Limb Remote Ischemic Preconditioning for Intestinal and Pulmonary Protection during Elective Open Infrarenal Abdominal Aortic Aneurysm Repair

A Randomized Controlled Trial

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ABSTRACT

Background: Remote ischemic preconditioning (RIPC) may confer the cytoprotection in critical organs. The authors hypothesized that limb RIPC would reduce intestinal and pulmonary injury in patients undergoing open infrarenal abdominal aortic aneurysm repair.

Methods: In this single-center, prospective, double-blinded, randomized, parallel-controlled trial, 62 patients undergoing elective open infrarenal abdominal aortic aneurysm repair were randomly assigned in a 1:1 ratio by computerized block randomization to receive limb RIPC or conventional abdominal aortic aneurysm repair (control). Three cycles of 5-min ischemia/5-min reperfusion induced by a blood pressure cuff placed on the left upper arm served as RIPC stimulus. The primary endpoint was arterial–alveolar oxygen tension ratio. The secondary endpoints mainly included the intestinal injury markers (serum intestinal fatty acid–binding protein, endotoxin levels, and diamine oxidase activity), the markers of oxidative stress and systemic inflammatory response, and the scores of the severity of intestinal and pulmonary injury.

Results: In limb RIPC group, a/A ratio was significantly higher than that in control group at 8, 12, and 24 h after cross-clamp release (66 ± 4 *vs.* 45 ± 4, $P = 0.003$; 60 ± 6 *vs.* 37 ± 4, $P = 0.002$; and 60 ± 5 *vs.* 47 ± 6, $P = 0.039$, respectively). All biomarkers reflecting intestinal injury increased over time, and there was significant differences between limb RIPC and control group ($P < 0.001$). The severity of intestinal and pulmonary injury was decreased by limb RIPC ($P = 0.014$ and $P = 0.001$, respectively).

Conclusions: Limb RIPC attenuates intestinal and pulmonary injury in patients undergoing elective open infrarenal abdominal aortic aneurysm repair without any potential risk.

What We Already Know about This Topic

- Ischemic preconditioning is a physiologic mechanism whereby tissues exposed to a brief period of ischemia–reperfusion (I/R) develop resistance to subsequent ischemic insult
- Some studies suggest that I/R in distant tissues may confer the same protection—remote ischemic preconditioning (RIPC)

What This Article Tells Us That Is New

- In 62 patients undergoing elective open infrarenal abdominal aneurysm repair, limb RIPC (three cycles of 5 min I/R on the upper arm) attenuated pulmonary (alveolar–arterial oxygen tension ratio) and intestinal injury

IT has been recognized that multiple organ dysfunction syndrome is a major cause of morbidity and mortality after abdominal aortic aneurysm (AAA) surgery and contributes to approximately 25% of all deaths in elective AAA repair.[1] It is postulated that aortic cross-clamping during open AAA repair may cause ischemia–reperfusion (I/R) injury of the intestine and subsequently results in the translocations of bacteria and endotoxin across intestinal mucosal barrier, leading to the systemic releases of reactive oxygen species (ROS) and inflammatory cytokines, which not only damage gut itself but also harm distant organs, including heart, kidney, and lung.[2–4]

Ischemic preconditioning is a physiologic mechanism whereby tissues exposed to a brief period of nonlethal I/R develop resistance to subsequent ischemic insult.[5] However,

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ischemic preconditioning itself might lead to deterioration of organ function or cause complications, such as plaque embolization, especially when arteries are intermittently occluded, which also limit its clinical applicability.[6] Recently, a more clinically relevant stimulus is afforded by remote ischemic preconditioning (RIPC), which has been described that brief I/R in distant tissues, usually skeletal muscle, may confer the same cytoprotection in critical organs.[7–13] Although the mechanisms through which RIPC confers organ protection remains unclear, the recent evidences indicated that humoral, neurogenic, and systemic inflammatory mediators produced by preconditioning might transmit the RIPC stimulus from the source tissue to the target and thereby protect the remote region or organ.[14–16]

So far, there have been some trials of RIPC in cardiovascular surgery but these mainly focused on RIPC's potential for myocardial and renal protection during cardiac surgery and open AAA repair.[9–13] However, clinical information regarding the effects of RIPC, particularly limb RIPC, on other organs such as gut and lung after open AAA repair is lacking.

The purpose of this study was to evaluate clinical use of limb RIPC in providing intestinal and pulmonary protection after elective open infrarenal AAA repair in a randomized trial. Intestinal protection was assessed by the serum levels of intestinal fatty acid–binding protein (I-FABP), a sensitive marker of early intestinal ischemia,[17] and endotoxin reflecting intestinal mucosal permeability, and the activity of diamine oxidase (DAO) in serum, which is used as an index for small intestinal mucosal injury.[18] Meanwhile, pulmonary protection was evaluated by arterial–alveolar oxygen tension ratio (a/A ratio), alveolar–arterial oxygen tension difference (A-aDO_2), and respiratory index (RI).[19] Markers of systemic inflammation and oxidative stress were measured as well.

Materials and Methods

A single-center, double-blinded, prospective, randomized, parallel-group controlled trial following the CONSORT statement was conducted on patients undergoing elective open infrarenal AAA repair. Written informed consent was obtained from each participant. The study protocol was reviewed and approved by the Research Ethics Committee of the First Affiliated Hospital, Sun Yat-Sen University (Guangzhou, China). The trial has been registered at the end of the study (NCT01344239, June 2011).

Patients

The study was conducted at the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China. Between January 2008 and June 2011, adult patients were consecutively invited to participate in the current trial at the time that they were scheduled for elective open infrarenal AAA repair. Patients older than 80 yr or suffering any of the following symptoms or diseases were excluded: myocardial infarction within 3 months, any angina pain within 48 h of repair procedure, ejection fraction less than 40%, poor pulmonary function (PaO_2 < 60 mmHg), chronic obstructive pulmonary disease, history of inflammatory bowel disease, history of diarrhea (≥2 liquid stools per day for ≥2 days) within 1 week of surgery, and intestinal chronic inflammatory disease.

