Limb Remote Ischemic Preconditioning Attenuates Lung Injury after Pulmonary Resection under Propofol–Remifentanil Anesthesia

A Randomized Controlled Study

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ABSTRACT

Background: Remote ischemic preconditioning (RIPC) may confer the protection in critical organs. The authors hypothesized that limb RIPC would reduce lung injury in patients undergoing pulmonary resection.

Methods: In a randomized, prospective, parallel, controlled trial, 216 patients undergoing elective thoracic pulmonary resection under one-lung ventilation with propofol–remifentanil anesthesia were randomized 1:1 to receive either limb RIPC or conventional lung resection (control). Three cycles of 5-min ischemia/5-min reperfusion induced by a blood pressure cuff served as RIPC stimulus. The primary outcome was $Pa_{O_2}/F_{I_{O_2}}$. Secondary outcomes included other pulmonary variables, the incidence of in-hospital complications, markers of oxidative stress, and inflammatory response.

Results: Limb RIPC significantly increased $Pa_{O_2}/F_{I_{O_2}}$ compared with control at 30 and 60 min after one-lung ventilation, 30 min after re-expansion, and 6 h after operation (238 ± 52 *vs.* 192 ± 67, $P = 0.03$; 223 ± 66 *vs.* 184 ± 64, $P = 0.01$; 385 ± 61 *vs.* 320 ± 79, $P = 0.003$; 388 ± 52 *vs.* 317 ± 46, $P = 0.001$, respectively). In comparison with control, it also significantly reduced serum levels of interleukin-6 and tumor necrosis factor-α at 6, 12, 24, and 48 h after operation and malondialdehyde levels at 60 min after one-lung ventilation and 30 min after re-expansion (all $P < 0.01$). The incidence of acute lung injury and the length of postoperative hospital stay were markedly reduced by limb RIPC compared with control (all $P < 0.05$).

Conclusion: Limb RIPC attenuates acute lung injury *via* improving intraoperative pulmonary oxygenation in patients without severe pulmonary disease after lung resection under propofol–remifentanil anesthesia. **(ANESTHESIOLOGY 2014; 121:249-59)**

NON–SMALL-CELL lung carcinoma is a leading cause of mortality in most countries.[1] Surgical resection provides the best chance of survival in the early stage of the disease.[2] Despite recent advances in surgical techniques, perioperative anesthetic management, and intensive care management, acute lung injury (ALI) after major thoracic surgery remains the leading cause of death from pulmonary surgery.[3] Previous reports of ALI after major thoracic surgery is 2 to 8% and postoperative adult respiratory distress syndrome (ARDS) is 2 to 5%.[4–6]

The pathogenesis of ALI after pulmonary resection has not been fully elucidated. However, ischemic/reperfusion (I/R) injury of the operated lung has been demonstrated as one of the most vital factors causing and aggravating ALI and ARDS.[7,8] During one-lung ventilation (OLV), the operated lung remains atelectatic and also hypoperfused due to the hypoxic pulmonary vasoconstriction (HPV). After the bronchial block is ended, the subsequent oxygen re-entry through the airways causes reactive pulmonary vascular dilatation, and the lung reperfusion starts. The prompt lung re-expansion and tissue reperfusion may generate a large number of reactive oxygen species and inflammatory cytokines, which will most likely lead to ALI after pulmonary resection.[8,9]

What We Already Know about This Topic

- Remote ischemic preconditioning has been shown to be beneficial to organ function in some experimental paradigms.

What This Article Tells Us That Is New

- In a randomized, prospective, parallel, controlled trial of patients who were undergoing lung resection procedures with one-lung ventilation, one group of the randomized patients received limb ischemia in three cycles of 5 min of ischemia with 5 min of reperfusion. The patients receiving limb ischemia had a significant decrease in acute lung injury.

Limb remote ischemic preconditioning (RIPC) is a physiologic mechanism whereby skeletal muscles exposed to a transient sublethal episode of I/R develop resistance to subsequent ischemic insult of remote vital organs.[10] In recent years, limb RIPC has been expanded to different organs, representing a general form of organ protection against the detrimental effects of acute I/R injury.[11–13]

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Although the mechanisms *via* which RIPC confers organ protection remains unclear, the latest evidences indicated that humoral, neurogenic, and systemic inflammatory mediators produced by preconditioning might transmit the RIPC stimulus from the source tissue to the target one, and thereby protect the remote tissue or organ.[14–18] More interestingly, animal experiments showed that limb RIPC could mitigate lung injury induced by prolonged lower limb I/R or by hemorrhagic shock/resuscitation in rats.[19,20] We recently reported that limb RIPC could attenuate lung injury in patients undergoing elective open infrarenal abdominal aortic aneurysm repair *via* inhibiting oxidative stress and release of inflammatory cytokines.[21] However, whether or not limb RIPC can confer pulmonary protection after pulmonary resection in patients with lung cancer is unclear.

On the basis of the previous studies, we hypothesized that limb RIPC would reduce the lung injury in patients undergoing elective pulmonary resection and used a prospective, randomized, clinical trial to clarify this hypothesis. The primary outcome of the study was to compare P_{O_2}/F_{IO_2}, a variable reflecting the severity of lung dysfunction between the patients receiving RIPC and the control patients. The secondary outcome was to compare other selected pulmonary variables, incidences of in-hospital complications including ALI, malondialdehyde, and inflammatory cytokines between the groups.

