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ORIGINAL ARTICLE

Remote ischemic preconditioning and incidence of postoperative atrial fibrillation

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Abstract

Objectives. Although remote ischemic preconditioning (RIPC) has shown favorable effects on ischemia–reperfusion injury, much remains unknown of its mechanisms and clinical significance. We hypothesized that RIPC would reduce the incidence of postoperative atrial fibrillation (POAF) following coronary artery bypass graft (CABG) surgery. In addition, we investigated whether RIPC could induce alterations of circulating microRNA in blood plasma. *Design.* This is a single-center, double-blind, randomized controlled trial. 92 adult patients referred for first-time isolated CABG surgery were randomly assigned to either RIPC ($n = 45$) or control ($n = 47$). The RIPC-stimulus comprised three 5-min cycles of upper arm ischemia, induced by inflating a blood pressure cuff to 200 mmHg, with an intervening 5 min reperfusion. Heart rhythm was assessed by telemetry. MicroRNA expression was assessed in plasma by real-time polymerase chain reaction. *Results.* Of the 92 patients included in the study, 27 patients developed POAF (29%). 17 of these patients belonged to the RIPC group (38%), and 10 to the control group (21%). There were no significant alterations of microRNA expression. *Conclusions.* We did not observe a reduced incidence of POAF by RIPC before CABG surgery. Larger multi-center studies may be necessary to further clarify this issue.

Key words: *coronary artery bypass, ischemic preconditioning, postoperative period, preoperative care*

Introduction

The release of cardiac enzymes during coronary artery bypass graft (CABG) surgery indicates myocardial injury and has been associated with adverse clinical outcomes (1,2), including a higher risk of developing postoperative atrial fibrillation (POAF) (3). Myocardial injury during CABG surgery may be attributed to several mechanisms, most importantly perioperative cross-clamping of the aorta leading to myocardial ischemia and ischemia–reperfusion injury. In this context, ischemic preconditioning (IP) may provide a novel strategy for cardiac protection.

IP emerged as a cardioprotective phenomenon in 1986 when Murry et al. (4) found that multiple brief ischemic episodes applied to the heart before a potentially lethal ischemic insult, reduced the size of infarction by greater than 50%. This could not be explained by increased blood flow via collateral circulation. The authors concluded that they had discovered a new phenomenon triggered by ischemia, which provides protection against ischemic cell death. In 1993, regional IP was demonstrated by Przyklenk et al. (5). They showed that brief ischemic episodes (4 * 5 min followed by 5 min of reperfusion) of the left circumflex coronary artery significantly reduced the size of myocardial infarction following a subsequent sustained occlusion of the left anterior descending coronary artery. Intramyocardial protection across coronary territories was thereafter extended beyond the heart to remote ischemic preconditioning (RIPC), when it became apparent that the same cardioprotection could be recreated even if the ischemic stimulus was applied distant to the heart (6).

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RIPC may represent an easy, harmless and cost-effective method of improving cardiac protection in open heart surgery (7). Recently it was shown that RIPC preserves mitochondrial function in atrial myocardium (8), and even improve the prognosis of patients undergoing elective CABG surgery (9). However, the effect of RIPC on the development of POAF is still unclear.

POAF is the most common complication after CABG surgery. POAF occurs in 20–40% of patients undergoing open heart surgery and is associated with increased postoperative mortality, postoperative stroke and prolonged hospitalization (10,11). Moreover, POAF constitutes an independent risk factor for late mortality and cerebrovascular morbidity (12).

MicroRNA (miR) are a group of small regulatory RNAs that have been demonstrated to influence cardiac arrhythmia and ischemia–reperfusion injury (13). It was recently found that RIPC was associated with altered miR expression in the right atrium during CABG surgery (14).

This study was designed to investigate the hypothesis that RIPC reduces the incidence of POAF after CABG surgery. Secondarily, we aimed to assess if RIPC affects circulatory miR expression in blood plasma.

Material and methods

This is a prospective randomized controlled trial conducted at the Department of Cardiothoracic Surgery at St. Olav's University Hospital in Trondheim. Ninety-two adult patients with coronary artery disease referred for CABG surgery were recruited. Approval was obtained from the Regional Committee for Medical Research Ethics (2011/2525REK midt) and the trial is registered at ClinicalTrials.gov under identification number NCT01740102.

