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Effect of remote ischemic preconditioning with postconditioning on postoperative lung function in patients undergoing cardiac surgery involving cardiopulmonary bypass

심폐우회술을 이용한 심장 수술 환자에서 원격 허혈성 전조건화 및 후조건화가 수술 후 폐기능에 미치는 영향

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의학과 마취통증의학 전공

민 정 진

Abstract

Background: Remote ischemic preconditioning is a protective mechanism in which transient ischemia to a distant organ protects the subsequent sustained ischemia-reperfusion injury of a target organ. We hypothesized that remote ischemic preconditioning with postconditioning (RIPC) might alleviate the pulmonary dysfunction after cardiac surgery involving cardiopulmonary bypass (CPB).

Methods: A total of 76 patients who underwent elective cardiac surgery involving CPB were randomized into the control group or RIPC group. In the RIPC group, four cycles of 5-min ischemia and 5-min reperfusion were administered two times to the upper limb: before CPB and after CPB. The primary endpoint was to compare the lung function evaluated by PaO_2/F_IO_2 ratio and the secondary endpoint was to compare the other pulmonary variables between the two groups at postoperative 6, 12, 18, 24 hours.

Results: The mean PaO_2/ F_IO_2 value was significantly higher in the RIPC group than in the control group at 24 hour after operation (290 ± 96 *vs*. 387 ± 137, p = 0.001) and the proportion of patients under mechanical ventilation longer than 48 hours was significantly higher in the control group (23 % *vs*. 3 % , $p < 0.05$). However, there were no significant differences on other parameters including oxygenation at other time points, systemic inflammatory markers, postoperative mechanical ventilation time and duration of ICU stay.

Conclusion: RIPC improved oxygenation at postoperative 24 hours and decreased the number of patients requiring ventilator care longer than 48 hours in patients undergoing elective cardiac surgery involving CPB. However, to determine the clinical significance of these protective effects, further studies would be required.

Keywords: remote, ischemic, preconditioning, postconditioning, lung, oxygenation

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Contents

List of Tables

List of Figures

Introduction

Despite the improvements of surgical techniques, materials and intraoperative and postoperative care, pulmonary dysfunction after cardiac surgery involving cardiopulmonary bypass (CPB) is still common and complicates the postoperative recovery. After cardiopulmonary bypass, the lungs of the patients are injured by various degrees and 8-15% of patients need to be mechanically ventilated for more than 48 hours.[1] Although most of the injuries may be subclinical functional changes, some of the patients went into more severe complications such as adult respiratory distress syndrome.[2, 3]

Although the etiology of the pulmonary dysfunction after cardiopulmonary bypass is thought to be multifactorial including intra- and extra-CPB factors,[4] [5] pulmonary ischemia-reperfusion injury is one of the main contributors because pulmonary arterial blood flow is arrested during CPB. During CPB, pulmonary endothelium and adjacent parenchymal tissues often receive the most prolonged ischemic insult than any other organs. [6]

Remote ischemic preconditioning (RIPC) is the protective mechanism in which transient ischemia of distant organs protects the subsequent sustained ischemia-reperfusion injury of target organs. This could be induced by a simple and noninvasive technique such as transient limb ischemia using pneumatic cuff. [7] In the previous animal studies, RIPC showed powerful protective effect on various organs including heart, lung, liver, kidney, spinal cord and skeletal muscle. [8-14] In human, many clinical studies showed protective effect of RIPC mainly on myocardium. [15, 16] However, with regard to lung protection, the number of randomized clinical studies was relatively small and the effect or time course of the RIPC is still less conclusive despite of the several studies published.[17-19]

We evaluated the protective effect of RIPC on pulmonary function after cardiac surgery involving CPB in this single center substudy of our previous RIPC effect on clinical outcome study, a prospective randomized clinical trial conducted at two tertiary centers in patients undergoing cardiac surgery. In this study, remote ischemia was induced twice, before (preconditioning) and after CPB (postconditioning), using pneumatic cuff in the upper limb to augment the protective effects. Our primary endpoint was to compare the lung function evaluated by PaO_2/ F_IO_2 ratio and the secondary endpoint was to compare other pulmonary variables or inflammatory markers between the two groups.

Methods

Patients

As described elsewhere, our previous RIPC Effect on Clinical Outcome study was a prospective, randomized trial of control versus RIPC effect on postoperative major adverse outcomes in 1280 patients who underwent elective cardiac surgery at two tertiary care centers (Seoul National University Hospital and Asan Medical Center).

The current substudy was conducted with a random subset of 76 patients among participants at Seoul National University Hospital of RIPC Effect on Clinical Outcome study.

