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Original Article

Combination of Continuous Positive Airway Pressure and Air Reinflation during One-Lung Ventilation Attenuates Lung Injury Following Esophagectomy: A Randomized Clinical Trial

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ABSTRACT

Background: One-lung ventilation (OLV) is routinely used in esophagectomy to facilitate surgery. Lung injury may be induced by a "multiple-hit" mechanism. The aim of this study was to determine whether combined intervention using continuous positive airway pressure (CPAP) and air reinflation can reduce lung injury after OLV.

Methods: Patients scheduled for esophagectomy were enrolled in this prospective study. These patients were assigned randomly to four different groups. In the control group (N=24), the collapsed lung was reinflated with 80% oxygen. In the air reinflation group (N=25), room air was used to regain two-lung ventilation. In the CPAP group (N=24), 5 cm H_2O CPAP was administered to the contralateral lung during OLV. In the CPAP+AIR group (N=24), the contralateral lung received CPAP during OLV, and room air was used for reinflation of the lung. Plasma malondialdehyde (MDA), superoxide dismutase (SOD), tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8) levels were measured at baseline (10 minutes after two lung ventilation) and 3 hours after reinflation. Bronchoalveolar lavage fluid (BALF) was obtained 30 minutes after lung re-expansion for measurements of surfactant apoprotein A (SP-A) and surfactant apoprotein C (SP-C). Computerized tomography was used to precisely detect micro-atelectasis on the fourth postoperative day.

Results: Compared with the control group, CPAP and combined intervention increased arterial oxygen pressure levels 60 minutes after OLV (164±43 vs. 217±43; 164±43 vs. 216±52, P<0.05). The plasma MDA level in the air reinflation group was lower and SOD level was higher than those in the control group 3 hours after lung reinflation (P<0.05). The CPAP group had a lower plasma IL-8 level, a less atelectasis and a higher SP-A level in BALF (P<0.05) as compared to the control group. In the CPAP+AIR group, the plasma levels of MDA, IL-6, and IL-8, and atelectatic area reduced (7.9±3.9% vs. 4.4%±3.3%, P<0.05), while levels of SOD, SP-A, and SP-C increased (P<0.05) when compared with the control group.

Conclusions: CPAP combined with air reinflation increased arterial oxygen pressure levels during OLV, reduced oxidative stress and inflammation, and minimized atelectasis following esophagectomy.

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One- lung ventilation (OLV) is routinely used in esophagectomy to facilitate surgical procedures. Postoperative lung injury may be induced by a "multiple- hit" mechanism (1). OLV induces hyperperfusion and over ventilation of the ventilated lung, which injury the lung through micro- barotrauma (2). Collapse and subsequent re- expansion of the collapsed lung may also result in pulmonary insult. Hypoxia may be encountered in the practice of OLV (3). Continuous positive airway pressure (CPAP) is an effective means of improving oxygenation during OLV, and CPAP levels of as little as 3 cm H_2O have been shown to be sufficient for this purpose (4, 5). However, recent studies have shown that reinflation of the collapsed lung after OLV leads to oxidative and inflammatory reaction (6, 7). Further research is thus required to determine whether use of CPAP during OLV can attenuate oxidative and inflammatory response, and ultimately minimize lung injury.

During OLV, the collapsed lung is hypoperfused, and is subjected to some degree of ischemia. Re-expansion and reperfusion of the lung adds further insult. It is common for patients to be ventilated with a high fraction of respired oxygen (FiO_2) of 80% or even 100% at the time of reperfusion. In a rabbit model of lung reperfusion, it was found that hyperoxic ventilation at reperfusion may worsen lung reperfusion injury, as compared to reventilation with room air (8). We hypothesized that in clinical situations, use of a low FiO_2 during reinflation would modify reperfusion injury, as compared with 80% oxygen ventilation.

Atelectasis appears in almost 90% of patients who receive general anesthesia. A study in humans revealed that high FiO_2 promoted pulmonary atelectasis after general anesthesia (9). It was therefore suggested that lower FiO_2 should be used to minimize absorption atelectasis. These studies were conducted in two-lung ventilation (TLV) situations. It seems likely that application of air reinflation in OLV is more critical compared with TLV because of re-expansion.

Multiple factors are involved in the process of postoperative lung injury. It is difficult to achieve optimum lung protective effects via single intervention technique in clinical situations. This clinical trial evaluated lung injury both as it is related to the method of carrying out OLV, and in regaining bilateral lung ventilation. The aim of this prospective randomized trial was to determine whether combined intervention with CPAP and air reinflation would reduce lung injury after OLV. The impact of CPAP and air reinflation on oxygenation, oxidative stress, inflammatory response, and atelectasis was evaluated.