Patients

Patients above 18 years of age, scheduled to undergo elective, isolated, primary CABG surgery with cardiopulmonary bypass (CPB) were eligible for the study. Patients were excluded from consideration if they had severe pulmonary disease, renal failure (GFR $<$ 30 mL/min/1.73 m^2) liver failure, peripheral vascular disease affecting the upper limbs or atrial fibrillation in their case history. Patients above 80 years of age and patients who used sulfonylurea derivatives were also excluded as these medications may abrogate the cardioprotection elicited by RIPC (15). We obtained written informed consent from all patients in the study. Those included were randomized to either undergo RIPC or to participate in the control group. Randomization was done using an Internet-based randomization application created by the Unit of Applied Clinical Research at the Norwegian University of Science and Technology (NTNU). Figure 1 shows the trial profile. One hundred patients scheduled for elective CABG surgery were assessed for eligibility, of which four patients refused to participate. The remaining 96 patients consented to participate and were randomized to RIPC or control. After randomization, four patients had to be excluded due to administrative reasons. Ultimately, 92 patients were analyzed within RIPC ($n = 45$) or control ($n = 47$).

The RIPC protocol was applied after induction of anesthesia, before surgery. During this period, both patients in the RIPC- and control group had a blood pressure cuff placed on their right upper arm. RIPC consisted of three cycles of 5 min right upper arm ischemia, which was induced by inflating a blood pressure cuff to 200 mmHg, with an intervening 5 min of reperfusion during which the cuff was deflated. Patients in the control group had a deflated cuff placed on the right upper arm throughout the same period. Patients, cardiac surgeons, the investigator and the staff at both the ward and intensive care unit were all blinded to treatment allocation. Theater nurses and anesthetists were present during the RIPC- or control procedure and were consequently not blinded.

Perioperative management

All patients were premedicated with paracetamol (1.5 g) and either morphine hydrochloride (5–10/0.2–0.4 mg) or diazepam (10 mg) 20–40 min before

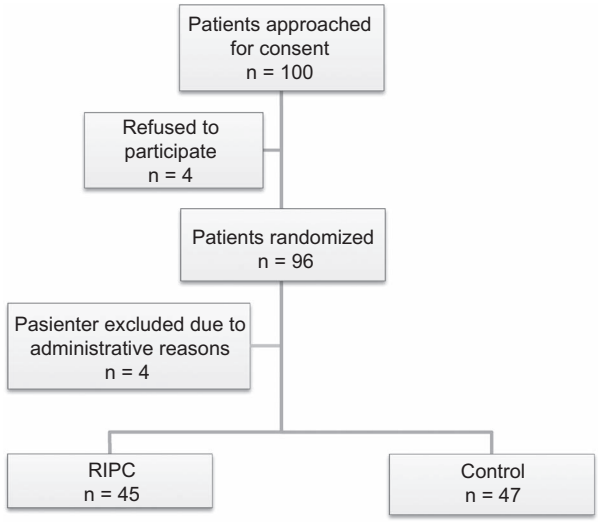

Figure 1. Trial profile. RIPC, remote ischemic preconditioning.

general anesthesia. Anesthesia was induced with fentanyl (0.3–0.5 mg), thiopentone sodium (125–200 mg), and a neuromuscular blocking agent (vecuronium, cisatracurim or pancuronium). Anesthesia was thereafter maintained with repetitive doses of fentanyl (total dose 1.0–1.2 mg), isoflurane (1–2%) during mechanical ventilation and propofol (3 mg/kg/h) during CPB. In addition, vasoactive agents were used as required. The patients were kept sedated (propofol 1 mg/kg/h) and mechanically ventilated for a few hours after the end of surgery in the cardiothoracic intensive care unit.

Surgical technique was equivalent for both treatment groups. Standard non-pulsatile CPB was performed using a membrane oxygenator with ascending aortic and two-stage venous cannulation. During the operation mild systemic hypothermia (32–34°C) was maintained and heparin (3 mg/kg) was administered in order to achieve an activated coagulation time above 480 s. The left internal mammary artery and saphenous veins were used as graft conduits. The coronary anastomoses were constructed on CPB during aortic cross-clamping, using intermittent ante- and/or retrograde cold-blood cardioplegia (St.Thomas Solution, Martindale Pharmaceuticals, Essex, UK). Cardioplegia was repeated every 20 min. Protamine (200–300 mg) was used to reverse the effect of heparin.

Postoperative atrial fibrillation

All participants were monitored by continuous five-lead telemetry until the fifth postoperative day. From day 5 until hospital discharge, pulse was checked twice daily. Telemetry was reinstituted if arrhythmia was detected clinically. Any episode of atrial fibrillation lasting more than 1 min during postoperative hospitalization was classified as POAF. All arrhythmias were noted on patients' surveillance charts by nurses at the ward. In addition, one of the authors, blinded to group identity, examined the patient's surveillance charts, medical records and discharge summaries to ensure that all episodes of POAF were recorded. Some of the patients were transferred to their local hospital 3–5 days postoperatively. To register episodes of POAF that occurred after the transfer, a blinded collaborator at each of these hospitals reported back whether POAF occurred.