Materials and Methods

A single-center, prospective, randomized, clinical trial was conducted on patients undergoing elective thoracic surgery for pulmonary resection. Written informed consent was obtained from each participant. This study was approved by the Research Ethics Committee of the First Affiliated Hospital, Sun Yat-Sen University (Guangzhou, China). The trial has been registered after the beginning of the study (NCT01307085).

Patients

Between July 2011 and June 2013, 216 adult patients scheduled for elective thoracotomy and pulmonary resection for clinical stage I or II non–small-cell lung cancer as assessed by computer tomography scan were recruited. Eligible patients, aged between 18 and 65 yr with an anticipant long period of intraoperative OLV (>60 and <120 min) were consecutively invited to participate in the current trial. All invited patients met the criteria for the American Society of Anesthesiologists physical status I to II category. The exclusion criteria included cardiac disease categorized as New York Heart Association classes II to IV, preoperative severe impairment of respiratory function (arterial oxygen tension [Pa_{O_2}] <60 mmHg or forced expiratory volume in 1 s <50% predicted), pre-existing coagulopathy or thrombocytopenia, previously received chemotherapy or radiation therapy or immunotherapy, systemic or local active infections (either clinically defined or suggested by evidence such as increased C-reactive protein levels, leukocytosis, or a body temperature of >38°C), peripheral vascular disease affecting the upper limbs, and administration of vitamins, nonsteroidal anti-inflammatory agent, or corticosteroid within 3 months.

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 sealed in numbered and opaque envelopes, and each treatment allocation was revealed by the anesthesiologists 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 allowed to release the intervention of study subjects' intervention to the surgical staff. The patients, the postoperative team, and clinical and research staff 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, postoperative outcome data, and death within 90 days of surgery were recorded carefully for all patients.

Intervention: Limb RIPC Protocol

The limb RIPC protocol was applied after the anesthetic induction and before the start of surgery. The limb RIPC consisted of three cycles: 5 min of left upper arm ischemia induced by an automated cuff-inflator placed on the left upper arm with inflation to 200 mmHg, followed by 5 min of reperfusion during which the cuff was deflated. A similar method was described in detail for inducing RIPC for myocardial protection during coronary artery bypass graft surgery.[12] The control group had a deflated cuff on the left upper arm for 30 min.

Anesthetic and Surgical Management

Forced vital capacity and forced expiratory volume in the first second were assessed preoperatively using a hand-held spirometer (Spirolab II; SDI Diagnostics, Rome, Italy). Chest radiograph was taken the day before surgery as part of the routine assessment and also taken every morning on each of the first 3 postoperative days and when clinically indicated.

Operative and anesthesia techniques were standardized for the purpose of this trial. None of the patients received premedication. All patients underwent general anesthesia combined with epidural anesthesia. 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 16-French catheter was placed in the urinary bladder immediately after induction of anesthesia to

monitor the urine output. Induction of anesthesia was initiated with intravenous propofol (1.5 mg/kg), rocuronium (0.6 to 0.9 mg/kg), and fentanyl (4 μg/kg). Anesthesia was maintained with a continuous infusion of propofol (4 to 8 $mg \cdot kg^{-1} \cdot h^{-1}$) and remifentanil (0.2 to 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$), aiming at a bispectral index of 40 to 50. Rocuronium was administered for further muscle relaxation as clinically indicated. After induction of anesthesia, an appropriate size of left- or right-sided double-lumen endotracheal tube (Ireland Blue Line Endobronchial Tube 37 or 39 French; Covidien IIC, Mansfield, MA) was intubated and its position was precisely confirmed using a fiber-optic bronchoscope (BF-MP60; Olympus, Tokyo, Japan) before and after the patients turned to the lateral decubitus position. During two-lung ventilation and OLV, all patients were ventilated following the same protocol with a tidal volume of 6 ml/kg per ideal body weight and fraction of inspired oxygen (F_{IO_2}) 1.0 and 5 cm H_2O positive end-expiratory pressure. Respiratory rates were adjusted to maintain the arterial carbon dioxide between 35 and 45 mmHg. During OLV, if the SP_{O_2} decreased to less than 95%, the following procedures were performed according to the established course to raise SP_{O_2}: (1) ensure that the delivered F_{IO_2} is 1.0; (2) check position of double-lumen tube or blocker using fiber-optic bronchoscopy; (3) ensure that cardiac output is optimal; (4) apply a recruitment maneuver to the ventilated lung; (5) apply continuous positive airway pressure of 1 to 2 cm H_2O to the nonventilated lung; (6) apply intermittent reinflation to the nonventilated lung; and (7) conduct severe or precipitous desaturation: resume two-lung ventilation (if possible). Need for the practice would result in removing the patient from the study.

Standardized fluid replacement and vasopressor treatment were applied preoperatively to maintain stable hemodynamics. Before the operation, a thoracic epidural catheter was inserted at T4-T5 or T5-T6 level for postoperative pain management. To make sure that the patients had a working epidural analgesia, pain scores were recorded during the first 3 postoperative days by using the visual analog scale rating from 0 (no pain at all) to 10 (worst possible pain).

