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ORIGINAL

F. Stüber
H. Wrigge
S. Schroeder
S. Wetegrove
J. Zinserling
A. Hoeft
C. Putensen

Kinetic and reversibility of mechanical ventilation-associated pulmonary and systemic inflammatory response in patients with acute lung injury

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F. Stüber · H. Wrigge · S. Schroeder
S. Wetegrove · J. Zinserling · A. Hoeft
C. Putensen (✉)
Department of Anesthesiology
and Intensive Care Medicine,
University of Bonn, Sigmund-Freud-Str. 25,
53105 Bonn, Germany
e-mail: putensen@uni-bonn.de
Tel.: +49-228-2874118
Fax: +49-228-2879122

Abstract *Objective:* To investigate the kinetic and reversibility of mechanical ventilation-associated pulmonary and systemic inflammatory response in patients with acute lung injury (ALI). *Design:* Prospective observational cross-over study. *Setting:* Intensive care unit of a university hospital. *Patients:* Twelve mechanically ventilated patients with ALI. *Interventions:* Mechanical ventilation was transiently changed from a lung protective setting with PEEP of 15 cmH_2O and a V_T of 5 ml/kg predicted body weight to a more conventional ventilatory setting with PEEP of 5 cmH_2O and V_T of 12 ml/kg predicted body weight for a period of 6 h. *Measurements and results:* We examined the profile of interleukin (IL)-1β, IL-1 receptor antagonist, IL-6, IL-10, and tumor necrosis factor in the plasma of all patients, and in the bronchoalveolar lavage (mini-BAL) fluid of six of these patients. Measurements were performed at baseline, 1 h, and 6 h after each change of the ventilatory setting. Switching to conventional mechanical ventilation was associated with a higher PaO_2 (P <0.05) and a marked increase (P <0.05) of measured plasma cytokines in patients with and without mini-BAL with a maximum after 1 h. Similarly, intraalveolar cytokine concentrations increased with conventional mechanical ventilation. While plasma cytokine levels returned to baseline values, intraalveolar cytokine concentrations further increased when lung protective mechanical ventilation was reestablished. *Conclusions:* In patients with ALI, initiation of low PEEP and high V_T mechanical ventilation is associated with cytokine release into circulation which occurred within 1 h. It is independent from BAL procedures and can be reversed by reinstitution of lung protective mechanical ventilation.

Keywords Acute respiratory distress syndrome · Acute lung injury · Positive pressure ventilation · Protective mechanical ventilation · Inflammatory cytokines

Introduction

Acute lung injury (ALI) is associated with an insult to endothelial and epithelial cells in the lung resulting in release of mediators, increased vascular- and alveolar permeability, interstitial edema formation, alveolar collapse, and thereby arterial hypoxemia [1, 2, 3]. Positive pressure ventilation, commonly used to improve gas exchange, may further aggravate preexisting lung injury including pneumothorax, alveolar edema, and alveolar rupture [4, 5].

Mechanical ventilation with high positive end-expiratory pressure (PEEP) and low tidal volumes (V_T) has been suggested to prevent tidal collapse and overdistension of lung units during ALI [6, 7]. This lung-protective ventilatory strategy has been shown to improve gas ex-

change and outcome in patients with severe acute respiratory distress syndrome (ARDS) [8, 9]. A recent randomized multicenter trial in patients with ALI has demonstrated a decrease in mortality of more than 20% by limiting V_T to 6 ml/kg predicted body weight [10]. However, it is unclear how lung-protective ventilatory strategies reduce mortality in patients with ALI. In vitro experiments demonstrate that mechanical stress to lungs cells enhances the production of inflammatory mediators after inflammatory activation [11]. In animal models of ALI, mechanical ventilation with low PEEP and high V_T has been found to increase intraalveolar levels of inflammatory mediators when compared to a lung-protective ventilatory strategy [12]. Recently, Ranieri et al. [13] observed higher systemic and intraalveolar levels of pro-inflammatory mediators in patients ventilated with a conventional strategy when compared to patients ventilated according to a lung-protective strategy. However, the kinetic and reversibility of a systemic inflammatory response by injurious mechanical ventilation is unknown in patients with ALI.

