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Effects of propofol and desflurane anaesthesia on the alveolar inflammatory response to one-lung ventilation†

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Background. One-lung ventilation (OLV) induces a pro-inflammatory response including cytokine release and leucocyte recruitment in the ventilated lung. Whether volatile or i.v. anaesthetics differentially modulate the alveolar inflammatory response to OLV is unclear.

Methods. Thirty patients, ASA II or III, undergoing open thoracic surgery were randomized to receive either propofol 4 mg kg^{-1} h^{-1} (n=15) or 1 MAC desflurane in air (n=15) during thoracic surgery. Analgesia was provided by i.v. infusion of remifentanil (0.25 μg kg^{-1} min^{-1}) in both groups. The patients were mechanically ventilated according to a standard protocol during two-lung ventilation and OLV. Fibre optic bronchoalveolar lavage (BAL) of the ventilated lung was performed before and after OLV and 2 h postoperatively. Alveolar cells, protein, tumour necrosis factor α (TNFα), interleukin (IL)-8, soluble intercellular adhesion molecule-1 (sICAM), IL10, and polymorphonuclear (PMN) elastase were determined in the BAL fluid. Data were analysed by parametric or non-parametric tests, as indicated.

Results. In both groups, an increase in pro-inflammatory markers was found after OLV and 2 h postoperatively; however, the fraction of alveolar granulocytes (median 63.7 *vs* 31.1%, $P<0.05$) was significantly higher in the propofol group compared with the desflurane group. The time courses of alveolar elastase, IL-8, and IL-10 differed between groups, and alveolar TNFα (7.4 *vs* 3.1 pg ml^{-1}, $P<0.05$) and sICAM-1 (52.3 *vs* 26.3 ng ml^{-1}, $P<0.05$) were significantly higher in the propofol group.

Conclusions. These data indicate that pro-inflammatory reactions during OLV were influenced by the type of general anaesthesia. Different patterns of alveolar cytokines may be a result of increased granulocyte recruitment during propofol anaesthesia.

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Mechanical ventilation with a tidal volume (V_T) of 10 ml kg^{-1} is recommended[1] during one-lung ventilation (OLV) to avoid atelectasis, to minimize intrapulmonary shunt, and to maintain sufficient gas exchange.[2]

Experimental and clinical studies have shown that mechanical ventilation with increased V_T and airway pressures induced a pro-inflammatory reaction in the intra-alveolar compartment characterized by an increased capillary permeability and pulmonary oedema with diffuse alveolar damage.[3] OLV with a V_T of 10 ml kg^{-1} resulted in increased alveolar concentrations of tumour necrosis factor (TNF)α, interleukin (IL)-8, and polymorphonuclear (PMN) elastase, protein, albumin, and leucocytes in patients

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undergoing thoracic surgery.[4] Lung immune function is influenced by pre-existing systemic and lung diseases, medications, preoperative tobacco use, and the type and extent of surgical trauma.[5–7] However, it is currently not known if the pulmonary immune effects of volatile or i.v. anaesthetics vary during and after OLV.

Desflurane offers excellent characteristics for fast-track anaesthesia.[8] Emergence after pulmonary surgery is twice as fast with desflurane as with sevoflurane or isoflurane allowing more rapid emergence and earlier recovery of cognitive and psychomotor functions.[9] Desflurane acts as a bronchodilator; this resulted in a reduction of peak inspiratory pressure and increase in dynamic compliance at 1 MAC concentration,[10] suggesting protective effects on mechanical forces applied to lung tissue.

The objective of this prospective, randomized, single-blinded clinical study was to evaluate the effects of general anaesthesia on the pulmonary inflammatory response to OLV. We hypothesized that desflurane and propofol do not have different effects on lung immune function during and after thoracic surgery.

Methods

The study protocol was approved by the local Ethics Committee of the Otto-von-Guericke-University, Magdeburg, and written informed consent was obtained from all patients.

Thirty adult patients, ASA II or III, with normal lung function undergoing elective open thoracic surgery using OLV were included in the study.

