Original Article

Effect of Remote Ischemic Preconditioning on Myocardial Ischemia in Patients Undergoing Coronary Artery Bypass Graft Surgery: A Randomized Controlled Trial

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Objective: To determine whether the remote ischemic pre-conditioning (RIPC) reduces myocardial ischemia in patients undergoing elective coronary artery bypass graft (CABG) surgery.

Materials and Methods: The present study was a single-center, triple-blinded, randomized controlled trial. Fifty patients undergoing elective coronary artery bypass graft surgery were assigned to either RIPC or control treatment. Ischemic pre-conditioning consisted of three cycles of 5-minute of lower limb ischemia and reperfusion (cuff inflation and deflation) after anesthesia induction. Myocardial ischemia was assessed based on serum high-sensitivity cardiac troponin T (hs-cTnT).

Results: There was no significant difference in hs-cTnT levels between the RIPC group and the control group. Furthermore, there were no significant differences in inotropic drug use, acute kidney injury, mechanical ventilation time, hospital stay, or 30-day mortality. However, patients in the RIPC group had a significantly shorter length of stay in the intensive care unit (ICU).

Conclusion: Although RIPC did not reduce myocardial ischemia after CABG surgery, it did decrease the length of patients' stays in the ICU.

Keywords: Remote ischemic preconditioning, Coronary artery bypass graft, Myocardial ischemia, Troponin

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Coronary artery disease is a common condition and one of the leading causes of death. Coronary artery bypass graft (CABG) surgery is a major surgery that is performed in cardiac centers worldwide. Current data show that most patients who suffered from coronary artery disease tend to be older and have more co-morbid diseases, which can complicate this kind of surgery. There are various intraoperative factors that can adversely affect surgical outcomes, a major one of which is myocardial ischemia. Thus, it is necessary to develop new cardioprotective interventions to protect the heart during CABG surgery and improve patient morbidity and mortality[1]. Ischemic pre-conditioning is a concept that was introduced over three decades ago as a strategy to protect organs during surgery. Remote ischemic pre-conditioning (RIPC) is performed by introducing brief episodes of non-lethal ischemia to remote organs, such as the limbs, and inducing reperfusion prior to inducing a sustained episode of lethal ischemia and reperfusion (for example, cross clamping the aorta during cardiac surgery). This provides subsequent protection against ischemia-induced myocardial injury by operating through the humoral or neural pathways[2]. Myocardial ischemia was assessed by measuring serum troponin release post-operatively. The release of troponin is related not only to myocardial ischemia but also to other cardiovascular events in the post-operative period. RIPC is a simple, low cost, and non-invasive technique that may provide powerful myocardial

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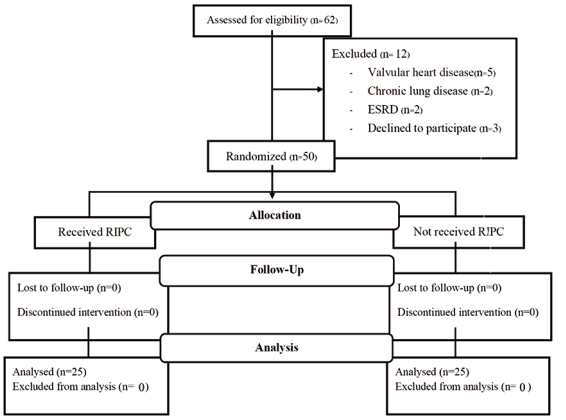

Figure 1. Study protocol.

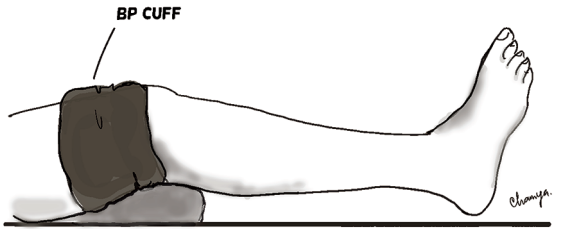

Figure 2. Remote ischemic preconditioning (RIPC).

protection during CABG surgery[3]. However, findings regarding the role of RIPC in cardioprotection remain inconclusive.

Objective

The aim of the present study was to investigate whether RIPC is an effective technique of myocardial protection in patients undergoing elective CABG surgery.

