Effects of Volatile and Intravenous Anesthesia on the Alveolar and Systemic Inflammatory Response in Thoracic Surgical Patients

Thomas Schilling, M.D., Ph.D., D.E.A.A.,* Alf Kozian, M.D., Ph.D.,* Mert Senturk, M.D.,† Christof Huth, M.D.,‡ Annegret Reinhold, Ph.D.,§ Göran Hedenstierna, M.D., Ph.D.,‖ Thomas Hachenberg, M.D., Ph.D.#

ABSTRACT

Background: One-lung ventilation (OLV) results in alveolar proinflammatory effects, whereas their extent may depend on administration of anesthetic drugs. The current study evaluates the effects of different volatile anesthetics compared with an intravenous anesthetic and the relationship between pulmonary and systemic inflammation in patients undergoing open thoracic surgery.

Methods: Sixty-three patients scheduled for elective open thoracic surgery were randomized to receive anesthesia with 4 mg · kg^{-1} · h^{-1} propofol (n = 21), 1 minimum alveolar concentration desflurane (n = 21), or 1 minimum alveolar concentration sevoflurane (n = 21). Analgesia was provided by remifentanil (0.25 μg · kg^{-1} · min^{-1}). After intubation, all patients received pressure-controlled mechanical ventilation with a tidal volume of approximately 7 ml · kg^{-1} ideal body weight, a peak airway pressure lower than 30 cm H_2O, a respiratory rate adjusted to a $Paco_2$ of 40 mmHg, and a fraction of inspired oxygen lower than 0.8 during OLV. Fiberoptic bronchoalveolar lavage of the ventilated lung was performed immediately after intubation and after surgery. The expression of inflammatory cytokines was determined in the lavage fluids and serum samples by multiplexed bead-based immunoassays.

Results: Proinflammatory cytokines increased in the ventilated lung after OLV. Mediator release was more enhanced during propofol anesthesia compared with desflurane or sevoflurane administration. For tumor necrosis factor-α, the values were as follows: propofol, 5.7 (8.6); desflurane, 1.6 (0.6); and sevoflurane, 1.6 (0.7). For interleukin-8, the values were as follows: propofol, 924 (1680); desflurane, 390 (813); and sevoflurane, 412 (410). (Values are given as median [interquartile range] pg · ml^{-1}). Interleukin-1β was similarly reduced during volatile anesthesia. The postoperative serum interleukin-6 concentration was increased in all patients, whereas the systemic proinflammatory response was negligible.

Conclusions: OLV increases the alveolar concentrations of proinflammatory mediators in the ventilated lung. Both desflurane and sevoflurane suppress the local alveolar, but not the systemic, inflammatory responses to OLV and thoracic surgery.

What We Already Know about This Topic

- Alveolar and systemic inflammatory mediators are found in patients undergoing one-lung ventilation

What This Article Tells Us That Is New

- The alveolar cytokine release in the ventilated lung was decreased in patients undergoing elective open thoracic surgery when sevoflurane and desflurane were administered compared with the administration of propofol as the anesthetic

IN patients who undergo lung resection, mechanical ventilation and the surgical procedure may induce alveolar and systemic inflammatory responses.[1] Consequently, one-lung ventilation (OLV) increases the concentrations of alveolar macrophages and granulocytes, proteins, proinflammatory cytokines, and adhesion molecules (*i.e.*, soluble intercellular adhesion molecule-1, tumor necrosis factor (TNF) α, interleukin [IL] 8, and polymorphonuclear granulocyte elastase) in the alveoli of the ventilated lung.[2] Similarly, temporary lung collapse and surgical manipulation enhance the expression of inflammatory mediators.[3,4] The proinflammatory responses of the ventilated and collapsed

* Assistant Professor in Cardiac and Thoracic Anesthesia, † Assistant Professor in Anesthesia, Department of Anesthesiology and Intensive Care Medicine, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany. ‡ Professor of Surgery and Chair, Department of Cardiovascular and Thoracic Surgery, Otto-von-Guericke-University Magdeburg. § Research Immunologist, Institute of Molecular and Clinical Immunology, Otto-von-Guericke-University Magdeburg. ‖ Professor in Clinical Physiology and Head of the Research Department of Clinical Physiology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden. # Professor of Anesthesia and Chair, Department of Anesthesiology and Intensive Care Medicine, Otto-von-Guericke-University Magdeburg.

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Address correspondence to Dr. Schilling: Department of Anesthesiology and Intensive Care Medicine, Otto-von-Guericke-University, Leipziger Strasse 44, D-39120 Magdeburg, Germany. thomas.schilling@med.ovgu.de. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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lung can be modified by the inhalational anesthetics desflurane and sevoflurane, respectively.[4,5]

However, the modification of alveolar cytokine release by different inhalational anesthetics has not been evaluated in a defined ventilatory setting during OLV, which includes pressure-controlled ventilation[6] with low tidal volumes,[7] limitation of inspired oxygen concentrations,[8] limitation of inspiratory pressure and intraoperative fluid load,[9] use of repetitive alveolar recruitment maneuvers,[10] and positive end-expiratory pressure.[11] In addition, there are no data on the relationship between pulmonary and systemic inflammation in these patients.

Therefore, the objectives of the current clinical study were to compare the potential modulation of alveolar and systemic proinflammatory cytokine expression by desflurane or sevoflurane with total intravenous anesthesia (propofol) and to analyze the pulmonary and systemic effects of OLV and thoracic surgery.

The following null hypothesis was tested: the administration of desflurane, sevoflurane, or propofol does not affect the proinflammatory response after thoracic surgery.

Materials and Methods

The study was designed as a prospective, randomized, blinded clinical observation. The Institutional Review Board of Otto-von-Guericke-University Magdeburg, Magdeburg, Germany, approved the study protocol and patient management. Written informed consent was obtained from all patients.

