

Randomized Controlled Trial

Randomized controlled trial of remote ischemic preconditioning and atrial fibrillation in patients undergoing cardiac surgery

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Abstract

AIM

To study whether remote ischemic preconditioning (RIPC) has an impact on clinical outcomes, such as post-operative atrial fibrillation (POAF).

METHODS

This was a prospective, single-center, single-blinded,

randomized controlled study. One hundred and two patients were randomized to receive RIPC (3 cycles of 5 min ischemia and 5 min reperfusion in the upper arm after induction of anesthesia) or no RIPC (control). Primary outcome was POAF lasting for five minutes or longer during the first seven days after surgery. Secondary outcomes included length of hospital stay, incidence of inpatient mortality, myocardial infarction, and stroke.

RESULTS

POAF occurred at a rate of 54% in the RIPC group and 41.2% in the control group ($P = 0.23$). No statistically significant differences were noted in secondary outcomes between the two groups.

CONCLUSION

This is the first study in the United States to suggest that RIPC does not reduce POAF in patients with elective or urgent cardiac surgery. There were no differences in adverse effects in either group. Further studies are required to assess the relationship between RIPC and POAF.

Key words: Chronic ischemic heart disease; Cardiac surgery; Coronary artery disease; Other treatment; Remote ischemic preconditioning; Post-operative atrial fibrillation

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Core tip: This is the first study in the United States to suggest that remote ischemic preconditioning does not reduce post-operative atrial fibrillation in patients with elective or urgent cardiac surgery.

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INTRODUCTION

Post-operative atrial fibrillation (POAF) is the most common arrhythmia after coronary artery bypass grafting (CABG)^[1]. Despite improvement in medical therapy, surgical technique, and anesthesia, POAF occurs in 25%-40% of patients undergoing CABG and valve surgery^[1-4]. POAF remains challenging to prevent, treat, or cure^[5], and contributes to increased short and long term mortality^[6,7], stroke^[8], an increase in length of hospital stay^[9], intensive care unit readmission, and treatment costs^[10]. Some factors associated with POAF include a patient's preoperative status, age, and

preexisting electrocardiogram abnormalities^[11]. Intra-operative stress also plays a key role, due to occurrence of reperfusion, inflammation, oxidative stress, and/or hemostasis^[12-14]. Most POAF episodes occur within the first 6 d following cardiac surgery, with the peak incidence on the second or third post-operative day, coinciding with the peak of systemic inflammation caused by surgery and with atrial stretch^[8].

Remote ischemic preconditioning (RIPC) is one strategy that has shown a myocardial protective effect during CABG and heart valve surgery^[15-17]. It was first described in 1986 in a dog model, where RIPC provided a protective effect on the myocardium that was later subjected to a sustained bout of ischemia^[18]. RIPC was shown to reduce the incidence of ischemic reperfusion ventricular arrhythmias^[19]. There is evidence that RIPC can preserve mitochondrial function and influences myocardial microRNA expression of the right atrium, potentially decreasing the incidence POAF after CABG surgery^[20,21]. In addition, the efficacy of preconditioning to reduce myocardial injury in cardiac surgery and percutaneous coronary interventions has also been demonstrated^[22].

There is growing evidence that AF is associated with increased inflammation^[23,24], and Jannati *et al*^[25], demonstrated that myocardial ischemic preconditioning by aortic cross-clamping in patients undergoing CABG reduced the incidence of POAF.

Currently, there is no optimal preconditioning protocol or tool being utilized during cardiac surgery and aortic cross-clamping may increase the risk of embolic stroke, particularly in elderly patients^[26]. We conducted a randomized clinical trial to assess if RIPC can reduce POAF after CABG, with or without concomitant valve surgery or valve surgery alone.

MATERIALS AND METHODS

Study design

This study was a prospective, single-center, single-blinded, randomized controlled trial. The trial was registered with www.clinicaltrials.gov (NCT01500369).

Patient population

Patients who were undergoing non-emergent cardiac surgery were screened and recruited from the cardiac surgical service.

Eligibility

Eligible patients were adults greater than 18 years old who were referred for elective or urgent CABG, with or without valve surgery, or valve surgery alone between April 2011 and October 2013.

