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ORIGINAL ARTICLE

Effects of sevoflurane and propofol on pulmonary inflammatory responses during lung resection

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Abstract
Purpose Pulmonary inflammatory reactions are affected by one-lung ventilation (OLV) and anesthetic agents. However, the effects of anesthetic agents on pulmonary inflammatory reactions may vary. Our previous investigations suggested that inflammatory reactions were more pronounced in the dependent lung during lung resection under general anesthesia with propofol and remifentanil. Therefore, in the present study we attempted to determine the difference in pulmonary inflammatory reaction using either sevoflurane or propofol in both dependent and nondependent lungs during OLV.
Methods Forty adult patients undergoing elective lung resection were randomized to receive either propofol ($n = 20$) or sevoflurane ($n = 20$) as the main anesthetic agent. Intraoperative analgesia was provided by remifentanil in both groups. Epithelial lining fluid (ELF) was obtained from each lung using a bronchoscopic microsampling method. ELF and plasma levels of inflammatory cytokines were measured using multiplexed bead-based immunoassays before and after OLV.
Results Epithelial lining fluid levels of interleukin (IL)-1β, IL-6, and IL-8 were significantly increased in the dependent lung and the nondependent lung after OLV compared with baseline levels ($P < 0.05$). Moreover, IL-6 ELF level in the dependent lung was significantly higher in the propofol group than in the sevoflurane group after OLV ($P < 0.001$).
Conclusion One-lung ventilation induced inflammatory responses of the bronchial epithelia in the dependent lung and the nondependent lung during lung resection. Moreover, this inflammatory response was significantly suppressed by sevoflurane compared with propofol. Furthermore, the antiinflammatory effect of sevoflurane was more pronounced in the dependent lung than in the nondependent lung during OLV.

Keywords One-lung ventilation · Propofol · Sevoflurane · Pulmonary inflammation · Cytokine

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Introduction

Pulmonary inflammatory reactions during and after lung resection may increase the risk of pulmonary complications, thus resulting in higher morbidity and mortality rates [1–5]. During lung resection, pulmonary inflammatory reactions can be induced by multiple factors, including mechanical damage from surgical manipulation, one-lung ventilation (OLV)-induced atelectasis and reexpansion, or damage induced by high inspiratory oxygen concentration or high inspiratory pressure as a result of mechanical ventilation [2, 5–9].

Studies have shown that bronchial epithelia express various immune molecules [10, 11]. OLV increases the concentration of alveolar macrophages and granulocytes,

proteins, and inflammatory cytokines [7]. IL-8 is an important chemo-attractant that affects the recruitment of granulocytes and alveolar macrophages [12]. Alveolar macrophages not only act as phagocytes but also secrete biologically active products, thereby playing a significant role in regulating pulmonary inflammatory reactions [13, 14]. Evidence is mounting to suggest that increased levels of these inflammatory cytokines can be clinically relevant to pulmonary complications following thoracic surgery [1–5].

In a previous study, we showed that the extent of pulmonary inflammation in the dependent lung was higher than in the nondependent lung during lung resection [6]. Other clinical studies have reported that OLV-induced pulmonary inflammatory reactions can be modified by both inhalation and intravenous anesthetic agents [2, 15, 16]. However, potential differences in immunomodulatory effect between the ventilated dependent lung and the collapsed nondependent lung have yet to be fully evaluated. Therefore, we hypothesized that the extent of the immunomodulatory effects incurred by the administration of anesthetic agents may differ in the dependent lung and the nondependent lung during thoracic surgery.

Assessment of the pulmonary biochemical environment using bronchoalveolar lavage fluid (BALF) analysis can provide valuable pathophysiological 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 to measure biochemical constituents in the epithelial lining fluid (ELF) of small airways [6, 17]. In the current clinical study, we used the bronchoscopic microsampling method to obtain ELF from each lung.

The aims of this study were to compare the pulmonary or systemic effects of sevoflurane with propofol and to investigate whether the pulmonary immunomodulatory effect might differ in the dependent lung and the nondependent lung during thoracic surgery.

