

Effects of Mechanical Ventilation on Release of Cytokines into Systemic Circulation in Patients with Normal Pulmonary Function

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Background: **Mechanical ventilation with high tidal volumes (V_T) in contrast to mechanical ventilation with low V_T has been shown to increase plasma levels of proinflammatory and anti-inflammatory mediators in patients with acute lung injury. The authors hypothesized that, in patients without previous lung injury, a conventional potentially injurious ventilatory strategy with high V_T and zero end-expiratory pressure (ZEEP) will not cause a cytokine release into systemic circulation.**

Methods: **A total of 39 patients with American Society of Anesthesiologists physical status I–II and without signs of systemic infection scheduled for elective surgery with general anesthesia were randomized to receive mechanical ventilation with either (1) V_T = 15 ml/kg ideal body weight on ZEEP, (2) V_T = 6 ml/kg ideal body weight on ZEEP, or (3) V_T = 6 ml/kg ideal body weight on positive end-expiratory pressure of 10 cm H_2O. Plasma levels of proinflammatory and antiinflammatory mediators tumor necrosis factor, interleukin (IL)-6, IL-10, and IL-1 receptor antagonist were determined before and 1 h after the initiation of mechanical ventilation.**

Results: **Plasma levels of all cytokines remained low in all settings. IL-6, tumor necrosis factor, and IL-1 receptor antagonist did not change significantly after 1 h of mechanical ventilation. IL-10 was below the detection limit (10 pg/ml) in 35 of 39 patients. There were no differences between groups.**

Conclusions: **Initiation of mechanical ventilation for 1 h in patients without previous lung injury caused no consistent changes in plasma levels of studied mediators. Mechanical ventilation with high V_T on ZEEP did not result in higher cytokine levels compared with lung-protective ventilatory strategies. Previous lunge damage seems to be mandatory to cause an increase in plasma cytokines after 1 h of high V_T mechanical ventilation. (Key words: Inflammation; lung; mediators; ventilator-associated lung injury.)**

POSITIVE pressure ventilation is commonly applied in patients undergoing general anesthesia to assure adequate ventilation and gas exchange. Conventional mechanical ventilation still uses low positive end-expiratory pressure (PEEP) levels with high tidal volumes (V_T) ranging between 10 and 15 ml/kg ideal body weight.[1–4] However, positive pressure ventilation alone or in combination with preexisting lung disease may contribute considerably to lung injury, including pneumothorax, alveolar edema, and alveolar rupture.[5,6]

Mechanical ventilation with PEEP titrated above the lower inflection pressure of a static pressure–volume curve and low V_T has been suggested to prevent tidal collapse and overdistension of lung regions during severe acute respiratory distress syndrome (ARDS).[7] This lung-protective ventilatory strategy has been shown to improve gas exchange and outcome in patients with ARDS.[8] Recently, Ranieri *et al.*[9] observed higher systemic and intraalveolar levels of proinflammatory cytokines in ARDS patients during mechanical ventilation with low PEEP and high V_T when compared with a lung-protective strategy. Therefore, it has been speculated that conventional mechanical ventilation may induce release of inflammatory mediators and thereby contribute to lung injury.[10] *In vitro* experiments have demonstrated that mechanical stress to lung cells is associated with release of inflammatory mediators.[11,12] However, acute lung injury or ARDS itself causes an inflammation of the lungs with increased systemic and intraalveolar concentrations of the proinflammatory cytokines.[13] It is unclear whether mechanical ventilation alone or only in the presence of acute lung injury can release inflammatory cytokines into systemic circulation.

We hypothesized that, in patients with normal lungs, mechanical ventilation with high V_T does not induce a release of cytokines into the systemic circulation. To test this hypothesis, we measured proinflammatory and anti-inflammatory cytokines in the plasma of anesthetized patients with healthy lungs while they were mechanically ventilated with lung-protective or conventional strategies.

