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Original Article

# Cardioprotective Effect of Extended Remote Ischemic Preconditioning in Patients Undergoing Coronary Artery Bypass Grafting: A Randomized Clinical Trial

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## Abstract

**Background:** The cardioprotective effect of ischemic preconditioning has been known for many years. Since the temporary ischemia in the heart may cause lethal cardiac effects, the idea of creating ischemia in organs far from the heart such as limbs was raised as remote ischemic preconditioning (RIPC). We hypothesized that the extension of RIPC has more cardioprotective effect in patients undergoing coronary artery bypass graft (CABG) surgeries.

**Methods:** In this triple-blind randomized clinical trial study, 96 patients were randomly divided into 3 groups and two blood pressure cuffs were placed on both upper and lower extremities. In group A, only upper extremity cuff and in group B upper limb and lower limb cuff was inflated intermittently and group C was the control group. RIPC was induced with three 5-min cycles of cuff inflation about 100 mmHg over the initial systolic blood pressure before starting cardiopulmonary bypass. The primary endpoints were troponin I and creatine phosphokinase-myoglobin isoenzyme (CK-MB).

**Results:** Six hours after the termination of CPB, there was a peak release of the troponin I level in all groups (group A=4.90 ng/ml, group B=4.40 ng/ml, and group C=4.50 ng/ml). There was a rise in plasma CK-MB in all groups postoperatively and there were not any significant differences in troponin I and CK-MB release between the three groups.

**Conclusion:** RIPC induced by upper and lower limb ischemia does not reduce postoperative myocardial enzyme elevation in adult patients undergoing CABG.

**Trial Registration Number:** IRCT2012071710311N1

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**Keywords** ● Ischemic preconditioning ● Coronary artery bypass ● Troponin I

## What's Known

- Remote ischemic preconditioning (short episodes of ischemia and reperfusion in a distant target organ) could reduce tissue injury during surgery.

## What's New

- Limb ischemic preconditioning is cardioprotective in patients undergoing on-pump coronary artery bypass graft surgery.

## Introduction

Adult cardiac surgeries have been shown to be associated with increased mortality and morbidity resulting from acute myocardial injury.[1] Although cardioplegic arrest is induced during cardiac surgery, the incidence of complications such as peri-operative myocardial infarction remains high (9.8%).[2] Therefore, to

protect the patients against such complications, additional strategies should be considered. Increased myocardial tolerance to prolonged ischemia is of concern, especially in high-risk populations such as patients of extreme age, diabetic individuals, and patients required to have prolonged cross-clamp time.[3]

Ischemic preconditioning is an approach for reduction in myocardial injury during CABG surgery, during which the induction of cycles of non-lethal myocardial ischaemia and reperfusion before a potentially lethal heart ischaemia can cause cardioprotection. Cardioprotection can be obtained from two types of ischemic preconditioning, local or remote. Because in local preconditioning, we need to induce ischaemia in the target organ, that may stimulate heart dysfunction as well as inappropriate myocardial protection, its clinical usefulness is limited. In recent years, remote ischemic preconditioning (RIPC) which is a less invasive method with the same cardioprotective effect was established. In this phenomenon, short episodes of ischemia and reperfusion in distant non-cardiac tissues could reduce the effects of subsequent prolonged ischemia in myocardium. In other word, brief ischemia of distant tissue renders the myocardium resistant to subsequent lethal ischemia. Manifesting immediately after the stimulus and lasting for 2 hours, the primary phase of protection is referred to as "early ischemic preconditioning", while the second phase also known as "second window of protection" or "late ischemic preconditioning" manifests itself 24 to 48 hours later lasting for at least 48 to 72 hours.[4]

In 1993, Przyklenk for the first time introduced RIPC in myocardial tissue.[4] The results of his study showed that ischemia induced in kidneys followed by reperfusion can protect myocardial tissue from prolonged ischemia and reduce the infarct size. Moreover, animal studies indicated that brief ischemia-reperfusion of the gut, kidneys, mesentery, and limbs would reduce myocardial infarct size. Skeletal preconditioning has been the subject of human studies with beneficial effects on myocardial protection, possibly through the regulation of endothelial protection.[5]