Materials and methods

The study utilized a prospective, randomized, single-blinded clinical design. The Institutional Review Board of Juntendo University Hospital approved the study protocol. All patients were included in this study after providing written informed consent.

Participants

Forty consecutive adult patients undergoing thoracic surgery with OLV were studied. Operations were performed at Juntendo University Hospital, and included lobectomy ($n = 27$ patients) and partial lung resection ($n = 13$ patients). Lung resections were performed through a standard posterolateral or an anterolateral thoracotomy. All patients were classified as physical status I or II in accordance with the American Society of Anesthesiologists (ASA).

Exclusion criteria

Exclusion criteria included cardiac disease categorized as NYHA classes II–IV; preoperative severe impairment of respiratory function such as a vital capacity <50% or a forced expiratory volume in 1 s <50% of that predicted; preexisting coagulopathy or thrombocytopenia (platelet count less than 100,000/μl); 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 evident or suggested by markers of infection such as elevated C-reactive protein levels, leukocytosis, or a body temperature >38°C).

Randomization

Patients were randomly assigned to a propofol group ($n = 20$) or a sevoflurane group ($n = 20$) using a list of random numbers generated by computer software (Microsoft Excel; Microsoft Corporation, Redmond, WA, USA).

Anesthesia

No patients received premedication. All patients underwent general anesthesia combined with epidural anesthesia. Before the operation, a thoracic epidural catheter was inserted between the T4–T5 and the T6–T7 intervertebral space for postoperative pain management.

Propofol and remifentanil were used for total intravenous anesthesia in the propofol group. 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) was used to facilitate orotracheal intubation. Following 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). Rocuronium was administered for further muscle relaxation, as clinically indicated.

In the sevoflurane group, induction of anesthesia was initiated by inhalation of 5% sevoflurane by deep breathing and a continuous infusion of remifentanil at 0.5 μg/kg/min. Rocuronium (0.6–0.9 mg/kg) was used to facilitate orotracheal intubation. Anesthesia was maintained with

sevoflurane (0.8–1.0 minimum alveolar concentration) and remifentanil (0.2–1.0 μg/kg/min).

For postoperative pain management, patients were administered 1 μg/kg fentanyl (intravenous) and 5–8 ml 0.375% ropivacaine (intraepidural) before the discontinuation of anesthetic agents, followed by an intraepidural 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 Fr. 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 was greater than 90%. Respiratory rate was adjusted to maintain normocapnia. The collapsed lung was not inflated periodically. No patients required intermittent continuous positive airway pressure on the nondependent lung to maintain oxygenation during OLV.

Electrocardiogram, oxygen saturation (SpO_2), invasive arterial blood pressure, end-tidal carbon dioxide pressure, rectal body temperature, and urine output were monitored continuously 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 surgical procedures were complete, the previously collapsed lung was reinflated until visible atelectatic areas were resolved with a peak airway pressure below 25 cmH_2O. All patients were extubated in the operating room and transferred to a postanesthesia care unit or the intensive care unit.

Bronchoscopic microsampling

ELF was obtained from each lung using the bronchoscopic microsampling method before OLV (denoted as 'before') as the baseline level, and 15 min after terminating OLV (denoted as 'after'). A bronchofiberscope was inserted into each lung through an endotracheal tube and placed on the bronchus at a point that was 7 cm distal to the bifurcation of the trachea. A bronchoscopic microsampling probe (BC-401C; Olympus) was inserted into the lungs through the channel of the bronchofiberscope; it consisted of a 1.8-mm-outer-diameter polyethylene sheath and an inner 1.1-mm-diameter cotton probe attached to a stainless steel guidewire. 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 absorption of ELF, the inner probe was withdrawn and stored at −80°C until analysis. Peripheral blood was collected from an arterial catheter before and after OLV, simultaneous with ELF sampling.

Measurement of cytokines

After obtaining ELF, the bronchoscopic microsampling probe was sectioned at 3.0 cm from its tip, introduced in a pre-weighed tube, weighed, and frozen at −80°C until analysis. A diluted solution for measuring cytokines was prepared by adding 500 μl saline to the tube containing the frozen probe. The solution was then vortexed for 1 min. Afterward, the probe was dried and reweighed to measure the recovered ELF volume, and the dilution factor was calculated. We also measured the OD_{280nm} of 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 protein in ELF.