MATERIALS AND METHODS

Study Population

The protocol was approved by the medical ethics committee of the affiliated hospital of Luzhou Medical college, and was registered in the Chinese clinical test registration center, with the registration number ChiCTR- TRC- 11001402. Informed consent was obtained from all patients. Patients scheduled for esophagectomy were eligible for this study provided they agreed to postoperative analgesia. Exclusion criteria included New York Heart Association class (NYHA) III or IV, preexisting chronic obstructive pulmonary disease with preoperative forced expiratory volume (FEV1) of less than 80% in 1 second. Patients with coronary artery disease, morbid obesity (body mass index >35 kg/m^2), cerebrovascular disease, or severe liver or renal malfunction were also excluded. Exit criteria included patient pulse oxygen saturation (SpO_2) less than 90%, or surgery time less than 2 hours.

Perioperative Management

All patients received routine anesthesia, which included intravenous propofol (initially 2-3 mg/kg and subsequently 50-100 μg/kg/min), fentanyl (2-3 μg/kg) and remifentanil (0.1-0.2 μg/kg/min), and cisatracurium (0.2 mg/kg). A fiberoptic bronchoscope was employed for the insertion of the double-lumen tube. Mechanical ventilation was carried out using FiO_2 (fraction of inspiration O_2) of 0.8, a tidal volume (V_T) of 9 ml/kg for TLV, and 7 ml/kg for OLV. The respiratory rate was adjusted to maintain arterial blood carbon dioxide partial pressure ($PaCO_2$) at a level of 35 and 45 mm Hg throughout the surgery. OLV was initiated at the start of surgery, and was terminated when the definitive part of the surgical procedure ended. Ohmeda CAM anesthesia gas monitor (Datex-Ohmeda Inc., Tewkes-

bury, MA) was used to monitor the anesthesia gas and oxygen concentration.

All operations were carried out by the same experienced surgical team, which were also blinded to the trial protocol in this study. Surgical procedures included esophagectomy and esophageal reconstruction. The patients and the technician who performed the biomarker assays were also blinded to the randomization grouping.

Extubation was performed when the following criteria were fulfilled: (1) the patients were conscious and sufficiently alert; (2) SpO_2>95% when breathing room air; and (3) $PaCO_2$ was less than 50 mm Hg. All patients received intravenous patient controlled analgesia with fentanyl and tramadol, and visual analogue scale (VAS score) was recorded.

Trial Protocol

Patients were assigned randomly to four groups. Randomization was performed using computer generated random numbers, enclosed in sealed envelopes. In the control group (Control), OLV was initiated at the start of surgery, and the collapsed lung was reinflated with 80% oxygen. In the air reinflation group (AIR), room air was used to recover TLV, and to maintain ventilation for 5 minutes, followed by TLV with 80% oxygen. In the CPAP group, 5 cm H_2O continuous CPAP with 80% oxygen was administered to the contralateral lung, and 80% oxygen was used for recovery of TLV. In the CPAP and AIR group (CPAP + AIR), the contralateral lung received CPAP with 80% oxygen during OLV, and room air was used to reinflate the lung and maintain ventilation during TLV.

A Simple Lightweight CPAP-Delivery Device

The CPAP-delivery device used in this trial was according to a previous study (10). It was composed with a three-way stopcock (Yi Xinda, Shenzhen, China) and a funnel-shaped piece of tube tightly connected to the proximal end of the bronchial lumen of a double-lumen tube. A pressure gauge (Fuyang Huayi meter factory, Hangzhou, China) was connected via a second stopcock for monitoring CPAP levels. The oxygen-flow rate was measured with an electrical flow meter (Novametrix Medical Systems, Wallingford, CT, USA) (11). All the materials used in this study are easy to acquire.

Blood Gas Analysis

Blood gas analysis and hemodynamic variables were measured and recorded at four time points: (1) 1 minute before initiation of OLV; (2) 30 minutes after initiation of OLV; (3) 60 minutes after initiation of OLV; (4) at the termination of OLV.

Bronchoalveolar Lavage Fluid (BALF)

Bronchoalveolar lavage fluid (BALF) was obtained 30 minutes after lung re-expansion using a flexible fiber-bronchoscope as described in a previous study. Seven successive 20-ml aliquots of 37 ℃ saline were instilled and aspirated immediately with 50 mm Hg suction (recovery 69 ± 23 ml). BALF was centrifuged at 1,500 g for 10 minutes at 4 ℃. Cell-free BALF supernatant was stored at -80 ℃ for measurements of surfactant apoprotein A (SP-A) and surfactant apoprotein C (SP-C).

