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Implications of Remote Ischemic Preconditioning on Liver Function in Adults Undergoing Cardiac Surgery: Randomized Controlled Trial

Running title: Remote Ischemic Preconditioning on Liver Function in Adults Cardiac Surgery
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Eligibility of the study:
This prospective, double-blinded, randomized controlled clinical study was conducted at Assiut University Hospitals in the Cardiothoracic Surgery Theater and postoperative ICU, after receiving approval from the Medical Ethics Committee, Faculty of Medicine, Assiut University, Assiut, Egypt under the number (IRB 17200518) and ClinicalTrials.Gov registration ID:(NCT04647370). All participants signed a written informed consent before inclusion. The study followed the ethics and guidelines of the Declaration of Helsinki.
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Abstract

Background: Many therapeutic strategies for protection against ischemic reperfusion and one of them is Remote ischemic preconditioning (RIPC) which is an alternative to ischemic conditioning but it has not yet been extensively studied. While RIPC may attenuate myocardial injury during cardiac surgery, its beneficial effects on different organs are still unclear. We hypothesized that RIPC would improve postoperative liver function in adults undergoing cardiac surgery.

Materials and Methods: 90 patients undergoing on-pump cardiac surgery were randomly assigned to two groups. Group A (study group, 45 patients) received RIPC, while Group B (control group, 45 patients) received a pseudo-RIPC. The primary outcome was RIPC on liver function, while secondary outcome was its effect on renal function.

Results: There was an insignificant difference between the two groups regarding the primary outcome, measured by liver function tests (Alanine aminotransferase (ALT)- Aspartate aminotransferase (AST)-Alkaline Phosphatase (ALP), albumin, Bilirubin (total, direct, and indirect) or clinical indicators such as jaundice, encephalopathy, and bleeding tendency. With respect to renal function, there was an insignificant difference in serum level of blood urea nitrogen (BUN) and creatinine between the two groups, except for on the 3rd postoperative day as serum creatinine and BUN were significantly lower in the RIPC group.

Conclusions: Our study demonstrates that in adults undergoing on-pump cardiac surgery, RIPC did not provide a significant beneficial effect in terms of liver or renal function outcomes, except for significantly lower kidney function tests in the RIPC group on day three postoperatively.

Keywords: RIPC, Liver function, Adult cardiac surgery.

Introduction:

During on-pump cardiac surgery, Ischemic injury and reperfusion is frequent in organs other than the heart and is associated with increased morbidity, hospital stay, and mortality [1-3]. CardioPulmonaryBypass (CPB) is a source of metabolic and physiological stress on the liver as catecholamines which are released upon the start of (CPB) decrease hepatic arterial flow and hepatic perfusion[4]and as we know the liver receives a double supply from the portal system and hepatic artery. This explains the liver's ability to be resistant to necrosis from hypoperfusion as it extracts about 95% of oxygen from the blood [5].

Multiple theories tried to explain the pathophysiology of postoperative liver dysfunction one of them can be explained by cell ischemia and necrosis from ischemic reperfusion injury [6]. Also, many drugs which are given perioperatively may cause hepatic damage[7] and alterations in hemodynamics, this may be reflected in a transient liver dysfunction typically peaking on third postoperative day. The severity varies widely from transient liver dysfunction to fulminant liver failure, especially with prolonged CPB time[8].

Studies for the protection of vital organs to avoid ischemic perfusion damage are not standardized yet. However, Remote ischemic preconditioning (RIPC) was applied by **Schmidt et al** during cardiac ischemia in form of cycles of ischemia for short periods then reperfusion is allowed in organs away

from the heart and is considered a beneficial technique to attenuate ischemic reperfusion injury in vital organs[9],[10].

