



Remote ischaemic preconditioning ameliorates sinus rhythm restoration rate through Cox maze radiofrequency procedure associated with inflammation reaction reduction

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Received: 4 December 2018 / Revised: 7 February 2019 / Accepted: 22 February 2019 / Published online: 5 March 2019
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Abstract

Remote ischaemic preconditioning (RIPC) as adjuvant to selective heart surgery attenuates cardiac injury and atrial fibrillation (AF) occurrence. We investigated its effect on sinus rhythm (SR) restoration rate in permanent AF patients undergoing Cox maze (CM) radiofrequency ablation with concomitant mitral valve surgery. From May 2013 to May 2017, 206 patients with rheumatic valve disease concomitant with permanent AF were randomized to receive prosthesis valve replacement and CM radiofrequency ablation procedure with ($n = 104$) or without ($n = 102$) RIPC (intermittent arm ischaemia through three cycles of 5-min inflation, followed by 5-min deflation of a blood pressure cuff). The primary end point of the study was freedom from cumulative AF without using antiarrhythmic drugs 1 year after operation; the secondary end points included inflammation reaction index over 48 h postoperatively and clinical outcomes. Baseline characteristics and preoperative data did not differ between groups. The SR restoration rates were significantly higher in the RIPC group, 85.6%, 83.7%, and 82.7%, than those in the control group, 72.5%, 70.6%, and 69.6%, at discharge, 6 months and 12 months, respectively, after the radiofrequency ablation procedure ($P < 0.05$). The serum concentration of high sensitivity C-reactive protein and neutrophil–lymphocyte ratio were significantly decreased at 12 h, 24 h, and 48 h postoperatively in the RIPC group compared to those in the control group ($P < 0.05$). RIPC induced by brief ischaemia and reperfusion of the arm ameliorated SR restoration rate in patients with permanent AF through CM radiofrequency ablation procedure and was associated with reduction of postoperative systemic inflammation reaction index.

Keywords Atrial fibrillation · Cox maze procedure · Heart valve disease · Remote ischaemic preconditioning · Sinus rhythm restoration rate

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00395-019-0723-4>) contains supplementary material, which is available to authorized users.

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Introduction

Since the modified Cox maze (CM) radiofrequency procedure became recognized as an effective method of restoring normal sinus rhythm (SR) in patients who suffered atrial fibrillation (AF), it has been recommended at the time of

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concomitant mitral operations, according to clinical practice guidelines [3]. Although criticized as requiring more operative time and a high degree of complexity, the additional procedure has been found to result in AF burden relief, haemodynamic performance improvement, a reduction in stroke complications, and even improved long-term survival [1]. A method to improve the efficacy of the surgical CM radiofrequency procedure remained to be determined due to its modest SR restoration rate in patients with permanent AF [29]. It had been demonstrated that operative trauma and ischaemia and reperfusion led to oxidative stress and the production of proinflammatory molecules, resulting in endothelial and leukocyte activation, the release of NADPH oxidases, nitrous oxide production and reactive oxygen species generation, and the development of postoperative atrial fibrillation (POAF) [8]. Randomized studies suggested that preoperative anti-inflammatory prophylaxis had significant clinical benefits in cardiopulmonary bypass (CPB) patients by decreasing the risk of new onset AF, and results were encouraging for reducing bleeding, length of hospital stay, and mortality [28].

Remote ischaemic preconditioning (RIPC) by brief episodes of ischaemia and reperfusion in a remote organ or vascular territory provides protection from injury caused by myocardial ischaemia and reperfusion [12]. In patients undergoing coronary artery bypass graft surgery (CABG), there was a significantly lower incidence of POAF after RIPC compared with the control procedure via preservation of mitochondrial respiration function [23]. Based on the underlying evidence of RIPC on reducing the POAF, we investigated the effect of RIPC on SR restoration rate and postoperative inflammation reaction index in patients undergoing CM radiofrequency ablation with concomitant heart valve replacement.