We hypothesized that in patients with ALI mechanical ventilation with low PEEP and high V_T induces reversible pulmonary release of inflammatory mediators. To test this hypothesis, we examined the profile of pro- and anti-inflammatory mediators in the alveolar lavage fluid and plasma of patients with ALI ventilated with a lung-protective strategy that were transiently switched to mechanical ventilation with low PEEP and high V_T.

Materials and methods

The protocol was approved by the local ethics committee. Since informed consent from patients could not be obtained, permission for asking consent from the next of kin was granted by the legal authorities. All patients included had informed consent thus granted by relatives, and all survivors later gave written consent for scientific use of the recorded data. As this study – which has important implications for future management of acute lung injury – bore no direct benefit for the patients examined, relatives were fully informed about risks of BAL. Instead of a standard BAL procedure using up to 150 ml of saline, a reduced volume of fluid was employed for a mini-BAL (20 ml) in order to exclude the risk of substantially deteriorating pulmonary function by bronchial fluid instillation. Close monitoring of pulmonary function (continuous pulse oximetry, blood gas analyses) and hemodynamics (continuous measurement of arterial blood pressure, central venous pressure, and EKG) was performed throughout the study. The study was conducted between December 1998 and July 1999.

Twelve mechanically ventilated patients with ALI were studied. The criteria of the American-European Consensus Conference were used to define ALI [14]. Patients with a history of chronic lung or heart disease and those with sepsis were not included in the study. In addition, a critical pulmonary or cardiac function documented by an FiO_2/PaO_2 ratio <200 or need of catecholamines for inotropic support was considered as a non-inclusion/exclusion criterion in order to prevent possible further deterioration of a critical lung function by BAL procedures. Organ Failure Score [15] and Simplified Acute Physiologic Score [16] were assessed at study entry.

Routine clinical management of the patients included the use of a radial artery catheter and a central venous catheter. Heart rate (HR) was obtained from the electrocardiogram. Systemic blood pressure (Psa) and central venous (Pcv) pressures were transduced (Combitrans; Braun, Melsungen, Germany) and recorded. All patients received a continuous intravenous infusion of sufentanil and midazolam as clinically required. During the study, fluid replacement and infusion of all drugs remained unchanged.

Parameters of mechanical ventilation

Protective ventilatory support was provided with a positive end-expiratory pressure (PEEP) of 15 cmH_2O and a V_T of 5 ml/kg predicted body weight using a standard ventilator (Evita, Dräger, Lübeck, Germany). During the transient conventional mechanical ventilation PEEP was set at 5 cmH_2O and V_T at 12 ml/kg predicted body weight. Respiratory rate and cycle time were set to maintain an arterial PCO_2 between 35 mmHg and 50 mmHg and an inspiratory to expiratory time ratio of 1:1. The FiO_2 was adjusted to exceed a PaO_2 of 70 mmHg. Switching to conventional ventilation was maintained for 6 h before resuming the initial settings. All ventilatory parameters were recorded from ventilator readings.

Physiologic gas analysis

Arterial blood gases and pH were determined immediately after sampling with standard blood gas electrodes (ABL; Radiometer, Copenhagen, Denmark). Oxygen saturation (SO_2) and hemoglobin (Hb) in each sample were analyzed using spectrophotometry (OSM3; Radiometer, Copenhagen, Denmark).

Cytokine measurements

Bronchoalveolar lavages (BAL) were performed using a bronchoscope with an aliquot of 20 ml sterile isotonic saline in segments of the right upper lobe. When an infiltrate was present in the chest radiography, BAL was performed in an unaffected lobe. The aspirated BAL fluid was centrifuged at 500 *g* for 15 min and the supernatants stored at –70 °C. Arterial EDTA blood samples of 5 ml were centrifuged at 1,500 *g* for 10 min, the plasma aspirated and stored at –70 °C. Cytokines were detected in EDTA plasma and in BAL fluid with commercially available enzyme-linked immunoabsorbent assays (ELISA). IL-6 and TNF were determined with ELISA kits obtained from Biosource company (Biosource company, Ratingen, Germany). IL-10, IL-1β, and IL-1ra were measured using ELISA kits from R&D Systems (R&D Systems, Minneapolis, Minn., USA). Analysis by ELISA was performed strictly according to the suppliers guidelines.

Protocol

Patients were on ventilatory support for at least 24 h before inclusion into the study. A 6 h equilibration period followed the institution of lung-protective mechanical ventilation before baseline measurements.