Materials and Methods

Study design

The present study was a single-center, triple-blinded, randomized controlled trial in patients undergoing elective CABG surgery for the first time. The study received approval from the authors' Institution's Ethics Committee, and written informed consents were obtained from all recruited patients.

The subjects of the present study were patients undergoing conventional CABG surgery at the Srinagarind Hospital and Queen Sirikit Heart Center of the Northeast at Khon Kaen University (Thailand).

Patient selection and randomization

The inclusion criteria were patients age 18 to 70 years and diagnosis with coronary artery disease that required an elective CABG. Exclusion criteria were cardiogenic shock or cardiac arrest during the current admission, conditions requiring other cardiac procedures such as valvular heart disease, history of cardiac operation, significant peripheral arterial disease affecting the lower limbs, end-stage renal disease (ESRD) or glomerular filtration rate (GFR) of less than 15 ml per minute, pregnancy, and chronic lung disease.

The sample size of the present study was determined based on the results of a previous study[4] to achieve a power of 80% and 95% confidence interval. Between November 2016 and April 2017, there were 62 eligible patients, 12 of whom were excluded due to not fulfilling the inclusion criteria.

Patients were divided into two groups based on block of four randomizations, the RIPC group (25 patients) and the control group (25 patients). The group codes were kept in secured envelopes and attached to the patients' charts. The secured codes were opened in the operating room by the circulating nurse. Blinding was also a consideration for the patient, surgeons, nurses who cared for the patient during the post-operative period, and the researcher who analyzed the data. The study protocol is demonstrated in Figure 1.

Interventions

RIPC and control protocols were initiated after anesthesia induction. RIPC was conducted with one standard blood pressure cuff placed on the right or left upper thigh. The cuffs were then simultaneously inflated to 200 mmHg and left inflated for five minutes. They were then deflated to 0 mmHg and left uninflated for five minutes. This cycle was repeated twice so that the total duration of the RIPC protocol was 15 minutes (Figure 2). The control group received the same protocol, but the cuff was not inflated when the attached bulb was squeezed. This procedure was performed by a scrub nurse before the surgeon arrived and began the operation.

Surgical technique

All of the patients received the same general anesthesia and median sternotomy. The left internal mammary artery (LIMA) was harvested in all patients, and the greater saphenous vein or radial artery was harvested according to the conditions and indications of each patient. Standard cardiopulmonary bypass (CPB) was established, and heparin was given to achieve activated clotting time (ACT) of more than 480 seconds. Systemic mild hypothermia with a body

temperature of 32°C to 34°C was conducted. The aortic cross-clamp was applied, and the antegrade cardioplegia was used as needed. When distal anastomosis was performed completely, the patient was rewarmed, and then the aorta was partially clamped for proximal anastomosis. Following anastomoses of the grafts, CPB was discontinued and protamine was used to achieve heparin reversal.

Study endpoints

The primary endpoint of the present study was myocardial ischemia, which was assessed by measuring total 72-hour serum high-sensitivity cardiac troponin T (hs-cTnT) levels. The secondary endpoints were the necessity of post-operative inotropic drugs, duration of ventilator assistance, acute kidney injury as assessed based on increases in serum creatinine levels, length of intensive care unit (ICU) per hospital stay, and early mortality.

Definitions

Cardiovascular death was defined as death due to a known cardiovascular cause.

Early mortality was defined as in-hospital death or death within 30 days after the operation.

Myocardial ischemia was defined as decreased blood flow to the heart muscle (myocardium) due to partial or complete blockage of a coronary artery or low perfusion condition.

Peri-operative myocardial infarction was indicated by biomarker (high-sensitive troponin T) values more than five times of the 99th percentile of the normal reference range during the first 72 hour following CABG, when associated with the appearance of new pathological Q-waves or new left bundle branch block (LBBB), or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium.

Acute kidney injury was defined as an abrupt, within hours, decrease in kidney function. The diagnosis of acute kidney injury was based on a sudden decrease in GFR, as reflected by an acute rise in serum creatinine levels or a decline in urine output over a given time interval.

