

The Effects of Different Ventilatory Settings on Pulmonary and Systemic Inflammatory Responses During Major Surgery

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Mechanical ventilation with high tidal volumes (V_T) and zero or low positive end-expiratory pressure increased mediator release to inflammatory stimuli or acute lung injury. We studied whether mechanical ventilation modifies the inflammatory responses during major thoracic or abdominal surgery. Sixty-four patients undergoing elective thoracotomy ($n = 34$) or laparotomy ($n = 30$) were randomized to receive either mechanical ventilation with $V_T = 12$ or 15 mL/kg ideal body weight, respectively, and zero end-expiratory pressure, or $V_T = 6$ mL/kg ideal body weight with positive end-expiratory pressure of 10 cm H_2O . In 62 patients who completed the study, arterial oxygenation was not different between groups. Tumor necrosis

factor, interleukin (IL)-1, IL-6, IL-8, IL-10, and IL-12 were determined by cytometric bead array in plasma after 0, 1, 2, and 3 h and in tracheal aspirates after 3 h of mechanical ventilation. Data were log-transformed and analyzed using parametric or nonparametric tests, as indicated. All plasma mediators increased more during abdominal than during thoracic surgery, although the differences were small. However, neither time course nor concentrations of pulmonary or systemic mediators differed between the two ventilatory settings. Our data suggest that the ventilatory settings we studied do not affect inflammatory reactions during major surgery within 3 h.

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Major abdominal and thoracic surgery alters immune functions in the perioperative course of elective surgery (1–4). Previous studies have suggested that the amount of mediator release depends on the degree of surgical trauma (1,4). In addition, patients who developed pulmonary infections after esophagectomy already had higher serum levels of inflammatory markers intraoperatively (1).

Clinical studies suggest that mechanical ventilation can modify inflammatory responses in patients with acute lung injury (5). In such patients, with existing pulmonary and systemic inflammation, ventilation with tidal volumes (V_T) of 10–15 mL/kg ideal body

weight and low-to-moderate levels of positive end-expiratory pressure (PEEP) was associated with increased intraalveolar and systemic levels of inflammatory mediators (5–7). In contrast, mechanical ventilation with moderate-to-high levels of PEEP and low V_T of approximately 6 mL/kg ideal body weight assured adequate gas exchange, decreased intraalveolar and systemic mediator levels, and improved outcome (5–8). Experimental data suggest that mechanical ventilation with higher V_T and zero end-expiratory pressure (ZEEP) induces not only cytokine release (9–11) but also translocation of cytokines from the lungs to the systemic circulation and even vice versa (12). In addition, inflammatory responses to mechanical stress caused by mechanical ventilation were aggravated by inflammatory co-stimulation (9).

In contrast to patients with acute lung injury having a continuing systemic inflammatory reaction, short-term mechanical ventilation alone of adult patients with healthy lungs did not induce a systemic inflammatory response (13). However, it is not known whether mechanical ventilation will aggravate production and/or translocation of cytokines released by an inflammatory co-stimulus such as major surgery.

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Therefore, we studied pulmonary and systemic mediator levels depending on ventilatory settings in patients undergoing major thoracic or abdominal surgery as a clinical model of ventilator-associated lung injury.

Methods

Approval of the Bonn University Ethics Committee for the study protocol was obtained and all patients gave written informed consent before inclusion in the study.

Sixty-four adult patients scheduled for major elective thoracic ($n = 34$) or abdominal ($n = 30$) surgery under general anesthesia were eligible to participate in the study. Patients with immunosuppression by drugs or patient's preoperative underlying condition and those with an increased white blood cell count or clinical signs of a systemic or pulmonary infection before surgery were not included in the study.