Patient Characteristics

The patients scheduled for open thoracic surgery and OLV were randomly allocated to propofol, desflurane, or sevoflurane anesthesia. A total of 87 consecutive patients were considered for inclusion in the study. Sixty-three adults with normal lung function, scheduled for elective open thoracic surgery, were eligible to participate.

The exclusion criteria applied were as follows: persistent tobacco abuse, body mass index greater than 35 kg/m^2, history of treatment with immunodepressant drugs in the 6 weeks before surgery, cardiac failure (New York Heart Association class greater than II), clinically relevant obstructive or restrictive lung diseases (vital capacity or forced expiratory volume in 1 s lower than 50% of the predicted values), pulmonary hypertension (mean pulmonary arterial pressure greater than 25 mmHg), or preexisting coagulation disorders. Patients with evidence of pulmonary or systemic infections (clinically defined or increased C-reactive protein serum concentrations greater than 5 mg/l, leukocytosis greater than 10.0 gigaparticles/liter, or body temperature higher than 37°C) were also excluded.

The preoperative screening was performed by the same physician (T.S.) to ensure consistent application of the following criteria: complete medical history, physical examination findings, measurements of body weight and height, electrocardiogram, chest X-ray, pulmonary function test results, echocardiographic findings, and the results of arterial blood gas analysis.

General Anesthetic Management

All patients were orally premedicated with 0.1 mg/kg midazolam 2 h before anesthesia. Before intubation, a thoracic epidural catheter was inserted (Th4/5 to Th7/8). The position of the catheter tip was verified by a test dose of 3 ml bupivacaine, 0.5%, with adrenaline (5 μg/ml). Continuous epidural analgesia started with ropivacaine, 0.2%, and sufentanil (1 μg/ml) immediately after OLV. Analgesia was maintained for 2–4 days until the chest tubes were removed.

In all patients, both a radial artery catheter (Angiocath G20; Becton Dickinson, Heidelberg, Germany) and a central venous catheter (B. Braun, Melsungen, Germany) were inserted.

Standard intraoperative fluid therapy consisted of crystalloid infusion (4–6 $ml \cdot kg^{-1} \cdot h^{-1}$, E156; Serumwerk Bernburg, Bernburg, Germany). Intraoperative volume deficits were replaced by additional administration of a colloid solution (2–4 $ml \cdot kg^{-1} \cdot h^{-1}$, hydroxyethyl starch 6 130/0.42 RAc; Serumwerk Bernburg), as required. All patients received a single dose of 2 g cefotiam for prophylactic antibiosis.

After surgery, the patients were admitted to the intensive care unit and monitored for 24 h. Postoperative sedation was maintained with remifentanil (0.1–0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and intermittent intravenous administration of midazolam (2–4 mg) until extubation. Fluids and blood transfusions were given to maintain urine output at 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$ and a hemoglobin concentration of 6.0 mM or greater with respect to a maximum positive fluid balance lower than 20 ml/kg in the first 24 h after surgery.

All patients were assessed daily regarding clinical signs of general and, especially, pulmonary complications after surgery.

Randomization

Randomization assignment of patients to propofol anesthesia (propofol group, n = 21), desflurane inhalation (desflurane group, n = 21), or sevoflurane inhalation (sevoflurane group, n = 21) was performed with a list of random numbers that was generated by the random function of computer software (EXCEL®; Microsoft Corp, Redmond, WA). The list contained the natural numerals 1, 2, and 3. These numbers were allocated as follows: 1, propofol; 2, desflurane; and 3, sevoflurane administration.

In the propofol group, general anesthesia was induced with propofol (1.5–2 mg/kg) and remifentanil (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Tracheal intubation was facilitated by administration of cisatracurium (0.1 mg/kg). Anesthesia was maintained by a continuous infusion of propofol (3–5 $mg \cdot kg^{-1} \cdot h^{-1}$), remifentanil (0.1–0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and *cis*-atracurium (1–2 $\mu g \cdot kg^{-1} \cdot min^{-1}$). In patients who were allocated to the volatile anesthesia groups, anesthesia was induced as previously described but was maintained with desflurane (ap-

proximately 1 minimum alveolar concentration per air) or sevoflurane (approximately 1 minimum alveolar concentration per air),[12] remifentanil (0.1–0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and *cis*-atracurium (1–2 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

Airway Management and Ventilation Setup

A left- or right-sided double-lumen endobronchial tube (Broncho-Cath® 39 or 41 Charrieré; Mallinckrodt Medical Ltd, Athlone, Ireland) was inserted in all patients. The correct position of the double-lumen tube was confirmed by fiberoptic bronchoscopy (bronchoscope BF-3C40; OD, 2.8 mm; Olympus Europe, Hamburg, Germany). The lung was recruited through vital capacity maneuvers (alveolar recruitment maneuver) with airway pressures of 40 cm H_2O applied to the whole lung for approximately 7–10 s before and after each bronchoscopic manipulation.

The patients were ventilated by pressure-controlled ventilation, provided by a closed-circuit anesthesia ventilator (Zeus®; Dräger, Lübeck, Germany). The tidal volume was set to 6 ml/kg. The peak inspiratory pressure was limited to 30 cm H_2O. The fraction of inspired oxygen was adjusted to maintain oxyhemoglobin saturation at greater than 95% (fraction of inspired oxygen, 0.4–0.5 before OLV; fraction of inspired oxygen, 0.6–0.7 during OLV) and the respiratory rate to keep the $Paco_2$ between 36 and 44 mmHg. The positive end-expiratory pressure was set to 5 cm H_2O. Gas concentrations and airway pressures were measured at the proximal end of the endobronchial tube using the ventilator-integrated functions. During OLV, the ventilation settings were maintained; and positive end-expiratory pressure was not reduced.

