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Chapter 8

Mechanical Ventilation with Lower Tidal Volumes and PEEP Prevents Alveolar Coagulation in Patients without Lung Injury

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Abstract

Background: Alveolar fibrin deposition is a hallmark of acute lung injury, resulting from activation of coagulation and inhibition of fibrinolysis. Previous studies have shown that mechanical ventilation with high tidal volumes may aggravate lung injury in patients with sepsis and acute lung injury. We sought to determine the effects of mechanical ventilation on the alveolar hemostatic balance in patients without pre-existent lung injury.

Methods: Patients, scheduled for an elective surgical procedure (lasting ≥ 5 hours), were randomized to mechanical ventilation with either higher tidal volumes of 12 ml/kg predicted body weight and no positive end-expiratory pressure (PEEP) or lower tidal volumes of 6 ml/kg and 10 cmH_2O PEEP. After induction of anesthesia and 5 hours later bronchoalveolar lavage fluid and blood samples were obtained, and markers of coagulation and fibrinolysis were measured.

Results: In contrast to mechanical ventilation with lower tidal volumes and PEEP (n = 21), the use of higher tidal volumes without PEEP (n = 19) caused activation of bronchoalveolar coagulation, as reflected by a marked increase in thrombin-antithrombin complexes, soluble tissue factor, and factor VIIa after 5 hours of mechanical ventilation. Mechanical ventilation with higher tidal volumes without PEEP caused an increase in soluble thrombomodulin in lavage fluids and lower levels of bronchoalveolar activated protein C in comparison to lower tidal volumes and PEEP. Bronchoalveolar fibrinolytic activity did not change by either ventilation strategy.

Conclusions: Mechanical ventilation with higher tidal volumes and no PEEP promotes procoagulant changes, which are largely prevented by the use of lower tidal volumes and PEEP.

Introduction

Pulmonary inflammation is characterized by local generation of proinflammatory mediators and a procoagulant shift of the alveolar hemostatic balance, promoting fibrin depositions within the airways [1,2]. Indeed, disturbances in alveolar fibrin turnover have been demonstrated in patients with pneumonia [3-6] and acute respiratory distress syndrome (ARDS) [4,7]. Whereas fibrin formation may aid in host protection, such as the containment of infectious agents during pulmonary infection and in maintaining or repairing the endothelial-epithelial barrier, on the other hand, coagulation products such as thrombin and fibrin have significant proinflammatory properties, potentially compromising pulmonary integrity and function [1,2]. In its most extreme form bronchoalveolar fibrin formation may compromise pulmonary function, as may occur with severe ARDS.

In severe lung injury, ventilatory support is almost invariably mandatory, but it is increasingly recognized that mechanical ventilation itself may aggravate or even initiate lung injurious processes [8,9]. The so-called ventilator-associated lung injury is characterized by several pathophysiological sequelae, including local generation of inflammatory mediators, constituting a pulmonary environment which is highly proinflammatory. Another hallmark of ventilator-associated lung injury in patients with severe lung injury is the activation of bronchoalveolar coagulation [3,6]. In patients with ARDS mechanical ventilation with lower tidal volumes improves patient survival [10], most likely by limiting generation of proinflammatory mediators, both locally in the lungs and systemically [11]. It is unknown whether (mechanical ventilation induced) alterations in the alveolar hemostatic balance contribute to outcome in mechanically ventilated patients. Moreover, there is ongoing debate on whether patients without pre-existent lung injury would benefit from mechanical ventilation with lower tidal volumes, since large clinical trials have only investigated patients with acute lung injury and ARDS in the intensive care unit. Recently, the pulmonary and systemic inflammatory effects of mechanical ventilation were investigated in patients during major surgery, showing little alterations in the inflammatory responses [12,13].

The aim of the current study was to characterize the effects of mechanical ventilation on the alveolar hemostatic balance. A randomized controlled trial was performed comparing two mechanical ventilation strategies in patients without pre-existent lung injury who were scheduled for a major surgical procedure.

Methods

Patients

The study protocol was approved by the Medical Ethics Committee of the University of Amsterdam, and informed consent was obtained from all patients. Adult patients were eligible if scheduled for a surgical procedure of ≥ 5 hours, and all involved physicians (surgeon, anesthesiologist, pulmonologist) consented with the study procedures, assuring safety of the patient. Exclusion criteria included a history of any lung disease, use of immunosuppressive medication, recent infections, previous thrombo-embolic disease, recent admission to the intensive care unit for ventilatory support, and participation in another clinical trial.

