Original Article

The Effect of Remote Ischemic Preconditioning on the Incidence of Acute Kidney Injury in Patients Undergoing Coronary Artery Bypass Graft Surgery: A Randomized Controlled Trial

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What's Known

• Remote ischemic preconditioning which is the transient ischemia and reperfusion of a limb showed protective effects against kidney injury in some previous studies.

What's New

• We found that remote ischemic preconditioning did not reduce the incidence of postoperative acute kidney injury, nor did it improve short-term clinical outcomes including postoperative liver function, atrial fibrillation, the length of hospital and intensive care unit stay, and inpatient mortality in patients undergoing on-pump coronary artery bypass graft surgery.

Abstract

Background: Remote ischemic preconditioning (RIPC) protects other organs from subsequent lethal ischemic injury, but uncertainty remains. We investigated if RIPC could prevent acute kidney injury (AKI) in patients undergoing coronary artery bypass graft (CABG) surgery.

Methods: This parallel-group, double-blind, randomized, controlled trial was done on adults undergoing elective or urgent on-pump CABG surgery from 2013 to 2017 in Shiraz, Iran. Patients were allocated to RIPC or control groups through permuted blocking. The patients in the RIPC group received three cycles of 5 min ischemia and 5 min reperfusion in the upper arm after induction of anesthesia. We placed an uninflated cuff on the arm for 30 min in the control group. The study primary endpoint was an incidence of AKI. Secondary endpoints included short-term clinical outcomes. We compared categorical and continuous variables using Pearson χ^2 and unpaired t tests, respectively. P<0.05 was considered significant.

Results: Of the 180 patients randomized to RIPC (n=90) and control (n=90) groups, 87 patients in the RIPC and 90 patients in the control group were included in the analysis. There was no significant difference in the incidence of AKI between the groups (38 patients [43.7%] in the RIPC group and 41 patients [45.6%] in the control group; relative risk, 0.96; 95% confidence interval, 0.69 to 1.33; P=0.80). No significant differences were seen regarding secondary endpoints such as postoperative liver function, atrial fibrillation, and inpatient mortality.

Conclusion: RIPC did not reduce the incidence of AKI, neither did it improve short-term clinical outcomes in patients undergoing on-pump CABG surgery.

Trial Registration Number: IRCT2017110537254N1.

Introduction

Acute kidney injury (AKI) following coronary artery bypass graft (CABG) surgery is a major complication occurring in 1% to 53% of

patients (depending on how it is defined) with the pooled rate of 18.2% and 2.1% of them requiring renal replacement therapy.[1] Cardiopulmonary bypass (CPB)-associated AKI increases the mortality by about 2-4 fold regardless of AKI definition.[1] It is also associated with the increased risk of postoperative stroke, acute myocardial infarction, cardiac tamponade, heart failure, lengthened intensive care unit (ICU), and hospital stays.[2-5] Even minor elevations of postoperative serum creatinine have been associated with a significant increase in 30-day mortality, from a 3-fold increase risk for a small elevation of up to 0.5 mg/dL from baseline to an 18-fold increase risk of death with a Serum creatinine rise greater than 0.5 mg/dL.[6]

The pathogenesis of CPB-associated AKI is complicated and includes hemodynamic, inflammatory, and other mechanisms that interact at a cellular level.[7] To date, despite the presence of several experimental preventive strategies, none has demonstrated conclusive efficacy in the prevention of AKI after cardiac surgery.[8-10]

Remote ischemic preconditioning (RIPC) is a phenomenon in which brief ischemia of one organ or tissue provokes a protective effect, which can reduce the mass of infarction caused by vessel occlusion and reperfusion.[11, 12] In CABG surgery, cardiomyocyte injury caused by myocardial protection failure is predominantly responsible for the adverse outcomes. RIPC have been shown to reduce the troponin release 24 h postoperatively in children undergoing corrective surgery for congenital heart disease.[13] Other studies have demonstrated that RIPC using brief ischemia and reperfusion of the upper limb could reduce myocardial injury in adult patients undergoing CABG surgery.[14-16]

Because of the similarities between the mechanisms of ischemia-reperfusion injury produced by RIPC and those proposed for AKI after CPB,[17-19] we decided to test the hypothesis that RIPC could prevent AKI in patients undergoing CABG surgery.