Exclusion criteria included any preoperative rhythm detected other than a sinus rhythm, a history of AF, New York Heart Association IV congestive heart failure, cardiogenic shock, emergent CABG and/or valve surgery, bleeding diathesis, patients taking K(+) ATPase channel blockers (sulphonylureas), and women of child-

bearing age. Patients were contacted by the primary investigator or a cardiology fellow to explain the study and obtain consent. This occurred during the 24-h period after undergoing cardiac catheterization (urgent care patients) or during a pre-op office visit (elective surgery patients). Patients who were interested gave written informed consent. Trial approval was obtained from the Institutional Review Board and the study is registered at <http://www.clinicaltrials.gov>; identifier NCT01500369. Upon consent, participants were randomized during the pre-operative period to either the treatment or control group.

Blinding

Patient blinding: Patients were randomly assigned to a treatment strategy (RIPC/no RIPC) in the operative room during the 45-min pre-operation period. Randomization occurred after patients were anesthetized; thus, patients were unaware of their treatment assignment.

Physician blinding: Since randomization and the RIPC procedure were conducted preoperatively, we expect that the surgeons were unaware of patient treatment assignment, and an effort was made to prevent surgeon knowledge of which group was selected.

Randomization process

The randomization schedule was developed by the institution's statistical core facility and patients were randomized according to a computer-generated randomization procedure. Patients were randomized using blocks in sizes 4 and 6, administered in a random fashion.

Consecutively-numbered envelopes were created and populated with a patient identification and the treatment assignment, based on the random block. The envelopes were kept in a locked cabinet. When an eligible patient was identified, consented, and moved to the pre-operative area, the staff member would select the next envelope in the consecutive list and give it to the research nurse. The research nurse would open the envelope and proceed as indicated on the enclosed form.

Study procedures

For all study participants, anesthesia was induced with intravenous propofol (0.5-2 mg/kg), midazolam (0.04-0.05 mg/kg), fentanyl (1-5 μ g/kg), and rocuronium (0.6-1 mg/kg), and maintained with isoflurane. On-pump surgical revascularization was achieved through a median sternotomy. The internal thoracic arteries, radial arteries, and saphenous veins were used as grafts. Heparin was administered to achieve an activated clotting time longer than 400 s. Standard non-pulsatile cardiopulmonary bypass with a membrane oxygenator was used with an ascending-aortic and two-stage venous cannulation. During cardiopulmonary bypass, moderate hemodilution with a hematocrit of approximately 25%

and mild systemic hypothermia (32 °C) were maintained. Retrograde warm blood cardioplegia was used for all distal anastomoses. Proximal anastomoses were constructed with partial side clamping of the ascending aorta. Bypass graft flow was assessed with an ultrasonic transit time-flow measurement probe. After reperfusion and weaning from cardiopulmonary bypass, protamine was administered for heparin reversal. For hemodynamic support, inotropes and/or vasopressors were infused as required.

RIPC, for those in the study arm, took place after induction of anesthesia and prior to skin incision during which time the patient was prepped, draped, and prepared for surgery using the following protocol.

Treatment group: Patients in the treatment group received 3 sequential sphygmomanometer cuff inflations on their right upper arm after induction of anesthesia in the operating room. The cuff was inflated to 200 mmHg for five minutes each occasion, with a period of five minutes deflation between inflations. The entire RIPC phase lasted 30 min.

Control group: Patients in the control group had the sphygmomanometer cuff placed on their right upper arm, but the cuff was not inflated. Similar to patients in the treatment group, patients in the control group had to undergo the same 30 min delay before the initiation of a skin incision.

Outcome events

Primary outcome: The primary outcome was POAF lasting for five minutes or longer during the first seven days after surgery. This outcome was assessed by using patient's hospital records as well as the Society of Thoracic Surgery (STS) database which records outcomes up until 30 d after surgery.

Secondary outcomes: Secondary outcomes such as length of hospital stay, inpatient death, myocardial infarction (MI), and stroke were recorded during the study follow-up period. Additionally, using the STS definitions for perioperative outcomes (Table 1), the 30-d death, MI, stroke, and readmission were obtained from the institutional STS database.

Adverse outcomes: Adverse events were documented after the initiation of the protocol.