Statistical analysis

Data were presented as mean ± standard deviation or median. The significant differences between the two groups were assessed using a Student's t-test or Mann-Whitney U-test. Categorical data were compared using a chi-squared test or Fisher's exact

Table 1. Patient demographic data

Parameters	Control (n=25) n (%)	RIPC (n=25) n (%)	p-value
Sex: male	13 (52.00)	19 (76.00)	0.140
Age (year); mean±SD	61.16±8.00)	59.76±11.95	0.629
BMI (kg/m^2); mean±SD	23.99±3.52	23.52±4.34	0.677
Smoking	11 (44.00)	14 (56.00)	0.572
History of angina	20 (80.00)	22 (88.00)	0.440
History of TIA/CVA	1 (4.00)	2 (8.00)	1.000
Underlying disease			
DM	14 (56.00)	14 (56.00)	1.000
HT	18 (72.00)	16 (64.00)	0.544
Dyslipidemia	8 (32.00)	5 (20.00)	0.333
CKD	2 (8.00)	2 (8.00)	1.000
NYHA class			
NYHA I	3 (12.00)	2 (8.00)	0.637
NYHA II	17 (68.00)	20 (80.00)	0.333
NYHA III	5 (20.00)	3 (12.00)	0.440
CCS angina class			
CCS I	8 (32.00)	3 (12.00)	0.088
CCS II	17 (68.00)	22 (88.00)	0.088
EuroSCORE II; mean±SD	0.9±0.08	1.1±0.10	0.587
Drug history			
Aspirin	23 (92.00)	25 (100)	0.490
Statin	23 (92.00)	22 (88.00)	1.000
Nitrates	13 (52.00)	13 (52.00)	1.000
β-blockers	13 (52.00)	14 (56.00)	0.777
ACEI/ARBs	9 (36.00)	7 (28.00)	0.544
Insulin	4 (4.00)	3 (12.00)	0.609
Inotrope	0 (0.00)	0 (0.00)	N/A
History of intermittent claudication	0 (0.00)	0 (0.00)	N/A
ABI >1	25 (100)	25 (100)	N/A
Ejection fraction (%); median ((IQR)	60 (53 to 66)	56 (43 to 68)	0.415
CAG			0.017
DVD	1 (4.00)	3 (12.00)	0.609
TVD	19 (76.00)	9 (36.00)	0.004
TVD with LM	5 (20.00)	13 (52.00)	0.018

RIPC=remote ischemic preconditioning; BMI=body mass index; TIA=transient ischemic attack; CVA=cerebrovascular accident; DM=diabetes mellitus; HT=hypertension; CKD=chronic kidney disease; NYHA=New York Heart Association; CCS=Canadian Cardiovascular Society; EuroSCORE=European System for Cardiac Operative Risk Evaluation; ACEI=angiotensin-converting-enzyme inhibitor; ARBs=angiotensin II receptor blockers; ABI=ankle-brachial index; CAG=coronary angiography; DVD=double vessel disease; TVD=triple vessel disease; LM=left main; SD=standard deviation; IQR=interquartile range; N/A=not available

Table 2. Intraoperative data

Parameters	Control (n=25) n (%)	RIPC (n=25) n (%)	p-value
Aortic cross clamp time (minute); median (IQR)	90.5 (76.5 to 118)	94 (70 to 110)	0.555
CPB time (minute); median (IQR)	148 (120 to 184)	140 (110 to 163)	0.177
Partial aortic cross clamp (minute); median (IQR)	20 (9 to 26)	21.5 (14 to 30)	0.368
Number of grafts; median (IQR)	4 (3 to 5)	4 (3 to 5)	0.620
LIMA usage	25 (100)	25 (100)	N/A
Radial artery usage	3 (37.50)	4 (57.14)	0.542
GEA usage	0 (0.00)	1 (20.00)	0.455
SVG usage			0.268
1	4 (17.39)	4 (20.00)	1.000
2	6 (26.09)	9 (45.00)	0.194
3	10 (43.48)	7 (35.00)	0.571
4	3 (13.04)	0 (0.00)	0.236
Coronary endarterectomy	1 (4.35)	2 (8.00)	1.000
Operative time (hour); median (IQR)	5 (5 to 6)	5 (5 to 6)	0.769

RIPC=remote ischemic preconditioning; IQR=interquartile range; CPB=cardiopulmonary bypass; LIMA=left internal mammary artery; GEA=gastroepiploic artery; SVG=saphenous vein graft; N/A=not available

Table 3. Post-operative troponin levels

Troponin level	RIPC (n=25) Mean±SD	Control (n=25) Mean±SD	p-value
At 0 hour	834.56±650.18	864.88±713.98	1.000
At 12 hours	871.08±538.99	1,388.04±1,653.01	0.152
At 24 hours	636.12±446.82	901.96±1,000.72	1.000
At 48 hours	488.12±315.91	774.40±821.10	1.000
At 72 hours	423.00±217.97	865.40±967.60	1.000