After baseline measurements the lung-protective ventilatory strategy was changed to low PEEP and high V_T mechanical ventilation. Following 6 h of mechanical ventilation with low PEEP and high V_T, patients were switched back to the lung-protective mechanical ventilation. Measurements of plasma cytokines and cardiopulmonary variables were performed at baseline following 6 h of lung-protective mechanical ventilation, 1 h and 6 h after the switch to low PEEP and high V_T mechanical ventilation, and 1 h and 6 h after reestablishing lung-protective mechanical ventilation (Fig. 1). In a subgroup of six patients (with mini-BAL) BAL was

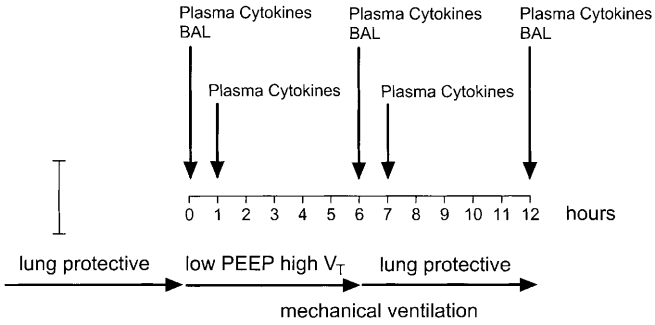

Fig. 1 Study design and time course of measurements and interventions

performed after sampling for plasma cytokines and measurements of cardiopulmonary variables at baseline, 6 h of low PEEP and high V_T mechanical ventilation, and 6 h after reestablishing lung-protective mechanical ventilation. In the six other patients (without mini-BAL) all measurements were performed except mini-BAL to determine possible influence of the BAL procedure on systemic or local mediator release.

Preparation of the study was started in July 1997. At that time outcome data from studies testing standard high tidal volume ventilation versus low tidal volume ventilation [10] were not yet available.

Statistical analysis

Results are expressed as mean±standard error of the mean (SE). Data were analyzed by the Friedman test followed by post hoc analysis using Duncan's multiple range test and Kruskal-Wallis test as indicated. Differences were considered to be statistically significant for $P < 0.05$.

Results

There were no statistically significant differences in the demographic and clinical data between patients of both groups (Table 1). Changes in ventilatory and cardiopul-

Table 1 Demographic and clinical data of patients included in this study

	Patients with mini-BAL	Patients without mini-BAL
Number of patients	6	6
Age, years	40±5	47±8
Gender M/F	3/3	4/2
SAPS (mean±SE)	16±1	15±3
Survivors *n* (%)	5(83)	6(100)
Diagnosis		
Peritonitis *n* (%)	3(50)	2(33)
Multiple trauma *n* (%)	1(17)	3(50)
Others *n* (%)	2(33)	1(17)
Organ failure *n*[a]		
1	1	2
2	5	4
Ventilatory support before study entry days	3±2	5±2

[a] assessed using the Organ Failure Score [15]

Table 2 Cardiopulmonary variables. Values are mean±SE. (*BAL* mini-bronchoalveolar lavage, *FiO_2* inspiratory fraction of oxygen, *PEEP* positive end-expiratory pressure, *P_{ei}* end-inspiratory airway pressure, *V_T* tidal volume, *PaO_2* arterial oxygen tension, *$PaCO_2$* arterial carbon dioxide tension, *HR* heart rate, *Psa* mean systemic arterial pressure, *Pcv* mean central venous pressure)