All patients received a standard premedication with midazolam. Anesthesia was performed using propofol, remifentanyl, and cisatracurium. Patients who underwent thoracotomy were tracheally intubated with a double-lumen tube (Mallinckrodt, Athlone, Ireland) to allow single-lung ventilation. Mechanical ventilation was provided with an anesthesia ventilator connected to a circle system (Julian[®]; Dräger, Lübeck, Germany) using a fraction of inspired oxygen of 0.30 and 1.0 during single-lung ventilation. Routine perioperative monitoring included measurement of invasive arterial and central-venous blood pressures (AS/3[®]; Datex-Ohmeda, Helsinki, Finland). End-tidal fractions of carbon dioxide were monitored using infrared absorption capnography (Julian[®]; Dräger). Arterial blood gases, oxygen saturation, hemoglobin, and pH were determined immediately after sampling with standard blood gas electrodes (ABL; Radiometer, Copenhagen, Denmark) or spectrophotometry (OSM3; Radiometer).

Ventilatory Measurements

Gas flow and airway pressure were measured at the proximal end of the tracheal tube with a standard monitor for ventilatory measurements (CP 100; Bicore, Irvine, CA). All signals were sampled with an analog/digital converter board (PCM-DAS16S/12, Computer Boards Inc., Mansfield, MA) installed in a personal computer. Digitized signals were stored on magnetic media for off-line analysis. Inspiratory time and ventilatory cycle time were identified by analyzing the gas flow curve. V_T and minute ventilation were derived from the integrated gas flow signal.

Cytokine and Chemokine Measurements

Arterial ethylenediaminetetraacetic acid blood samples of 5 mL were centrifuged at 1500g for 5 min; the

plasma was aspirated and stored at -70°C . Tracheal fluid was aspirated after instillation of 10 mL of sterile isotonic saline. In thoracic surgery patients, fluid was always instilled and aspirated in the ventilated lumen of the double-lumen tube. The aspirated tracheal fluid was centrifuged at 500g for 15 min and the supernatants were stored at -70°C . Commercially available Cytometric Bead Array (BD Biosciences, Heidelberg, Germany), which allows simultaneous detection of multiple soluble analytes in a particle-based immunoassay, was used to quantitatively measure interleukin (IL)-8, IL-1 β , IL-6, IL-10, tumor necrosis factor (TNF)- α , and IL-12p70 protein levels in tracheal aspirate and serum samples. The assays were performed according to the manufacturer's instructions and were analyzed using the BD Cytometric Bead Array software.

Protocol

Baseline blood samples were obtained immediately after induction of anesthesia. Patients were then randomly (sealed envelopes) assigned to receive either mechanical ventilation with high V_T (12 or 15 mL/kg ideal body weight during thoracic or abdominal surgery, respectively) and ZEEP (high V_T and ZEEP group) or V_T of 6 mL/kg ideal body weight and PEEP of 10 cm H₂O (low V_T and PEEP group). The ventilator rate was adjusted to maintain Paco_2 between 35 and 45 mm Hg and ventilatory measurements were performed during stable conditions. In the thoracic surgery group, the ventilatory setting remained unchanged during one-lung ventilation but inspiratory pressure was limited to 35 cm H₂O. In case this pressure limit was reached, the setting was changed to pressure-limited ventilation with decelerating inspiratory flow usually allowing decreasing of pressure limit below the upper limit to meet the desired V_T . Additional blood was sampled 1, 2, and 3 h after initiation of mechanical ventilation finally followed by tracheal aspiration after 3 h only.

To detect differences in mediator levels between the two ventilatory settings with respect to the subgroups thoracic/abdominal surgery with the given two-sided parallel design at a significance level of 5% ($\alpha = 0.05$) with a probability of 80% ($\beta = 0.20$) based on an estimated difference of 0.84 of the parameter's mean SD , the number of patients to be studied in each group is at least 30.

