Effects of intense remote ischemic preconditioning in patients undergoing elective off-pump coronary artery bypass graft surgery: a pilot study

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Background
Remote ischemic preconditioning (RIPC) of the myocardium by upper-limb or lower-limb ischemia/reperfusion may reduce myocardial injury during cardiac surgery. We conducted a single-centered, prospective, randomized controlled trial to evaluate if intense RIPC by inducing ischemia/reperfusion in both the upper arm and thigh simultaneously can reduce myocardial injury in patients undergoing elective off-pump coronary artery bypass graft surgery.

Patients and methods
In total, 47 adult patients were randomized to receive either intense RIPC protocol (n=23) or control (n=24), after induction of general anesthesia but before the surgical incision. Patients in the RIPC group were subjected to three 5-min cycles of ischemia, induced by inflating two standard blood-pressure cuffs placed simultaneously on the upper arm and thigh to 200 mmHg, with an intervening 5 min of reperfusion, achieved by deflation of these cuffs. In the control group, the two blood-pressure cuffs were left uninflated for 30 min. Anesthesia was maintained with sevoflurane, remifentanil and rocuronium/cisatracurium. Perioperative myocardial injury was assessed by measuring serum levels of cardiac biomarkers [cardiac troponin I (cTnI), creatine kinase isoform-MB (CKMB), and N-terminal of the prohormone brain natriuretic peptide (NTproBNP)] preoperatively and at 24 and 72 h after the end of surgery.

Results
There was no significant difference in the postoperative release of cardiac biomarkers between the two groups: cTnI at 24 h [median (lower, upper quartiles), 1.16 (0.42, 4.69) ng/ml in RIPC vs. 0.83 (0.54, 1.93) ng/ml in controls, P=0.987] and at 72 h [0.28 (0.08, 1.79) ng/ml in RIPC vs. 0.48 (0.17, 2.34) ng/ml in controls, P=0.534]; CKMB at 24 h [4.2 (2.15, 14.15) ng/ml in RIPC vs. 7.3 (2.68, 12.5) ng/ml in controls, P=0.597] and at 72 h [1.6 (0.7, 4.85) ng/ml in RIPC vs 1.6 (0.9, 2.5) ng/ml in controls, P=0.902]; NTproBNP at 24 h [1510 (808, 3528) pg/ml in RIPC vs. 1584 (972, 3055) pg/ml in controls, P=0.958] and at 72 h [1459 (815, 3645) pg/ml in RIPC vs. 2677 (1292, 4804) pg/ml in controls, P=0.304]. There was no significant difference in inotrope score at the end of surgery (P=0.631) and duration of postoperative hospital stay (P=0.818) between the two groups.

Conclusion
Intense RIPC did not cause significant reduction in the postoperative release of cardiac biomarkers (cTnI, CKMB, and NTproBNP) in patients undergoing elective off-pump coronary artery bypass graft surgery.

Keywords:
cardiac biomarkers, coronary artery bypass graft surgery, intense remote ischemic preconditioning, myocardial injury, off-pump

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Introduction

Coronary artery bypass graft (CABG) surgery is a treatment modality for coronary artery revascularization in patients of coronary heart disease. CABG surgery can be performed by using the aid of cardiopulmonary bypass (CPB) or under the beating-heart technique without the use of CPB [off-pump coronary artery bypass graft surgery (OPCAB)]. Cardiac surgery in these patients is associated with increased risk of myocardial injury [as measured by troponin I or T, creatine kinase isoform-MB (CKMB)], which can cause adverse clinical outcomes [1–3]. Myocardial injury in these patients occurs due to the combined ischemia reperfusion injury (IRI) encountered during aorta cross-clamping, use of cardioplegia solution for cardiac arrest [4], coronary microembolization [5], and direct myocardial injury

due to handling of the heart. Although inflammatory response due to CPB [6] and myocardial IRI due to aortic cross-clamping and cardioplegia [7] are avoided in OPCAB, myocardial complications still occur [7]. These complications depend on factors like collateral circulation of coronary arteries, duration of coronary occlusion, and hemodynamic changes during anastomosis [8].

Several trials have shown that remote ischemic preconditioning (RIPC) can reduce the level of cardiac biomarkers in patients after cardiac surgery [7,9–15]. RIPC is the phenomenon in which brief nonlethal episodes of ischemia and reperfusion are applied to an organ such as kidney, liver or small intestine [16], or tissue such as skeletal muscle of the upper or lower limb [17] to protect the heart against myocardial injury caused by subsequent sustained acute lethal IRI [18]. The exact mechanism by which this safe [14], noninvasive, cheap, and easy technique of RIPC induces cardioprotection is still not clearly understood. Several theories describing the transfer of this cardioprotective stimulus from remote organ or tissue to the heart have been proposed [19,20].