All surgical procedures were performed by a single surgeon. Lung resection with systematic lymph node dissection was performed through a standard posterolateral muscle-sparing thoracotomy. Upon completion of the surgical procedures, positive pressure of 25 cm H_2O was applied to the nondependent or surgical lung for 5 s to assess bronchial stump air leak and to ensure lung expansion before closure of the thoracotomy. Then, the patient was extubated in the operating room and transferred to a postanesthesia care unit. In our study, all patients received pulse oximetry monitoring for 48 h after operation. Oxygen flow was titrated by the bedside clinician *via* either nasal cannulas to maintain a peripheral oxygen saturation of 95% or more. If patients were diagnosed with ALI/ARDS (Pa_{O_2}/F_{IO_2} <300), re-intubation and mechanical ventilation support were needed. A similar method for postoperative oxygen therapy was described in the study by Futier *et al.*[22]

Preparation of Blood Samples

Blood samples were collected for analysis at the following time points: T0 was after induction of anesthesia and just before OLV (baseline); T1 and T2 were 30 and 60 min after OLV was started but before resuming two-lung ventilation; T3 was 30 min after re-expansion; T4 to T7 were 6, 12, 24, and 48 h after operation, respectively. Venous blood was sampled from the jugular venous line and centrifuged within 20 min of collection at 2,000 rpm for 10 min at 4°C. Serum samples were stored at −80°C for subsequent analysis. Radial arterial blood was analyzed using a blood gas system (GEM Premier 3000; Instrumentation Laboratory, Bedford, MA).

Assessment of Lung Function

Lung function evaluation including Pa_{O_2}/F_{IO_2}, alveolar to arterial difference of oxygen tension ($A\text{-}aDO_2$), arterial–alveolar oxygen tension ratio (a/A ratio), and respiratory index was performed at the above sampling time points. During mechanical ventilation, the tidal volume, F_{IO_2}, peak and plateau airway pressure (P_{max} and P_{plat}), positive end-expiratory pressure, and respiratory compliance were obtained directly from the ventilator setting (S/5 Aespire 7900; Datex-Ohmeda, Madison, WI).

Postoperative lung injury was defined as pneumonitis, ALI, or ARDS occurring in the immediate postoperative period during hospitalization. ALI and ARDS were defined according to the American-European Consensus Conference on ARDS guidelines as: (1) sudden onset of respiratory distress; (2) radiographic infiltrates characteristic of pulmonary edema; (3) acute onset of hypoxemia with a Pa_{O_2}/F_{IO_2} less than 300 for ALI and less than 200 for ARDS; and (4) absence of hydrostatic pulmonary edema due to cardiac insufficiency or fluid overload, on the basis of pulmonary arterial catheterization, echocardiogram, laboratory data (creatine kinase-MB, troponin), clinical evaluation, or a combination of these.[23]

Evaluation of Inflammatory Response and Oxidative Stress

The levels of the inflammatory cytokines including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were measured using a quantitative sandwich enzyme-linked immunoassay with a commercially available kit (Jiancheng Bio-engineering Research Institute, Nanjing, China). The variables reflecting oxidative stress including malondialdehyde level in serum were analyzed using methods of thiobarbituric acid reaction. The lower detection limits for TNF-α, IL-6, and malondialdehyde were 0.5 pg/ml, 1.2 pg/ml, and 0.1 nmol/ml, respectively.

Primary and Secondary Study Outcomes

The primary outcome was Pao_2/Fio_2. The secondary outcomes included (1) other variables reflecting pulmonary injury (*e.g.*, a/A ratio, respiratory index), (2) the markers of oxidative stress and systemic inflammatory response, (3) postoperative hospital stay, (4) upper limb ischemia requiring intervention, (5) the incidence of ALI during hospitalization, and (6) the incidence of hospital complications in major organs, anastomosis leakage, sepsis, and death within 90 days of surgery.

Statistical Analysis

Sample size was calculated based on the results for Pao_2/Fio_2 reported previously.[24] With an expected difference of 20 mmHg between group means, an SD of 50 mmHg of the means, $\alpha = 0.05$, and $\beta = 0.8$, a sample size of 99 patients was required in each group. To compensate 10% cases for possible dropouts, a total 220 cases (110 for each group) were enrolled for study.

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 was compared by the Mann–Whitney *U* test. Inter- and intragroup mean values of pulmonary outcomes and biochemical serum markers were compared by repeated-measures ANOVA using Bonferroni correction as *post hoc* analysis. All *P* values were two-sided, and the statistical significance was defined as *P* value less than 0.05. Statistical analyses were conducted using the SPSS statistical software, version 16.0 (SPSS Inc., Chicago, IL).

Results

The CONSORT diagram was shown in figure 1. A total of 220 patients were assessed for eligibility, among them 216 were actually recruited and randomly assigned to the limb RIPC group (n = 108) or the control group (n = 108). Four patients were excluded from the data analysis, as one patient refused to participate, one patient had a history of thrombocytopenia, and two patients used vitamins within 3 months. Two hundred sixteen patients (108 in each group) completed the study and were included in the data analyses. No patients met difficulties in maintaining lung isolation with the double-lumen endotracheal tube. No patients required intermittent two-lung ventilation for SPo_2 less than 95% during surgery. No patients received intraoperative blood transfusion, and all patients were extubated at the end of the surgical procedure. No failure of epidural analgesia after an epidural catheter initial placement, defined as the need for additional intravenous opioids, was reported in the current study. The baseline characteristics and surgical data of the patients were summarized in table 1, and there was no statistically significant difference between the groups regarding either variable examined.