The protocol of this substudy was approved by the institutional review board and written informed consent was obtained from every patient. We enrolled patients aged from 18 to 80 years admitted to Seoul National University Hospital for elective open cardiac surgery involving cardiopulmonary bypass (CPB). Exclusion criteria were: emergent operation, a left ventricular ejection fraction less than 30 %, preoperative use of an inotropic agent or a mechanical assist device, severe hepatic or renal disease, recent myocardial infarction (within 7 days), preoperative significantly decreased pulmonary function (e.g. using mechanical ventilator, with oxygen therapy, tachypnea, orthopnea, active lung lesion on chest x-ray, the ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) less than 50% of predicted value, pulmonary artery hypertension (mean pulmonary artery pressure > 35 mmHg), any intracardiac shunts, recent systemic infection or sepsis (within 7 days), preoperative systemic or local steroid therapy.

Randomization and remote ischemic preconditioning with postconditioning protocol

On the morning of the surgery, patients were randomly allocated to either the RIPC group or to the control group according to the computerized randomization list. The surgeons and anesthesiologists were unaware of the patient allocation. The group allocation was blinded to the clinician and the investigators who were involved in the clinical care or the data collection until data analysis.

The remote ischemic preconditioning with postconditioning protocol was the same as for our previous clinical outcome study. Both preconditioning and postconditioning were induced by four cycles of 5-min ischemia and 5-min reperfusion in the upper limb using a pneumatic blood pressure cuff

inflated to a pressure of 200 mmHg by an anesthesia nurse who was not involved in the patient treatment. The remote ischemic preconditioning protocol was applied just after the induction of anesthesia before the start of the cardiopulmonary bypass and just after weaning from the CPB. In the control group, patients had the same pneumatic cuff in the upper limb and an anesthesia nurse did sham maneuver, that is, mimicked the maneuver to increase the pressure of the cuff with the three-way stopcock opened.

Anesthesia

All the patients were treated by a single anesthesiologist (YJ) and anesthetic techniques were standardized during the study. On arrival in the operating room, standard mornitoring devices consisting of 5-lead electrocardiogram electrodes, a blood pressure cuff and a pulse oximetry were applied and a radial arterial catheter was placed under lidocaine local anesthesia. A blood pressure cuff was wrapped around an upper arm approximately 3cm proximal to the elbow joint. A radial arterial line and a pulse oximetry were placed on the other side of the arm.

After 3 minutes of denitrogenation with 100% oxygen, anesthesia was induced with intravenous midazolam (0.15 mg/kg), sufentanil (1 μg/kg) and vecuronium (0.15 mg/kg). After endotracheal intubation, anesthesia was maintained with target-controlled intravenous infusion of propofol (1.5-3.5 μg/ml of target plasma concentration) and remifentanil (8-20 ng/ml of target plasma concentration). Propofol infusion was adjusted to achieve a bispectral index of 40-60. Remifentanil infusion was titrated according to the clinical situation. Vecuronium (1 μg/kg/min) was used for neuromuscular blockade.

Before and after CPB, the lungs were mechanically ventilated with a tidal volume of 8 ml/kg, an inspiratory to expiratory time ratio of 1:2, 20% end-inspiratory pause and fractional inspired oxygen of 50% with air by Drager Primus anesthesia machine (North American Drager, Telford, PA). Ventilatory rate was adjusted to maintain normocarbia (end-tidal carbon dioxide tension between 35 and 40 mmHg). This ventilator setting was maintained in the operating room except for the CPB duration. During CPB, the lungs were disconnected from the ventilator. Positive end-expiratory pressure (PEEP) was not applied and the vital capacity maneuver was not performed. During the surgery, patients received continuous monitoring consisted of 5-lead electrocardiography, pulse oximetry, radial arterial pressure, pulmonary arterial pressure, nasopharyngeal temperature, and transesophageal echocardiography.

Surgical techniques and Postoperative Management

All patients underwent surgical repairs using CPB established by

cannulation of the ascending aorta and both the superior and inferior vena cavae. Myocardial protection was maintained by cold high potassium blood cardioplegic solution and local cooling with iced slush. The aorta was cross-clamped after the onset of ventricular fibrillation and operations were performed under moderate hypothermia (28℃). The cardiopulmonary bypass duration, aorta cross-clamp time, total volume of infused fluids or blood products and total amount of urine output were recorded in every patient.

After surgery, all patients were transferred to the intensive care unit (ICU) and received standardized postoperative management according to the institutional guidelines. In the ICU, patients' lungs were ventilated with 60% oxygen using volume-controlled ventilation (Servo Ventilator 300; Siemens, Stockholm, Sweden) and a tidal volume of 9ml/kg with 5 cmH_2O of PEEP. Adjustment of respiratory rate was made to maintain normocarbia. Decisions for extubation and discharge from the ICU were made at the discretion of the attending cardiothoracic surgeons not aware of this study, according to the standardized ICU protocols of our institution. After extubation, a Venturi mask was applied to the patient to provide an accurate and constant inspiratory oxygen fraction (F_IO_2). The duration of the mechanical ventilation and the length of stay in the ICU were recorded.

