Cardioprotective Effect of Remote Ischemic Preconditioning with Postconditioning on Donor Hearts in Patients Undergoing Heart Transplantation: a single-center, double-blind, randomized controlled trial

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Abstract

Background: Cardioprotective effect of remote ischemic preconditioning (RIPC) in cardiovascular surgery is controversy. This study investigated whether RIPC combined with remote ischemic postconditioning (RIPostC) reduces myocardial injury on donor hearts in patients undergoing heart transplantation.

Methods: One hundred and twenty patients scheduled for orthotopic heart transplantation were enrolled and randomly assigned to an RIPC+RIPostC group (n=60) or a control (n=60) group. In the RIPC+RIPostC group, four cycles of 5-min ischemia and 5-min reperfusion were applied on the right upper limb by a cuff inflated to 200mmHg after anesthesia induction (RIPC) and 20 minutes after aortic declamping (RIPostC). Serum cardiac troponin I (cTnI) level was determined preoperatively and at 3, 6, 12, 24 h after aortic declamping. Postoperative clinical outcomes were recorded. The primary endpoint was comparison of the cTnI levels at 6 h after aortic declamping.

Results: Compare with the preoperative baseline, serum cTnI levels peaked at 6h after aortic declamping in two groups. Compare with the control group, RIPC+RIPostC significantly reduced the serum cTnI levels at 6h after aortic declamping (38.87±31.81 vs 69.30±34.13ng/ml, *P*=0.018). There was no significant difference in in-hospital morbidity and mortality between the two groups.

Conclusion: In patients undergoing orthotopic heart transplantation, RIPC combined with RIPostC reduced myocardial injury at 6h after aortic declamping，while we found no evidence of this function provided by RIPC+RIPostC could improve clinical outcomes

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Keywords: Ischemia; preconditioning; postconditioning; heart transplantation

Background

Myocardium is susceptible to ischemia/reperfusion injury (IRI) during cardiac surgery and is known to be associated with adverse outcomes [1, 2]. About 4000～5000 heart transplants are performed worldwide annually，IRI is an inevitable consequence of the heart transplantation[3, 4]. Although the long-term survival and quality of life of transplant recipients have improved significantly, strategies for myocardial protection and perioperative mortality rates haven't taken place substantial changes [5]. Therefore, efforts to devise the effective myocardial protective strategy continue for patients undergoing heart transplantation.

In early clinical studies, compared with ischemic preconditioning (IPC), remote ischemic preconditioning (RIPC) can be implemented through a simple, inexpensive and non-invasive technique such as using a pneumatic cuff to cause a transient limb ischemia [6]. Several clinical trials have shown that RIPC has a powerful protective effect on myocardial injury and significantly attenuated postoperative troponin

elevation in the surgeries of congenital cardiac, abdominal aortic, cardiac valve and coronary artery bypass graft (CABG[6-[Przyklenk, 1993 #13;Cheung, 2006 #7;Meybohm, 2015 #18]8]. In addition, it is probable that RIPC and remote ischemic postconditioning (RIPostC) protocol have additive protective effects. In this regard, compared with the control group, RIPC combined with RIPostC reduced postoperative serum cTnI elevation, whereas RIPC alone did not show a markedly difference in patients undergoing OPCAB surgery [9]. In the study of experimental animals, Andreka et al. [10] found that RIPostC also can provide cardioprotection. In clinical practice, Hong et al. [11] concluded that the protective effect of combined preconditioning and postconditioning can reduce myocardial enzyme elevation in patients receiving OPCAB surgery by 48.7%. Although RIPC +RIPostC is expected to exert an effective protective effect, the study of RIPC +RIPostC on heart transplantation has not been reported yet.

We therefore hypothesized that RIPC with RIPostC would reduce myocardial injury of donor hearts and improve clinical outcomes in patients undergoing heart transplantation.

Methods

This was a single-center, prospective, double-blind, randomized and controlled trial. This study was registered on Chinese Clinical Trial Registry (http://www.chictr.org.cn) with registration number ChiCTR-INR-16010234. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Medical Ethics Committee of Fuwai Hospital. Written informed consents were obtained from all participants prior to enrollment.