Statistical analysis

Treatment and control groups were compared on baseline characteristics to identify whether randomization was successful. Continuous variables were compared using 2-sample *t* tests or the non-parametric equivalent (Wilcoxon rank-sum test), while categorical variables were compared using Pearson χ^2 or Fisher's exact test. For dichotomous outcomes, logistic regression was used to adjust for group imbalances, when necessary. To examine whether treatment assignment influenced

Table 1 Society of thoracic surgery definitions for peri-operative outcomes

Outcomes	Definition
Stroke	If the patient had a central neurological deficit persisting postoperatively for > 72 h
Peri-operative MI	0-24 h post-operative: The CK-MB (or CK if MB not available) must be greater than or equal to 5 times the upper limit of normal, with or without new Q waves present in two or more contiguous ECG leads No symptoms required > 24 h post-operative: Indicate the presence of a peri-operative MI (> 24 h post-op) as documented by at least one of the following criteria: (1) Evolutionary ST-segment elevations (2) Development of new Q-waves in two or more contiguous ECG leads (3) New or presumably new LBBB pattern on the ECG (4) The CK-MB (or CK if MB not available) must be greater than or equal to 3 times the upper limit of normal

MI: Myocardial infarction; ECG: Electrocardiogram.

time to first occurrence of POAF, a log-rank test of the Kaplan-Meier survival functions was conducted.

RESULTS

A total of 102 patients were randomized between April 2011 and September 2013 (Figure 1). Sixty-nine point nine percent of the patients were males and 89% were Caucasian (Table 2). The mean age of patients in the RIPC and control group was 69.4 and 68.9 years, respectively. With the exception of diabetes mellitus, the two groups were balanced with respect to baseline characteristics. Study groups were also well balanced with respect to medication use including beta blocker and HMG-CoA reductase inhibitors (statins). 46% of the patients presented with acute coronary syndrome and 23.5% presented with stable angina and were well matched (Table 3).

POAF occurred at the rate of 54.0% in the RIPC group and 41.2% in the control group ($P = 0.23$). Expressed as a difference in proportions, the percent of patients experiencing POAF was 12.8% higher in the RIPC group compared with the usual care group (95%CI: -6.5%-32.1%). Although the presence of diabetes was significantly higher in the RIPC group, it was not associated with any outcome, and consequently, adjusting for diabetes in logistic regression models did not materially change the univariable results.

No post-operative MIs occurred in the RIPC group while 3.9% did in the control group, although this difference was not statistically significant ($P = 0.50$) (Table 4). There were only two deaths and two strokes for the entire study group and both occurred in the RIPC group. The 30-d readmission rates demonstrated no statistically significant difference between the two

Table 2 Baseline characteristics between control group and remote ischemic preconditioning group

Characteristic	Control (n = 51)	RIPC (n = 51)	P
Demographics			
Mean age (± SD)	68.9 (± 9.8)	69.4 (± 9.9)	0.77
Male % (n)	62.8 (32)	76.5 (39)	0.20
Caucasian % (n)	88.2 (45)	90.2 (46)	1.00
Mean BMI (± SD)	30.4 (± 7.6)	28.4 (± 5.2)	0.13
Co-morbidities			
Diabetes mellitus % (n)	39.2 (20)	62.7 (32)	0.029
Hypertension % (n)	84.3 (43)	82.4 (42)	1.00
Dyslipidemia % (n)	90.2 (46)	90.2 (46)	1.00
Heart failure % (n)	21.6 (11)	23.5 (12)	1.00
Atrial fibrillation % (n)	0.0 (0)	0.0 (0)	NA
AICD % (n)	0.0 (0)	2.0 (1)	1.00
CVA % (n)	3.9 (2)	5.9 (3)	1.00
TIA % (n)	2.0 (1)	7.8 (4)	0.36
PAD % (n)	9.8 (5)	21.6 (11)	0.17
CKD % (n)	23.5 (12)	23.5 (12)	1.00
Dialysis % (n)	2.0 (1)	2.0 (1)	1.00
Mean creatinine (± SD)	1.2 (± 1.1)	1.2 (± 0.7)	0.89
COPD % (n)	5.9 (3)	0.0 (0)	0.24
Tobacco use % (n)	17.6 (9)	27.5 (14)	0.34

AICD: Automatic implantable cardioverter-defibrillator; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CVA: Cerebrovascular accident; TIA: Transient ischemic attack; PAD: Peripheral arterial disease; RIPC: Remote ischemic preconditioning.

groups. The length of stay, left ventricular ejection fraction, and cross-clamp time demonstrated no significant difference between the control and RIPC groups.

