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Effect of remote ischemic preconditioning on myocardial injury and inflammatory response induced by ablation for atrial fibrillation: A randomized controlled trial

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ABSTRACT

Background: Remote ischemic preconditioning (RIPC) has been suggested to reduce postoperative release of cardiac and inflammatory markers in patients undergoing cardiac surgery. This study aimed to evaluate the effect of RIPC on nonischemic myocardial damage and inflammatory response in patients undergoing radiofrequency catheter ablation for paroxysmal atrial fibrillation (AF).

Methods: Seventy-two patients with drug-refractory paroxysmal AF undergoing radiofrequency catheter ablation were randomized into RIPC or control groups. RIPC (intermittent arm ischemia through four cycles of 5-min inflation and 5-min deflation of a blood-pressure cuff) was performed once daily on 2 consecutive days before the ablation and immediately before ablation. Cardiac troponin-I (cTnI), high-sensitive C-reactive protein (hs-CRP), and interleukin (IL)-6 levels were measured before RIPC/sham RIPC, after the ablation, and 24 and 72 h later. The early recurrence of atrial fibrillation (ERAF) in the two groups was observed over the subsequent 3 months.

Results: Radiofrequency ablation resulted in a significant rise in cTnI, hs-CRP, and IL-6 in both groups, which persisted for 72 h. The RIPC group showed a lower increase in cTnI ($P < 0.001$), hs-CRP ($P = 0.003$), and IL-6 ($P = 0.008$) than the control and tended to have a lower risk of ERAF (hazard ratio [HR] = 0.77, 95% confidence interval [CI]: 0.32–1.88).

Conclusions: These results show that RIPC before ablation for paroxysmal AF significantly reduces the increase in cTnI, hs-CRP, and IL-6 associated with the procedure and results in a lower risk of ERAF. These findings suggest that RIPC could provide cardioprotection against nonischemic myocardial damage.

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1. Introduction

Atrial fibrillation (AF) is the most common clinical arrhythmia and is associated with an increased risk of heart failure, thromboembolic events, and mortality. Radiofrequency catheter ablation for pulmonary vein (PV) antral isolation has become an effective therapeutic option to treat drug-refractory paroxysmal atrial fibrillation (AF) [1]; however, electrical PV isolation (PVI) by radiofrequency energy often causes extensive myocardial damage, which might result in a systemic and local inflammatory response [2,3]. Previous studies have suggested that proinflammatory processes initiated during ablation therapy have been implicated in the early recurrence of AF (ERAF) [4–6].

Remote ischemic preconditioning (RIPC), a noninvasive, simple procedure, can help a distant organ or tissue withstand subsequent prolonged ischemic events whereby using brief episodes of non-lethal ischemia [7,8]. Previous clinical trials have shown that RIPC provides cardiac protection against myocardial injury in patients undergoing cardiovascular surgery and percutaneous coronary intervention [9–12]. A recent study reported that upper-arm intermittent ischemia reduced the increase in platelet activation and reactivity induced by radiofrequency catheter ablation for paroxysmal AF [13]. In addition, it demonstrated that RIPC might reduce the incidence of postoperative AF during the first 3 days after coronary artery bypass surgery [14]; however, there are currently no data relating RIPC to nonischemic myocardial damage, such as myocardial injury induced by radiofrequency catheter ablation of AF.

The purpose of the present study was to determine whether RIPC has any effect on myocardial injury and inflammatory response induced by radiofrequency ablation of AF; and whether this consequence influences early recurrence of AF after ablation.

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2. Methods

2.1. Study design and population

This study was a prospective randomized controlled clinical trial. All patients provided written informed consent before the procedure, which was approved by the Medical Ethics Committee of Beijing Chao-Yang Hospital of Capital Medical University, China. Patients were randomized using a computer-generated list of randomized numbers, and allocation was concealed using numbered, sealed envelopes.

Seventy-two consecutive patients with paroxysmal AF referred for an initial catheter ablation procedure were enrolled between March 2015 and December 2015, and all the patients had at least two documented AF episodes within the preceding 12 months, either self-terminating within 7 days or cardioverted within 48 h of onset. At least one episode should have been documented under treatment with a class Ic or III antiarrhythmic drug. Participants were randomized to receive either RIPC or a sham intermittent ischemia (control) before ablation.