Methods

Patient recruitment and allocation

This study was approved by the Ethics Committee of Sichuan Provincial People's Hospital, and written informed consent was obtained preoperatively from all participants. A total of 206 consecutive adult patients from May 2013 to May 2017 were recruited and randomly assigned by computerized block randomization to receive procedures with ($n = 104$) versus without ($n = 102$) RIPC, which was performed by intermittent arm ischaemia through three cycles of 5-min inflation and 5-min deflation of a blood pressure cuff after induction with the combination of propofol and fentanyl venous anaesthesia [30]. The control group without RIPC received only a blood pressure cuff on the arm without inflation. Patients undergoing non-emergency, primary

mitral valve (MV), and/or aortic valve (AV) replacement simultaneously with the surgically modified CM radiofrequency ablation procedure were recruited. The eligibility criteria included (1) adult heart valve disease with left atrium (LA) ≤ 70 mm, (2) presenting with chronic AF, defined as AF lasting longer than 6 months without spontaneous conversion, and (3) surgical CM radiofrequency ablation was simultaneously performed with mitral valve and/or aortic valve replacement procedure. Patients were excluded from this study if there was concomitant infective endocarditis or anti-inflammation therapy or a requirement for additional CABG [27]. Patients suffering from embolism on limb arteries were also rejected. The study primary end point was freedom from cumulative AF 1 year after operation, measured by a 24 h Holter-ECG recording; secondary end points included inflammation index over 48 h postoperatively and in-hospital clinical outcomes.

Operative approach

All procedures were performed by senior surgeons via a median sternotomy using cardiopulmonary bypass with bicaval venous drainage during moderate hypothermia (28–32 °C) on an arrested heart, with a total of 2000 mL antegrade HTK cardioplegia delivered to arrest the heart in both groups. The LA appendage was amputated and then oversewn from the epicardial side. The modified radiofrequency ablation procedure aimed to mimic most of the incisions and sutures of classical CM procedure. The procedure was performed with either one of the two bipolar radiofrequency devices at the discretion of the operator (AtriCure Inc, West Chester, Ohio, Cardioblate; Medtronic, Minneapolis, MN, USA).

The right-sided procedure was performed on an oblique right atriotomy before aortic cross-clamping (ACC). Ablation lines were created between the superior and inferior caval cannulation sites. Additional lines were drawn from the medial aspect of the base of the excised right atrial appendage into the annulus of the tricuspid valve and from the caudal end of the surgical incision at the atrioventricular groove to the posterior part of the annulus of the tricuspid valve. Three ablation lines for the right atrium were preceded on the intercaval, inferior cavotricuspid isthmus through the coronary sinus and Waterston's groove. The interatrial septal part of the procedure was performed in a later stage of the operation, just before opening the left atrium, to prevent tearing of the septum. In the left atrium, the LA appendage was amputated, oversewn from the epicardial surface with double-layer suture using 4/0 polypropylene at its orifice and reinforced with ablation around the orifice. The left and right pulmonary veins were encircled, and a connecting line between both islands of pulmonary veins was drawn across the left atrial roof and floor. Ablation lines were also

performed from the ablation line isolating the left pulmonary vein to the base of the left atrial appendage amputation site and to the posterior mitral valve annulus. In addition, the Marshall ligament was ablated. Induction of transmural lesions was visually estimated intraoperatively and was assumed when the endocardium turned whitish during ablation and the warning sound of successful transmural ablation started. Left atrial size reduction was performed when LA > 60 mm. To ensure complete blocking of the ablation lines, each bipolar radiofrequency lesion was created by ablation at least three times with a clamp to ensure lesion transmural. After completing the valve(s) replacement operation, the LA was closed and the aortic clamp was removed. Temporary epicardial wires introduced into the right ventricle wall were attached on the chest wall at the end of the operation.

