Remote ischemic preconditioning for myocardial protection during single valvular heart surgery: a randomized-controlled trial

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Objectives
This study aimed to investigate the potential of remote ischemic preconditioning (RIPC) in myocardial protection after elective single valve replacement.
Patients and methods
Forty patients were randomized to single valve replacement (mitral or aortic) with RIPC or conventional single valve replacement (control). The RIPC protocol was induced by four (5 min) cycles of upper limb ischemia and (5 min) reperfusion using a blood-pressure cuff. Troponin I level at 30 min preoperatively, 3, 6, 12, and 24 h postoperatively, operative time, the duration of cardioplegia, aortic cross-clamping time, cardiopulmonary bypass time, the length of ICU stay, ventilation time, dose of inotropic support requirements, and hemodynamic parameters (central venous pressure, urine output, and mean arterial pressure) were recorded.
Results
The RIPC group showed a highly significant decrease in serum troponin level at 6, 12, and 24 h postoperatively. There were no significant differences between groups in operative time, duration of cardioplegia, cross-clamping duration, cardiopulmonary bypass time, and hemodynamic parameters. The length of ICU stay and ventilation time showed a nonsignificant decrease in the RIPC group. Total inotropic support in the first 24 h postoperatively showed a highly significant reduction in the RIPC group.
Conclusion
RIPC reduced the total amount of troponin I significantly postoperatively; also, it decreased the inotropic support needed postoperatively and nonsignificantly improved the ventilation time and ICU stay time.

Keywords:
myocardial protection, remote ischemic preconditioning, single valvular heart surgery

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Introduction

Cardiac function is crucial for cardiac surgery. It is, therefore, necessary to find novel approaches to improve cardiac function in cardiac surgery patients [1]. When the coronary supply is interrupted, the size of the resulting infarct is proportional to the duration of ischemia [2]. Cardiac surgery is associated with a certain risk of end-organ ischemia and reperfusion injury [3], which is estimated to be responsible for up to 30% of infarct size [4]. This has led to a search for cytoprotective mechanisms that make the myocardium less vulnerable to such damage [5]. Inducing nonlethal and brief ischemia before the period of prolonged ischemia has been considered a tool for increasing the heart's resistance to ischemia–reperfusion injury [6–8]. Subsequently, preconditioning the heart with ischemia was shown to maintain its cardioprotective abilities even when the nonlethal ischemic stimulus was not applied directly to the targeted tissue, but to any distant site of the organism, hence the idea of [remote ischemic preconditioning (RIPC)] [9]. In cardiac surgery, where the timing of global ischemia and reperfusion periods is predictable, the application of RIPC seemed to be a perfect solution [10]. This technique was used for the first time in pediatric patients undergoing corrective surgery for congenital heart disease, in whom it was shown to reduce troponin release 24 h postoperatively [11]. This study aimed to determine whether RIPC could induce myocardial protection in single valve replacement patients.

Patients and methods

This study was approved by the local ethical committee of Benha University.

Informed written consent was obtained from every patient before enrollment in the study.

To investigate the potential of RIPC on myocardial protection after elective single valve replacement

(mitral or aortic), we conducted a prospective, randomized, controlled, double-blind study comparing valve replacement with RIPC vs. conventional valve replacement (control). In the RIPC group, the RIPC protocol was induced by four cycles of upper limb ischemia and reperfusion using a blood-pressure cuff over the patient's arm inflated to a pressure 15 mmHg higher than the systolic arterial blood pressure. The duration of each cycle was 5 min. This technique was started after induction of anesthesia to be finished from 5 to 10 min before initiation of bypass. In the control group, patients underwent sham placement of the blood-pressure cuff around the upper arm without inflation.

Patients were randomized using an online randomization program (http://www.randomizer.org/) and concealed using sealed, opaque envelopes. The allocation was shown by the operating surgeon by opening the top envelope before surgery. Patients and data collectors not present in the operating theater were blinded to assignment of patients.

Patients with airway and/or parenchymal lung disease, severe pulmonary hypertension requiring vasopressor support before induction, immunodeficiency, hematological disorders, hepatic or renal impairment, pregnancy, morbid obesity, diabetic, patients with myocardial ischemia or infarction, patients with peripheral vascular disease, and patients receiving drugs that interfered with the mechanism of RIPC, i.e. sulfonylureas, nicorandil, or propofol were excluded from the study.