	Lung protective ventilation		Low PEEP – high V_T ventilation				Lung protective ventilation			
	Baseline		1 h		6 h		1 h		6 h	
	Without BAL	With BAL	Without BAL	With BAL	Without BAL	With BAL	Without BAL	With BAL	Without BAL	With BAL
PEEP cmH_2O	15	15	5	5	5	5	15	15	15	15
P_{ei} cmH_2O	26±1	27±2	31±2*	31±2*	30±2*	32±2*	26±1	27±1	26±1	26±1
V_T ml	408±13	395±14	1020±43*	1005±40*	1012±42*	996±38*	387±17	391±19	391±17	397±20
V_T ml/kg	4.9±0.2	4.9±0.2	12.0±0.9*	12.1±0.8*	12.0±0.8*	12.0±0.8*	4.7±0.2	4.9±0.2	4.9±0.2	4.9±0.2
FiO_2	0.43±0.02	0.44±0.01	0.46±0.03	0.47±0.02	0.48±0.03	0.40±0.04	0.45±0.02	0.46±0.02	0.45±0.02	0.46±0.03
PaO_2 mmHg	98±7	95±8	76±6*	75±5*	78±7*	77±8*	101±9	96±8	103±9	98±8
$PaCO_2$ mmHg	43±1	43±1	37±2	36±1	38±1	38±2	42±2	44±2	42±2	44±2
PHa	7.38±0.01	7.37±0.01	7.44±0.01	7.43±0.01	7.42±0.01	7.42±0.01	7.37±0.01	7.38±0.01	7.38±0.01	7.37±0.01
HR/min	95±5	99±5	94±4	96±4	93±5	99±5	98±5	99±4	95±5	98±5
Psa mmHg	76±2	74±2	80±3	81±3	82±3	82±3	74±2	77±2	77±2	75±2
Pcv mmHg	14±3	15±3	13±3	13±2	14±3	13±2	14±2	15±3	15±3	14±2

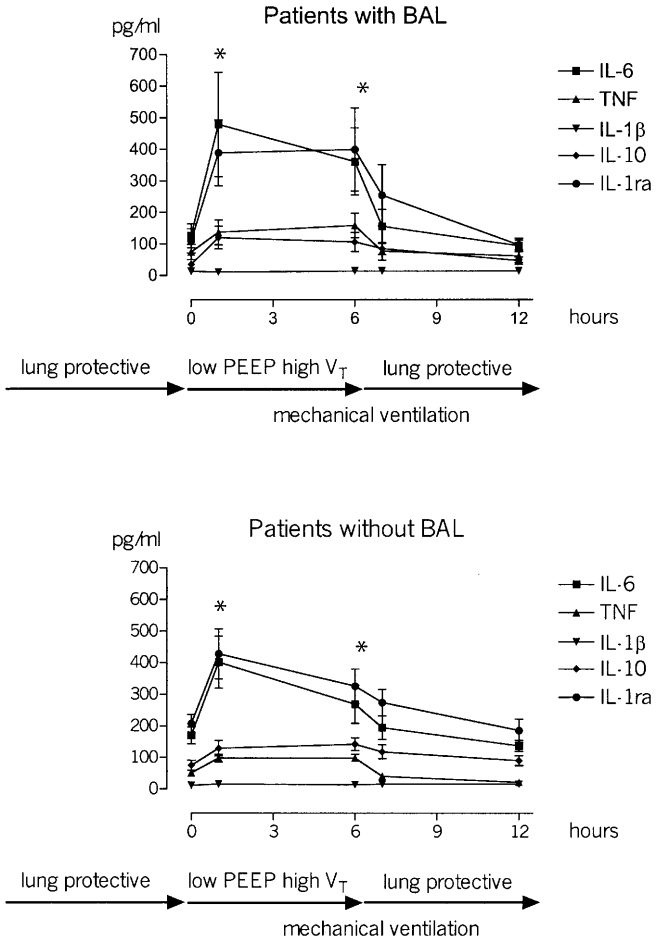

Fig. 2 Plasma interleukin (IL)-1β, IL-1ra, IL-6, IL-10, and tumor necrosis factor (TNF) measured in twelve patients with ALI ventilated with a lung-protective strategy (PEEP 15 cmH_2O, V_T 5 ml/kg predicted body weight) that was transiently switched to low PEEP and high V_T mechanical ventilation (PEEP 5 cmH_2O, V_T 12 ml/kg predicted body weight). In six patients bronchoalveolar lavage (min-BAL) was performed (*upper part*) after sampling for plasma cytokines whereas in the six other patients measurements were performed without mini-BAL (*lower part*). *P <0.05 for all cytokines except IL-1β when compared to baseline cytokine levels at 0 h (Friedmann test and post hoc analysis). No statistically significant difference in cytokine levels was found between patients with and without mini-BAL (Kruskal-Wallis test)