Results are expressed as mean \pm SD unless otherwise stated. All statistical analyses were performed using a statistical software package (STATISTICA for Windows 6.0; StatSoft, Inc., Tulsa, OK). Data were tested for normal distribution with the Shapiro-Wilks W test and analyzed by using one-way or repeated-measures analysis of variance. Data of plasma mediators were analyzed separately after \log_{10} transfor-

Table 1. Demographic and Clinical Data

	Abdominal surgery		Thoracic surgery	
	High V _T ZEEP	Low V _T PEEP	High V _T ZEEP	Low V _T PEEP
Number of patients	15	15	17	15
Age (yr)	62 ± 9	59 ± 15	59 ± 14	55 ± 16
Sex (M/F)	11/4	12/3	12/5	11/4
Smoker	9	8	9	8
Ideal body weight (kg)	70 ± 7	70 ± 9	62 ± 11	68 ± 8
ASA physical status (I/II/III)	0/12/3	1/8/6	0/13/4	0/11/4

V_T = tidal volume, ZEEP = zero end-expiratory pressure, PEEP = positive end-expiratory pressure, M = male, F = female.

mation to achieve homoscedasticity (homogenous variances of data sets) and normal distribution. Groups were analyzed by Tukey's *post hoc* test only when a significant F ratio was obtained, with differences either within the same type of surgery or within the same ventilatory setting between surgery. Because mediator concentrations in tracheal aspirates still differed significantly from normal distribution even after log₁₀ transformation, these data were analyzed using the Mann-Whitney U-test. Although this study was not designed to control for the influence of possible cofactors, such as age, gender, and smoking status, the potential influence of these factors was studied by backward regression together with the factors mode of ventilation and surgery. Differences were considered to be statistically significant if *P* < 0.05.

Results

Patients

Two patients in the thoracic surgery and low V_T group had to be excluded for technical reasons, leaving 62 patients who completed the study. There were no statistically significant differences in demographic or clinical data among groups (Table 1). Types of surgery performed during the study are listed in Table 2.

Ventilation and Respiration

Ventilatory and respiratory variables are shown in Table 3. During mechanical ventilation with low V_T, a higher ventilator rate (*P* < 0.001) was required to achieve the desired PaCO₂ range, compared with high V_T mechanical ventilation, whereas minute ventilation and inspiratory/cycle time ratio were not significantly different between groups. Mean airway pressure was higher during mechanical ventilation with low V_T and PEEP (*P* < 0.001). In patients who underwent thoracic surgery, maximal airway pressure was higher in the low V_T and PEEP group (*P* < 0.05). Duration of one-lung ventilation in relation to total time of surgery was not different (high V_T, ZEEP group 39% ± 16% versus

Table 2. Types of Surgery

Type of surgery	High V _T ZEEP	Low V _T PEEP
Abdominal surgery		
Liver	5	5
Gastric and bowel	5	5
Pancreatic	3	1
Other	2	4
Thoracic surgery		
Lobectomy	9	6
Partial lobectomy	4	5
Medistinal tumor	1	3
Esophageal	3	1

V_T = tidal volume, ZEEP = zero end-expiratory pressure, PEEP = positive end-expiratory pressure.

34% ± 13% low V_T, PEEP group). During one-lung ventilation, mean and maximal airway pressures increased in the high V_T mechanical ventilation group (*P* < 0.05 and *P* < 0.01, respectively) whereas all other spirometric variables were not different compared with two-lung ventilation (Table 3). PaO₂/fraction of inspired oxygen was not statistically different between ventilatory settings and surgery groups but was lower during one-lung ventilation (*P* < 0.05 high V_T and ZEEP, *P* < 0.01 low V_T and PEEP group, respectively). In the abdominal but not in the thoracic surgery group, PaCO₂ was higher and pH was lower in patients ventilated with lower V_T and PEEP as compared with higher V_T and ZEEP (*P* < 0.01).

Inflammatory Mediators

During both major abdominal and thoracic surgery, overall statistical analysis revealed an increase in measured plasma inflammatory mediators over time (*P* < 0.001). However, the time course of systemic mediator concentrations did not differ significantly between the two ventilation settings (Fig. 1, A and B, A-F, respectively). By backward regression, no significant influence of the potential cofactors age, smoking history, and gender was observed. Concentrations of measured inflammatory mediators in tracheal aspirate