After surgery, the double-lumen tube was replaced by a standard single-lumen tube for postoperative ventilatory support.

Surgical Procedures

Open thoracic surgical procedures were applied for established or suspected malignancies (carcinomas and metastases). Lung resections were performed through a standard posterolateral or an anterolateral muscle-sparing thoracotomy.

Hemodynamic Measurements

Cardiopulmonary data (*i.e.*, heart rate, mean arterial pressure, central venous pressure, and arterial blood gas concentrations) were recorded and evaluated at three stages: (1) during two-lung ventilation before thoracic surgery, (2) 25 min after the start of OLV, and (3) after the surgical procedure.

Cardiac output measurements were performed using a continuous cardiac output monitor (Vigileo; Edwards Lifesciences, S.A., Nyon, Switzerland), which was connected to the radial artery catheter.

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) of the dependent ventilated lung was performed by passing the fiberoptic bronchoscope through the endobronchial tube and wedging the tip into a segmental bronchus of the left- or right-sided lower lobe or the middle lobe. Different segments were randomly chosen for repetition of BAL. Lavage was performed by sequential instillation and gentle aspiration of isotonic sodium chloride solution (10-ml portions, with a total of 40 ml) after intubation, before thoracotomy, and 30 min after the surgical procedure.

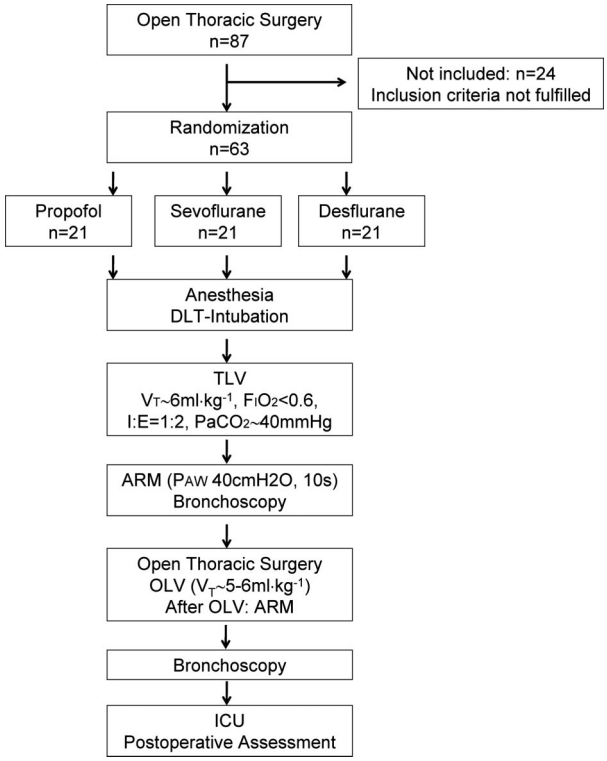

Fig. 1. Study protocol. ARM = alveolar recruitment maneuver; DLT = double lumen tube; F_{IO_2} = fraction of inspired oxygen; ICU = intensive care unit; I:E = inspiration:expiration; OLV = one-lung ventilation; P_{AW} = airway pressure; V_T = tidal volume.

Preparation of BAL Fluid and Serum Samples

The lavage fluid was filtered through sterile gauze filters, collected on ice in siliconized containers, and immediately centrifuged (at 250*g* for 10 min at 4°C). The samples of arterial blood were allowed to clot on ice and were also centrifuged (at 200*g* for 10 min at 4°C). After centrifugation, aliquots of serum and lavage fluid (500 μl) were immediately frozen and stored at −80°C until analysis.

Measurement of Cytokine Concentrations

The concentrations of TNF-α and IL-1β, IL-6, IL-8, IL-10, and of IL-12p70 in the BAL fluids and serum samples were determined using a quantitative multiplexed bead-based immunoassay for inflammatory mediators that allows the quantification of multiple cytokines simultaneously (BD Cytometric Bead Array, Human Inflammatory Cytokines Kit, catalog No. 551811; Becton Dickinson).

The samples of each subject were analyzed in duplicate in the same assay run. The assays were run on the basis of the manufacturer's instructions by an investigator blinded to the randomization (A.R.). Six bead populations with distinct fluorescence intensities were coated with capture antibodies specific for IL-8, IL-1β, IL-6, IL-10, TNF-α, and IL-12p70 proteins. The beads were mixed together to form the bead array that was resolved in the red channel of a flow cytometer (FACSCalibur; Becton Dickinson). The cytokine concentrations were calculated by interpolation from standard curves using computer software (CellQuest Pro; Becton Dickinson).

The sensitivities of the immunoassays were as follows: TNF-α, 3.7 pg/ml; IL-1β, 7.2 pg/ml; IL-6, 2.5 pg/ml; IL-8, 3.6 pg/ml; IL-10, 3.3 pg/ml; and IL-12p70, 1.9 pg/ml.

Statistical Analysis

Statistical analysis was performed using computer software (SPSS, version 17; SPSS Inc., Chicago, IL). On the basis of previous studies,[2,5] 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 16 subjects per group were needed to detect a difference of more than 40% in alveolar cytokine concentrations. The changes of alveolar TNF-α and IL-8 concentrations were defined as primary variables.

The data were tested for normal distribution with the Shapiro-Wilks W test. Normally distributed variables were presented as mean ± SD (for hemodynamic, ventilation, and gas exchange data). These variables were analyzed by a repeated-measures one-way ANOVA with *post hoc* Bonferroni correction.