There are different types of preconditioning. Limb preconditioning has gained popularity among practitioners because it is considered feasible, noninvasive, and as effective as local conditioning.[6] Limb-induced RIPC is of particular interest in that it involves applying a tourniquet to a limb with intervals of inflation and deflation before a sustained ischemic period of the heart or other vital organs is achieved. This topic has been the subject of recent meta-analyses, with heterogenic results, especially in adult cardiac surgery.[7,8] However, there are only a few studies investigating the possible sources of such heterogeneity. On the other hand, cardioprotection by RIPC for adult patients undergoing cardiac surgery has been recently studied by many researchers, performing randomized controlled trials (RCTs), with mixed results.[9-16] Although RIPC has been shown to effectively reduce cardiac injury associated with ischemia-reperfusion, the idea of RIPC extension has not been the subject of human studies. Therefore, the authors of the present study conducted a randomized controlled trial with the aim of examining the cardioprotective effect of RIPC and its extension on patients undergoing on-pump coronary artery bypass graft (CABG) surgery.

## Patients and Methods

### *Trial Design*

This was a double-blind clinical randomized controlled trial, which was done from September 2012 to July 2013. The staff involved in clinical care and members collecting and analyzing data along with the randomization operator were blind to group allocation. The study protocol was approved by the institutional review board (IRB) of the Shiraz University of Medical Sciences, and the approval of the Ethics Committee was achieved before the study was commenced. All participants gave their written informed consent. The study protocol was registered at the Iranian registry of clinical trials (www.IRCT.IR) in August 2012 with the registration number IRCT2012071710311N1.

### *Participants*

The study population included patients with coronary artery disease in the age range of 50-85 years and baseline troponin I concentration <0.03 ng/ml candidated for elective CABG surgery (on-pump) at Nemazee Hospital, Shiraz, Iran. The exclusion criteria were history of cardiogenic shock or cardiac arrest during the current admission, positive history of myocardial infarction in the last 4 weeks, decreased left ventricular ejection fraction (<30%), positive history of significant peripheral vascular disease, insulin dependent diabetes, body mass index >35 Kg/m$^2$, concomitant non-cardiac surgery, advanced carotid artery disease, significant hepatic dysfunction defined as bilirubin >20 µmol/L or INR >2.00, significant pulmonary disease defined by FEV1 <40% predicted, renal

failure with a GFR <30 mL/min/1.73 $m^2$, and also simultaneous treatment with glibenclamide or nicorandil that could hinder the cardioprotection induced by RIPC.

*Intervention Induction of Remote Ischemic Preconditioning*

Ninety-six eligible patients were allocated into 3 equal groups with random numbers. A random assignment approach was taken using the research randomized program (available at: http://www.randomizer.org/form.htm) to generate random numbers. Two blood pressure cuffs were placed on both upper and lower extremities. In group A, patients were assigned to receive solitary right upper extremity ischemia as the preconditioning method. The RIPC protocol in this group comprised of cycles of upper limb ischemia each lasting for 5 minutes. The ischemia was induced using a sterile 15 cm wide blood pressure cuff, which was placed on the right upper arm. The cuff was inflated up to 100 mmHg above systolic arterial pressure and each interval of ischemia was followed by a 5 min intervening reperfusion period during which the cuff was deflated.[17] These cycles were repeated three times in total.

In group B, the RIPC protocol included cycles of 5 min ischemia induced on the right upper limb while the cuff placed on the lower extremity was deflated. Afterwards, 5 min intervals of ischemia on the lower extremity were induced, using a 15 cm wide sterile cuff inflated up to 100 mm above systolic arterial pressure while the previously inflated cuff on the upper extremity was deflated. The cycles were repeated three times in all.

In the control group C, the cuffs were not inflated. This procedure was performed by an operating room technician, who also carefully checked the proper functioning of the inflating device before and after usage, but was otherwise not involved in the study. In both groups A and B, the RIPC was applied after anesthesia induction and baseline measurements. In all of the patients, RIPC was induced within 30 minutes of the initiation of cardiac bypass.

*Anesthetic and Surgical Management*

Atrial lines were inserted before induction of anesthesia under local anesthesia and sedation. Anesthesia was induced with midazolam (Exir Pharmaceutical Co., Broujerd, Iran) (0.1 mg/kg), opioids including morphine (Darou Pakhsh Pharma Chem Co., Tehran, Iran) (0.2 mg/kg), sufentanil (Mylan Pharmaceuticals Inc., Pennsylvania, USA) (0.2 µg/kg), propofol (Fresenius Kabi AG, Homburg, Germany) as required doses and the muscle relaxant pancuronium (Nani Pharmaceuticals Pvt. Ltd., New Delhi, India). Anesthesia was maintained using isoflurane (Piramal Critical Care Inc., PA, USA).