Patients aged 18 to 70 years with end-stage heart diseases scheduled for primary orthotopic heart transplantation between January 2017 and August 2018 at Fuwai Hospital, Beijing, China were screened and considered for random allocation. Exclusion criteria were preoperative mechanical circulatory support, peripheral vascular disease affecting the upper limbs, redo heart transplantation. Moreover, patients taking the antidiabetic sulphonylurea or glibenclamide were also excluded because these agents have been shown to abolish preconditioning induced by ischemic preconditioning [12].

On the day of surgery, eligible patients were randomly allocated to receive either RIPC+RIPostC or sham RIPC+RIPostC (control) before heart transplantation. Randomization was performed with opaque envelopes that concealed the group allocation. A research fellow, not involved in medical treatment or data analysis performed the enrollment, group assignment, and intervention. Patients, cardiac surgeons, and postoperative intensive care staffs were all blinded to treatment.

Remote ischemic conditioning was applied after anesthesia induction (RIPC) and 20 minutes after aortic declamping (RIPostC), which consisted of four 5-min cycles of right upper limb ischemia induced by a cuff inflated to 200 mmHg with an intervening 5 min of reperfusion during which the cuff was deflated. Patients in the control group underwent the sham placement of the cuff around the right upper arm without inflation. Blood samples were collected for measurement of serum cardiac troponin I (cTnI) levels before surgery and at 3, 6, 12, 24h after removal of the aortic cross clamp.

Premedication, anesthesia, perfusion, cardioplegia, and surgical techniques were standardized. Electrocardiography (ECG), pulse oximetry, nasopharyngeal and bladder temperature, arterial blood pressure, central venous pressure, and pulmonary artery pressure were monitored continuously. Anesthesia was induced with intravenous etomidate (0.2-0.3 mg/kg), cisatracurium (0.2-0.3 mg/kg) or rocuronium (0.6-1.5 mg/kg), sufentanyl (1-2 μg /kg), and midazolam (0.2-1mg/kg), and maintained with propofol (0.05–0.08 mg/kg/min), sufentanyl(300μg-500μg) and muscle relaxants(10mg/h). Low concentration of sevoflurane (0.5-1%) was used if necessary (during central lines implantation).

Orthotopic heart transplantation was conducted through median sternotomy. Standard non-pulsatile cardiopulmonary bypass (CPB) with a membrane oxygenator was used. During CPB, moderate systemic hypothermia (nasopharyngeal temperature 28°C) was maintained. The recipient's heart was removed. Orthotopic heart transplantation was performed using a double-venous technique. All patients received basiliximab (20mg) before incision for immune induction. Methylprednisolone (500mg) was used twice before incision and after aortic declamping.

The primary endpoint was to compare serum cTnI levels at 6 h after aortic declamping between two groups. Secondary endpoints were comparison of serum cTnI levels at 3, 12, 24 h after aortic declamping and postoperative clinical outcomes including in-hospital death, new onset stroke, renal failure requiring dialysis, mechanical circulatory support, arrhythmia requiring treatment, re-operation for any cause, gastrointestinal bleeding, mechanical ventilation time, ICU length of stay, postoperative hospital length of stay.

The clinical outcomes were derived from the Society of Thoracic Surgeons (STS) database registry [13]. New onset stroke was defined as a new ischemic or hemorrhagic cerebrovascular accident with focal neurological deficit persisting >24 h and confirmed by brain computed tomography imaging. Re-operation for any cause included re-exploration for bleeding and surgical reintervention. Mechanical circulatory support was defined as postoperative use of an intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO). Arrhythmia requiring treatment included ventricular fibrillation, ventricular tachycardia, and atrial fibrillation requiring intervention. Data were obtained from medical records and reviewed by two cardiologists who did not participate in the study.

Statistical analysis of data

Sample size was calculated according to our pilot study, serum cTnI level was 66±23 ng/ml at 6 h after aortic decamping in the control group. We hypothesized RIPC with RIPostC significantly reduced serum cTnI levels by 30% and assuming a 5% dropout rate. To achieve 80% power at a two-sided significance level of 5%, a total of 120 patients was needed.