In case of nonnormal distribution (alveolar and serum cytokine concentrations), the results were displayed as box plots (median and interquartile range, 25 to 75 percentile). These data were logarithmically transformed to achieve homogeneous variances of data sets (homoscedasticity). The sequential changes of alveolar and serum cytokine concentrations in each group were assessed by a repeated-measures general linear model (type III sums of squares) after transformation. Subsequent between-group comparisons were performed by two-way ANOVA using the independent variables "group" and "time." *Post hoc* multiple comparisons were performed by the Bonferroni procedure. However, the alveolar concentrations of TNF-α, IL-1β, and IL-10 remained heteroscedastic even after transformation. Therefore, these data were analyzed by a nonparametric Friedman test and subsequently by a Kruskal–Wallis H-test, with adjustment of α levels for repeated measurements.

No data were lost during the experiment or were missed in the statistical analysis. In some cases, mediator concentrations were lower than the detection limits of the assays. These data were included in the statistical analysis, with a value of $P < 0.01$.

The differences were considered statistically significant for all procedures if $P < 0.05$.

Results

Patient Characteristics

Of 87 consecutive patients scheduled for elective open thoracic surgery, 63 enrolled into the study (fig. 1). Thus, 24 patients were excluded, most for the reason of immunodepressant ther-

Table 1. Patient Characteristics and Intraoperative Variables

Variables	Propofol Group (n = 21)	Desflurane Group (n = 21)	Sevoflurane Group (n = 21)
Biometric Data			
Age, yr	64 (21–78)	60 (24–83)	63 (29–78)
Male/Female Ratio	15:6	13:8	13:8
Actual Weight, kg	79 (50–120)	78 (53–124)	76 (48–110)
Height, cm	172 (159–187)	171 (147–195)	171 (153–182)
Body Mass Index, kg/m^2	26 (20–34)	26 (19–32)	25 (18–35)
Predicted Body Weight, kg	73 (50–96)	72 (56–101)	70 (53–91)
No. of Former Smokers	11	10	9
ASA II/III/IV	2:15:4	5:14:2	3:14:4
Preoperative FVC, % Predicted	88 (56–111)	89 (59–116)	88 (67–108)
Preoperative FEV_1, % Predicted	75 (51–98)	74 (52–96)	77 (59–96)
Preoperative Pa_{O_2}, mmHg	75 (60–100)	77 (59–96)	78 (64–93)
Preoperative Pa_{CO_2}, mmHg	38 (32–47)	37 (29–43)	38 (32–46)
Intraoperative Data			
Right-sided Thoracotomy	14	13	11
Left-sided Thoracotomy	7	8	10
Lobectomy or Pneumonectomy	12	6	7
Atypical Pulmonary Resection	9	15	14
Duration of Surgery, min	122 (48–252)	102 (50–257)	109 (39–196)
Time of OLV, min	64 (23–179)	59 (29–90)	58 (25–124)
Transfused Blood*/Patients	5/5	4/4	4/4

Data are given as the median (range) unless otherwise indicated.

* Leukocyte-depleted erythrocyte concentrates.

ASA = American Society of Anesthesiologists; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; OLV = one-lung ventilation.

Table 2. Administration of Anesthetic Drugs

Variable	Two-lung Ventilation after Intubation			One-lung Ventilation at 25 min			Two-lung Ventilation after Surgery		
	Propofol, $mg \cdot kg^{-1} \cdot h^{-1}$ (n = 21)	Desflurane, % by Volume (n = 21)	Sevoflurane, % by Volume (n = 21)	Propofol, $mg \cdot kg^{-1} \cdot h^{-1}$ (n = 21)	Desflurane, % by Volume (n = 21)	Sevoflurane, % by Volume (n = 21)	Propofol, $mg \cdot kg^{-1} \cdot h^{-1}$ (n = 21)	Desflurane, % by Volume (n = 21)	Sevoflurane, % by Volume (n = 21)
Anesthetic Drug	3.9 ± 1.2	5.5 ± 0.5	1.6 ± 0.4	4.2 ± 1.3	5.6 ± 0.8	1.8 ± 0.4	3.8 ± 1.0	5.2 ± 0.6	1.7 ± 0.3
Remifentanil, $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.19 ± 0.08	0.17 ± 0.07	0.15 ± 0.07	0.22 ± 0.05	0.22 ± 0.06	0.20 ± 0.09	0.19 ± 0.07	0.16 ± 0.08	0.18 ± 0.09

Data are given as mean ± SD.

apy (*i.e.*, steroids or cytostatic drugs). All enrolled patients completed the study successfully. Table 1 presents the biometric data of patients and the details of thoracic surgery. The patient characteristics were evenly distributed between the groups.

The different surgical procedures included lobectomy, pneumonectomy, and atypical pulmonary resection. There were no associations between cytokine release and type or duration of surgery and OLV. The mean doses of the administered anesthetics are presented in table 2.

All patients had an uneventful postoperative course. They were extubated in a median of 1.2 h after admission to the intensive care unit. There were no differences in time to extubation, fluid balance, morbidity, postoperative chest infections, and length of hospital stay. The use of blood products did not differ between the study groups. There was no association between cytokine concentrations and administration of erythrocyte concentrates.

Hemodynamic and Ventilation Variables

The time courses of ventilation, gas exchange (table 3), and hemodynamic data (table 4) did not differ between the patients who were anesthetized with either intravenous or volatile anesthetics. After initiation of OLV, airway pressures increased ($P < 0.001$), whereas minute ventilation and inspiratory/cycle time ratios were unaltered compared with two-lung ventilation. Respiratory compliance and Pa_{O_2} decreased in all patients during surgery ($P < 0.001$). No patient was excluded for the need of ventilatory settings outside the defined protocol during OLV.