Table 3. Ventilatory and Respiratory Variables

	Abdominal surgery		Thoracic surgery		Thoracic surgery, one-lung ventilation ^a	
	High V _T ZEEP	Low V _T PEEP	High V _T ZEEP	Low V _T PEEP	High V _T ZEEP	Low V _T PEEP
Rate (L/min)	6 ± 1	16 ± 4*	8 ± 1	16 ± 3*	8 ± 2	16 ± 6*
V _T (mL)	1339 ± 191	550 ± 69*	1016 ± 180	548 ± 72*	1028 ± 195	528 ± 93*
V _E (L/min)	9.2 ± 1.3	9.5 ± 2.7	8.5 ± 1.4	10.0 ± 1.8	8.5 ± 2.1	9.2 ± 2.0
T _I /T _{TOT}	0.35 ± 0.04	0.37 ± 0.07	0.38 ± 0.05	0.37 ± 0.07	0.34 ± 0.01	0.40 ± 0.07
Paw _{mean} (cm H ₂ O)	7 ± 1	13 ± 1*	6 ± 2	14 ± 2*	9 ± 2	15 ± 3*
Paw _{max} (cm H ₂ O)	22 ± 4	21 ± 3	19 ± 4	24 ± 5†	26 ± 4	28 ± 4
Pao ₂ /Fio ₂ (mm Hg)	314 ± 62	306 ± 88	341 ± 162	411 ± 128	213 ± 72‡	242 ± 124§
Paco ₂ (mm Hg)	36 ± 3	42 ± 3*	40 ± 5	44 ± 5	38 ± 4	44 ± 7†
pH	7.42 ± 0.03	7.35 ± 0.04*	7.40 ± 0.04	7.38 ± 0.04	7.41 ± 0.04	7.37 ± 0.05†

All values are means ± SD.

V_T = tidal volume, ZEEP = zero end-expiratory pressure, PEEP = positive end-expiratory pressure, V_E = minute ventilation, T_I = inspiratory time, T_{TOT} = inspiratory + expiratory time, Paw_{mean} = mean airway pressure, Paw_{max} = maximal airway pressure, Pao₂ = arterial blood oxygen tension, Fio₂ = inspiratory oxygen gas fraction, Paco₂ = arterial blood carbon dioxide tension.

^a Spirometric variables during one-lung ventilation were measured in 23 of 32 patients receiving thoracic surgery.

* P < 0.01 and † P < 0.05 compared with high V_T at ZEEP mechanical ventilation group of same surgery type.

‡ P < 0.05 and § P < 0.01 one-lung compared with two-lung ventilation in thoracic surgery group.