All statistical analyses were performed using SPSS version 20.0 (IBM Corp, Armonk, NY). The Shapiro-Wilk test was used to assess the normality of the distribution. For normally distributed data, all data were described as mean ± SD. Nonparametric data were described as median and interquartile ranges, and categorical data were described as the number of patients and relative frequency of the patient. Normally

distributed variables were compared between groups with independent-sample T test. Continuous variables that were not normally distributed were analyzed with nonparametric test (Mann-Whitney *U*). Categorical variables were compared between groups with Chi-square test or Fisher exact test if the resulting matrixes contained cells with expected count <5. All tests were two-sided and a p value of $P<0.05$ was regarded as significant. The analysis was by intention to treat.

Results

During the study period, 144 patients were screened for eligibility, among whom 120 met the inclusion criteria and were randomizd to either the RIPC+RIPostC group (n=60) or to the control group (n=60).24 patients were excluded (5 preoperative IABP support,3 redo heart transplantation and 16 refused to participate) (Figure 1).

The baseline characteristics of the two groups were comparable (Table 1). There was no difference in donor heart ischemia time and the details of orthotopic heart transplantation surgery between two groups (Table 2). No unintended effects or harm related to the RIPC+RIPostC were detected.

Myocardial Injury

Baseline preoperative serum cTnI level was comparable between two groups. Serum cTnI levels significantly increased in both groups after the procedure and peaked at 6h after aortic declamping. RIPC+RIPostC significantly reduced the peak cTnI levels (at 6h) (38.87±31.81 vs 69.30±34.13ng/ml, $P=0.018$). There was no significant difference in the levels of serum cTnI at other postoperative time points (Table 3).

Clinical Outcomes

There was no significant difference in in-hospital mortality, length of ICU stay, mechanical ventilation time, and other clinical outcomes between two groups (Table 4).

Discussion

The present study is the first demonstration of the effectiveness of RIPC combined with RIPostC in patients undergoing orthotopic heart transplantation. It showed that RIPC+RIPostC can reduce serum cTnI levels in donor heart ischemia at 6h after aortic declamping, but we found no evidence of this function provided by RIPC+RIPostC could improve clinical outcomes after surgery, compared with the control group.

Ever since the first RIPC study [6] which demonstrated a strong preventing IRI and myocardial protective effect, substantial RIPC studies have been performed due to the RIPC technique is simple, inexpensive and non-invasive. In early clinical studies, RIPC predominantly reduced postoperative myocardial enzyme levels in cardiovascular surgery patients. Hausenloy et al. [14] induced RIPC by lower limb ischemia in

patients undergoing on-pump CABG, and they illustrated that it attenuated myocardial injury at 6, 12, 24, and 48 h after surgery. Furthermore, this effect has also been confirmed by our preceding meta-analysis by Yang et al. [15], but mortality, morbidity, and other clinical outcomes in patients did not improve. However, several studies [16-18] have failed to demonstrate beneficial effects of RIPC in this kind of patients including two multicenter randomized clinical trials of larger sample size in cardiac surgery reported by Hausenloy et al. [16] and Meybohm et al. [17]

There are several explanations for our results. The study tested the myocardial protective effect of RIPC+RIPostC in patients undergoing orthotopic heart transplantation, those who may benefit highly from an effective preventive strategy. In the aforementioned research (Hausenloy et al .and Meybohm et al.), most of the patients were undergoing CABG, some patients undergoing valve or ascending-aorta replacement or combined procedures. Postoperative complications of these types of surgery are inherently less than those of orthotopic heart transplantation. In addition, most patients have experienced preconditioning for IRI before CABG. Thus, the beneficial clinical effect of RIPC may be limited during CABG and valve or ascending-aorta replacement or combined procedures. In recent clinical studies, they found that RIPC significantly reduced the rate of acute kidney injury compared with no ischemic preconditioning, and renal replacement therapy were required in high-risk patients undergoing cardiac surgery [19]. It is highly likely that such preconditioning is more effective in non-ischemic heart patients with high risk and high complication rate than in patients without these factors.

