (27.5%)	>0.999
Other valve (alone)	4 (5.0%)	4 (5.0%)	>0.999
Aorta surgery (alone)	2 (2.5%)	4 (5.0%)	0.681
Other procedures (alone)	4 (5.0%)	5 (6.3%)	0.732
Combined procedures	27 (33.8%)	31 (38.8%)	0.511
Coronary artery bypass graft	5 (6.3%)	5 (6.3%)	>0.999

Data are presented as mean (SD), or number (proportion). RIPC, remote ischemic preconditioning; EuroSCORE II European System for Cardiac Operative Risk Evaluation II.

Cardiac surgery with CPB can cause global myocardial ischemia–reperfusion injury, the presence of which can be quantified by measuring cardiac enzymes and is associated with worse clinical outcomes. RIPC is a non-invasive, inexpensive, and powerful therapeutic intervention for inducing cardioprotection in patients undergoing cardiac surgery; previous studies have shown that RIPC reduces peri-operative myocardial injury and possibly improves prognosis [3,4]. However, the clinical effects of delayed RIPC have not been adequately studied. Wagner et al. first reported that the delayed phase of RIPC could reduce peri-operative myocardial injury in cardiac surgery [14]. However, this effect was not evident in the study by Pavione et al., which was performed in children undergoing CPB [15]. We performed a meta-analysis of clinical trials assessing delayed RIPC in adults undergoing cardiac surgery, including the present study and the previous study of Wagner et al., using data from a total of 226 patients (see Supplemental Figure Content, which demonstrates the results of meta-analysis). Delayed RIPC reduced post-operative new-onset atrial fibrillation (odds ratio [OR] = 0.558; 95% CI, 0.319–0.977; p = 0.041). However, it did not reduce post-operative myocardial infarction, ventricular arrhythmia, or delirium.

Table 2
Intra-operative characteristics.

	Delayed RIPC (n = 80)	Control (n = 80)	p value
Time from RIPC or sham to aorta cross clamp (h)	29.5 (5.8)	29.3 (6.9)	0.837
Time from RIPC or sham to reperfusion (h)	31.9 (5.9)	31.8 (6.7)	0.923
Aortic cross-clamp duration (min)	145.2 (59.0)	149.2 (58.7)	0.663
Cardiopulmonary bypass duration (min)	228.4 (85.8)	233.4 (79.2)	0.707
Duration of surgery (min)	447.4 (142.2)	445.7 (134.8)	0.937

Data are presented as mean (SD). RIPC, remote ischemic preconditioning.

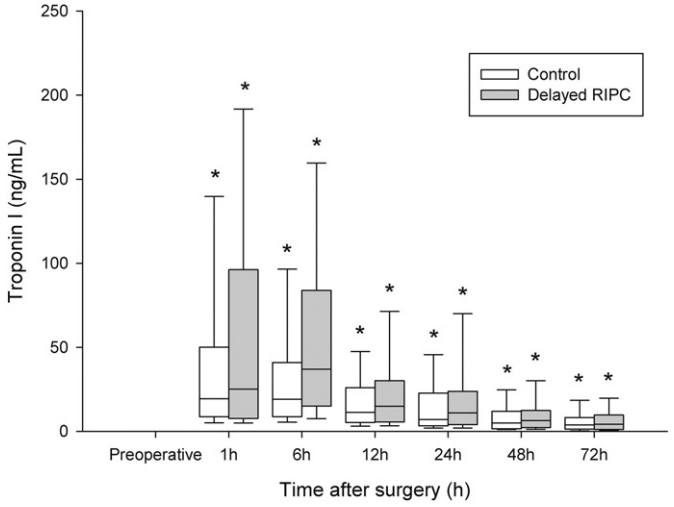

Fig. 2. Peri-operative concentrations of serum troponin I. Data are presented as the median and quartiles. Error bars indicate the 90th and 10th percentiles. Asterisks indicate significant changes compared with the pre-operative value (* $p < 0.05$). RIPC, remote ischemic preconditioning.