Study Protocol

All patients received routine anesthesia according to protocol, including intravenous propofol (2-3 mg/kg, thereafter 6-12 mg/kg/h), fentanyl (2-3 μg/kg, thereafter as required), and rocuronium (as required); and epidural bupivacaine (0.125%) / fentanyl (2.5 μg/ml). The ventilatory protocol consisted of volume-controlled mechanical ventilation, at an inspired oxygen fraction of 0.40, inspiratory to expiratory ratio of 1:2, and a respiratory rate adjusted to normocapnia. Randomization was performed by drawing a pre-sealed envelope; patients were randomized to mechanical ventilation with either tidal volumes of 12 ml/kg (predicted body weight (PBW), calculated according to the formula as described before) [10] and no positive end-expiratory pressure (PEEP) or 6 ml/kg PBW and 10 cmH_2O PEEP. Anesthesiologists were allowed to change the ventilation protocol at any timepoint upon surgeon's request, or if there was any concern on patient's safety. If the surgical procedure exceeded 5 hours, anesthesiologists were allowed to change the ventilation strategy after the second sampling (blood and bronchoalveolar lavage). Patients were followed until hospital discharge or death.

Bronchoscopy and bronchoalveolar lavage were performed twice on all patients: the first just after initiation of mechanical ventilation in either the right middle lobe or lingula, the second performed in the contralateral lung 5 hours thereafter, either peri-operatively or directly postoperatively. Lavage fluid was obtained as previously described [3,5,14]. In short, the bronchoalveolar lavage was performed by an experienced pulmonologist in a standardized fashion according to the guidelines of the American Thoracic Society, using a flexible fiberoptic video-bronchoscope. Seven successive 20 ml aliquots of pre-warmed normal saline were instilled and aspirated immediately with low suction (general recovery 10-15 ml). For coagulation assays, sodium citrate and benzamidin were added to the lavage fluids to a final concentration of 10 mM and 20 mM, respectively. Citrated (0.109 M) blood samples were drawn prior to both lavages, and hourly blood gas analyses were performed. Cell free supernatants were stored at -80°C until analysis.

Assays for coagulation and fibrinolysis

Thrombin-antithrombin complex (TATc), soluble tissue factor, factor VIIa, tissue-type plasminogen activator (tPA), plasminogen activator inhibitor type 1 (PAI-1), plasminogen activator activity, soluble thrombomodulin and activated protein C (APC) concentrations were measured as described before [15-17].

Statistical Analysis

The required sample size was calculated from data from our previous investigations on pulmonary hemostasis [3,6]. To detect differences in bronchoalveolar TATc concentrations in the study groups at a two-sided significance level of 5 percent with a power of 80 percent, the number of patients to be studied in each group was at least 19.

Baseline characteristics of the randomized patient groups were compared with Student t test or Mann-Whitney U test, where appropriate. For categorical data $\chi 2$ test was used. Differences within groups were analyzed with a Wilcoxon signed-rank test for paired samples comparing t = 5 versus t = 0 hours, Mann-Whitney U test was used to compare the changes over time between the two randomization groups. All results are expressed as mean ± SD. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS 12.0 (SPSS, Chicago, IL).

Results

Patients

Seventy-four consecutive patients who were scheduled for an elective surgical procedure of 5 hours or more were screened in the period December 2003 through March 2005 (**figure 1**). Twenty-eight patients were excluded, leaving 46 patients for randomization. Five patients were randomized but excluded from final analysis, because the initial surgical procedure was converted by the surgeon into another shorter operation (< 3 hours), and only one bronchoalveolar lavage was performed. One patient was randomized but no lavages were performed upon the surgeon's request after induction of anesthesia. In total 40 patients completed the study protocol. There were no major differences between both randomization groups with regard to baseline characteristics (**table 1**). In particular, peak pressures were not different between the study groups during 5 hours of mechanical ventilation.