Materials and Methods

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

Thirty-nine adult patients classified as American Society of Anesthesiologists physical status I or II scheduled for elective extrathoracic surgery with general anesthesia (table 1) were eligible to participate in the study.[14] Patients with history or clinical signs of lung disease, history of smoking, age older than 65 yr, immunosuppression by drugs or underlying condition, elevated leu-

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Table 1. Demographic and Clinical Data

Parameter	High V_T ZEEP	Low V_T ZEEP	Low V_T PEEP
Number of patients	13	13	13
Age (yr)	46 ± 19	49 ± 14	49 ± 14
Gender (M/F)	7/6	8/5	7/6
Ideal body weight (kg)	65 ± 15	61 ± 8	63 ± 10
ASA I/II (n)	5/8	3/10	3/10
Scheduled surgery			
Abdominal	5	6	6
Bone	1	1	1
Vascular	4	2	1
Other	3	4	5

V_T = tidal volume; ZEEP = zero end-expiratory pressure; PEEP = positive end-expiratory pressure; ASA = American Society of Anesthesiologists.

kocyte count, or clinical signs of a systemic infection were not included in the study.

All patients received a standard premedication of 7.5 mg midazolam orally on the day of surgery. Anesthesia was induced using thiopental (4–6 mg/kg administered intravenously) and fentanyl (1–2 μg/kg administered intravenously). Thereafter, cis-atracurium (0.10–0.15 mg/kg administered intravenously) was given to facilitate tracheal intubation. Mechanical ventilation was provided with an anesthesia ventilator connected to a circle system (Julian, Dräger, Lübeck, Germany) with a fresh gas flow of air–oxygen at 4 l/min and an inspiratory fraction of oxygen of 0.30. Anesthesia was maintained with 0.5 minimum alveolar concentration of isoflurane and supplemental doses of fentanyl as required. Routine perioperative monitoring included measurement of noninvasive blood pressure, pulse oximetry, and electrocardiogram (CS/3, Datex-Ohmeda, Helsinki, Finland). End-tidal fractions of carbon dioxide and isoflurane were measured using infrared absorption capnography (Julian, Dräger). All patients received infusion of 1.5 l of crystalloid fluids during the study period to assure hemodynamic stability.

Ventilatory Measurements

Gas flow was measured at the proximal end of the tracheal tube with a heated pneumotachograph (No. 2; Fleisch, Lausanne, Switzerland) connected to a differential pressure transducer (Huba Control, Würenlos, Switzerland). Airway pressure was measured at the proximal end of the tracheal tube with another differential gas–pressure transducer (SMT, Munich, Germany). All signals were sampled with an analog–digital converter board (PCM-DAS16S/12, Mansfield, MA) installed in a personal computer. Digitized signals were plotted in real time on the computer screen and stored on magnetic media for offline analysis. V_T and minute ventilation were derived from the integrated gas flow signal.

Cytokine Measurements

Venous EDTA blood samples of 5 ml were centrifuged at 1,500*g* for 5 min, and the plasma was aspirated and stored at −70°C. Commercially available enzyme-linked immunosorbent assays were used to measure plasma levels of interleukin (IL)-6, tumor necrosis factor (TNF) (Biosource, Ratingen, Germany), IL-10, and IL-1 receptor antagonist (R&D Systems, Minneapolis, MN). All enzyme-linked immunosorbent assay analyses were performed with strict adherence to the manufacturers' guidelines.

Protocol

All patients remained supine throughout the study period. Baseline measurements were obtained immediately before induction of anesthesia.

After induction of anesthesia, patients were randomly assigned to receive either mechanical ventilation with V_T of 15 ml/kg ideal body weight and zero end-expiratory pressure (ZEEP) (high V_T, ZEEP group), a V_T of 6 ml/kg ideal body weight and ZEEP (low V_T, ZEEP group), or a V_T of 6 ml/kg ideal body weight and 10 cm H_2O PEEP (low V_T, PEEP group). The ventilator rate was adjusted to maintain end-tidal carbon dioxide partial pressure between 35 and 45 mmHg. After ventilation with the assigned mode was stable for 1 h, the measurements were repeated. Thereafter, data collection was concluded and the surgical procedure was allowed to commence.