Randomization and Masking

Before the trial, randomized treatment allocations with no further stratification were generated by an independent person using a computer random number generator with a 1:1 allocation using blocks of varying sizes. Allocation details were stored in numbered, sealed, and opaque envelopes. Treatment allocation was revealed by anesthesiologists by opening the envelope on the morning of surgery and supervised by an independent statistician. None of the anesthesiologists participated in the data assessment or analysis and were not allowed to report study subjects' intervention to the intensive care unit (ICU) and surgical staff. Patients, investigators, surgeons, critical care teams, and individuals participating in data analysis were all blinded to group allocation. The trial was monitored by an independent data and safety monitoring board. Group allocation was not revealed until the final statistical analysis was completed. Baseline characteristics, intraoperative variables, and details of the postoperative course were recorded carefully for all patients.

Intervention: Limb RIPC Protocol

The limb RIPC protocol was applied after anesthetic induction and before the start of surgery. The limb RIPC was induced by placing a blood pressure cuff on the left upper arm of patients for three inflating–deflating cycles: 5 min inflating to 200 mmHg followed by a 5-min reperfusion with deflating the cuff. A similar method has been described for inducing RIPC for myocardial protection during coronary artery bypass graft surgery.[9] The control group had an uninflated cuff placed on the left upper arm for 30 min.

Anesthetic and Surgical Management

FVC and FEV_1 were assessed preoperatively using a handheld spirometer (Spirolab II; SDI Diagnostics, Rome, Italy). A chest radiograph was taken the day before surgery as part of the routine assessment. Another chest radiograph was taken 4 h after surgery. In addition, Glasgow Aneurysm Score was assessed for each patient before operation to ensure that operative risk between groups was similar.[20]

Operative and anesthetic techniques were standardized for the purpose of this trial. Before induction of general anesthesia, an epidural catheter was inserted at T12-L1 or L1-L2 level using a midline or paramedian approach in all patients, through which a test dose of 5 ml of 1% lidocaine

was given. After 15 min, the quality of the epidural analgesia was assessed using cold discrimination. If pain relief was inadequate, the position of the epidural catheter was adjusted or a new catheter was placed if necessary. The anesthesia staff was instructed not to use the epidural catheters intraoperatively. A catheter was placed in the internal jugular vein for monitoring the central venous pressure, and a radial artery cannula was also inserted for measuring the arterial pressure and sampling the arterial blood gas. A 14-Fr catheter was placed in the urinary bladder immediately after induction of anesthesia to monitor the urine output.

Both test and control groups of patients were given general anesthesia with intravenous propofol (1.5 mg/kg), cisatracurium (0.2 mg/kg), and fentanyl (2 μg/kg). Maintenance of anesthesia was achieved with a continuous infusion of propofol (3–6 mg kg^{-1} h^{-1}) and remifentanil (0.2–0.4 μg kg^{-1} min^{-1}). Patients were intubated with a 7.5-mm cuffed endotracheal tube, and the ventilation parameters were standardized (respiratory rate, 12–15 breaths/min; tidal volume, 8–10 ml/kg; fraction of inspired oxygen, 1.0) to achieve 35–45 mmHg of $ETCO_2$ in the expired air. In this study, patients received 5 cm H_2O positive end-expiratory pressure initially. If the patients' PaO_2 was less than 80 mmHg, regular attempts would be made to increase it, in 2 cm H_2O increments, to achieve the goal (PaO_2 > 80 mmHg, SpO_2 > 95%). But the maximal positive end-expiratory pressure was not more than 10 cm H_2O. Standardized fluid replacement consisted of 10 ml/kg lactated Ringer's solution applied preoperatively and 6 ml kg^{-1} h^{-1} of the solution applied preoperatively. Colloid was given to obtain a stable heart rate, central venous pressure of 8–10 cm H_2O, a steady mean arterial pressure, and a urine output more than 1 ml kg^{-1} h^{-1}. Packed erythrocytes were transfused as necessary to maintain a circulating hemoglobin level approximately 10 g/dl. Cell saver or other autologous blood salvage was not used in the current study.

In the operation, an abdominal midline incision was used and the small intestine was placed in a plastic gut bag and retracted to the right side of the abdominal wound to easily expose the infrarenal aorta. The plastic gut bag was carefully tightened partially to prevent protrusion but avoid strangulation of the small intestine. The aorta and the iliac vessels were prepared, isolated, and clamped after systemic heparinization. The aortic cross-clamping in all cases was under renal artery and lasted 30–60 min. Reconstruction using either a tube or bifurcated Dacron graft depended on the size of the aneurysm. The procedure was consistently performed by the same surgeon.

Postoperative Management

At the end of surgery, the patients were routinely transferred to ICU for weaning from artificial ventilation. The epidural catheter infusions were begun immediately on entry to ICU. The loading dose was 6 ml of 0.25% bupivacaine with 2 mg morphine, and during the first three postoperative days, all patients received epidural analgesia with a mixture of bupivacaine 0.125% and 0.1 mg/ml morphine with a basal rate of 2 ml/h, bolus doses of 3–5 ml, and a lockout interval of 20 min. To make sure that those patients had a working epidural analgesia, postoperative pain was assessed at rest and movement during postoperative days 1, 2, and 3 by using the visual analog scale rating from 0 (no pain at all) to 10 (worst possible pain). In ICU, crystalloid fluid replacement was infused at 2 ml kg^{-1} h^{-1} to maintain a stable heart rate, central venous pressure of 8–10 cm H_2O, and a steady mean arterial pressure. In addition, blood was given to maintain hemoglobin more than 10 g/dl. Extubation was managed according to the standard ICU protocols by the ICU staff. ICU extubation protocol included adequate oxygenation ($PaO_2 \geq 60$ mmHg, $PaCO_2 \leq 50$ mmHg on a fraction of inspired oxygen ≤40%, positive end-expiratory pressure ≤8 cm H_2O), systolic blood pressure greater than 90 mmHg without vasopressor support, heart rate greater than 60 beats/min, absence of significant metabolic/respiratory acidosis (pH ≥ 7.3), adequate hemoglobin level (8–10 g/dl), and spontaneous breathing (spontaneous VT ≥ 4 ml/kg, respiratory rate ≤ 35 per min). For each patient, the postoperative ventilator support time and ICU and hospital-free days were recorded.

