Heart, Lung and Circulation (2016) **25,** 484–492
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2015.09.008

ORIGINAL ARTICLE

Pulmonary Protective Effects of Remote Ischaemic Preconditioning with Postconditioning in Patients Undergoing Cardiac Surgery Involving Cardiopulmonary Bypass: A Substudy of the Remote Ischemic Preconditioning with Postconditioning Outcome trial

Jeong Jin Min, MD [a,1], Jun-Yeol Bae, MD [a], Tae Kyong Kim, MD [a], Jun Hyun Kim, MD [b], Ho Young Hwang, MD, PhD [c], Kyung-Hwan Kim, MD, PhD [c], Hyuk Ahn, MD, PhD [c], Ah Young Oh, MD, PhD [d], Jae-Hyon Bahk, MD, PhD [a], Deok Man Hong, MD, PhD [a,2], Yunseok Jeon, MD, PhD [a,2*]

[a]Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, Seoul, Korea
[b]Department of Anesthesiology and Pain Medicine, Inje University Ilsan Paik Hospital, Gyeonggi, Korea
[c]Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul, Korea
[d]Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi, Korea

Received 27 April 2015; received in revised form 16 August 2015; accepted 20 September 2015; online published-ahead-of-print 17 October 2015

Background The RISPO (Remote Ischemic Preconditioning with Postconditioning Outcome) trial evaluated whether remote ischaemic preconditioning (RIPC) combined with remote ischaemic postconditioning (RIPostC) improves the clinical outcomes of patients undergoing cardiac surgery. This substudy of the RISPO trial aimed to evaluate the effect of RIPC with RIPostC on pulmonary function in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).

Methods Sixty-five patients were enrolled (32: control and 33: RIPC-RIPostC). In the RIPC-RIPostC group, four cycles of 5 min ischaemia and 5 min reperfusion were administered before and after CPB to the upper limb. Peri-operative PaO_2/F_IO_2 ratio, intra-operative pulmonary shunt, and dynamic and static lung compliance were determined.

Results The mean PaO_2/ F_IO_2 was significantly higher in the RIPC-RIPostC group at 24h after surgery [290 (96) *vs.* 387 (137), p = 0.001]. The incidence of mechanical ventilation for longer than 48h was significantly higher in

*Corresponding author at: Department of Anesthesiology and Pain medicine, Seoul National University Hospital, Daehakro 101, Jongno-gu, Seoul, Korea, 110-744. Tel.: +82 10 9016 2940; fax: +82 2 747 5639, Email: jeonyunseok@gmail.com

[1] Jeong Jin Min moved from Seoul National University Hospital to Samsung Medical Center, Sungkyunkwan University School of Medicine during the study period.

[2] Drs. Hong DM and Jeon Y contributed equally as the corresponding author of this manuscript.

the control group (23% *vs.* 3%, $p < 0.05$). However, there were no significant differences in other pulmonary profiles, post-operative mechanical ventilation time, and duration of intensive care unit stay.

Conclusions In our study, RIPC-RIPostC improved the post-operative 24h PaO_2/F_IO_2 ratio. Remote ischaemic preconditioning-Remote ischaemic postconditioning has limited and delayed pulmonary protective effects in cardiac surgery patients with CPB.

Keywords Complication • Post-operative • Ischaemic preconditioning • Ischaemic postconditioning • Cardiac surgical procedures • Lung injury

Remote ischaemic preconditioning (RIPC) is the protective mechanism by which transient ischaemia of distant organs or tissues protects the target organ from sustained ischaemia-reperfusion injury [1]. This protection can be induced by a simple and non-invasive technique such as transient limb ischaemia using a pneumatic cuff. In previous animal studies, RIPC showed powerful protective effects on various organs including the heart, lungs, liver, kidneys, spinal cord, and skeletal muscles [2–6]. In early clinical trials, RIPC reduced myocardial enzyme levels in cardiac and non-cardiac surgery patients [7–9]. Subsequent meta-analysis revealed that RIPC significantly reduced troponin levels in cardiac surgery patients [10]. However, most of the earlier studies were designed to evaluate biomarkers such as troponin.

To evaluate the clinical effects of RIPC, the RISPO (Remote Ischemic Preconditioning with Postconditioning Outcome) trial was conducted on 1,280 patients who underwent elective cardiac surgery at two tertiary care centres [11]. In the RISPO trial, remote ischaemic postconditioning (RIPostC) was added to RIPC after the ischaemic period (cardiopulmonary bypass [CPB] or coronary anastomoses) to augment the protective effect. The primary endpoint was the composite of major adverse outcomes including death, myocardial infarction, arrhythmia, stroke, coma, renal failure or dysfunction, respiratory failure, cardiogenic shock, gastrointestinal complication, and multiorgan failure. When comparing the RIPC with RIPostC and the control group, RIPC with RIPostC did not reduce the composite outcome, and there were no differences in each major adverse outcome and hospital stays between the two groups.

Although RIPC is thought to induce a systemic protective effect, the pulmonary protective effect of RIPC remains to be determined. Prior research on the pulmonary protective effects of RIPC includes few randomised clinical trials and results are inconclusive regarding the effects or the time course [8,12–16]. In the RISPO trial, we attempted to enrol a large number of patients; however, the study included heterogeneous surgeries and patients with variable pre-operative pulmonary functions. Moreover, respiratory profiles at various time points during the study could not be measured.

Therefore, to evaluate whether pulmonary function is affected by RIPC with RIPostC at various time points in patients undergoing cardiac surgery with CPB, we conducted this substudy.

Methods

This is a subgroup study of the RISPO trial [11]. The details of the RISPO trial have been published. This subgroup study protocol is registered at ClinicalTrials.gov (NCT01144585).

Study Population

All patients enrolled in this substudy were part of the RISPO trial, which aimed to evaluate whether RIPC combined with RIPostC improved the clinical outcomes of cardiac surgery patients. The RISPO study was performed in two tertiary care centres (Seoul National University Hospital and Asan Medical Center) on elective cardiac surgery patients regardless of CPB use. In the present substudy, only patients with CPB from Seoul National University Hospital were enrolled. The additional exclusion criteria for this substudy were significantly decreased pre-operative pulmonary functions such as mechanical ventilator support, pre-operative oxygen therapy, tachypnoea, orthopnoea, active lung lesions on chest radiograph, a ratio of forced expiratory volume in 1 sec to forced vital capacity (FEV_1/FVC) less than 50% of predicted value, pulmonary artery hypertension (mean pulmonary artery pressure >35 mmHg), intracardiac shunts, and pre-operative systemic or local steroid therapy.

Study Design

In the RISPO study, eligible patients were randomly allocated to the RIPC with RIPostC (RIPC – RIPostC) group or the control group using a computer-generated list in variable permuted blocks of four and six. The randomisation list was generated by an independent statistician and was stored in concealed envelopes. The group assignment was blinded to all patients, medical personnel, and investigators except the anaesthesia nurses who performed the RIPC and RIPostC processes. In the RIPC-RIPostC group, four cycles of 5 min ischaemia and 5 min reperfusion were administered to the upper limb before CPB for RIPC and after CPB for RIPostC. Limb ischaemia was performed with a blood pressure cuff inflated to 200 mmHg. In the control group, the blood pressure cuff was applied around the upper limb with no pressure applied to the cuff.

Anaesthesia was induced with intravenous midazolam and sufentanil and maintained with propofol and remifentanil. Muscle relaxation was obtained using vecuronium. An inhalational anaesthetic agent was avoided to prevent