Inflammatory cytokine levels in ELF were measured using a cytometric bead array system (CBA Human Inflammatory Cytokines Kit; Becton–Dickinson, Franklin Lakes, NJ, USA).The system included six fluorescently distinguishable capture microbeads coated with antibodies against six analytes: tumor necrosis factor (TNF)-α, IL-1β, IL-6, IL-8, IL-10, and IL-12p70. This method detected cytokines bound onto microbeads by use of an 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 was used to measure plasma cytokine levels before and after OLV. Serum was prepared from blood samples by centrifugation at 1,000 *g* for 10 min and measured without dilution.

Statistical analysis

Data were statistically evaluated by use of the paired *t* test and one-way analysis of variance (ANOVA) with post hoc Bonferroni correction. Statistical differences were considered to be significant if $P < 0.05$. Correlation was determined by the Pearson's correlation coefficient. Power calculation using a two-sided design at a significance level of 5% ($\alpha = 0.05$) and a power of 80% ($\beta = 0.20$) revealed that at least 14 patients per group were needed. Therefore, we enrolled 20 patients per group to increase the power of the current study. Analyses were performed with the statistical software program GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA).

Table 1 Patient characteristics and surgical data

	Propofol group ($n = 20$)	Sevoflurane group ($n = 20$)
Age (years)	61.7 ± 13.5	62.9 ± 13.8
Sex (M/F)	15/5	16/4
BMI (kg/m^2)	22.2 ± 2.9	22.3 ± 3.1
Right/left-sided thoracotomy	11/9	13/7
Lobectomy/partial resection	13/7	14/6
PIP during OLV (cmH_2O)	22.9 ± 1.4	22.5 ± 2.5
Duration of OLV (min)	142.1 ± 54.8	151.0 ± 80.7
Duration of surgery (min)	166.4 ± 59.8	175.0 ± 83.9
Duration of anesthesia (min)	245.0 ± 59.8	248.6 ± 96.3

Data are expressed as mean ± SD

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

Results

Clinical characteristics

Table 1 depicts the characteristics and surgical data of the 40 patients divided into two experimental groups. Data are expressed as mean ± SD. Clinical characteristics were distributed evenly between the groups. All patients were extubated after surgery in the operating room, and their postoperative course was uneventful.

The expression of inflammatory mediators

Figure 1 shows ELF levels of IL-1β, IL-6, and IL-8 at each sampling point in the dependent lung and the nondependent lung for the two experimental groups. Data are expressed as mean ± SD. Inflammatory level was expressed as cytokine amount per 1 mg protein in ELF. The levels of TNF-α, IL-10, and IL-12p70 were below the minimum quantifiable level of the measuring methods at each sampling point. However, ELF levels of IL-1β, IL-6, and IL-8 significantly increased in the dependent lung and the nondependent lung after OLV in both groups, compared with their baseline levels ($P < 0.05$). The dependent lung ELF level of IL-6 was significantly higher in the propofol group than in the sevoflurane group after OLV ($P < 0.001$).

The magnitude of cytokine expression in ELF after OLV showed a progressive increase with prolonged duration of OLV in both groups (Figs. 2, 3). There was a correlation between the increase in the level of IL-1β, IL-6, or IL-8 and the duration of OLV in the dependent lung and the nondependent lung after OLV. The plasma cytokine levels of TNF-α, IL-1β, IL-6, IL-8, IL-10, and IL-12p70 were undetectable.

Discussion

In the current study, the ELF levels of IL-1β, IL-6, and IL-8 were significantly increased both in the dependent and the nondependent lungs during thoracic surgery. The level of IL-6 in the dependent lung was significantly higher in the propofol group than that in the sevoflurane group after OLV. However, the levels of inflammatory cytokines in the nondependent lung were not significantly different between the two groups. The ELF level of cytokine expression indicated a local inflammatory response because the plasma cytokine levels remained undetectable during surgery.

The major finding of this study was that sevoflurane suppressed proinflammatory cytokine release in the ventilated dependent lung after OLV, and did so more effectively than propofol. Furthermore, the immunomodulatory effect of sevoflurane seemed to be potentially greater in the dependent lung than in the nondependent lung during OLV.