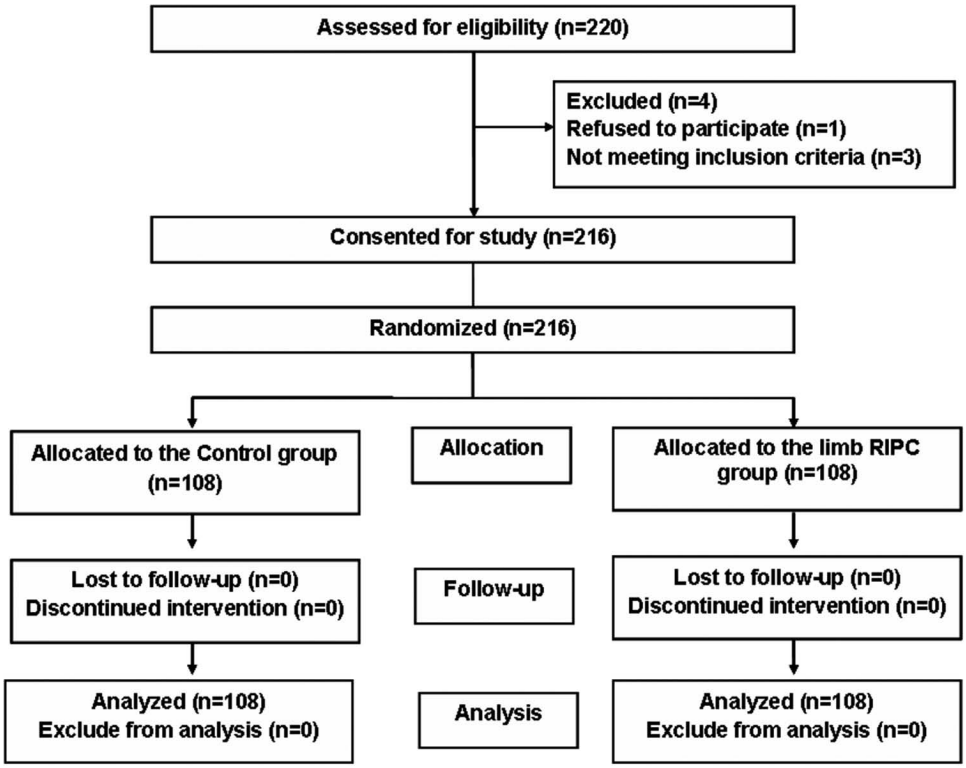

Fig. 1. Study flow diagram showing the flow of participants through each stage of the randomized trial. RIPC = remote ischemic preconditioning.

Table 1. Preoperative and Intraoperative Characteristics

	Limb RIPC Group (n = 108)	Control Group (n = 108)	*P* Value
Age (yr)	56 ± 9	59 ± 8	0.73
Weight (kg)	68 ± 12	64 ± 13	0.56
Sex, males	82 (76%)	76 (70%)	0.35
ASA score	2 (2–3)	2 (2–3)	0.91
Right-side surgery	49 (45%)	55 (51%)	0.41
Procedure			0.41
Wedge resection	30 (27%)	35 (32%)	
Lobectomy	80 (73%)	75 (68%)	
Preoperative FVC (% predicted)	90 (82–100)	88 (79–100)	0.39
Preoperative FEV_1 (% predicted)	89 (80–97)	86 (78–98)	0.42
Preoperative FEV1/FVC (%)	79 (74–85)	83 (79–89)	0.78
Preoperative Pao_2 (mmHg)	92 (87–100)	89 (85–98)	0.80
Preoperative $PaCO_2$ (mmHg)	37 (35–42)	36 (34–44)	0.92
Smoking, No. (%)			0.79
Current smokers	52 (48%)	56 (52%)	
Ex-smokers	45 (42%)	38 (35%)	
Never smoked	11 (10%)	14 (13%)	
Associated illness, No. (%)			
Hypertension	24 (22%)	29 (27%)	0.43
Diabetes mellitus	15 (14%)	23 (21%)	0.15
Previous myocardial infarction	6 (5%)	10 (9%)	0.29
Crystalloid (ml)	1,302 ± 236	1,583 ± 305	0.37
Colloid (ml)	300 ± 65	320 ± 50	0.63
Urine (ml)	430 ± 120	550 ± 170	0.17
Estimated blood loss (ml)	200 (100–250)	220 (100–300)	0.75
Intraoperative blood transfusion (ml)	0	0	1
Duration of anesthesia (min)	210 (200–230)	200 (180–220)	0.56
OLV duration (min)	100 (90–110)	90 (85–110)	0.67
Operation time (min)	180 (160–200)	170 (150–200)	0.70

Continuous data are reported as mean ± SD or median (interquartile range). Categorical data are given as counts (percentages).

ASA = American Society of Anesthesiologists; FEV_1 = forced expired volume in 1 s; FVC = forced vital capacity; OLV = one-lung ventilation; $PaCO_2$ = arterial carbon dioxide partial tension; PaO_2 = arterial oxygen; RIPC = remote ischemic preconditioning.

Postoperative data were summarized in table 2. All patients survived 90 days after operation. The incidences of cardiovascular complications were not significantly different between the limb RIPC group and the control group ($P = 0.39$). The length of postoperative hospital stay in the limb RIPC group was significantly shorter compared with that in the control group (6 [5, 8] day *vs.* 9 [7, 10] day, $P = 0.03$]. In the limb RIPC group, five of the patients had ALI after operation, whereas in the control group 13 patients had ALI ($P = 0.04$). Pain scores obtained from the two groups also were similar. No signs of upper arm pain, function disability, or sensory disability were observed postoperatively, and the incidence of hospital complications did not differ between the groups (all $P > 0.05$).