Exclusion criteria were persistent tobacco abuse or a history of treatment with immunosuppressant drugs within 3 months prior to surgery, cardiac failure or clinically relevant obstructive or restrictive lung diseases [vital capacity (VC) or forced expiratory volume in 1 s (FEV_1) $<50\%$ of the predicted values], pulmonary hypertension [mean pulmonary artery pressure (MPAP) >30 mm Hg], or pre-existing coagulation disorders. Patients with evidence of pulmonary or systemic infections (clinically defined or elevated C-reactive protein levels, leucocytosis, or body temperature $>37^{\circ}C$) were also excluded.

Preoperative screening of all patients was done by the same physician to ensure consistency in obtaining complete history, physical examination, measurements of actual weight and height, ECG, chest X-ray, pulmonary function tests, echocardiography, and arterial blood gas analysis.

All patients were premedicated with diazepam 0.15 mg kg^{-1} given orally 2 h before anaesthesia. Before the operation, a thoracic epidural catheter was inserted (T4/5 to T6/7) and the position verified with a test dose consisting of 3 ml of bupivacaine 0.5% with adrenaline, 5 μg ml^{-1}. Epidural analgesia was started after OLV with ropivacaine 0.2% and sufentanil 1 μg ml^{-1}, and was maintained for 2–4 days until the chest tubes had been removed. A radial artery catheter and a pulmonary arterial catheter (B. Braun, Germany) were inserted in all patients. Intraoperative fluid therapy included crystalloid and colloid infusion, 7 ml kg^{-1} h^{-1} and 5 ml kg^{-1}, respectively. All patients received a single dose of cefotiam 2 g.

The patients were randomly allocated to receive propofol ($n=15$) or desflurane ($n=15$) anaesthesia by random numbers (Microsoft EXCEL®).

In the propofol group, general anaesthesia was induced with propofol 1.5–2 mg kg^{-1} and remifentanil 0.25 μg kg^{-1} min^{-1}. Tracheal intubation was facilitated by administration of cis-atracurium 0.1 mg kg^{-1}. Anaesthesia was maintained with a continuous infusion of propofol 2–4 mg kg^{-1} h^{-1}, remifentanil 0.1–0.4 μg kg^{-1} min^{-1}, and cis-atracurium 2 μg kg^{-1} min^{-1}. In the desflurane group, anaesthesia was induced as above but maintained with desflurane 1MAC in air, remifentanil 0.1–0.35 μg kg^{-1} min^{-1}, and cis-atracurium 2 μg kg^{-1} min^{-1}.

A left- or right-sided double-lumen endobronchial tube (DLT, Broncho-Cath® 39 or 41 Ch., Mallinckrodt Medical Ltd, Ireland) was inserted and the correct position confirmed using a fibreoptic bronchoscope. The patients were ventilated with a V_T of 10 ml kg^{-1} (actual body weight), fraction of inspired oxygen (FI_{O_2}) of 0.45 in air, PEEP 5 cm H_2O, and the respiratory rate adjusted to maintain Pa_{CO_2} between 4.8 and 5.8 kPa (CiceroEM®, Dräger, Germany). A V_T of 10 ml kg^{-1} and FI_{O_2} of 0.8 to 1.0 was used during OLV to achieve a $Pa_{O_2}>10.6$ kPa, and the respiratory rate adjusted to maintain a Pa_{CO_2} of 4.8–5.8 kPa. PEEP was set to zero during OLV and peak inspiratory pressures were limited to 35 cm H_2O.

Desflurane concentrations, fresh gas flow, and airway pressures were measured at the proximal end of the endobronchial tube (Capnomac-Ultima®, Datex-Ohmeda, Finland).

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

After surgery, double-lumen tubes were changed to standard single-lumen tubes for postoperative ventilatory support and bronchoalveolar lavage (BAL). Patients were admitted to the intensive care unit and monitored for at least 24 h. Postoperative sedation was maintained with remifentanil 0.1–0.25 μg kg^{-1} min^{-1} and intermittent administration of midazolam 2–4 mg as required. Fluids and blood transfusions were given as required to maintain central venous pressure (CVP) $\geq$3 cm H_2O, urine output $\geq$1 ml kg^{-1} h^{-1}, and haemoglobin concentration $\geq$6.0 mmol l^{-1}.