Cannulation of the ascending aorta and right atrium was performed after median sternotomy and pericardiotomy. After heparin (Darou Pakhsh Pharma Chem Co., Tehran, Iran) administration, standard CPB was started using a disposable hollow fiber oxygenator. Isoflurane was given via a Dräger Vapor 2000 (Drägerwerk AG & Co., Lübeck, Germany) integrated into the CPB machine. Cardiac arrest was induced using antegrade cold crystalloid cardioplegia after aortic cross clamping. A single interval of aortic cross-clamping was used during side clamping to perform proximal anastomoses. Using α-stat regulation of blood pH, core temperature was allowed to decrease spontaneously. Phenylephrine was administered to maintain on-pump blood pressure greater than 55 mmHg. Atrial catheter blood samples were collected at the time of cannulation and again 15 min after releasing the cross clamp.

After construction of all the grafts, CPB was ceased and heparin effect was antagonized using protamine (C.P. Pharmaceuticals, Wrexham, UK). During CPB and after surgery, hemoglobin concentration was maintained at levels >7 g/dl and over 9 g/dl, respectively. All of the patients received similar postoperative care in the same intensive care unit. Collection and analysis of all laboratory and clinical data were performed by personnel blinded to group assignment.

*Outcomes*

The effect of RIPC on myocardial injury was assessed based on primary and secondary outcomes. Changes in levels of biochemical markers (troponin I and CK-MB) after surgery were considered as primary outcomes. Arterial blood samples were obtained for the assessment of troponin I (cTnI) immediately before anesthesia induction and 6, 24 and 48 hours after termination of CPB. Creatine kinase-myoglobin isoenzyme (CK-MB) was measured before anesthesia induction, immediately after coronary bypass, and 24, 48, and 72 hours after CPB. Using the immunochemiluminescence method (Architect i2000SR, Abbot Diagnostics, USA), values of the plasma troponin I were determined quantitatively (upper normal limit 0.3 ng/ml). Plasma CK-MB activity was measured using chemical IFCC-DGKC photometry. Secondary outcomes were short term clinical determinants, including the rate and duration of inotrope infusion, the presence of cardiac arrhythmias

after CPB discontinuation, and the number of the patients supported with an intra-aortic balloon pump (IABP) or DC shock for separation from CPB.

*Statistical Analysis*

By using the power static software collection (SSC), with a power of 80%, α level of 0.05, consideration of variance 2.66 and mean difference 1.87 in BE, the appropriate sample size for each group was determined to be at least 32 patients (total of 96 patients).

The statistical analysis was performed using SPSS version 20 software for MAC OS (IBM Corp.). The quantitative data were expressed in absolute mean±SD (standard deviation). For comparison of quantitative data, paired t-test for dependent samples, one-way ANOVA and repeated measures ANOVA were used for comparison of the three groups. Values of $P<0.05$ were considered statistically significant.

## Results

The consort diagram is depicted in figure 1. The baseline characteristics of the patients are reported in four main categories, including demographics, cardiac status, intraoperative status, and medications (table 1). There were no statistically significant differences between the study and control groups regarding baselines. Assessment of data regarding baseline biomarkers of myocardial injury showed that all of the patients had values of troponin I <0.3 ng/ml (upper normal range of the assay). Data showed a rise in the value of troponin I in all of the groups, which could be due to myocardial injury (table 2). After 6 hours of completing cardio-pulmonary bypass, there was a peak release in the level of troponin I in all groups (group A: 4.90 (ranged 0.34-25) ng/ml, group B: 4.40 (ranged 0.50-25) ng/ml and group C: 4.50 (ranged 0.63-25) ng/ml). As indicated in table 2, in all of the groups there was a significant decrease in the value of troponin I measured at 24 and 48 hours after CPB.

There were no statistically significant differences between the study and control groups regarding concentrations of troponin I, neither before nor at any time after CPB (measured up to 48 hours after CPB) (table 3). Similar results were shown in the total troponin I released over 48 hours after surgery (table 3, figure 2).