Lung function assessment

Respiratory function data were obtained at 6 time points: just after anesthesia induction before sternotomy (T_{base}), after the sternal closure ($T_{sternum}$), 6, 12, 18, 24 hours after ICU arrival (T_{ICU6}, T_{ICU12}, T_{ICU18}, T_{ICU24}). The tidal volume (TV), fraction of inspired oxygen (F_IO_2), peak and plateau pressure of airway (P_{peak}, $P_{plateau}$), and positive end expiratory pressure (PEEP) were recorded from the Drager Primus anesthesia machine (North American Drager, Telford, PA) in operating room and Servo Ventilator 300 (Siemens, Stockholm, Sweden) in ICU at each 6 time points. Data of arterial and mixed venous blood gas analysis were also recorded at the same time. The following standard equations were used to estimate the lung function.

Static lung compliance (C_{static}) = $TV/(P_{plateau} – PEEP)$;

Dynamic lung compliance ($C_{dynamic}$) = $TV/(P_{peak} – PEEP)$;

Intrapulmonary shunt (Q_S/Q_T) = $(CcO_2 – CaO_2)/(CcO_2 – CvO_2)$

CcO_2 = end-capillary oxygen content

CaO_2 = arterial oxygen content

CvO_2 = mixed venous oxygen content

Inflammatory markers measurement

As one of the routine critical care, blood samples for complete blood counts, serum electrolyte, serum C-reactive protein (CRP), liver and renal panel

analysis were drawn by surgeons every morning until discharge from ICU. The value of serum CRP, white blood cell (WBC) counts and percentage of neutrophil counts on postoperative day 1, 2, 3 and 5 were also recorded.

Statistical analysis

The sample size was calculated on the basis of the PaO_2/F_IO_2 ratio of the RIPC and the control group in our pilot study. At least 34 patients in each group were needed to detect the PaO_2/F_IO_2 ratio differences of 58 between two groups in independent t-test with a power of 0.8 and significance at the two-sided 5% level. Since we considered a drop-out rate as approximate 10% during the study, 76 patients were enrolled for randomization. All data were expressed as number of patients or mean ± standard deviation (SD). Significance of differences between the two groups was assessed using the Student *t*-test, Mann-Whitney U test, Repeated-measures analysis of variance (RM-ANOVA) or Generalized estimation equation (GEE) as appropriate. Bonferroni correction was applied when significant interactions were found. Categorical data were compared using χ^2 or Fisher's exact test. $P < 0.05$ was considered to be statistically significant. Statistical analysis was performed using the Statistical Product and Service Solutions software version 18.0 (SPSS Institute, Chicago, IL).

Results

Patients and clinical outcome

Among the patients who were having cardiac surgery involving CPB and enrolled in the clinical outcome parent study, eighty-six patients were recruited and assessed for enrollment and ten of them were excluded because they met the exclusion criteria. Of the seventy-six patients who were randomly allocated to two groups, sixty-five patients finished the study (thirty-two in the control group and thirty-three in the RIPC group)(Fig 1). The baseline patients' characteristics were comparable between the two groups (Table 1). There were no significant differences between the groups in the operation names, duration of the mean cardiopulmonary bypass and aortic cross-clamp time, total amounts of infused intravenous fluid volume or blood products, and total amount of urine output during the operations (Table 2).

After surgery, mean duration of mechanical ventilation and the length of stay in ICU was not significantly different between the groups (Table 2) but the proportion of patients under mechanical ventilation longer than 48 hours was significantly higher in the control group (23 % *vs*. 3 % , $p<0.05$)(Fig 2).

Lung Function

PaO_2/F_IO_2, intrapulmonary shunt, static (in the operation room) and dynamic lung compliance (in both operation room and ICU) at 6 time intervals are presented in Table 3. At baseline, PaO_2/F_IO_2 was comparable between two groups. The mean PaO_2/F_IO_2 value was significantly higher in the RIPC group than the control group only in the T_{ICU24} (290 ± 96 vs 387 ± 137, $p = 0.001$)(Fig 3). There were no significant differences in dynamic lung compliance, static compliance, and intrapulmonary shunt between the groups at $T_{sternum}$ and T_{ICU6} (Table 3). From T_{ICU6} to T_{ICU24}, many patients were extubated in both groups so we could not compare the lung compliances and intrapulmonary shunt between the groups after T_{ICU6}.

Inflammatory markers

We compared the serum CRP values, WBC counts and segmented neutrophil fraction. There were no significant differences in the preoperative values between two groups. The peak value of the serum CRP and WBC counts reached on the postoperative day 2 and the highest fraction of the segmented neutrophil fraction was measured on the postoperative day 1 in both groups. Postoperative serum CRP value, WBC counts and percentage of segmented neutrophil counts were not significantly different between two groups on the postoperative 1, 2, 3, and 5 day (Table 4).

