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ORIGINAL ARTICLE

The effect of one-lung ventilation upon pulmonary inflammatory responses during lung resection

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Abstract
Purpose One-lung ventilation (OLV) is commonly used during thoracic surgery. Clinical studies using bronchoalveolar lavage fluid analysis have demonstrated that OLV induces pulmonary inflammatory reactions in the ventilated dependent lung. However, few clinical studies have investigated such inflammatory reactions in the dependent lung compared with the collapsed nondependent lung. Here we used a bronchoscopic microsampling method to obtain epithelial lining fluid (ELF) from each lung, and then compared the inflammatory reactions in the dependent lung and the nondependent lung during thoracic surgery.
Methods Twenty adult patients were studied. All patients underwent thoracic surgery using OLV. Propofol and remifentanil were used for total intravenous anesthesia. A double-lumen endotracheal tube was used to perform OLV. ELF was obtained from each lung using the bronchoscopic microsampling method. ELF levels of inflammatory mediators, tumor necrosis factor α, interleukin (IL)-1β, IL-6, IL-8, IL-10, and IL-12p70 were measured using ELISA before and after OLV.
Results ELF levels of IL-1β, IL-6, and IL-8 were significantly increased in the dependent lung and the nondependent lung at the end of surgery compared with their baseline levels ($p < 0.05$). ELF level of IL-6 was significantly higher in the dependent lung than in the nondependent lung at the end of surgery ($p = 0.019$).
Conclusions One-lung ventilation induced inflammatory responses of the bronchial epithelia in the dependent lung and the nondependent lung during thoracic surgery. In addition, these inflammatory responses were more augmented in the dependent lung than in the nondependent lung.

Keywords One-lung ventilation · Epithelial lining fluid · Bronchoscopic microsampling · Pulmonary inflammation · Cytokine

Introduction

One-lung ventilation (OLV) is commonly used in thoracic surgery. During OLV, pulmonary inflammatory reactions can be induced by multiple factors such as mechanical damage due to surgical manipulation, OLV-induced atelectasis and re-expansion, damage by high oxygen tension, or by high inspiratory pressure due to mechanical ventilation [1–5].

Some studies have shown that bronchial epithelia express various immune molecules [6, 7]. Inflammatory cytokines, tumor necrosis factor α, interleukin (IL)-1β, IL-6, and IL-8 are important chemoattractants that affect the recruitment of neutrophils and alveolar macrophages. Alveolar macrophages not only act as phagocytes but also secrete biologically active products, thereby play a

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significant role in regulating pulmonary inflammatory reactions [8–10]. By expressing these inflammatory mediators, the bronchial epithelium may play an important role in the initiation and exacerbation of an inflammatory response in the airway. An increase in these inflammatory cytokines can be clinically relevant to pulmonary complications following thoracic surgery [2, 3, 11, 12].

Some clinical studies have analyzed bronchoalveolar lavage fluid (BALF) and reported OLV-induced pulmonary inflammatory reactions in the ventilated dependent lung [1, 13]. However, few clinical studies have compared inflammatory reaction differences between the ventilated dependent lung and the collapsed nondependent lung.

Assessment of the pulmonary biochemical environment using BALF analysis can provide valuable pathophysiologic information. However, complications including hypoxia may limit the serial examination of BALF, particularly in patients undergoing thoracic surgery using OLV. In earlier studies, a less invasive and quantitative bronchoscopic microsampling probe was developed in order to measure biochemical constituents in the epithelial lining fluid (ELF) of small airways [14, 15]. This enabled us to obtain ELF from each lung during OLV.

We hypothesized that the extent of OLV-induced inflammatory responses may differ in the dependent lung and the nondependent lung during thoracic surgery. The aims of this study were to: (1) examine OLV-induced effects in the dependent lung and the nondependent lung, and (2) compare inflammatory reactions in the dependent lung and the nondependent lung during thoracic surgery.

Since a lateral position can induce a gravitational shift in blood distribution in the lungs [16], we also hypothesized that inflammatory responses may differ between the upper lung and the lower lung while in a lateral position. We therefore investigated an additional patient group to evaluate the effect of a lateral position upon the pulmonary inflammatory reaction.

In the first part of our study (study I), we investigated the effects of OLV upon pulmonary inflammatory responses during lung resection. In the second part (study II), we also investigated the effect of lateral position on the pulmonary inflammatory reaction as a control study.

Materials and methods

Study I: the pulmonary inflammatory effect of one-lung ventilation

Participants

Twenty consecutive adult patients undergoing thoracic surgery with OLV were studied, after providing written informed consent. The study was approved by our institutional review board. Operations were performed at Juntendo University Hospital in 2009 and included lobectomy ($n = 13$ patients) and partial lung resection ($n = 7$ patients). Lung resections were performed through a standard posterolateral or an anterolateral thoracotomy. All patients met the criteria for the American Society of Anesthesiologists physical status I–II category.