Patients and Methods

Study Design

The Ethics Committee of Shiraz University of Medical Sciences (SUMS) approved this double-blind randomized controlled clinical trial (IR.SUMS.MED.REC.1395.61) and it was carried out at Nemazee and Shahid Faghihi Teaching Hospitals, which are the tertiary referral centers for CABG surgery affiliated to SUMS from November 2013 to February 2017 in Shiraz, Iran. All patients participating in the study signed the written informed consent form. The study was conducted in accordance with the Declaration of Helsinki Principles. An investigator who was independent of the study randomized the patients to RIPC or control groups (allocation ratio 1:1) by using a computer-generated list of randomized numbers through permuted blocking. The independent investigator did the allocation concealment by means of consecutively-numbered opaque envelopes populated with a patient identification and the treatment assignment. When an eligible patient was transferred to the pre-operative area, the study coordinator chose the next envelope in the consecutive list and gave it to the research nurse. The research nurse opened the sealed envelope and started the procedure as it was indicated.

The patients, anesthetists and cardiac surgeons, staff on ICU and cardiac wards, and the investigator collecting and analyzing the data were all blinded to treatment allocation. The trial was registered at irct.ir (IRCT2017110537254N1) and clinicaltrials.gov (NCT02981680).

Inclusion and Exclusion Criteria

Adult patients (>18 years of age) who were candidates for elective or urgent on-pump CABG surgery at Nemazee and Shahid Faghihi Teaching Hospitals were recruited. Exclusion criteria were end-stage renal disease (receiving hemodialysis or glomerular filtration rate <15 ml/min/1.73 m^2), abnormal liver function tests, known peripheral vascular disease of the upper extremities, planned off-pump surgery, pregnancy, and inability to sign the informed consent.

Intervention

After induction of anesthesia and prior to skin incision, RIPC and control protocols were started. The patients in the RIPC group received three sequential sphygmomanometer cuff inflations on their right upper arms. The cuff was inflated by the investigator nurse up to 200 mmHg for five minutes each occasion, with five minutes of deflation in between the inflations. The entire pre-conditioning phase lasted 30 minutes. The patients in the control group had the sphygmomanometer cuff placed on their right upper arms, but the cuff was not inflated. Similar to the patients in the treatment group, those in the control group underwent the same 30-minute delay before initiation of the skin incision.

Surgical Procedure

In order to minimize the differences in surgical techniques, all the patients were operated by the same surgeon. Anesthesia was induced

with intravenous propofol (Dongkook Pharm., Korea) (2-3 mg/kg), midazolam (Caspian Tamin, Iran) (0.1-0.2 mg/kg), sufentanil (Aburaihan, Iran) (0.5-1 µg/kg), and pancuronium (Darou Pakhsh, Iran) (0.15-0.2 mg/kg), and maintained with either isoflurane (Piramal Critical Care, USA) or intravenous propofol. Mild hypothermic CPB (32-34 °C) was used in all patients; PaCO2 was maintained at 35-40 mm Hg, and mean arterial pressure (MAP) was maintained between 50-90 mm Hg. The temperature was allowed to drift downwards without active cooling, and rewarming did not exceed 37 °C. MAP was controlled with vasoactive agents at the discretion of the anesthetist. Blood cardioplegia was administered at the discretion of the cardiac surgeon. For all patients who received proximal grafts, a single cross-clamp was used. The patients who agreed about transfusion received packed red blood cells if the hematocrit was less than 20%, and the surgeon and anesthetist agreed that transfusion was indicated. Postoperatively, the patients were transferred to the Cardiovascular Intensive Care Unit and were managed with the goals of hemodynamic stability, analgesia, and early extubation by means of a weaning pathway.