Table 1 Baseline characteristics of patients

	LV_T/PEEP (n = 21)	**HV_T/ZEEP** (n = 19)
Age, mean ± SD, yr	62 ± 9.8	61 ± 9.5
Male, n (%)	14 (67)	14 (74)
ASA, median (range)	2 (1-4)	2 (1-3)
Height, mean ± SD, cm	176 ± 8.7	174 ± 10.0
Weight, mean ± SD, kg	79 ± 14.4	76 ± 13.7
PBW, mean ± SD, kg	70 ± 9.5	69 ± 10.6
Tobacco use, n (%)	9 (43)	6 (32)
Surgical procedure	5 Whipple's Procedure*	8 Whipple's Procedure*
	5 Laparoscopic Radical Prostatectomy	7 Laparoscopic Radical Prostatectomy
	6 Hemihepatectomy	3 Hemihepatectomy
	2 Retroperitoneal Tumor Resection	1 Colon Conduit
	2 Total Pancreatectomy	
	1 Open Prostatectomy†	

* Whipple's procedure is a pancreatico-duodenectomy. † The open prostatectomy was performed after an initial laparoscopic approach. ASA = American Society of Anesthesiologists (physical status classification); PBW = predicted body weight; HV_T/ZEEP = higher tidal volumes/zero positive end-expiratory pressure; LV_T/PEEP = lower tidal volumes/positive end-expiratory pressure.

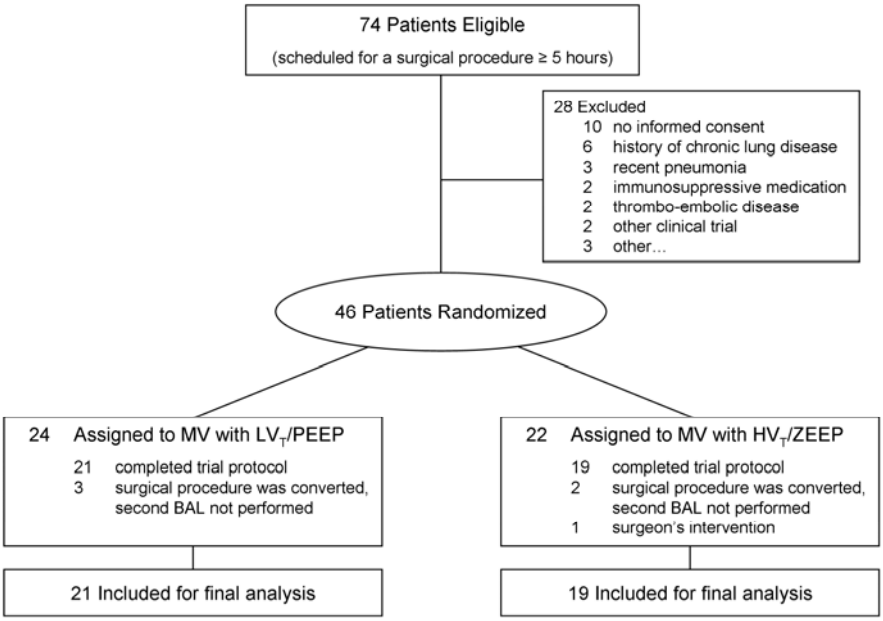

Figure 1 CONSORT diagram. MV = mechanical ventilation; BAL = bronchoalveolar lavage; HV_T/ZEEP = tidal volumes of 12 ml/kg predicted body weight and no positive end-expiratory pressure; LV_T/PEEP = tidal volumes of 6 ml/kg predicted body weight and 10 cmH_2O positive end-expiratory pressure.

Table 2 Peri-operative parameters

	LV_T/PEEP (n = 21)	**HV_T/ZEEP** (n = 19)
MV duration, mean ± SD, min	304 ± 35	308 ± 52
Blood loss, median (IQR), ml	1550 (800-2325)	1000 (463-1675)
Transfused red cells, median (IQR), units	0 (0-1.5)	0 (0-1)
Transfused plasma, median (IQR), units	0 (0-0)	0 (0-0)
Colloids, median (IQR), l	0.5 (0.5-1.5)	0.5 (0.5-1.5)
Chrystalloids, median (IQR), l	4.5 (2.75-5.75)	4.0 (2.5-5.5)
Lowest Hb, mean ± SD, mmol/l†	6.0 ± 1.2	6.2 ± 1.0
Highest SBP, mean ± SD, mmHg	122 ± 17	135 ± 21*
Lowest SBP, mean ± SD, mmHg	82 ± 9.6	87 ± 14.9

MV = mechanical ventilation; IQR = interquartile range; Hb = hemoglobin; HV_T/ZEEP = higher tidal volumes/zero positive end-expiratory pressure; LV_T/PEEP = lower tidal volumes/positive end-expiratory pressure; SBP = systolic blood pressure. * Difference from LV_T/PEEP ($p < 0.05$). † Hemoglobin, 1 mmol/L = 1.61 g/dL.