Exclusion criteria

Exclusion criteria included cardiac disease categorized as NYHA classes II–IV; preoperative severe impairment of respiratory function, such as a vital capacity of <50% or a forced expiratory volume in one second of <50% of that predicted; pre-existing coagulopathy or thrombocytopenia; and preoperative nonsurgical supplemental treatments such as chemotherapy, radiation therapy, or immunotherapy. Patients were excluded if they had systemic or local active infections (either clinically defined or suggested by evidence such as elevated C-reactive protein levels, leukocytosis, or a body temperature >38°C).

Anesthesia

None of our patients received premedication. All patients underwent general anesthesia combined with epidural anesthesia. Before the operation, a thoracic epidural catheter was inserted between the T4/5 and the T6/7 intervertebral spaces for postoperative pain management.

Propofol and remifentanil were used for total intravenous anesthesia. Induction of anesthesia was initiated with intravenous propofol, using a target-controlled infusion technique with a target concentration of 3–5 μg/ml, and a continuous infusion of remifentanil at 0.5 μg/kg/min. Rocuronium (0.6–0.9 mg/kg) facilitated orotracheal intubation. Following orotracheal intubation, patients were placed in a lateral position. Anesthesia was maintained with propofol (at target concentrations of 2–4 μg/ml) and remifentanil (0.2–1.0 μg/kg/min). For further muscle relaxation, rocuronium was administered, as clinically indicated.

For postoperative pain management, patients were administered 1 μg/kg of fentanyl (intravenous) and 5–8 ml of 0.375% ropivacaine (intra-epidural) before the discontinuation of anesthetic agents, followed by intra-epidural continuous infusion of 0.2% ropivacaine (2–5 ml/h).

OLV was achieved with a left- or right-sided double-lumen endotracheal tube (Blue Line® Endobronchial Tube 37 or 39 Fr; Smiths Medical, St Paul, MN, USA). Correct positioning of the tube was confirmed using a bronchofiberscope (BF-MP60; Olympus, Tokyo, Japan). Pressure-controlled ventilation with 5 cmH_2O positive end-expiratory pressure (PEEP) was used for bilateral lung ventilation and

for OLV. During OLV, peak inspiratory pressure was maintained below 30 cmH_2O with a tidal volume of 6–8 ml/kg, and FIO_2 was maintained between 0.6 and 1.0 to ensure oxygen saturation of >90%. Respiratory rate was adjusted to maintain normocapnia. The collapsed lung was not inflated periodically. None of our patients required intermittent continuous positive airway pressure on the nondependent lung in order to maintain oxygenation during OLV.

Electrocardiogram, oxygen saturation, invasive arterial blood pressure, end-tidal carbon dioxide pressure, rectal body temperature, and urine output were continuously monitored during anesthesia. Arterial blood gas analyses were performed, as clinically required. Crystalloids were used for hydration, in accordance with clinical needs. None of our patients required blood transfusion.

After completing the surgical procedures, the previously collapsed lung was re-inflated until visible atelectatic areas were resolved with a peak airway pressure of below 25 cmH_2O. All patients were extubated in the operating room and transferred to a post-anesthesia care unit or intensive care unit.

Bronchoscopic microsampling

ELF was obtained from each lung using the bronchoscopic microsampling method before OLV (i.e., baseline) and 15 min after terminating OLV (i.e., end of surgery). A bronchofiberscope was inserted into each lung through an endotracheal tube. The fiberscope was placed on the bronchus 7 cm distal to the bifurcation of the trachea. A bronchoscopic microsampling probe (BC-401C; Olympus, Tokyo, Japan) was inserted into the lungs through the channel of the bronchofiberscope. The probe consisted of a 1.8 mm outer-diameter polyethylene sheath and an inner 1.1 mm cotton probe attached to a stainless steel guide wire. The probe was inserted into the channel of the bronchofiberscope, and the inner probe was advanced slowly into the distal airway until it made contact with the mucosal surface. ELF was obtained from each bronchus under direct observation. After absorbing ELF, the inner probe was withdrawn and stored at −80°C until analysis. Peripheral blood was collected from an arterial catheter before OLV and at the end of surgery, simultaneous with ELF sampling.

Measurement of cytokines

After obtaining ELF, the bronchoscopic microsampling probe was sectioned at 3.0 cm from its tip, introduced into a pre-weighed tube, weighed, and frozen at −80°C until analysis. A diluted solution for measuring cytokines was prepared by adding 500 μl of saline to the tube containing the frozen probe. The solution was then vortexed for 1 min. Afterwards, the probe was dried and weighed again to measure the recovered ELF volume, and the dilution factor was calculated. We also measured OD_{280nm} for each sample to standardize protein concentrations of all samples using bovine serum albumin as the standard. Inflammatory level was expressed as the amount of cytokine per 1 mg of protein in ELF.

Inflammatory cytokine levels in ELF were measured using a cytometric bead array system (CBA Human Inflammatory Cytokines Kit; Becton, Dickinson and Company, Franklin Lakes, NJ, USA).The system included six fluorescently distinguishable capture microbeads coated with antibodies against six analytes: TNFα, IL-1β, IL-6, IL-8, IL-10, and IL-12p70. The method detected cytokines bound onto microbeads by enzyme-linked immunosorbent assay (ELISA). Using the cytometric bead array system, the minimum quantifiable level of cytokines was 20 pg/ml.