However, RIPC was developed to protect the myocardium against ischemic reperfusion Injury; its benefits have been demonstrated in organs such as kidneys, liver, and lungs. Nowadays, increasing evidence of the RIPC effect in attenuating ischemic injury in the myocardium in cardiac surgery[11, 12]. But, the beneficial role on different organs during cardiac surgery needs further investigations[13, 14] In this study we hypothesized RIPC would improve postoperative liver function in adults undergoing cardiac surgery

Materials and Methods:

Patients of both sexes, aged 18 to 70 years, who were candidates for on-pump cardiac surgery were included in the study. Patients who refused or asked for withdrawal at any time during the study or with any cause of potential liver dysfunction (including right-side heart failure, gallbladder diseases, hepatitis), pregnancy, history of neuropathy or vasculopathy of the extremities, prolonged cardiopulmonary bypass (CPB) time of more than 120 minutes, and previous cardiac surgery were excluded from the study.

Study design and randomization: 90 patients undergoing on-pump cardiac surgery were randomly allocated (using a computer-generated table) into one of two groups (45 patients per group).

Allocation: group assignment was kept in well-sealed opaque envelopes which were opened by the researcher only after patient enrollment. Participants, data collectors in the ward, and the ICU staff were all blinded to the group assignment. As this trial is a protocol-based process, the treating clinicians could not be blinded to the trial arm allocation.

1. Group A (Study group, 45 patients): RIPC was performed, consisting of three cycles of 5-minute inflation of a blood pressure cuff to 200 mmHg (or at least 50 mmHg higher than the systolic arterial pressure) on one arm, followed by 5 minutes of reperfusion with the cuff deflated.
2. Group B (Control group, 45 patients): A pseudo-RIPC intervention was performed, consisting of three cycles of one-arm pseudo-ischemia (5-minute blood pressure cuff inflation to 20 mmHg, followed by 5 minutes of cuff deflation.

Outcomes: the effect of RIPC on liver function as a primary outcome and on renal function as a secondary outcome.

Anesthetic technique: Preoperative visits and assessments were routinely applied to all our patients, and a peripheral intravenous (IV) line was inserted in all patients. Premedication was administered via IV midazolam (2-3 mg).

Upon admission to the operating theater, we started with standard monitoring, including a 5-lead ECG, pulse oximetry, and non-invasive blood pressure monitoring. An arterial line was inserted under local anesthesia (2 ml of lidocaine 2%) using complete aseptic conditions. Preoxygenation for 3 minutes, followed by induction using opioid: fentanyl (1-2 µg/kg), IV anesthetic: propofol (2 mg/kg), and muscle relaxant: atracurium (0.5 mg/kg).

After intubation with appropriate size endotracheal tube and fixed at an appropriate length, and mechanical ventilation was initiated using volume control ventilation with parameters adjusted according to the patient's body weight. Capnography and a temperature probe were connected, and central venous and urinary catheters were inserted under aseptic conditions. The patient was in the supine position, with padding to protect bony prominences.

Maintenance of anesthesia with sevoflurane in an oxygen/air mixture, along with continuous infusions of opioid: fentanyl (1-2 µg/kg/hr) and muscle relaxant: atracurium (0.005-0.01 mg/kg/min).

Before skin incision, RIPC was performed in Group A, and in Group B, a pseudo-RIPC intervention was performed as outlined above. After skin incision and before sternotomy a bolus dose of fentanyl