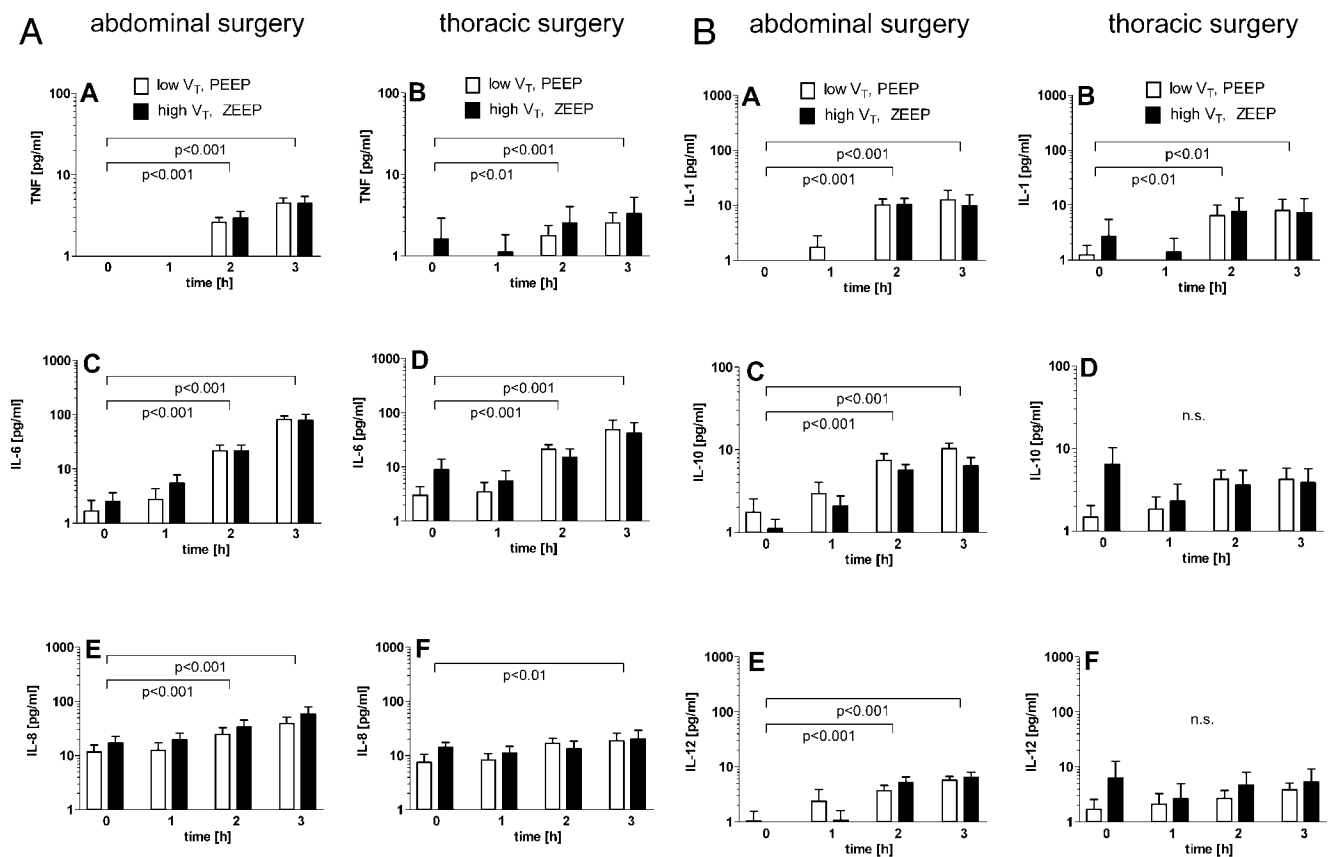


Figure 1. Both A and B (A–F, respectively) show time course of inflammatory markers in the plasma of patients during abdominal (left side) and thoracic (right side) surgery. V_T = tidal volume, PEEP = positive end-expiratory pressure, ZEEP = zero end-expiratory pressure, TNF = tumor necrosis factor, IL = interleukin.

were comparable between mechanical ventilation groups (Fig. 2). An absolute increase in systemic mediator concentrations was larger in the abdominal than in the thoracic surgery group (*P* < 0.05, Fig. 3A),

although the differences were small. The concentrations of pulmonary mediators (except IL-10) were not different after 3 h of abdominal or thoracic surgery (Fig. 3B).

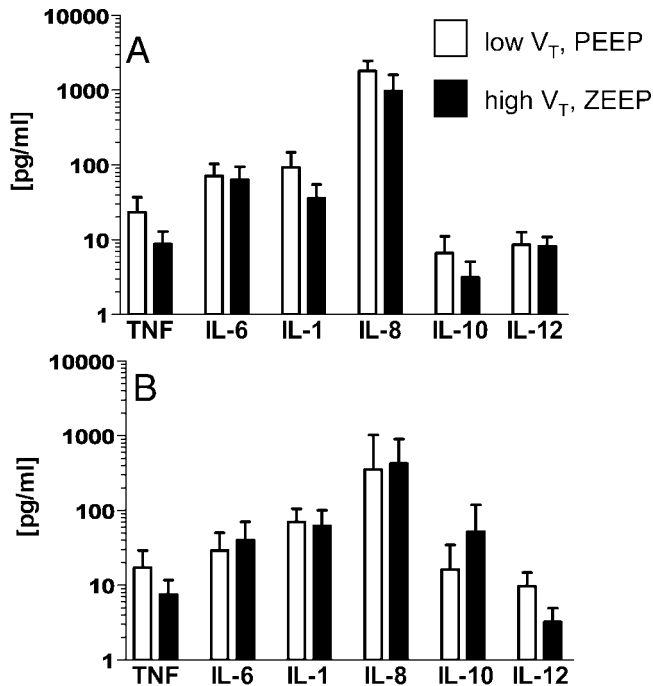


Figure 2. Concentrations of measured inflammatory markers in the tracheal aspirate after 3 h of mechanical ventilation and (A) abdominal surgery or (B) thoracic surgery. V_T = tidal volume, PEEP = positive end-expiratory pressure, ZEEP = zero end-expiratory pressure, TNF = tumor necrosis factor, IL = interleukin.