Statistics

To detect differences in cytokine plasma levels between the ventilatory settings 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 0.85 of the parameter's mean SD, a minimum of 39 patients were to be studied.

Results are expressed as mean ± SD. All statistical analysis were performed using a statistical software package (Statistica for Windows 5.1, StatSoft, Inc., Tulsa, OK). Data were tested for normal distribution with the Sharpiro-Wilks W test. Ventilatory variables were analyzed using a one-way analysis of variance. When a sig-

Table 2. Ventilatory Variables*

Parameter	High V_T ZEEP	Low V_T ZEEP	Low V_T PEEP
Ventilatory rate (l/min)	6.3 ± 0.7	22.9 ± 4.0†	22.3 ± 5.3†
V_T (ml)	1,024 ± 210	411 ± 53†	430 ± 71†
V_E (l/min)	6.5 ± 1.3	9.3 ± 1.6†	9.4 ± 1.9†
T_I (s)	4.6 ± 0.7	1.3 ± 0.3†	1.3 ± 0.4†
T_E (s)	5.0 ± 0.5	1.4 ± 0.2†	1.5 ± 0.5†
T_I/T_E	0.48	0.47	0.46
Paw_{mean} (cm H_2O)	6.6 ± 3.5	5.3 ± 1.4	12.7 ± 0.5†§
Paw_{max} (cmH_2O)	16.1 ± 4.9	12.1 ± 3.3‡	17.9 ± 1.5‖
PET_{CO_2} (mmHg)	36 ± 3	41 ± 3‡	41 ± 5‡

* Values are mean ± SD.

† $P < 0.001$ and ‡ $P < 0.05$ compared with high tidal volume (V_T) at zero end-expiratory pressure (ZEEP) mechanical ventilation group. § $P < 0.001$ and ‖ $P < 0.005$ between low V_T mechanical ventilation groups.

PEEP = positive end-expiratory pressure; V_E = minute ventilation; T_I = inspiratory time; T_E = expiratory time; Paw_{mean} = mean airway pressure; Paw_{max} = maximum airway pressure; PET_{CO_2} = end-tidal partial pressure of carbon dioxide.

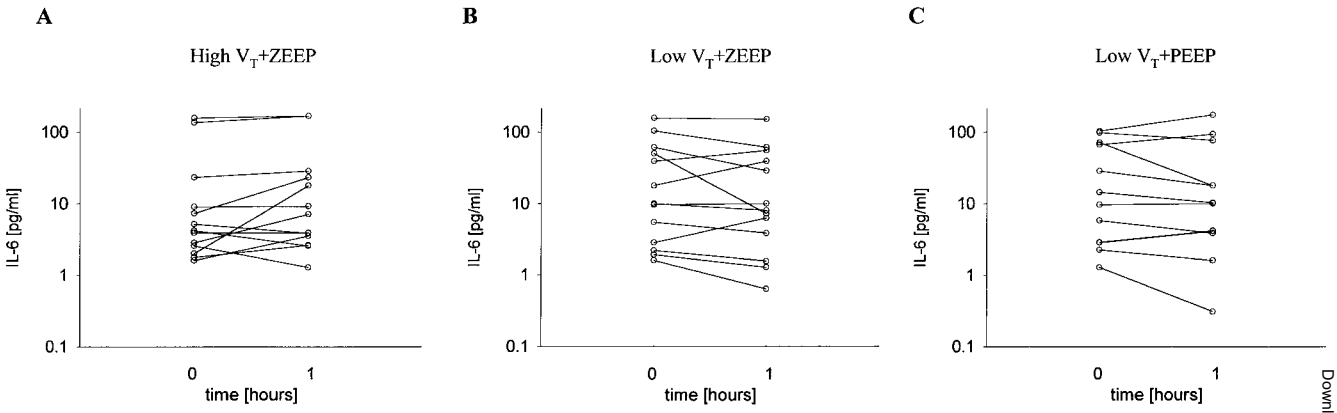

Fig. 1. Changes in interleukin (IL)-6 plasma levels before and 1 h after initiation of mechanical ventilation. (*A*) High-tidal-volume (V_T) mechanical ventilation; (*B* and *C*) low-V_T mechanical ventilation settings. ZEEP = zero end-expiratory pressure; PEEP = positive end-expiratory pressure.