Preparation of Blood Samples

Blood samples were collected for analysis at the following time points: before surgery (baseline), 30 min, 4, 8, 12, and 24 h after cross-clamp release (reperfusion). Venous blood was sampled from the jugular venous line and centrifuged at 2700 rpm for 15 min. Serum samples were stored at –70°C for subsequent analysis. Radial arterial blood was analyzed using a blood gas system (GEM Premier 3000, Instrumentation Laboratory, Bedford, MA).

Assessment of Intestinal Injury

Intestinal injury was assessed by measuring the serum concentrations of I-FABP and endotoxin and the activity of DAO at predetermined time points. The concentration of I-FABP was measured by enzyme-linked immunosorbent assay according to the instruction manual (ADL Co., Mukwonago, WI). The concentration of endotoxin was determined using a quantitative Limulus amoebocyte lysate chromogenic assay (Ruicheng Bioengineering Research Institute, Shanghai, China). DAO activity was assessed using a sandwich enzyme-linked immunoassay with a commercially available kit (HuiJia Bioengineering Research Institute, Xiamen, China).

To evaluate the patients' intestinal function after aneurysm repair, a modified intestinal dysfunction score based on previously described methods was used.[21] Because patients usually start enteral feeding from the third day after AAA surgery in our center, the recording of intestinal injury score was initiated from 72 h after operation.

Assessment of Pulmonary Injury

Pulmonary function evaluation included a/A ratio, A-aDO_2, and respiratory index at corresponding time points. Respiratory compliance was measured for 8 h after operation. During mechanical ventilation, the VT, fraction of inspired oxygen (FiO_2), Pmax, Pplat, and positive end-expiratory pressure were obtained directly from the ventilator setting (S/5 Aespire 7900; Datex-Ohmeda, Madison, Wisconsin). The following formulas were used to determine pulmonary function:

$$\text{Static lung compliance(Cs)} = \text{VT} / (\text{Pplat} - \text{PEEP})$$

$$\text{Dynamic lung compliance (Cd)} = \text{VT} / (\text{Pmax} - \text{PEEP})$$

$$\text{a / A ratio} = \text{PaO}_2 / \text{PAO}_2$$

$$\text{A} - \text{aDO}_2 = \text{PAO}_2 - \text{PaO}_2 = 713\text{FiO}_2 - \text{PaCO}_2 / 0.8 - \text{PaO}_2$$

$$\text{RI} = \text{A} - \text{aDO}_2 / \text{PaO}_2$$

Similarly, a pulmonary injury score based on previously described methods was collected.[22] The recording of pulmonary injury score was initiated 8 h after surgery, because the collections of some parameters involved in the score must rely on mechanical ventilation and patients were usually extubated in the following morning in ICU.

Evaluation of Inflammatory Response and Oxidative Stress

The levels of the inflammatory cytokines, including tumor necrosis factor-α and interleukin-6, were measured using a sandwich enzyme-linked immunoassay with a commercially available kit (Jiancheng Bioengineering Research Institute, Nanjing, China). The variables reflecting oxidative stress, including malondialdehyde level and superoxide dismutase (SOD) activity in serum, were analyzed using methods of thiobarbituric acid reaction and the generation of an artificial chromophore, respectively.

Primary and Secondary Study Outcomes

The primary outcome was a/A ratio. Secondary outcomes included: (1) other variables reflecting pulmonary injury (A-aDO_2, respiratory index); (2) the biomarkers reflecting intestinal injury (serum I-FABP, endotoxin levels, and DAO activity); (3) the scores of the severity of intestinal and pulmonary injury; (4) the markers of oxidative stress and systemic inflammatory response; (5) ventilator support time; (6) ICU- and hospital-free days; (7) new arrhythmia, defined as any duration at any time in the postoperative period on the basis of a rhythm strip or 12-lead electrocardiogram; (8) perioperative myocardial infarction, defined as new Q waves of 0.04 ms and/or a reduction in R waves more than 25% in at least two contiguous leads on electrocardiogram; (9) the diagnosis of congestive heart failure was based on symptoms and signs of pulmonary congestion and abnormal results on chest radiograph; (10) neurologic events, diagnosis of stroke was made if there was evidence of new neurologic deficit with morphologic substrate confirmed by computed tomography or nuclear magnetic resonance imaging; (11) renal failure, defined as the diagnosis of renal dysfunction significant requiring postoperatively established hemofiltration; and (12) upper limb ischemia requiring intervention.

Statistical Analysis

Because there are no exact incidences of intestinal injury induced by open AAA repair available, sample size was determined based on a previous study in which a mean a/A ratio reflecting pulmonary function of 0.3 at 12 h after surgery in patients undergoing elective AAA repair was found.[19] Therefore, with an expected difference of 0.1 between-group means in the current study, an SD of 0.1 of the means, significance at the two-side 5% level and a power of 80%, a sample size of 26 was necessary. To compensate for 20% cases for possible dropouts, a total of 31 cases were enrolled in each group.