High-sensitivity C-reactive protein (CRP) level and NLR value over 48 h

Baseline blood samples were obtained early in the morning, normally 1–3 days before surgery, and then collected at the three consecutive postoperative time points (12 h, 24 h, and 48 h after procedure). Serum concentrations of high sensitivity C-reactive protein (hs-CRP) were determined by a particle-enhanced immunoturbidimetric assay using an ultrasensitive kit (Orion Diagnostica, Espoo, Finland). The normal interval of detection was 0 mg/L to 5.0 mg/L. The neutrophil–lymphocyte ratio (NLR), defined as the ratio of absolute counts of neutrophils and lymphocytes, was calculated through regular blood test results for the same time points as hs-CRP was detected.

The level of serum cardiac troponin I (TnI)

The sample for determination of troponin I (TnI) protein level was conventionally drawn and determined 12 h after the procedure in the intensive care units.

Patient follow-up

The patients undergoing CM radiofrequency ablation immediately received a microinfusion pump of 600 mg amiodarone on the operative day and 300 mg on the next day. The subsequent administration protocol for oral amiodarone was 600 mg/day for 10 days, then 400 mg/day for 10 days, and finally 200 mg/day for 70 days. Patients were discharged from the hospital, and continuous oral anticoagulation with warfarin sodium was administered with a target international normalized ratio of 1.8–2.5 for at least 6 months. Patients were followed up at 3, 6, and 12 months and annually postoperatively. The follow-ups included regular telephone interview, annual consultation meeting, and outpatient visit. Each visit consisted of detailed history, a routine

clinical, electrocardiogram, echocardiographic evaluations and laboratory testing. Oral amiodarone was discontinued for all patients followed by a 3-month blanking period. A 24 h Holter-ECG recording was prescribed beforehand to be completed at discharge, 6 months, and 12 months after radiofrequency ablation. There were two patients in both groups receiving additional follow-up with a 24 h Holter-ECG due to the presence of symptoms suggestive of arrhythmia after the 3-month blanking period. The detection results also indicated that these patients suffered AF recurrence. The ECGs were analysed to determine the SR if there was presence of electrical atrial activity (P wave). Any one of the following three rhythms was considered no SR restoration: any documented AF, atrial flutter, or atrial tachycardia lasting > 30 s. Patients with postoperatively detected AF, atrial flutter, or paroxysmal atrial tachycardia were managed with the rate control strategy 6 months after operation.

Statistical analysis

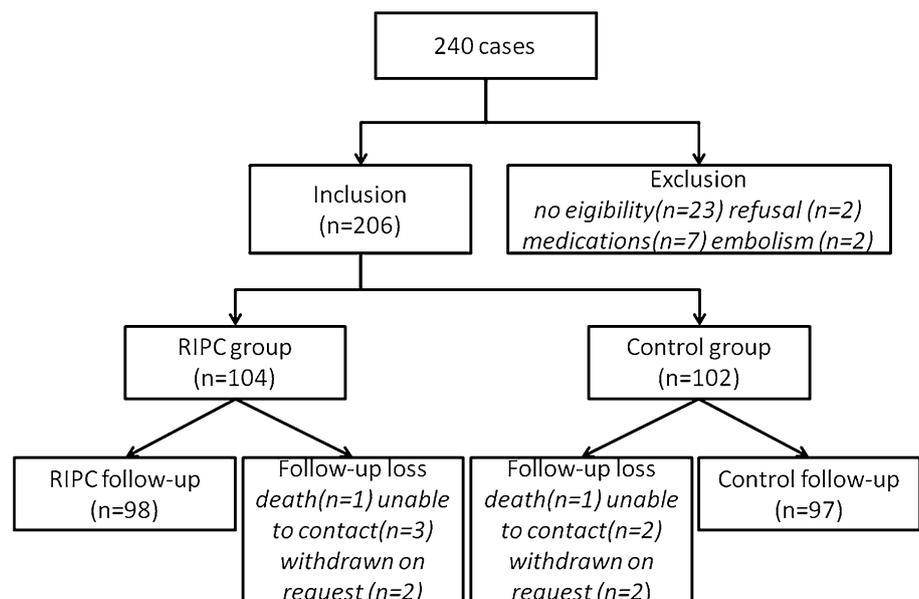
All statistical analyses were performed with SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean value \pm standard deviation (SD). Categorical variables were expressed as frequencies and percentages, with outcomes compared using the χ^2 or the Fisher exact test. Continuous outcomes were compared using the Student's independent samples *t* test for means of normally distributed continuous variables and the Mann–Whitney *U* nonparametric test for skewed distributions, as appropriate based on parametric test assumptions. Sinus rhythm restoration was compared between groups using ANOVA. A *P* value < 0.05 was considered to be statistically significant.

