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Article

Effects of Remote Ischemic Preconditioning on Delirium and Neurological Function in Patients Undergoing Cardiac Surgery: A Multicenter Randomized Controlled Trial

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Abstract

Background: Postoperative delirium (POD) and neurological dysfunction are very common following cardiac surgery and deteriorate the patient's prognosis and the outcome of surgical procedures. A clinically effective management strategy or drug is not yet available for POD. Additionally, it is unknown whether remote ischemic preconditioning (RIPC) has neuroprotective and anti-delirium benefits in patients who undergo cardiac surgery. **Methods**: This study examined whether RIPC can improve POD and neurological function in cardiac surgery patients. We screened 510 consecutive adult patients aged 18 and older who underwent cardiac surgery between January 2018 and December 2022. Then, 448 of these patients were recruited in the trial as the intention to treat (ITT) group, who were then randomly assigned to receive either a control (n = 223) or RIPC treatment (n = 225). The primary outcome measures were hospitalization postoperative delirium, six-month modified Rankins scale (mRS), hospital cerebral infarction, 30-day overall mortality, neuron-specific enolase (NSE) and S-100b levels, related adverse effects, hospital costs, and hospital stay. **Results**: A statistically significant variation was not observed between the two groups in terms of the baseline clinical data. In contrast to the control group, the POD in the RIPC group was considerably alleviated. RIPC treatment also decreased the levels of NSE and S-100b, which alleviated nerve injury. The adverse impacts of RIPC-induced objective indicators of tissue or neurovascular damage were similar in both groups, showing no significant variations between the two. The hospital stays and hospitalization costs also decreased significantly in the RIPC-treated patients. **Conclusion**: The study findings suggested that RIPC may benefit cardiac surgery patients by reducing POD, alleviating injury, and lowering hospital expenditures and length of stay. Cardiac surgery patients can be treated with RIPC, which is an effective and safe technique.