In the preoperative room, an intravenous line was inserted and midazolam (0.01–0.02 mg/kg) was administered to all patients; then, the arterial line was inserted. Patients were transported to operative room and routine monitoring was performed. Anesthesia was induced with thiopental (4–7 mg/kg), pancuronium bromide 0.08 mg/kg, and fentanyl 10 mcg/kg. After adequate preoxygenation, a suitable-size endotracheal tube was inserted. Anesthesia was maintained with inhaled isoflurane 1 MAC in 100% oxygen and top-up doses of pancuronium bromide 0.02 mg/kg every 30 min. All patients underwent the surgical procedure using standard cardiopulmonary bypass techniques with blood cold cardioplegia. None of the patients studied received perioperative steroids.

The primary outcome measure was the troponin I level measured at the following intervals: 30 min before the operation, and 3, 6, 12, and 24 h postoperatively.

The secondary outcomes included operative time (measured from induction of anesthesia till skin closure), duration of cardioplegia (measured from application of cardioplegia till aortic declamping), aortic cross-clamping time (time from application of the aortic clamp till aortic declamping), cardiopulmonary bypass time (time from connecting the patient to extracorporeal circulation till termination of cardiopulmonary bypass by re-establishing the normal physiological function of the heart), length of ICU stay (time from the arrival of the patient to the ICU till transferring the patient to the ward), ventilation time (time from connecting the patient to the ICU ventilator till extubation), dose of inotropic (adrenaline) support requirements: inotropic support at each time was quantified by calculating the inotropic (adrenaline support, hemodynamic parameters (central venous pressure and mean arterial blood pressure), and urine output measured every 2 h for 24 h postoperatively.

Statistical analysis

Statistical analysis was carried out using the SPSS (version 16; SPSS Inc., Chicago, Illinois, USA). Descriptive variables are presented as means and SD and compared using the unpaired Student *t*-test. Categorical data are expressed as numbers and percentage and compared using the χ^2-test. A *P*-value less than 0.05 was considered statistically significant, whereas a *P*-value less than 0.01 was considered statistically highly significant. On the basis of a pilot study of the first eight patients, the sample size was calculated using G*power (version 3.1.7; Universitat Kiel, Kiel, Germany) to a power of 80% and a two-sided α error of 0.05. The effect size was 0.925. We estimated that 20 patients would be required per group.

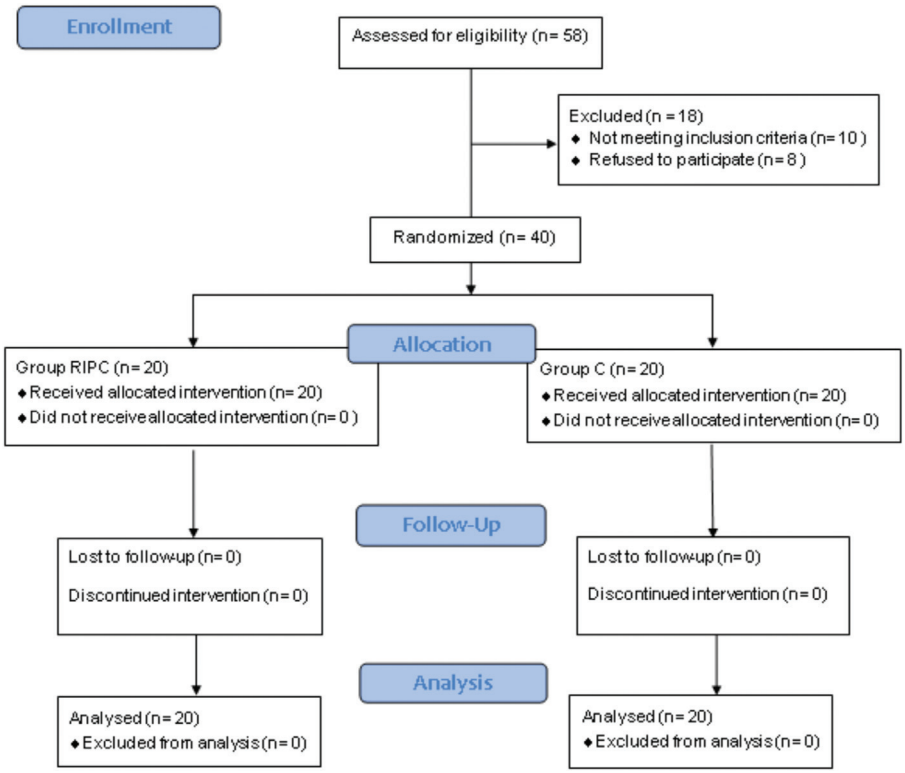
Results

Between February 2011 and December 2014, all patients referred for elective single valve replacement (mitral or aortic) at Benha University hospitals were invited to participate in our trial. Eight patients refused to participate, 10 were excluded (fulfilled the exclusion criteria), and 40 patients were allocated randomly to either one of two groups: group RIPC (20 patients) or group C (20 patients). All patients received the intended treatment, completed the study protocol, and were included in the analysis (Fig. 1).