Biomarker Assays

Arterial blood samples were collected from an indwelling arterial catheter for measurements of serum malondialdehyde (MDA), superoxide dismutase (SOD), tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), interleukin-8 (IL-8), and interleukin-6 (IL-6) levels at baseline (10 minutes after TLV) and 3 hours after reinflation. This plasma was centrifuged at 1,000 g for 15 minutes at 4 ℃. Supernatant was collected and stored at -80 ℃ until measurements were performed. Enzyme-linked immunoassays were used for measurements of these markers, and biomarker assays were performed using assay kits (Jianchen Bioengineering Institute, Nanjing, China) according to the manufacturer's instructions.

Computed Tomography

On the fourth postoperative day, patients were transported to the Department of Radiology for computed tomography (CT) scans. To avoid inter-observer variation, CT analysis was performed by the same investigator who was blinded to the patient's study group. Patients were told to lie in the supine position and raise their arms above their heads during CT scans. The examination was carried out at resting expirato-

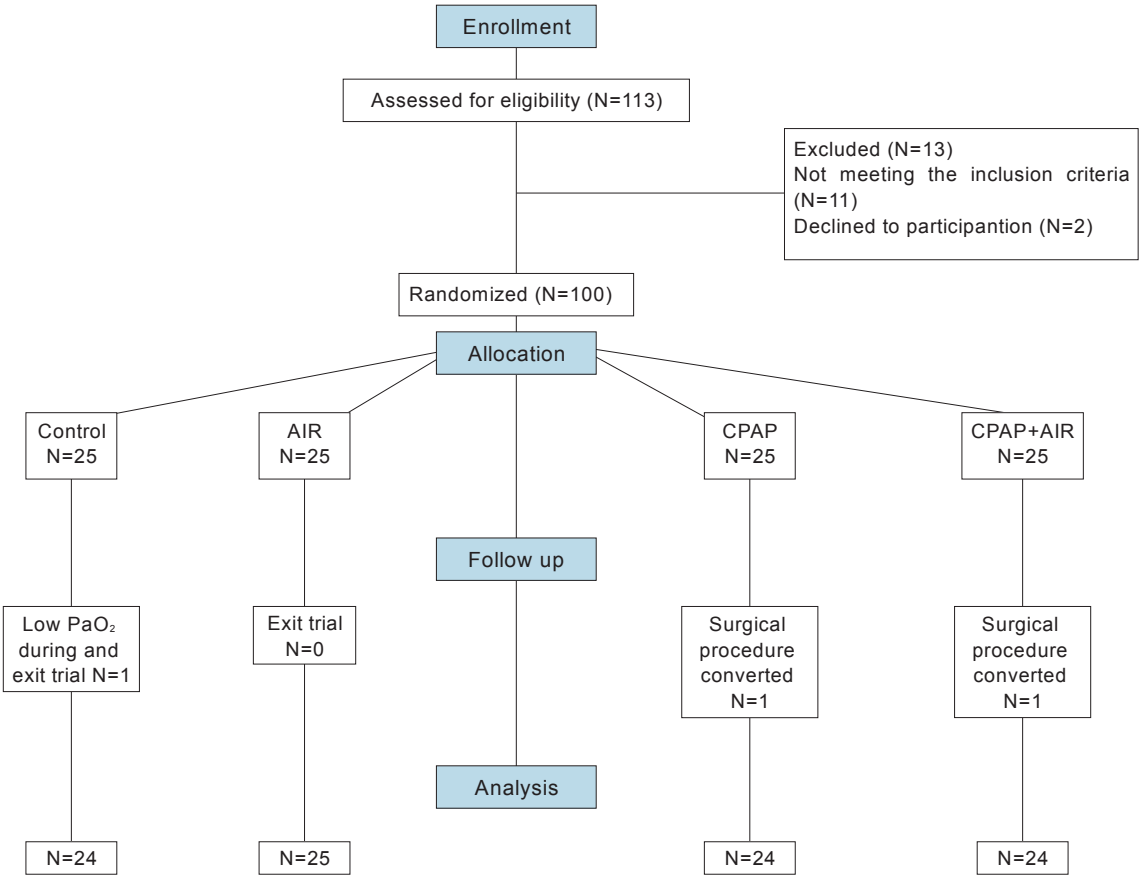

Figure 1. Participant Flow Diagram.

ry lung volume (11). Exposure time was 9 seconds for a 12 cm volume scan at 280 mA and 120 kV. Images were reconstructed with a slice thickness of 1.0 cm and a 512 × 512 matrix. The patients received a total estimated effective radiation dose of 1.5 millisieverts. Analysis of atelectasis and pulmonary aeration were done at 1 cm and 5 cm above the top of the left diaphragm. Lung area was delineated manually from the inner margins of the thoracic cage. Standard definitions of lung aeration according to attenuation values in Hounsfield Units (HU) were used. Aerated lung area was classified by volume elements with attenuation values between -100 HU and -1,000 HU, and atelectasis was defined by values between + 100 and -100 HU (12). The amount of atelectasis was expressed as atelectatic area and the percentage of the total lung area.