Keywords

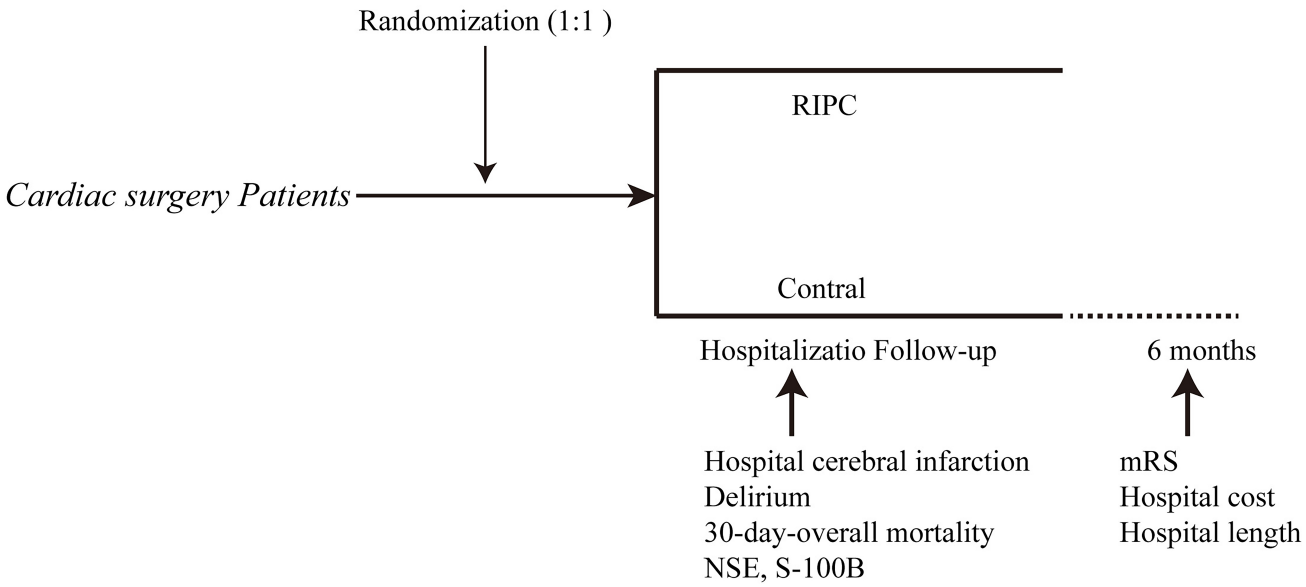
cardiac surgery; RIPC; RCT; outcome

Introduction

There is a high prevalence of postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) in patients who have undergone cardiac surgery under general anesthesia [1]. After cardiovascular surgery, POD and POCD are the most common acute and transient brain disorders, occurring in approximately 30% of patients in intensive care units (ICUs) [2,3]. Up to 53% of patients who undergo cardiac surgery develop POD, according to a previous report [4]. Our earlier research demonstrated that POD is independently related to death, long-term cognitive decline, prolonged hospital stays, and higher healthcare expenses [5,6]. Therefore, the prevention of POD after cardiac surgery is very important.

The pathophysiologic mechanism of delirium includes endothelial damage, microthrombosis, cerebrovascular vasospasm, cerebral hypoperfusion, systemic neuroinflammation, and blood–brain barrier (BBB) injury [3]. Pharmacological interventions have been extensively explored in the literature (such as statins and melatonin) for preventing POD, but their effectiveness has been debated. Extensive research has indicated that nonpharmacological interventions help improve cerebral blood flow and endothelial function and are critically involved in the conditions of patients undergoing cardiac surgery [7,8].

Murry *et al*. [9] published the first study on ischemic preconditioning (IPC) in 1986, which was defined as repeated transient myocardial ischemia that reduces subsequent long-term myocardial ischemia–reperfusion damage. Subsequent studies have shown that IPC can reduce the incidence and severity of postischemia arrhythmia, promote cardiac function recovery after overall cardiac ischemia, and lower the risk of ischemia–reperfusion injury (IRI) [10–12]. Masada *et al*. [13] reported that IPC technology can alleviate brain edema, BBB disruption, and neurologic deficits and decrease the infarction volume after is-



Graphical Abstract

chemic stroke. Saber *et al.* [14] also reported that following traumatic brain injury (TBI), mice treated with remote ischemia conditioning showed attenuated acute lung injury. The heart and brain are extremely vulnerable to ischemia damage; thus, several adjustments are required in clinical treatment. It is difficult to perform IPC directly. Additionally, the specific efficacy and safety remain undetermined. Therefore, a new concept of remote ischemic preconditioning (RIPC) refers to the implementation of transient ischemic prestimulation in distant organs such as limbs to improve the tolerance of other important target organs to subsequent fatal ischemic injury, which is an effective method to protect tissues and organs from the influence of ischemia–reperfusion (IR). A randomized controlled trial (RCT) demonstrated that the RIPC technique can significantly reduce intraoperative troponin I (cTnI) levels and reduce the incidence of renal impairment, myocardial infarction, and myocardial damage [15]. Wang *et al.* [16] reported that with RIPC via upper limb ischemia, patients undergoing off-pump coronary artery bypass graft surgery require a shorter mechanical ventilation time and a reduction in postoperative myocardial enzyme production and proinflammatory cytokine production. Meybohm *et al.* [17] reported that RIPC had no positive effects on neurocognitive performance, intraoperative myocardial dysfunction, or long-term outcomes in a large group of cardiovascular surgery patients undergoing propofol anesthesia. According to a recent meta-analysis of RCTs, RIPC should not be regularly used in individuals who have undergone cardiac surgery since it was unable to avoid the risk of POD or POCD [18]. Until now, there have been no studies on the clinical value and safety of RIPC treatment on delirium and neurological function in cardiac surgery patients, and there is a lack of good-quality prospective RCTs.

The effectiveness and safety of RIPC are yet unknown due to the special characteristics of cardiac surgery patients. Therefore, we tested the hypothesis that cardiac surgery patients who received RIPC preoperatively would have a better outcome.