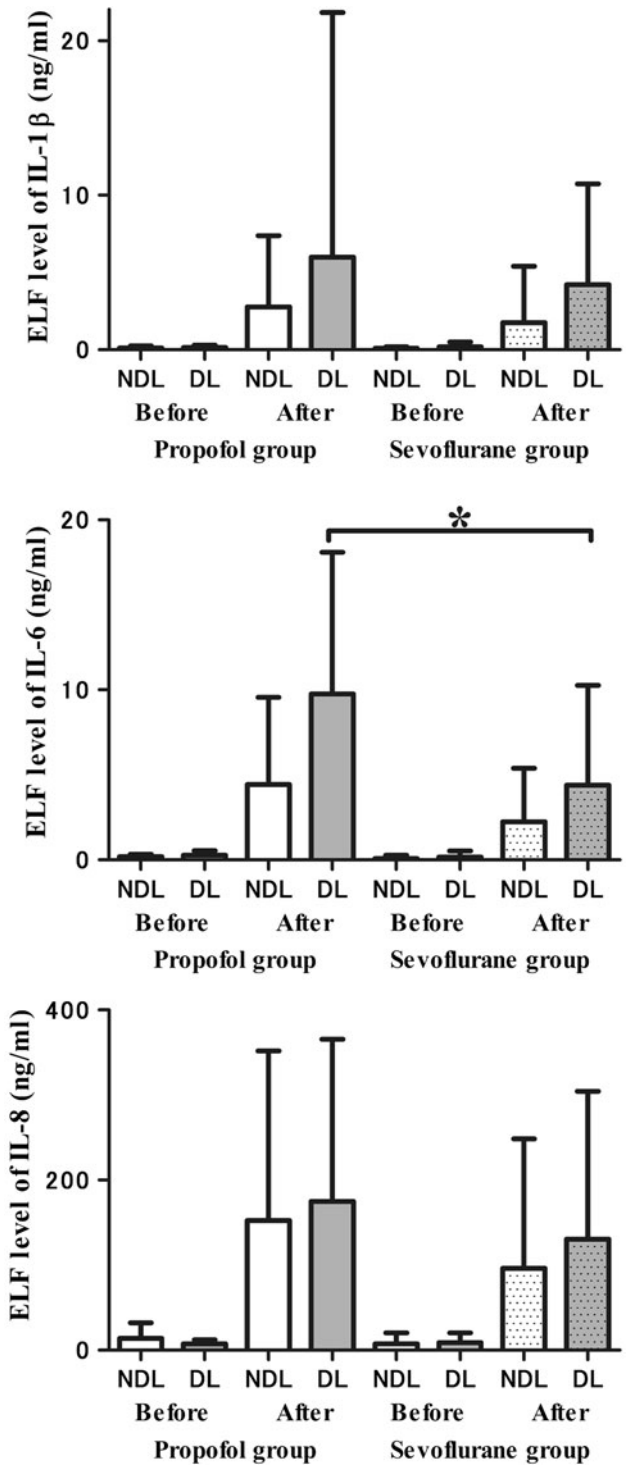
Acute pulmonary inflammatory responses represent alveolar damage on the basis of a ventilation-induced lung injury [18]. Damage of the alveolocapillary unit may lead to an increase in alveolar permeability, greater influx of protein and albumin, and recruitment of granulocytes and macrophages into the alveolar space [7, 15]. These processes of immune activation were related to alveolar proinflammatory cytokine release. Recent studies have suggested that ELF levels of cytokines such as IL-1β, IL-6, and IL-8 were clinically relevant to pulmonary complications after thoracic surgery [1, 2, 5].

We consider that multiple pulmonary factors are able to induce inflammatory reactions, such as mechanical damage caused by surgical manipulation, OLV-induced atelectasis and reexpansion, damage resulting from high inspiratory oxygen concentration, and high inspiratory pressure as a result of mechanical ventilation.

Higher oxygen concentrations and inspiratory pressure are generally used during OLV than during bilateral lung ventilation. It is also accepted that ventilation with an inspiratory oxygen concentration above 60% can lead to pulmonary injury [19, 20].