Central venous pressure increased in all patients during OLV (table 4). Heart rate, mean arterial pressure, and cardiac

Table 3. Ventilation and Gas Exchange Data at Different Time Points: During Two-lung Ventilation before Surgery, during One-lung Ventilation, and during Postoperative TLV

Variable	TLV, Preoperatively			One-lung Ventilation at 25 min			TLV, Postoperatively		
	Propofol (n = 21)	Desflurane (n = 21)	Sevoflurane (n = 21)	Propofol (n = 21)	Desflurane (n = 21)	Sevoflurane (n = 21)	Propofol (n = 21)	Desflurane (n = 21)	Sevoflurane (n = 21)
MV/min	6.4 ± 1.1	6.7 ± 1.1	6.4 ± 1.5	6.5 ± 1.3	6.8 ± 1.6	6.8 ± 2.1	6.5 ± 1.3	7.0 ± 1.5	6.5 ± 1.0
RR/min	12.8 ± 1.7	13.3 ± 1.5	13.2 ± 1.5	13.4 ± 2.5	13.4 ± 1.6	15.4 ± 4.1	12.8 ± 2.0	13.0 ± 1.2	13.0 ± 2.2
V_T, ml/kg ABW	6.4 ± 1.0	6.4 ± 1.0	6.3 ± 1.1	6.2 ± 1.1	6.5 ± 0.8	6.0 ± 0.9	6.4 ± 1.0	6.5 ± 0.9	6.5 ± 0.9
V_T, ml/kg PBW	7,1 ± 1.1	7.2 ± 0.9	6.9 ± 1.2	6.8 ± 1.1	7.0 ± 0.7	6.7 ± 0.9	7.1 ± 1.1	7.3 ± 0.8	7.2 ± 0.9
P_{AW} peak, cm H_2O	16 ± 6	18 ± 4	17 ± 6	26 ± 7*	25 ± 6†	25 ± 8‡	19 ± 6	20 ± 5	19 ± 5
P_{AW} plateau, cm H_2O	15 ± 5	16 ± 3	15 ± 6	23 ± 8*	24 ± 6†	23 ± 7‡	17 ± 5	18 ± 5	17 ± 4
PEEP, cm H_2O	3.0 ± 1.3	3.2 ± 1.3	3.4 ± 1.1	2.3 ± 1.1	2.6 ± 1.4	3.1 ± 1.5	3.4 ± 1.4	3.8 ± 1.5	3.8 ± 1.4
C, ml/cm H_2O	50 ± 19	52 ± 18	52 ± 21	31 ± 13*	29 ± 10†	32 ± 13‡	45 ± 17	46 ± 19	49 ± 16
F_{IO_2}	0.52 ± 0.1	0.53 ± 0.1	0.55 ± 0.1	0.69 ± 0.1*	0.67 ± 0.1†	0.69 ± 0.1‡	0.55 ± 0.1	0.59 ± 0.1	0.59 ± 0.1
Pa_{O_2}, mmHg	183 ± 102	153 ± 60	175 ± 51	97 ± 43*	79 ± 20†	104 ± 44‡	210 ± 86	169 ± 65	185 ± 66
Pa_{CO_2}, mmHg	43 ± 7	40 ± 4	40 ± 5	43 ± 8	40 ± 5	39 ± 7	42 ± 5	44 ± 6	41 ± 7
Sa_{O_2}, %	99 ± 2	98 ± 1.5	99 ± 1	95 ± 2.5*	94 ± 4†	96 ± 3‡	99 ± 1	98 ± 1	99 ± 1

Data are given as mean ± SD in each group.

* Differences within the propofol group. † Differences within the desflurane group. ‡ Differences within the sevoflurane group.

ABW = actual body weight; C = dynamic compliance; F_{IO_2} = fraction of inspired oxygen; MV = minute ventilation; P_{AW} = airway pressure; PBW = predicted body weight; PEEP = positive end-expiratory pressure; RR = respiratory rate; Sa_{O_2} = arterial oxygen saturation; TLV = two-lung ventilation; V_T = tidal volume.

Table 4. Hemodynamic Data at Different Time Points: During Two-lung Ventilation before Surgery, during One-lung Ventilation, and during Postoperative TLV

	TLV before Surgery			One-lung Ventilation at 25 min			TLV, Postoperatively		
Variable	Propofol (n = 21)	Desflurane (n = 21)	Sevoflurane (n = 21)	Propofol (n = 21)	Desflurane (n = 21)	Sevoflurane (n = 21)	Propofol (n = 21)	Desflurane (n = 21)	Sevoflurane (n = 21)
Heart Rate, beats/min	67 ± 13	70 ± 11	75 ± 14	74 ± 12	75 ± 15	75 ± 10	72 ± 13	72 ± 15	74 ± 11
MAP, mmHg	65 ± 12	64 ± 11	68 ± 12	72 ± 18	69 ± 10	70 ± 11	74 ± 18	70 ± 10	71 ± 13
CVP, mmHg	8.1 ± 4.2	7.2 ± 2.6	8.2 ± 3.6	10.1 ± 4.4*	10.2 ± 3.6†	10.4 ± 3.3‡	8.4 ± 3.9	8.0 ± 2.7	6.8 ± 3.1
CO, l/min	5.1 ± 1.1	5.1 ± 0.8	4.7 ± 0.9	5.6 ± 1.3	5.3 ± 0.6	5.0 ± 0.9	5.1 ± 1.3	5.2 ± 0.7	5.2 ± 1.0
Hb, mM	7.2 ± 0.8	7.2 ± 1.2	7.3 ± 1.1	6.9 ± 0.6	7.1 ± 1.0	7.0 ± 1.1	6.7 ± 0.6	6.9 ± 1.0	6.9 ± 1.1

Data are given as mean ± SD in each patient group.

* Differences within the propofol group ($P = 0.001$). † Differences within the desflurane group ($P < 0.001$). ‡ Differences within the sevoflurane group ($P = 0.022$).

CO = cardiac output; CVP = central venous pressure; Hb = hemoglobin concentration; MAP = mean arterial pressure; TLV = two-lung ventilation.

output remained unchanged. Postoperative values of hemodynamic and ventilation parameters were not different between the groups and when compared with preoperative two-lung ventilation values.