Methods

Study Design

A parallel-arm, randomized experiment was carried out in Wuxi Taihu Hospital, Wuxi Minci Hospital, Wuxi People's Hospital, and the affiliated hospital of Jiangnan University (Jiangsu, China) from January 2018 to December 2022. In this investigation, the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) were adhered to [19]. We screened 510 consecutive adult patients aged 18 and older who underwent cardiac surgery and enrolled 488 of these patients. The Wuxi Taihu Hospital's Clinical Research Ethics Committees approved the current study (ethics approval number: 2017-YXLL-0231), which was conducted in full compliance with the Declaration of Helsinki (registration number wxth-2018-009765, date: 09 January 2018). We requested signed informed consent from the involved patient's immediate family members or patients. Patients were allocated by randomization (1:1) to the intervention or control group. Additionally, four cycles of 5 min of ischemia and 5 min of reperfusion of an upper extremity were performed on each patient in the RIPC group. To perform the procedure, the nurse anesthetist used an electronic tourniquet device (Tourniquet 4500 ECL, made by VBM Medizintechnik, Sulz am Neckar, Germany). Five minutes were spent inflating the tourniquet to 200 mmHg, deflating it, and reperfusing it for five minutes. The tourni-

quet was inflated 15 mmHg higher if the patient's systolic blood pressure (SBP) surpassed 185 mmHg. Before entering the operating room, the intervention was carried out, and before making the skin incision, the last ischemia and reperfusion cycle was accomplished. RIPC was performed according to a previous study [20]. In the control groups, the patients received standard preoperative, intraoperative, and postoperative care. Six months after the operation, the last checkup was conducted.

Patients Enrolled in the Study and Sample Selection Procedures

The criteria for inclusion were as follows: (1) 18- to 80-year-old patients; (2) the diagnosis was clear and required cardiovascular surgery; (3) selected at random to receive RIPC or control; and (4) preoperative consciousness was clear and neurological function assessment could be completed. The exclusion criteria were as follows: (1) patients who were unlikely to be salvaged upon admission; (2) age <18 or >80 years old; (3) cognition impairment (montreal cognitive assessment-basic (MOCA-B) test was abnormal); (4) recent acute myocardial infarction, history of stroke or transient ischemic attack, structural brain abnormalities, carotid artery stenosis $>50\%$, left ventricular ejection fraction $<30\%$ left ventricular ejection fraction; (5) severe cervical, chest and abdominal multiple injuries; and (6) multiorgan failure.

Randomization and Concealment

A computerized system used permuted blocks based on an allocation list to generate random numbers (in a one-to-one ratio) using SPSS software (version: 20.0) (SPSS Institute, Hefei, Anhui, China). To maintain the research's integrity and blindness, an independent statistician who was not a part of the study team handled the statistical work. Prenumbered envelopes were utilized to collect data from the random sampling procedure and were maintained at the research center until the investigation was finished. Participants and patients/families were not informed which RIPC/control was being used in the experiment. We gathered details about the patient's demographics, health history, and relevant investigation results.

Blood Samples and Plasma Testing

A preoperative sample and a postoperative sample were taken from the cubital vein. As soon as these samples were collected, they were centrifuged immediately. Plasma S-100b levels were tested in samples that had been held at 80 °C until batch assessment, and neuron-specific enolase (NSE) levels were tested in fresh plasma samples.

Evaluation of Outcomes

A masked independent diagnosis and evaluation committee evaluated all clinical and radiographic data as well as all medical interventions. A member of this committee was a trained researcher who had completed clinical training before the start of the study and was not involved in patient care before the study started. The incidence of hospitalization delirium following surgery served as the primary endpoint. The first postoperative assessment of delirium was performed approximately 24 h after surgery twice daily [21]. The Confusion Assessment Method (CAM) was applied to assess delirium, and the specific approaches corresponded to our earlier research [21]. The secondary endpoints included (1) hospital cerebral infarction detected using computed tomography (CT) and/or magnetic resonance imaging (MRI), (2) 30-day overall mortality, (3) six-month modified Rankins scale (mRS) scores, and (4) NSE levels and plasma S-100b levels.

Safety Evaluation and Complications

Objective signs of tissue or neurovascular damage were among the most frequent RIPC complications. Two physicians and nurses who were blinded to the research protocol conducted a physical exam to confirm all complications, including palpation of distal radial pulses, visual inspection for local edema, erythema, and skin lesions, and palpation for tenderness. Furthermore, for the first 14 days, we monitored the associated complications daily.