A high inspiratory pressure resulting from mechanical ventilation can also damage the dependent lung during OLV [21]. Experimental data have shown that high pulmonary capillary pressure was accompanied by deterioration of the alveolar–capillary barrier [22, 23]. Some studies have also demonstrated that intraoperative mechanical ventilation with a high tidal volume is associated with an increased risk of respiratory failure [7, 8, 24, 25].

OLV-induced atelectasis and reexpansion has been suggested to induce ischemia–reperfusion injury [26]. The nondependent lung remains completely atelectatic for a period of time, accompanied by hypoperfusion from hypoxic pulmonary vasoconstriction (HPV). A lack of ventilation to the



◀ **Fig. 1** Changes in the epithelial lining fluid levels of interleukin-1β, interleukin-6, and interleukin-8 during lung resection. 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 before and after one-lung ventilation (OLV) in the ventilated dependent lung (DL) and the collapsed nondependent lung (NDL) for two groups. ELF levels of IL-1β, IL-6, and IL-8 increased significantly in the dependent lung [propofol group: IL-1β ($P = 0.047$), IL-6 ($P < 0.001$), IL-8 ($P < 0.001$); sevoflurane group: IL-1β ($P = 0.011$), IL-6 ($P = 0.003$), IL-8 ($P = 0.004$)] and in the nondependent lung [propofol group: IL-1β ($P = 0.017$), IL-6 ($P = 0.002$), IL-8 ($P = 0.006$); sevoflurane group: IL-1β ($P = 0.049$), IL-6 ($P = 0.005$), IL-8 ($P = 0.012$)] after OLV, compared with their baseline levels. *Asterisk* indicates the dependent lung ELF level of IL-6 was significantly higher in the propofol group than in the sevoflurane group after OLV ($P < 0.001$). Data are expressed as mean ± SD

collapsed lung might exacerbate reperfusion injury. De Leyn et al. [27] found greater lactate concentrations and lower ATP concentrations in isolated ischemic rabbit lungs that were deflated rather than inflated. Hamvas et al. [28] further studied ischemia–reperfusion lung injury in dogs and identified that ventilation or static inflation attenuated lung injury.

Madjdpour et al. [29] 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 [29].

Some previous studies have also demonstrated that the longer the duration of OLV, the more the pulmonary inflammatory responses were enhanced. Our present data support these earlier findings [2, 6, 30].

Serum cytokine concentrations observed in the present study were not accompanied by the alveolar proinflammatory response. This result confirms previous clinical data demonstrating that different ventilation modes with low or high tidal volumes did not change the concentration of plasma cytokines [31]. In addition, a single inflation with a peak airway pressure of 40 cmH_2O for 7–30 s did not affect plasma cytokine levels in mechanically ventilated patients [32, 33]. However, these results were in direct contrast to data arising from patients undergoing esophagectomy [4]. According to this study, mechanical ventilation with a lower tidal volume was associated with reduced plasma cytokine levels. The systemic inflammatory response may depend on the invasiveness of the surgical procedure [34], and it appears to be smaller after lung resection than esophagectomy.

The release of IL-6 in the dependent lung was significantly suppressed during sevoflurane administration compared with total intravenous propofol anesthesia in the current study. Recent in vitro data suggested that sevoflurane reduces the accumulation of neutrophils and the release of inflammatory mediators in endotoxin-injured alveolar epithelial cells [35, 36]. Reversible inhibition of pulmonary cytokine gene expression has also been observed following sevoflurane exposure [37]. The underlying mechanism for this type of immunomodulation is thought to involve interaction with inducible nitric oxide synthetase by reversible inhibition of voltage-dependent calcium channels and subsequent reductions in intracellular