2.2. Exclusion criteria

Exclusion criteria were as follows: 1) <18 years old; 2) left atrial size >55 mm; 3) previous ablation for AF or intracardiac thrombus; 4) valvular heart disease, thyroid disease, any acute or chronic inflammatory or allergic disease, autoimmune disease, or malignancy; 5) corticosteroid or other immunosuppressive or immunomodulatory therapy; or 6) severe hepatic and renal failure and acute cardiovascular or cerebrovascular events (e.g., myocardial infarction, acute coronary syndrome, stroke) within the previous 3 months. A detailed clinical history was recorded from all patients, including an assessment of cardiovascular risk factors and characteristics of AF episodes. None of the patients took anti-inflammatory drugs during the study period.

2.3. RIPC and control interventions

RIPC or sham intermittent forearm ischemia (control group) was performed once daily for 2 consecutive days before the procedure and immediately before ablation. A blood pressure cuff was placed in the standard position on the upper arm of all patients. RIPC was induced by four cycles of upper-limb ischemia (5-min blood-pressure cuff inflation to ≥200 mm Hg, but at least 15 mm Hg higher than the patient's actual systolic arterial pressure, followed by 5-min cuff deflation). For the control group, the sham RIPC was performed as follows: the cuff was inflated for similar cycles at 10 mm Hg for 5 min with 5-min intervals [13].

2.4. Catheter ablation

Antiarrhythmic drugs were discontinued five half-lives before the procedure in all patients, except for amiodarone, which was discontinued for at least 8 weeks before ablation. Warfarin was discontinued 3 days before the procedure. Low molecular-weight heparin was used subcutaneously twice daily as bridge therapy until the evening before the procedure. Within 48 h of AF ablation, transthoracic echocardiography and multislice computerized tomography (CT) were performed to evaluate the left atrium and the anatomy of the PVs. Surface electrocardiograms (ECG) and bipolar intracardiac electrograms were monitored continuously and data stored on a computer-based digital recording system (LabSystem PRO, Bard Electrophysiology, Lowell, MA, USA). Bipolar electrograms were filtered from 30 to 500 Hz. A multielectrode catheter was positioned in the coronary sinus for recording electrograms and atrial pacing.

All patients underwent wide-area circumferential PVI. After a single transseptal puncture was performed under fluoroscopic guidance, a dose of 100 U/kg heparin sodium was administered; thereafter, additional boluses of heparin were infused to maintain an activated clotting time of between 250 and 350 s, which was checked at 30-min intervals throughout the procedure. An endocardial map of the left atrium (LA) was created with the CARTO 3 electroanatomic mapping system (Biosense Webster, Inc., Diamond Bar, CA, USA) and then merged with the pre-acquired multislice CT imaging. PV potentials were recorded with the Lasso Nav circular mapping catheter (Biosense Webster, Inc., Diamond Bar, CA, USA) before, during, and after antral ablation. The ThermoCool SmartTouch irrigated radiofrequency ablation catheter (Biosense Webster, Inc., Diamond Bar, CA, USA) was used to perform ablation. Irrigated radiofrequency energy was delivered with a target temperature of 43 °C, a power between 30 and 35 W, and an irrigation rate of 30 mL/min. The procedural end point was complete isolation of the PVs with a bidirectional conduction block between LA and PVs.

Fentanyl was administered in cases of chest pain during the procedure. No clinically relevant hemodynamic perturbations requiring medical interventions occurred during the procedure on any patient.

2.5. Blood sampling and analysis

Blood samples were obtained from a peripheral vein of each patient at four different time points as follows: 1) at baseline before RIPC/sham intermittent ischemia, 2) immediately after the end of the ablation procedure, 3) 24 h after the procedure, and 4) 72 h after the procedure. Blood was collected into collection tubes without anticoagulant and allowed to clot for 30 min at room temperature before centrifugation at 4.0 °C/1000*g* for 15 min. Serum aliquots were kept at −80 °C to await analysis. Each aliquot was analyzed once, and none were refrozen.

