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Multiorgan protection of remote ischemic perconditioning in valve replacement surgery

Qinghua Hu, MD, Wanjun Luo, MD, Lingjin Huang, MD, Rimao Huang, MD, Ri Chen, MD, and Yang Gao, MD*

Department of Cardiothoracic Surgery, Xiangya Hospital, Central-South University, Changsha, Hunan, China

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ABSTRACT

Background: Remote ischemic perconditioning (RIPerc) is a new alternative of remote ischemic conditioning and has not been well studied. RIPerc attenuates myocardial injury when applied during cardiac surgery. However, its protective effects on other organs remain unknown.

Materials and methods: Patients with rheumatic heart disease undergoing valve replacement surgery were randomized into the RIPerc group ($n = 101$) or the control group ($n = 100$). RIPerc was achieved by three cycles of 5-min ischemia–5-min reperfusion in the right thigh during surgery. Clinical data and the levels of injury biomarkers for the heart, lungs, liver, and kidneys within 48 h after surgery were compared using one-way or repeated measurement analysis of variance.

Results: In the RIPerc group, the release of serum cardiac troponin I (128.68 ± 102.56 *versus* 172.33 ± 184.38, $P = 0.04$) and the inotropic score (96.4 ± 73.8 *versus* 121.5 ± 89.6, $P = 0.032$) decreased compared with that of the control; postoperative drainage (458.2 ± 264.2 *versus* 545.1 ± 349.0 ml, $P = 0.048$) and the incidence of acute lung injury was reduced (36.6% *versus* 51%, $P = 0.04$), and the extent of hyperbilirubinemia was also attenuated. No significant difference was observed in the levels of biomarkers for renal injury and systemic inflammation response.

Conclusions: RIPerc applied during the valve replacement surgery induced multiple beneficial effects postoperatively including reduced drainage and myocardial damage, lower incidence of acute lung injury, and attenuated hyperbilirubinemia.

1. Introduction

During cardiac surgery, acute ischemic–reperfusion (I/R) injury in organs other than the heart is not uncommon and is associated with increased mortality and prolonged hospital stays [1–3]. Studies in search of effective medications for preventing the organs from I/R injury are far from satisfying yet. However, remote ischemic conditioning (RIC) that is triggered by applying several cycles of brief I/R in distant organs is emerging as a promising therapeutic strategy to attenuate I/R injury in target organs [4]. The ability to recapitulate RIC protection using the upper or lower limbs instead of internal organs facilitates the translation of RIC into clinical practice [5]. Although RIC was originally developed to protect myocardium against I/R injury; its protective effects have been subsequently demonstrated in many noncardiac organs such as the lungs, liver, and kidneys. To date, growing evidence suggests that

* *Corresponding author*. Department of Cardiothoracic Surgery, Xiangya Hospital, Xiangya Road 87, Changsha, Hunan 410078, China. Tel.: +86 13787177889; fax: +86 073184327247.
E-mail address: luo3478@aliyun.com (W. Luo).

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RIC attenuates myocardial injury in cardiac surgery [6,7]. However, its protective effects on other organs during cardiac surgery are still controversial and need further investigations [8,9].

Remote ischemic perconditioning (RIPerc) was introduced by Schmidt *et al.* [10] by applying RIC during cardiac ischemia. RIPerc is a new alternative of RIC and differs in terms of the timing of intervention from remote ischemic preconditioning (RIPC) and postconditioning (RIPost), RIPC being applied before and RIPost after the index ischemic event. Compared with RIPC and RIPost, RIPerc is less studied but it is more practicable in clinical settings. Botker *et al.* [11] showed that RIPerc triggered by intermittent arm ischemia during ambulance transfer for primary coronary angioplasty significantly increased myocardial salvage index. The RIPOST-MI study revealed that RIPerc applied immediately before revascularization in patients with ST segment in electrocardiography-elevation myocardial infarction reduced infarct size [12]. Our group previously demonstrated that RIPerc reduced myocardial injury in patients undergoing valve replacement surgery evidenced by lower release of cardiac troponin I (cTnI) and that it was superior to RIPC [13]. However, to our knowledge, the assumed protective effects of RIPerc on other organs besides the heart have not been tested in cardiac surgery.