Postoperatively, all patients were assessed daily for clinical signs of pulmonary complications.

Cardiopulmonary variables [heart rate (HR), mean arterial pressure (MAP), MPAP, central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), and arterial and mixed venous blood gases] were recorded continuously and evaluated at three stages: during two-lung ventilation (TLV) before thoracic surgery, 20 min after start of OLV, and immediately postoperatively.

BAL of the dependent ventilated lung was performed by passing a fibre optic bronchoscope (Olympus models BF-P40, BF3-C40) through the endobronchial tube and wedging the tip into a segmental bronchus of the left-sided lower lobe or the right lower or middle lobes. Different randomly chosen segments were subjected to BAL during each procedure. BAL was performed by sequential instillation of normal saline (10 ml portions; a total of 60 ml), and gentle aspiration on three occasions: 30 min after intubation before thoracotomy, immediately at the end of the surgical procedures, and 2 h postoperatively.

Lavage fluid was filtered through sterile gauze filters, collected on ice in siliconized containers and centrifuged immediately at 200 *g* for 10 min. The supernatants were snap-frozen and kept at −80°C until analysis. The cell pellets were resuspended in ice-cold phosphate buffer with 0.01% sodium azide and 2% bovine serum for staining and counting (Neubauer cell counting chamber). The differentiation of BAL leucocyte subpopulations was performed by flow cytometry.

All samples from each patient were analysed in duplicate in the same assay run according to the manufacturer's instructions by the same investigator blinded to randomization. Concentrations of interleukin (IL) 8, IL10, and of soluble intercellular adhesion molecule (sICAM)-1 in the BAL fluids were determined by commercially available quantitative sandwich enzyme immunoassays (Quantikine®, R&D Systems Ltd, Germany). TNFα and PMN cell elastase immunoassays were purchased from Immunotech, France and Milenia Biotech, Germany, respectively. Protein concentrations were measured by colorimetric detection assay (Micro BCA™ Protein Assay Reagent Kit, Pierce, USA). Albumin concentrations were estimated by nephelometry (BN 2000, Dade/Behring, Germany).

Statistical analysis was performed using SPSS (Chicago, IL, USA). Power calculations were based on previous data,[4] and an estimated 15 patients per group were needed to detect differences in alveolar cytokine concentrations and alveolar leucocyte count between propofol and desflurane anaesthesia using a two-sided design at a significance level of 5% ($\alpha=0.05$) with a probability of 80% ($\beta=0.20$).

Data were tested for normal distribution with the Shapiro-Wilks *W* test. Normally distributed variables are presented as mean (SD) (cardiopulmonary and ventilation data) or as median [IQR] in the case of non-normal distribution. Normally distributed data were analysed by a repeated measures one-way analysis of variance with *post-hoc* Bonferroni correction. Non-normally distributed cytokine data were logarithmically transformed to achieve homogeneous variances; however, cytokine concentrations in BAL fluids still differed from normal distribution even after log transformation. Sequential changes of these variables with time in each group were confirmed by a repeated measures general linear model (type III sums of squares). The differences between the two groups before and after OLV were assessed by calculation of the differences in each parameter and evaluation by linear regression analysis.

Differences were considered to be statistically significant for all procedures if $P<0.05$.

Results

A total of 30 patients were enrolled into the study. Patient characteristics and details of thoracic surgery are given in Table 1. There were no differences in the patient characteristics between the groups. The mean doses used were 4.1 (1.4) mg kg^{-1} h^{-1} for propofol, and 5.6 (0.4) vol% for desflurane.

Operations performed were lobectomy ($n=15$), pneumonectomy ($n=3$), and atypical pulmonary resection ($n=12$). All patients had an uneventful postoperative course. Patients were extubated 1–3 h (mean 1.6 h) after the third bronchoscopy. There were no differences in time to extubation, morbidity, postoperative chest infections, and in the length of hospital stay between both groups.

Six of 30 patients received 1 or 2 units of packed red blood cells (EC) intraoperatively. One patient in the propofol group received four ECs postoperatively. There were no differences in the use of blood products between the study groups and no correlations between alveolar cytokine concentrations and administration of EC.