nificant F ratio was obtained, differences between the means were isolated with the *post hoc* Tukey multiple comparison test. Because cytokine data were not normally distributed, a two-way analysis of variance was performed after $\log_{10}$ transformation to permit the application of a parametric test. Differences were considered to be statistically significant at P values less than 0.05.

Results

There were no statistically significant differences in the demographic or clinical data between patients of the studied groups (table 1).

Ventilatory variables are shown in table 2. During mechanical ventilation with low V_T, a higher ventilator rate ($P < 0.001$) and a higher minute ventilation ($P < 0.001$) were required to achieve the desired end-tidal carbon dioxide partial pressure range, compared with high V_T mechanical ventilation. Increase in ventilatory rate was associated with a reduction of inspiratory time and expiratory time ($P < 0.05$), whereas the inspiratory time/expiratory time ratio remained unchanged. Peak airway pressure was lowest during mechanical ventilation with low V_T at ZEEP. In the presence of PEEP, mechanical ventilation with low V_T resulted in the highest mean airway pressure. End-tidal carbon dioxide partial pressure was lowest during mechanical ventilation with high V_T at ZEEP.

Cytokine plasma levels are shown in figures 1–3. The response of the cytokine levels to starting mechanical ventilation was neither significantly different between the three ventilatory strategies nor statistically different after 1 h of ventilation in each individual group. Plasma levels of IL-10 remained below the detection limit (10 pg/ml) in 35 of 39 patients both at baseline and after 1 h of mechanical ventilation.

Discussion

This study was designed to evaluate the effects of different ventilatory strategies on the release of inflammatory mediators into the systemic circulation of anesthetized patients who had healthy lungs. We were unable to detect statistically significant differences in cytokine release between potentially injurious and protective ventilatory strategies after 1 h of ventilation.

Mechanical ventilation is usually provided by using

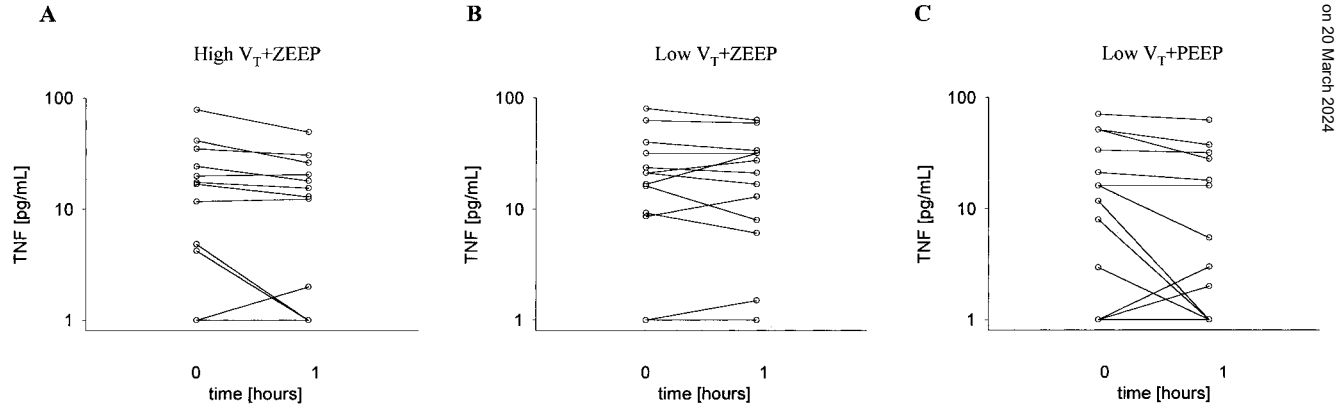

Fig. 2. Tumor necrosis factor (TNF) plasma concentrations before and 1 h after initiation of mechanical ventilation for the three different ventilatory treatment groups. V_T = tidal volume; ZEEP = zero end-expiratory pressure; PEEP = positive end-expiratory pressure.