There are several mechanisms for RIPC and RIPostC technique applied in orthotopic heart transplantation in animal. In a study of heart porcine transplantation, researchers found that hind limb preconditioning in a recipient animal provided significant cardioprotection effect for the subsequently transplanted and denervated donor heart [20]. Furthermore, Konstantinov et al. [21] demonstrated that RIPC of the recipient animal decreased IRI in the donor heart following orthotopic heart transplantation via a K^+ATP channel. RIPostC is considered to recruit a completely different mechanism of RIPC during the reperfusion period, the mechanism of RIPostC remains to be determined [22]. Combined with our results, we speculated that humoral mechanisms like plays a crucial role when RIPC and RIPostC technique using in orthotopic heart transplantation.

Another possible confounding factor in our results is using of propofol for anesthetic maintenance. The effect of RIPC and RIPostC may have been less affected by the use of propofol in our study, compared with other researches utilizing RIPC alone.Given that RIPostC protocol have additive cardioprotective effects，maybe it can offset a part of negative effect of propofol . In addition, the dose of propofol was low (0.05–0.08 mg/kg/min) in present study, large doses of sufentanyl and sevoflurane assisted meanwhile. Taken together, several promising effects were conducted in this study, although the use of propofol anesthesia.

The study has some limitations. First, this was a single-centre study including a relatively small sample size of patients participating in a randomized controlled trial. Orthotopic heart transplantation surgery is a highly complex procedure and demanding for both the surgeon and the anesthesiologist. Therefore, it

was unrealistic to conduct a multicentre trial. Second, serum cTnI is sensitive and specific biomarkers for detecting of myocyte injury, its level can reflect the amount of myocardial destruction. In spite of a significant reduction of serum cTnI levels were observed in our study, this may be due to the number of patients enrolled was probably too small, which means that a larger scale trial is needed. Third, long-term clinical outcomes were not investigated.

Conclusion

The present study is the first demonstration of RIPC with RIPostC in patients undergoing orthotopic heart transplantation, which showed that RIPC with RIPostC can reduce the release of myocardial injury marker serum cTnI levels at 6 h after aortic decamping. Further study with different clinical outcomes as primary endpoints and follow-up data are clearly warranted.

Abbreviations

RIPC: remote ischemic preconditioning；RIPostC: remote ischemic postconditioning；

cTnI：cardiac troponin I；IRI：ischemia/reperfusion injury (IRI); CABG: coronary artery bypass grafting

Declarations

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Availability of data and materials

Data are available from the authors upon reasonable request with permission from Fuwai Hospital.

Authors' contributions

GYW conceived of the study, participated in the design of the study, supervise the study and revise the manuscript. YZ participated in the design of the study and revise the manuscript.LJY participated in the design of the study and drafted the manuscript. YMC helped analyse the data and draft the manuscript.

HZ performed the statistical analysis, data interpretation. ZRF, CYZ, and GYL participated in the data collection. SS and JL helped with study conduct. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The local ethical committee approval was obtained from Fuwai Hospital，Approval NO：2016-836．Written informed consents were obtained from all participants before enrollment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Baseline characteristics

	RIPC+RIPostC (n=60)	Control (n=60)
Demographics		
Age (years)	46.5±16.2	47.1±12.4
Male	45 (75%)	44 (73.3%)
BMI	21.6±3.7	21.4±3.2
Distribution of primary diseases		
Coronary heart diseases	10(16.7%)	9(15%)
Cardiomyopathy		
Dilated cardiomyopathy	29(48.3%)	32(53.3%)
Hypertrophic cardiomyopathy	5(8.3%)	7(11.7%)
Restrictive cardiomyopathy	3(5%)	3(5%)
ARVC	6(10%)	3(5%)
Alcoholic cardiomyopathy	1(1.7%)	1(1.7%)
Peripartum cardiomyopathy	0	1(1.7%)
Noncompaction of ventricular myocardium	2(3.3%)	1(1.7%)
Valvular heart disease	3(5%)	2(3.3%)
Behcet disease	1(1.7%)	0
Myocarditis	0	1(1.7%)
Risk factors and comorbidities		
Hypertension	7 (23%)	6 (20%)
Diabetes mellitus	13 (21.7%)	10 (16.7%)
Hypercholesterolemia	12 (20%)	12 (12%)
Previous myocardial infarction	6 (10%)	4 (13%)
Previous stroke	6 (10%)	6 (10%)
Previous atrial fibrillation	20 (33.3%)	20 (33.3%)
Previous cardiac surgery	6 (10%)	8 (13.3%)
Cardiac status		
Left-ventricular ejection fraction (%)		
>55%	4(6.7%)	3(5%)
35%-55%	8(13.3%)	12(20%)