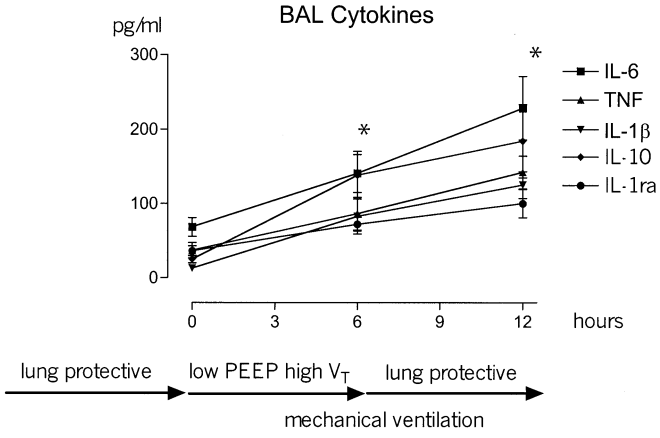

Fig. 3 Interleukin (IL)-1β, IL-1ra, IL-6, IL-10, and tumor necrosis factor (TNF) concentration in the alveolar fluid measured in six patients with ALI ventilated with a lung-protective strategy that was transiently switched to low PEEP and high V_T mechanical ventilation. *P <0.05 for all cytokines when compared to baseline cytokine levels at 0 h (Friedmann test and post hoc analysis)

monary variables are shown in Table 2. During lung-protective mechanical ventilation end-inspiratory airway pressure (P_{ei}) was lower (P <0.05) than during low PEEP and high V_T mechanical ventilation in all patients. The ventilator rate had to be increased (P <0.05) to maintain the target range of $PaCO_2$ during lung-protective mechanical ventilation resulting in comparable minute ventilation. PaO_2 was lowest (P <0.05) during low PEEP and high V_T mechanical ventilation. Heart rate, Psa, Pcv, $PaCO_2$, and pH remained essentially unchanged for all tested conditions.

Cytokine plasma levels are shown in Fig. 2. Plasma levels of TNF, IL-6, IL-10, and IL-1ra were moderately elevated in all patients during lung-protective mechanical ventilation. IL-1β levels remained below 20 pg/ml throughout the study. Switching to low PEEP and high V_T mechanical ventilation was associated with a marked increase (P <0.05) in all plasma cytokines except for IL-1β regardless of whether BAL was performed or not. Plasma cytokine levels remained elevated in all patients during low PEEP and high V_T mechanical ventilation. One hour after reestablishing lung-protective mechanical ventilation, IL-6 plasma levels were reduced (P <0.05). All other previously elevated cytokines (TNF, IL-10, IL-1ra) showed a tendency towards lower values. After 6 h of protective mechanical ventilation, systemic cytokine levels decreased (P <0.05) to values comparable to baseline measurements in all patients.

Intraalveolar cytokine levels for the six patients with BAL are shown in Fig. 3. Low PEEP and high V_T mechanical ventilation was associated with an increase in intraalveolar cytokines including IL-1β. While plasma cytokine levels decreased (P <0.05), intraalveolar cytokine concentrations increased further (P <0.05) when lung-protective mechanical ventilation was reestablished. Performance of BAL did not induce a statistically significant difference in plasma cytokine levels when comparing patients undergoing or not undergoing BAL (P >0.05)

Discussion

This study was designed to evaluate the effect of different ventilatory strategies on the release of inflammatory

mediators in patients with ALI. Lung-protective mechanical ventilation was associated with moderately elevated plasma levels of inflammatory cytokines. Mechanical ventilation with low PEEP and high V_T provoked an inflammatory reaction, as reflected by a marked increase of pro- (TNF, IL-6) and anti-inflammatory (IL-1ra, IL-10) cytokines in the plasma. Similarly, intraalveolar cytokine concentrations increased with low PEEP and high V_T mechanical ventilation. While plasma cytokine levels decreased to initial values, intraalveolar cytokine concentrations increased further when lung-protective mechanical ventilation was reestablished.