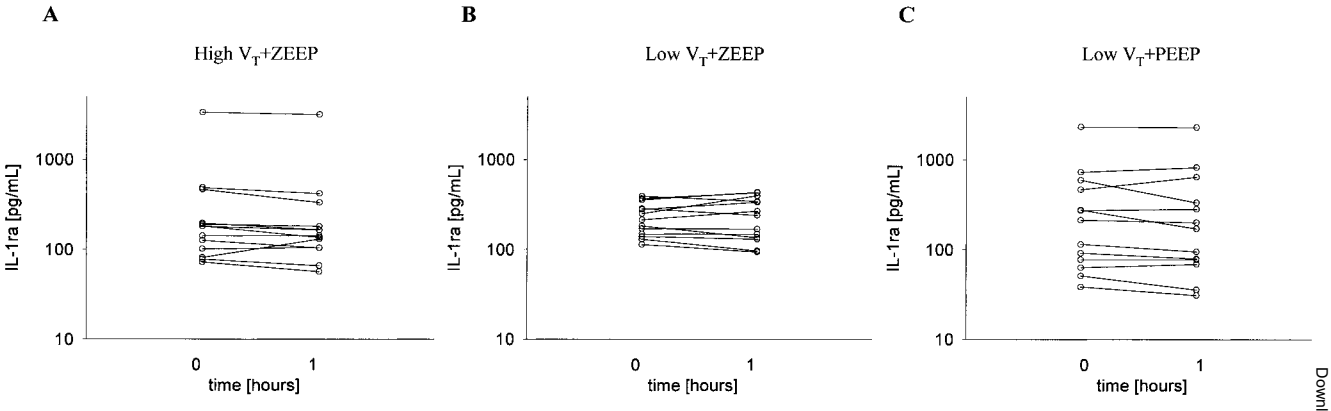

Fig. 3. Plasma levels of interleukin (IL)-1 receptor antagonist before and after 1 h of mechanical ventilation with high-tidal-volume (V_T) or two different low-tidal-volume mechanical ventilation settings. ZEEP = zero end-expiratory pressure; PEEP = positive end-expiratory pressure.

low PEEP levels with high V_T ranging between 10 and 15 ml/kg ideal body weight.[1–4] Based on experimental data, mechanical ventilation with high V_T has been claimed to overdistend functional lung units and contribute to direct lung damage.[6] Mechanical stress such as shear stress has been found to induce production of inflammatory cytokines in isolated endothelial,[15] epithelial,[16] and macrophage cells.[17] Experimental and clinical studies have investigated the production of inflammatory mediators in injured lungs induced by various ventilatory strategies.[9,11,12,17–20] Based on these findings, inflammatory cytokines have been implicated as contributors to ventilator-associated lung injury.[21] A recent multicenter trial of 861 patients demonstrated a reduction in mortality by 22% and lower systemic cytokine levels when V_T was reduced from 12 to 6 ml/kg ideal body weight. [22]

We studied the effect of different ventilatory strategies on systemic cytokine levels during anesthesia before elective surgery. Although our patients had an essentially normal pulmonary function, previous computed tomography studies have clearly demonstrated alveolar collapse and atelectasis soon after induction of anesthesia and mechanical ventilation in previously healthy patients,[23,24] which can be prevented with a PEEP of 10 cm H_2O.[25] Thus, the lung-protective ventilatory settings in this study should have prevented tidal alveolar collapse and overdistension, whereas the potentially injurious ventilatory should have not.[23] The latter has been suggested to result in shear forces with transmural pressures of up to 100 cm H_2O applied to lung cells. [26]