The haemodynamic variables, and ventilation and gas exchange variables showed no differences between the propofol and desflurane group. During OLV, mean and maximal airway pressures increased significantly from preoperative TLV in all patients. Minute volume ventilation and inspiratory/cycle time ratios also revealed no differences. Intraoperatively recorded values of PEEP (1–4 cm H_2O) were not different between both groups.

Table 1 Patient characteristics and surgical data. *Leucocyte-depleted erythrocyte concentrates. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; Pa_{O_2}, arterial oxygen tension; Pa_{CO_2}, arterial carbon dioxide tension. Data are given as median (range) or numbers

Variables	Propofol group $n=15$	Desflurane group $n=15$
Age (years)	62 (38–76)	62 (40–72)
Sex (M/F)	10/5	11/4
Weight (kg)	78 (55–106)	76 (52–112)
Height (cm)	171 (159–188)	171 (152–195)
Former smokers	11	7
Preoperative FVC (% predicted)	91 (67–108)	92 (78–100)
Preoperative FEV_1 (% predicted)	77 (64–91)	79 (62–92)
Preoperative Pa_{O_2} (kPa)	9.6 (7.7–11.9)	9.8 (8.4–11.5)
Preoperative Pa_{CO_2} (kPa)	4.9 (4.4–5.6)	5.0 (4.5–5.8)
Right-sided thoracotomy	7	8
Left-sided thoracotomy	8	7
Lobectomy/pneumonectomy	8	10
Atypical pulmonary resection	7	5
Operation time (min)	128 (77–168)	111 (65–185)
OLV duration (min)	65 (47–108)	61 (39–114)
Transfused units of blood*/patients	8/3	6/4