Only a few studies have been done regarding the effect of RIPC in OPCAB [7,8]. Hong *et al.* [8] reported that RIPC induced by upper-limb ischemia caused statistically insignificant reduction in the postoperative release of myocardial enzyme, troponin I, in patients undergoing OPCAB. Hong *et al.* [7] conducted another randomized controlled trial in OPCAB patients and demonstrated that RIPC with remote ischemic postconditioning (RIPost) by lower-limb ischemia decreased postoperative troponin I release by almost 50%.

The aim of our study was to determine if intense RIPC, induced by simultaneous upper-limb and lower-limb ischemia and reperfusion, can reduce postoperative myocardial injury assessed by the release of cardiac troponin I (cTnI), CKMB, and N-terminal of the prohormone brain natriuretic peptide (NTproBNP) in patients undergoing OPCAB.

Patients and methods

This was a single-centered, prospective, randomized controlled trial carried out in Tongji Medical College, Huazhong University of Science and Technology, over a period of 10 months (from December 2014 to September 2015). After obtaining approval by the institutional ethics committee, written informed consent was obtained from all the patients. In total, 47 adult patients (≥18 years) scheduled for elective isolated first-time OPCABG surgery were enrolled in the study and randomly divided into two groups, RIPC or control. Randomization was done using a computer-generated table of random numbers. Patients with age more than 80 years, history of cardiogenic shock or cardiac arrest during current admission, unstable angina, acute or recent myocardial infarction (within 7 days) or any other reason for increased preoperative cardiac troponins, preoperative inotropic support or any kind of mechanical assist device, left ventricular ejection fraction less than 30%, pregnancy, significant peripheral vascular disease affecting the upper or lower limbs, significant hepatic impairment (bilirubin >20 mmol/l, international normalized ratio>2.0), renal failure with a glomerular-filtration rate less than 30 ml/min/1.73 m^2 or pulmonary disease, or concomitant treatment with glibenclamide or nicorandil (these antidiabetic drugs can inhibit ATP-sensitive K^+-channel conductance and interfere with cardioprotective properties of RIPC) [21] were excluded from our study.

After arrival in the operation theater, the patient was properly positioned and a peripheral venous cannula was inserted. ECG monitoring was done with five-lead ECG and pulse-oximetry monitoring was done continuously. An arterial cannula was inserted into the left radial artery before induction of anesthesia and continuous arterial pressure monitoring was done.

General anesthesia was induced with intravenous etomidate, sufentanil with or without midazolam. The trachea was intubated and mechanical ventilation started with oxygen with or without air. Anesthesia was maintained with inhaled sevoflurane and remifentanil infusion. Intravenous rocuronium or cisatracurium was used for muscle relaxation during induction as well as maintenance.

After induction of anesthesia, RIPC was induced in the RIPC group by applying two standard-size blood-pressure cuffs to the arm and thigh simultaneously and inflating the cuff to 200 mmHg for 5 min (ischemia). This was followed by deflation of the cuffs for 5 min (reperfusion). This cycle of ischemia and reperfusion was repeated for three cycles. In the control group, blood-pressure cuffs were placed simultaneously on the arm and thigh and left uninflated for 30 min. RIPC stimulus was applied after the induction of general anesthesia but before the first surgical incision. RIPC protocol was performed and completed before the first surgical

incision. Central venous access was established in the internal jugular vein. Central venous pressure and nasopharyngeal temperature were monitored continuously.

All patients were treated with heparin to maintain activated clotting time greater than 450 s during anastomosis. CABGs were established using internal thoracic artery or saphenous vein graft in the beating heart (without using CPB). After completion of anastomosis, the effect of heparin was reversed using protamine sulfate. The patient was transferred to the ICU after surgery.

The primary endpoint of this study was the extent of perioperative myocardial injury assessed by serum concentration of cTnI, CKMB, and NTproBNP. These were measured preoperatively and at 24 and 72 h after the end of surgery.