As shown in table 3, the hemodynamic variables, arterial pH, and $PaCO_2$ were also similar between the two groups at any observational points (all $P > 0.05$). The airway pressures increased and pulmonary compliance decreased with the initiation of OLV; however, static lung compliance and dynamic lung compliance in limb RIPC group were significantly higher than those in the control group at 30 and 60 min after OLV was started (all $P < 0.05$). As shown in figure 2A, Pao_2/FIO_2 in the limb RIPC group was significantly higher than that in the control group at 30 and 60 min after OLV was started, 30 min after re-expansion, and 6 h after operation (238 ± 52 *vs.* 192 ± 67, $P = 0.03$; 223 ± 66 *vs.* 184 ± 64, $P = 0.01$; 385 ± 61 *vs.* 320 ± 79, $P = 0.003$; 388 ± 52 *vs.* 317 ± 46, $P = 0.001$, respectively), and there was a significant difference between groups (ANOVA analysis: P (group) = 0.03, P (time) < 0.001, P (group–time interaction) < 0.001]. Similarly, there was a significant difference in a/A ratio between groups (ANOVA analysis: P (group) = 0.002, P (time) < 0.001, P (group–time interaction) < 0.001) (fig. 2B). Moreover, respiratory index and $A\text{-}aDO_2$ in the limb RIPC group was significantly lower than those in the control group at 30 and 60 min after OLV was started, 30 min after re-expansion, and 6 h after operation (all $P < 0.05$) (fig. 2, C and D).

In addition, the plasma IL-6 level was measured over time (fig. 3A), which was low (10 to 15 pg/ml) at 60 min after OLV was started in both groups but significantly increased at 30 min after re-expansion and peaked 12 h after operation. However, the IL-6 levels in the limb RIPC group were lower than those in the control group at 6, 12, 24, and 48 h after operation (all $P < 0.05$). Different from the changes of IL-6

Table 2. Postoperative Data

	Limb RIPC Group (n = 108)	Control Group (n = 1 08)	*P* Value
Pain score			
POD1	1.6 ± 0.8	1.7 ± 0.4	0.63
POD2	1.9 ± 0.7	2.1 ± 0.6	0.56
POD3	1.8 ± 0.6	2.0 ± 0.9	0.38
Postoperative hospital stay	6 (5–8)	9 (7–10)	0.03
Hospital complication			
Cardiovascular complications	8 (7.4%)	5 (4.6%)	0.39
Renal complications	0	0	1
Liver complications	0	0	1
Neuralgic events	0	0	1
Upper limb ischemia requiring intervention	0	0	1
Sepsis	0	0	1
Death	0	0	1
Abnormal chest radiograph, postoperatively			
Atelectasis	9 (8.3%)	11 (10.1%)	0.63
Infiltration	13 (12%)	19 (17.6%)	0.25
ALI	5 (4.6%)	13 (12.0%)	0.04
ARDS	4 (3.6%)	6 (5.5%)	0.51

Continuous data are reported as mean ± SD or median (interquartile range). Categorical data are given as counts and percentages. Hospital complications were complications developed postoperatively during the hospital stay; cardiovascular complications were an increased cardiac enzyme or newly developed arrhythmia requiring treatment; renal complications were an increased serum creatinine or decreased estimated glomerular filtration rate; and liver complications were aspartate aminotransferase or alanine aminotransferase >200 U/l or total bilirubin >3 mg/dl.

ALI = acute lung injury; ARDS = adult respiratory distress syndrome; POD = postoperative day; RIPC = remote ischemic preconditioning.

levels, the plasma TNF-α level gradually increased during the whole observational period and sharply peaked at 48 h after surgery (fig. 3B). Likewise, there was a significant difference in TNF-α level between the groups at 6, 12, 24, and 48 h after surgery (all $P < 0.05$).

As shown in figure 3C, the serum malondialdehyde levels at 30 min after OLV was started did not differ between the two groups ($P > 0.05$). It increased transiently at 60 min after OLV was started and returned to the baseline values 12 h after surgery for both groups. However, the malondialdehyde levels at 60 min after OLV was started, 30 min after re-expansion in the limb RIPC group, were lower than those in the control group (All $P < 0.05$).

Discussion

In this prospective, randomized, and controlled trial, the overall incidence of postoperative ALI was 12.0% in patients undergoing pulmonary resection. This result is in agreement with the findings of previous reports.[5,6] More valuably, for the first time, an apparent trend was observed toward protection from pulmonary injury in the patients who were randomized to limb RIPC.

The concept of RIPC was first introduced by Przyklenk *et al.*[25] as the initial study suggested that one vascular bed could precondition another vascular bed in dogs. The later studies suggested that transient ischemia of the limb could also induce protection for organs against subsequent I/R injury. Limb RIPC is a particular protocol whereby a brief ischemia in limbs protects distant tissue or organs from prolonged ischemia through either humoral mediators or neuronal pathway.[26] Its noninvasive nature and promising experimental results have led to numerous clinical studies validating organ-protective effects of limb RIPC. However, regarding lung protection, there are some conflicting results. For example, one study showed that limb RIPC did not improve postoperative oxygenation in children undergoing cardiac surgery.[11] Another recent study also suggested that RIPC did not provide significant pulmonary benefit after complex valvular cardiac surgery.[27] Different from the two researches, it was demonstrated that repeated limb RIPC improved postoperative lung compliance accompanied by reduced inflammatory reaction in infants after cardiac surgery.[28] We recently also found that limb RIPC improved oxygenation in adult patients undergoing elective open infrarenal abdominal aortic aneurysm repair.[21] Obviously, the conflicting results could be related to different experimental protocols and research subjects.