Baseline levels of CK-MB fell within the normal range in all of the groups with no significant difference. There was a rise in plasma CK-MB in all groups postoperatively (table 4), which also

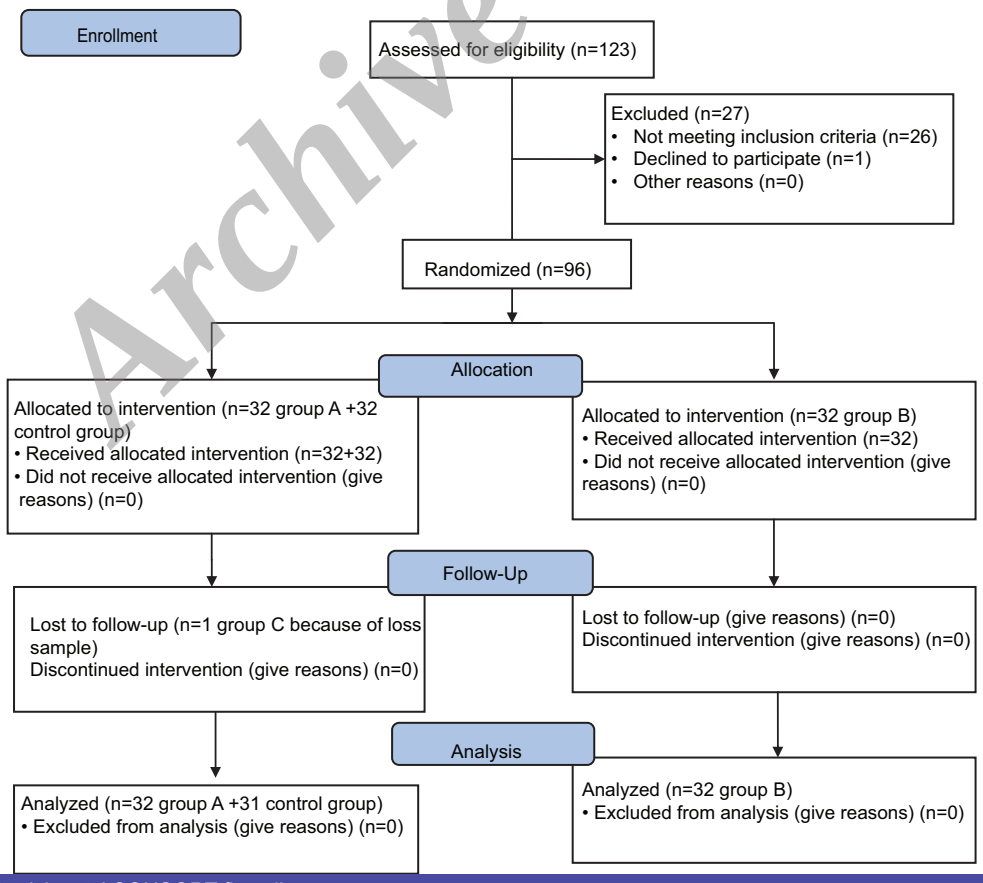


**Figure 1:** Participants' CONSORT flow diagram.

**Table 1:** Demographics and baseline characteristics of the patients in the study groups

| Variable | Group A (32) | Group B (32) | Group C (32) | P value |
|---|---|---|---|---|
| Demographics | | | | |
| Age (years) | 59.88±10.30 | 63.41±11 | 62.58±10.70 | 0.390 |
| Gender (male/female) % | 59.4% | 56.3% | 32.3% | 0.063 |
| BMI (Kg/m$^2$) | 26.11±4.89 | 22.96±3.32 | 24.50±5.44 | 0.150 |
| Cardiac status | | | | |
| LV ejection fraction (%) | 52.3±9.7 | 49.8±9.9 | 52.3±7.4 | 0.459 |
| NYHA functional class | | | | |
| Class II | 10 (31.2) | 14 (43.8) | 12 (37.5) | 0.330 |
| Class III | 22 (68.8) | 18 (56.2) | 19 (59.4) | 0.531 |
| Class IV | 0 | 0 | 0 | - |
| Intraoperative status | | | | |
| Cross clamp time (min) | 34.17±7.37 | 31.19±7.24 | 29.17±6.93 | 0.090 |
| Bypass time (min) | 59.11±15.57 | 52.33±13.94 | 51.68±11.58 | 0.200 |
| Number of grafts | 2.25±0.44 | 2.19±0.39 | 2.28±0.45 | 0.560 |
| Medication | | | | |
| $Ca^{2+}$ blockers | 4 (12.5%) | 4 (12.5%) | 2 (6.2%) | 0.430 |
| β-Blockers | 27 (84.3%) | 25 (78.1%) | 29 (92.6%) | 0.481 |
| ACE-inhibitors | 18 (56.2%) | 19 (59.3%) | 26 (81.2%) | 0.765 |
| Nitrates | 24 (75%) | 22 (68.7%) | 26 (81.2%) | 0.623 |
| Diuretics | 14 (43.7%) | 12 (37.5%) | 10 (31.2%) | 0.663 |