Sample Size and Statistical Analysis

Power calculation was based on previous studies on ventilator-associated lung injury in esophagectomy (13). We calculated that 24 patients had to be included in each group to detect a difference in mean IL-6 concentration of 50%, an estimated SD of 60%, with a two-sided significance level of 0.05 and power of 80%. All quantitative data are expressed as means ± SD. Male, ASA physical status, Smoke, and Stage pTNM (UICC) were expressed as a percentage, and differences between groups were compared using chi-square or Fisher exact tests. The intra group comparisons of respiratory and hemodynamic data at different time points were done using repeated measures analysis of variance (ANOVA). If significant differences between and within groups were found, multiple comparison with Bonferroni correction was applied. Differences with the rest of the data were examined by one-way ANOVA followed by the least-significant difference (LSD) test. $P<0.05$ was considered statistically significant. All analyses were carried out using SPSS version 13.0 (SPSS Inc, Chicago,

Table 1. Demographic Data, Duration of OLV, Intraoperative Blood Loss, Intraoperative Fluid Administration, and VAS Score.

Group	Control (N=24)	AIR (N=25)	CPAP (N=24)	CPAP+AIR (N=24)
Age (year)	60.3±9.3	59.7±7.2	59.4±8.1	57.3±10.6
Male, N (%)	21 (87.5)	20 (80)	20 (83.3)	21 (87.5)
BMI (kg/m^2)	22.2±2.2	22.1±2.5	22.3±2.8	21.6±2.4
ASA physical status, N (%)				
I	6 (25)	4 (16)	7 (29.2)	5 (20.8)
II	17 (70.8)	19 (76)	15 (62.5)	16 (66.7)
III	1 (4.2)	2 (8)	2 (8.3)	3 (12.5)
Smoke, N (%)	14 (58.3)	17 (68)	16 (66.7)	15 (62.5)
FEV1 (%)	95.5±12.8	95.6±12.3	97.0%±13.1	96.3±11.9
FVC (%)	98.6±12.1	99.8±13.2	97.5±11.4	99.4±16.6
FEV1/ FVC (%)	77.9±5.7	76.1±5.1	75.7±6.1	75.8±6.3
Stage pTNM (UICC), N (%)				
I	7 (29.2)	6 (24)	4 (16.6)	7 (29.2)
II	13 (54.2)	16 (64)	17 (70.8)	12 (50)
III	4 (16.6)	3 (12)	3 12.5)	5 (20.8)
OLV duration (minute)	97±28	95±21	98±13	101±15
Intraoperative blood loss (ml)	498±274	512±318	523±381	536±297
Intraoperative fluid administration (ml)	3179±696	3337±809	3188±849	3179±927
VAS score of postoperative day 1	2.2±1.7	2.3±1.9	2.1±1.3	2.4±1.5
VAS score of postoperative day 4	1.3±0.9	1.5±1.1	1.1±1.2	1.4±0.7

Data are expressed as means±SD except for male, ASA physical status, smoke, and stage pTNM (UICC).
There were no statistically significant differences in all variables between groups.
ASA, American Society of Anesthesiologists; pTNM (UICC), postoperative pathologic staging of union for international cancer control; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; OLV, one-lung ventilation; VAS, visual analogue scale.

IL, USA).

RESULTS

Patients

From November 2010 to December 2012, patients scheduled for selective esophagectomy were consecutively recruited into this study (Figure 1). Of 113 eligible patients, 100 were randomly allocated into four groups. Patients in these four groups had comparable demographic data. Two patients randomized into the CPAP and CPAP + AIR groups were excluded from final analysis, because their intended surgical procedures were converted to palliative operations, which took much less time (<2 hours). One patient in the control group had unstable partial pressure of arterial oxygen (PaO_2) during OLV, and CPAP had to be applied. In total, 97 patients completed the study protocol. There was no difference in the VAS scores of these patients postoperatively (Table 1).