The cytometric bead array system measured plasma cytokine levels before OLV and at the end of surgery. Serum was prepared from blood samples by centrifugation at $1000\times g$ for 10 min and measured without dilution.

Study II: the pulmonary inflammatory effect of a lateral position

Five patients exhibiting acetabular dysplasia and undergoing rotational acetabular osteotomy were studied. All patients met the criteria for the American Society of Anesthesiologists physical status I–II category. None of our patients received premedication. All patients underwent general anesthesia combined with epidural anesthesia. Before the operation, a lumbar epidural catheter was inserted at either the L1/2 or the L2/3 intervertebral space. Total intravenous anesthesia was performed with propofol and remifentanil, as previously described for study I. A left-sided double-lumen endotracheal tube was used to prevent sample contamination. Following anesthetic induction, the patient was placed in a lateral position. Bilateral lung ventilation with 5 cmH_2O PEEP was maintained throughout the operation. The peak inspiratory pressure was maintained below 30 cmH_2O with a tidal volume of 8–10 ml/kg and an FIO_2 of 0.4–0.6. The respiratory rate was adjusted to maintain normocapnia.

ELF was obtained from each lung using the bronchoscopic microsampling method before and after surgery. A cytometric bead array system measured the levels of inflammatory cytokines in the ELF. We measured OD_{280nm} for each sample to standardize protein concentrations of all samples, as previously described for study I. We then compared the expression of the inflammatory cytokines in ELF from each lung.

Statistical analysis

Statistical results are presented as the median (25th–75th), with statistical significance ($p < 0.05$) determined by the Mann–Whitney U test or the Wilcoxon signed-rank test. Correlation was determined by the Spearman's correlation coefficient by rank. Parametric data are expressed as the mean ± standard error of the mean in tables. All analyses were performed with the statistical software program GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA).

Results

Study I: the pulmonary inflammatory effect of one-lung ventilation

Clinical characteristics

Table 1 depicts the characteristics and surgical data of the 20 patients. All patients were extubated after surgery in the operating room and experienced uneventful postoperative recoveries.

Table 1 Thoracic surgery: patient characteristics and surgical data

Age (years)	61.4 ± 3.0
Sex (M/F)	14/6
BMI (kg/m^2)	22.1 ± 0.7
Right/left-sided thoracotomy	10/10
Lobectomy/partial resection	13/7
PIP during OLV (cmH_2O)	23.0 ± 0.3
Duration of OLV (min)	140.6 ± 12.6
Duration of surgery (min)	164.4 ± 13.6
Duration of anesthesia (min)	242.7 ± 13.4

Data are expressed as mean ± standard error of the mean (SEM)

BMI body mass index, *PIP* peak inspiratory pressure, *OLV* one-lung ventilation

The expression of inflammatory mediators in ELF

Figure 1 shows the ELF levels of IL-1β, IL-6, and IL-8 at each sampling point in the dependent lung and the non-dependent lung. Inflammatory level was expressed as cytokine amount per 1 mg of protein in ELF. The levels of other cytokines were undetectable at each sampling point.