Figure 1. CONSORT diagram.
†Pulmonary hypertension with mean pulmonary artery pressure > 35 mmHg.
HTN, hypertension; ASD, atrial septal defect; VSD, Ventricular septal defect; CPAP, continuous positive airway pressure; RIPC, remote ischemic preconditioning; RIPostC, remote ischemic postconditioning; PAC, pulmonary arterial catheter; TR, tricuspid regurgitation; PASP, pulmonary artery systolic pressure; TCA, total circulatory arrest; PEEP, positive end expiratory pressure; TEE, trans esophageal echocardiography.

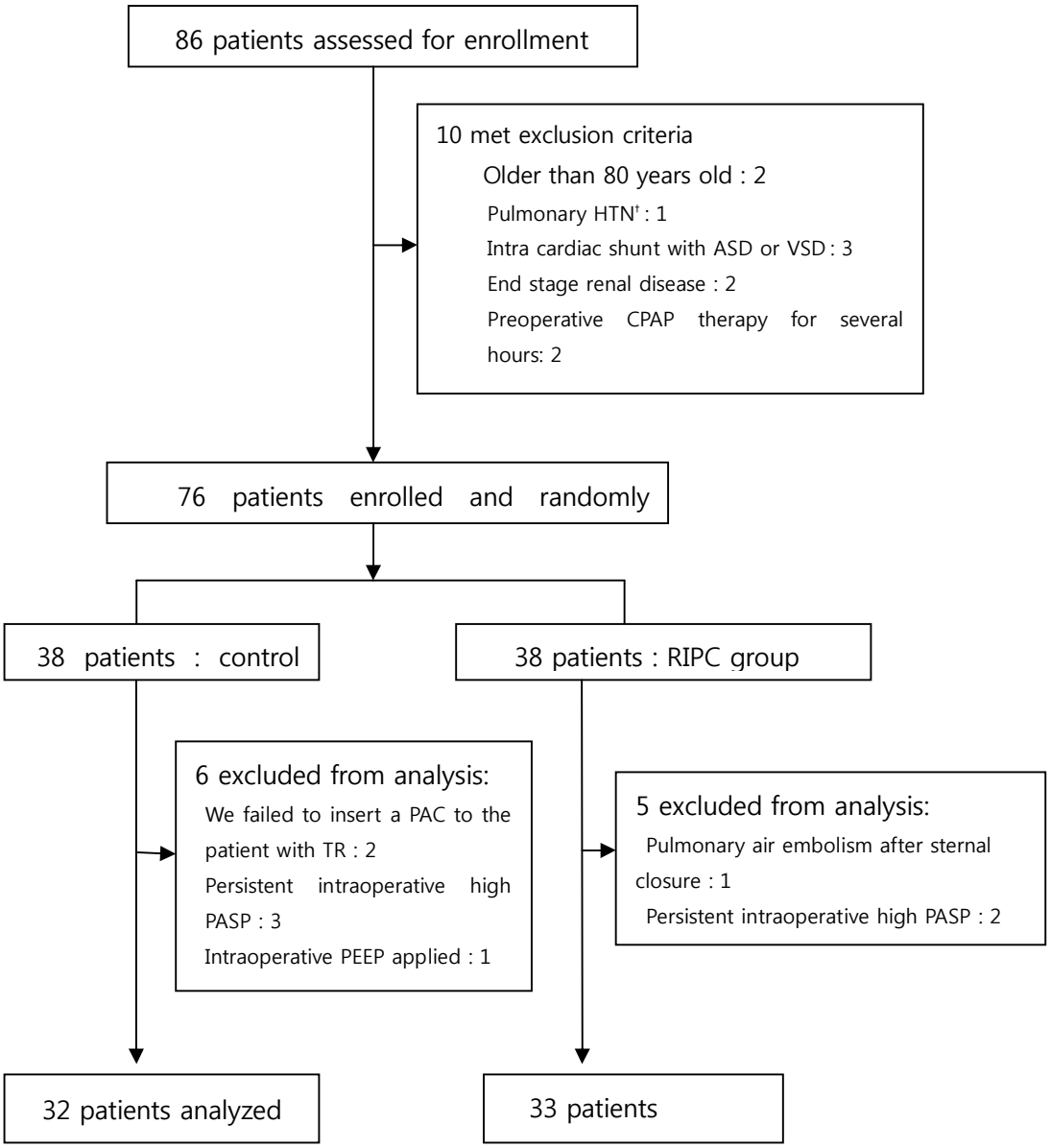
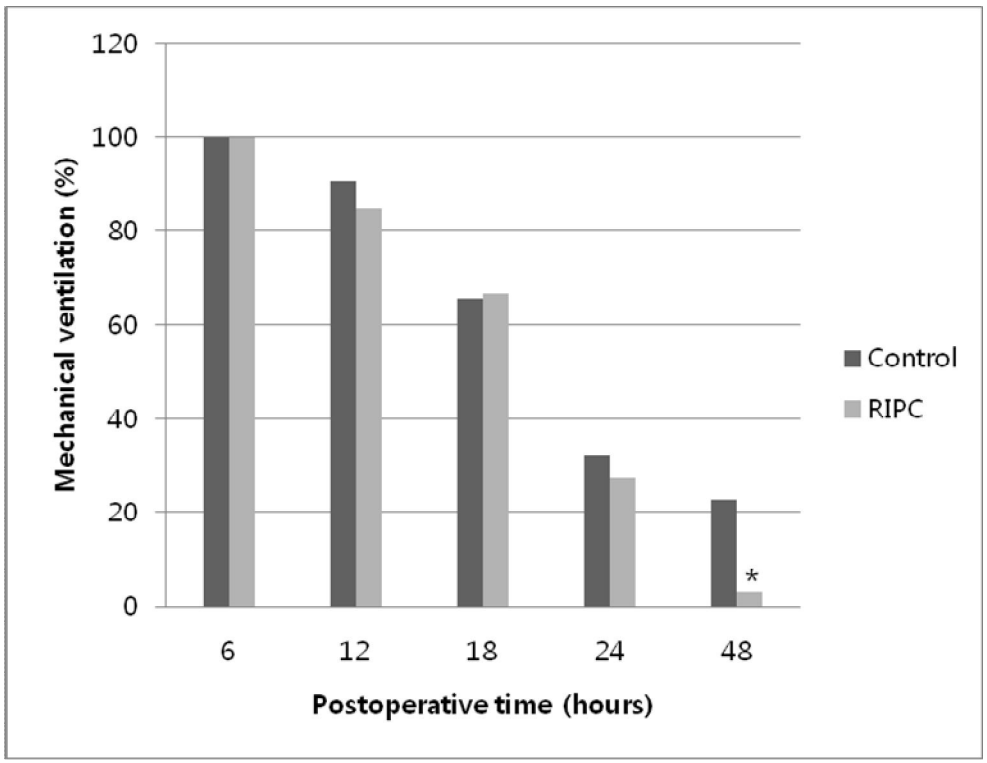