There were no significant differences between groups in the demographic characteristics of the patients (Table 1).

Serum troponin level in blood showed a highly significant decrease at 6, 12, and 24 h postoperatively

Figure 1



Consort flow diagram. RIPC, remote ischemic preconditioning.

in the RIPC group in comparison with group C (Table 2).

There were no significant differences between groups in operative time, duration of cardioplegia, cross-clamping time, and cardiopulmonary bypass time (Table 3).

Duration of ICU and ventilation time showed a nonsignificant decrease in the RIPC group in comparison with group C (Table 4).

Total inotropic support in the first 24 h postoperatively showed a highly significant reduction in the RIPC group compared with group C (Table 4).

The hemodynamic parameters showed nonsignificant changes between groups (Figs 2–4).

Table 1 Demographic characteristics of patients [mean±SD and *n* (%)]

	Group RIPC	Group C	*P*-value
Age	39.3±10.75	36.1±8.05	0.29
Sex			
♂	9 (45)	8 (40)	0.75
♀	11 (55)	12 (60)	
Weight (kg)	70.25±17.02	70.4±11.3	0.97
Height (cm)	166.7±15.57	169.9±4.7	0.09
ASA			
II	8 (40)	7 (35)	0.74
III	12 (60)	13 (65)	

RIPC, remote ischemic preconditioning.

Table 2 Comparison of groups in terms of the serum troponin level (mean±SD)

	Group RIPC	Group C	*P*-value
Preoperatively	0.01±0	0.01±0	0.15
Postoperatively (h)			
3	3.37±1.85	4.2±1.87	0.15
6	3.12±1.47	5.39±1.23	<0.001**
12	2.61±0.99	4.97±1.62	<0.001**
24	2.03±1.06	4.91±1.91	<0.001**

RIPC, remote ischemic preconditioning. **Highly significant.

Discussion

This study shows the myocardial protective effects of RIPC in patients undergoing single valve replacement through decreasing the serum troponin level postoperatively, also reducing the inotropic support needed postoperatively for these patients and improving the ventilation time and ICU stay time. For serum troponin, this study is in agreement with that of Xie *et al.* [1], who found that there was a significant reduction in serum troponin I concentrations in patients treated with RIPC postoperatively, and also consistent with Venugopal *et al.* [12], who found that RIPC decreased perioperative troponin T release during the 72 h after

Table 3 Comparison of groups in the intraoperative measurement (mean±SD)

	Group RIPC	Group C	*P*-value
Operative time (min)	237.5±21.67	244.25±26.72	0.385
Time of cardioplegia (min)	45±15.39	48.5±15.65	0.48
Cross-clamping time (min)	62.5±19.63	76±25.37	0.068
Cardiopulmonary bypass time (min)	91.5±24.28	95.25±16.1	0.57

RIPC, remote ischemic preconditioning.

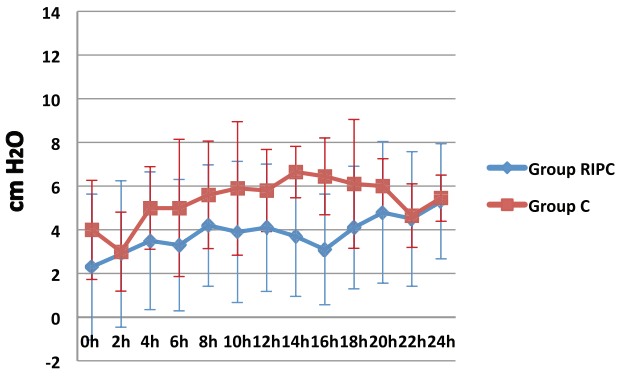
Table 4 Comparison of groups in intensive care unit measurements (mean±SD)

	Group RIPC	Group C	*P*-value
ICU time (h)	51±4.96	56.3±11.71	0.07
Ventilation time (h)	6.1±1.74	6.7±0.92	0.18
Adrenaline (ng/kg/min)	55.76±17.29	81.86±19.17	0.001**

RIPC, remote ischemic preconditioning. **Highly significant.