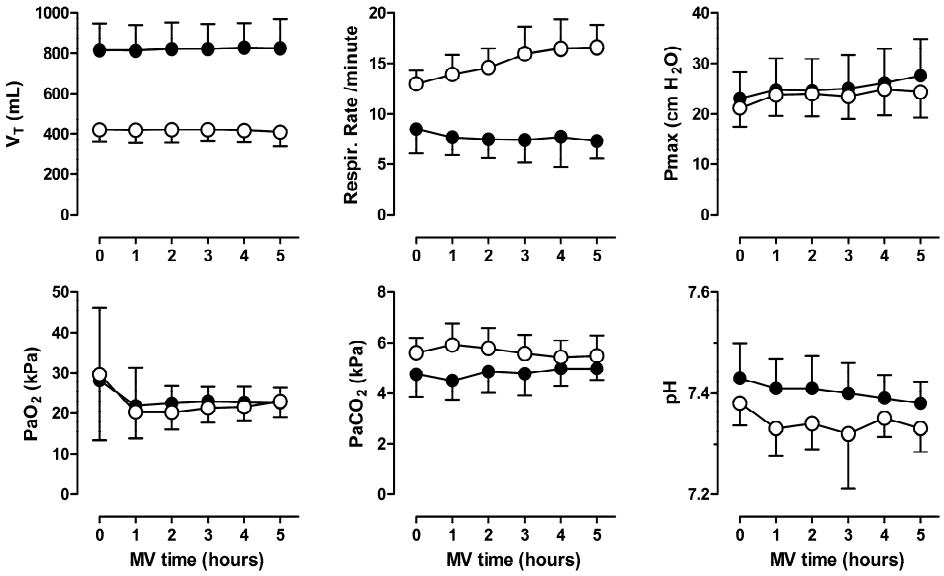

Figure 2 Peri-operative parameters. Tidal volumes (V_T), respiratory rate (Respir. Rate), maximal airway pressures (Pmax), PaO_2, $PaCO_2$ and pH in patients ventilated with lower tidal volumes and positive end-expiratory pressure (*open symbols*, n = 21) and patients ventilated with higher tidal volumes and no positive end-expiratory pressure (*closed symbols*, n = 19). MV = mechanical ventilation. Data are mean ± SD.

Bronchoalveolar Coagulation and Fibrinolysis

Mechanical ventilation with higher tidal volumes and zero PEEP (HV_T/ZEEP) caused activation of bronchoalveolar coagulation, as reflected in a marked increase in TATc, soluble tissue factor, and factor VIIa after 5 hours of mechanical ventilation (all $p < 0.001$ vs. t = 0; **figure 3**). In patients ventilated with lower tidal volumes and 10 cmH_2O PEEP (LV_T/PEEP), only soluble tissue factor was slightly elevated ($p < 0.01$ vs. t = 0; **figure 3B**) and far less pronounced than in patients with HV_T/ZEEP ($p < 0.001$ between groups).

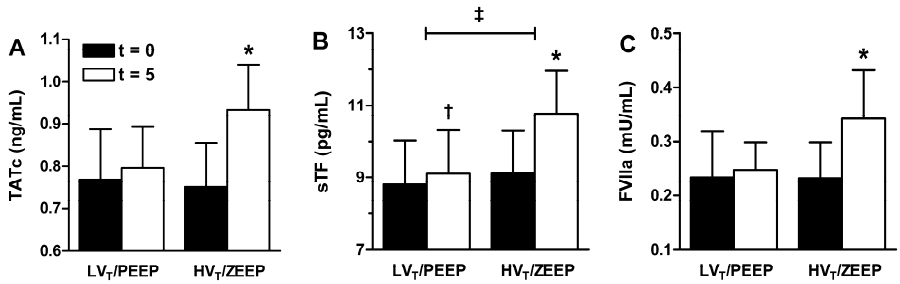

Figure 3 Thrombin-antithrombin complexes (TATc, ***A***), soluble tissue factor (sTF, ***B***), and factor VIIa (FVIIa, ***C***) in bronchoalveolar lavage fluid recovered at baseline (t = 0) and after 5 hours (t = 5) from patients mechanically ventilated with 6 ml/kg and 10 cmH_2O positive end-expiratory pressure (LV_T/PEEP, n = 21) or with 12 ml/kg and zero positive end-expiratory pressure (HV_T/ZEEP, n = 19). * Difference from t = 0 in HV_T/ZEEP ($p < 0.001$). † Difference from t = 0 in LV_T/PEEP ($p < 0.01$). ‡ Intergroup difference ($p < 0.001$). Data are mean ± SD.