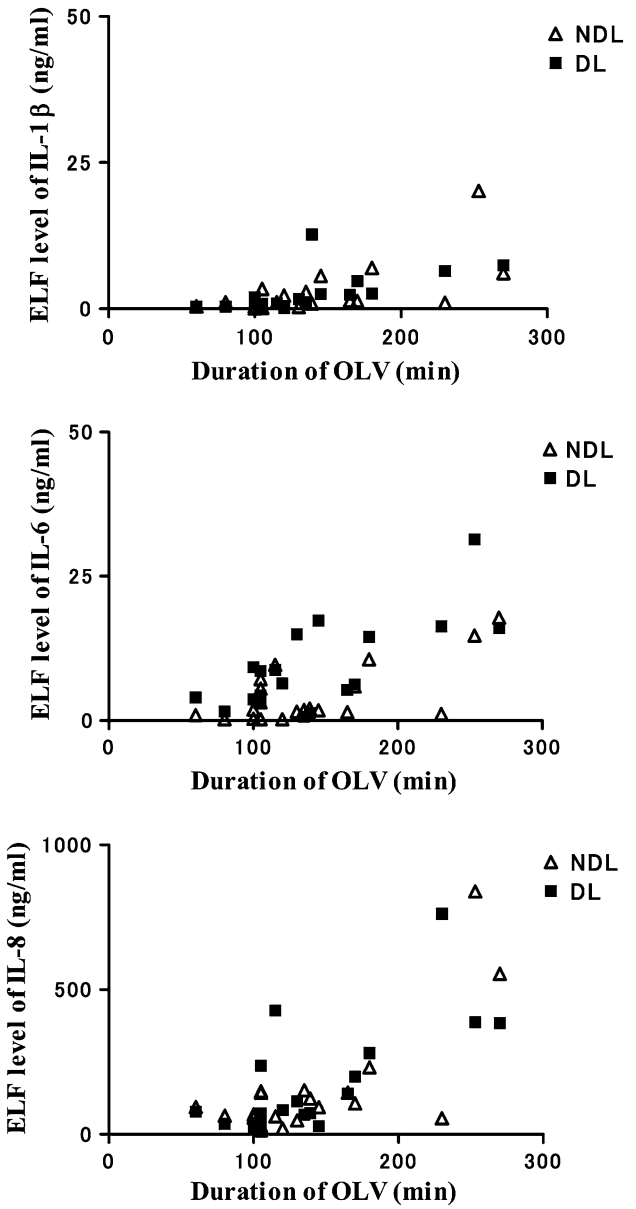


Fig. 2 Correlation between increase in interleukin-1β, interleukin-6, or interleukin-8 and the duration of one-lung ventilation in both lungs of the propofol group. There was a correlation between the increase in the levels of IL-1β, IL-6, or IL-8 and the duration of one-lung ventilation (OLV) in both the ventilated dependent lung (DL) and the collapsed nondependent lung (NDL) after OLV. For IL-1β, $r = 0.568$, $P = 0.009$ for the dependent lung; $r = 0.644$, $P = 0.002$ for the nondependent lung. For IL-6, $r = 0.724$, $P < 0.001$ for the dependent lung; $r = 0.669$, $P = 0.001$ for the nondependent lung. For IL-8, $r = 0.702$, $P < 0.001$ for the dependent lung; $r = 0.729$, $P < 0.001$ for the nondependent lung