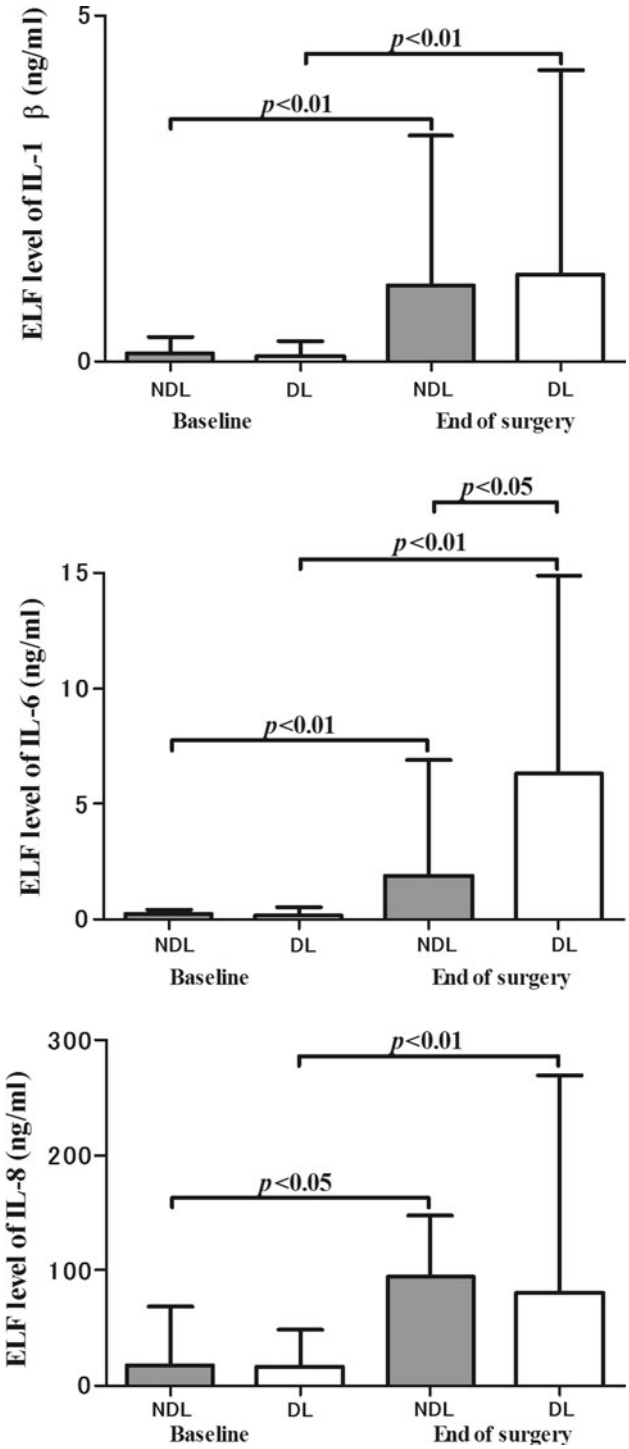

Fig. 1 Changes in the epithelial lining fluid levels of interleukin-1β, interleukin-6, and interleukin-8 during thoracic surgery. Thoracic surgery was associated with changes in the levels of interleukin (IL)-1β, IL-6, and IL-8 in the epithelial lining fluid (ELF). *Graphs* show the levels of these interleukins at each time point in the ventilated dependent lung (DL) and the collapsed nondependent lung (NDL). ELF levels of IL-1β, IL-6 and IL-8 increased significantly in the dependent lung [IL-1β ($p < 0.001$), IL-6 ($p < 0.001$), IL-8 ($p < 0.001$)] and in the nondependent lung [IL-1β ($p < 0.001$), IL-6 ($p = 0.001$), IL-8 ($p = 0.029$)] at the end of surgery, compared with their baseline levels. The ELF level of IL-6 was significantly higher in the dependent lung than in the nondependent lung at the end of surgery ($p = 0.019$). Data are expressed as the median (25th–75th)

However, ELF levels of IL-1β, IL-6 and IL-8 significantly were increased in the dependent lung and the nondependent lung at the end of surgery compared with their baseline levels ($p < 0.05$). The ELF level of IL-6 was significantly higher in the dependent lung than in the nondependent lung at the end of surgery ($p = 0.019$).

The magnitude of cytokine expression at the end of surgery showed a progressive increase with prolonged duration of OLV (Fig. 2). There was a correlation between the increase in the level of IL-1β or IL-6 and the duration of OLV in the dependent lung and the nondependent lung at the end of surgery. For IL-1β in the dependent lung, $r = 0.482$, $p = 0.032$; and for IL-1β in the nondependent lung, $r = 0.495$, $p = 0.026$. For IL-6 in the dependent lung, $r = 0.467$, $p = 0.038$; and for IL-6 in the nondependent lung, $r = 0.466$, $p = 0.038$. For IL-8, there was no correlation in the dependent lung ($r = 0.225$), whereas there was a correlation in the nondependent lung ($r = 0.517$, $p = 0.020$). The plasma cytokine levels of tumor necrosis factor α, IL-1β, IL-6, IL-8, IL-10, and IL-12p70 were undetectable.

Study II: the pulmonary inflammatory effect of a lateral position

Table 2 depicts patient characteristics and surgical data. All patients were extubated following surgery in the operating room and had uneventful postoperative recovery periods. Inflammatory level was expressed as cytokine amount per 1 mg of protein in ELF. ELF levels of the cytokines tumor necrosis factor α, IL-1β, IL-6, IL-8, IL-10, and IL-12p70 did not significantly differ between the upper and lower lung at each sampling point (Fig. 3).