Neither mechanical ventilation strategies were associated with changes in broncho-alveolar plasminogen activator activity (both within groups and between groups), despite a slight upregulation of PAI-1 with HV_T/ZEEP ($p < 0.05$ vs. t = 0; **Figure 4**). tPA was increased in both groups (both $p < 0.001$ vs. t = 0; **Figure 4C**), slightly more in HV_T/ZEEP ventilation ($p < 0.05$ between groups).

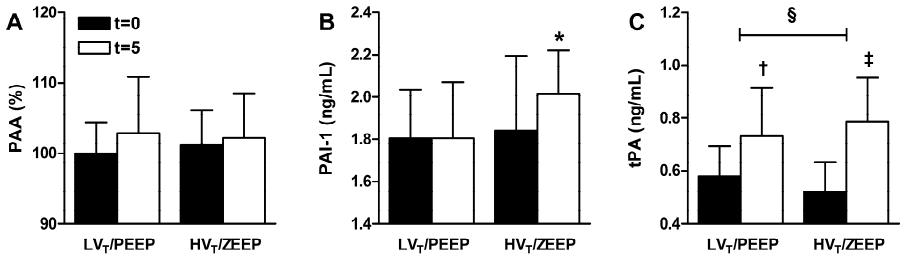

Figure 4 Plasminogen activator activity (PAA, ***A***), plasminogen activator inhibitor type-1 (PAI-1, ***B***), and tissue-type plasminogen activator (tPA, ***C***) in bronchoalveolar lavage fluid recovered at baseline (t = 0) and after 5 hours (t = 5) from patients mechanically ventilated with 6 ml/kg and 10 cmH_2O positive end-expiratory pressure (LV_T/PEEP, n = 21) or with 12 ml/kg and zero positive end-expiratory pressure (HV_T/ZEEP, n = 19). * Difference from t = 0 in HV_T/ZEEP ($p < 0.05$). † Difference from t = 0 in LV_T/PEEP ($p < 0.001$). ‡ Difference from t = 0 in HV_T/ZEEP ($p < 0.001$). § Intergroup difference ($p < 0.05$). Data are mean ± SD.

There was a trend towards lower levels of bronchoalveolar APC with HV_T/ZEEP as apposed to a trend towards higher APC with LVT/PEEP (**figure 5A**). Between group analysis did show a difference in changes of APC levels over time ($p < 0.05$ between groups). Mechanical ventilation with HV_T/ZEEP caused an increase in soluble thrombomodulin as measured in lavage fluids ($p < 0.05$ vs. t = 0; **figure 5B**), which was not with LV_T/PEEP.

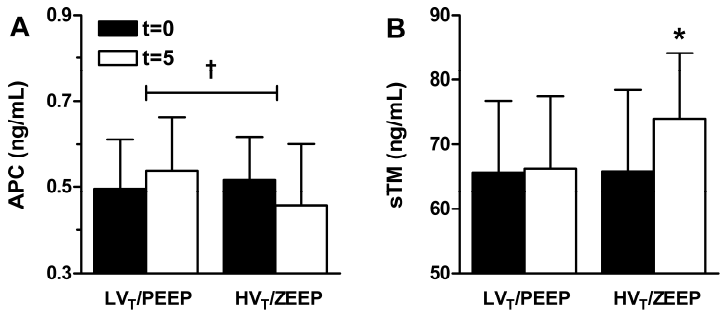

Figure 5 Activated protein C (APC, ***A***) and soluble thrombomodulin (sTM, ***B***) in bronchoalveolar lavage fluid recovered at baseline (t = 0) and after 5 hours (t = 5) from patients mechanically ventilated with 6 ml/kg and 10 cmH_2O positive end-expiratory pressure (LV_T/PEEP, n = 21) or with 12 ml/kg and zero positive end-expiratory pressure (HV_T/ZEEP, n = 19). * Difference from t = 0 in HV_T/ZEEP ($p < 0.05$). † Intergroup difference ($p < 0.05$). Data are mean ± SD.