2.6. Markers of myocardial injury

Myocardial damage was determined by measuring cardiac troponin I (cTnI). CTnI was analyzed using a heterogeneous immunoassay module (Siemens Healthcare Diagnostics Inc., Newark, DE, USA). For this assay, the lowest concentration measurable was 0.04 ng/mL and the 99th percentile concentration was 0.07 ng/mL according to the manufacturer's instructions.

2.7. Markers of inflammatory response

Inflammatory response was determined by measuring interleukin (IL)-6 and high-sensitive C-reactive protein (hs-CRP). Serum levels of IL-6 were measured using enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA). The minimum detectable concentrations were determined by the manufacturer as 0.70 pg/mL. The intra-assay and inter-assay variations were ≤4.2% and ≤6.4%, respectively. Serum concentrations of hs-CRP were determined by a particle-enhanced immunoturbidimetric assay using an ultrasensitive kit (Orion Diagnostica, Espoo, Finland). The lower rate of detection was 0.25 mg/L and the upper normal limit was 3.0 mg/L.

2.8. Post-ablation follow up

Patients were followed up for 3 months, starting from the day of the ablation procedure (no blanking period was applied). The main outcome measure was AF recurrence. The patients underwent continuous, in-hospital electrocardiography monitoring for 3 days after the procedure. Warfarin (target international normalized ratio, 2.0–3.0) or novel oral anticoagulants were continued after the procedure for a minimum of 3 months. No antiarrhythmic drugs (class I or III) were allowed after the procedure except for those patients with highly symptomatic ERAF.

A clinical assessment, 12-lead electrocardiography, and Holter monitoring for 24-h were routinely performed on all patients at each of the 1.0-, 2.0-, and 3.0-month follow-up visits in a dedicated arrhythmia outpatient clinic. Twelve-lead electrocardiography and 24-h Holter electrocardiography were also performed when any patient reported to have palpitations. Patients were also instructed to contact the study center and to go to the emergency room whenever they felt symptoms consistent with arrhythmia. ERAF was defined as >30 s AF/atrial flutter (AFL)/atrial tachycardia (AT) within the first 3.0 months after the ablation procedure. No patient was lost to follow up, and all patients continued their required outpatient visits and monitoring.

2.9. Statistical analyses

Continuous variables were expressed as the mean ± SD and compared using Student's *t*-test if their distribution did not significantly deviate from the normal distribution (tested with the Kolmogorov–Smirnov test). If significant deviation from the normal distribution was found, continuous variables were expressed as the median (interquartile range) and were compared using nonparametric tests (the Wilcoxon and Mann–Whitney U tests). Categorical variables were expressed as percentages and numbers and were compared using the chi-squared test. A generalized linear model for repeated measures was applied to compare the curves of myocardial damage and inflammatory markers throughout the radiofrequency procedure between the two groups. In case of global significant differences, post hoc multiple comparisons were made between and within the groups using unpaired and paired *t*-tests, respectively. A multivariate analysis was conducted to evaluate the predictors of AF recurrence using Cox regression. SPSS v. 17 was used (SPSS, Inc., Chicago, IL, USA) for analysis of the data and $P < .05$ (two sided) was considered statistically significant.

3. Results

3.1. Subject characteristics

The present study comprised 72 subjects (age: 65.4 ± 9.4 years; male/female 35/37). The main clinical characteristics of the two groups are summarized in Table 1. There were no significant differences in subject characteristics between the two groups; they were well balanced with regard to main clinical and laboratory characteristics, drug therapy, and characteristics of AF episodes, as well as the main findings concerning the radiofrequency ablation procedure. No surgical complications occurred in any patient.

3.2. Myocardial injury marker

Changes of cTnI in the two groups are summarized in Table 2, and its trends in relation to AF ablation are shown in Fig. 1. There were no significant differences of serum cTnI concentrations between the two groups under basal conditions. The level of cTnI increased significantly in both groups during the radiofrequency ablation ($P < .001$), and

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