As shown in table 2, the PaO_2 decreased at 30 minutes, 60 minutes, and the end of OLV in four groups as compared to 1 minute before OLA ($P<0.05$). The PaO_2 levels were improved in both the CPAP and the CPAP + AIR groups during OLV, compared to the Control and AIR group ($P<0.05$). The OLV increased the inspiratory plateau pressure (Pplat) in all patients ($P<0.05$). There were no differences among groups with respect to $PaCO_2$, MAP, and HR ($P>0.05$).

Oxidative Stress

As shown in figure 2, the plasma MDA content which is an index of lipid peroxidation was significantly reduced in the AIR group and CPAP + AIR group, as compared with the control group ($P<0.05$). At the same time, levels of the antioxidant SOD were significantly increased in the above two groups ($P<0.05$). There were no differences between the three intervention groups

Table 2. Respiratory and Hemodynamic Variables.

	1 minute before OLV				OLV 30 minutes				OLV 60 minutes				OLV end			
Group	Control	AIR	CPAP	CPAP+AIR	Control	AIR	CPAP	CPAP+AIR	Control	AIR	CPAP	CPAP+AIR	Control	AIR	CPAP	CPAP+AIR
PaO_2 (mm Hg)	372±51	381±48	379±50	384±57	150±43 *	156±54 *	193±44 *#†	189±51 *#†	164±43 *	169±55 *	217±43 *#†	216±52 *#†	175±43 *	182±57 *	229±44 *#	237±57 *#†
$PaCO_2$(mm Hg)	41±3	40±4	39±3	40±3	41±3	40±3	42±8	40±3	42±4	41±4	43±6	41±4	44±3	42±5	43±4	42±5
Pplat (cm H_2O)	15±3	16±3	16±3	15±3	23±4*	23±3*	22±3*	21±4*	23±3*	22±4*	22±4*	21±3*	22±4*	22±3*	21±4*	20±3*
MAP (mm Hg)	84±11	83±10	87±9	89±12	84±11	86±13	87±14	88±11	85±10	86±11	87±12	89±13	87±12	88±13	90±13	84±9
HR (beat/minute)	69±5	70±6	68±7	71±9	68±7	67±8	66±9	68±6	74±5	71±6	68±7	71±9	76±11	73±10	72±9	77±11

Data are expressed as means±SD; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; MAP, mean arterial pressure; Pplat, inspiratory plateau pressure.
*P<0.05 vs. 1 minute before OLV, #P<0.05 vs. Control, †P<0.05 vs. AIR.

(P>0.05).

Cytokine Levels

A marked inflammatory response occurred after esophagectomy. Indeed, there was an increase over time in blood levels of all cytokines (Figure 2) except TNF-α, which remained below the detection level of 5 pg/ml throughout the study (data not shown). The plasma level of IL-1β was also below a detectable level. Compared with the control group, the IL-6 level decreased in the CPAP + AIR group, and the IL-8 level decreased in the AIR and CPAP + AIR groups (P< 0.05) (Figure 3). No difference was found between the three intervention groups (P>0.05).

Atelectasis

Four days after esophagectomy, most patients had signs of atelectasis. Areas of atelectasis were largest in the basal lung, close to the diaphragm, and were relatively minor near the lung apex. Significant smaller atelectatic areas were found in both basal and apical levels in the CPAP group and CPAP + AIR group, when compared with the control group (P<0.05). There were no differences between AIR, CPAP and AIR + CPAP groups (P>0.05). The values from both lungs at the two levels of CT evaluation were shown in table 3, and examples of CT scans were shown in figure 4.

SP-A and SP-C Levels in BALF

As shown in figure 5, the SP-A level of BALF in the CPAP+AIR group was significant higher (P< 0.05), and the SP-C level of BALF in both the CPAP group and the CPAP+AIR group also significantly increased, when compared with the control group (P<0.05). No difference was found between the three intervention groups in respect to SP-A and SP-C levels (P>0.05).

DISCUSSION

This study has shown that CPAP combined with air reinflation attenuated lung injury after esophagectomy. Inflammatory response and oxidative stress was reduced in the combined intervention group. Moreover, CPAP combined with air reinflation was associated with a lower level of surfactant apoprotein in BALF, and smaller vol-

umes of pulmonary atelectasis.