Results

Baseline data

We assessed 240 patients for eligibility, of whom 206 patients were enrolled into the study and randomized to receive either the RIPC (*N* = 104) or control (*N* = 102) procedure. Among the excluded causes, 23 patients did not meet the inclusion and exclusion criteria. The other causes consisted of receiving preoperative antibiotic therapy (*n* = 5), oral glucocorticoid, or non-steroidal anti-inflammatory drugs (*n* = 2) and declined participation (*n* = 2). Two other patients presented with limb artery embolism. The follow-ups on heart rhythm were obtained for 95% of all included patients (RIPC group: 98; control group: 97). The loss to follow-up was due to failure to contact patients or obtain results (see Fig. 1). No significant differences

Fig. 1 Study flowchart



were found between the two groups with respect to baseline characteristics (Table 1).

RIPC ameliorated postoperative hs-CRP and NLR levels

Serum levels of inflammatory factors, represented by hr-CRP and the NLR value, did not differ significantly between the two groups preoperatively, but increased significantly after the procedure. Significant elevation of hr-CRP and NLR was observed in both groups postoperatively. However, the levels of hr-CRP and NLR at 12 h, 24 h, and 48 h postoperatively were significantly lower in the RIPC group than those in the control group ($P < 0.05$, Table 2). No statistically significant difference in TnI was observed 12 h after the procedure in the RIPC group compared to the control group.

RIPC improved the early postoperative clinical outcomes

Although there were no significant differences in cardiopulmonary bypass (CPB) and aortic artery clamp (ACC) procedure times (PT) between the two groups, chest tube drainage volume, ventilation time, and intensive care unit (ICU) stay were significantly lower in the RIPC group than in the control group. However, the in-hospital stay was not significantly different between groups. There were no in-hospital deaths, but there was one case of postoperative 30-day death in each group.

RIPC sustained the sinus rhythm restoration rate

The SR restoration rates were significantly better in the RIPC group, 85.6%, 83.7%, and 82.7%, than those in the control group, 72.5%, 70.6%, and 69.6%, at discharge, 6 months, and 12 months, respectively, after the radiofrequency ablation procedure ($P < 0.05$ for all) (Table 3). Two patients in each group suffered severe atrium ventricular block and accepted permanent pacemaker implantation. There were two cases of stroke occurrence in each group postoperatively during the hospital stay, and there were two cases of stroke occurrence in group A and five cases in Group B after hospital discharge ($P > 0.05$).

Discussion

This study demonstrated that RIPC resulted in an increase in SR restoration rate for permanent AF patients undergoing modified radiofrequency CM procedure with concomitant heart valve(s) replacement. The increase in SR conversion rate presented by RIPC was accompanied by a reduction in the level of hs-CRP and NLR.