Costs and Length of Hospital Stay Following Surgery

We compared the length of hospital stay, length of stay in the ICU, and cost of treatment between the two groups.

Sample Size Estimates

In our preliminary experiment, the primary endpoint showed that 39% of patients in the control group had delirium, compared with 26% of patients in the RIPC group. An alpha of 0.05, 80% statistical power, and 10% loss to follow-up were recorded to calculate the sample size. Then, 444 patients were enrolled (222 per category). In the end, 225 and 223 patients were recruited to the RIPC and control groups, respectively.

Statistical Analysis

Data on baseline conditions and outcomes were input into the database by an experienced research nurse. Information was collected using handwritten forms and then uploaded to a password-protected digital database. Continuous variables are presented as the means with standard deviations. SPSS software was employed to execute all analyses of statistical data. The evaluation of quantitative data was

performed utilizing independent-sample *t* tests. Qualitative data were compared with the chi-square test or Fisher's exact *t* test. The significance level was established at $p < 0.05$.

Results

We screened 510 consecutive adult patients aged 18 and older who underwent cardiac surgery, out of whom 448 were randomly assigned to receive either a control (n = 223) or RIPC treatment (n = 225). Wuxi Taihu Hospital enrolled 149 patients, Wuxi Minci Hospital enrolled 135 patients, Wuxi People's Hospital enrolled 109 patients, and the affiliated hospital of Jiangnan University enrolled 55 patients. Open blindness was not observed during the study period. In addition, the baseline data did not exhibit any significant variation between the two groups (Table 1). After including all patients in the analysis, an intention-to-treat (ITT) analysis was performed (Fig. 1). On 31 May 2023, the last patient chosen at random had their final visit.

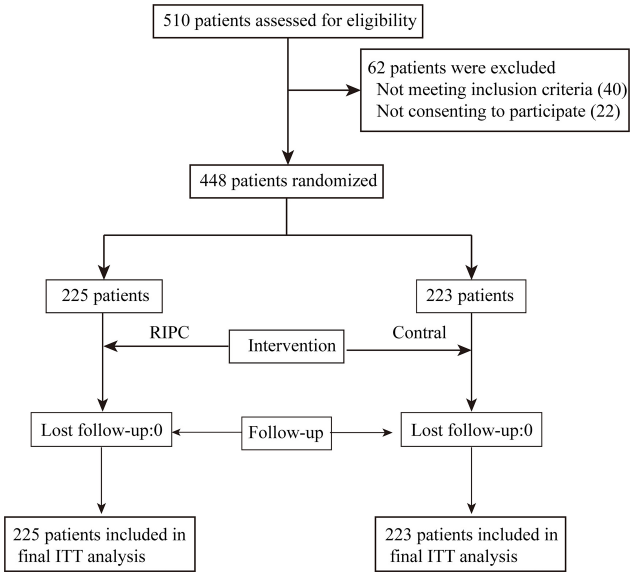


Fig. 1. Trial profile. ITT, intention-to-treat; RIPC, remote ischemic preconditioning.

The Primary Endpoint

For the duration of hospital stay follow-up, 59 (26.22%) RIPC-treated patients and 79 (35.43%) who received the control treatment developed POD, and the difference was statistically significant ($p = 0.035$, Fig. 2).

The Secondary Endpoints

After RIPC treatment, the NSE levels (34.18 ± 7.62 *vs.* 37.81 ± 8.19, $p < 0.001$) and plasma S-100b levels (1529.14 ± 338.08 *vs.* 1726.14 ± 342.15, $p < 0.001$) in the RIPC-treated patients showed significant improvement in contrast to those in the control group (Table 2). Additionally, the RIPC group's incidence of cerebral infarction was considerably lower relative to that in the control group (4.0% *vs.* 9.42%, $p = 0.022$). We found that 30-day overall mortality and six-month mRS scores were similar between the two groups, and the difference was insignificant ($p > 0.05$, Table 2).