was administered as needed.
Before cannulation and the initiation of CPB, 400 units/kg Heparin was given, with activated clotting time (ACT) monitoring. If ACT exceeded 400 seconds, vascular lines were secured, and CPB was initiated.
The perfusionist gradually increased pump flow to 2-2.5 L/min/m², aiming for a mean arterial pressure of 60-70 mmHg.After initiation of CPB and aortic cross-clamp, the cold potassium cardioplegia was administrated in a dose of 20 ml /kg every 30 minutes.
Monitoring of CPB was targeting perfusion in form of mean arterial blood pressure of 60 to70 mm Hg, normal acid-base balance, accepted hematocrit values, less than 200 mg/dL blood glucose levels, temperature management according to type and length of surgery, and follow up ACT and adjust the dose of heparin accordingly. Anesthesia during CPB was maintained via total intravenous anesthesia (TIVA) with IV anesthetic: propofol (50-100 µg/kg/min), opioid: fentanyl (1-2 µg/kg/hr), and muscle relaxant: atracurium (0.005- 0.01 mg/kg/min).
Weaning from CPB after finishing the surgical procedure, after confirming that the accepted body temperature was 37°C, and the heart rhythm was stable (usually 80–100 beats/min). Laboratory values were checked to ensure they were within acceptable limits, including normal pH, ionized calcium, potassium, and hematocrit. Adequate ventilation with 100% oxygen was resumed, and all monitors were rechecked.
After weaning from CPB, bleeding was controlled, bypass cannulas were removed, and anticoagulation was reversed using protamine (1 mg of protamine per 100 units of heparin), administered slowly over 5–10 minutes. The ACT was monitored to ensure it returned to baseline following protamine administration. Once hemostasis was judged acceptable and the patient remained hemodynamically stable, the chest was closed.
Transportation to postoperative I.C.U: the patient was transported sedated, intubated, and mechanically ventilated under standard monitoring to the postoperative ICU.
Data collection in the form of Demographic data and clinical data: Age-sex-body mass index(BMI) – DM -hypertension-renal impairment-viral serology (HBV-HCV)
Preoperative data: baseline laboratory investigations (Alanine aminotransferase (ALT)- Aspartate aminotransferase (AST)-Alkaline Phosphatase (ALP)- Albumin-Bilirubin(total, direct and indirect) – serum creatinine –BUN)
Intraoperative data: type of surgery (Coronary artery bypass graft (CABG) or valve replacement or both), Time for (Aortic cross-clamping – CardioPulmonaryBybass(CPB)– Operation)
Post-operative data : clinical signs of liver cell failure: Jaundice–Bleeding tendency–Encephalopathy and laboratory investigations for 3 days :((ALT)- (AST)-(ALP)- Albumin-Bilirubin(total, direct and indirect) –serum creatinine –BUN)
Sample Size: Drawing from the findings of a previous study [8].the mean ±SD of total bilirubin on the 3rd postoperative day after (CABG) surgery was found to be 1.2±0.4. Based on a power of 80% and a confidence level of 95%, the required sample size was calculated as 44 per group, considering that a 20 % reduction in total bilirubin was clinically relevant so we enrolled 45 patients per group.
Statistical analysis: we used SPSS (version 27) for data collection and analysis. We utilized The Kolmogorov-Smirnov test and the Shapiro test to evaluate the distribution of data normality and all data were not normally distributed. Categorical variables were described by number and percent (No., %) whereas continuous variables were described by mean ± standard deviation "SD" or median (interquartile range “Q1-Q3”). Chi-square test and Fisher exact test were used to compare categorical variables between the two groups where comparing between continuous variables by the Mann–Whitney U test for nonparametric variables. A two-tailed $p < 0.05$ was considered statistically significant.

Results:

120 patients were undergoing on-pump cardiac surgery, and 30 of them didn't meet our inclusion criteria and were excluded, Figure 1 demonstrates the CONSORT flow diagram with the 90 patients who completed the study.