The event rate for POAF, based on Kaplan-Meier analysis, was not significantly different between the RIPC and control group ($P = 0.13$) (Figure 2). No adverse events related to RIPC occurred.

DISCUSSION

In our study that assessed the effect of RIPC on clinical outcomes in patients undergoing elective or urgent cardiac surgery, we found that RIPC did not reduce POAF. In addition, there were no statistically significant differences in secondary outcomes, including post-operative MI and stroke and no adverse events were reported with RIPC.

The Effect of Remote Ischemic Preconditioning on Clinical Outcomes in CABG Surgery (ERICCA) study randomized 1216 patients who underwent CABG to RIPC vs control and demonstrated that at one year there was no statistically significant difference in the primary clinical outcome (cardiovascular clinical death, MI, stroke and coronary revascularization)^[27]; no data regarding POAF were provided. Previous studies to date have largely evaluated the impact of RIPC on surrogate markers of clinical outcomes. RIPC has been evaluated in patients undergoing percutaneous coronary intervention to reduce myocardial injury^[28], reduce contrast-induced nephropathy^[29], and myocardial salvage in

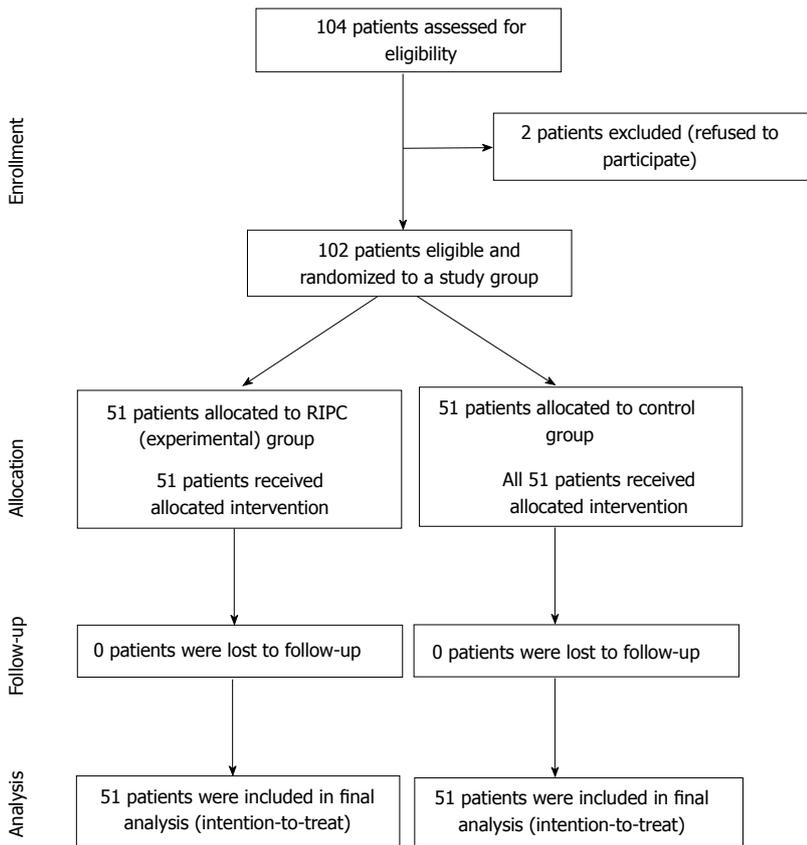


Figure 1 Randomization and follow up of patients. RIPC: Remote ischemic preconditioning.