Rheumatic heart disease is still a major component of heart valvular diseases in the developing countries [14]. Most patients have long histories of heart failure before surgery, which makes their organs more vulnerable to acute I/R injury. However, the studies about the protective effects of RIC in such patients are rather limited. Therefore, in the present study, we chose patients with rheumatic valvular disease undergoing valve replacement surgery as our subjects and performed a randomized clinical trial to investigate whether RIPerc is capable of conferring protection on other organs besides the heart.

2. Materials and methods

2.1. Study design

We performed a single-center, randomized, prospective, and double-blinded study. Based on $\alpha = 0.05$, $1-\beta = 0.9$, and the preliminary results of serum cTnI and creatinine (Scr), the estimated sample size was 30 for cTnI and 100 for Scr. Between March of 2012 and May of 2014, 237 patients with rheumatic valvular diseases admitted to our hospital for valve replacement surgery were randomized into the RIPerc group ($n = 101$) or the control group (Con) ($n = 100$). The inclusion and exclusion process was illustrated in Figure 1. Patients with coronary artery disease, previous heart surgery history, need for atrial fibrillation ablation, infective endocarditis, peripheral vascular diseases, hypertension, diabetes or abnormal hepatic, and renal or pulmonary function were excluded. Patients taking aspirin, corticosteroids, angiotensin-converting enzyme inhibitors, or statin were also excluded. A 12-cm-wide blood pressure cuff was placed around the right thigh before anesthesia in the operating room for all patients. In the RIPerc group, after cross-clamping the aorta, the cuff was immediately inflated to 600 mm Hg—in accordance with the orthopedic standard for blocking the blood flow of the lower limb—for 5 min followed by 5-min reperfusion interval and it was repeated three times. For the Con, the cuff was only slightly inflated. Patients, surgeons, perfusionists, intensive care unit staff, and laboratory technicians were blinded to which group the patients were allocated. Biomarkers that indicate the extent of injury for lungs, liver, and kidneys were measured within 48 h after surgery. These biomarkers were our primary outcome measurements, whereas serum cTnI as a specific myocardial injury marker was determined to confirm the effectiveness of RIPerc applied during surgery.

2.2. Ethical issue

The study was approved by the Ethic committee of Xiangya Hospital, Central-South University, China. It was performed in compliance with the Declaration of Helsinki. Written informed consents from patients were obtained before inclusion.

2.3. Anesthesia and surgery

The procedures of anesthesia and surgery were previously described in detail [13]. Briefly, general anesthesia was induced by intravenous midazolam and vecuronium bromide and maintained by fentanyl and propofol together with intermittent inhalation of isoflurane. The same surgeon and perfusionist team performed each surgery. Median sternotomy, standard cardiopulmonary bypass (CPB), and moderate hypothermia (28°C–31°C) were used. The cardiac arrest was achieved by intermittent antegrade perfusion of 1:4 cold crystalloid-blood cardioplegia. The mitral valve replacement was done via a transseptal approach, and the aortic valve replacement was carried out via a transverse aortotomy.

2.4. Clinical data

All patients received standard postoperative care. For hemodynamic support, dopamine and/or dobutamine were used as the first-line inotropes and epinephrine or isoproterenol or norepinephrine as the second-line. No hemostatic agents were used except protamine used to antagonize the effects of heparin. The data of ventilation time, intensive care duration, inotropes requirement, drainage, urine output, x-ray, electrocardiography, arterial blood gas, and complications during hospital stay were collected. The inotropic score was assessed with the formula: (dopamine + dobutamine × 1) + (milrinone × 15) + (epinephrine + norepinephrine + isoproterenol × 100) [15]. All patient follow-up continued for at least 30 d after surgery.

2.5. Blood samples

Blood samples were taken from peripheral veins at different time points: preoperative (T0), 12 (T12), 24 (T24), and 48 h (T48) after surgery. All blood sample analyses were performed in accordance with standard procedures at the laboratory of Xiangya Hospital. The concentration of cTnI was measured by enzyme-linked immunosorbent assays according to the supplier's instructions (Jidan Biotechnology Co, Nanjing, China) using an analyzer (ELX800; BIO-TEK Instruments Inc, Winooski, VT).