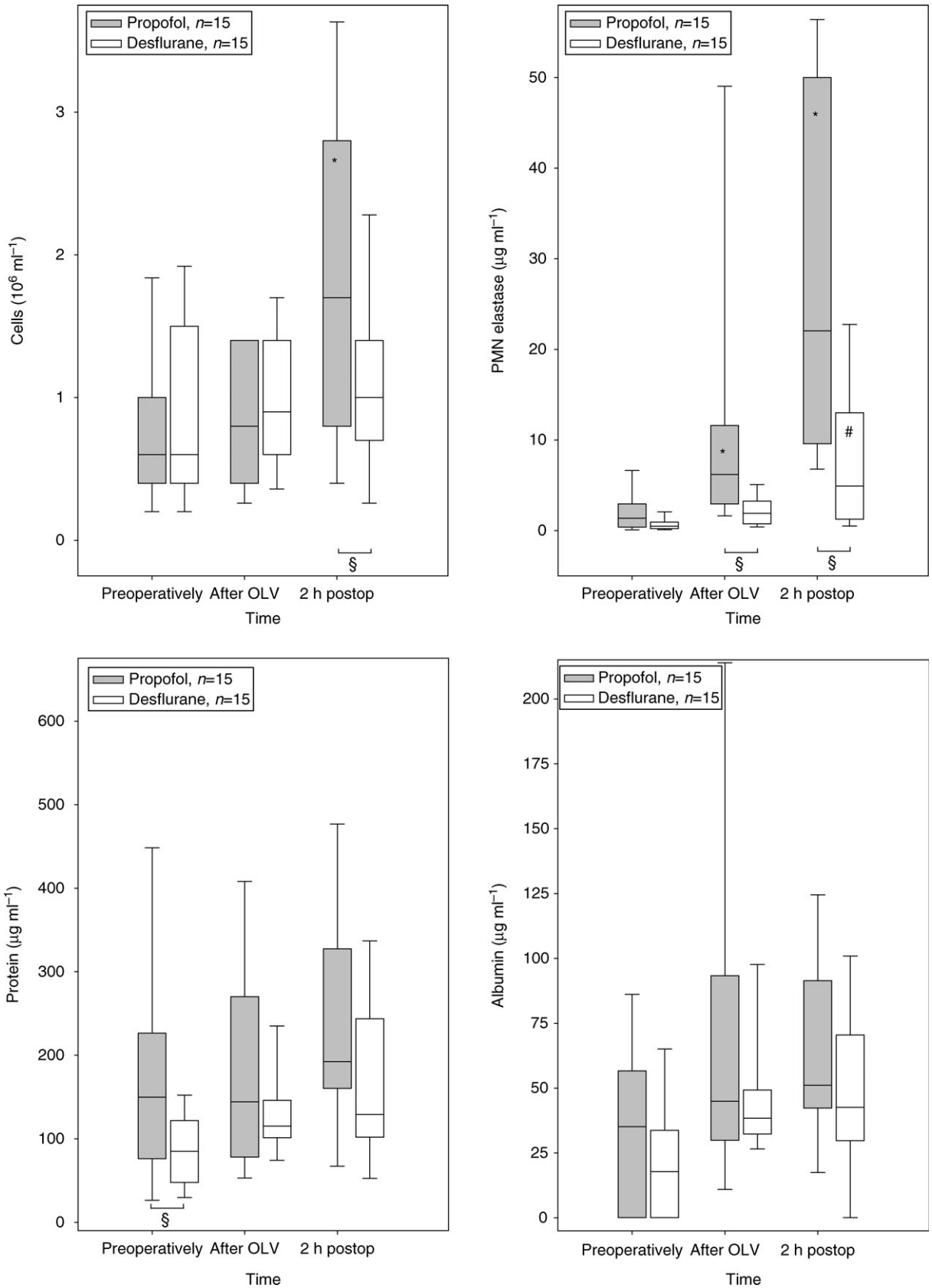

Fig 1 Concentrations of cell numbers, polymorphonuclear (PMN) elastase, protein, and albumin in bronchoalveolar lavage (BAL) fluids of patients undergoing one-lung ventilation (OLV) during thoracic surgery. Data are presented as ranges, medians, and IQR; * indicates significant differences within the propofol group, # indicates changes within the desflurane group, § indicates differences between both groups, $P<0.05$.

Table 2 Differentiation of BAL (bronchoalveolar lavage) cells. OLV, one-lung ventilation; TLV, two-lung ventilation. Data are presented as median [IQR]. *$P<0.05$ within the propofol group, ‡$P<0.05$ between both groups

Variable	TLV, preoperatively		After OLV		TLV, 2 h postoperatively	
	Propofol group $n=15$	Desflurane group $n=15$	Propofol group $n=15$	Desflurane group $n=15$	Propofol group $n=15$	Desflurane group $n=15$
Intra-alveolar cells (10^6 ml^{-1})	0.60 [0.6]	0.60 [1.1]	0.80 [1.0]	0.90 [0.8]	1.7 [2.0]*‡	1.0 [0.7]‡
Alveolar macrophages (%)	38.8 [29.9]	45.8 [28.8]	30.9 [22.9]	37.4 [35.2]	26.0 [34.7]	43.4 [35.4]
Alveolar granulocytes (%)	24.3 [20.2]	19.4 [33.4]	28.8 [29.3]‡	19.9 [15.9]‡	63.7 [52.9]*‡	31.1 [31.7]‡
Alveolar lymphocytes (%)	15.6 [12.9]	18.2 [21.1]	14.6 [15.8]	17.1 [24.8]	4.5 [14.9]*	10.4 [14.5]

An increase of MPAP, PAOP, CVP, and shunt (Qs/Qt) during OLV compared with baseline was observed in all patients, with no significant differences between the groups. HR, MAP, and cardiac index remained unchanged.

Pre- and postoperative values of haemodynamic and ventilation parameters were not different in both groups in comparison with preoperative TLV.

The recovery rate for BAL did not differ between groups or time points [desflurane group: 34(10) ml, 33(12) ml, and 30(7) ml; propofol group: 31(9) ml, 33(7) ml, and 31(6) ml, respectively].

During and after OLV, an increase in total intra-alveolar cells and proinflammatory mediators was demonstrated in the BAL fluids. The time course of immune parameters, as analysed by linear regression, was not influenced by ASA status, age, gender, smoking history, left- or right-sided thoracotomy, duration of OLV, and duration of surgery.