Study Primary Endpoint

The study primary endpoint was an incidence of AKI defined as any elevation of Serum creatinine level of ≥0.3 mg/dl above the preoperative value, or ≥50% increase from the preoperative value within 72 h after surgery. Blood samples for Serum creatinine were taken preoperatively and at 24, 48, and 72 h post-surgery. We used the creatinine-based criterion of the Acute Kidney Injury Network (AKIN) for the definition of AKI. AKI was classified as stage I if there was an increase in Serum creatinine ≥0.3 mg/dl or an increase of 150% up to 200% of baseline; stage II for an increase above 200% up to 300% of baseline; and stage III for an increase to above 300% of baseline.[20]

Study Secondary Endpoints

The study secondary endpoints included the followings:

Renal replacement therapy (RRT) requirement: The incidence of patients requiring RRT during the postoperative period until they got discharged.

Postoperative liver function: We measured serum aspartate aminotransferase (AST),

Enrollment

Assessed for eligibility (n=186)

Excluded (n=6)
• Not meeting inclusion criteria (n=6)

Randomized (n=180)

Allocation

Allocated to RIPC (n=90)
• Received RIPC (n=87)
• Did not receive RIPC (surgery was cancelled) (n=3)

Allocated to control (n=90)
• Received control (n=90)
• Did not receive RIPC (n=0)

Follow-Up

Lost to follow-up (n=0)

Discontinued intervention (n=0)

Lost to follow-up (n=0)

Discontinued intervention (n=0)

Analysis

Analysed (n=87)
• Excluded from analysis (n=0)

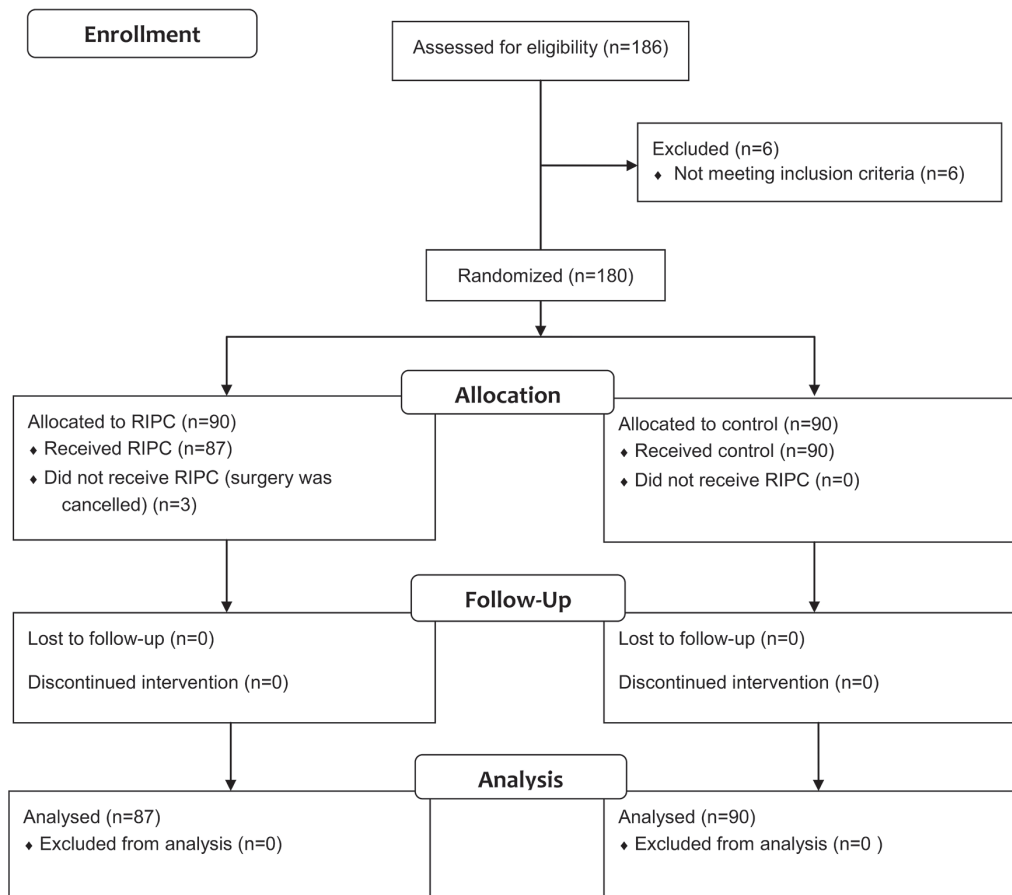Analysed (n=90)
• Excluded from analysis (n=0)

Figure 1: The figure shows the CONSORT flowchart. RIPC, remote ischemic preconditioning.

alanine aminotransferase (ALT), total bilirubin (TBIL), and albumin preoperatively and at 24 h post-surgery.