Figure 2. The proportion of patients under postoperative mechanical ventilation



*p<0.05

Figure 3. Changes of pulmonary oxygenation.
Data are expressed as mean ± SD. *p<0.01

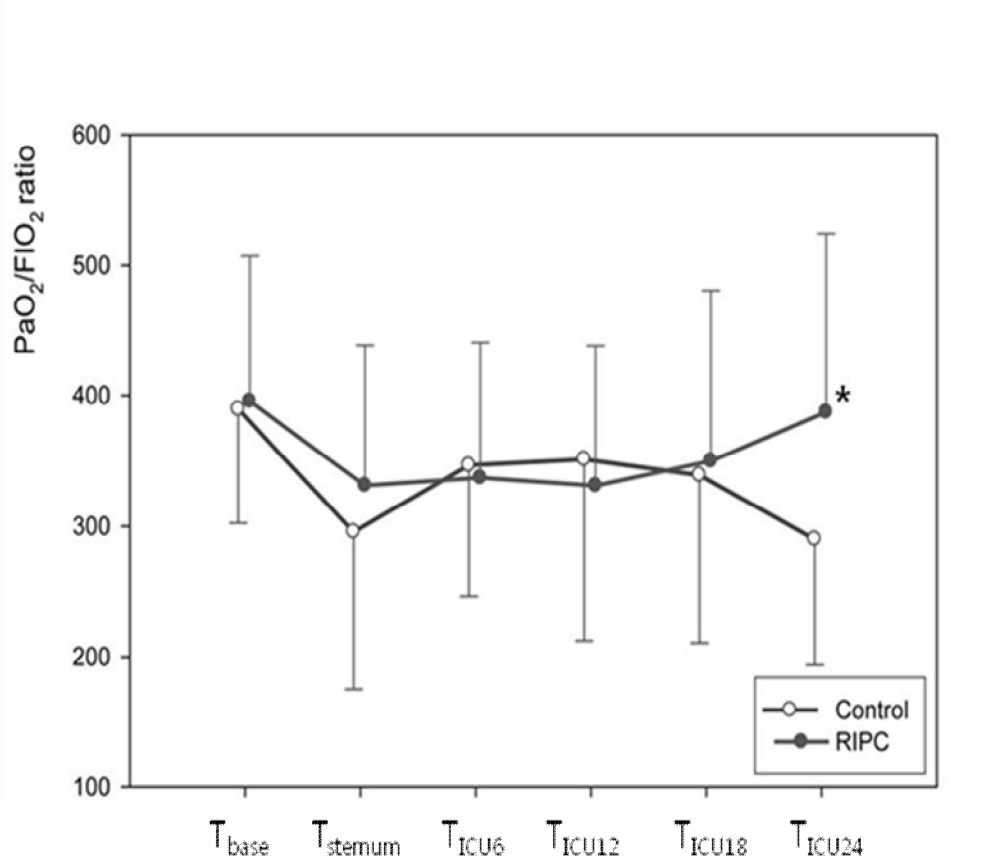


Table 1. Baseline patient characteristics

*Pulmonary hypertension with NYHA/WHO functional classification class I.
NYHA, New York Heart Association; WHO, World Health Organization; LV EF, left ventricular ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotension receptor blocker; CCB, calcium channel blocker

	Control (n=32)	RIPC (n=33)	p-value
Gender (male/female)	20/12	17/16	0.37
Age (years)	64 ± 14	58 ± 13	0.09
Weight (kg)	60 ± 8	62 ± 11	0.67
Height (cm)	164 ± 10	160 ± 9	0.15
Body Mass Index (kg/m^2)	22 ± 3	24 ± 3	0.08
Underlying disease			
Hypertension	14 (44 %)	11 (33 %)	0.39
Diabetes mellitus	3 (9 %)	2 (6 %)	0.62
Cardiac arrhythmia	7 (22 %)	9 (27 %)	0.61
Coronary disease history	1 (3 %)	1 (3 %)	0.98
Pulmonary hypertension*	2 (6 %)	0 (0 %)	0.15
Previous stroke	3 (9 %)	2 (6 %)	0.62
History of smoking	6 (19 %)	4 (12 %)	0.46
Preoperative LV EF(%)	59 ± 11	57 ± 10	0.47
Medications			
ACE inhibitor	7 (22 %)	7 (21 %)	0.95
ARB	5 (16 %)	3 (9 %)	0.42
CCB	7 (22 %)	5 (15 %)	0.49
BB	4 (13 %)	6 (18 %)	0.53
Nitrate	2 (6 %)	4 (12 %)	0.41
Euroscore	7 ± 3	6 ± 3	0.07

Table 2. Clinical outcome data

MVR, mitral valve replacement; TAP, tricuspid annuloplasty; AVR, aortic valve replacement; TVR, tricuspid valve replacement; CPB, cardiopulmonary bypass; ACC, aorta cross clamp; MV, mechanical ventilation; ICU, intensive care unit;

	Control (n=32)	RIPC (n=33)	p-value
Operation name			
Valvuloplasty only	5 (16 %)	6 (18 %)	0.78
Valve replacement	21 (66 %)	26 (79 %)	0.27
MVR only or MVR + TAP	2 (6 %)	4 (12 %)	0.67
AVR only	3 (9 %)	8 (24 %)	0.18
AVR + ascending aorta replacement	12 (38 %)	7 (21 %)	0.24
Double valve replacement	3 (9 %)	7 (21 %)	0.18
TVR	1 (3 %)	0 (0 %)	0.31
Ascending aorta surgery only	3 (9 %)	0 (0 %)	0.11
Others	3 (9 %)	1 (3 %)	0.35
Pseudoaneurysm resection	1 (3 %)	0 (0 %)	0.31
Left atrial thrombectomy	1 (3 %)	0 (0 %)	0.31
Aortic root remodelling	1 (3 %)	0 (0 %)	0.31
Cardiac tumor excision	0 (0 %)	1 (3 %)	0.32
Redo operation	2 (6 %)	7 (21 %)	0.14
Operating room			
CPB duration (min)	189 ± 65	195 ± 70	0.66
ACC duration (min)	116 ± 48	128 ± 55	0.29
infused crystalloid (ml)	909 ± 470	851 ± 452	0.57
infused colloid (ml)	955 ± 456	967 ± 468	0.90
Used blood products (ml)	1917 ± 1424	1811 ± 1342	0.73
Urine output	1844 ± 1047	2109 ± 1308	0.38
ICU			
MV duration (hours)	32 ± 38	25 ± 36	0.15
ICU stay (hours)	73 ± 56	56 ± 37	0.44
Hospital stay (days)	18 ± 14	15 ± 10	0.37

Table 3. Peri-operative changes of pulmonary variables
*: p<0.05 vs Control group