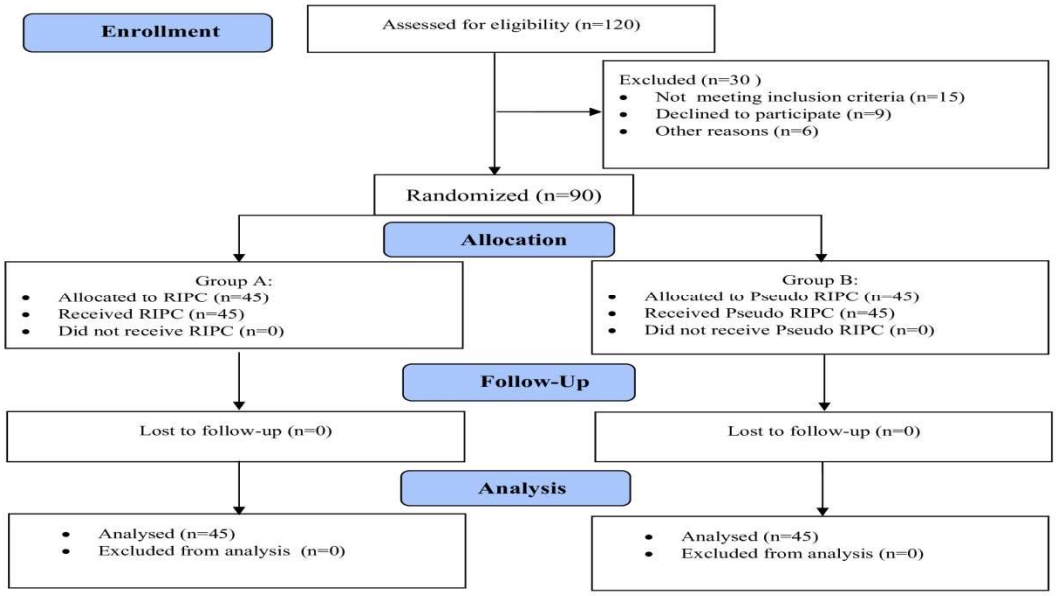

Figure1:CONSORT flow diagram

Both groups had non-significant differences regarding demographic and baseline clinical data (age, sex, BMI, DM, Hypertension, renal impairment, viral serology(HBV, HCV)) as shown in (Table 1). Also, as regards as type of surgery and intraoperative data as time for cross-clamp and CPB time and total operative time in both groups had non-significant differences as shown in (Table 2)

Table 1: Demographic data and baseline clinical data between two groups:

	Group A(n=45)	**Group B(n=45)**	**P. value**
Age (Years) Mean ± SD	50.64±10.85	50.47±11.24	0.868
Sex			
Male	26(57.8%)	29(64.4%)	0.517
Female	19(42.2%)	16(35.6%)	
BMI Mean ± SD	27.95±5.71	27.58±4.04	0.900
DM			
Yes	10(22.2%)	10(22.2%)	1.000
No	35(77.8%)	35(77.8%)	
Hypertension			
Yes	15(33.3%)	12(26.7%)	0.490
No	30(66.7%)	33(73.3%)	
Renal impairment			
Yes	0(0%)	3(6.7%)	0.078

No	45(100%)	42(93.3%)	
Serology (HBV, HCV) -ve +ve	 45(100%) 0(0%)	 45(100%) 0(0%)	-

Group A (study group), Group B (control group), Data are presented as number (%) and mean ±SD or median and IQ range, P value < 0.05 is considered statistically significant.BMI for body mass index, DM for diabetes mellitus, HBV for hepatitis B virus, and HCV for hepatitis C virus.

Table 2: Type of surgery and intraoperative data between two groups:

	Group A(n=45)	**Group B(n=45)**	**P. value**
Type of surgery: CABIG Valve replacement CABIG, Valve replacement	 16(35.6%) 29(64.4%) 0(0%)	 23(51.1%) 20(44.4%) 2(4.4%)	0.086
Aortic cross-clamp time Mean ± SD	87.62±10.91	89.73±10.01	0.358
CBP time Mean ± SD	105.04±11.52	106.2±10.55	0.692
Operative time Mean ± SD	6.4±0.99	6.38±1.11	0.902

Group A (study group), Group B (control group), Data are presented as number (%) and mean ±SD or median and IQ range, p-value < 0.05 is considered statistically significant.CABIG for Coronary artery Bypass Graft surgery, Aortic cross-clamp time presented in minutes, CPB for cardiopulmonary bypass and presented in minutes, Operative time presented in hours