Continuous data were expressed as mean ± SD or median (25% percentile, 75% percentile) of patients and compared with independent *t* test or Mann–Whitney *U* test, respectively. Categorical data were expressed as frequency or percentage and compared with Fisher exact test or the chi-square test where appropriate. The state of smoking and the scores of the severity of intestinal or pulmonary injury were compared by the Mann–Whitney *U* test. To account for repeated measurements from the intestinal injury biomarkers, the MANOVA model was used to identify the differences within and between the groups. If group differences over time are to be interpreted, then further *post hoc* strategies comparisons were performed using the Hotlling T^2 test. All other data, including the pulmonary outcomes, the hemodynamic data, and biochemical serum markers, were analyzed using two-way repeated-measures ANOVA with Bonferroni correction for both within-group and between-group comparisons. All *P* values were two-sided, and the statistical significant level was 0.05. Statistical analyses were conducted using the SPSS statistical software, version 16.0 (SPSS Inc., Chicago, IL).

Results

The CONSORT diagram is depicted in figure 1, and patient data are listed in table 1. Sixty-nine patients were assessed for eligibility, of whom 62 were actually recruited and randomly assigned to limb RIPC group (n = 31) or control group (n = 31). All patients completed the study with no patients lost to follow-up. Patients' baseline characteristics, total operation time, aortic cross-clamping time, aneurysm diameter, and Glasgow Aneurysm Score were comparable in both groups. There was no documented case in which no block was obtainable after an epidural catheter initial placement and no failure of epidural analgesia, defined as the need for additional intravenous opioids, was reported in the current study.

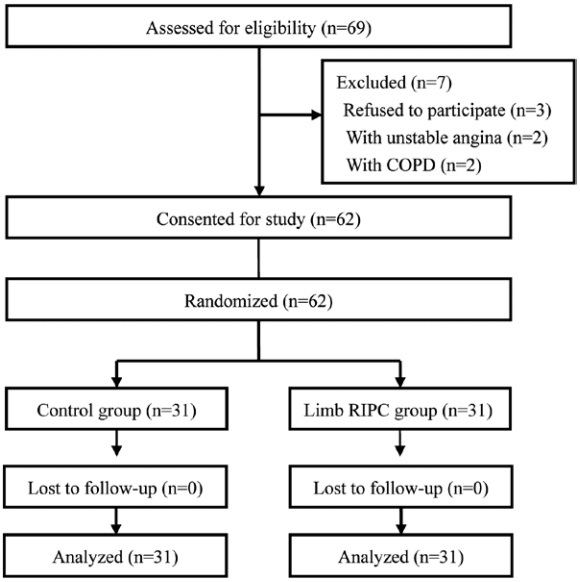

Fig. 1. CONSORT diagram showing the flow of participants through each stage of the randomized trial. COPD = chronic obstructive pulmonary disease; RIPC = remote ischemic preconditioning.

Postoperative data are summarized in table 2. All patients survived 30 days after operation. In the limb RIPC group, two of the patients had a new myocardial infarction, four patients experienced arrhythmia, and none of the patients had severe intestinal and pulmonary injury, whereas in the control group only one patient had a new myocardial infarction, three patients experienced new arrhythmia, one of the patients had a severe intestinal injury, and two experienced severe pulmonary injury. None of the patients in the two groups had cerebrovascular injury or renal damage requiring hemofiltration. No signs of upper arm pain, function disability, or sensory disability were observed postoperatively. In each case, radial artery pulse was normal and Allen's test was negative 1 month after hospital discharge.

As shown in table 2, there were no significant differences in fluid balance and transfusion requirement between the groups during the operation and 24 h after surgery. The vasoconstrictor usage was similar between groups (all $P > 0.05$). The ventilator support time and ICU-free days were both shorter in the limb RIPC group compared with control group [640 (306–920) min *vs.* 519 (275–778) min, $P = 0.04$ and 2 (2–4) day *vs.* 3 (2–5) day, $P = 0.03$, respectively], but there were no distinct differences in the length of hospital-free days ($P = 0.28$).

Pulmonary Injury

As shown in table 3, there were no significant differences in hemodynamic variables, arterial pH, and $PaCO_2$ between the two groups at any of the observing time points (all $P > 0.05$). However, there were significant differences in variables reflecting pulmonary injury between groups (all $P < 0.01$). In limb RIPC group, a/A ratio was significantly higher than that in control group at 8, 12, and 24 h after cross-clamp release (66 ± 4 *vs.* 45 ± 4, $P = 0.003$; 60 ± 6 *vs.* 37 ± 4, $P = 0.002$; and 60 ± 5 *vs.* 47 ± 6, $P = 0.039$, respectively). Similarly, Cs and Cd in limb RIPC group were significantly higher than those in control group at 4 and 8 h after cross-clamp release (all $P < 0.05$). Moreover, respiratory index and $A\text{-}aDO_2$ in limb RIPC group were significantly lower than those in control group at 8, 12, and 24 h after cross-clamp release (all $P < 0.05$).

As shown in table 2, the severity of the pulmonary injury in limb RIPC patients were lower than those of control patients at 8 h after cross-clamp release ($P = 0.001$, Mann–Whitney *U* test).

Table 1. Preoperative and Intraoperative Characteristics

	Limb RIPC (n = 31)	Control (n = 31)
Age (yr)	62 ± 7	67 ± 8
Weight (kg)	68 (65–72)	61 (58–68)
Sex, males	29 (93%)	26 (84%)
Preoperative FVC (l)	4.2 (3.8–4.4)	4.3 (3.9–4.6)
Preoperative FEV_1 (l)	3.2 (3.0–3.4)	3.3 (3.1–3.5)
PaO_2 (mmHg)	82 ± 5	84 ± 6
$PaCO_2$ (mmHg)	37 ± 3	36 ± 2
Smoking, No. (%)		
Current smokers	7 (23%)	6 (19%)
Ex-smokers	15 (48%)	19 (62%)
Never smoked	9 (29%)	6 (19%)
Associated illness, No. (%)		
Hypertension	24 (77%)	18 (58%)
Diabetes mellitus	14 (45%)	9 (29%)
Previous myocardial infarction	5 (16%)	8 (26%)
Glasgow Aneurysm Score	65 (56–72)	63 (54–70)
Preoperative medications, No. (%)		
β-blockers	16 (52%)	19 (61%)
Calcium channel antagonist	10 (42%)	7 (23%)
ACE inhibitor	9 (29%)	6 (19%)
Statin	13 (35%)	16 (52%)
Duration of anesthetic (min)	290 ± 40	275 ± 45
Cross-clamp time (min)	62 ± 9	58 ± 14
Aneurysm diameter (mm)	72 ± 9	69 ± 12
Median operating time (min)	150 ± 20	137 ± 17

There are no statistically significant differences between groups on either variable listed. Continuous data are reported as mean ± SD or median (25% percentile, 75% percentile). Categorical data are given as counts (percentages).