Mechanical ventilation with PEEP is commonly used to provide adequate alveolar ventilation and to recruit non- or poorly ventilated lung units and improve arterial oxygenation. Increasing PEEP has been shown to correspond to a significant increase in aerated lung tissue observed by computer tomography, decrease in venous admixture, and improvement of arterial oxygenation [17]. Therefore, adequate levels of PEEP should recruit initially nonventilated lung units and prevent progressive loss of gas exchange area. In contrast, until recently conventional mechanical ventilation used low PEEP levels with high V_T ranging between 10 ml/kg and 15 ml/kg ideal body weight [6, 10, 18, 19, 20]. Based on experimental data mechanical ventilation with high V_T has been claimed to over-distend functional lung units and contribute to direct lung damage [21]. However, several randomized clinical trials could not demonstrate any advantage or even improved outcome when just low V_T of 7 ml/kg body weight were used to avoid alveolar overdistension during positive pressure inflation in patients with ARDS [19, 20]. In this context, this study was designed to illuminate pathophysiological changes concerning release of inflammatory mediators by switching the PEEP and tidal volume in ALI patients. Once our study was completed, a multi-center trial in more than 800 patients with ALI demonstrated more than 20% improvement in mortality by reduction in V_T from 12 ml/kg to 6 ml/kg ideal body weight and, thereby, demonstrating the clinical importance of avoiding pathophysiologic sequelae induced by high tidal ventilation. [10]. Whereas in these investigations PEEP levels remained essentially unchanged, Amato et al. [6, 18] suggested higher PEEP to prevent alveolar collapse at end-expiration, while minimizing the end-inspiratory lung volume by using smaller V_T [6, 7, 18, 22]. This lung protective mechanical ventilation has been shown to improve gas exchange and decreased mortality in patients with ARDS [6, 7, 18, 22]. In our patients, mechanical ventilation with PEEP of 5 cmH_2O and V_T of 12 ml/kg predicted body weight may have caused end-expiratory alveolar collapse and overdistension. This has been suggested to result in shear forces with transmural pressures of up to 100 cmH_2O applied to lung cells [23]. Compatible with previous findings [6, 18], lung protective mechanical ventilation in our patients with PEEP of 15 cmH_2O and V_T of 5 ml/kg predicted body weight improved arterial oxygenation. As a result, our patients fulfilled the criteria for ALI during lung-protective mechanical ventilation and for ARDS during low PEEP and high V_T mechanical ventilation [14]. However, ALI and ARDS represent only different levels of pulmonary gas exchange disturbance caused by a similar inflammatory reaction leading to increased vascular and alveolar permeability, interstitial edema formation, and alveolar collapse [14].

Patients with ARDS rarely die of hypoxia and/or hypercarbia but commonly develop a systemic inflammatory response that culminates in multiple organ system dysfunction syndrome and death [1, 24, 25]. Recent research has shown that cytokines and other inflammatory agents significantly promote organ damage on a cellular level [26] and that cytokine plasma levels correlate with the degree of organ failure in ALI patients [27].

Inflammatory mediators including cytokines can be synthesized and released by lung cells due to a variety of stimuli [11, 28, 29]. In patients, during ARDS, concentrations of TNF, IL-1β, IL-6, and IL-8 in the alveolar fluid increase and remain elevated in non-survivors [30, 31, 32, 33]. In addition, BAL itself has been shown to effect a significant increase in plasma cytokines levels [34] but is considered a safe procedure in ALI and ARDS patients [35, 36, 37]. In the present study, comparison of plasma cytokine levels in patients with or without mini-BAL (20 ml] did not reveal a statistically significant difference suggesting that the increase in plasma cytokine levels were due to changes of ventilator settings. Furthermore, mechanical stress such as shear stress has been found to induce production of inflammatory cytokines in isolated endothelial [28], epithelial [29], and macrophage cells [11]. Therefore, inflammatory cytokines may be involved in ventilation-associated lung injury.

Several studies reported findings regarding the production of inflammatory mediators in the lungs induced by various injurious ventilatory strategies [11, 12, 13, 38]. Stretching and pressurizing of cultivated alveolar macrophages by cyclic changes in airway pressure simulating clinical mechanical ventilation has been observed to increase cellular secretion of pro-inflammatory cytokines [11]. Similarly, mechanical ventilation with low PEEP and high V_T has been found in isolated lung preparations to induce release of pro-inflammatory cytokines into the alveolar fluid [12, 38] and into the perfusate [38]. However, recent studies in animals [39] and humans [40] indicate that mechanical ventilation of normal lungs alone is not associated with an inflammatory response. These observations suggest that injurious ventilatory strategies may aggravate a pulmonary and systemic inflammatory cytokine response. In a prospective ran-