As regards liver function tests: both groups had insignificant differences regarding preoperative baseline and first 3 days of postoperative liver function tests (AST, ALT, ALP, Albumin, Bilirubin (total, direct, and indirect) as shown in(Table 3) and regarding postoperative liver dysfunction: both groups had insignificant differences regarding postoperative clinical signs of liver dysfunction in form of jaundice, encephalopathy, and bleeding tendency as shown in (Table 4). For Renal function tests: both groups had insignificant differences regarding preoperative baseline,1st and 2nd postoperative day kidney function tests (Creatinine, BUN). But as regards as 3rd postoperative day there were statistically significantly lower in RIPC group (group A) than in group B as shown in (Table 5)

Table 3: liver function tests between two groups:

	Preoperative		**Day 1**		**Day 2**		**Day 3**	
	Group A	**Group B**	**Group A**	**Group B**	**Group A**	**Group B**	**Group A**	**Group B**

	(n=45)	(n=45)	(n=45)	(n=45)	(n=45)	(n=45)	(n=45)	(n=45)
AST								
Mean±SD	22.76±6.37	23.37±11.54	82.49±40.84	66.56±25.59	84.22±55.84	61.47±22.33	77.02±54.46	57.02±22.04
P. value	*0.569*		*0.140*		*0.110*		*0.419*	
ALT								
Mean±SD	22.47±7.45	22.21±12.64	54.96±25.83	56.87±24.23	48.44±26.17	54±25.11	41.24±19.85	49.02±24.66
P. value	*0.460*		*0.616*		*0.288*		*0.099*	

ALP								
Mean ± SD	95.18 ± 36.81	98.13 ± 41.25	96.84 ± 28.23	92.31 ± 25.46	97.71 ± 27.07	87.36 ± 23.99	92.64 ± 33.09	86.04 ± 38.35
P. value	*0.774*		*0.916*		*0.121*		*0.272*	
Albumin								
Mean ± SD	4.1 ± 0.36	3.94 ± 0.49	3.78 ± 0.49	3.7 ± 0.49	3.6 ± 0.29	3.56 ± 0.49	3.74 ± 0.5	3.58 ± 0.46
P. value	*0.113*		*0.577*		*0.533*		*0.098*	
Tot								

albilirubin								
Mean ± SD	0.66 ± 0.19	0.65 ± 0.24	0.81 ± 0.2	0.88 ± 0.26	0.78 ± 0.27	0.83 ± 0.27	0.82 ± 0.47	0.82 ± 0.29
P. value	*0.587*		*0.146*		*0.231*		*0.211*	
Indirectbilirub								

in								
Mean ± SD	0.5 ± 0.16	0.48 ± 0.19	0.58 ± 0.2	0.68 ± 0.29	0.56 ± 0.24	0.64 ± 0.28	0.56 ± 0.34	0.61 ± 0.24
p. value	*0.507*		*0.090*		*0.133*		*0.090*	
Direct bilirubin								
Mean ± SD	0.17 ± 0.07	0.17 ± 0.07	0.22 ± 0.08	0.2 ± 0.06	0.22 ± 0.1	0.21 ± 0.08	0.26 ± 0.25	0.21 ± 0.11
P. va	*0.897*		*0.214*		*0.584*		*0.675*	

l u e				

Group A (study group), Group B (control group), Data are presented as number (%) and mean ±SD or median and IQ range, P value < 0.05 is considered statistically significant. AST for Aspartate aminotransferase(U/L) (0-34), ALT for Alanine aminotransferase (U/L)) (0-45), ALP for alkaline transferase (U/L)(46-116), Albumin in (mg/dl)(3.5-5.5)and Total bilirubin in (mg/dl) (0.2-1), indirect bilirubin in (mg/dl)(.2-.8) *and direct bilirubin in (mg/dl)*(0-0.2)*).*

Table 4: postoperative clinical signs of liver dysfunction between two groups:

	Group A (n=45)	**Group B (n=45)**	**P. value**
Jaundice Yes No	 2(4.4%) 43(95.6%)	 3(6.7%) 42(93.3%)	0.645
Encephalopathy Yes No	 2(4.4%) 43(95.6%)	 3(6.7%) 42(93.3%)	0.645
Bleeding tendency Yes No	 7(15.6%) 38(84.4%)	 10(22.2%) 35(77.8%)	0.419

Group A (study group), and Group B (control group), Data are presented as numbers (%), and a p-value < 0.05 is considered statistically significant.