BMI: Body mass index; LV: Left ventricle; NYHA: New York heart association; Data are presented as mean±SD or number (%)

**Table 2:** Cardiac troponin levels in groups (ng/ml)

| Time group | N | Mean±SD | Minimum | Maximum |
|---|---|---|---|---|
| Before RIPC | | | | |
| 1 | 32 | 0.127±0.0646 | 0.100 | 0.350 |
| 2 | 32 | 0.107±0.0299 | 0.100 | 0.254 |
| 3 | 31 | 0.107±0.0277 | 0.100 | 0.242 |
| Total | 95 | 0.114±0.0448 | 0.100 | 0.350 |
| 6-hr after CPB | | | | |
| 1 | 32 | 4.965±4.855 | 0.340 | 25.00 |
| 2 | 32 | 4.468±4.431 | 0.502 | 25.00 |
| 3 | 31 | 4.570±4.302 | 0.637 | 25.00 |
| Total | 95 | 4.669±4.495 | 0.340 | 25.00 |
| 24-hr after CPB | | | | |
| 1 | 32 | 4.437±6.968 | 0.100 | 25.00 |
| 2 | 32 | 4.232±5.437 | 0.000 | 25.00 |
| 3 | 31 | 3.686±4.462 | 0.664 | 25.00 |
| Total | 95 | 4.123±5.676 | 0.000 | 25.00 |
| 48-hr after CPB | | | | |
| 1 | 32 | 2.420±5.658 | 0.100 | 25.00 |
| 2 | 32 | 2.434±3.936 | 0.100 | 18.04 |
| 3 | 31 | 1.866±2.394 | 0.321 | 11.28 |
| Total | 95 | 2.244±4.191 | 0.100 | 25.00 |

RIPC: Remote ischemic preconditioning; CPB: Cardiopulmonary bypass; hr: Hours; Data are presented as mean±SD

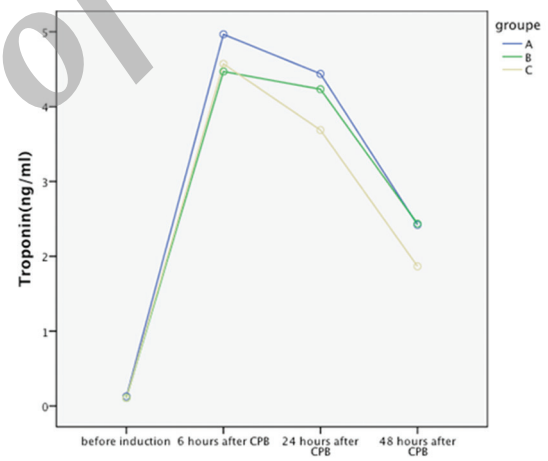


**Figure 2:** Mean plasma troponin I changes before and after cardiac surgery. Six hours after cardiopulmonary bypass, there was a peak in troponin I in all groups but there were no statistically significant differences between the study and control groups. CPB: Cardiopulmonary bypass.

shows myocardial injury during the surgery. The highest level of CK-MB in group A was observed during the first 24 hours after surgery. In the alternating upper- and lower-extremity ischemia and the control group (groups B and C), the CKMB peak release appeared after cardiopulmonary pump (group A: 64 (ranged 38.50-89.60) ng/ml, group B: 51.70 (ranged 35-68.40) ng/ml, and group C: 57.90 (ranged 42.90-72.80) ng/ml) (table 4). There were no statistical significant differences between the control group and any of the study groups regarding CK-MB at any time after surgery (table 5, figure 3).