	T_{base}	$T_{sternum}$	T_{ICU6}	T_{ICU12}	T_{ICU18}	T_{ICU24}
PaO_2/FIO_2						
Control	389 ± 87	296 ± 121	347 ± 101	351 ± 139	339 ± 129	290 ± 96
RIPC	396± 112	331 ± 107	337 ± 104	331 ± 107	350 ± 131	387 ± 138*
C_{STATIC}						
Control	44 ± 10	33 ± 11				
RIPC	44 ± 11	38 ± 14				
$C_{DYNAMIC}$						
Control	34 ± 8	31 ± 8	43 ± 13			
RIPC	34 ± 7	30 ± 9	40 ± 14			
Shunt						
Control	9 ± 5	18 ± 13	13 ± 7			
RIPC	9 ± 5	13 ± 7	14 ± 7			

Table 4. Inflammatory markers

	Serum CRP (mg/dl)	WBC counts (n/μL)	Neutrophil counts(%)
Preoperative			
control	0.4 ± 0.7	6095 ± 1767	56.1 ± 10.9
RIPC	0.2 ± 0.2	6016 ± 1416	58.7 ± 10.7
Postoperative day 1			
control	5.7 ± 3.7	10714 ± 3870	88.5 ± 3.9
RIPC	6.1 ± 4.0	11123 ± 5204	89.1 ± 3.5
Postoperative day 2			
control	13.0 ± 8.2	13536 ± 5421	86.6 ± 5.1
RIPC	14.2 ± 9.2	14287 ± 5987	87.4 ± 4.6
Postoperative day 3			
control	12.7 ± 11.2	12797 ± 5041	86.3 ± 5.6
RIPC	12.3 ± 9.3	12462 ± 5091	83.8 ± 6.8
Postoperative day 5			
control	6.8 ± 7.4	11179 ± 4783	74.9 ± 11.1
RIPC	6.4 ± 4.9	10774 ± 3780	72.0 ± 7.5

Values are described in mean± SD.
RIPC, remote ischemic preconditioning with postconditioning; CRP, C reactive protein; WBC, white blood cell.

Discussion

In this study, the remote ischemic preconditioning with postconditioning significantly improved pulmonary oxygenation at postoperative 24 hour compared to the control group in patients undergoing elective cardiac surgery with CPB. However, it did not improve the oxygenation at other time points, nor did it reduce the postoperative systematic inflammatory responses, mean duration of postoperative mechanical ventilation or the length of ICU stay.

Since the first RIPC study that showed a strong myocardial protective effect, a number of RIPC studies, which showed conflicting results, have been performed because the RIPC protocol was simple, cost-benefit and noninvasive. With regard to the pulmonary protective effect of RIPC, there have been several experimental animal studies[8-14] and a few clinical human studies[17-19]. In a preclinical randomized study with pigs, RIPC group showed improved lung compliance, less pulmonary resistance changes than control group during reperfusion (at 1hour and 3 hour after CPB).[9] In another experimental sheep study, RIPC group showed higher PaO_2/FIO_2 ratio and lower pulmonary vascular resistance than control group until 2 hours after the final reperfusion injury. [10]

In human, there have been two clinical studies on children undergoing cardiac surgery using CPB. Cheung et al. showed that the 6 hour postoperative airway resistance was significantly lower in the RIPC group[18] and in another limb ischemic preconditioning study on infants, the RIPC group had significantly higher lung compliance, lower respiratory index ($P(A\text{-}aDo_2)/PaO_2$) and lower inflammatory cytokines at postoperative 2, 4, 12, 24 hours.[19] As our study, there were no significant differences in ventilator support time or duration of ICU stay in the previous studies.

Although we used the similar RIPC protocol and we even added the postconditioning for more intensive protection, significantly improved pulmonary oxygenation presented only at postoperative 24 hour in current study. There are several possible explanations for this limited pulmonary protective effect. Unlike above mentioned two clinical studies on infants and children [18, 19], we studied with adult patients whose mean age was 61. There have been several investigations about blunted response to preconditioning in aged hearts compared to the young hearts due to the defects within the signaling cascade of preconditioning.[20, 21] Another adult study of remote ischemic preconditioning plus postconditioning with lower limb ischemia protocol showed no significant pulmonary benefit after complex valvular heart surgery.[17] Their mean age of the patients was late fifties. However, in addition to the patients' age, they used volatile anesthetic

agents in both groups for anesthesia maintenance and this also could contribute to the absence of the differences between two groups because volatile anesthetics are known to have preconditioning effects.

For another factor explaining our result is the two phase protection of ischemic conditioning. There was no significant difference in PaO_2/F_IO_2 ratio until postoperative 24 hours in this study. This result is thought to be consistent with the late-phase protection which Loukogeorgakis SP et al. demonstrated about the time-course of protection by RIPC. [22] Considering that Zhou et al. treated RIPC twice (at 24 hour and 1 hour before the surgery), their early pulmonary protective effect before postoperative 24 hours might be due to late-phase protective effect contributed by the RIPC applied 1 day ago. [19] In the animal studies mentioned above, the authors measured the effect of RIPC just 1 to 3 hours after CPB and the protective result may correspond to the early protection phase of RIPC. [22] Delayed phase of RIPC had not been observed because some animals died before postoperative 24 hours and the authors measured the outcome data no longer than postoperative 6 hours.