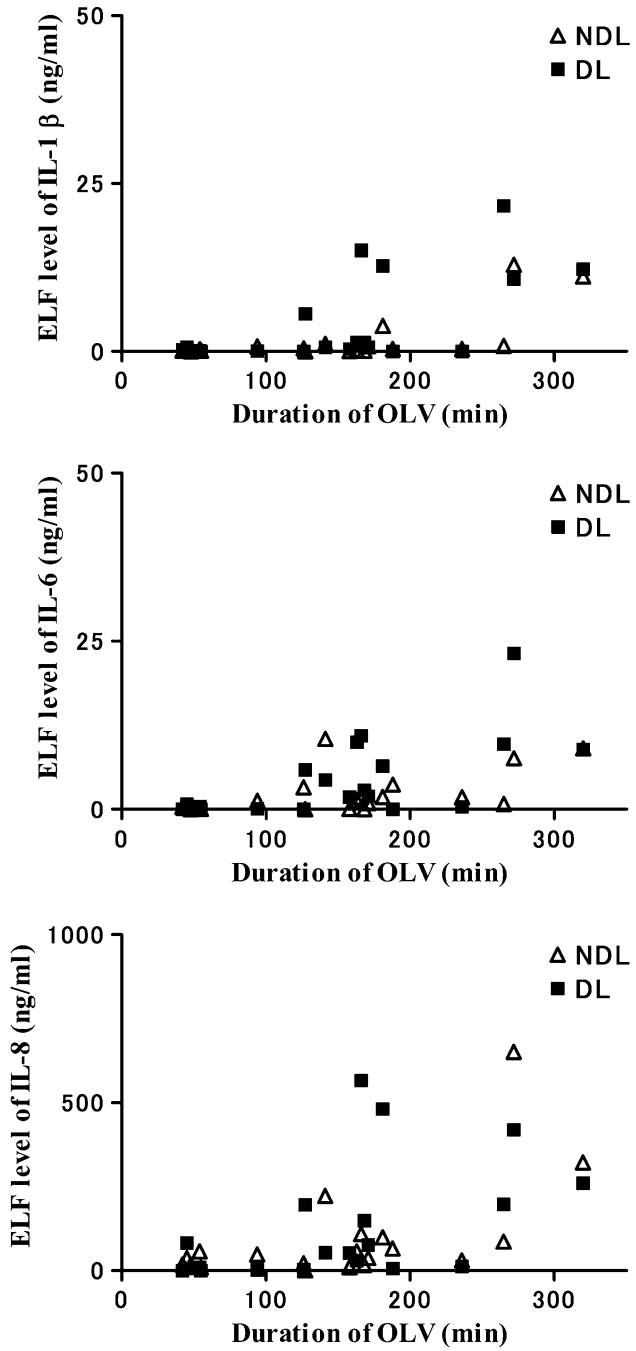


Fig. 3 Correlation between increase in interleukin-1β, interleukin-6, or interleukin-8 and the duration of one-lung ventilation in both lungs of the sevoflurane group. There was a correlation between the increase in the levels of IL-1β, IL-6, or IL-8 and the duration of one-lung ventilation (OLV) in both the ventilated dependent lung (DL) and the collapsed nondependent lung (NDL) after OLV. For IL-1β, $r = 0.622$, $P = 0.003$ for the dependent lung; $r = 0.643$, $P = 0.002$ for the nondependent lung. For IL-6, $r = 0.632$, $P = 0.003$ for the dependent lung; $r = 0.540$, $P = 0.014$ for the nondependent lung. For IL-8, $r = 0.489$, $P = 0.029$ for the dependent lung; $r = 0.577$, $P = 0.008$ for the nondependent lung

calcium concentration [38]. Urner et al. [39] reported that fluorinated groups mediated the immunomodulatory effects of sevoflurane in acute cell injury.

A recent clinical study demonstrated that cytokine concentrations in BALF from the nondependent lung

were significantly suppressed during sevoflurane administration compared with propofol [2]. However, the immunomodulatory effect of sevoflurane was significant only in the dependent lung in our current dataset. Our present data may therefore imply that the immunomodulatory effect of sevoflurane is potentially greater in the dependent lung than in the nondependent lung during OLV. Several factors might be considered to underlie this issue. During OLV, blood distribution is increased in the dependent lung as a result of HPV and the gravitational shift caused by the lateral position [40]. Furthermore, the alveolar epithelial cells are influenced by direct contact of sevoflurane in the dependent lung during OLV [35, 36].

In summary, OLV in patients undergoing lung resection promotes the production and release of proinflammatory substances in the alveoli of both the dependent lung and the nondependent lung. Moreover, the administration of sevoflurane significantly suppresses pulmonary proinflammatory response in the ventilated dependent lung, to a greater extent than propofol. Finally, these observations were likely to be related to the more enhanced immunomodulatory effect of sevoflurane in the dependent lung than the nondependent lung.