ACE = angiotensin-converting enzyme; FEV_1 = forced expired volume in 1 second; FVC = forced vital capacity; $PaCO_2$ = arterial carbon dioxide partial tension; PaO_2 = arterial oxygen; RIPC = remote ischemic preconditioning.

Table 2. Intraoperative and Postoperative Data

	Limb RIPC Group (n = 31)	Control Group (n = 31)	*P* Value
Intraoperative			
Crystalloid (ml)	2,257 (2,000–2,500)	2,379 (2000–2,500)	0.63
Colloid (ml)	1,062 (500–1500)	1,217 (500–1,500)	0.56
p-RBC transfusion (ml)	417 (240–560)	504 (310–770)	0.38
FFP (ml)	217 (100–200)	254 (200–400)	0.46
Estimate blood loss (ml)	670 ± 350	698 ± 430	0.84
Urine output (ml)	750 (580–920)	520 (400–660)	0.16
Number of patients transfused	16 (51%)	14 (45%)	0.61
24 h after operation			
Crystalloid (ml)	3,205 (3,000–3,200)	3,469 (2,800–3,400)	0.66
Colloid (ml)	650 ± 110	770 ± 170	0.57
Packed erythrocytes transfusion (ml)	250 ± 50	328 ± 120	0.35
FFP (ml)	100 ± 50	250 ± 100	0.12
Vasoconstrictors usage	1 (3%)	4 (13%)	0.17
Ventilator support time (min)	519 (275–778)	640 (306–920)	0.04
ICU-free days	2 (2–4)	3 (2–5)	0.03
Hospital-free days	10 (7–12)	13 (7–14)	0.28
Intestinal injury grade			0.014
Normal	3 (9%)	1 (3%)	
Mild intestinal injury	21 (68%)	14 (45%)	
Moderate intestinal injury	7 (23%)	15 (49%)	
Severe intestinal injury	0	1 (3%)	
Pulmonary injury grade			0.001
Normal	10 (32%)	4 (13%)	
Mild pulmonary injury	17 (55%)	11 (35%)	
Moderate pulmonary injury	4 (13%)	14 (45%)	
Severe pulmonary injury	0	2 (7%)	
Myocardial infarction	2 (6.4%)	1 (3.2%)	0.50
Arrhythmia	4 (9.6%)	3 (9.6%)	0.46
Congestive cardiac failure	0	1 (3.2%)	0.48
Renal failure	0	0	
Neuralgic events	0	0	
Upper limb ischemia requiring intervention	0	0	
Death	0	0	

Continuous data are reported as mean ± SD or median (25% percentile, 75% percentile). Categorical data are given as counts and percentages.

FFP = fresh frozen plasma; ICU = intensive care unit; p-RBC = packed red blood cell; RIPC = remote ischemic preconditioning.

Intestinal Injury

As the results of intestinal injury evaluation by MANOVA showed, there was significant interaction effect between time and group (F = 58.98, P < 0.001). Furthermore, Hotlling T^2 testing showed that the between-group differences of intestinal injury markers occurred over the whole observational period (P < 0.001). As shown in figure 2A, limb RIPC reduced the I-FABP release over the 24 h after cross-clamp release. Moreover, serum I-FABP concentrations in limb RIPC group were significantly lower than those in control group at 30 min and 4 h after cross-clamp release (95.2 ± 22.5 pg/ml *vs.* 236.5 ± 35.0 pg/ml, P = 0.001 and 193.2 ± 23.0 pg/ml *vs.* 344.2 ± 40.4 pg/ml, P=0.003, respectively). Similarly, as shown in figure 2B and 2C, serum endotoxin levels and DAO activity were lower in the limb RIPC patients during 24 h after cross-clamp release compared with the control group (all P < 0.001).

As shown in table 2, 72 h after cross-clamp release, limb RIPC significantly reduced the severity of the intestinal injury in comparison to the control (P = 0.014, Mann–Whitney U test).

Evaluation of Systemic Inflammatory Response

As shown in figure 2D, the interleukin-6 levels peaked 12 h after the release of cross-clamp in both groups. However, the levels in limb RIPC group were lower than those in the control at 8, 12, and 24 h (all P < 0.05). Different from the changes of interleukin-6 levels, tumor necrosis factor-α level gradually increased over the whole observational period and sharply peaked 24 h after the release of the cross-clamp. Similarly, there was significant difference between groups (P < 0.001) (fig. 2E).