Incidence of postoperative atrial fibrillation (AF): This was defined as the incidence of new-onset AF lasting for five minutes or longer during the first 72 h after surgery. This outcome was assessed by using continuous telemetry and electrocardiogram (EKG). EKG was done by a blinded staff nurse on a daily basis and in case of detecting AF on the telemetry, and then analyzed by a blinded investigator.

Table 1: Preoperative characteristics of remote ischemic preconditioning group and control group

	Control (N=90)	RIPC (N=87)	P
Age, year	64.5±10.7[a]	62.8±10.9	0.3
Male sex, no. (%)	50 (55.6)	52 (59.8)	0.6
Body mass index, kg/m^2	23.6±3.6	24.0±3.5	0.5
Preoperative creatinine, mg/dL[b]	1.1±0.3	1.1±0.3	0.7
GFR <60 ml/min/1.73m^2, no. (%)[c]	33 (36.7)	25 (28.7)	0.3
Preoperative liver function			
AST, U/L	33.0±28.8	38.7±55.3	0.4[d]
ALT, U/L	33.8±26.2	33.3±30.8	0.7[d]
TBIL, mg/dL	1.0±0.5	1.0±0.7	0.2[d]
Albumin, g/dL	4.2±0.5	4.2±0.4	0.9
Preexisting conditions			
Hypertension, no. (%)	57 (63.3)	64 (73.6)	0.1
Diabetes mellitus, no. (%)	33 (36.7)	29 (33.3)	0.6
Hyperlipidemia, no. (%)	52 (57.8)	43 (49.4)	0.3
Smoking, no. (%)	29 (32.2)	34 (39.1)	0.3
Opium addict, no. (%)	15 (16.7)	20 (23.0)	0.3
Recent Myocardial infarction (≤7 days), no. (%)	14 (15.6)	8 (9.2)	0.2
Anemia, no. (%)[e]	32 (35.6)	27 (31.0)	0.5
Atrial fibrillation, no. (%)	2 (2.2)	1 (1.1)	0.9[f]
Stroke, no. (%)	2 (2.2)	4 (4.6)	0.4[f]
TIA, no. (%)	1 (1.1)	0 (0)	0.9[f]
Preoperative medications			
Statin, no. (%)	83 (92.2)	82 (94.3)	0.6
Aspirin, no. (%)	83 (92.2)	76 (87.4)	0.3
Clopidogrel, no. (%)	30 (33.3)	35 (40.2)	0.3
Diuretic, no. (%)	18 (20.0)	20 (23.0)	0.6
ACE-I or ARB, no. (%)	68 (75.6)	70 (80.5)	0.4
Beta-blocker, no. (%)	78 (86.7)	75 (86.2)	0.9
Nitrate, no. (%)	81 (90.0)	74 (85.1)	0.3
Calcium channel-blocker, no. (%)	16 (17.8)	22 (25.3)	0.2
Biguanide, no. (%)	15 (16.7)	15 (17.2)	0.9
Sulfonylurea, no. (%)	15 (16.7)	11 (12.6)	0.5
Insulin, no. (%)	6 (6.7)	3 (3.4)	0.5[f]
NSAID, no. (%)	3 (3.3)	3 (3.4)	0.9[f]
Ejection fraction			0.5
>55%, no. (%)	15 (16.7)	18 (20.7)	
35-55%, no. (%)	69 (76.7)	60 (69.0)	
<35%, no. (%)	6 (6.7)	9 (10.3)	
Coronary angiogram ≤5 days before, no. (%)	26 (28.9)	24 (27.6)	0.9
Type of CABG			0.9
Elective, no. (%)	46 (51.1)	45 (51.7)	
Urgent, no. (%)	44 (48.9)	42 (48.3)	
NYHA class	3.6±0.6	3.8±0.4	0.2[d]