OLV is widely used in thoracic surgery to facilitate surgical procedures. During OLV, pulmonary oxidation and inflammation may be induced by a multiple-hit mechanism which includes mechanical damage, atelectasis and re-expansion, high oxygen tension, and high inspiratory pressure of the ventilated lungs (13). During lung re-expansion, the sudden reintroduction of oxygen into the collapsed lung results in a burst of reactive oxygen species (ROS) generation, which increases tissue damage through lipid peroxidation. As lipid peroxidation requires oxygen supply, a study using hemorrhagic shock models has suggested that restriction of oxygen levels in initial reperfusion may reduce lung injury (14). The collapsed lung remains hypoxic and hypoperfused during OLV, and re-ventilation and reperfusion of the collapsed lung induces "second hit" injury, mainly through oxygen free radicals (15). MDA and SOD were used as markers as they are respectively a good indicator of lipid peroxidation and a major endogenous antioxidative enzyme. OLV increased plasma MDA levels and reduced SOD levels. Compared with the control group, air reinflation, and air reinflation combined with CPAP intervention increased antioxidative enzyme SOD level while suppressing MDA levels. CPAP did not change the MDA and SOD levels. Our result suggested that the sudden reintroduction of oxygen was the source of ROS generation, and a gradual re-exposure of hypoperfused lungs to O_2 was thus recommended to minimize the peroxidation.

The second finding in this study is that CPAP reduced inflammation. Previous findings and our results showed that OLV increased inflammation (16). CPAP and combined CPAP with air reinflation decreased IL-6 and IL-8 levels 3 hours after resuming TLV in our study, which suggests that CPAP, and combined intervention with CPAP and air reinflation can attenuate pulmonary inflammatory responses in patients undergoing esophagectomy. Two other proinflammatory cytokines TNF-a and IL-1β, however were barely detectable in this study. One possible explanation is that TNF-α and IL-1β peak levels precede IL-6 and IL-8, and have short half-lives after the inflammatory hit (17). Sampling 3 hours after re-expansion may therefore fail to detect these two early cytokines. In addition, this study found that CPAP promoted oxygenation during OLV, being in accordance with findings in previous studies (4, 5).

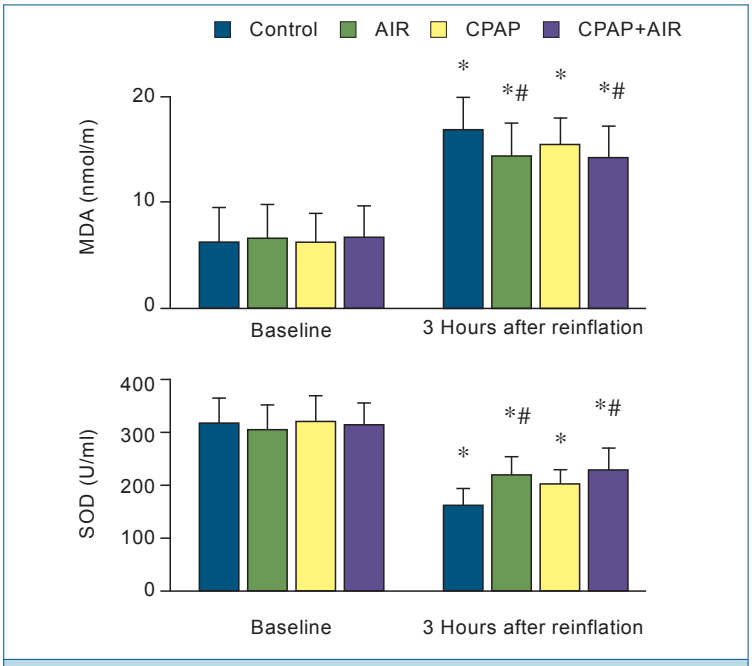

Figure 2. Plasma MDA and SOD Levels.
Data are expressed as means±SD. *P<0.05 compared with baseline values; #P<0.05 compared with control group.