Systemic Hemostasis

During surgery both systemic procoagulant and fibrinolytic activity were increased. In patients ventilated with HV_T/ZEEP, there was an increase in TATc (6.1 $\pm$ 0.76 vs. 5.78 $\pm$ 1.10 ng/ml, $p < 0.05$) and plasminogen activator activity (103 $\pm$ 5.9 vs. 99 $\pm$ 6.5 %, $p < 0.01$); in patients ventilated with LV_T/PEEP, there was also an increase in TATc (5.63 $\pm$ 1.13 vs. 4.86 $\pm$ 1.09 ng/ml, $p < 0.01$), but only a trend towards higher plasminogen activator activity (102 $\pm$ 8.7 vs. 99 $\pm$ 6.6 %). The changes over time were not different between the two mechanical ventilation strategies.

Postoperative Course

In the post-operative recovery, 28 patients had follow-up chest radiographs. There were no differences in post-operative arterial blood gas analyses (HV_T/ZEEP vs. LV_T/PEEP): pO_2 15.5 $\pm$ 5.6 vs. 16.4 $\pm$ 7.1 kPa, pCO_2 5.7 $\pm$ 0.6 vs. 5.6 $\pm$ 0.7 kPa, and pH 7.36 $\pm$ 0.053 vs. 7.34 $\pm$ 0.051. There were no differences in incidence of pulmonary complications (e.g., acute lung injury, pneumonia) between the two study groups; in each study group, there was one patient requiring prolonged mechanical ventilation for respiratory failure after surgery. One patient ventilated with LV_T/PEEP died postoperatively of multiple organ failure after complicated hemihepatectomy. All other patients were discharged home.

Discussion

Although mechanical ventilation with lower tidal volumes is generally considered to be protective in patients with acute lung injury, there is ongoing debate on the ideal tidal volumes in patients without pre-existent lung injury. We here demonstrated that

mechanical ventilation has significant effects on bronchoalveolar hemostasis: although the duration of mechanical ventilation was only 5 hours, and no differences were observed in clinical parameters during the surgical procedure or in the recovery phase, local procoagulant activity was increased in the group of patients with non-injured lungs ventilated with 12 ml/kg and without the use of PEEP. Furthermore, we showed that mechanical ventilation with lower tidal volumes and PEEP can largely prevent these procoagulant changes. Simultaneously, there is upregulation of plasminogen activation, which is not immediately reflected in increased fibrinolytic activity, perhaps – at least in patients ventilated with HV_T/ZEEP – because of inhibitory effects of PAI-1. And finally, we demonstrated that mechanical ventilation with HV_T/ZEEP causes generation of more soluble fragments of thrombomodulin in the bronchoalveolar spaces, potentially leading to an impaired activation of the protein C system. In summary, mechanical ventilation with HV_T/ZEEP seems to promote fibrin depositions within the airways by three mechanisms: increased procoagulant activity via the extrinsic pathway, a relative insufficiency of the anticoagulant protein C system, and inhibition of fibrinolysis by PAI-1.

A "multiple-hit" model of lung injury can be theorized whereby predisposing conditions, like injurious mechanical ventilation during surgery, may result in pulmonary inflammation (the “primary hit”). Then, several “second hits”, like transfusion of blood products [18], prolonged (injurious) mechanical ventilation [11,19], aspiration [10,20], shock or sepsis [10,20] and ventilator-associated pneumonia [21] may all cause additional lung injury, finally resulting in full-blown ARDS with high morbidity and mortality. Although the present study was not designed to investigate clinical outcome, no differences were observed in the postoperative course between the study groups. However, the alterations in bronchoalveolar hemostasis may indicate that mechanical ventilation potentially has harmful effects, even in patients without acute lung injury.