ACE-I: Angiotensin-converting enzyme inhibitor; ALT: Alanine aminotransferase; ARB, angiotensin-receptor blocker; AST: Aspartate aminotransferase; CABG, coronary artery bypass grafting; GFR: Glomerular filtration rate; NSAID: Nonsteroidal anti-inflammatory drug; NYHA: New York Heart Association; TBIL: Total bilirubin; [a]The values are mean±SD; [b]To convert values for creatinine to μmol/l, multiply by 88.4; [c]GFR is estimated by an equation developed by the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration; [d]Mann-Whitney U test; [e]Anemia was defined as a hemoglobin level of less than 13 g/dL in men and less than 12 g/dL in women; [f]Fisher's exact test

Incidence of postoperative stroke, which is defined as a new ischemic or hemorrhagic cerebrovascular accident with neurological deficit lasting >24 h during the postoperative period until the discharge time.

Length of ICU and hospital stay, measured as the total duration in days of the length of stay in ICU and in hospital.

Rate of death, during the hospital stay until the discharge time.

Statistical Analysis

Based on the previous data and according to definition of AKIN, the incidence of post-CABG AKI in the control and RIPC groups was 47% and 20%, respectively.[21] Therefore, the study required a sample size of 54 patients per intervention group to provide the statistical power of 80% with a two-sided significance level of 0.05. However, we increased our sample size to 90 patients in each study group to accommodate any withdrawal or missing data points.

Baseline characteristics of the RIPC and control groups were compared as to identify whether randomization was successful. For comparing continuous variables, unpaired t test or the non-parametric equivalent (Mann-Whitney U test) was used. We compared categorical variables by using Pearson χ^2 test (or Fisher's exact test when the expected value was <5). A $P<0.05$ was considered significant.

Statistical analysis was performed using SPSS Software, version 23.0 (SPSS, Inc., Chicago, IL, USA).

Results

Of the 186 patients assessed for eligibility

Table 2: Intraoperative characteristics of remote ischemic preconditioning group and control group

	Control (N=90)	RIPC (N=87)	P
CPB time, min	54.0±11.7[a]	53.0±13.0	0.6
Aortic cross-clamp time, min	29.3±8.8	28.4±7.8	0.5
Anesthetic agent			0.8
Isoflurane, no. (%)	8 (8.9)	7 (8.0)	
Propofol, no. (%)	82 (91.1)	80 (92.0)	
Number of grafts	2.8±0.6	2.8±0.6	0.6
PRBCs transfused, mL	433.3±267.1	356.3±268.6	0.07[b]
Lowest hematocrit, %	22.2±4.1	23.6±3.7	0.02
Need to use vasopressors, no. (%)	85 (94.4)	83 (95.4)	0.9[c]

CPB: Cardiopulmonary bypass; PRBCs: Packed red blood cells; [a]The values are mean±SD; [b]Mann-Whitney U test; [c]Fisher's exact test

Table 3: Postoperative outcome data of remote ischemic preconditioning group and control group

	Control (N=90)	RIPC (N=87)	Effect Size	P
Primary endpoint				
AKI, no. (%)	41 (45.6)	38 (43.7)	0.02	0.8
Stage I, no. (%)	32 (35.6)	32 (36.8)		
Stage II, no. (%)	7 (7.8)	6 (6.9)		
Stage III, no. (%)	2 (2.2)	0 (0)		
Secondary endpoints				
RRT, no. (%)	0 (0)	0 (0)	-	-
Postoperative liver function				
AST, U/L	50.1±38.7[a]	49.0±54.8	0.02	0.8[b]
ALT, U/L	32.2±21.9	35.8±65.7	0.03	0.6[b]
TBIL, mg/dL	1.3±0.7	1.2±0.9	0.10	0.2[b]
Albumin, g/dL	3.3±0.4	3.3±0.5	0.03	0.7[b]
New-onset AF, no. (%)	9 (10.0)	8 (9.2)	0.01	0.9
Stroke, no. (%)	0 (0)	0 (0)	-	-
Hospital stay, days	6.1±6.6	5.5±3.4	0.13	0.09[b]
ICU stay, days	3.1±3.4	3.2±3.6	0.06	0.4[b]
Hospital death, no. (%)	2 (2.2)	2 (2.3)	0.003	0.9[c]