<35%	47(78.3%)	45(75%)
Previous pacemaker	18(30%)	16(26.7%)
Preoperative medication		
Warfarin	8(13.3%)	12(20%)
β blocker	50(83.3%)	52(86.7%)
Lipid-lowering agent	3(5%)	8(13.3%)
ACE inhibitors or ARB	30(50%)	11(18.3%)
Aldosterone receptor blocker	46(76.7%)	57(95%)
Digitalis	16(26.7%)	49(81.7%)
Nitrates	5(8.3%)	12(20%)
Anti-diabetic drugs	6(10%)	8(13.3%)
Inotropic drugs	23(38.3%)	46(76.7%)

Data are mean ± SD or number (%).

BMI, body mass index; ARVC, arrythmogenic right ventricular cardiomyopathy; ACE, angiotensin converting enzyme; ARB, angiotensin-II-receptor blocker; NYHA, New York Heart Association; RIPC, remote ischemic preconditioning; RIPostC, remote ischemic postconditioning.

Table 2. Intraoperative characteristics

	RIPC+RIPostC (n=60)	Control (n=60)	P value
Length of surgery (h)	5.9±1.2	6.1±1.4	0.397
Donor heart ischemia time (h)	5.3±1.9	4.9±1.6	0.191
CPB time (min)	215±50	233±64	0.090
Aortic cross-clamp duration (min)	70.7±18.1	74.8±17.5	0.211
Reperfusion time (min)	130.3±34.0	139.3±43.7	0.211
Defibrillation after aortic declamping	18 (30%)	12 (20%)	0.225
Intraoperative ECMO	3 (5%)	3 (5%)	1.000

Data are mean±SD or number (%).

CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; RIPC, remote ischemic preconditioning; RIPostC, remote ischemic postconditioning.

Table 3. cTnI levels

	RIPC + RIPostC (n=60)	Control (n=60)	*P* value
T1 (before surgery)	0.05(0.26, 0.11)	0.04(0.02, 0.97)	0.340
T2 (3 hours after aortic declamping)	44.08±32.19	51.99±36.53	0.263
T3 (6 hours after aortic declamping)	38.87±31.81	69.30±34.13	0.018
T4 (12 hours after aortic declamping)	33.64±31.79	43.73±32.95	0.125
T5 (24 hours after aortic declamping)	30.17±26.34	31.40±26.21	0.742

Data are number of median(quartiles) or mean±SD.

cTnI, cardiac troponin I; RIPC, remote ischemic preconditioning; RIPostC, remote ischemic postconditioning.