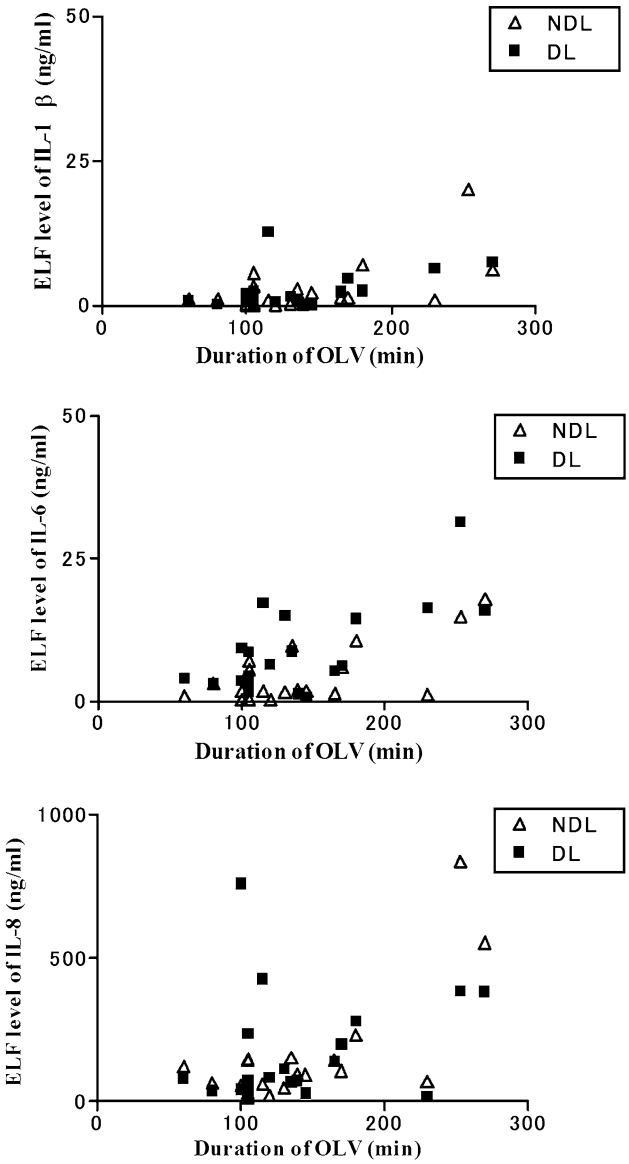

Fig. 2 Correlation between the increase in interleukin-1β, interleukin-6, or interleukin-8 and the duration of one-lung ventilation in both lungs at the end of surgery. There was a correlation between the increase in interleukin (IL)-1β or IL-6 levels and the duration of one-lung ventilation in both the ventilated dependent lung (DL) and the collapsed nondependent lung (NDL) at the end of surgery. For IL-1β, $r = 0.482$, $p = 0.032$ for the dependent lung; and $r = 0.495$, $p = 0.026$ for the nondependent lung. For IL-6, $r = 0.467$, $p = 0.038$ for the dependent lung; and $r = 0.466$, $p = 0.038$ for the nondependent lung. There was no correlation between IL-8 level and the duration of one-lung ventilation in the dependent lung ($r = 0.225$), but a correlation did exist with the nondependent lung ($r = 0.517$, $p = 0.020$)

Discussion

In study I, we demonstrated that ELF levels of IL-1β, IL-6 and IL-8 were significantly increased in the dependent lung and the nondependent lung at the end of thoracic surgery, compared with their baseline levels. We also demonstrated that the ELF level of IL-6 was significantly higher in the dependent lung than in the nondependent lung.

Our data suggest that, during thoracic surgery, OLV induces inflammatory responses of the bronchial epithelia in the dependent lung and the nondependent lung. Inflammatory responses were more augmented in the dependent lung than in the nondependent lung, as indicated by the higher ELF level of IL-6 in the dependent lung at the end of surgery. ELF level of cytokine expression indicated a local inflammatory response, since the plasma cytokine levels were undetectable during surgery.

The duration of OLV is a most important factor in promoting pulmonary inflammatory responses, as shown in previous studies [2, 17, 18]. These earlier studies demonstrated a significant correlation between the extent of pulmonary inflammatory response and the duration of

Table 2 Rotational acetabular osteotomy: patient characteristics and surgical data

Age (years)	40.2 ± 4.6
Sex (M/F)	0/5
BMI (kg/m^2)	21.1 ± 0.9
Right/left lateral position	1/4
PIP during lateral position (cmH_2O)	17.4 ± 1.1
Duration of surgery (min)	170.2 ± 15.3
Duration of lateral position (min)	199.8 ± 16.6
Duration of anesthesia (min)	235.8 ± 14.8

Data are expressed as mean ± standard error of the mean (SEM)

BMI body mass index, *PIP* peak inspiratory pressure

OLV. Our present data were compatible with these findings.

The lateral position is thought to induce differences in pulmonary perfusion and ventilation in the lungs because of the gravitational shift [16]. However, recent studies show that there are other factors that affect pulmonary perfusion and ventilation while in the lateral position. The underlying structure of the bronchial and pulmonary vascular anatomy with asymmetrical branching is now considered an important factor in causing differences in pulmonary perfusion and ventilation in the lungs while in the lateral position [19, 20].

We hypothesized that heterogeneity in the lungs may induce different levels of inflammatory responses between the upper lung and the lower lung while in the lateral position. Despite heterogeneity, our present data suggested that the lateral position did not result in a significant difference in the pulmonary inflammatory reaction between the upper and lower lungs during bilateral lung ventilation in study II.

Based on this finding, we do not believe that the lateral position itself augmented the inflammatory responses in the dependent lung in study I. We believe that multiple pulmonary factors induced inflammatory reactions, such as mechanical damage due to surgical manipulation, OLV-induced atelectasis and re-expansion, or damage due to a high inspiratory oxygen concentration or a high inspiratory pressure due to mechanical ventilation. A higher oxygen concentration and a higher inspiratory pressure were utilized in study I than in study II. Therefore, we believe these factors are important in inducing inflammatory responses in the dependent lung.

The ventilation of the dependent lung with an inspiratory oxygen concentration of >60% can lead to pulmonary injury [21–24]. Oxygen toxicity of the lung is a well-recognized complication of prolonged exposure to a high inspiratory oxygen concentration and is characterized by histopathologic changes similar to an acute lung injury. Oxygen toxicity may occur during OLV with a high inspiratory oxygen concentration (even for a short period of time); it also involves ischemia–reperfusion injury and oxidative stress [25].