References

1. Yamaguchi K, Sugasawa Y, Takeuchi K, Kugimiya T, Kumakura S, Iwanuma Y, Kajiyama Y, Tsurumaru M, Nagaoka I, Inada E. Effects of sivelestat on bronchial inflammatory responses after esophagectomy. Int J Mol Med. 2011;28:187–92.
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. 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.
4. 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.
5. Baudouin S. Lung injury after thoracotomy. Br J Anaesth. 2003;91:132–42.
6. Sugasawa Y, Yamaguchi K, Kumakura S, Murakami T, Kugimiya T, Suzuki K, Nagaoka I, Inada E. The effect of one-lung ventilation upon pulmonary inflammatory responses during lung resection. J Anesth. 2011;25:170–7.
7. 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.
8. 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.
9. 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.
10. 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;278:572–9.
11. 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.
12. Sheeran P, Hall GM. Cytokines in anaesthesia. Br J Anaesth. 1997;78:201–19.
13. 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.
14. 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.
15. 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.
16. Schilling T, Kozian A, Senturk M, Huth C, Reinhold A, Hedenstierna G, Hachenberg T. Effects of volatile and intravenous anesthesia on the alveolar and systemic inflammatory response in thoracic surgical patients. Anesthesiology. 2011;115:65–74.
17. 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.
18. Slutsky AS. Lung injury caused by mechanical ventilation. Chest. 1999;116:9–15.
19. Halliwell B. Reactive oxygen species in living systems: source, biochemistry, and role in human disease. Am J Med. 1991;91:14–22.
20. Clark J. Pulmonary limits of oxygen tolerance in man. Exp Lung Res. 1988;14:897–910.
21. Whitehead T, Slutsky A. The pulmonary physician in critical care: ventilator induced lung injury. Thorax. 2002;57:635–42.
22. 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.
23. 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.
24. 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.
25. 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.

26. 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.
27. De Leyn P, 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. (discussion 1079).
28. 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.
29. 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;284:360–7.
30. 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.
31. Wrigge H, Zinserling J, Stüber F, von Spiegel T, Hering R, Wetegrove S, Hoeft A, Putensen C. Effects of mechanical ventilation on release of cytokines into systemic circulation in patients with normal pulmonary function. Anesthesiology. 2000;93:1413–7.
32. Puls A, Pollok-Kopp B, Wrigge H, Quintel M, Neumann P. Effects of a single-lung recruitment maneuver on the systemic release of inflammatory mediators. Intensive Care Med. 2006;32:1080–5.
33. Talmor D, Sarge T, Legedza A, O'Donnell CR, Ritz R, Loring SH, Malhotra A. Cytokine release following recruitment maneuvers. Chest. 2007;132:1434–9.
34. Craig SR, Leaver HA, Yap PL, Pugh GC, Walker WS. Acute phase responses following minimal access and conventional thoracic surgery. Eur J Cardiothorac Surg. 2001;20:455–63.
35. Suter D, Spahn DR, Blumenthal S, Reyes L, Booy C, Z'graggen BR, Beck-Schimmer B. The immunomodulatory effect of sevoflurane in endotoxin-injured alveolar epithelial cells. Anesth Analg. 2007;104:638–45.
36. Steurer M, Schläpfer M, Z'graggen BR, Booy C, Reyes L, Spahn DR, Beck-Schimmer B. The volatile anaesthetic sevoflurane attenuates lipopolysaccharide-induced injury in alveolar macrophages. Clin Exp Immunol. 2009;155:224–30.
37. Takala RS, Soukka H, Salo MS, Kirvelä O, Kääpä P, Aantaa R. Gene expression of pulmonary cytokines after sevoflurane or thiopentone anaesthesia in pigs. Acta Anaesthesiol Scand. 2006;50:163–7.
38. Tschaikowsky K, Ritter J, Schröppel K, Kühn M. Volatile anesthetics differentially affect immunostimulated expression of inducible nitric oxide synthase: role of intracellular calcium. Anesthesiology. 2000;92:1093–102.
39. Urner M, Limbach LK, Herrmann IK, Müller-Edenborn B, Roth-Z'graggen B, Schlicker A, Reyes L, Booy C, Hasler M, Stark WJ, Beck-Schimmer B. Fluorinated groups mediate the immunomodulatory effects of volatile anesthetics in acute cell injury. Am J Respir Cell Mol Biol. 2011;45:617–24.
40. Lohser J. Evidence-based management of one-lung ventilation. Anesthesiol Clin. 2008;26:241–72.