Secondary endpoints of this study were duration of postoperative hospital stay and inotrope requirement during surgery, as calculated by inotrope score at the end of surgery, adapted from a study by Ko *et al.* [22]:

$$\begin{aligned}\text{Inotrope score} &= \left[\text{dosages of dopamine} + \text{dobutamine } (\text{in } \mu\text{g/kg/min})\right] \\ &+ \left[\text{dosages of epinephrine} + \text{norepinephrine} + \text{isoproterenol } (\text{in } \mu\text{g/kg/min})\right]\times 100 \\ &+ \left[\text{dosages of milrinone } (\text{in } \mu\text{g/kg/min})\right]\times 15 .\end{aligned}$$

Data were analyzed using SPSS, version 20.0 (SPSS, Chicago, Illinois, USA). Continuous data were expressed as mean±SD or median (lower–upper quartiles). Categorical data were presented as number (percentage). Comparison between two groups was done using independent *t* test for normally distributed data (BMI and total duration of surgery) and Mann–Whitney *U* test for non-normally distributed data (age, cardiac enzyme levels, inotrope score, and duration of hospital stay). Categorical data were compared using χ^2 test or Fisher's exact test wherever appropriate. *P* value less than 0.05 was considered to be statistically significant.

Results

A total of 59 patients, scheduled for elective OPCABG surgery, were screened for eligibility in this study. Four patients were excluded: one had a pacemaker, one had heart failure during current admission, one had a high preoperative troponin I value, and one had a right-sided mediastinal tumor. Written informed consent was obtained from the remaining 55 patients and they were randomized to receive either RIPC protocol (n=27) or control (n=28). Three patients of the RIPC group and two patients of the control group had to be excluded because of additional use of propofol/dexmedetomidine to maintain the depth of anesthesia. CPB was used during operation in one patient of the RIPC group and two patients of the control group, so these three patients were excluded. So, the final number of patients included in our study was 47, n=23 in the RIPC group and n=24 in the control group (Fig. 1).

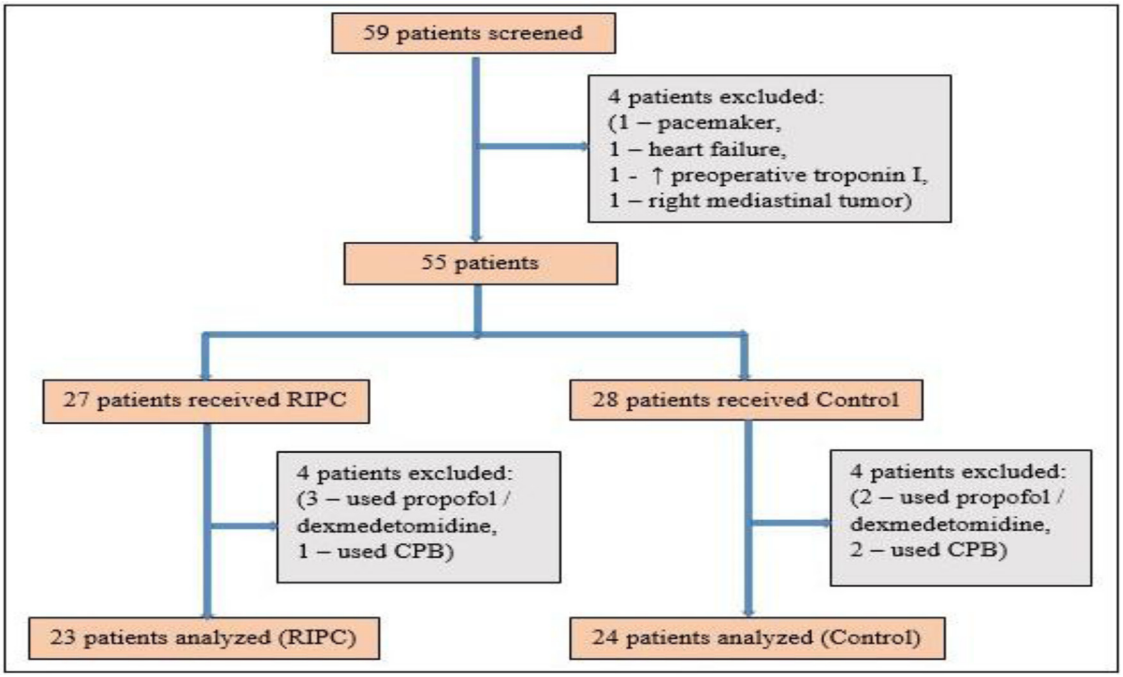
There was no difference in the baseline characteristics between the two groups (Table 1). Intraoperative features (duration of surgery and number of grafts used) and secondary outcomes (inotrope score at the end of surgery and duration of postoperative hospital stay) were similar in patients of the two groups (Table 2). RIPC protocol was applied to the right upper and lower limbs in all the patients, except one patient in the RIPC group, where the left side was used. Two deaths were reported in the control group. One patient died on 15th postoperative day due to multiple-organ-dysfunction syndrome and another patient died on 42nd postoperative day due to septic shock. There were no untoward effects of the RIPC protocol in either group.