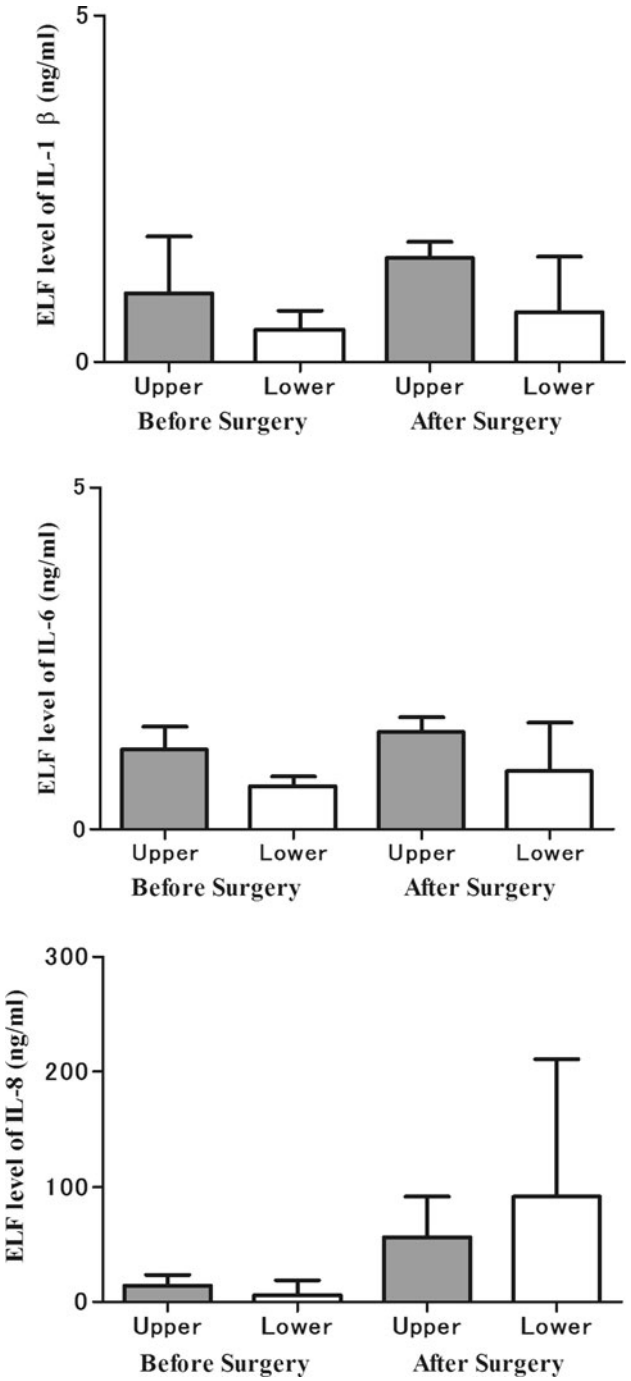

Fig. 3 Changes in the epithelial lining fluid levels of interleukin-1β, interleukin-6, and interleukin-8 during rotational acetabular osteotomy. Changes in the levels of interleukin (IL)-1β, IL-6, and IL-8 in epithelial lining fluid (ELF) while in a lateral position are shown. *Graphs* show the upper lung (*upper*) and the lower lung (*lower*) levels before and after surgery. ELF levels of cytokines were not significantly different between the upper lung and the lower lung at each time point. Data are expressed as the median (25th–75th)

A higher inspiratory pressure generally tends to be used during OLV than during bilateral lung ventilation. A high inspiratory pressure resulting from mechanical ventilation can also damage the dependent lung [26, 27]. Experimental data show that a high pulmonary capillary pressure is accompanied by the deterioration of the alveolar–capillary barrier [28, 29]. The terms "barotrauma" and "volutrauma" are closely related [27]. Some studies have demonstrated that intraoperative mechanical ventilation with a high tidal volume is associated with an increased risk of respiratory failure [1, 4, 30, 31]. Recent guidelines emphasize the importance of limiting the inspiratory pressure and the degree of alveolar distension for a given alveolar pressure [32].

OLV-induced atelectasis and re-expansion might induce ischemia–reperfusion injury [33]. This could explain the underlying mechanisms of inflammation in both the dependent lung and the nondependent lung [3, 34]. The nondependent lung remains completely atelectatic for a period of time, which is accompanied by hypoperfusion due to hypoxic vasoconstriction. A lack of ventilation to the collapsed lung might exacerbate reperfusion injury. De Leyn et al. [35] found greater lactate concentrations and lower ATP concentrations in isolated ischemic rabbit lungs that were deflated rather than inflated. Hamvas et al. [36] further studied ischemia–reperfusion lung injury in dogs and identified that ventilation or static inflation attenuated lung injury.

Madjdpour et al. [37] showed that acute hypoxia resulted in inflammatory changes in the lung. Alveolar hypoxia in the nondependent lung during OLV leads to the augmented expression of adhesion molecules on alveolar epithelial cells, an increase in albumin leakage, and enhanced expression of inflammatory mediators, which are mainly macrophage dependent. Alveolar macrophages may play a pivotal role in inflammatory mechanisms during hypoxia-induced lung injury. Alveolar damage following hypoxia is biphasic; it starts with the lack of oxygen and is then exacerbated during reoxygenation [37].