Analysis of Alveolar and Systemic Inflammatory Mediators

Figure 2 presents alveolar concentrations of the proinflammatory mediators TNF-α (fig. 2A), IL-1β (fig. 2B), IL-6

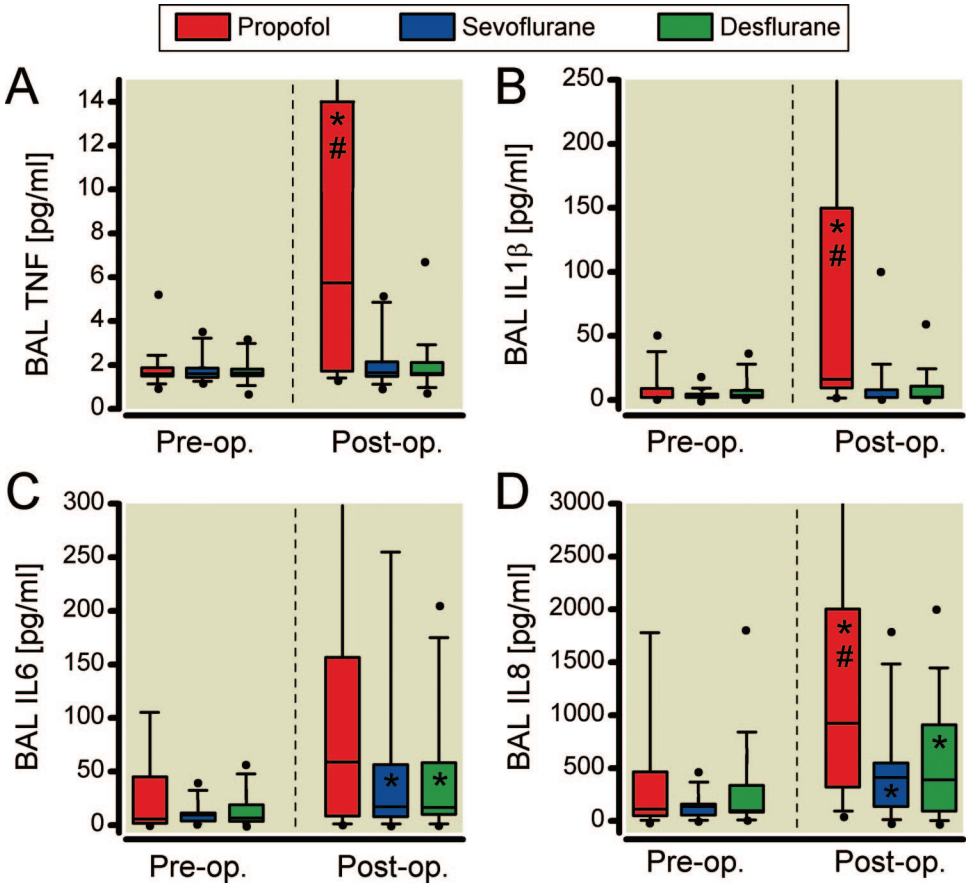

Fig. 2. The time-dependent changes of the intraalveolar concentrations of tumor necrosis factor (TNF)-α (*A*), interleukin (IL)-1β (*B*), IL-6 (*C*), and IL-8 (*D*) in patients undergoing one-lung ventilation and open thoracic surgery. Data are given as medians, ranges, and interquartile ranges (25 to 75 percentile). The black dots indicate the outliers in each group. The symbol * indicates differences within a single study group, and # marks differences between the propofol and both volatile anesthesia patient groups. BAL = bronchoalveolar lavage; Post-op = postoperatively; Pre-op = preoperatively.