In our patients, we did not observe consistent differences in proinflammatory and antiinflammatory cytokine plasma levels depending on different ventilatory strategies, and all levels were still within the variability observed in healthy volunteers.[27] Therefore, our findings appear to be in contrast with previous experimental[12] and clinical[9,28] observations, indicating a marked systemic inflammatory response in the presence of an injurious ventilatory strategy using low PEEP and high V_T. Variation in the systemic cytokine concentrations observed during injurious mechanical ventilation may be attributed to the difference in the design and the experimental conditions of the individual studies. Tremblay *et al.*[12] found pronounced production of cytokines induced by injurious mechanical ventilation in animals pretreated with intravenous lipopolysaccharides,[1] whereas pressure stretching of cultivated alveolar macrophages in absence of lipopolysaccharides as an inflammatory costimulus could not induce TNF and IL-6 excretion.[17] These findings support our observation that mechanical ventilation seems to induce no inflammation in normal lungs, but may well augment lung inflammation to clinically important levels in preinjured or infected lungs. In agreement with our findings, in rats without lung injury, mechanical ventilation with V_T set at 10 ml/kg did not affect bronchoalveolar lavage fluid content of IL-1α, IL-1β, IL-6, macrophage inflammatory protein-2, and TNF when compared with spontaneous breathing,[19] whereas in a rat model with hydrochloric acid instillation–induced lung injury, mechanical ventilation with V_T of 16 ml and ZEEP resulted in a marked increase in TNF and macrophage inflammatory protein-2 when compared with V_T of 9 ml and PEEP of 5 cm H_2O.[1]

Unfortunately, we cannot draw conclusions on lung tissue cytokine concentrations on the basis of plasma cytokine levels. Previous studies suggest that an increase in alveolar–capillary permeability is required for translocation of mediators, including cytokines, from the lungs into the circulation.[29,30] Because inflammatory mediators cause an increase in vascular and alveolar permeability, a relevant accumulation of cytokines in the lungs should have resulted in an increased release of cytokines into the blood and alveolar fluid.

It is also important to note that we tested each ventilatory strategy only for 1 h. Experimental data have demonstrated that intraalveolar expression of TNF gene[31] and increased TNF levels in the systemic circulation[11] can be found after 1 h of injurious mechanical ventilation in lung injury models. Preliminary clinical data in patients with injured lungs indicate that maximal

increase in alveolar and systemic cytokine concentrations occurs within 1 h after initiating mechanical ventilation with low PEEP and high V_T.[28] Therefore, the lack of an increase in plasma cytokines during injurious mechanical ventilation in our patients should not be attributed to a time-related component on the cytokine release. However, we did not study long-term effects of mechanical ventilation on cytokine production in healthy lungs or the effects of mechanical ventilation combined with a surgical intervention, which itself may cause an inflammatory response or even bacteremia.

General anesthesia itself has been suggested to modulate the inflammatory response during mechanical ventilation.[32] Recent experimental data suggest that inflammatory response to mechanical ventilation may be aggravated by inhalation of volatile anesthetics after 2 h.[19] Studies comparing the immune response to standardized elective surgery in patients during propofol *versus* isoflurane anesthesia have revealed no differences[33] or a minimally diminished systemic inflammatory response with propofol and alfentanil when compared with isoflurane and nitrous oxide anesthesia.[34] Anesthesia in all of our patients was provided with isoflurane and fentanyl. Therefore, it is unlikely that anesthesia has a major influence on our results after a study period of only 1 h.

Our data suggest that in essentially normal lungs of anesthetized patients, short-term mechanical ventilation with high V_T in the presence or absence of PEEP induces no clinical relevant increase in systemic proinflammatory and antiinflammatory cytokines. This observation is indirect evidence that mechanical ventilation seems to induce no inflammation in normal lungs, but may well augment lung inflammation to clinically important levels in preinjured or infected lungs as previously shown.

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