Lastly, in addition to the preconditioning, we also performed the remote ischemic postconditioning just after the CPB to intensify the protective effect. In the several previous animal studies, sharing mechanistic similarities, postconditioning was as effective as preconditioning to attenuate the ischemia-reperfusion injury.[23] [24] However, as we conducted the RIPC procedure twice (right before and after the CPB), the total tourniquet time was longer than previous studies. There have been several studies about tourniquet ischemia-induced lung injury. Abel Wakai et al. showed that after tourniquet-induced reperfusion injury, there was a significant increase of neutrophil and monocyte activation which was transient, lasted no longer than 4 hours.[25] In another study of Joseph M. Klauner et al., after 2 hours of bilateral hind limb tourniquet ischemia in sheep, there was a significant increase in the lung lymph flow and proteinaceous exudates and leukosequestration in lung histology.[26] So, as one of the possible reasons for the limited protective effect of RIPC in our study, the longer tourniquet time induced acute inflammatory reaction might had offset the early pulmonary protective effect of RIPC.

The limitation of this study is that we evaluated the postoperative lung function no longer than postoperative 24 hours. Considering that the late phase protective effect of RIPC presents 12 to 24 hours after RIPC application and is sustained for 48 to 72 hours,[22] as we conducted RIPC also with postconditioning, the protective effect of RIPC may have existed after postoperative 24 hours. However, the duration of postoperative evaluation was limited because many of the patients were extubated and the pulmonary catheters were removed within the postoperative 24 hours.

Additional limitation is that this is a substudy of a multicenter randomized controlled parent study. As the random number list was made for the parent study and we partly included patients undergoing cardiac surgery involving CPB, complete randomization might not have been achieved. Nevertheless, there were no significant differences in baseline characteristics between two groups.

In conclusion, RIPC improved oxygenation at postoperative 24 hours and decreased number of the patients requiring ventilator care for more than 48 hours in patients undergoing elective cardiac surgery involving CPB. However, to determine the clinical significance of these protective effects, further studies would be required.

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국문 초록

배경 및 목적 : 원격 허혈성 조건화는 허혈이 예상되는 장기로부터 원위부의 다른 장기를 짧은 시간동안 허혈-재관류 시킴으로써, 목표 장기를 후속되는 보다 긴 기간의 허혈로부터 보호하기 위해 개발된 방법이다. 본 연구에서는 원격 허혈성 전조건화 및 후조건화가 심폐우회술을 이용한 심장 수술을 받는 환자에서 수술 후 폐 기능 보호 효과가 있을 것이라 가정하였다.

방법 : 심폐우회술을 이용한 심장 수술을 받는 환자 76명을 대조군과 원격 허혈성 전조건화 및 후조건화군으로 무작위 배정하였다. 원격 허혈성 전조건화 및 후조건화군에는 한쪽 상지에 혈압 측정 커프를 거치하여 심폐우회술 전 후에 5분 허혈 - 5분 재관류 과정을 한 주기로 총 4주기씩 2회 시행하였다. 마취 유도 후, 흉골 봉합 후, 중환자실 이송 6시간 후, 12시간 후, 18시간 후, 24 시간 후의 6시점에서 PaO_2/F_IO_2 ratio 및 호흡기 지표들을 계산하여 두 그룹에서의 폐 기능 변화를 비교 평가하였다.

결과 : 대조군에 비해 원격 허혈성 전조건화 및 후조건화 군에서 수술 종료 24시간 후 PaO_2/F_IO_2 ratio 평균값이 유의하게 높았고 (290 ± 96 *vs.* 387 ± 137, p = 0.001) , 중환자실에서 48시간 이상 기계환기가 필요한 환자 비율은 유의하게 낮았다 (23 % *vs.* 3 % , p < 0.05). 그러나, 수술 후 24시간 이외 시점에서의 PaO_2/F_IO_2 ratio, 그 밖의 호흡기적 지표들, 수술 후 평균 기계 환기 시간 및 중환자실 재원 기간에서는 두 군간에 유의한 차이가 없었다.

결론 : 심폐우회술을 이용한 심장 수술 환자에서 원격 허혈성 전조건화 및 후조건화가 수술 24시간 후 폐 산소화를 향상시켰고, 중환자실에서 48시간 이상 기계 환기가 필요한 환자 수를 감소시켰다. 그러나 이와 같은 보호 효과의 임상적 유의성에 대하여는 추가적인 연구가 필요할 것으

로 생각된다.

주요어: 원격, 허혈성, 전조건화, 후조건화, 폐, 산소화

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