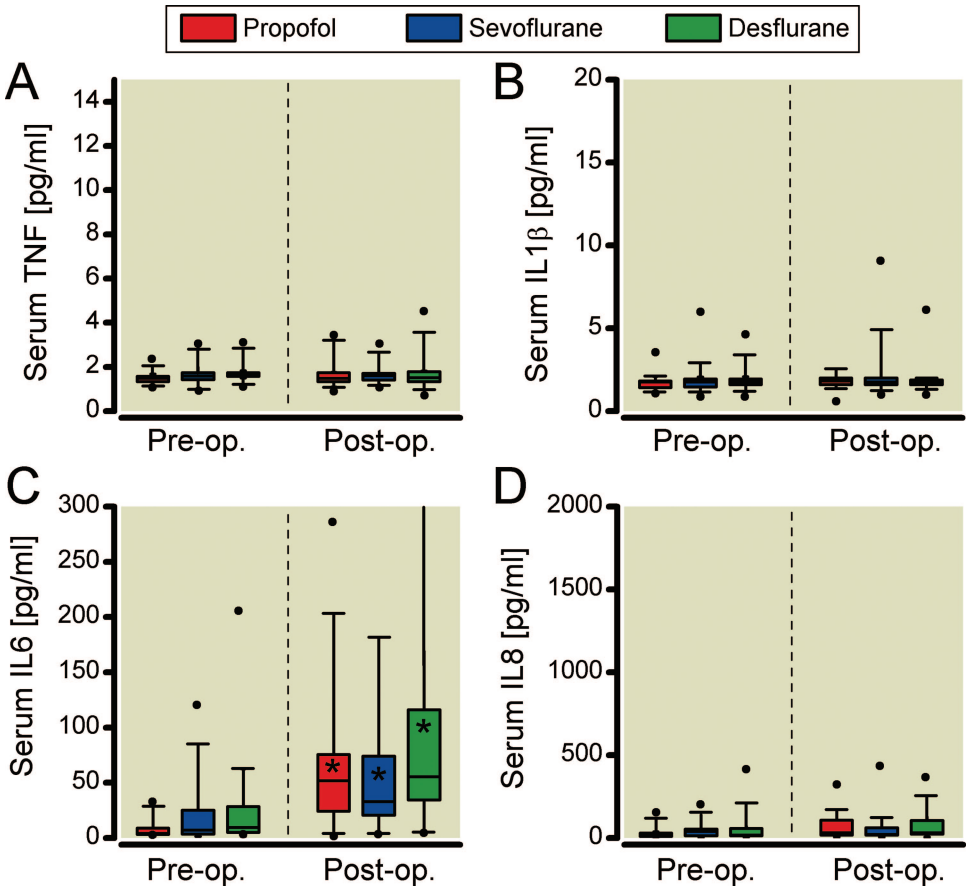

Fig. 3. The changes of the serum tumor necrosis factor (TNF)-α (*A*), interleukin (IL)-1β (*B*), IL-6 (*C*), and IL-8 (*D*) concentrations in the different patient groups. Data are displayed as ranges, medians, and interquartile ranges (25 to 75 percentile). The black dots indicate the outliers in each group. The symbol * marks the differences within the propofol, sevoflurane, or desflurane group. Post-op = postoperatively; Pre-op = preoperatively.

(fig. 2C), and IL-8 (fig. 2D) in the dependent lung before and after OLV and thoracic surgery. Postoperatively, the proinflammatory cytokines TNF-α ($P = 0.001$), IL-1β ($P = 0.002$), and IL-8 ($P = 0.025$) were more increased in patients during propofol administration compared with both volatile anesthesia groups. The alveolar concentrations of IL-6 and IL-8 were enhanced in the ventilated lung after OLV ($P = 0.001$).

Figure 3, A–D, illustrates that the systemic expression of TNF-α, IL-1β, and IL-8 was nonsignificant. However, the postoperative serum concentration of IL-6 was increased in all patient groups after thoracic surgery ($P < 0.001$).

OLV and thoracic surgery did not affect the alveolar and systemic expression of antiinflammatory IL-10 (fig. 4, A and B) or IL-12p70 protein (fig. 4, C and D).

Discussion

The principal finding of the current study is that the volatile anesthetics desflurane and sevoflurane suppress the proinflammatory cytokine release in the ventilated lung after OLV. The intravenous anesthetic propofol does not exert this alleviating effect on alveolar cytokines. The postoperative responses to OLV and thoracic surgery are different in the lung and in the peripheral blood: the systemic expression of IL-6 is enhanced in all patients, but the serum concentrations of TNF-α, IL-8, IL-1β, IL-10, and IL-12p70 are not increased.

Acute proinflammatory reactions become evident in all types of thoracic surgery.[13] These have been well described in relation to acute lung injury and the adult respiratory distress syndrome.[14] The lung damage probably represents the pulmonary manifestation of an inflammatory response on the basis of a ventilation-induced alveolar injury.[15] Likewise, histopathological signs of diffuse alveolar damage after OLV were established in a porcine study.[16] The damage of the alveolocapillary unit may lead to changes in alveolar permeability, influx of protein and albumin, and recruitment of granulocytes and macrophages into the alveolar space.[2,5] The activation of immune cells results in a characteristic proinflammatory response and in decompartmentalization of cytokines into circulation.[17]

The activation of alveolar cells and subsequent mediator release are caused by enhanced mechanical forces during ventilation,[18–19] which are common in OLV. The delivery of

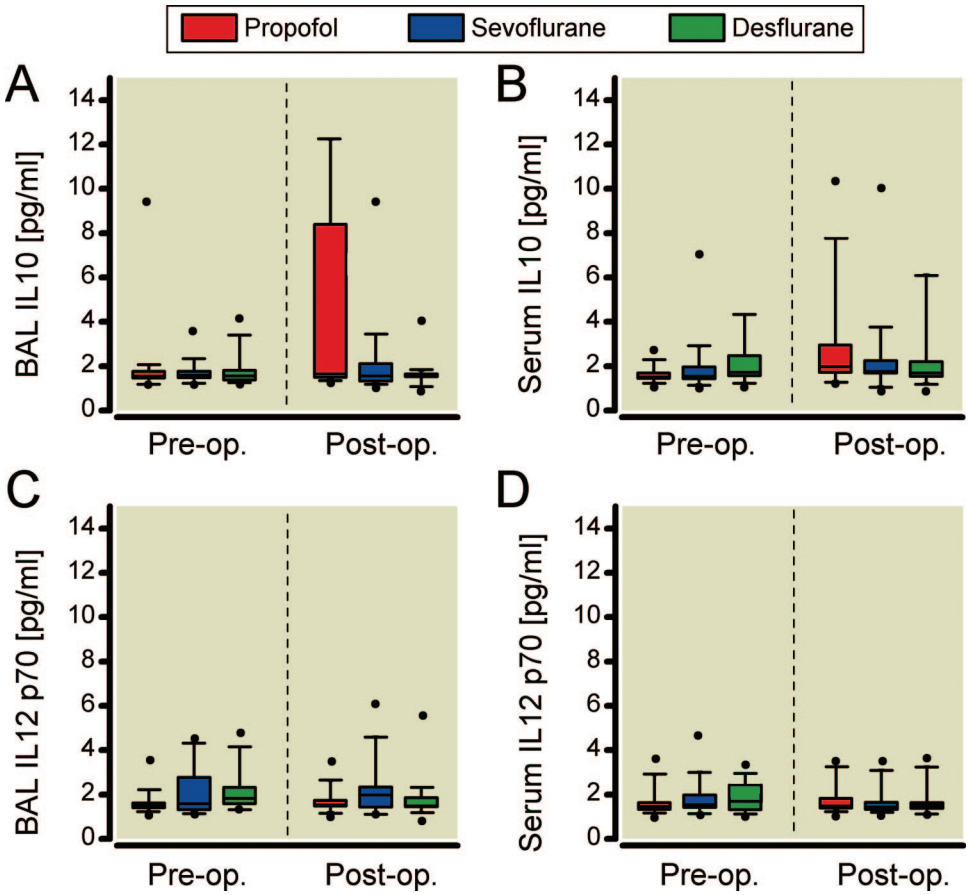

Fig. 4. Intraalveolar and serum concentrations of interleukin (IL)-10 (*A* and *B*) and IL-12p70 (*C* and *D*) in the different patient groups before and after thoracic surgery. Data are displayed as ranges, medians, and interquartile ranges (25 to 75 percentile). The black dots indicate the outliers in each group. BAL = bronchoalveolar lavage; Post-op = postoperatively; Pre-op = preoperatively.