Table 3. Hemodynamic Data and the Variables Reflecting Lung Function

	Group	Baseline	30 min After Reperfusion	4 h After Reperfusion	8 h After Reperfusion	12 h After Reperfusion	24 h After Reperfusion	*P* Value
MAP (mmHg)	Control	94 ± 10	88 ± 10	89 ± 7	92 ± 9	88 ± 6	82 ± 11	0.46
	limb RIPC	96 ± 12	87 ± 7	90 ± 11	97 ± 8	86 ± 8	92 ± 7	
HR (beats/min)	Control	73 ± 5	78 ± 13	79 ± 8	74 ± 13	89 ± 14	86 ± 10	0.32
	limb RIPC	76 ± 6	82 ± 9	77 ± 7	88 ± 16	78 ± 11	84 ± 13	
CVP (mmHg)	Control	6 ± 1	11 ± 3	9 ± 3	9 ± 2	10 ± 3	9 ± 2	0.23
	limb RIPC	5 ± 2	10 ± 3	8 ± 3	8 ± 2	9 ± 2	8 ± 3	
Arterial pH	Control	7.41 ± 0.03	7.32 ± 0.03	7.40 ± 0.03	7.39 ± 0.02	7.38 ± 0.02	7.35 ± 0.02	0.88
	limb RIPC	7.39 ± 0.02	7.33 ± 0.02	7.35 ± 0.02	7.38 ± 0.01	7.36 ± 0.02	7.37 ± 0.01	
$PaCO^2$ (mmHg)	Control	37 ± 1	38 ± 2	38 ± 2	37 ± 2	38 ± 2	38 ± 1	0.91
	limb RIPC	37 ± 1	37 ± 1	39 ± 2	38 ± 1	38 ± 2	39. ± 1	
PaO^2 (mmHg)	Control	373 ± 147	349 ± 78	302 ± 30	193 ± 44*	177 ± 28*	206 ± 29*	0.35
	limb RIPC	384 ± 131	358 ± 93	332 ± 27	290 ± 28#	265 ± 33#	280 ± 27#	
a/A ratio (%)	Control	70 ± 4	69 ± 5	58 ± 5	45 ± 4*	37 ± 4*	47 ± 6*	<0.01
	limb RIPC	69 ± 5	66 ± 3	69 ± 4	66 ± 4#	60 ± 6#	60 ± 5#	
Cs ($ml \cdot cm^{-1} \cdot H_2o$)	Control	99 ± 12	88 ± 7	62 ± 14*	59 ± 10*			<0.01
	limb RIPC	102 ± 10	95 ± 9	89 ± 8#	83 ± 7*#			
Cd ($ml \cdot cm^{-1} \cdot H_2o$)	Control	59 ± 6	56 ± 4	41 ± 6*	31 ± 4*			<0.01
	limb RIPC	54 ± 4	53 ± 5	50 ± 6#	47 ± 3*#			
RI	Control	0.32 ± 0.05	0.45 ± 0.06	0.47 ± 0.05	0.88 ± 0.21*	1.33 ± 0.28*	1.1 ± 0.22*	<0.01
	limb RIPC	0.35 ± 0.03	0.40 ± 0.05	0.42 ± 0.03	0.45 ± 0.06#	0.90 ± 0.26*#	0.8 ± 0.10*#	
A-aDO^2 (mmHg)	Control	162 ± 47	156 ± 58	172 ± 40	205 ± 47*	210 ± 43*	222 ± 46*	<0.01
	limb RIPC	144 ± 32	138 ± 30	152 ± 37	142 ± 38#	165 ± 35*#	177 ± 42*#	

Continuous data are presented as means ± SD.

* $P < 0.05$ *versus* baseline, # $P < 0.05$ *versus* control group.

a/A ratio = arterial–alveolar; A-aDO_2 = alveolar–arterial oxygen tension difference; Cd = dynamic lung compliance; Cs = static lung compliance; CVP = central venous pressure; HR = heart rate; MAP: mean arterial pressure; RI = respiratory index oxygen tension ratio; RIPC = remote ischemic preconditioning.

Analysis of Lipid Peroxidation

As shown in figure 2F, the serum malondialdehyde levels in both groups increased transiently in the first 12 h after the release of cross-clamp and returned to the baseline values 24 h after reperfusion. However, malondialdehyde levels at 8 and 12 h after cross-clamp release in limb RIPC group were lower than those in control group (5.8 ± 0.5 nmol/ml *vs.* 6.2 ± 0.5 nmol/ml, $P = 0.039$ and 5.7 ± 0.7 nmol/ml *vs.* 6.4 ± 0.5 nmol/ml, $P = 0.002$, respectively).

Figure 2G shows that SOD activity in both groups peaked 8 h after cross-clamp release and the activity of SOD was significantly different between groups ($P = 0.02$). It was of interest for limb RIPC group that the SOD activity 24 h after cross-clamp release was even higher than the baseline value ($P = 0.02$). In addition, SOD activity in limb RIPC group at 8 and 12 h after cross-clamp release was higher than that in control group (143.9 ± 30.6 nmol/ml *vs.* 112.5 ± 23.3 nmol/ml, $P = 0.022$ and 123.2 ± 24.7 nmol/ml *vs.* 95.9 ± 29.0 nmol/ml, $P = 0.001$, respectively).

Discussion

In this prospective, randomized, and controlled trial, significant occurrence of intestinal and pulmonary injury in patients undergoing open infrarenal AAA repair was demonstrated. Meanwhile, we for the first time observed a significant trend toward protection from intestinal and pulmonary injury in those patients randomized to limb RIPC.

The concept of RIPC was first introduced by Przyklenk *et al.*[23] The initial study suggested that one vascular bed could precondition another vascular bed in dogs. The basic concept was followed by additional studies suggesting that transient ischemia of the limb could also induce protection for organs against subsequent I/R injury.