Discussion

In this clinical study, comparing high V_T and ZEEP mechanical ventilation with low V_T and PEEP ventilation in patients during major thoracic or abdominal surgery, we found no differences in pulmonary or systemic levels of inflammatory markers depending on ventilatory strategy. Apparently, and in contrast to animal models with ZEEP and end-inspiratory pressures >40 cm H_2O (10,12), no translocation of mediators, such as IL-8, depending on the ventilatory setting occurred, thus suggesting that compartmentalization was maintained in our patients.

Our findings seem to be in contrast to basic research demonstrating initiation or perpetuation of local and systemic inflammatory responses to injurious ventilatory strategies using high V_T and/or low or zero PEEP (5,9,11,14,15). High V_T mechanical ventilation resulted in increased production of proinflammatory cytokines within a few hours whereas low V_T and high PEEP ventilatory strategies were associated with reduced mediator levels.

Clinically, it was demonstrated that low V_T ventilation of 6–8 mL/kg ideal body weight with moderate (7,16) or high levels of PEEP (8) can decrease mortality in acute lung injury or acute respiratory distress syndrome when compared with mechanical ventilation with high V_T of at least 12 mL/kg ideal body weight, and that this correlates with lower pulmonary and/or

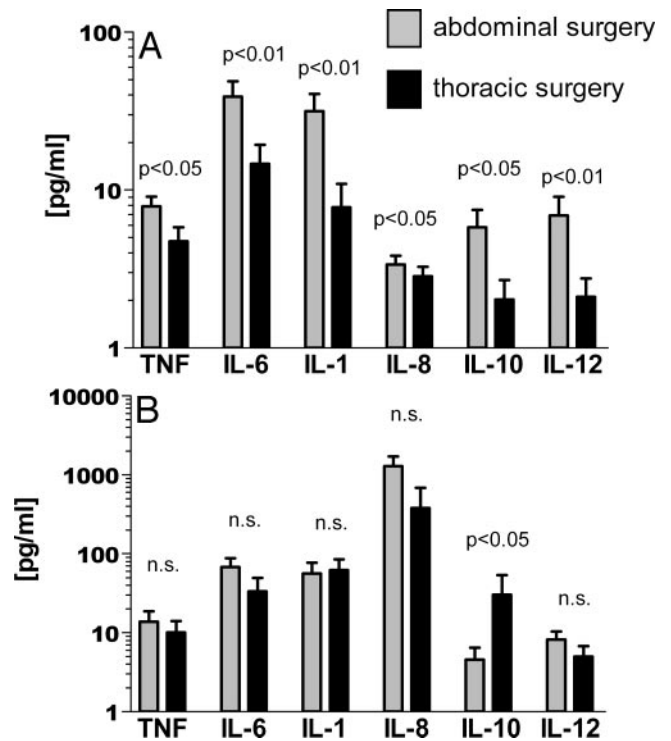


Figure 3. Comparison of absolute plasma concentration increases (differences between values after 3 h and baseline) (A) and absolute tracheal aspirate levels after 3 h of mechanical ventilation (B) between abdominal and thoracic surgery. Data of ventilatory treatment groups were pooled here. TNF = tumor necrosis factor, IL = interleukin, n.s. = not significant.

systemic mediator concentrations (5,6). Thus, although ample evidence indicates that mechanical ventilation may alter an existing inflammatory response in patients with acute lung injury, it is not entirely clear whether mechanical ventilation alone can stimulate cytokine production from healthy lungs. In patients with normal lungs ventilated without surgical co-stimuli for one hour, we did not observe changes in the plasma levels of inflammatory mediators (13). Plötz et al. (17) reported an increase in pulmonary TNF and IL-6 levels in anesthetized infants during diagnostic heart catheterization after two hours of conventional mechanical ventilation (17). Unfortunately, the authors did not control for the factors mechanical ventilation, anesthesia, radiation, and the use of a contrast agent.