RIPC=remote ischemic preconditioning; CI=confidence interval; SD=standard deviation

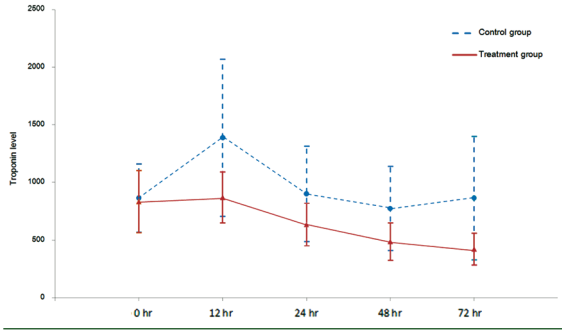

Figure 3. Serum hs-cTnT levels.

test. The generalized estimating equation (GEE) method using the first-order autocorrelation was applied to compare repeated measurements of troponin levels within a single subject. The interaction between group and time was tested using a 0.05 level of significance. All tests were 2-tailed, and p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using Stata, version 10 (StataCorp LP, College Station, TX, USA).

Results

The authors assessed 62 patients for eligibility (see Figure 1). Twelve patients were excluded from the study. Fifty patients were enrolled and randomized to either the RIPC (n=25) or control (n=25) group and included in the final analysis. There was no significant difference between the two groups in terms of baseline characteristics (Table 1). The mean age of the patients in both groups was approximately 60 years. Most patients presented with angina, and more than half of the patients in both groups had underlying diabetes mellitus and hypertension. Most patients in both groups had triple vessel involvement. Triple vessel with left main disease was more common in the RIPC group.

Both groups were similar in terms of intra-operative characteristics. There were no statistically significant differences with regard to aortic cross-clamp time, CPB time, number of grafts, or operative time (Table 2).

There were marked elevations in hs-cTnT levels in both groups at 0, 12, 24, 48, and 72 hours after the

Table 4. Postoperative data

Parameters	Control (n=25) Median (IQR)	RIPC (n=25) Median (IQR)	p-value
EKG, n (%)			
New-onset Q wave	0 (0.00)	0 (0.00)	N/A
New-onset LBBB	0 (0.00)	0 (0.00)	N/A
AF	9 (36.00)	6 (24.00)	0.305
IABP usage, n (%)	2 (8.00)	0 (0.00)	0.490
Inotrope usage (hour)	65.5 (39.0 to 120.0)	45.5 (21.5 to 51.0)	0.137
Duration of ventilator assistance (hour)	17 (15 to 48)	16 (15 to 19)	0.349
Peak creatinine at			
Day 1	1.1 (0.9 to 2.0)	1.0 (0.7 to 1.7)	0.539
Day 2	1.0 (0.8 to 1.7)	0.9 (0.8 to 1.6)	0.703
Day 3	0.9 (0.7 to 1.5)	0.9 (0.7 to 1.2)	0.800
Length of ICU stay (days)	4 (3.5 to 5.5)	3 (3 to 4)	0.004
Length of hospital stay (days)	14 (12 to 17)	13 (11 to 16)	0.402
30-day mortality, n (%)	0 (0.00)	0 (0.00)	N/A

RIPC=remote ischemic preconditioning; IQR=interquartile range; EKG=electrocardiogram; LBBB=left bundle branch block; AF=atrial fibrillation; IABP=intra-aortic balloon pump; ICU=intensive care unit; N/A=not available

operation (Table 3). Levels peaked at 12 hours after the operation in all patients. A linear graph (Figure 3) revealed that troponin levels in the RIPC group were lower than in the control group at all-time points, but this difference was not statistically significant.

Post-operative period data are presented in Table 4. The duration of stay in ICU was significantly longer in the control group. None of the patients in the present study developed post-operative renal dysfunction. There were no operative deaths up to 30 days post-operatively, in either group. The inotrope requirement, duration of ventilator support, and duration of ICU and hospital stay were similar between the two groups.