Although the exact mechanisms of pulmonary injury after lung resection with OLV have not been fully elucidated, it is most likely that the etiology is multifactorial including mechanical damage due to surgical manipulation and high airway pressure, biochemical injury resulting from high oxygen tension, and OLV-induced atelectasis and re-expansion.[29–33] Among these factors, an I/R-like response resulting from re-expansion of a previously collapsed lung after OLV may be a key factor. It was reported that this I/R-like response could result in biochemical and functional changes including the releases of a large number of reactive oxygen species and inflammatory cytokines not only in the previously collapsed lung but also in the contralateral lung and the remote organs.[34] To date, no direct evidence

Table 3. Hemodynamic Data and the Variables Reflecting Lung Function

Variable	Basline	30 min after OLV	60 min after OLV	30 min after Expansion	6 h after Operation	12 h after Operation	24 h after Operation	48 h after Operation
MAP (mmHg)								
Control group	74 ± 15	78 ± 19	80 ± 20	82 ± 14	87 ± 16	85 ± 17	82 ± 16	79 ± 18
Limb RIPC group	68 ± 17	74 ± 17	78 ± 14	77 ± 16	89 ± 19	84 ± 15	83 ± 13	81 ± 15
HR (beats/min)								
Control group	73 ± 15	78 ± 13	79 ± 18	74 ± 13	84 ± 20	87 ± 19	83 ± 14	84 ± 15
Limb RIPC group	76 ± 18	72 ± 19	77 ± 16	88 ± 16	88 ± 17	85 ± 16	80 ± 12	83 ± 14
CVP (mmHg)								
Control group	4 ± 2	7 ± 3	9 ± 4	8 ± 2	9 ± 3	7 ± 3	5 ± 2	7 ± 3
Limb RIPC group	5 ± 2	8 ± 3	9 ± 3	7 ± 3	8 ± 4	7 ± 4	6 ± 2	6 ± 3
Arterial pH								
Control group	7.38 ± 0.02	7.32 ± 0.03	7.30 ± 0.03	7.39 ± 0.02	7.37 ± 0.02	7.39 ± 0.01	7.38 ± 0.02	7.40 ± 0.03
Limb RIPC group	7.40 ± 0.02	7.31 ± 0.02	7.33 ± 0.02	7.38 ± 0.03	7.40 ± 0.03	7.41 ± 0.02	7.36 ± 0.02	7.38 ± 0.01
$Paco_2$ (mmHg)								
Control group	37 ± 2	41 ± 4	44 ± 3	35 ± 2	40 ± 4	41 ± 3	38 ± 2	37 ± 3
Limb RIPC group	37 ± 3	43 ± 4	43 ± 5	37 ± 3	39 ± 3	38 ± 4	37 ± 2	38 ± 3
Cs (ml/cm H_20)								
Control group	53 ± 10	28 ± 6*	22 ± 8*	37 ± 6				
Limb RIPC group	56 ± 12	30 ± 8*	28 ± 7*	40 ± 7				
Cd (ml/cm H_20)								
Control group	50 ± 11	24 ± 5*	21 ± 4*	33 ± 5				
Limb RIPC group	55 ± 9	27 ± 7*	25 ± 6*	37 ± 6				

Continuous data are presented as means ± SD or median (interquartile range).

*$P < 0.05$ *vs.* baseline.

Cd = dynamic lung compliance; Cs = static lung compliance; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; OLV = one-lung ventilation; $Paco_2$ = arterial carbon dioxide partial tension; RIPC = remote ischemic preconditioning.

is noted that HPV alone causes lung injury after the pulmonary resection. During OLV, the operated lung not only remains atelectatic but also hypoperfused because of HPV.[35,36] Although HPV decreases the shunt fraction and attenuates hypoxemia,[37,38] it could be an aggravating factor for lung injury when ventilation is restored because the pulmonary re-expansion promotes the re-entry of oxygen through the airways, causing the release of excessive oxidative radicals.[36] Therefore, HPV could be one of the potential mechanisms of ALI during lung resection with OLV, which needs further study to provide direct evidence.

In the current study of assessing the protective effect of limb RIPC on lung injury in patients undergoing elective pulmonary resection, Pao_2/Fio_2 was chosen as the primary variable because it is a useful parameter for detecting impaired intrapulmonary gas exchange and oxygenation. Dynamic lung compliance is also one of the commonly measured variables in association with lung injury.[39] The current study proved a positive effect of limb RIPC that mitigated the decrease of Pao_2/Fio_2 and the reduction of dynamic lung compliance during thoracic surgery, which indicates that limb RIPC can improve intraoperative oxygenation. Interestingly, limb RIPC not only improved the primary end point compared with the control group but also reduced the incidence of ALI after pulmonary resection.

It has been demonstrated that limb RIPC reduces an inflammatory response by up-regulation of cyto-protective genes and down-regulation of proinflammatory genes related to the pathogenesis of I/R injury.[40,41] TNF-α and IL-6 are established proinflammatory cytokines that are associated with postoperative pulmonary dysfunction and prolonged mechanical ventilation.[42–44] Thus, the serum levels of TNF-α and IL-6 were investigated in the current study. In this study, the IL-6 levels before OLV were negligible in both groups; however, they significantly increased at 30 min after re-expansion. The current study showed that limb RIPC significantly reduced the increase in serum IL-6 level at the end of surgery. This result suggests a possibility that ongoing postoperative insult offsets the immune-modulatory effect of limb RIPC during thoracic surgery and/or that there was no persistent or inducing anti-inflammatory effect of limb RIPC in the postoperative period.