In the propofol group, the number of intra-alveolar cells increased over time (Fig. 1). In contrast, the cell numbers in the desflurane group did not change significantly from baseline after OLV and 2 h postoperatively during TLV. Postoperative alveolar cell numbers were higher in the propofol group than in the desflurane group.

The differentiation of BAL cells using their light scattering properties revealed that the proportion of alveolar granulocytes and lymphocytes differed between both groups, whereas the fraction of alveolar macrophages remained constant. A significant increase of granulocytes and a decrease of lymphocytes were seen in the propofol group 2 h postoperatively (Table 2).

The median BAL protein and albumin concentrations increased in both groups over time; however, protein concentrations were significantly lower in the desflurane group during preoperative TLV (Fig. 1). In all patients, increases of the alveolar concentrations of PMN elastase (Fig. 1), IL8, and TNFα (Fig. 2) were observed during and after OLV. The pro-inflammatory effects of OLV were significantly lower in the desflurane group. Likewise, the increases of alveolar PMN elastase and IL8 were significantly less pronounced in the desflurane group. Alveolar sICAM-1 did not change during and after OLV. However, sICAM-1 concentrations were significantly lower in the desflurane group before and after OLV, and 2 h postoperatively (Fig. 2).

Intra-alveolar IL-10 concentrations decreased significantly in the propofol group, but remained unchanged during and after desflurane anaesthesia (Fig. 2). The quantity of alveolar IL-10 was lower in patients receiving desflurane, and this difference was statistically significant between the study groups ($P<0.05$).

Discussion

The study demonstrates that OLV with $V_T=10$ ml kg^{-1} induced a pro-inflammatory reaction in the dependent ventilated lung. The immune response was attenuated by desflurane anaesthesia as indicated by different alveolar concentrations of sICAM-1, and of PMN elastase, IL-8, and IL-10 before and after OLV. Propofol anaesthesia resulted in a relative increase of the alveolar granulocyte fraction and a decrease of alveolar lymphocytes which may explain the different cytokine patterns in both groups.

At baseline, during preoperative TLV, higher concentrations of protein, TNFα, IL-10, and sICAM-1 were found in the propofol group, whereas alveolar IL-8, PMN elastase, albumin concentrations, and cell numbers were not different between the groups. Linear backward regression analysis provided no significant influence of factors such as ASA status, age, gender, smoking history, genetic factors, polymorphisms of cytokines, and localization of thoracic surgery. Thus, the results can be attributed to the administration of propofol. Since the first BAL had to be performed with a delay after intubation, patients had already received propofol for 30 min. The study design reflects daily clinical algorithms and therefore differences in baseline measurements were inevitable.

Volatile anaesthetics had been shown to produce dose and time-dependent immunomodulatory effects. Whereas in healthy subjects the effects of halogenated agents are transient, experimental data suggested inhibitory effects on neutrophil function.[11] In rat alveolar epithelial type II cells, halothane, enflurane, and isoflurane reduced the secretion of IL-6, macrophage inflammatory protein-2 (MIP-2), and monocyte chemoattractant protein-1 (MCP-1) in a time- and dose-dependent manner; in association with a decrease in MIP-2 and TNFα mRNA expression.[12] The underlying mechanism seemed to be an