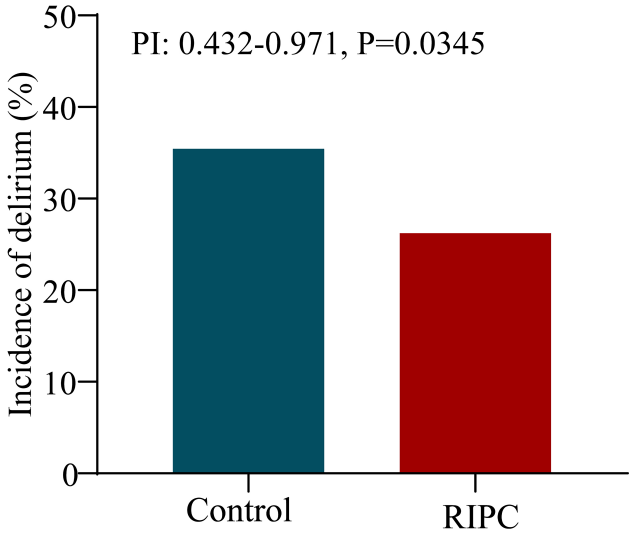


Fig. 2. The primary endpoint.

Safety Assessment

Objective signs of tissue or neurovascular damage were among the most frequent RIPC-related side effects. In seven patients, there was a hematoma at the site of placement of the cuff, but no hemoglobin levels were decreased. There were fifteen cases of transient cyanosis and nine cases of transient erythema following RIPC; no signs of acute limb ischemia were found. Deep vein thrombosis occurred in 21 patients in the RIPC group and 16 patients in the control group (Table 3). The differences in terms of possible side effects between the two groups were insignificant.

Postoperative Hospital Stays and Hospitalization Costs

The average length of stay between the RIPC and control groups differed significantly, with the RIPC group's value being 14.28 days and the control group's being 15.37 days ($p = 0.017$). The RIPC group's hospitalization costs were US$5750, substantially less than that in the control group (US$6410) ($p = 0.024$, Table 4).

Discussion

The study's findings confirm the potential of RIPC to greatly alleviate POD in patients undergoing cardiac surgery. However, RIPC did not improve neurological

Table 1. Comparison of baseline data.

	RIPC Group (n = 225)	Control Group (n = 223)	*p*
Age (Year, mean ± SD)	47.6 ± 10.8	48.2 ± 11.3	0.566
Gender, no. (%)			0.759
Male	132 (58.67%)	134 (60.09%)	
Female	93 (41.33%)	89 (39.91%)	
BMI (kg/cm^2, mean ± SD)	21.2 ± 1.8	21.4 ± 2.0	0.266
Left ventricular ejection fraction <50%, n (%)	47 (20.89%)	43 (19.28%)	0.608
Preoperative medications, n (%)			
Clopidogrel	53 (23.56%)	59 (26.46%)	0.478
Aspirin	225 (100.00%)	223 (100.00%)	1.000
b-blocker	184 (81.78%)	173 (77.58%)	0.269
Angiotension Converting Enzyme (ACE) inhibitor	159 (70.67%)	164 (73.54%)	0.497
Statin	198 (88.00%)	182 (81.61%)	0.060
Systolic blood pressure (mmHg)	122 ± 32.6	121 ± 31.5	0.742
Diastolic blood pressure (mmHg)	74 ± 19.5	73 ± 20.7	0.599
Valve surgery	152 (67.56)	161 (72.20)	0.284
Combined surgery	64 (28.44)	57 (25.56)	0.492
Smoking history, no. (%)			0.340
Yes	109 (48.44%)	98 (43.95%)	
No	116 (51.56%)	125 (56.05%)	
Living environment, no. (%)			0.396
Town	107 (47.56%)	115 (51.57%)	
Countryside	118 (52.44%)	108 (48.43%)	
Past medical history, no. (%)			
Hypertension	173 (76.89%)	161 (72.20%)	0.254
Hyperlipidemia	145 (64.44%)	153 (68.61%)	0.350
Diabetes	95 (42.22%)	87 (39.01%)	0.489
Preoperative biomarker			
NSE levels (ng/mL)	8.95 ± 2.37	9.27 ± 2.44	0.160
S-100b (ng/L)	126.42 ± 35.71	123.39 ± 33.08	0.352
Surgical method			
Coronary Artery Bypass Grafting (CABG)	87 (38.67%)	94 (42.15%)	0.452
CABG & others	44 (19.56%)	38 (17.05%)	0.491
Aortic valve replacement	42 (18.67%)	45 (20.18%)	0.686
Mitral valve replacement	25 (11.11%)	29 (13.00%)	0.538
Tricuspid valve replacement	17 (7.55%)	12 (5.38%)	0.350
Aneurysm repair	10 (4.44%)	5 (2.24%)	0.195
Operation time (min)	257.13 ± 52.17	249.84 ± 49.83	0.131
Aortic clamping time (min)	79.66 ± 18.43	77.48 ± 17.46	0.200
CPB time (min)	114.26 ± 29.65	117.91 ± 31.22	0.205