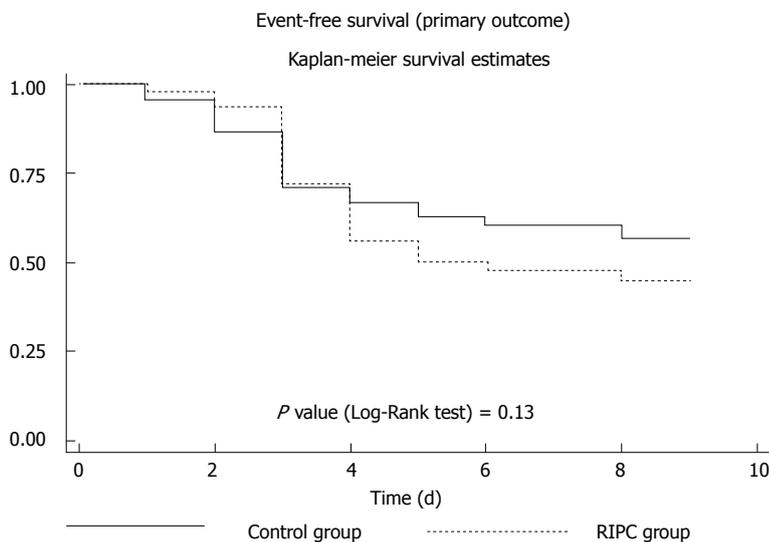


Figure 2 Kaplan-Meier estimates of the probability of remaining free from post-operative atrial fibrillation, according to study group. RIPC: Remote ischemic preconditioning.

ST-segment elevation MI^[30]. Specifically, in patients undergoing cardiac surgery, RIPC has been known to decrease myocardial injury measured by cardiac troponin release^[31,32]. At the same time, several other trials have failed to show improvement in surrogate outcomes with the implementation of RIPC^[33,34], and this can be attributed to variable protocols, medications, surgical, and anesthetic regimens. It is also difficult to

draw any conclusions regarding clinical outcomes from these studies as they were included only as secondary outcomes, often under-powered and had varying definitions of clinical outcomes^[35]. Thus, no trials have been published demonstrating that RIPC significantly reduced clinical endpoints in patients undergoing cardiac surgery^[36].

The rate of POAF in our study was higher than

Table 3 Baseline medications and clinical presentation in the control group and remote ischemic preconditioning group

Characteristic	Control (n = 51)	RIPC (n = 51)	P
Medications % (n)			
Alpha blockers	7.8 (4)	2.0 (1)	0.36
Beta blockers	78.4 (40)	80.4 (41)	1.00
ACE-inhibitors	37.3 (19)	41.2 (21)	0.84
Aspirin	90.2 (46)	90.2 (46)	1.00
Statins	84.3 (43)	86.3 (44)	1.00
Clinical presentation % (n)			
Stable angina	23.5 (12)	23.5 (12)	1.00
Unstable angina	25.5 (13)	25.5 (13)	1.00
Positive stress test	27.5 (14)	25.5 (13)	1.00
Non-STEMI	19.6 (10)	17.6 (9)	1.00
STEMI	0.0 (0)	2.0 (1)	1.00
Valve without CAD	17.6 (9)	27.5 (14)	0.34

ACE: Angiotensin converting enzyme; CAD: Coronary artery disease; RIPC: Remote ischemic preconditioning; STEMI: ST-elevation myocardial infarction.

expected in both groups, which could be related to the small sample size and the presenting co-morbidities. Additionally, the absolute numbers of secondary outcomes recorded were quite small and therefore, are only exploratory at this stage. The unreliability of studies with small study samples is well-known^[37,38]. Even if significant results had emerged from our study, regardless of direction of effect, we would caution against the over-interpretation of results, since small studies often produce large effects that frequently defy replication^[39]. To our knowledge, this is the first study undertaken in the United States to assess the relationship of RIPC with POAF. Although this small study found no significant association of RIPC with clinical outcomes, it serves as an addition to the sparse literature on RIPC and clinical outcomes and would be of value when additional small studies are published. Meta-analyses of randomized controlled studies could yield a more accurate estimation of the true relationship between RIPC and POAF by combining patients and increasing sample power.