I/R injury is accompanied by reactive oxygen species generation, and OLV during thoracic surgery is a powerful free radical generator due to hypoxia/reoxygenation. A previous study on lobectomy in patients with lung cancer showed that lung re-expansion from OLV provoked more severe oxidative injuries than surgical intervention by measuring malondialdehyde, a product of lipid peroxidation. Moreover, increasing durations of OLV result in increased levels of markers of oxidative stress.[8] Cellular damage after a hypoxic insult is biphasic, initiating with the lack of oxygen and exacerbating during reoxygenation. There is now abundant evidence that reoxygenation injury is the structural damage caused by the overwhelming generation of free radicals. They interact with cellular structural molecules provoking dysfunction mostly to endothelial cells. The formation of these reactive species can, at toxic levels, cause molecular and ultimately cellular damage

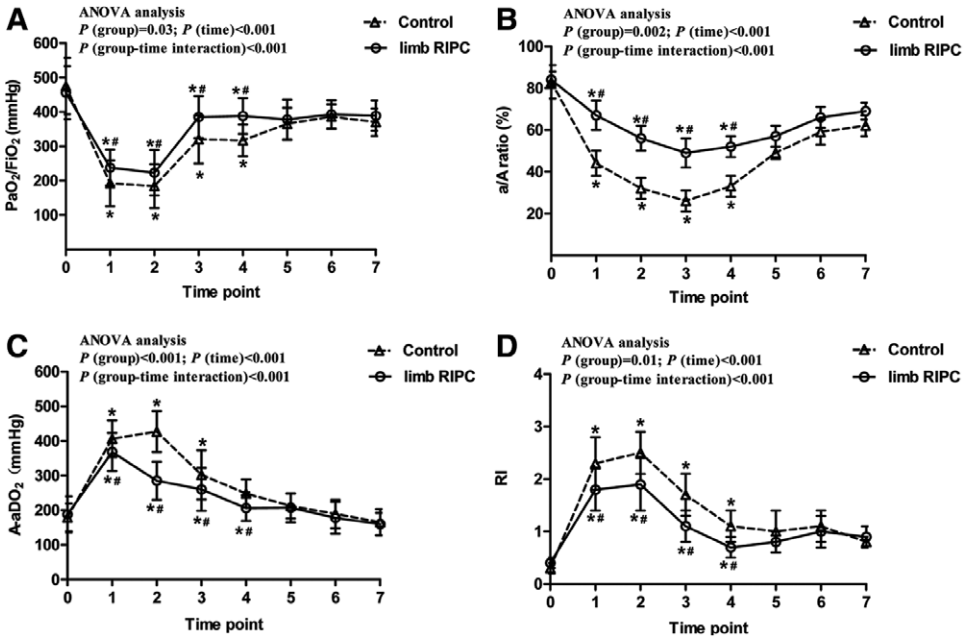

Fig. 2. Variables of lung function at various time points in patients undergoing pulmonary resection with or without limb remote ischemic preconditioning (RIPC). n = 108 for each group. (*A*) Pao_2/Fio_2; (*B*) a/A ratio; (*C*) A-aDO_2; (*D*) respiratory index (RI). Data are represented as mean ± SD. *$P < 0.05$ *versus* baseline; #$P < 0.05$ *versus* control. a/A ratio = arterial–alveolar oxygen tension ratio; A-aDO_2 = alveolar to arterial difference of oxygen tension; T0 = after induction of anesthesia and just before one-lung ventilation (OLV) (baseline); T1 = 30 min after OLV was started, and just before resuming two-lung ventilation; T2 = 60 min after OLV, 30 min after OLV was started, and just before resuming two-lung ventilation; T3 = 30 min after re-expansion; T4 to T7: 6, 12, 24, and 48 h after operation, respectively.

and could contribute to lung injury after thoracotomy. Williams *et al.*[45] and Lases *et al.*[46,47] have both produced evidence of oxidative damage in patients undergoing pulmonary resection. Misthos *et al.*[8] have recently published further evidence to support the concept that oxidative stress contributes to lung damage after lung resection. These workers measured plasma malondialdehyde in plasma as a surrogate marker for oxygen free radicals in patients undergoing lung resection. In this study, patients with lung cancer had a higher production of oxygen free radicals compared with that in a control population. The magnitude of oxidative stress as measured by raised malondialdehyde levels was related to the use of OLV and the duration of OLV. Lung re-expansion after a period of OLV also provoked severe oxidative stress, and thus supporting the concept of reperfusion injury. Moloney *et al.*[48] have, in addition, demonstrated increased levels of leukotriene B4, hydrogen peroxide, and hydrogen ions in exhaled breath condensates after lobectomy for lung cancer. This provides further evidence of the pulmonary inflammation and oxidative stress response after lung cancer surgery. In the current study, we showed that lung re-expansion from OLV provoked severe oxidative injuries through measuring malondialdehyde level in patients with lung cancer undergoing pulmonary resection, but malondialdehyde levels at 60 min after OLV was started and 30 min after re-expansion in limb RIPC group were lower than those in control group, which suggested that the limb RIPC provides protective effects on ALI after pulmonary resection *via* an antioxidant pathway. Another notable finding of the current study was that limb RIPC significantly shortened the length of postoperative hospital stay, even though most patients only received wedge resections. It could be attributable to the antioxidant and anti-inflammatory effects of limb RIPC as the above mentioned.