ACE, Angiotension Converting Enzyme; BMI, body mass index; CABG, Coronary Artery Bypass Grafting; NSE, neuron-specific enolase; CPB, cardiopulmonary bypass.

function after 6 months of follow-up. Interestingly, we found that RIPC can alleviate NSE levels and plasma S-100b levels at early time points, which are biomarkers of nerve damage, and it also decreased hospitalization stay and hospitalization costs. Additionally, the incidence of serious side effects was not increased significantly.

Remote ischemic preconditioning (RIPC) involves intermittent ischemia and reperfusion of the distal organ to protect the target vital organ from subsequent lethal IR injury, and several organs and illnesses have been tested for RIPC [22,23]. Numerous preclinical and clinical studies have demonstrated that RIPC protects the organ [24]. Additionally, little is known about the mechanisms by which RIPC provides organ protection; however, it is involved in neural, humoral, and immunological pathways. Following the RIPC operation, the treated group of rats exhibited superior performance in the water maze test compared to the untreated group, and immunostaining analysis revealed a reduction in the number of nerve cell casualties within the hippocampal region of the treated group

Table 2. Comparison of the secondary endpoints.

	RIPC group (n = 225)	Control group (n = 223)	*p*
NSE levels (ng/mL)	28.46 ± 6.15	31.08 ± 6.79	<0.001
S-100b (ng/L)	998.26 ± 186.17	1213.08 ± 205.19	<0.001
Cerebral infarction	9 (4.0%)	21 (9.42%)	0.022
mRS	0.77 ± 1.52	0.78 ± 1.59	0.501
30-day-overall mortality	7 (3.11%)	5 (2.24%)	0.569

mRS, modified Rankins scale.

Table 3. Comparison of the Safety evaluation.

	RIPC group (n = 225)	Control group (n = 223)	*p*
Hematoma in lower limb	7 (3.11%)	NA	NA
Cyanosis in lower limb	15 (6.67%)	NA	NA
Erythema in lower limb	9 (4.0%)	NA	NA
Deep vein thrombosis	21 (9.33%)	16 (7.17%)	0.407

NA, not applicable.

[25]. Recent research has revealed that the TNF-related apoptosis-inducing ligand (TRAIL) T receptor performs a critical function in the apoptosis of nerve cells, and its expression can be inhibited by RIPC, decreasing the brain infarct volume and neuronal death [26]. According to earlier research, IPC may have multiple neuroprotective effects. First, RIPC locally produces substances that have a protective effect by activating neural pathways that reach brain tissue and then activate receptors within the brain tissue [27,28]. Second, local chemicals or enzyme-linked reactions are generated during ischemia and reperfusion of distal organs, which subsequently traverse the circulatory pathway to activate receptors and facilitate signal transduction, ultimately mediating neuroprotective effects [29]. In the present study, we also found that RIPC can improve neurological function, decrease the incidence of delirium, and improve cerebral infarction. Previous animal studies illustrated that RIPC may modulate inflammatory responses [30], oxidative stress [31], apoptotic processes [32], and neuroprotection [32–34]. The complex interplay between these pathways is thought to be crucial to organ protection. We also found that the levels of the inflammatory factor NSE and plasma S-100b decreased significantly after RIPC treatment in this study.