MicroRNA

Blood samples were obtained immediately before and approximately 30 min after RIPC or placebo from 10 randomly selected patients in each treatment group. RNA-isolation and quantitative reverse transcription-polymerase chain reaction were performed at Exiqon Services, Vedbaek, Denmark. MiRs from plasma were polyadenylated and reverse transcribed into cDNA in a single reaction and run on the miRCURY LNA^{TM} Universal RT miRNA PCR Human panel I and II (Exiqon Services, Denmark). Amplification was performed in a Roche LightCycler 480 (Roche Diagnostics Ltd., Switzerland). Reactions yielding a crossing point (Cp) value within 5 Cp values of the negative controls were removed and data was normalized based on the average of the assays detected in all samples.

Statistical analysis

For categorical variables, chi-square test or Fisher's exact test was used for between-group comparison and descriptive data is given as a percentage. Continuous variables, expressed as mean ± standard deviation (SD), were compared between groups using the Student's t-test for independent samples. All statistical analyses were performed using version 20 of the SPSS software (SPSS Inc., Chicago, IL, USA). A two-tailed p-value lesser than 0.05 was considered significant. Bonferroni correction for multiple testing was applied to miR analyses. The sample size was calculated using the results of a previous study of RIPC by our group (8). We took into consideration that the incidence of POAF in our department generally is somewhat lower than 48%, which was the case for the control group in this study. Calculations yielded a sample size of 45 patients per group, assuming an incidence of POAF of 40% in controls and 14% in RIPC.

Results

Postoperative atrial fibrillation

There was no difference in baseline patient characteristics between the two groups (Table I). Per- and postoperative data are summarized in Table II. Perioperative data such as CPB time, aortic cross-clamp time and the number of distal anastomoses did not differ between the groups. Nor were any significant differences detected between the groups postoperatively. A total of 27 patients developed POAF (29%), of which 17 patients belonged to the control group (38%) and 10 to RIPC (21%). The median onset of POAF was on day 2 (Figure 2). The hospital stay was on average 7 days for patients in the control group and 8 days in the RIPC group. One patient in each group suffered an ischemic stroke. Two patients underwent re-operation due to bleeding; both patients belonged to the control

Table I. Patient characteristics.

	RIPC ($n=45$)	Control ($n=47$)	*P*-value
Age (years)	64.2 ± 7.8	64.4 ± 8.6	0.885
Female (%)	6.7	8.5	1.000
BMI (kg/m²)	28.3 ± 4.5	27.4 ± 3.3	0.289
History of smoking (%)	64.4	70.2	0.555
Diabetes mellitus (%)	17.8	27.7	0.259
Ustable angina (%)	8.9	4.3	0.430
Hypertension (%)	57.8	53.2	0.658
Peripheral vascular disease (%)	2.2	10.6	0.204
COPD (%)	11.1	6.4	0.481
Previous stroke (%)	8.9	8.5	1.000
Previous AMI (%)	44.4	38.3	0.549
Previous PCI (%)	15.6	19.1	0.649
EuroSCORE	1.5 ± 1.2	1.8 ± 2.2	0.437
Ejection fraction (%)	52.0 ± 9.9	53.3 ± 10.6	0.541

Data are presented as percentages for discontinuous variables and as means ± standard deviation (SD) for continuous variables.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; EuroSCORE, European System for Cardiac Operative Risk Evaluation; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

group. There was no mortality within 30 days in either group. No adverse consequences were observed due to the RIPC protocol.

MicroRNA

One hundred and five miRs were detected in all samples, with an average detection of 282 miRs per samples. Unsupervised analysis revealed no evident clustering according to groups or treatment, and supervised analyses did not yield any significant between-group or within-group differences in samples between the two time points.

Table II. Per- and postoperative data.

	RIPC ($n=45$)	Control ($n=47$)	*P*-value
Peroperative data			
CPB time (min)	79.8 ± 21.3	71.8 ± 21.7	0.096
Cross-clamp time (min)	49.4 ± 16.3	44.3 ± 15.2	0.138
Distal anastomoses	3.7 ± 0.9	3.5 ± 1.0	0.320
Postoperative data			
POAF (%)	37.8	21.3	0.082
Reoperation for bleeding (%)	0.0	4.3	0.495
Length of stay (days)	7.9 ± 3.3	7.0 ± 2.1	0.174
Neurological event during hospital stay (%)	2.2	2.2	1.000
30day mortality (%)	0.0	0.0	1.000

Data are presented as percentages for discontinuous variables and as means ± standard deviation for continuous variables.
CPB, cardiopulmonary bypass; POAF, Postoperative atrial fibrillation

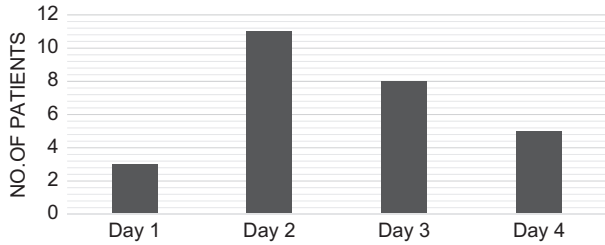

Figure 2. Onset of postoperative atrial fibrillation (POAF).