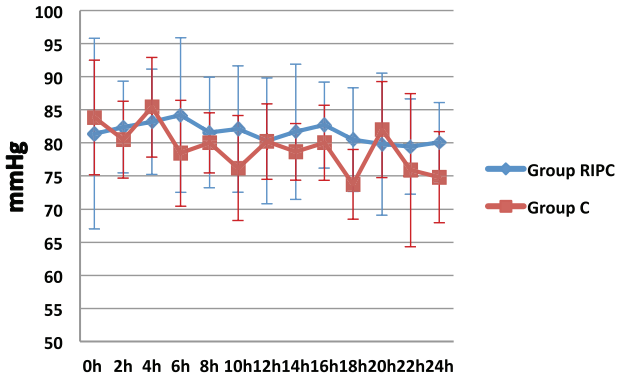
cardiac surgery. The present study is also consistent with the study of Venugopal *et al.* [13], who found that the area under the curve showed a decrease of 41%, and also consistent with Choi *et al.* [14], who found that RIPC reduces creatine kinase isoenzyme MB significantly postoperatively. This study is also in agreement with that of Cheung *et al.* [11], who concluded that there was a significant decrease in serum troponin postoperatively. However, our results in contrast to those of Hong *et al.* [15], which may be because of the use of the off-pump technique. Also, our results are in contrast to those of Rahman *et al.* [16], which may be because there is an argument in terms of the site of origin and significance of troponin release during on-pump cardiac surgery. Troponin release may be indicative of myofibrillar damage and myocyte necrosis or changes in sarcolemmal permeability with leakage from cytosolic pools. RIPC may protect against necrosis-related but not cytosolic release of troponin. Also, our results are in contrast to those of Li *et al.* [17], which may be because of less irreversible cardiocyte injury in valve replacement. In addition, the cTnI release reached the peak concentration half an hour later, rather than hours later reported in the literature. Also, our results are in contrast to those of Karuppasamy *et al.* [18], who found that patients undergoing CABG surgery RIPC do not receive myocardial protection and there was no association with changes in cytokines. This may be because of the use of only three cycles during RIPC, which perhaps did not induce the release of enough mediators to prepare the cardiac muscle. Our results are also in contrast to those of Wagner *et al.* [19], which may be because late-RIPC has a weaker effect than early RIPC.

Figure 2



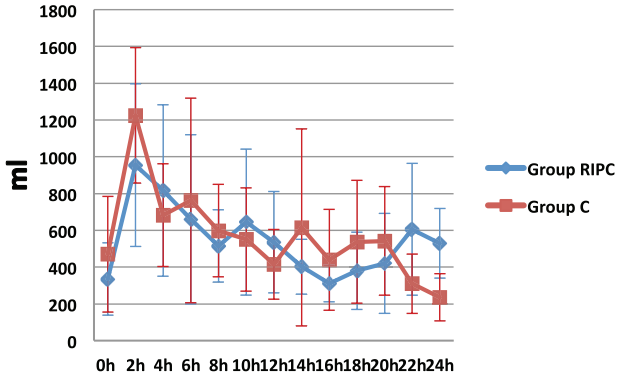
Comparison of groups in terms of central venous pressure. RIPC, remote ischemic preconditioning.

Figure 3



Comparison of groups in terms of mean arterial pressure. RIPC, remote ischemic preconditioning.

Figure 4



Comparison of groups in terms of urine output. RIPC, remote ischemic preconditioning.

In terms of the changes in ICU stay time and ventilation time, many studies [11,15–17,19–22] have documented that there was a nonsignificant difference in ICU stay time and ventilation time, which is consistent with our study. Our study is in contrast to that of Choi *et al.* [14], which may be

because RIPC is more efficient in protecting organs under direct and overt ischemia–reperfusion insult, resulting in organ damage associated with marked proinflammatory and oxidative stress, which leads to improvements in the recovery of the patients and reduction of ICU stay time.

In terms of the inotropic support requirements, this study is consistent with those of Cheung *et al*. [11], Luo *et al*. [20], and Wu *et al*. [22], who found that there was a significant reduction in inotropic support post operatively. Our study is in contrast to those of Thielmann *et al*. [21], Choi *et al*. [14], and Li *et al*. [17], who found that there was a nonsignificant decrease in inotropic support requirement postoperatively. This is may be because the mean age of the patients in this study is lower than that in these studies and different types of operation of this study made the RIPC protocol more effective in decreasing the inotropic requirement.

Conclusion

RIPC by upper limb brief ischemia and reperfusion reduced the total amount of troponin I significantly postoperatively; also, it decreased the inotropic support needed postoperatively and led to a nonsignificant improvement in the ventilation time and ICU stay time.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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