Considering the number of patients requiring inotrope and the duration of inotrope support in these patients, no significant statistical difference was observed. The only exception was the duration of epinephrine infusion, with a

**Table 3:** Comparison of cardiac troponin levels in groups

| | Sum of squares | df | Mean square | F | P value |
|---|---|---|---|---|---|
| Before RIPC | | | | | |
| Between groups | 0.008 | 2 | 0.004 | 2.156 | 0.122 |
| Within groups | 0.180 | 92 | 0.002 | | |
| Total | 0.189 | 94 | | | |
| 6-hr after CPB | | | | | |
| Between groups | 4.405 | 2 | 2.202 | 0.107 | 0.899 |
| Within groups | 1894.908 | 92 | 20.597 | | |
| Total | 1899.312 | 94 | | | |
| 24-hr after CPB | | | | | |
| Between groups | 9.461 | 2 | 4.730 | 0.144 | 0.866 |
| Within groups | 3019.325 | 92 | 32.819 | | |
| Total | 3028.786 | 94 | | | |
| 48-hr after CPB | | | | | |
| Between groups | 6.580 | 2 | 3.290 | 0.184 | 0.832 |
| Within groups | 1644.808 | 92 | 17.878 | | |
| Total | 1651.388 | 94 | | | |

RIPC: Remote ischemic preconditioning;
CPB: Cardiopulmonary bypass; hr: Hours

**Table 4:** CK-MB levels in groups (ng/ml)

| Time/group | N | Mean±SD | Minimum | Maximum |
|---|---|---|---|---|
| Before induction | | | | |
| 1 | 32 | 34.125±31.453 | 4.00 | 166.00 |
| 2 | 32 | 26.515±15.965 | 11.00 | 85.00 |
| 3 | 31 | 23.583±11.282 | 9.00 | 67.00 |
| Total | 95 | 28.122±21.700 | 4.00 | 166.00 |
| After coronary bypass | | | | |
| 1 | 32 | 56.906±31.032 | 8.00 | 181.00 |
| 2 | 32 | 51.968±15.224 | 29.00 | 109.00 |
| 3 | 31 | 52.548±20.482 | 16.00 | 96.00 |
| Total | 95 | 53.821±23.083 | 8.00 | 181.00 |
| 24-hr after CPB | | | | |
| 1 | 32 | 64.062±70.882 | 20.00 | 386.00 |
| 2 | 32 | 51.750±46.299 | 16.00 | 260.00 |
| 3 | 31 | 46.096±22.991 | 20.00 | 130.00 |
| Total | 95 | 54.052±50.886 | 16.00 | 386.00 |
| 48-hr after CPB | | | | |
| 1 | 32 | 35.462±28.964 | 10.00 | 142.00 |
| 2 | 32 | 38.562±43.852 | 11.00 | 247.00 |
| 3 | 31 | 29.664±17.605 | 9.00 | 104.00 |
| Total | 95 | 34.614±31.990 | 9.00 | 247.00 |
| 72-hr after CPB | | | | |
| 1 | 32 | 22.310±12.196 | 3.06 | 65.00 |
| 2 | 32 | 20.671±7.712 | 5.00 | 36.00 |
| 3 | 31 | 23.129±11.053 | 10.00 | 71.00 |
| Total | 95 | 22.025±10.427 | 3.06 | 71.00 |

CPB: Cardiopulmonary bypass; hr: Hours

significant difference between the two RIPC and the control group (group A: 0.02 and group C: 0.009 (P=0.008), group B: 0.03 and group C: 0.009 (P=0.005) (table 6).

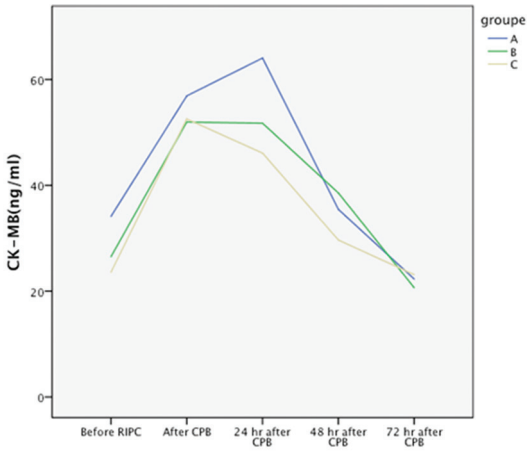


**Figure 3:** Mean plasma CK-MB changes before and after cardiac surgery. There were no statistical significant differences between the control and the study groups at any time after surgery. RIPC: Remote ischemic preconditioning, CPB: Cardiopulmonary bypass, hr: Hours.

## Discussion

The present study investigated whether RIPC and further extension of this method provides cardioprotective effects on ischemic injury in adults undergoing on-pump CAGB. Recently, researchers have focused on whether RIPC could serve as a way of reducing myocardial injury after a subsequent sustained episode of myocardial ischemia.