Medication

The patient's medication was examined for both groups. However no differences were found for the following group of drugs: Statins, Calcium antagonist, beta-blockers, ACE inhibitors, diuretics, aspirin, clopidogrel, brilique, warfarin, NO donors, metformin, insulin nor heparin.

Discussion

The primary aim of this study was to investigate whether RIPC can reduce POAF and improve clinical outcome after CABG surgery. The most important finding was that RIPC, mediated by transient upper limb ischemia, does not reduce the incidence of POAF in patients undergoing elective first-time CABG surgery.

Meta-analyses of randomized clinical trials (RCT) have been carried out to clarify the inconsistent results from RIPC trials. Their conclusion is that RIPC significantly reduces the release of biomarkers of myocardial injury (CK-MB/troponin T/I) following CABG surgery (16,17) and thus most likely has a cardioprotective effect. Thielmann et al. even showed an effect of RIPC on survival following coronary surgery (9). Our study failed to demonstrate any advantage of RIPC.

This in contrast to a study previously performed by our group (8), which showed a significantly reduced incidence of POAF among patients in the RIPC group compared to the control group (14% vs. 50%). However, as emphasized in our previous publication, the preceding study included a limited number of patients for the assessment of POAF, and the incidence of POAF within the control group was somewhat higher than normal. Despite of this we found our observation of interest and the present study was carried out to investigate these findings further.

This study includes low-risk patients. Patients above 80 years of age, redo-patients and patients with severe hepatic, renal or pulmonary disease were excluded to obtain a homogeneous cohort of patients. Additionally, there is evidence that the ability to

induce preconditioning is reduced in aged and diseased myocardium (18,19).

The volatile anesthetic isoflurane was used in all patients included in our study. As discussed by Karuppasamy et al. (20), volatile anesthetic agents have the ability to precondition the heart by activating ATP-dependent potassium channels (21) and may therefore interfere with the physiological mechanisms by which RIPC works. In this context Yetgin et al. (17) compared studies using volatile anesthetic agents with studies using a non-preconditioning anesthetic agent. Interestingly, they were unable to demonstrate additional benefit from RIPC when the aforementioned preconditioning agents were used as the anesthetic regime. In contrast, a significant decrease in myocardial biomarkers was found in studies using a non-preconditioning anesthetic agent. Although the exact significance of these findings is unclear, a possible explanation could be that both interventions act via similar pathways, reaching a plateau of protection (17). Since volatile anesthetics were used in this study it may represent a potential cofounder with regard to RIPC as a cardioprotective strategy. However, in a study by Venugopal et al. (22), and Thielmann et al. (9), a significant decrease of troponins was observed despite the use of halogenated anesthetic gases, suggesting that the effect of RIPC is additive to the cardioprotection afforded by iso- and sevoflurane (7). This was also the case in our previous RIPC-study where Slagsvold et al. (8) demonstrated that RIPC preserves mitochondrial respiration and prevents up-regulation of miR-1 in the right atrium during CABG surgery.

A secondary aim of this study was to investigate whether RIPC induces alterations of miR expression in blood plasma. We could not detect any differences of miR expression after RIPC. Our samples were obtained over a relatively short time interval (≈ 60 min between samples) and this may present too short of a time period to observe alterations of miR expression. Most previous studies investigating miR expression have found that the largest differences occur around 6 h after the applied stimulus (23). One may have suggested that sampling at a later time would provide useful in order to assess circulating miR expression after RIPC. However, we hypothesized that the interference of changes induced by medication administered preoperatively, along with surgical trauma, would decrease the likelihood of detecting alterations associated with RIPC in the current study.

Limitations

Our study assessed the effect of RIPC in low-risk patients below 80 years of age, and one may not exclude an effect in a higher-risk population. Studies of a substantially larger scale may be the necessary next step to thoroughly evaluate the clinical relevance of RIPC. Our results must therefore be interpreted with caution and the potential effect of RIPC on POAF requires further investigation. In this respect it is worth noting that large-scale multicenter randomized trials of RIPC in CABG surgery are currently underway to address this issue (24,25).

Conclusion

We conclude that RIPC does not reduce the incidence of POAF following CABG surgery in low-risk patients. Larger studies are needed to further clarify the effect of RIPC on POAF after CABG surgery.

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