the entire tidal volume to just one lung increases airway pressure and may promote cyclic airway closure and alveolar collapse that may be injurious to the lung.[20] Therefore, progressive alteration of the pulmonary inflammatory response was established during OLV.[2,5,21] The current study addresses the immediate inflammatory effects of a defined OLV setting but does not analyze its long-term effects.

The release of TNF-α, IL-8, and IL-1β was significantly decreased during desflurane and sevoflurane administration compared with total intravenous propofol anesthesia. The different alveolar cytokine expression indicates that inhalational and intravenous anesthetics have different effects on the pulmonary proinflammatory response. These findings confirm recent clinical data that have demonstrated that cytokine concentrations in lavage fluids from the ventilated[5] and nonventilated lung[4] are influenced by volatile and intravenous anesthetics. Moreover, *in vitro* studies[22] in endotoxin-injured alveolar epithelial cells describe that sevoflurane decreases neutrophil accumulation and inflammatory mediator release. Desflurane reduces the protein and messenger ribonucleic acid expression of intercellular and vascular adhesion molecules (*i.e.*, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1[23]) and of TNF-α[24] that may have attenuated the alveolar recruitment of granulocytes and decreased the cytokine response in patients during OLV.[5] Reversible inhibition of TNF-α, IL-6, and IL-1β gene expression is also observed after sevoflurane exposure.[25] The underlying mechanism is the interaction with inducible nitric oxide synthetase by reversible inhibition of voltage-dependent calcium channels and subsequent decreased intracellular calcium concentrations.[26] It has been proposed to be common in the action of volatile anesthetics.[27] Therefore, current data suggest that the immunodepressant effect is characteristic for the class of halogenated anesthetics in the lung. This is important because the administration of volatile anesthetics may prevent the organism from a systemic proinflammatory response and may improve the clinical outcome.[4]

The alveolar proinflammatory response was not accompanied by similar alterations of serum cytokine concentrations. This result confirms previous clinical data that demonstrate that different ventilation modes with low or high tidal volumes did not change the plasma concentrations of TNF-α, IL-6, IL-10, and IL-1 receptor antagonist in healthy patients.[28] In addition, a single inflation with an airway pressure of 40 cm H_2O for 7–30 s did not modify plasma concentrations of inflammatory mediators in mechanically ventilated patients.[29,30] However, the results are in contrast to

data of patients who underwent esophagectomy[31]: mechanical ventilation with a lower tidal volume was associated with reduced plasma concentrations of IL-1β, IL-6, and IL-8 at the end of OLV. The systemic inflammatory response likely depends on the invasiveness of the surgical procedure. It seems to be smaller after lung resection compared with esophagectomy.[13]

Monocytes/macrophages are considered to be the principal sources of the cytokines TNF-α, IL-1, IL-6, and IL-12. Alveolar macrophages are able to release more TNF-α but minor amounts of IL-1 compared with peripheral blood monocytes.[32] This difference may explain the nonsignificant systemic TNF-α and IL-1β release in response to OLV and thoracic surgery. In contrast to TNF-α and IL-1β, IL-12 is central to induction of T-cell–mediated immune responses to infections. The absence of IL-12 indicates the lack of infectious agents during OLV and the reduced number alveolar lymphocytes.[5]

However, the observed IL-6 serum concentrations are different from those of other cytokines. This can be explained by the fast release of IL-6 within minutes[33] by blood leukocytes. Although peak serum concentrations of other proinflammatory mediators are observed with delay after surgery,[34] IL-6 is constantly detected in the peripheral blood. Therefore, the increase of IL-6 may reflect the degree of tissue trauma. As a result, the IL-6 concentration is lower in less invasive and traumatic procedures.[13]

A major limitation of the current study is the short postoperative observation period. The long-lasting effects of intraoperatively administered anesthetic drugs could not be clarified. Nevertheless, the postoperative course was uneventful in all patients. Further limitations may include the comparison of different drugs and administration routes in the current study. However, in the volatile groups, equipotent dosages (1 minimum alveolar concentration) of sevoflurane or desflurane were used.[12] The dosage of propofol corresponds to previously published studies.[2,5]

Related to the study cohort, the number of surgical procedures was different between groups. However, there were no differences in duration of surgery or OLV. Moreover, the surgical procedure was not an independent factor in statistical analysis. Yet, it is possible that the effects of thoracic surgery become evident in the later postoperative course.

A methodological bias may result from the measurement of cytokines in BAL fluids. BAL may disturb the integrity of the distal airway. Protein and urea concentrations are not reliable dilution markers under these conditions. In particular, it cannot be excluded that cytokine release is influenced by airway manipulation, especially by insertion of the double-lumen tube and by BAL.

In summary, in patients undergoing open thoracic surgery, OLV induces the production and release of proinflammatory substances into the alveoli of the ventilated lung. The administration of halogenated volatile anesthetics, such as desflurane or sevoflurane, suppresses pulmonary cytokine release and has alleviating effects on alveolar TNF-α, IL-8, and IL-1β expression but not on the immediate systemic inflammatory response to OLV and thoracic surgery. It remains to be determined whether this attenuated proinflammatory reaction may affect the postoperative course.

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