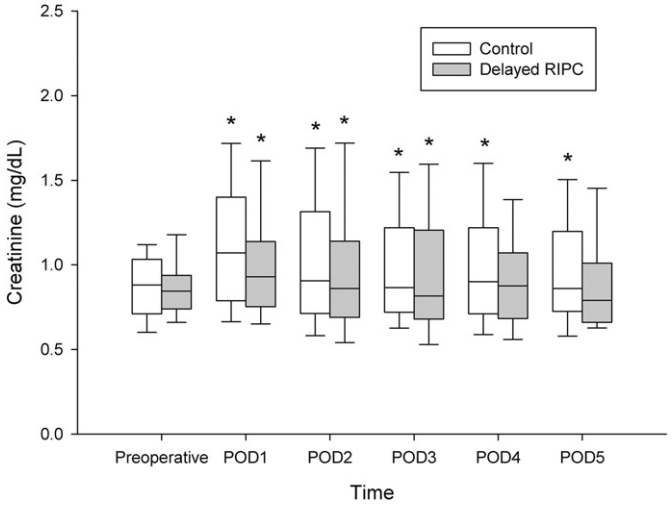

Fig. 3. Peri-operative concentrations of serum creatinine. Data are presented as the median and quartiles. Error bars indicate the 90th and 10th percentiles. Asterisks indicate significant changes compared with the pre-operative value (* $p < 0.05$). RIPC, remote ischemic preconditioning; POD, post-operative day.

Contrary to our study, a meta-analysis of clinical trial data on acute RIPC showed a myocardial protective effect [2], which could be due to various possibilities. First, acute RIPC may be more effective than delayed RIPC for myocardial protection. In a previous animal study, only acute RIPC decreased reperfusion-induced ventricular arrhythmias [16]. However, we did not compare early and delayed RIPC in this study. Second, previous acute RIPC studies with positive results were mostly performed in patients undergoing coronary artery bypass graft or uncomplicated single valve surgery [2,4,10], while in this study, 51 patients underwent complicated cardiac surgeries such as double or triple valve surgery, and aorta cross clamping time was much longer than in previous studies [3,4]. These findings raise the possibility that the myocardial protective effects of RIPC might be insufficient in complicated cardiac surgeries with significant myocardial injury.

The prevalence of AKIN class 1 AKI was significantly less in the delayed RIPC group compared to the control group in this study. It is well-known that AKI is frequent after cardiac surgery and is associated with morbidity and mortality [17]. Moreover, several studies have demonstrated the beneficial role of acute phase RIPC on kidney protection [6,7]. Interestingly, in a meta-analysis investigating RIPC in animal models, delayed RIPC was more effective than acute RIPC in preventing renal injury by ischemic reperfusion injury [18]. This is the first study to report the beneficial effects of delayed RIPC on post-operative AKI following cardiac surgery in humans. Considering that even a small increase in serum creatinine levels is associated with poor outcomes [17], our study suggests that delayed RIPC might be a therapeutic option to attenuate AKI.

In the present study, the rate of composite complications was lower in the delayed RIPC group than in the control group. It has been demonstrated that RIPC has systemic protective effects on various distal organs [1];

Table 3
Clinical outcomes.

	Delayed RIPC (n = 80)	Control (n = 80)	RR (95% CI)	p value
Mechanical ventilation time (h)	20 (15–46)	20 (16–46)		0.877
ICU length of stay (day)	4 (3–7)	4 (3–8)		0.525
Hospital length of stay (day)	14 (9–20)	14 (10–20)		0.874
Use of IABP or ECMO	8 (10.0%)	10 (12.5%)	0.800 (0.333–1.922)	0.617
Reoperation for bleeding	4 (5.0%)	6 (7.5%)	0.667 (0.196–2.273)	0.514
In-hospital mortality	2 (2.5%)	5 (6.3%)	0.400 (0.080–2.002)	0.246
Cardiovascular mortality	1 (1.3%)	4 (5.0%)	0.250 (0.029–2.188)	0.367
Myocardial infarction	0 (0.0%)	3 (3.8%)	NA	0.080
New-onset atrial fibrillation	27 (33.8%)	39 (48.8%)	0.692 (0.473–1.013)	0.054
Ventricular arrhythmia	21 (26.3%)	21 (26.3%)	1.000 (0.595–1.681)	>0.999
Stroke	1 (1.3%)	1 (1.3%)	1.000 (0.064–15.712)	>0.999
Post-operative delirium	18 (22.5%)	17 (21.3%)	1.059 (0.589–1.902)	0.848
Acute kidney injury	24 (30.0%)	38 (47.5%)	0.632 (0.421–0.948)	0.023
AKIN 1	15 (18.8%)	33 (41.3%)		
AKIN 2	5 (6.3%)	1 (1.3%)		
AKIN 3[a]	4 (5.0%)	4 (5.0%)		
RRT within 48 h	2 (2.5%)	2 (2.5%)	1.000 (0.144–6.926)	>0.999
RRT in-hospital	6 (7.5%)	6 (7.5%)	1.000 (0.337–2.969)	>0.999
Respiratory failure	6 (7.5%)	10 (12.5%)	0.600 (0.229–1.573)	0.292
Persistent cardiogenic shock	14 (17.5%)	14 (17.5%)	1.000 (0.510–1.960)	>0.999
Gastrointestinal complications	2 (2.5%)	3 (3.8%)	0.667 (0.114–3.883)	0.650
Composite complications[b]	52 (65.0%)	65 (81.3%)	0.800 (0.660–0.970)	0.020