	Preoperative		**Day 1**		**Day 2**		**Day 3**	
	Group A (n=45)	**Group B (n=45)**	**Group A (n=45)**	**Group B (n=45)**	**Group A (n=45)**	**Group B (n=45)**	**Group A (n=45)**	**Group B (n=45)**
Creatinine								
Mea	0.	0.	0.	0.	1.	0.	0.	0.

n ± SD	89 ± 0.21	83 ± 0.21	99 ± 0.24	92 ± 0.15	34 ± 1.87	87 ± 0.17	77 ± 0.3	85 ± 0.22
P. value	*0.577*		*0.340*		*0.566*		***0.006***	
BUN								
Mean ± SD	14.01 ± 4.54	13.78 ± 6.02	17.68 ± 4.35	15.95 ± 5.75	16.39 ± 4.11	16.01 ± 4.21	12.94 ± 2.27	17.24 ± 9.37
P. value	*0.733*		*0.098*		*0.674*		***0.048***	

Table 5: Renal function tests between two groups:

Group A study group, and Group B control group, data are presented as mean ±SD, Median (Q1-Q3), p-value < 0.05 is considered statistically significant.Creatinine in (mg/dl)(0.6-1.2), BUN for blood urea nitrogen in (mg/dl)(6-24)

Discussion:

This study's goal is to detect the benefits of remote ischemic preconditioning (RIPC) on functions of the liver and kidney in on-pump cardiac surgery patients. Our results demonstrated an insignificant difference between the two groups in all extracted data, except for a statistically significant reduction in serum creatinine and blood urea nitrogen (BUN) levels on third postoperative day in the RIPC group.

The study's primary outcome, which focused on liver function, showed insignificant differences between groups in terms of liver-related laboratory markers (AST, ALT, ALP, Albumin, and bilirubin) or clinical manifestations of liver dysfunction (such as jaundice, encephalopathy, and bleeding tendencies).

This finding suggests that, despite the well-known myocardial protective effects of RIPC, it may not extend to hepatic protection, at least in the context of our study. Several factors may explain this outcome. First, the liver may not be as responsive to RIPC as the myocardium due to its unique vascular anatomy and metabolic processes. While RIPC is thought to trigger endogenous protective

mechanisms, the liver's response to ischemia and reperfusion injury could be different from the heart's, which may account for the lack of benefit in liver function in this cohort.

Czigány, Turóczi, et al. showed that RIPC protected the liver in a model of rat from ischemic reperfusion injury and lower levels of liver enzymes in the RIPC group [15]. So the aim was to determine whether similar results could be replicated in our study.

Our findings indicate insignificant differences between two groups as regards as liver enzymes (AST, ALT, ALP), which were elevated in both groups but showed insignificant differences. Similarly, total, direct, and indirect bilirubin levels were elevated in both groups without significant differences. Both groups also exhibited decreases in albumin, again with no significant difference. Clinically, insignificant differences between two groups in form of jaundice, encephalopathy, or bleeding tendency

In line with **Hu Luo et al.** who studied (RIPC) role in surgeries for valve replacement, using biomarkers of liver injury (AST, ALT, and albumin). They found that postoperative levels of liver enzymes (AST, and ALT) significantly increased in two groups. While serum albumin levels decreased markedly. But, postoperative levels of total bilirubin were lower in the group of RIPC[16].