Previous studies showed that different anesthesia techniques could have different effects on inflammatory response and pulmonary function of perioperative patients with OLV.[44,49,50] In addition, it was reported that RIPC could confer myocardial protection for patients undergoing coronary artery bypass graft surgery under sevoflurane anesthesia but not propofol.[51] However, in the current study, we used total intravenous anesthesia with propofol–remifentanil in all patients. Thus, in the current study, RIPC reduces the lung injury under propofol–remifentanil anesthesia.

There are several limitations in the current study. First, because a trial with many thousands of patients after lung resection is required to detect the difference in clinical outcome with sufficient power, the current exploratory trial with a small scale was only designed to determine the effects of limb RIPC on subclinical pulmonary damage in patients undergoing lung resection. Second, although we have tried to exclude potential interferences from the trial, some factors such as genetic,[52] demographic, social, and other factors[53] could still interfere with the study results regarding accurately evaluating ALI. Third, the exact pathophysiology of ALI after lung resection is complex with many factors involved. In this study, we just explored the mechanisms

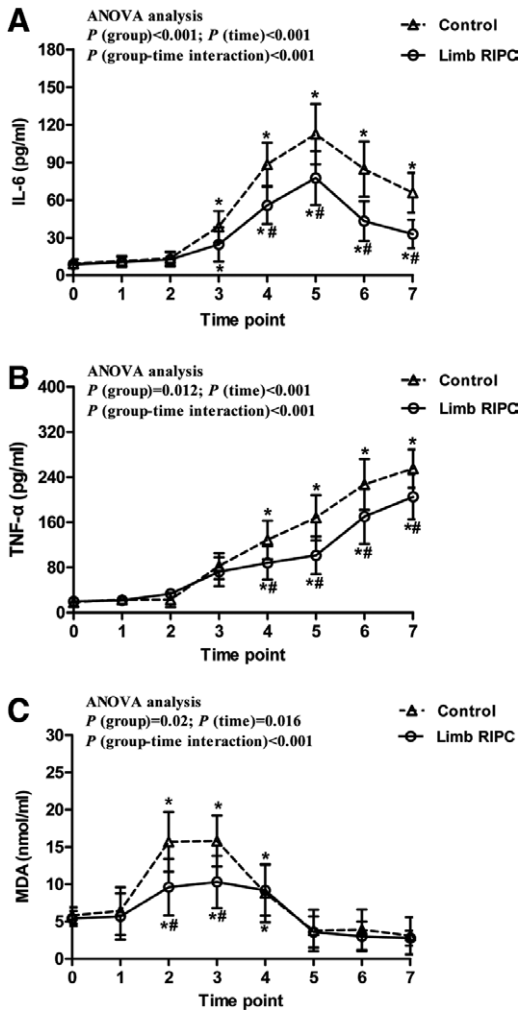

Fig. 3. Biomarkers reflecting inflammatory response and oxidative stress at various time points in patients undergoing pulmonary resection with or without limb remote ischemic preconditioning (RIPC). n = 108 for each group. (*A*) Interleukin-6 (IL-6) concentration; (*B*) tumor necrosis factor-α (TNF-α) concentration; and (*C*) serum malondialdehyde (MDA) concentration. Data are represented as mean ± SD. *$P < 0.05$ *versus* baseline; #$P < 0.05$ *versus* control. T0 = after induction of anesthesia and just before one-lung ventilation (OLV) (baseline); T1 = 30 min after OLV was started and just before resuming two-lung ventilation; T2 = 60 min after OLV, 30 min after OLV was started, and just before resuming two-lung ventilation; T3 = 30 min after re-expansion; T4 to T7: 6, 12, 24, and 48 h after operation, respectively.

related to oxidative stress and inflammatory response *via* which limb RIPC conferred its pulmonary protection. At last, our study did not evaluate the postoperative pulmonary variables because arterial blood gases were not routinely obtained unless clinically indicated.

In conclusion, this small, preliminary but novel study strongly implied that intermittent upper limb ischemia as a RIPC stimulus may improve intraoperative pulmonary function in patients without severe pulmonary disease after lung resection under propofol–remifentanil anesthesia. Our findings merit a larger trial to establish the effect of limb RIPC on clinical outcomes in the future.

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Competing Interests

The authors declare no competing interests.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Wine before Swine: Circe's Anticholinergic Potion

England's Anne Pratt depicted (ca.1860, *right*) the intoxicating beauty of the Nightshades Family, or Solanaceae, such as (1) Thornapple (*Datura*), and the (2) Stinking (henbane), (3) Woody (bittersweet), (4) Black (common), and (5) Deadly (belladonna) Nightshades. One or more plants like these and/or Mandrake (*Mandragora*) likely supplied deliriant anticholinergics for the wine-laced potion that J. M. Waterhouse painted (1891, *left*) witch-goddess Circe feeding to the shipmates of Odysseus (Ulysses). In high doses, such tropane alkaloidal mixtures of hyoscyamine, scopolamine, and atropine can kill; in low doses, these deliriants can induce hallucinations of flying or of transforming into animals. According to Homer's *Odyssey*, each drugged sailor (believed that he) was transformed into a pig (*left*, at Circe's feet) by the witch-goddess' anticholinergic potion. (Copyright © the American Society of Anesthesiologists, Inc.)

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