The proposed mechanism through which RIPC induces its protection, addresses the release into the systemic circulation of substances that exert multi organ protective effects.[17,18] Up-regulation of anti-inflammatory gene expression, suppression of pro-inflammatory genes, and reduction of neutrophil adhesion are events thought to result in cardioprotection in late ischemic preconditioning.[18,19] A series of experiments have positively confirmed that brief ischemia of kidney and intestine reduces the extent of myocardial infarctions.[20-22]

Although the safety and non-invasive nature of this method have made RIPC a theoretically brilliant protector of the myocardium, cardiac surgical literature includes conflicting results on this subject. It seems that whether RIPC could independently provide myocardial protection following surgical coronary revascularization is still unclear.

Although several other studies have emphasized that when using RIPC, postoperative troponin levels in adult patients following CABG surgery is decreased,[23,24] in this study, we found that RIPC induced by cycles of upper limb ischemia did not provide cardiac protection as represented by the

**Table 5:** Comparison of CK-MB levels in groups

| | Sum of squares | df | Mean square | F | Sig. |
|---|---|---|---|---|---|
| Before induction | | | | | |
| Between groups | 1,874.159 | 2 | 937.080 | 2.034 | 0.137 |
| Within groups | 42,390.324 | 92 | 460.764 | | |
| Total | 44,264.484 | 94 | | | |
| After coronary bypass | | | | | |
| Between groups | 464.593 | 2 | 232.296 | 0.431 | 0.651 |
| Within groups | 49,623.365 | 92 | 539.384 | | |
| Total | 50,087.958 | 94 | | | |
| 24-hr after CPB | | | | | |
| Between groups | 5,338.152 | 2 | 2669.076 | 1.031 | 0.361 |
| Within groups | 238,064.585 | 92 | 2587.659 | | |
| Total | 243,402.737 | 94 | | | |
| 48-hr after CPB | | | | | |
| Between groups | 1,281.358 | 2 | 640.679 | 0.621 | 0.540 |
| Within groups | 94,919.921 | 92 | 1031.738 | | |
| Total | 96,201.279 | 94 | | | |
| 72-hr after CPB | | | | | |
| Between groups | 98.992 | 2 | 49.496 | 0.450 | 0.639 |
| Within groups | 10,121.376 | 92 | 110.015 | | |
| Total | 10,220.368 | 94 | | | |

CPB: Cardiopulmonary bypass; hr: Hours

**Table 6:** Secondary outcomes: The rate and duration of inotrope infusion, presence of cardiac arrhythmias, number of the patients supported with intra-aortic balloon pump or DC shock

| | Group A | Group B | P value | Group A | Group C | P value | Group B | Group C | P value |
|---|---|---|---|---|---|---|---|---|---|
| Post op arrhythmias (number) | 2 | 4 | 0.390 | 2 | 2 | 0.970 | 4 | 2 | 0.420 |
| Pacemaker (number) | 1 | 1 | 1 | 1 | 1 | 0.980 | 1 | 1 | 0.980 |
| Epi (in OR) (mean) μg/kg/min | 0.020 | 0.030 | 0.550 | 0.020 | 0.009 | 0.008 | 0.030 | 0.009 | 0.005 |
| Nepi (in OR) (mean) μg/kg/min | 0.006 | 0.003 | 0.470 | 0.006 | 0 | 0.100 | 0.003 | 0 | 0.160 |
| Dop (in OR) (mean) μg/kg/min | 0.53 | 0.84 | 0.550 | 0.53 | 0.48 | 0.940 | 0.84 | 0.48 | 0.530 |
| DC Shock (number) | 1 | 2 | 0.660 | 1 | 0 | 0.300 | 2 | 0 | 0.750 |
| IABP (number) | 0 | 1 | 0.320 | 0 | 0 | 1 | 1 | 0 | 0.320 |
| Patients needed inotrope (in ICU) (number) | 15 | 18 | 0.460 | 15 | 14 | 0.890 | 18 | 14 | 0.380 |
| Duration of inotrope support (hr) | 9.5 | 13 | 0.600 | 9.5 | 13.9 | 0.360 | 13 | 13.9 | 0.910 |