Postoperative hyperbilirubinemia and elevated liver enzymes in cardiac surgery patients are common. A marked increase in liver biomarkers (bilirubin, AST, and ALT)was noted on third postoperative day but the exact explanation of postoperative liver dysfunction remains to be explained [17-19].
Similarly, secondary outcome in our study related to renal function, except for the observed lower serum blood urea nitrogen and creatinine on the third postoperative day in the RIPC group, did not show a significant difference. This reduction in serum BUN and creatinine suggests a potential benefit of RIPC in minimizing acute kidney injury (AKI).
A possible explanation for this finding is that RIPC may attenuate renal ischemia-reperfusion injury, as the kidneys are at high risk of oxidative stress and inflammatory responses during on-pump cardiac surgery. In line with existing literature that has suggested a protective role for RIPC in reducing the incidence of AKI in cardiac surgery patients [20].

Meanwhile no clear or consistent evidence across studies., **Walsh, Whitlock, et al** who studied RIPC in cardiac surgery risky patients, and **Hausenloy, Candilio et al.** who studied RIPC outcomes in Cardiac Surgery patients, both concluded that RIPC had insignificant differences in postoperative serum creatinine levels [21, 22], **Benstoem, Stoppe, et al**., who studied (RIPC) in coronary artery bypass grafting (CABG) surgery either alone or with valve replacement, along with **Hu, Luo et al**. in valve replacement surgery, and **Pinaud, Corbeau, et al**. in surgery for the aortic valve, RIPC did not demonstrate significant renal protective effects. Their studies reported insignificant differences in AKI incidence. [16, 23, 24]

Many studies have targeted a therapeutic approach to reduce the acute kidney injury incidence in cardiac surgery patients using various techniques of (RIPC), but the outcome has been quite inconsistent. Most serum laboratory biomarkers that are used for detection of acute kidney injury depend primarily on glomerular filtration rate (GFR), which can be affected by hemodynamics alteration, and volume status during the perioperative period.

The study's findings raise important questions about the broader applicability of RIPC in protecting organ systems other than the heart. While RIPC has shown promise in reducing myocardial injury, its effect on different organs, particularly the liver, remains uncertain.

In terms of clinical implications, the observed reduction in serum creatinine and BUN in the RIPC group suggests that this technique may have a modest benefit in preventing postoperative AKI. This finding warrants further investigation. Larger, multi-center trials with extended follow-up may help clarify the long-term impact of RIPC on renal function and determine if it can be a useful adjunctive therapeutic approach to prevent AKI in risky patients.

Limitations: our limitations of this study include that while the reduction in creatinine and BUN was statistically significant, its clinical significance remains uncertain, as the overall incidence of AKI and its impact on patient outcomes were not directly assessed in this study. Also, the RIPC was initiated after induction of anesthesia; therefore, more studies are needed for the assessment of the effects of RIPC before anesthesia. All patients with abnormal liver function before surgery, those undergoing cardiopulmonary bypass (CPB) for longer than 120 minutes, and patients requiring redo surgeries were excluded from the study. Consequently, the results cannot be generalized to all patients with valvular or coronary artery diseases. Finally, the lack of blinding of the treating clinicians, who were aware of the intervention, could introduce bias in the interpretation of clinical outcomes, though the data collectors were blinded to group allocation.

Conclusion: In conclusion, while this study did not demonstrate significant protective effects of RIPC on liver function, there was a notable reduction in serum creatinine and BUN on the third postoperative day in the RIPC group, suggesting a potential benefit in preventing AKI.

Abbreviations:(RIPC): Remote Ischemic Preconditioning,(BUN): Blood Urea Nitrogen, (ALT): Alanine aminotransferase,(AST): Aspartate aminotransferase,(ALP): Alkaline Phosphatase (CPB): CardioPulmonaryBypass, Intravenous(IV), ECG: Electrocardiogram,(ACT)**:** Activated Clotting Time,(TIVA): Total Intravenous Anesthesia, HBV: Hepatitis B virus, HCV: Hepatitis C virus,(CABG): Coronary Artery Bypass Graft,(SPSS): Statistical Package for the Social Sciences,(SD): Standard Deviation,(AKI): Acute kidney Injury,(GFR): Glomerular Filtration Rate.

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