Data are presented as median (interquartile range) or number (proportion). [a] includes RRT, [b] composite complications include in-hospital death, myocardial infarction, new onset atrial fibrillation, stroke, acute kidney injury, respiratory failure, and persistent cardiogenic shock, and gastrointestinal complication. CI, confidence interval; RR, relative risk; RIPC, remote ischemic preconditioning; ICU, intensive care unit; IABP, intraaortic balloon pump; ECMO, extracorporeal membrane oxygenation; AKIN, Acute Kidney Injury Network; RRT, renal replacement therapy; NA, not applicable.

however, in our previous clinical trial on 1280 cardiac surgery patients, acute RIPC did not decrease composite complications [12]. Recent multicenter trials also failed to show relevant clinical benefits of acute RIPC in cardiac surgery [19,20]. The authors suggested that lack of standardization of peri-operative anesthesia may have affected the efficacy of RIPC. Then, delayed RIPC 24 to 48 h prior to the cardiac surgery may be more practical in the clinical setting compared with the acute RIPC which may be affected by multiple confounders such as propofol during the surgery. Also, we hypothesize that delayed RIPC does not result in the transient harmful effects of RIPC techniques leading to inflammation and coagulation [21,22]; if true, this suggests that delayed RIPC may be more beneficial in cardiac surgery patients compared with acute RIPC. Although the study was not powered to assess the secondary endpoints, the rate of composite complications was lower in the delayed RIPC group than in the control group. Also, there were trend of reduction of in-hospital mortality, cardiovascular mortality, myocardial infarction and new-onset atrial fibrillation.

The exact mechanisms underlying the organ protective signal transfer from remote ischemic stimuli to distal organs are not yet clear; however, neuronal and humoral transmission are widely suggested [1]. Time-dependent transcription and synthesis of cardioprotective mediators or neuronal release of a signal molecule may account for the two distinct windows of organ protection in RIPC [1,9]. Unlike acute RIPC, delayed RIPC requires the synthesis of new proteins such as nitric oxide synthase, cyclooxygenase-2, aldose reductase, and antioxidant enzymes [8,9]. Through its systemic effects, delayed RIPC may provide distal organ protection, such as kidney protection, as found in this study. While the acute preconditioning effect lasts only 2–3 h, delayed preconditioning has a longer duration of protection, ranging from 3 to 4 days [8,9]. It is not always easy in cardiac surgeries even in elective cases that ischemia–reperfusion injury occur on the exact protective time window. It may be one of the reasons for the inconsistent results of RIPC in previous clinical studies. This longer time window may be more beneficial in a real clinical setting, such as during long aorta cross clamp durations in complex cardiac surgeries in which peri-operative ischemic insults do not always occur within 2–3 h after preconditioning.

This study had several limitations. First, study was not powered to detect AKI or composite outcomes, and the findings should be interpreted with caution. Second, confounders such as patient age, sex, comorbidities, and drugs may have affected the study outcomes. In this study, patients with diabetes were excluded since release of a humoral cardioprotective factor is attenuated in diabetic patients [23]. Beta blockers are known to inhibit preconditioning pathways [23]; however, use of beta blockers was comparable between groups. Third, the ischemic preconditioning protocol is not standardized and, under certain conditions, the RIPC stimulus may be insufficient to elicit cardioprotection. For example, optimal site, timing, and duration of the ischemic preconditioning are not definite. Fourth, the choice of anesthetics can be a major confounder in surgical settings. We avoided volatile anesthetics because inherent preconditioning might be fully exploited by a volatile anesthetic itself [24]. Kottenberg et al. reported that propofol may interfere with the cardioprotective effects of RIPC [25]. However, several studies reported a significant decrease in myocardial injury following RIPC under propofol anesthesia [3,5,10]. Thus, more evidence is needed to clarify the effects of propofol on RIPC effects. Moreover, larger multicenter randomized clinical trials are required to fully elucidate the effects of delayed RIPC on clinical outcomes.

In summary, delayed RIPC did not provide cardioprotective effects in patients undergoing cardiac surgery with CPB, but reduced AKI and composite complications.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.10.111.

Conflicts of interest

None.

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