The preoperative concentration of all three cardiac biomarkers (cTnI, CKMB, and NTproBNP) was similar between the two groups. Baseline concentration of cTnI was less than or equal to 0.207 ng/ml in both RIPC and control patients. All three cardiac enzyme levels increased postoperatively in both the groups. But, RIPC failed to cause a significant difference in postoperative release of cTnI, CKMB, and NTproBNP at 24 and 72 h after surgery when compared with the control group (Table 3).

Discussion

Our study demonstrated that RIPC, induced by brief ischemia and reperfusion of both upper and lower limbs with standard blood-pressure cuffs, did not cause a significant difference in the postoperative release of cTnI, CKMB, and NTproBNP in patients undergoing

Figure 1



Trial profile. RIPC, remote ischemic preconditioning; CPB, cardiopulmonary bypass.

Table 1 Patient characteristics

	RIPC (*N*=23)	Control (*N*=24)	*P* value
Demographics			
Age (years)	64 (52, 70)	64 (58, 67)	0.945
Sex			
Male	17 (73.9)	17 (70.8)	0.813
Female	6 (26.1)	7 (29.2)	
BMI (kg/m^2)	23.95±2.89	23.60±2.72	0.674
Risk factors			
Diabetes mellitus	5 (21.7)	5 (20.8)	1
Hypertension	15 (65.2)	15 (62.5)	0.846
Stroke	0	1 (4.2)	1
Smoking			0.666
Active smokers	2 (8.7)	4 (16.7)	
Nonsmokers	21 (91.3)	20 (83.3)	
NYHA class			
Class I	1 (4.3)	1 (4.2)	0.286
Class II	8 (34.8)	12 (50)	
Class III	11 (47.8)	11 (45.8)	
Class IV	3 (13)	0	
CCS class			
Class I	1 (4.3)	2 (8.3)	0.094
Class II	8 (34.8)	11 (45.8)	
Class III	5 (21.7)	9 (37.5)	
Class IV	9 (39.1)	2 (8.3)	
LVEF			
>55%	20 (86.96)	20 (83.33)	1
35–55%	3 (13.04)	4 (16.67)	
<35%	0	0	

Data given as *n* (%), mean±SD, or median (lower, upper quartile). CCS, Canadian Cardiovascular Society; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RIPC, remote ischemic preconditioning.

elective OPCABG surgery. This result was comparable to few previous studies that also reported no significant reduction in the release of cardiac enzymes with RIPC after cardiac surgery [8,23–27].

Hong and colleagues had conducted two trials, one in 2010 [8] and another in 2012 [7], to study the effect of RIPC in OPCAB. The authors had demonstrated no benefit with RIPC in the first trial, while significant cardioprotection with RIPC+RIPost in the second trial. The differences between these two trials were that RIPC was induced in the upper limb and inhalational anesthesia was used in the first trial, while RIPC+RIPost was induced in the lower limb and total intravenous anesthesia was used in the second trial. In our study, RIPC protocol was induced simultaneously in both upper and lower limbs and sevoflurane was used for maintenance of anesthesia in all the patients.

The degree of myocardial injury that occurs due to ischemia reperfusion during cardiac surgery can be quantified by the perioperative release of cardiac biomarkers [10]. Elevated levels of these cardiac enzymes cTnT [2,28], cTnI [1,3], and CKMB [29] may be associated with poor short-term and long-term clinical outcomes after cardiac surgery. Several studies have shown that RIPC decreased the release of cardiac biomarkers after CABG surgery [7,9–15,30], congenital cardiac [31], adult

Table 2 Intraoperative details and outcomes

	RIPC (*N*=23)	Control (*N*=24)	*P* value
Duration of surgery (min)	279.57±51.24	285±46.70	0.705
Number of grafts			
One	3 (13)	4 (16.7)	0.361
Two	13 (56.5)	8 (33.3)	
Three	7 (30.4)	11 (45.8)	
Four	0	1 (4.2)	
Inotrope score	3.22 (2.17, 5.77)	3.85 (2.28, 6.48)	0.631
Postoperative hospital stay (days)	13.89 (12.03, 16.82)	13.8 (12.55, 16.63)	0.818
Number of deaths	0	2 (8.33)	

Data given as *n* (%), mean±SD, or median (lower, upper quartile). RIPC, remote ischemic preconditioning.