Epi: Epinephrine; Nepi: Norepinephrine; Dop: Dopamine; IABP: Intra-aortic balloon pump; hr: Hours, DC shock: Direct current shock; ICU: Intensive care unit; op: Operation; OR: Operation room

values of cardiac biomarkers (troponin and CK-MB). These results agree with findings of Lomivorotov's study where eighty patients were assigned to remote preconditioning or control treatment following CABG surgery.[14,25] Although short-term RIPC improved hemodynamics in Lomivorotov's study, it did not reduce myocardial injury after CABG surgery.[14] Also, two other studies confirm the same effect of RIPC. Rahman found that there is no difference in cTnT level in RIPC and control groups.[9] Another study by Hoole showed RIPC has a neutral effect on left ventricular functions (such as wall motion score, ischemic segment tissue velocities, tissue Doppler velocities and peak systolic strain) during dobutamine stress echocardiography.[26]

Moreover, a RCT investigating RIPC effects on myocardial function in children undergoing cardio-pulmonary bypass has shown that cardiac troponin I levels were significantly different between groups.[27]

In Hong`s study, although RIPC reduced the total amount of troponin I in off-pump CABG surgery patients by 26%, it did not reach statistical significance.[28]

In discussing the results of our study, it should be mentioned that in 2009, Rahman described RIPC as the best hope for myocardial protection in cardiac surgery.[9,25] However, the results of other large clinical trials published within a year following this statement failed to demonstrate significant cardiac protection through the use of RIPC in CABG surgery.[9,28]

Studies have shown that troponin level reduced by RIPC, but not in a statistically significant amount. As shown here, neither troponin nor CK-MB release had a statistical difference in the studied groups. Finally, a recent systematic review and meta-analysis investigating 10 papers and 693 participants has shown that RIPC significantly decreases postoperative troponin concentration following open cardiac surgery.[29] Most studies in this review involved CABG surgery and the results could be comparable. Although in RIPC group, troponin level 12 hours after operation decreased, there was some controversy in statistical analysis of studies probably due to the degree of blinding.

In other words, there were mild treatment effects in blinded studies or even no statistically significant effect of RIPC on troponin concentrations. As the participants and medical personnel were fully blinded in our controlled trial, this explains that our results failed to support treatment effects in favor of RIPC in CABG surgery. This is consistent with previous surveys demonstrating that in RCTs, blinding has resulted in smaller estimates of treatment effect.

Another important aspect of our study concerns the extension of preconditioning to more than one distant limb. Considering the dominant theories of preconditioning, reaching the level where an organ is able to start an endogenous protection at cellular level requires a certain degree of stimulation.[30] Therefore, it would be conceivable that the collective effect of subsequent upper and lower limb ischemia should induce a potentially more consistent and effective overall cell protection. We had hypothesized that the extension of ischemia to more than one distant limb (subsequent upper and lower limb ischemia) would further enhance the protective effects of RIPC. However, there were no statistically significant differences between the study and control groups regarding plasma levels of biomarkers of myocardial injury, neither before nor at any time after CPB (measured until 48 hours after CPB). In our study of patients who underwent CABG surgery, RIPC could not decrease myocardial injury.

Although, the extension of RIPC from the current method was never studied before, studies of whole body preconditioning with ether-derived volatile anesthetics show a decrease in the release of biomarkers associated with myocardial cell death and myocardial dysfunction in patients undergoing CABG surgery. One study revealed that application of volatile anesthetics for the patients[31] mimicking a combination of before and after anesthetic conditioning, most markedly protected the myocardium of patients under CABG surgery. There were no significant differences between the two groups. However, comparing group C with other groups in the current study, we found a significant difference in duration of epinephrine support after surgery. It seems that RIPC and its extension do not have any effect on the short-term hemodynamic status of the patients, which is contrary to the result of Lomivorotov's study.

In our study, all patients received isoflurane as an anesthetic agent during surgery. Therefore, we could not assess the preconditioning effect of isoflurane. In other words, RIPC could not produce more additive effect in association with isoflurane.

The limitations of our study were, (i) we did not differentiate the effects of RIPC on high and low risk patients, (ii) we could not evaluate the clinical effect of RIPC on cardiac function and (iii) isoflurane was used as the sole anesthetic in our study that has cardioprotective effects and can affect the result of the study.

## Conclusion

In this study, RIPC induced by subsequent upper and lower limb ischemia did not reduce the postoperative myocardial enzyme elevation in adult patients undergoing CABG surgery. Although a recent meta-analysis has advocated the cardioprotective role of RIPC following CABG surgery, as discussed earlier, it is proposed that further studies with a larger number of patients may be needed. Moreover, the extension of RIPC into more than one distant limb may be the subject of interest for further studies.

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