AF is a risk factor for long-term mortality, thromboembolism complications, and tricuspid regurgitation, and it also has an adverse effect on the degree of improvement when considering left ventricular function [26]. Surgical ablation is a favourable option for patients with AF undergoing concomitant cardiac surgery [9]. Although the surgical ablation technology for the CM procedure is routinely suggested for permanent AF patients with concomitant valve diseases in our surgical department, the modest SR conversion rate

Table 1 Baseline characteristics

Characteristics	RIPC (n = 104)	Control (n = 102)	P value
Female, n (%)	66 (63.5%)	55 (53.9%)	0.203
Age, mean (SD), (years)	52 ± 11	54 ± 11	0.204
BMI, (kg/m ²)	22.8 ± 2.5	22.9 ± 2.7	0.636
AF duration, months	22 ± 8	22 ± 7	0.929
Cardiothoracic ratio	0.60 ± 0.07	0.61 ± 0.05	0.397
Left atrium diameter, mm	55 ± 8	56 ± 6	0.466
Left ventricular end-diastolic dimension, mm	51 ± 7	53 ± 7	0.180
Left ventricular ejection fraction (%)	55 ± 8	55 ± 7	0.927
NYHA function class, n			0.302
II	30	20	
III	53	59	
IV	21	23	
Procedure-involved type			0.677
Mitral valve	49	45	
Mitral + aortic valve	55	57	
Tricuspid valvuloplasty style			0.843
No	16	13	
Tread	28	27	
Ring	60	62	
Prosthesis implantation type			0.331
Biological	28	35	
Mechanical	75	67	
Euroscore, mean (SD)	2.7 ± 1.4	2.8 ± 1.5	0.580
Preoperative medication			
Anti-inflammatory drugs	0	0	
Statin	0	0	
Aspirin	0	0	
NOACS	0	0	
Warfarin	0	0	
Amiodarone	0	0	
Low molecular weight heparin	21	17	0.514
Beta blocker	69	63	0.493
Digoxin	73	68	0.586
Diuretic	104	102	1.0
Postoperative medication			
Diuretic	104	102	1.0
Warfarin	104	102	1.0
Amiodarone	104	102	1.0
Beta blocker	62	45	0.672
Digoxin	20	17	0.718

Data are expressed as the mean ± standard deviation (SD) or as number (%)

NYHA New York Heart Association (classification), BMI body mass index, NOACS novel oral anticoagulants

remained to be further improved. Measures to enhance the SR conversion rate during the CM procedure have been reported, such as irrigated catheter application of amiodarone during ablation [14].

A growing body of evidence suggests that inflammation and fibrosis contribute to the pathogenesis of AF.

Differential expression profiles of proinflammatory genes, such as oxidative stress, were presented between SR and AF and between maintained SR and recurrent AF after the CM procedure [25]. Anti-inflammatory therapy was introduced to decrease the risk of POAF in dogs, induced by lateral right atriotomy [15]. The incidence of POAF has

Table 2 The value of inflammation reaction and injury index between the two groups

Variables	RIPC (<i>n</i> = 104)	Control (<i>n</i> = 102)	<i>P</i> value
The amount of cardioplegic solution	2000 mL	2000 mL	1.0
CPB time	119 ± 25	121 ± 28	0.657
ACC time	84 ± 24	84 ± 25	0.973
Procedure time	223 ± 32	227 ± 33	0.329
hs-CRP, mg/L			
Basal (mean rank)	140.29	102.72	0.849
12 h after procedure	30.7 ± 12.2	39.9 ± 14.7	<0.001
24 h after procedure	70.9 ± 20.9	80.5 ± 19.2	0.001
48 h after procedure	111.9 ± 27.4	124.1 ± 25.5	0.001
Neutrophil–lymphocyte ratio			
Basal	2.6 ± 1.0	2.8 ± 1.0	0.095
12 h after procedure	3.9 ± 1.1	4.4 ± 0.9	0.002
24 h after procedure	5.7 ± 1.6	6.2 ± 1.7	0.024
48 h after procedure	8.7 ± 2.3	9.7 ± 2.8	0.005
TnI, 12 h after procedure, ng/mL	10.5 ± 4.1	10.6 ± 3.8	0.978
Ventilation time (h)	15 ± 9	18 ± 10	0.019
Blood drainage (mL)	728 ± 204	798 ± 162	0.006
ICU stay (h)	28 ± 12	33 ± 17	0.022
In-hospital stay (days)	8.0 ± 1.3	8.3 ± 1.2	0.102