Our present data suggest that factors leading to inflammation during OLV can be more significant in the dependent lung than in the nondependent lung.

Padley et al. studied patients undergoing open thoracic surgery who developed postoperative acute respiratory distress syndrome. Preoperative and postoperative CT scans demonstrated that lung tissue density increased at a significantly higher rate in the ventilated lung than in the operated lung, indicating a virtually asymmetric lung injury [38]. Recent studies suggest that ELF levels of cytokines such as IL-1β, IL-6 and IL-8 are clinically relevant to pulmonary complications after thoracic surgery [2, 3]. Our present data suggest that increased expression of cytokines is possibly related to postoperative injury in the dependent lung.

In summary, OLV may promote the production and release of proinflammatory substances in the alveoli of the dependent lung and the nondependent lung during thoracic surgery. Furthermore, inflammatory responses were more augmented in the dependent lung than in the nondependent lung at the end of surgery. These pulmonary inflammatory responses, as indicated by increased cytokine expression, may be relevant to postoperative complications in the dependent lung.

Conflict of interest None.

References

1. Schilling T, Kozian A, Huth C, Bühling F, Kretzschmar M, Welte T, Hachenberg T. The pulmonary immune effects of mechanical ventilation in patients undergoing thoracic surgery. Anesth Analg. 2005;101:957–65.
2. De Conno E, Steurer M, Wittlinger M, Zalunardo M, Weder W, Schneiter D, Schimmer R, Klaghofer R, Neff T, Schmid E, Spahn D, Z'graggen B, Urner M, Beck-Schimmer B. Anesthetic-induced improvement of the inflammatory response to one-lung ventilation. Anesthesiology. 2009;110:1316–26.
3. Baudouin S. Lung injury after thoracotomy. Br J Anaesth. 2003; 91:132–42.
4. Fernández-Pérez E, Keegan M, Brown D, Hubmayr R, Gajic O. Intraoperative tidal volume as a risk factor for respiratory failure after pneumonectomy. Anesthesiology. 2006;105:14–8.
5. von Bethmann A, Brasch F, Nüsing R, Vogt K, Volk H, Müller K, Wendel A, Uhlig S. Hyperventilation induces release of cytokines from perfused mouse lung. Am J Respir Crit Care Med. 1998;157:263–72.
6. Madjdpour C, Oertli B, Ziegler U, Bonvini J, Pasch T, Beck-Schimmer B. Lipopolysaccharide induces functional ICAM-1 expression in rat alveolar epithelial cells in vitro. Am J Physiol Lung Cell Mol Physiol. 2000;278:L572–9.
7. Voigtsberger S, Lachmann R, Leutert A, Schläpfer M, Booy C, Reyes L, Urner M, Schild J, Schimmer R, Beck-Schimmer B. Sevoflurane ameliorates gas exchange and attenuates lung damage in experimental lipopolysaccharide-induced lung injury. Anesthesiology. 2009;111:1238–48.
8. Bless NM, Huber-Lang M, Guo RF, Warner RL, Schmal H, Czermak BJ, Shanley TP, Crouch LD, Lentsch AB, Sarma V, Mulligan MS, Friedl HP, Ward PA. Role of CC chemokines (macrophage inflammatory protein-1 beta, monocyte chemoattractant protein-1, RANTES) in acute lung injury in rats. J Immunol. 2000;164:2650–9.
9. Vozzelli MA, Mason SN, Whorton MH, Auten RL. Antimacrophage chemokine treatment prevents neutrophil and macrophage influx in hyperoxia-exposed newborn rat lung. Am J Physiol Lung Cell Mol Physiol. 2004;286:L488–93.
10. Beck-Schimmer B, Schwendener R, Pasch T, Reyes L, Booy C, Schimmer RC. Alveolar macrophages regulate neutrophil recruitment in endotoxin-induced lung injury. Respir Res. 2005;6:61.
11. Michelet P, D'Journo X, Roch A, Doddoli C, Marin V, Papazian L, Decamps I, Bregeon F, Thomas P, Auffray J. Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study. Anesthesiology. 2006;105:911–9.
12. D'Journo X, Michelet P, Marin V, Diesnis I, Blayac D, Doddoli C, Bongrand P, Thomas P. An early inflammatory response to