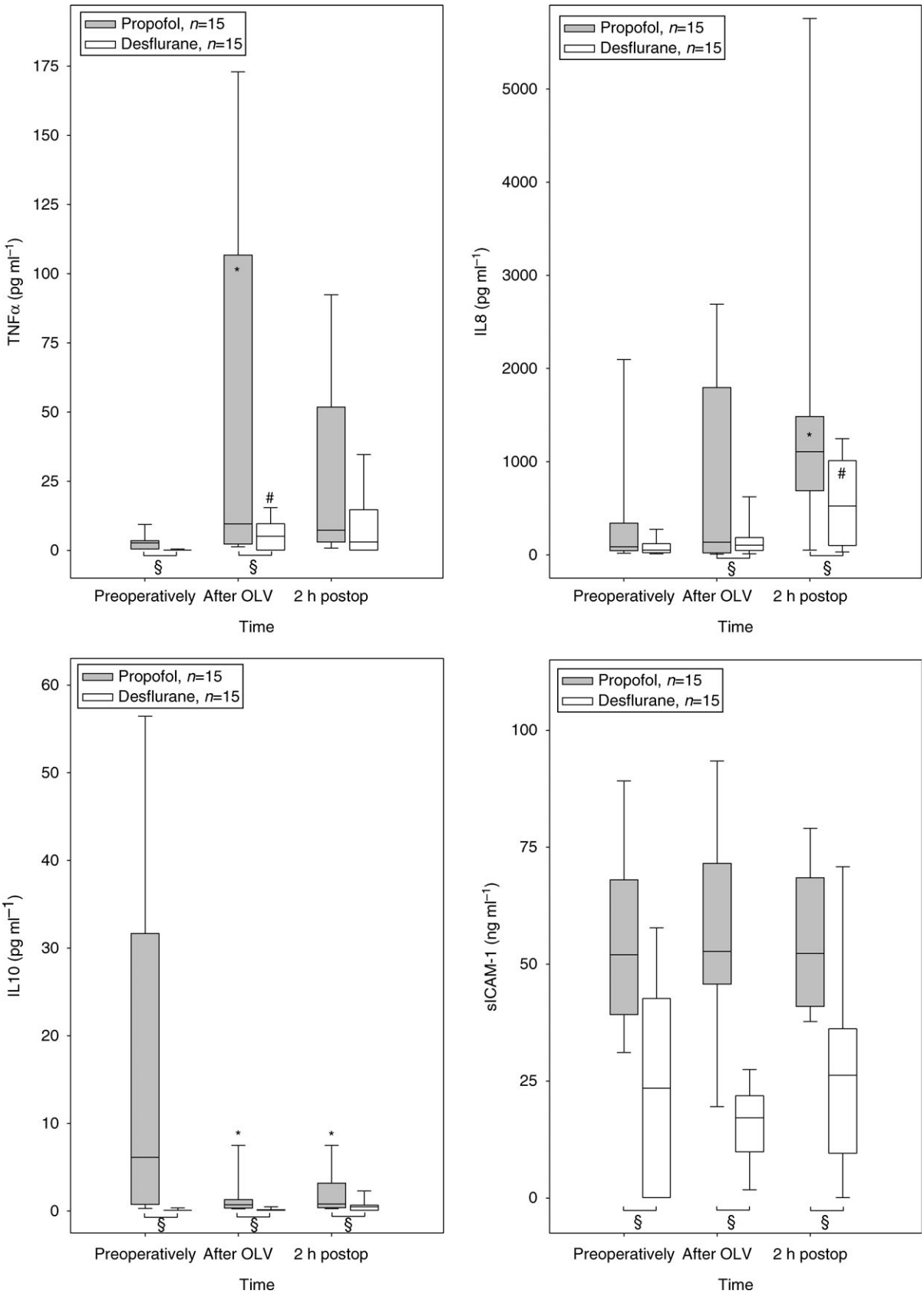

Fig 2 Time-dependent changes of the concentrations of the alveolar inflammatory markers tumour necrosis factor (TNF)α, interleukin (IL)-8, IL-10, and soluble intercellular adhesion molecule (sICAM)-1 before one-lung ventilation (OLV), after OLV, and 2 h postoperatively in the bronchoalveolar lavage (BAL) fluids. Mediator concentrations are presented as ranges, medians, and IQR; * indicates significant differences within the propofol group, # indicates changes within the desflurane group, § indicates differences between both groups, $P<0.05$.

interaction with inducible nitric oxide synthetase by reversible inhibition of voltage-dependent calcium channels and subsequently decreased intracellular calcium concentrations. In contrast, exposure to volatile anaesthetics and mechanical ventilation increased proinflammatory cytokine gene expression in rats.[5] However, inconsistent data of decreased or even improved immune function may be a result of different patient populations, methodology, and laboratory techniques.[13]

In the present study, the alveolar pro-inflammatory response indicates an impaired integrity of the alveolo-capillary membrane. During OLV, transmural pulmonary capillary pressures[14] were most likely increased in the dependent lung as indicated by increased MPAP, PAOP, and CVP during OLV. Experimental data showed that high pulmonary capillary pressures were accompanied by deterioration of the alveolo-capillary barrier.[15–17]