In 1997, Birnbaum *et al.*[24] published the first study confirming that transient limb ischemia could reduce ischemic myocardial damage. Subsequently, Cheung *et al.*[7] described the first clinical application of remote preconditioning in human beings, in which four cycles of 5-min ischemia/5-min reperfusion at lower limb using a blood pressure cuff in children undergoing cardiac surgery significantly reduced the myocardial injury. In addition, multiple clinical observations about RIPC's protective effects on tissues and organs were reported; however, negative results concerning remote preconditioning in the heart in coronary artery bypass graft surgery were also reported.[25] To date, however, only two studies have investigated the effects of RIPC on organ injury after open AAA repair.[12,13] In these studies, RIPC was induced by two cycles of intermittent cross-clamping of the

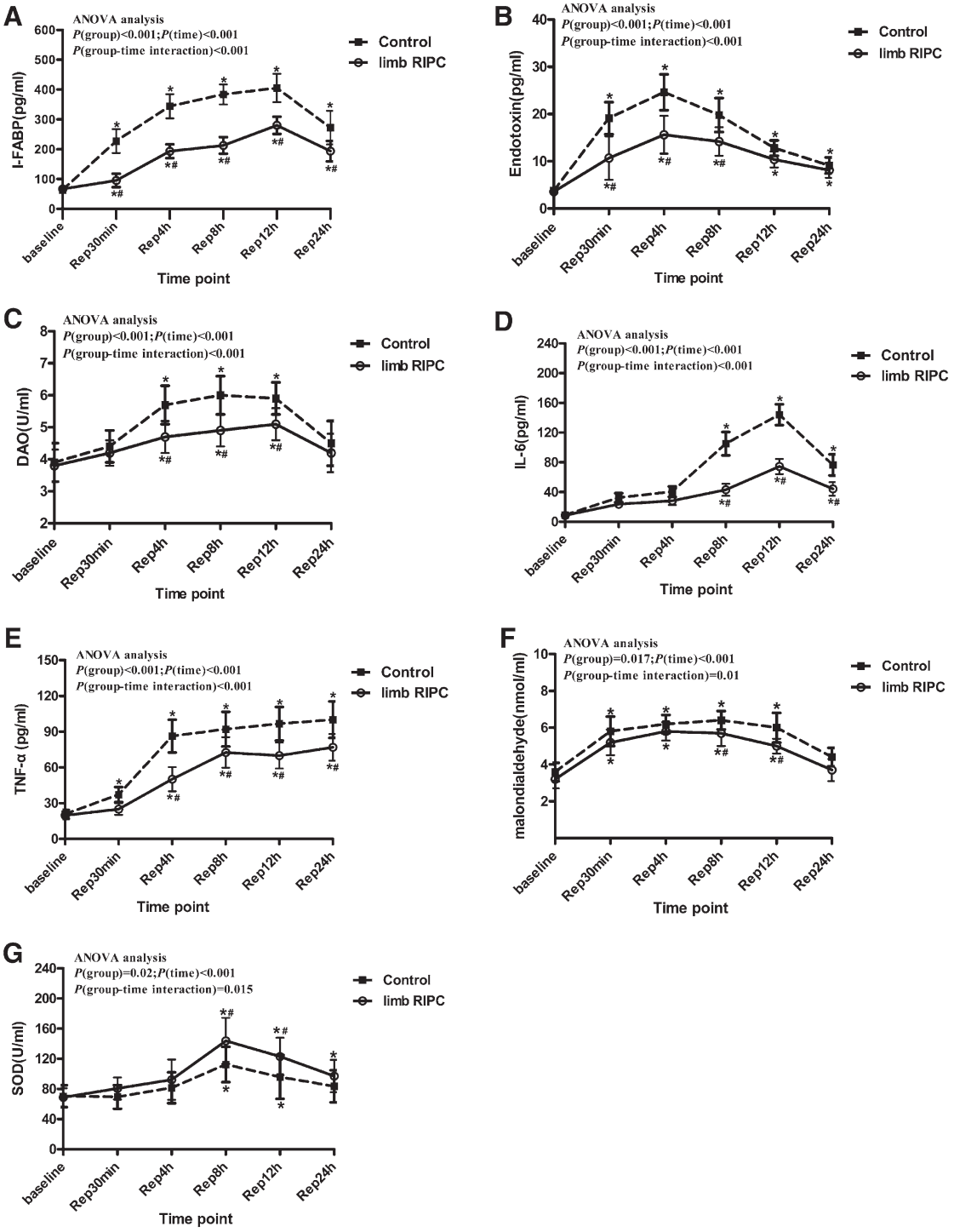

Fig. 2. Biomarkers of intestinal injury and variables reflecting oxidative stress and inflammatory response at various time points in patients undergoing open infrarenal AAA repair with or without limb RIPC. n = 31 for each group. *A*: serum I-FABP concentration; *B*: serum endotoxin level; *C*: serum DAO activity; *D*: IL-6 concentration; *E*: TNF-α concentration; *F*: Serum malondialdehyde concentration; *G*: SOD activity. Data are represented as mean ± SD. * $P < 0.05$ *versus* baseline; # $P < 0.05$ *versus* control. AAA = abdominal aortic aneurysm; DAO = diamine oxidase; I-FABP = intestinal fatty acid–binding protein; IL-6 = interleukin-6; Rep = reperfusion; RIPC = remote ischemic preconditioning; SOD = superoxide dismutase; TNF-α = tumor necrosis factor-α.

common iliac with 10 min of ischemia followed by 10 min of reperfusion, and the protective potential of RIPC on myocardial and renal injury was assessed. Ali *et al.*[12] found that RIPC significantly reduced the incidence of myocardial and renal injury in comparison to the control. In contrast, Walsh *et al.*[13] found that although control patients' median

urinary retinol-biding protein level was five times greater than those in RIPC group at 3 h postoperatively, there were no statistically significant differences in renal outcome indices. In addition, there were several concerns with this particular RIPC maneuver in the above two studies. First, intermittent cross-clamping of the common iliac may cause plaque thrombus and potential blood vessel injury. Second, one of the two observations showed that cross-clamping of the common iliac might cause severe acute lower limb ischemia, which occurred in 18% of the RIPC group.[13] To avoid potential complications resulting from cross-clamping of the common iliac, therefore, in the current study, a blood pressure cuff was used to induce upper limb RIPC. We found that this maneuver did not develop significant peripheral vascular disease. Moreover, the obvious advantages of this technique include its noninvasive nature and ease of application. In addition, the "non-local" effect of limb RIPC may afford widespread protection against organs I/R injury, which has been demonstrated by previous studies.[7]