domized investigation, Ranieri et al. [13] observed in patients with ARDS lower systemic and intraalveolar levels of pro-inflammatory cytokines following 36 h of lung-protective mechanical ventilation, when compared to mechanical ventilation with PEEP of 6 cmH_2O and a V_T of 11 ml/kg ideal body weight. In contrast to our patients with moderately increased cytokine plasma concentrations at baseline, these ARDS patients already had markedly elevated baseline cytokine plasma levels [13]. Furthermore, the reversibility of a mechanical ventilation-induced systemic inflammatory cytokine response may be difficult to evaluate on the basis of previous studies because systemic and intraalveolar concentrations of the pro-inflammatory cytokines were determined after prolonged application of injurious ventilatory strategies during the investigations [12, 13, 38]. In our study, patients were transiently ventilated with low PEEP and high V_T, while mini-BAL was only performed on a random basis in some patients. Therefore, our results should reflect essentially the effect of a mechanical ventilation with low PEEP and high V_T on the kinetic and reversibility of the pro- and anti-inflammatory cytokines release in the lungs.

In our patients, low PEEP and high V_T mechanical ventilation was consistently accompanied by a reversible increase of systemic pro- and anti-inflammatory cytokine levels regardless of whether BAL was performed or not. Consistent with previous experimental [12, 38] and clinical investigations [13], our findings demonstrate that an injurious ventilatory strategy using low PEEP and high V_T can induce a systemic inflammatory response. These observations have been attributed to induction, synthesis, and release of cytokines from lung tissue during mechanical ventilation [12, 13, 38]. Recently, the lung macrophage was identified as the important mechanosensor responding to pressure-stretching cyclic load with secretion of inflammatory cytokines [11]. The decrease in plasma cytokine levels to initial values and further increase in intraalveolar cytokine concentrations when lung-protective mechanical ventilation was reestablished suggests that the various lung cells in the alveolus and pulmonary vasculature may respond different to an injurious ventilatory strategy. Compatible with this concept, Tremblay et al. [12] observed release of inflammatory cytokines even in alveolar macrophage-depleted rat lungs during injurious ventilatory regimen. Furthermore, a pressure-stretching stimulus has been shown in isolated endothelial and interstitial lung cells to induce a release of inflammatory mediators [28]. Absence of a decline in intraalveolar cytokine levels after discontinuation of low PEEP and high V_T mechanical ventilation might be explained by an ongoing release of cytokines from macrophages or epithelial cells due to damage to alveolar structures. In animals receiving intratracheal instillation of bacteria, low PEEP and high V_T mechanical ventilation has been demonstrated to increase bacterial translocation from the alveolus into the blood [41]. Haitsma et al. have recently demonstrated translocation of TNF from the systemic compartment to the lungs and vice versa during injurious ventilation in rats [42]. A similar mechanism may have resulted in an increased transfer of cytokines from the alveolus into the blood and induced the systemic cytokine response in our patients during low PEEP and high V_T mechanical ventilation. However, our data clearly demonstrate that the low PEEP and high V_T mechanical ventilation-induced systemic cytokine response can be reversed by lung-protective mechanical ventilation. Unfortunately, the results of our study only quantify intraalveolar and plasma inflammatory cytokine levels and do not allow us to draw conclusions on the distinct cellular sources of cytokine release or presumably associated biological effects.

Mechanical ventilation with tidal volumes of 5 ml/kg to avoid end-inspiratory overinflation may result in hypercapnia and respiratory acidosis [6, 9]. To deliver the two ventilatory strategies in our patients with comparable minute ventilation, $PaCO_2$ and pH ventilatory rate had to be significantly reduced during low PEEP and high V_T mechanical ventilation. Consequently, $PaCO_2$ and pH remained essentially unchanged throughout the study and therefore cannot sufficiently explain the magnitude of cytokines release associated with low PEEP and high V_T mechanical ventilation. Although arterial oxygenation deteriorated during low PEEP and high V_T mechanical ventilation it is unlikely that this small decrease in PaO_2 can explain the marked increase of pro-and anti-inflammatory cytokines in the plasma [43].

In conclusion, the results of this study demonstrate that mechanical ventilation with low PEEP and high V_T induces release of pro- and anti-inflammatory cytokines into the alveolar space and the blood after only 1 h. Lung-protective mechanical ventilation designed to minimize cyclic closing and overdistension of lung units can reverse this systemic inflammatory response. The decrease in plasma cytokine levels to baseline values associated with further increase in intraalveolar cytokine concentrations when lung-protective mechanical ventilation is reestablished suggests that cells in the alveolus and pulmonary vasculature may respond differently to an injurious ventilatory strategy.

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