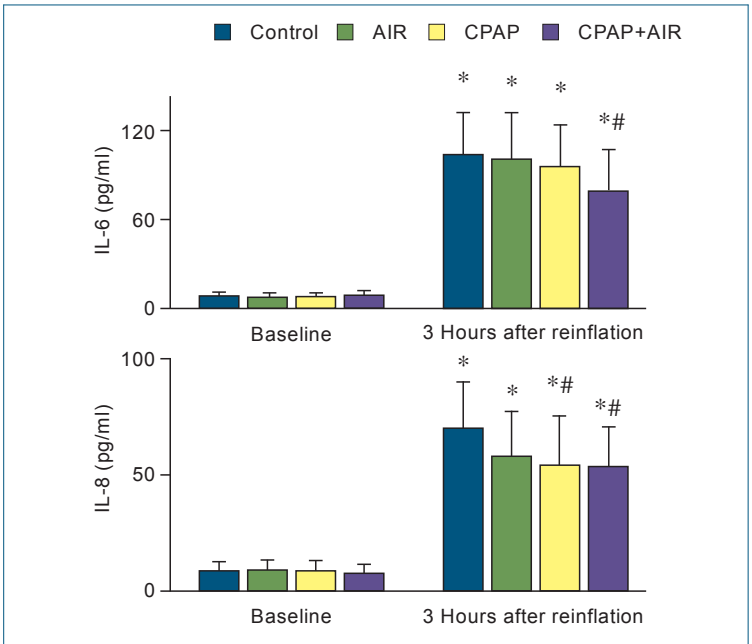

Figure 3. Plasma IL-6 and IL-8 Levels.
Data are expressed as means±SD. *P<0.05 compared with baseline values; #P<0.05 compared with control group.

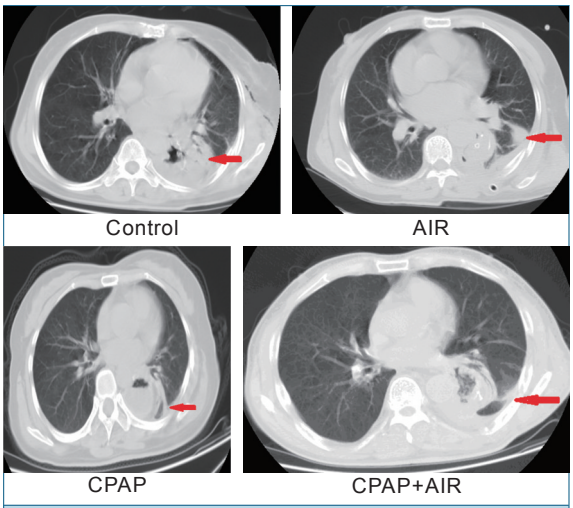

Figure 4. Representative CT Images of Lungs in Four Groups.
CT levels were positioned 1 cm above the diaphragm. The red arrows point to atelectatic areas.

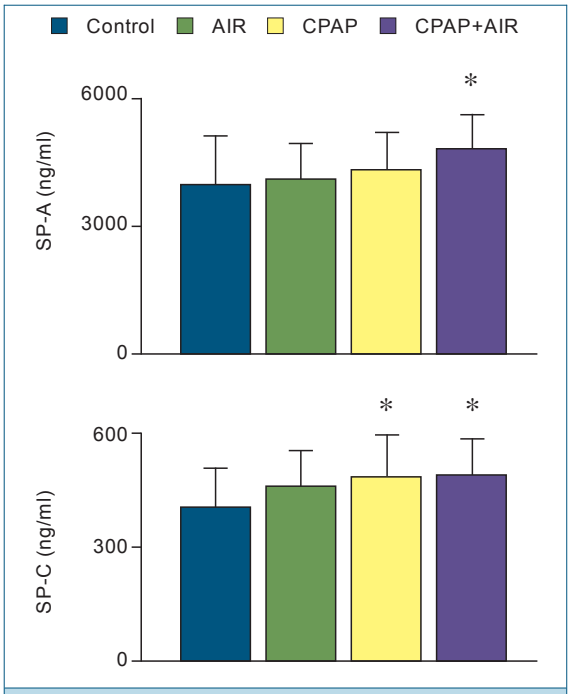

Figure 5. SP-A and SP-C Levels in BALF.
Data are expressed as means ± SD. *P<0.05 vs. control group.

Table 3. Operative Atelectasis in the Four Groups.

	Control (N=24)	AIR (N=25)	CPAP (N=24)	CPAP+AIR (N=24)
Basal level				
(%)	7.9±3.9	6.1±3.5	5.6±3.9*	4.4±3.3*
(cm^2)	10.1±4.5	8.8±4.2	8.2±4.4	7.4±4.3*
Upper level				
(%)	2.3±1.7	1.7±1.5	1.4±1.4*	1.1±1.3*
(cm^2)	3.3±1.9	2.6±1.8	2.1±1.9*	1.9±1.8*

Data are expressed as means ± SD, atelectatic volume is given as a percentage of total lung volume. *P<0.05 as compared with the Control group. The basal level of evaluation is 1 cm above the top of the diaphragm, and the upper level is 5 cm higher than the basal level.