There have been several reports of intestinal injury after open AAA repair.[26–28] However, because there are no specific and sensitive variables for the detection of the intestinal injury, the definitive diagnosis of intestinal injury in clinical setting is difficult and often delayed. The urine excretion ratio of lactulose and mannitol is usually used as the indirect indicator of intestinal permeability in research, but it is not sensitive enough in critically ill patients. To improve the accuracy of the evaluation of intestinal injury, three different markers that respectively reflect intestinal injury from different aspects, together with the intestinal dysfunction score, were used in the current study. Among these markers, I-FABP is a 15-kd protein that is uniquely located at the tips of intestinal mucosal villi. It contains approximately 2–3% of protein of enterocyte and is generally undetectable in the peripheral circulation, but it will increase rapidly when intestinal mucosal injury occurs. I-FABP has been shown to be a sensitive marker of early intestinal ischemia.[29,30] To our knowledge, the release of I-FABP has not been measured in patients undergoing open AAA repair. The second marker reflecting intestinal injury was serum DAO activity, which is used as an index of small intestinal mucosal injury, because it is particularly high in the upper portion of small intestinal villi.[18] In addition, the serum endotoxin level was used to reflect the intestinal permeability in the current study. We found that the serum level of I-FABP began to increase at the early phase of open infrarenal AAA repair, accompanied by increases in DAO activity and serum endotoxin level 4 h after surgery. This indicated that intestinal injury occurred very early during operation and still existed after surgery, which was also supported by postoperative high incidence (49%) of moderate intestinal injury. Of interest, the current results showed that limb RIPC not only significantly attenuated the clinically relevant markers of intestinal injury but also reduced the scores of the intestinal injury severity, implying a novel finding that limb RIPC could confer intestinal protection after open infrarenal AAA repair.

Paterson *et al.*[31] reported that AAA repair was followed by a reduced pulmonary elastance. Since then, pulmonary injury has been taken into consideration as an important risk factor affecting the outcome of patients after open AAA repair.[32] In agreement with previous reports, our series also showed significant postoperative pulmonary dysfunction across both patient groups, but we for the first time demonstrated that pulmonary dysfunction was significantly attenuated in the RIPC patients. The mechanisms through which open repair of infrarenal AAA induces intestinal and pulmonary injuries remain unclear. Because the procedure usually involves small-bowel manipulation, clamping and unclamping of aorta and inferior mesenteric artery, and hypovolemia due to excessive blood loss or inadequate resuscitation, I/R in intestine and lower limbs could occur. Because the gut has been referred to as "the motor of multiple organ dysfunction syndrome," intestinal injury caused by AAA repair could contribute to lung injury in the current study.[33] We previously demonstrated in a rat model that intestinal I/R led to significant intestinal injury accompanied with systemic releases of inflammatory cytokines and ROS, thereby resulting in injury in distant organs, including lung.[34–36] In addition, lower limb I/R could also promote the releases of inflammatory cytokines and ROS.[37] Similarly, some clinical observations also showed that lipid peroxidation caused by ROS production and inflammatory response induced by the release of inflammatory cytokines played important roles in organ injury during conventional and endovascular repair of AAA.[38] In accordance with the previous reports, the current study also showed that open repair of infrarenal AAA caused markedly systemic inflammatory response evidenced by increases in serum levels of interleukin-6 and interferon-α and lipid peroxidation manifested by increases in serum malondialdehyde level and reduction of SOD activity, further suggesting that lipid peroxidation and inflammatory response may, at least in part, play important roles in organ injury during open AAA repair.

The mechanisms through which RIPC produces beneficial effects on organs suffering from I/R have not been fully elucidated. Theories include the concept that humoral substances such as adenosine or bradykinin produced by preconditioning are released into the systemic circulation and then protect the remote organ.[24] Other mechanistic factors proposed include erythropoietin, activation of the adenosine-5'-triphosphate–sensitive potassium channel,[39] nitric oxide,[40] delta 1-opioid, and free radicals.[41] Another theory is that ischemic preconditioning of one region or organ induces a generalized catecholamine stimulation or a sympathomimetic nerve stimulation that then mediate protection. The current study showed that RIPC could suppress the releases of ROS and inflammatory mediators, which partly supported the above notion. Further studies investigating the exact mechanisms of RIPC protection in the patients are mandatory.

There are several limitations in the current study. First, because there is no acknowledged standard for the diagnosis of

intestinal and pulmonary injury, we could not obtain the exact data about the incidence of intestinal and pulmonary injury. Moreover, because a trial with sufficient power to detect large differences in clinical outcome after infrarenal AAA repair would require many thousands of patients, the current exploratory trial was only designed to determine the effects of limb RIPC on subclinical pulmonary and intestinal damage in patients undergoing open infrarenal AAA repair. Second, because the effects of RIPC on heart[12] and kidney[13] after open infrarenal AAA repair have already been investigated as mentioned above, the current study specially focused on the effects of RIPC on intestine and lung. Nevertheless, further investigation is still warranted to elucidate the impact of limb RIPC on other organs during open repair of infrarenal AAA and other clinical settings. Third, it is worthy of further investigation on which mode of RIPC, upper or lower limb RIPC or intermittent cross-clamping of the common iliac, is more effective for protection of organs, and what ischemic extent could confer better beneficial effects. At last, although we have tried to exclude potential interferences, some factors such as anesthetic agents,[42] ages,[43] diabetes,[44] and preoperative statin therapy[45] could interfere with the effects of RIPC, which might have confounded the results.

In conclusion, this small novel but preliminary study strongly implied that intermittent upper limb ischemia as a RIPC stimulus may potentially confer intestinal and pulmonary protection during elective open infrarenal AAA repair. However, large clinical trials are needed to further investigate its use during major surgeries.

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