Table 4. Postoperative characteristics and clinical outcomes

Variables	RIPC+RIPostC (n=60)	Control (n=60)	*P* value
Length of ICU stay (d)	3.85(3, 5.83)	4(3, 6)	0.628
ICU stay >7d	10(16.7%)	8(13.3%)	0.609
ICU stay >14d	6(10%)	4(6.7%)	0.509
Mechanical ventilation time (h)	35(22, 44.5)	28.5(22, 41.75)	0.389
Mechanical ventilation time >48h	12(20%)	11(18.3%)	0.747
Mechanical ventilation time >72h	9(15%)	4(6.7%)	0.125
Postoperative hospital stay (d)	16(13, 22.5)	15(12.25, 22.75)	0.812
Postoperative hospital stay >28d	11(18.3%)	6(10%)	0.191
In-hospital death	2(3.3%)	0	0.496
New onset stroke	1(1.7%)	0	1.000
Renal failure requiring dialysis	2(3.3%)	1(1.7%)	1.000
IABP support	4(6.7%)	6(10%)	0.509
ECMO support	3(5%)	2(3.3%)	1.000
Atrial fibrillation	3(5%)	0	0.244
Use of a temporary pacemaker	4(6.7%)	0	0.119
Arrhythmia requiring treatment	4(6.7%)	1(1.7%)	0.364
Re-operation	3(5%)	3(5%)	1.000
Re-intubation	1(1.7%)	1(1.7%)	1.000
Tracheotomy	1(1.7%)	1(1.7%)	1.000
Pulmonary infection	14(23.3%)	24(40%)	0.050
Deep sternal infection	3(5%)	0	0.244
Gastrointestinal bleeding	3(5%)	0	0.244

Data are median (quartiles) or number (%).

ICU, intensive care unit; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; RIPC, remote ischemic preconditioning; RIPostC, remote ischemic postconditioning.

Figures

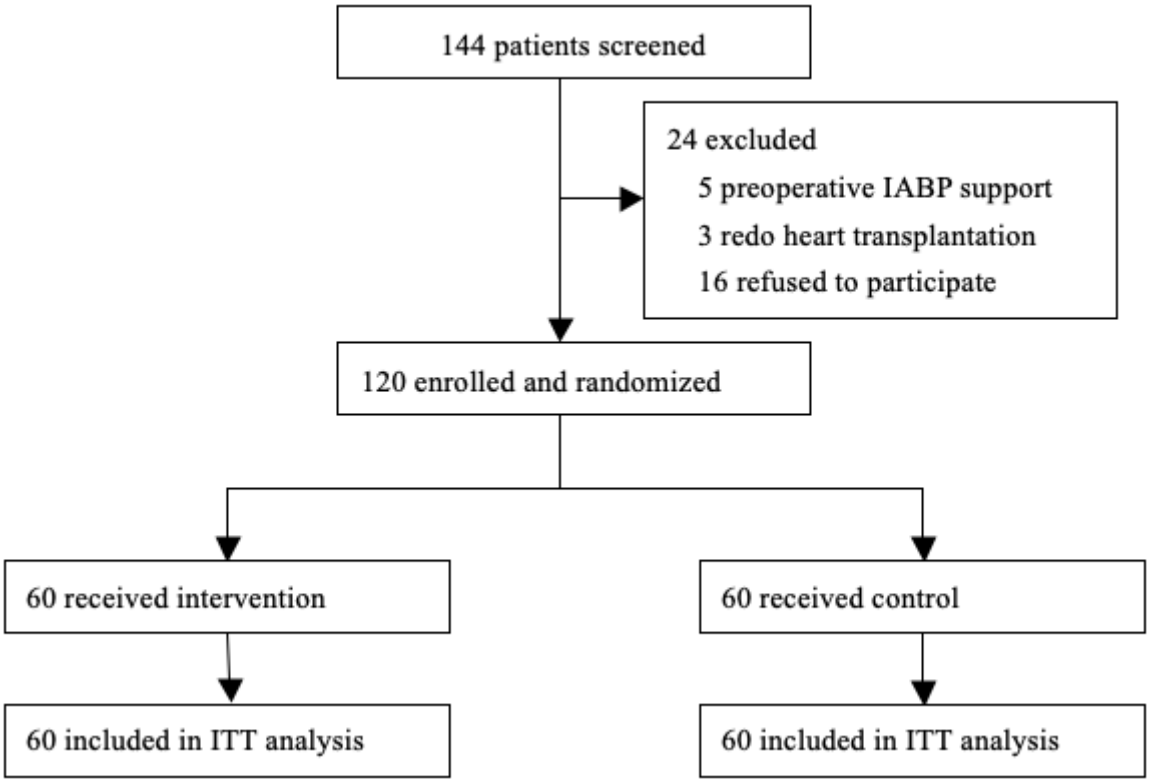

Figure 1

Flow Chart - IABP, intra-aortic balloon pump; ITT, intention to treat.