AF: Atrial fibrillation; AKI: Acute kidney injury; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ICU: Intensive care unit; RRT: Renal replacement therapy; TBIL: Total bilirubin; [a]The values are means±SD; [b]Mann-Whitney U test; [c]Fisher's exact test

(figure 1) from November 2013 to February 2017, six subjects were excluded because of end-stage renal disease. Thus, we randomized 180 patients to RIPC (n=90) and control (n=90) groups. Since three patients did not undergo surgery in the RIPC group, 177 patients were included in the intention-to-treat analysis, finally. With the exception of the lowest hematocrit percentage during surgery, study groups were balanced with respect to preoperative (table 1) and intraoperative characteristics (table 2).

Primary Outcome

There was no significant difference in the incidence of AKI within 72 h after surgery between the groups (38 patients [43.7%] in the RIPC group and 41 patients [45.6%] in the control group, relative risk, 0.96; 95% confidence interval (CI), 0.69 to 1.33; P=0.80) (table 3). 32 (35.6%) and 32 (36.8%) patients had stage I AKI, and seven (7.8%) and six (6.9%) had stage II AKI in the control and RIPC groups, respectively. Two (2.2%) patients in the control group had stage III AKI while it was not observed in the RIPC group.

Secondary Outcomes

No patients required renal replacement therapy before hospital discharge (table 3). The postoperative liver function including AST, ALT, TBIL, and albumin was not comparable between the groups. RIPC did not reduce the rate of new-onset AF in the first 72 h post-surgery (9 patients [10%] in the control group and eight patients [9.2%] in the RIPC group, P=0.86). No significant difference was found in the length of hospital stay, ICU stay, and the rate of hospital death between RIPC and control groups. Stroke did not occur in any patient during the postoperative period until discharge time (table 3).

Discussion

In this prospective, parallel-group, double-blind, randomized, controlled, clinical trial that was done on 180 patients in two centers to investigate the protective effect of RIPC on kidneys, we found that RIPC did not reduce the incidence of postoperative AKI. Moreover, no statistically significant differences were seen in secondary outcomes, including renal replacement therapy requirement, postoperative liver function, new-onset AF, stroke, length of hospital and ICU stay, and the rate of hospital death.

Despite our results, there are studies that have shown the protective effects of RIPC. In a clinical trial that was done by Zimmerman and others[21] on 120 adult patients undergoing elective CABG, valve surgery, or combined CABG and valve surgery, it was concluded that RIPC could prevent postoperative AKI (defined as a rise of serum creatinine of ≥0.3 mg/dl or ≥50% within 48 h after surgery) with a 27% absolute risk reduction. However, there was no significant difference in the changes of plasma neutrophil gelatinase-associated lipocalin (NGAL) (a highly sensitive biomarker of AKI) levels between RIPC and control groups. Candillio and others[22] showed that RIPC not only reduced the incidence of post-CABG AKI by 48% (10.0% RIPC vs 21.0% control; P=0.063), but also decreased the incidence of postoperative AF by 54% (11% RIPC vs 24% control; P=0.031) and length of ICU stay by 1 day (2.0 days RIPC [CI 1.0 to 4.0] vs 3.0 days control [CI 2.0 to 4.5]; P=0.043). However, most studies that reported positive effects of RIPC[13-15, 21-26] had used surrogate endpoints, were done in a single center and designed in a single-blinded way, had small study population, or were not standardized based on the type of anesthesia.