The third finding of this study is that CPAP diminished postoperative lung atelectasis. Atelectasis may compromise postoperative oxygenation and may increase pulmonary infection. CT was used to detect minimal atelectasis. We chose the fourth day after surgery to perform the CT scan, because pleural effusion significantly decreased, and the pleural drainage tube would be removed. Atelectasis was visible on CT four days after thoracotomy in most patients, and was most obvious near the diaphragm in the supine position, while decreased towards the apex. CPAP treatment and combination of CPAP and AIR reinflation reduced total lung atelectasis. Pulmonary surfactant is widely known to decrease alveolar surface tension and prevent atelectasis (18). To explore the mechanism underlying the decreases of atelectasis induced by CPAP intervention, we evaluated pulmonary SP-A and pulmonary SP-C levels in BALF. Consistent with the atelectatic changes found by CT scanning, BALF levels of SP-A and SP-C in the CPAP and CPAP + AIR groups were increased. Comparable with our findings, Veldhuizen and colleagues found an impairment of surfactant function following lung reperfusion, which might be reduced by maintaining ventilation (19). Wirtz and Dobbs further demonstrated that even a single stretch of alveolar type Ⅱ cells potentially stimulated surfactant secretion (20). Schütte and colleagues discovered that vascular distension and continued ventilation were protective in lung ischemia/reperfusion (21). During OLV, the independent lung is collapsed and atelectatic, and reperfusion and reinflation of the collapsed lung consume a large amount of pulmonary surfactant. By applying CPAP, the independent lung is distended, which may help to preserve pulmonary surfactant. In this study, CPAP intervention and CPAP combined with air reinflation increased BALF pulmonary surfactant levels, which is consistent with the decrease of atel-

ectatic areas. In contrast, it is argued that the benefit of intraoperative CPAP may not persist postoperatively (22). Ramelli et al investigated CPAP intervention on post pulmonary lobectomy patients. They found that intraoperative CPAP improved oxygenation in the first 24 hours after surgery, but had no beneficial effect on the overall incidence of pulmonary complications. In that study, the authors selected occurrence of lobar atelectasis as their index of observation, and found no difference between groups using chest X-ray. In the current study, with use of CT to precisely identify minimal areas of atelectasis, we demonstrated that the CPAP used alone or in combination with air reinflation reduced postoperative atelectasis. This discrepancy in findings may be attributed to the different sensitivity of chest X-ray and CT.

How does CPAP protect the lung during OLV? In a study using an isolated-perfused rat lung model, it was found that lung inflation during ischemia prevented lung reperfusion injury (23). Animal studies showed that ventilation or even static inflation attenuated lung injury, and promoted release of lung surfactant (24). Results of the current clinical study of humans undergoing esophagectomy were in accordance with those animal experiments, where expanding the lung (by CPAP) during OLV decreased inflammation, preserved pulmonary surfactant, and mitigated the injury.

Why did we select to test the use of two stones for one bird? A current proposal for lung injury takes the view that injury is induced by a "multiple-hit" mechanism (25). Mechanical ventilation during esophagectomy (including OLV) and surgical manipulation bring about the first hit (1), and reinflation may result in the second hit. In this trial, CPAP minimized the OLV hit, and air reinflation was targeted for mitigation of re-expansion injury. The results showed that this approach of combined intervention reduced inflammation and oxidative stress, and increased surfactant apoprotein. Moreover, this combined intervention increased arterial oxygen pressure levels during OLV and decreased atelectasis postoperatively. However, combination of the two interventions failed to further reduce lung injury, as compared to CPAP or air reflation alone in this study. The probable causes may be related to the limited protective effect of air reinflation, including almost ASA I-II patients, and the sample size calculation. During the first hit interval, other therapeutic measures such as reduction of V_T combined with positive end-expiratory pressure (PEEP) and lower FiO_2 have also been reported to be protective (6, 25). And the application of CPAP allows the use of lower FiO_2 without compromising intraoperative oxygenation.

Study Limitations

The CPAP used in this trial is not suitable for thoracoscopy procedures, which require better visualization during the procedure. A second potential shortcoming of this method is that there may still be areas of atelectasis identified by CT as high as $4.4\% \pm 3.3\%$ on the forth postoperative day even in the combined intervention group. One possibly explanation is that strict deep breathing exercises were not employed in this trial. Westerdahl and colleagues found that patients performing deep-breathing exercises after coronary artery bypass surgery had significantly smaller atelectatic areas as compared with the control group (11). A third limitation is patients with severe pulmonary diseases were not included in this study, so the conclusion was not suitable for those patients. Other limitations include lack of overall pulmonary complications, and length of hospital stay. However, we will address these issues in the future study.

In conclusion, this prospective, randomized clinical trail demonstrated that the combined intervention with CPAP and air reinflation reduced inflammation and oxidative stress, and decreased postoperative atelectasis, thus alleviating lung injury in patients undergoing esophagectomy.

Declaration of Interests

All authors have no financial support and potential conflicts of interest for this work.

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