According to a recent study, POD occurred in 20.55% (52/253) of patients following cardiovascular surgery, and its presence considerably lengthened hospital stays [35]. Following some previous studies, the present findings are valid. Despite several trials searching for treatments or medications to prevent POD, most of these studies had unfavorable outcomes [36–38]. The exact pathophysiologic mechanisms of delirium are not well known, making the diagnosis difficult and thus easily missed or misdiagnosed. The most widely used instrument for identification of delirium is the Confusion Assessment Method (CAM), validated in high quality studies including over 1000 patients with sensitivity of 94%, specificity of 89%, and high interrater reliability [39], which has been used in over 4000 published studies to 2001, and translated into at least 12 languages, has been adapted for use in the ICU [40]. There is increasing evidence that drugs or RIPC can ameliorate early brain injury (EBI), posttraumatic brain injury (TBI) or other acute central nervous system (CNS) diseases by inhibiting apoptosis, ferroptosis, oxidative stress, neuroinflammation, necrosis, necroptosis, and autophagy, which are among the most important public health issues [32,33,41–44]. Wu *et al*. [45] also reported that the effects of hypoxia preconditioning on neuronal loss and hypoxia tolerance in the cerebral cortex of rat's post TBI can be attenuated, and the process primarily involves the induction of Glucose transporter 1 (GLUT1) and Glucose transporter 3 (GLUT3) expression to boost the transportation of glucose. Gasparovic *et al.* [46] reported that there was a significant reduction in the pooled volume of ischemic brain lesions following RIPC after coronary artery bypass grafting, which also indicated that because of the drop in S-100b and NSE levels postoperatively, patients who underwent elective cardiopulmonary bypass (CPB)-assisted coronary artery bypass grafting or valve surgery exhibited favorable responsiveness to upper-limb RIPC [46]. Similarly, this study also approved a large-sample multicenter RCT to validate the clinical significance of RIPC on delirium and neurological function in patients following cardiac surgery, which can decrease postoperative delirium, alleviate nerve injury, decrease hospital costs and hospital stay, and lower cerebral infarctions. Hence, intermittent ischemic treatment of the distal limb or other parts of the body potentially prevents IRI in the brain. RIPC is the result of multipathway, multifactor, and multimolecular interactions, but the precise mechanism of action is yet unknown.

Several limitations were noted in this study, including the fact that it was an RCT conducted in an individual area. As a result, the results may not be generalizable. However, there may be differences in economic level and quality of

Table 4. Comparison of Postoperative hospital stays and costs.

	RIPC (n = 153)	Control (n = 151)	*p*
Hospitalization stays, day, mean ± SD	14.28 ± 4.31	15.37 ± 5.37	0.017
Hospitalization costs, US$ × 10^3, mean ± SD	5.75 ± 2.99	6.41 ± 3.14	0.024

health care in each region. The second limitation is that we only performed a six-month follow-up, and a long-term outcome evaluation may be needed. The study's limited sample size is another drawback. Additional multicenter RCTs need to be conducted in the future to evaluate the therapeutic effects of RIPC in patients undergoing cardiac surgery.

Conclusion

In summary, the findings from our trial provide conclusive evidence that RIPC can decrease the incidence of POD, alleviate nerve injury, and decrease hospital costs and hospital stays after cardiac surgery. Nonetheless, six months postoperatively, there was no significant variation in postoperative cognitive ability between the RIPC and control groups. This finding supports the execution of a large RCT with a functional primary endpoint for RIPC treatment at hospital admission for patients who have undergone cardiac surgery.

Availability of Data and Materials

The study protocol and individual participant data supporting the results reported are available from the corresponding authors upon reasonable request.

Author Contributions

RW performed the experiments and wrote the manuscript. XL, TL, and RW assisted in performing the experiments and prepared all the figures. RW designed the study and revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. These to meet the ICMJE authorship requirement.

Ethics Approval and Consent to Participate

The Wuxi Taihu Hospital's Clinical Research Ethics Committees approved the current study (ethics approval number: 2017-YXLL-0231), which was conducted in full compliance with the Declaration of Helsinki (registration number wxth-2018-009765, date: 09 January 2018). We requested signed informed consent from the involved patient's immediate family members. All patients provided consent for publication.

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Conflict of Interest

The authors declare no conflict of interest.

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