The results of this study are consistent with those of two large clinical trials: ERICCA trial and RIPHeart study.[27, 28] The ERICCA trial was a multicenter, controlled, clinical trial involving 1612 patients undergoing on-pump CABG (with or without valve surgery) using four 5-minute cycles of ischemia-reperfusion of the upper arm for preconditioning. At 12 months after randomization, there was no significant between-group difference in the cumulative incidence of the primary endpoint including death from cardiovascular causes, nonfatal myocardial infarction, stroke, and coronary revascularization (212 patients [26.5%] in the RIPC group and 225 patients [27.7%] in the control group; hazard ratio with ischemic preconditioning, 0.95; 95% CI, 0.79 to 1.15; P=0.58). Moreover, there was no significant difference in the preoperative myocardial injury, inotrope score, AKI, duration of stay in the ICU and hospital, distance on the 6-minute walk test, and quality of life. In the RIPHeart study that was done on 1403 patients undergoing elective cardiac surgery with cardiopulmonary bypass using intravenous propofol for total anesthesia, no significant difference was found between the RIPC and control groups in the rate of composite primary endpoint including death, myocardial infarction, AKI, and stroke up to the hospital discharge time (99 patients [14.3%] in the RIPC group and 101 [14.6%] in the control group, P=0.89). Furthermore, RIPC did not have any positive effects on the mechanical ventilation duration, new-onset of atrial fibrillation, the troponin release level, the incidence of postoperative delirium, and

the length of hospital or ICU stay. They did not observe any RIPC-related adverse events.

Why could RIPC not confer protective effects to patients undergoing CABG surgery? There is a probability that this preconditioning is less effective in patients whose hearts have been remodeled due to infarction, patients with diabetes, and in older patients. Moreover, since cardiopulmonary bypass has been known as a protective factor as well as hypothermia and cardioplegia, maybe achieving more protection is impossible.[29] Most important of all, the concomitant medications, especially the anesthetics, may interfere with RIPC. It seems that some anesthetics mimic the protective effect of RIPC but inhibit its protective effect simultaneously. In fact, propofol (the anesthetic agent used in more than 90% of the patients of our study), volatile anesthetic agents (used in less than 10% of the patients of our study), and opioids (used in most patients of this study) have all been known as factors that reduce or neutralize the protective effects of RIPC.[30-32] Thus, the best explanation for negative results of this study is that heart-protecting pharmacological agents may have masked the protective effects of RIPC and made it ineffectual.[33]

Our study had some limitations. First, although we measured serum creatinine for the diagnosis of AKI, we did not measure other biomarkers of renal injury such as plasma NGAL or serum cystatin C, which are highly sensitive and specific, and early-onset predictors of AKI.[34-36] In addition, inflammatory mediators associated with cardiopulmonary bypass were not measured in our study. Thus, we could not realize the relationship between the loss of protective effect of RIPC on the kidneys and the level of systemic inflammatory response in each individual. Therefore, it is recommended that these factors should be taken into account in future studies. Second, our definition of AKI, which is based on AKIN, does not consider the duration of serum creatinine elevation. Even though temporary elevation of serum creatinine predicts adverse outcomes,[37] a retrospective study in patients undergoing cardiac surgery revealed that the duration of postoperative AKI was directly associated with long-term mortality.[38] Therefore, the duration of postoperative AKI should be considered in further studies. Third, we used propofol as the anesthetic agent in more than 90% of our patients; an agent that is not used in some regions. Accordingly, we cannot generalize the results of this study to all CABG surgeries done worldwide. Finally, RIPC was done by using three consecutive 10 min cycles of ischemia and reperfusion of the upper arm (5 min of ischemia followed by 5 min of reperfusion in each cycle) in this study. Other RIPC protocols, such as RIPC in the lower limbs, more prolonged ischemia time, or more cycles, may be still protective.

Conclusion

In conclusion, RIPC with transient ischemia and reperfusion of the upper arm cannot reduce the incidence of postoperative AKI in patients undergoing CABG surgery and it seems that because of the confounding variables underlying the CABG surgery, RIPC is not a good strategy for AKI prevention.

Acknowledgment

Conflict of Interest: None declared.

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