Whereas in small animal models mechanical ventilation with sufficiently high V_T alone is able to trigger an inflammatory response, the somewhat conflicting observations in adults with and without previous pulmonary inflammation may be explained by a two-hit model. According to this model, pulmonary inflammation must already be present (first hit) for injurious mechanical ventilation (second hit) to aggravate the inflammatory response. The physiological basis for such a two-hit model may be given by the fact that

lungs from acute respiratory distress syndrome patients are inhomogeneously injured (18), so that the healthy alveoli may overinflate because the atelectatic alveoli produce no counterpressure (19). This hypothesis is supported by several experimental studies showing increased inflammatory responses to high V_T mechanical ventilation after an inflammatory first hit (9,10,20).

Previous studies have demonstrated a certain amount of alveolar collapse and atelectasis soon after induction of anesthesia and mechanical ventilation in previously healthy patients (21) which can be prevented with PEEP of 10 cm H_2O (22). Because the amount of atelectasis might even increase during surgery and lung volume is reduced during one-lung ventilation, high V_T could lead to inspiratory overdistension of lung units which is a contributing factor for ventilator-associated lung injury (23). Thus, the low V_T and PEEP ventilatory setting chosen in this study should have attenuated both the alveolar collapse and the overdistension in comparison to the high V_T and ZEEP setting (22).

Both of these settings may not reflect the average clinical setting mainly used in the operating room; however, this study was designed to investigate inflammatory effects of different ventilatory settings in a clinical model of ventilator-associated lung injury. In addition, ventilation with high V_T and ZEEP may still be used during one-lung ventilation (24), although recent experimental data suggest that ventilator-induced lung injury occurs with this setting (25).

If the two-hit theory were true, the lack of difference between the two ventilatory settings would suggest that even during thoracic surgery, only minimal lung injury was inflicted and that the inflammatory responses to major surgery were not a sufficient "first hit." This is in contrast to patients with acute lung injury already having pulmonary and systemic inflammation and requiring higher inspiratory airway pressures as did our patients with healthy lungs (5,6).

Surgical stimuli during major abdominal and thoracic surgery are associated with increased plasma levels of proinflammatory markers (1-4). In the present study, we extended those previous findings by showing that systemic, but not pulmonary cytokine levels are slightly higher during abdominal surgery. These differences, which likely are biologically insignificant, may be related to minor exposure to intestinal bacteria. Levels of all mediators, except IL-8 were rather low. The higher IL-8 levels are in line with other observations showing increased pulmonary and systemic IL-8 levels in patients undergoing esophagectomy (26,27).

It is of importance to note that we tested each ventilatory setting for only three hours. However, in previous experimental and clinical studies, this period of

time was sufficient to cause ventilation-induced mediator release. Experimentally, intraalveolar TNF expression (28) and increased TNF levels in the systemic circulation (10) occurred after one hour of high V_T mechanical ventilation in lung injury models. Clinically, in patients with acute lung injury, alveolar and systemic cytokine concentrations increased within one hour after initiating mechanical ventilation with low PEEP and high V_T (6). Therefore, and because we observed an inflammatory response to surgery within the study period of three hours, it is not likely that three hours was too short for ventilation-induced cytokine release to occur.

Our data suggest that, in uninjured normal lungs of patients during major abdominal or thoracic surgery, mechanical ventilation with high V_T and ZEEP does not increase the pulmonary or systemic inflammatory responses to surgery within three hours. This observation is indirect evidence for the two-hit hypothesis suggesting that high V_T and low PEEP mechanical ventilation may induce lung inflammation to clinically important levels in preinjured or infected lungs in the short term, as previously shown, but not in normal lungs even during major surgery.

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