CPB cardiopulmonary bypass, ACC aortic cross clamp, ICU intensive care unit

Table 3 Sinus rhythm restoration rate at follow-up

Variables	RIPC (<i>n</i> = 104)	Control (<i>n</i> = 102)	<i>P</i> value
Follow-up (months)	21 ± 7 (<i>n</i> = 98)	21 ± 5 (<i>n</i> = 97)	0.601
Death (cases)	1	1	1.0
Beta blocker with sinus rhythm (cases)	35	40	0.051
Digoxin with sinus rhythm (cases)	16	12	0.781
Warfarin with sinus rhythm (cases)	60	41	0.118
Diuretic with sinus rhythm (cases)	31	25	0.913
At discharge with sinus rhythm (cases)	85.6% (89)	72.5% (74)	0.021
6 months with sinus rhythm (cases)	83.7% (87)	70.6% (72)	0.025
12 months with sinus rhythm (cases)	82.7% (86)	69.6% (71)	0.027
Stroke during follow-up (cases)	2	5	0.277

been reported to be approximately 25–30% after CABG and 40–50% after valvular surgery, which peaked on postoperative day 2. There was mounting evidence to support a major role for inflammation and oxidative stress in the pathogenesis of POAF [33]. Both are consequences of using CPB and reperfusion following ischaemic cardioplegic arrest. Thus, we postulated that decreasing the incidence of POAF by attenuating inflammation reaction during the CM radiofrequency procedure through CPB could improve the SR conversion rate.

Multiple inflammatory markers have been studied as predictors of outcomes in AF including those with potential direct involvement in the pathogenesis, such as hs-CRP and NLR. The level of C-reactive protein in blood serum can rise over a 1000 times if stimulated by inflammation,

which normally does not exceed 10 mg/L (mean 0.8 mg/L). The concentration value doubles every 8 h and reaches its maximum in 36–50 h [2]. Specific inflammatory biomarkers, represented by hs-CRP and IL-6, were the predictors of adverse cardiac events in patients with severe mitral regurgitation undergoing valve procedures [7]. On the other hand, prophylactic treatment with a single dose of anti-inflammatory agent, a monoclonal antibody targeting interleukin-1 β , proved lower was better for the magnitude of the reduction of hs-CRP concentration in terms of all-cause mortality and cardiovascular outcomes [22]. In this study, we observed a lower increase in the level of hs-CRP in the RIPC group than in the control group at each postoperative time point, which was also linked to better clinical performance, such as lower volume of chest tube drainage, shorter ventilation time, and

shorter ICU stay, and this might reflect the slight extent of underlying inflammation reaction and stimulation during the procedure in the RIPC group.

The neutrophil–lymphocyte ratio (NLR), defined as the ratio of absolute counts of neutrophils and lymphocytes, usually represents the inflammation reaction index. As a measurable inflammatory biomarker, NLR was an additional tool in measuring severity and prognosis assessment of AF [21]. Elevated NLR is associated with a higher incidence of adverse outcomes after cardiac surgery [24]. An elevated preablation NLR was associated with increased AF recurrence after cryoballoon-based catheter ablation [6]. Our results supported that higher values of NLR were accompanied by lower SR conversion rates, which could imply the role of an inflammatory environment in the development of AF recurrence postablation.