oesophagectomy predicts the occurrence of pulmonary complications. Eur J Cardiothorac Surg. 2010;37:1144–51.
13. Schilling T, Kozian A, Kretzschmar M, Huth C, Welte T, Bühling F, Hedenstierna G, Hachenberg T. Effects of propofol and desflurane anaesthesia on the alveolar inflammatory response to one-lung ventilation. Br J Anaesth. 2007;99:368–75.
14. Ishizaka A, Watanabe M, Yamashita T, Ogawa Y, Koh H, Hasegawa N, Nakamura H, Asano K, Yamaguchi K, Kotani M, Kotani T, Morisaki H, Takeda J, Kobayashi K, Ogawa S. New bronchoscopic microsample probe to measure the biochemical constituents in epithelial lining fluid of patients with acute respiratory distress syndrome. Crit Care Med. 2001;29:896–8.
15. Koh H, Tasaka S, Hasegawa N, Asano K, Kotani T, Morisaki H, Takeda J, Fujishima S, Matsuda T, Hashimoto S, Ishizaka A. Vascular endothelial growth factor in epithelial lining fluid of patients with acute respiratory distress syndrome. Respirology. 2008;13:281–4.
16. Wilson WC, Benumof JL. Respiratory physiology and respiratory function during anesthesia. In: Miller RD, editor. Miller's anesthesia. 6th ed. Philadelphia: Elsevier/Churchill Livingstone; 2005. p. 679–722.
17. Misthos P, Katsaragakis S, Theodorou D, Milingos N, Skottis I. The degree of oxidative stress is associated with major adverse effects after lung resection: a prospective study. Eur J Cardiothorac Surg. 2006;29:591–5.
18. Tekinbas C, Ulusoy H, Yulug E, Erol M, Alver A, Yenilmez E, Geze S, Topbas M. One-lung ventilation: for how long? J Thorac Cardiovasc Surg. 2007;134:405–10.
19. Galvin I, Drummond G, Nirmalan M. Distribution of blood flow and ventilation in the lung: gravity is not the only factor. Br J Anaesth. 2007;98:420–8.
20. Chang H, Lai-Fook S, Domino K, Schimmel C, Hildebrandt J, Robertson H, Glenny R, Hlastala M. Spatial distribution of ventilation and perfusion in anesthetized dogs in lateral postures. J Appl Physiol. 2002;92:745–62.
21. Halliwell B. Reactive oxygen species in living systems: source, biochemistry, and role in human disease. Am J Med. 1991;91:14S–22S.
22. Winter P, Smith G. The toxicity of oxygen. Anesthesiology. 1972;37:210–41.
23. Clark J, Lambertsen C. Pulmonary oxygen toxicity: a review. Pharmacol Rev. 1971;23:37–133.
24. Clark J. Pulmonary limits of oxygen tolerance in man. Exp Lung Res. 1988;14(Suppl):897–910.
25. Lohser J. Evidence-based management of one-lung ventilation. Anesthesiol Clin. 2008;26:241–72.
26. Kolobow T, Moretti M, Fumagalli R, Mascheroni D, Prato P, Chen V, Joris M. Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. An experimental study. Am Rev Respir Dis. 1987;135:312–5.
27. Whitehead T, Slutsky A. The pulmonary physician in critical care. 7: Ventilator induced lung injury. Thorax. 2002;57:635–42.
28. Kozian A, Schilling T, Fredén F, Maripuu E, Röcken C, Strang C, Hachenberg T, Hedenstierna G. One-lung ventilation induces hyperperfusion and alveolar damage in the ventilated lung: an experimental study. Br J Anaesth. 2008;100:549–59.
29. Kozian A, Schilling T, Schütze H, Heres F, Hachenberg T, Hedenstierna G. Lung computed tomography density distribution in a porcine model of one-lung ventilation. Br J Anaesth. 2009;102:551–60.
30. Wolthuis E, Choi G, Dessing M, Bresser P, Lutter R, Dzoljic M, van der Poll T, Vroom M, Hollmann M, Schultz M. Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents pulmonary inflammation in patients without preexisting lung injury. Anesthesiology. 2008;108:46–54.
31. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000;342:1301–8.
32. Slutsky A. Mechanical ventilation. American College of Chest Physicians' Consensus Conference. Chest. 1993;104:1833–59.
33. Funakoshi T, Ishibe Y, Okazaki N, Miura K, Liu R, Nagai S, Minami Y. Effect of re-expansion after short-period lung collapse on pulmonary capillary permeability and pro-inflammatory cytokine gene expression in isolated rabbit lungs. Br J Anaesth. 2004;92:558–63.
34. Hamvas A, Palazzo R, Kaiser L, Cooper J, Shuman T, Velazquez M, Freeman B, Schuster D. Inflammation and oxygen free radical formation during pulmonary ischemia–reperfusion injury. J Appl Physiol. 1992;72:621–8.
35. De Leyn P, Lerut T, Schreinemakers H, Van Raemdonck D, Mubagwa K, Flameng W. Effect of inflation on adenosine triphosphate catabolism and lactate production during normothermic lung ischemia. Ann Thorac Surg. 1993;55:1073–8.
36. Hamvas A, Park C, Palazzo R, Liptay M, Cooper J, Schuster D. Modifying pulmonary ischemia–reperfusion injury by altering ventilatory strategies during ischemia. J Appl Physiol. 1992;73:2112–9.
37. Madjdpour C, Jewell U, Kneller S, Ziegler U, Schwendener R, Booy C, Kläusli L, Pasch T, Schimmer R, Beck-Schimmer B. Decreased alveolar oxygen induces lung inflammation. Am J Physiol Lung Cell Mol Physiol. 2003;284:L360–7.
38. Padley S, Jordan S, Goldstraw P, Wells A, Hansell D. Asymmetric ARDS following pulmonary resection: CT findings initial observations. Radiology. 2002;223:468–73.