Table 3 Serum levels of cardiac troponin I, creatine kinase isoform-MB, and N-terminal of the prohormone brain natriuretic peptide

	RIPC (*N*=23)	Control (*N*=24)	*P* value
cTnI (ng/ml)			
Preoperative	0.004 (0, 0.046)	0.0075 (0.0003, 0.027)	0.776
After 24 h	1.16 (0.42, 4.69)*	0.83 (0.54, 1.93)*	0.987
After 72 h	0.28 (0.08, 1.79)*†	0.48 (0.17, 2.34)*†	0.534
CKMB (ng/ml)			
Preoperative	0.9 (0.55, 1.25)	0.8 (0.4, 1)	0.254
After 24 h	4.2 (2.15, 14.15)*	7.3 (2.68, 12.5)*	0.597
After 72 h	1.6 (0.7, 4.85)†	1.6 (0.9, 2.5)*†	0.902
NTproBNP (pg/ml)			
Preoperative	278 (61, 917)	219 (59, 928)	0.908
After 24 h	1510 (808, 3528)*	1584 (972, 3055)*	0.958
After 72 h	1459 (815, 3645)*	2677 (1292, 4804)*	0.304

Data given as median (lower, upper quartile). CKMB, creatine kinase isoform-MB; cTnI, cardiac troponin I; NTproBNP, N-terminal of the prohormone brain natriuretic peptide; RIPC, remote ischemic preconditioning. *Significant increase when compared with preoperative value ($P<0.017$). †Significant decrease when compared with 24-h value ($P<0.017$).

valve [32], aortic surgeries [33], and PCI [34,35]. Only a very few of these trials have shown that RIPC can actually improve clinical outcome in these patients [14,15,36,37].

These conflicting results regarding cardioprotective features of RIPC may be due to the difference in RIPC protocols (number of cycles, upper or lower limb used, and timing of RIPC), anesthetic regimen (inhalational anesthesia or total intravenous anesthesia), presence of comorbid conditions, and surgical techniques used. A standard RIPC protocol and specific anesthesia regimen that has to be used for RIPC to be most effective in cardiac surgery has not been fully understood yet.

One study had shown that myocardial protection induced by combined ischemic preconditioning and postconditioning is greater than by preconditioning alone [7]. This study conducted by Hong and colleagues had reported almost 50% reduction in postoperative myocardial enzyme elevation in patients undergoing OPCAB with RIPC and RIPost. However, the RIPost protocol was not used in our study.

Inhaled anesthetic agents like sevoflurane can induce preconditioning by themselves and can attenuate the cardioprotective features of RIPC [38,39]. Hong *et al.* [8] had shown that RIPC under sevoflurane anesthesia failed to cause significant reduction in troponin-I levels in patients undergoing OPCAB. We also had used sevoflurane as a maintenance agent in all our patients.

It is known that an increase in myocardial enzyme levels after OPCAB is lesser than after on-pump CABG surgery [40,41]. Our study involved patients undergoing OPCAB, so cardioprotective features of RIPC may not have become apparent due to the lesser degree of myocardial injury in OPCAB as compared with conventional on-pump CABG surgery.

The beneficial effects of RIPC may not have become apparent because of the small number of patients in our study (*n*=47), which was the major

limitation of our study. Besides, cardiac biomarker (cTnI, CKMB, and NTproBNP) levels were measured preoperatively and at 24 and 72 h after the end of surgery. Various studies have reported cTnI levels measured at 20 [42] or 24 h [1] after the end of cardiac surgery or the first postoperative day [43] to be an independent predictor of perioperative myocardial injury and short-term, medium-term, and long-term mortality. But, the majority of clinical trials have measured these cardiac biomarkers at different postoperative time points (e.g. 6, 12, 24, 48, and 72 h) and shown that cardiac enzyme elevation is maximum at about 6 h after cardiac surgery [7,10,11]. Our study was unable to take into account the difference in postoperative release of cTnI, CKMB, and NTproBNP at 6, 12, and 48 h after OPCAB.

Conclusion

We found that intense RIPC, induced by brief ischemia and reperfusion of both the upper arm and thigh, did not cause a significant reduction in the postoperative release of cTnI, CKMB, and NTproBNP in patients undergoing elective OPCAB. Larger multicentered clinical trials with greater number of patients should be conducted in the future to evaluate the beneficial effect of this simple, safe, and easy technique of intense RIPC in patients undergoing on-pump and OPCAB.

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Conflicts of interest

There are no conflicts of interest.

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