There were several limitations to our study that may have contributed to it not resulting in a positive finding. First, the study was halted prematurely, due to the lack of financial support to continue recruitment, which led to a study with less power than intended. However, given a control POAF rate of 50% (as seen in this population), the study still had 70% power to detect a 25% percentage points difference. Second, there was a significantly higher percentage of patients with diabetes mellitus in the RIPC arm, which may have masked the beneficial effect of RIPC^[40]. However, this is unlikely to have significantly confounded the results as there was no change in the relationship of RIPC with outcomes even after adjustment using logistic regression analysis. Third, there is some recent evidence that patients given propofol may not gain protection from RIPC^[41,42], possibly related to its structure being similar

Table 4 Clinical outcomes in the control group *vs* remote ischemic preconditioning group

Characteristic	Control (n = 51)	RIPC (n = 51)	P
Primary endpoint			
POAF % (n)	41.2 (21)	54.0 (27)	0.23
Secondary endpoints			
Other arrhythmia % (n)	13.7 (7)	11.8 (6)	1.00
MI % (n)	3.9 (2)	0.0 (0)	0.50
Stroke % (n)	0.0 (0)	3.9 (2)	0.24
Mean EF (± SD)	53.1 (± 14.8)	50.5 (± 16.9)	0.43
Bleeding % (n)	21.6 (11)	28.0 (14)	0.50
Mean cross-clamp time (± SD)	88.7 (± 44.8)	93.0 (± 38.5)	0.61
In-hospital mortality % (n)	0 (0)	3.9 (2)	0.50
30-d mortality (after discharge) % (n)	0 (0)	0 (0)	1.0
30-d readmission % (n)	11.8 (6)	16.3 (8)	0.57
Mean LOS (± SD)	13.7 (± 7.8)	14.0 (± 7.7)	0.87

EF: Ejection fraction; LOS: Length of stay; MI: Myocardial infarction; POAF: Post-operative atrial fibrillation; RIPC: Remote ischemic preconditioning; STEMI: ST-elevation myocardial infarction.

to that of phenol-based radical scavengers. This study was started prior to the publication of the study by Kottenberg *et al.*^[41], and in our study, propofol was used for the induction of anesthesia, not for maintenance. As with the majority of RIPC studies^[35], we performed 3 cycles of RIPC, and in future trials it may be necessary to perform more than 3 cycles of blood pressure cuff inflation to provide clinical benefit. A final limitation is that warm cardioplegia has demonstrated a reduction in myocardial injury as compared to cold cardioplegia with similar clinical events^[43,44]. Given that all our patients received warm cardioplegia, this could have masked the benefit of RIPC.

Despite the fact that the results of this study suggest that there is no beneficial effect of RIPC on reducing POAF, RIPC still holds promise in improving clinical outcomes, based on "proof-of-concept" studies using cardiac biomarkers as primary endpoints^[31,45,46] and, due to the fact it is a simple, safe, non-invasive, and inexpensive intervention. Although it has been challenging to identify which groups of patients benefit from RIPC, further evaluation of RIPC to decrease post-operative events with carefully planned and funded studies with adequate power is warranted. Additionally, meta-analysis of small randomized controlled studies may also be useful in studying the relationship of RIPC and clinical outcomes, including POAF.

COMMENTS

Background

Remote ischemic preconditioning (RIPC) has been demonstrated to reduce perioperative myocardial injury following cardiac surgery (coronary artery bypass, with or without valve surgery).

Research frontiers

It is unknown whether it has an impact on clinical outcomes, such as post-operative atrial fibrillation, peri-operative myocardial infarction and stroke.

Innovations and breakthroughs

This is the first study in the United States evaluating these clinical outcomes following the use of RIPC with cardiac surgery.

Applications

Although this study did not suggest a clinically significant benefit with the use of RIPC, future meta-analyses of small randomized controlled studies may be useful in studying its relationship with clinical outcomes.

Terminology

RIPC is a strategy in which brief episodes of non-lethal ischemia and reperfusion are applied to the arm or leg in order to achieve myocardial protection from ischemic events.

Peer-review

This is an interesting manuscript about the effect of (PIPC on clinical outcomes such as post-operative atrial fibrillation (POAF), myocardial infarction, stroke, and mortality in 102 patients undergoing cardiac surgery. The data demonstrated that PIPC did not reduce POAF. In addition, there were no significant differences in post-operative myocardial infarction, stroke, and mortality between RIPC group and control group. Therefore, the authors have suggested that further evaluations of RIPC are required to decrease post-operative events.

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