Discussion

The cardioprotective effect of preischemic conditioning was first described in 1987[5]. This contributed to the development of RIPC, which is the protection against lethal acute ischemia and reperfusion injury by applying one or more cycles of brief, non-lethal ischemia and reperfusion to a remote organ or tissue such as an upper or lower limb. The actual mechanism of RIPC remains unclear, but most researchers believe that it may be related to neurohormonal factors. Neurohormonal are produced in response to the RIPC stimulus, which conveys the protective effect from the remote organ or tissue to the target organ[5-7].

The concept of RIPC has been applied in clinical practice for over two decades. Many studies have demonstrated the benefits of RIPC in terms of reducing the rates of myocardial injury and acute kidney dysfunction, as well as shortening the length of patients' stays in the ICU[8,9]. However, there have been some studies in which RIPC was not found to exhibit myocardial protection following surgical coronary revascularization[4,10,11].

In the present study, the authors found that RIPC did not reduce myocardial ischemia in patients underwent CABG surgery. There were no significant differences between the two groups in terms of plasma troponin T levels, which is a biomarker for myocardial ischemia, over the 72 hours period following surgery. However, troponin and creatinine levels were lower in the RIPC group at all-time points. This is consistent with the results of some previous studies. Rahman et al, for example, conducted a large randomized study of RIPC in CABG and failed to demonstrate any benefits of RIPC[12]. Their methodology differed from the present study in that they applied three 5-minute cycles of inflation and deflation of a blood pressure cuff placed on the upper arm, while the authors applied the pressure cuff to a lower limb.

Besides protecting the heart, RIPC may also useful in protecting other distant organs such as the kidneys. Hong et al found that RIPC reduced the incidence of renal impairment in patients undergoing

surgery for abdominal aortic aneurysm repair[9]. In the present study, creatinine levels in the RIPC group were lower than in the control group, but this difference was not statistically significant.

The authors also found beneficial effects of RIPC on the length of patients' stays in the ICU following cardiac surgery, which were approximately one day shorter in the RIPC group. This is consistent with the results of a study by Candilio et al, which applied RIPC protocol in patients undergoing CABG or valve surgery for two to five minute cycles of simultaneous upper arm and thigh cuff inflation and deflation, and found that RIPC reduced ICU stay by one day[8].

One potential explanation for the present study results relates to the RIPC stimulus itself, which may not be sufficient to promote cardioprotection under certain conditions. Most clinical studies have used a standard single-limb RIPC protocol consisting of one to three cycles of five minute of inflation and deflation of a cuff. Although, the authors used a more intense RIPC protocol consisting of three 5-minute cycles of simultaneous upper thigh cuff inflation and deflation, the authors did not find any benefit of RIPC. This is in contrast with the study by Hong et al mentioned above, which found that implementing a more intensive protocol yielded positive results. They reported significant reduction in myocardial injury in patients who underwent on pump beating heart CABG. They performed both RIPC and remote ischemic post conditioning (RIPostC), consisting of four cycles of five minutes ischemia and five minutes reperfusion on a lower limb before (RIPC) and after anastomoses (RIPostC). This suggests that the study protocol may affect to the outcome[9].

Limitations of the current study include patient-related factors that may have influenced the effectiveness of RIPC. Hassouna et al reported the mitochondrial dysfunction in diabetic patients causes the inability to respond to pre-conditioning[13], which is similar to the findings of a study by Ishihara et al that diabetes might prevent ischemic pre-conditioning[14]. In the present study, 56% of the patients in both groups were diabetic, which may have had a major effect on the outcome. In addition, the number of patients recruited was probably too small to enable detection of differences. The authors did not develop protocol for cardioplegia and anesthetic agents administration and did not perform subgroup analysis of the patients that received different cardioplegic solutions or anesthetic agents due to the relatively small number of patients.

Conclusion

RIPC did not reduce myocardial injury, acute kidney injury, post-operative arrhythmia, or inotrope or ventilator support in patients undergoing elective on-pump CABG but shortened patients' stays in the ICU.

What is already known on this topic?

Remote ischemic pre-conditioning is a simple, non-invasive technique to protect the myocardial injury in patients undergoing cardiac surgery by inducing a brief episode of limb ischemia prior to surgery. However, there is controversy regarding the benefits of RIPC.

What this study adds?

Remote ischemic pre-conditioning did not improve clinical outcomes in patients undergoing elective on-pump CABG. However, it shortened patients' stays in the ICU.

Acknowledgement

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Conflicts of interest

The authors declare no conflict of interest.

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