In patients who undergo off-pump CABG, induced by occluding the left anterior descending (LAD) twice for a 2-min period followed by 3-min reperfusion before bypass grafting of the first coronary vessel, ischaemic preconditioning protocol significantly suppressed heart rate elevation, the episodes of supraventricular tachycardia, and the incidence of ventricular tachycardia after surgery [31]. In contrast to direct local IPC, limb RIPC is a noninvasive technique with the advantages of easy application and a lack of ethical concerns. The signal transduction of RIPC is quite complex and is not clear in its details, but it involves physical and chemical stimulus and neuronal and humoral mediators which transfer the protective signal from the periphery to the heart and effector transduction mechanisms on the target organ [11, 12, 18].

In the translation of RIPC from bench to bedside, RIPC had inconsistent effects on the results of new onset of AF in patients undergoing CABG surgery [5, 20]. Although previous research indicated that longer ACC (more than 56 min) rather than other demographics, medications, and intraoperative variables during CABG procedure was facilitated by RIPC, we did not observe the difference in TnI [17]. On the one hand, we administered RIPC in the heart valve procedure in addition to the favourable cardioprotection from HTK cardioplegia. Propofol anaesthesia is known to abrogate cardioprotection of remote ischaemic conditioning in clinical trials, which is characteristic of reduced cardiac injury biomarker TnI [13, 19]. This study observed that RIPC ameliorated sinus rhythm restoration rate through Cox maze radiofrequency procedure associated with inflammation reaction reduction. We associated the enhancement of sinus rhythm restoration rate with the reduction of inflammation reaction. We also didn't observe indifference in cardiac injury biomarker TnI, which could be due to the effect of propofol anaesthesia. Thus, it is concluded that propofol anaesthesia could not interfere with the reduction of inflammation reaction in the way of signalling pathway.

In contrast to the RIPC trial in myocardial injury research, there was no documented report on the effect of RIPC when it was applied to maintain SR in AF patients undergoing surgical CM radiofrequency ablation. However, RIPC before radiofrequency catheter ablation for paroxysmal AF significantly reduced the increase in TnI, hs-CRP, and interleukin 6, and resulted in a lower early recurrence of AF [10]. In the rat stroke model, RIPC modulated inflammatory responses by induction of hypoxia-inducible factor 1 α [32]. In our previous experimental investigations, it was also stated that RIPC significantly reduced the inflammation reaction and oxidative stress reaction in the rat ischaemia reperfusion model [16]. Compared with strategies such as preoperative steroids for reducing POAF, RIPC was safer in clinical practice [4]. The potential inflammatory molecular targets which associated RIPC with successful SR maintenance after surgical AF ablation remained to be determined, but may provide clues for developing new potential therapeutic agents to improve the efficacy of AF conversion with medication.

Limitations

In the present study, some potential limitations deserve comment. First, a small sample size could underpower for definitive conclusions. Larger multi-centre studies may be necessary to further clarify this issue. Second, the patients lost to follow-up and death were regarded as having had AF. In fact, this could underestimate the SR restoration rate to some extent. The short duration of the Holter-ECG could provide insufficient precision for judging SR conversion. Third, we had only the regular blood test results from the hospital laboratory of inflammation index rather than other commercial reagents.

Conclusion

In conclusion, the novel strategy assisted by remote ischaemic preconditioning ameliorated the sinus rhythm restoration rate in patients undergoing surgical radiofrequency ablation for permanent atrial fibrillation and was associated with inflammation index reduction.

Acknowledgements This work was supported by the clinical study and translation grant of Sichuan Provincial People's Hospital (2017LY07) and the National Natural Science and Technology Foundation of China (81800274).

Author contributions The manuscript has not been submitted elsewhere and is not under consideration for publication. All authors have read and agreed with the submission of the manuscript. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Funding This work was supported by the clinical study and translation grant of Sichuan Provincial People's Hospital (2017LY07) and the National Natural Science and Technology Foundation of China (81800274).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All participants in the study gave written informed consent in accordance with the Declaration of Helsinki. Both studies were approved by the Ethics Committee of Sichuan Provincial People's Hospital, Chengdu, China.

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