TNFα and IL-8 represent the most important inflammatory mediators in alveolar macrophages and neutrophils. TNFα is principally produced by macrophages/monocytes; consequently, TNFα concentrations in BAL fluid reflect increased TNFα secretion by alveolar macrophages.[18] This observation is consistent with reported pulmonary histological changes including macrophage aggregation and neutrophil influx.[5 19 20] IL-8 binds to specific receptors on human neutrophils promoting the adherence of PMN cells. Neutrophils produce mediators such as elastase, leucotrienes, and free radicals which may exert potential toxicity to the lung tissue.[21]

Differentiation of BAL cells showed different concentrations of alveolar granulocytes, whereas the fraction of macrophages remained unchanged in both groups. The increase of granulocytes during propofol anaesthesia may facilitate higher alveolar concentrations of IL-8 and elastase in comparison with the desflurane group. The similar number of alveolar macrophages in all patients may explain the comparable time course of TNFα concentrations.

The accumulation of activated neutrophils in the lung is an early signal in the pulmonary inflammatory process. Highly lipid-soluble drugs such as propofol may influence neutrophil activation by reduction of polarization and chemotaxis, and inhibition of the respiratory burst in clinical concentrations.[22] The antioxidant properties of propofol are different from those of desflurane which increased BAL concentrations of malondialdehyde and decreased alveolar activities of glutathione peroxidase in mechanically ventilated pigs.[23] This suggests that oxidative stress is of less importance for alveolar inflammation during OLV.

The expression of ICAM-1 by alveolar epithelial cells was significantly decreased in the desflurane group over the entire study period. In many tissues, ICAM-1 interacts with lymphocyte function-associated antigen-1 (LFA-1) on neutrophils, and this interaction plays a critical role in neutrophil recruitment and activation.[24 25] Thus, volatile anaesthetics may prevent, at least partially, activation of alveolar epithelial cells.

Clinical evidence for pulmonary inflammatory reactions to thoracic surgery and OLV was indirectly provided recently. In patients undergoing lobectomy for lung cancer, concentrations of leucotriene B_4, hydrogen peroxide, and hydrogen ions in exhaled breath condensates increased significantly after lobectomy, indicating inflammation and oxidative stress.[26] However, analysis of exhaled biomarkers does not allow a differentiation between ventilated and non-ventilated lung after thoracotomy. Padley and colleagues[27] studied patients undergoing open thoracic surgery who developed postoperative acute respiratory distress syndrome (ARDS). Preoperative and postoperative CT scans demonstrated that lung tissue density increased significantly more in the ventilated lung than in the operated lung, indicating a truly asymmetric lung injury. Similarly, a recent retrospective study of patients undergoing elective pneumonectomy demonstrated that intraoperative mechanical ventilation with high tidal volumes was associated with increased risk of respiratory failure.[28]

The interpretation of cytokine concentrations in BAL fluids is difficult, because an unknown amount of cytokines remains within the cells. Evaluation of secreted cytokine concentrations is limited due to the lack of established dilution markers and of a reliable method for estimating the volume of the epithelial lining fluid. In addition, the integrity of the distal airway may be seriously deranged during BAL, and dilution markers such as protein concentrations are possibly less accurate under these conditions. It cannot be excluded that the different concentrations of protein, TNFα, and IL-10 before lung surgery are at least partially influenced by BAL.

Further limitations of the study include the sample size and the lack of true blinding during thoracic surgery. The relationship between cytokine profiles and organ damage or infectious complications could also not be clarified.

In summary, OLV promotes production and release of pro-inflammatory substances in the alveoli of the dependent lung. Volatile anaesthesia with desflurane has significant effects on alveolar cells, PMN-elastase, TNFα, IL-8, IL-10, and sICAM-1 concentrations. The cytokine pattern may follow the different alveolar recruitment of granulocytes during propofol and desflurane anaesthesia. The clinical impact of altered lung immune function during and after OLV, however, remains to be studied.

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