The presently described changes in pulmonary hemostasis are very similar as previously described in patients with pneumonia or ARDS [3-6], and human volunteers with endotoxin-induced pulmonary inflammation [17,22]. Consistently, increased procoagulant activity is reported, mostly related to the extrinsic coagulation pathway. It is likely that this activation is mediated by tissue factor expression on epithelial cells and mononuclear cells in the bronchoalveolar compartment. In the case of activation of epithelial and endothelial cells, either by pathogens, excessive inflammation, or – as probably is the case during mechanical ventilation – mechanical strain, there will be disruption of the endothelial-epithelial barrier. Transudation of plasma into the bronchoalveolar compartment will subsequently initiate coagulation within the airways. We speculate that this is the mechanism leading to immediate “sealing” of the damaged area, providing injury containment, and initiating other repair systems. Also, PAI-1 upregulation has been found consistently in patients with pneumonia [3-6], ARDS [4,7], and in our patients ventilated

with HV_T/ZEEP. Although in the current clinical settings, this did not lead to a suppression of fibrinolytic activity, it may well be possible that prolonged mechanical ventilation could lead to even higher levels of PAI-1 and more interference with fibrinolytic activity, as we demonstrated in patients developing ventilator-associated pneumonia [3,6]. tPA antigens levels were increased by ventilation with both low and high tidal volumes. This is in contrast to *in vitro* studies by dr. Günther's group in which various cell lines all showed a downregulation of tPA mRNA expression upon inflammatory stimuli [23]. The same group however reported in an in vivo model of endotoxin-induced lung injury, that tPA is indeed upregulated in both structural (alveolar type II cells, endothelial cells) and host defense cells (alveolar macrophages) in mouse lungs [24]. Also in our recent report on endotoxin-induced lung inflammation in human volunteers, increased levels of tPA were observed [17]. It is thought that this early activation of the fibrinolytic system is involved in tissue remodeling [25].

We have shown before that in patients with pneumonia protein C activation is suppressed, as well as after instillation of endotoxin in lungs of healthy volunteers [17,26]. Mechanical ventilation with HV_T/ZEEP induced shedding of sTM into the airspaces, which is generally believed to represent epithelial or endothelial damage. On the other hand, there was a trend towards lower levels of APC which was clearly opposite of the effect seen with LV_T/PEEP ventilation. Recombinant human APC (rhAPC) has been shown to reduce mortality in patients with severe sepsis [27], in whom protective effects are believed to be beyond its anticoagulant properties. Despite vast data from in vitro and animal studies, however, it is still unclear how rhAPC acts in vivo. Systemic administration of rhAPC has significant effects in the lungs [17,28], suggesting that pulmonary effects of rhAPC may contribute to patient survival. Indeed, in the pivotal phase III study in patients with sepsis, the majority of patients had a pulmonary origin and moreover, patients with pneumonia benefited mostly from rhAPC treatment [27,29,30].

All of the described effects shift the hemostatic balance towards a procoagulant side, promoting fibrin depositions in the airways. The question remains whether this reflects an adaptive mechanism with host protective functions, or whether it is a harmful process, predisposing the lungs to secondary complications or perhaps with long-term effects on pulmonary function. Fibrin deposition may be an important mechanism to repair endothelial or epithelial damage, however an exaggerated coagulation activation has been related to a number of detrimental sequelae. Coagulation products have important proinflammatory effects [31], and in addition, ongoing fibrin depositions inactivate surfactant proteins, causing alveolar instability and collapse. Importantly, various anticoagulant strategies have been shown to limit lung injury in experimental studies [32], but potential beneficial effects have to be confirmed in human patients.

To date, there have been few other reports on the effects of mechanical ventilation in patients with non-injured lungs. Gajic *et al*. [33,34] identified mechanical ventilation with higher tidal volumes as a risk factor for the development of acute lung injury in patients who did not have lung disease at the onset of mechanical ventilation. However, these patients were critically ill patients in an intensive care unit, developing ARDS after 48 hours or more. Wrigge *et al*. [12] recently showed that in patients undergoing major surgery with up to 3 hours of mechanical ventilation, the ventilation strategy did not affect pulmonary or systemic cytokine levels, suggesting that a brief period of mechanical ventilation does not affect patients without systemic inflammation. Most recently Wrigge *et al*. extended the duration of mechanical ventilation to 6 hours by selecting patients undergoing cardiac surgery [13]. Again, no systemic effects were observed, but postoperative levels of tumor necrosis factor alpha in bronchoalveolar lavage fluid were lower in patients ventilated with lower tidal volumes. However, measured cytokine levels were very low and highly variable. Therefore, we decided to lavage patients twice, immediately after initiation of mechanical ventilation, and 5 hours thereafter; this way, every patient would be his/her own control.

We here demonstrate for the first time that mechanical ventilation in patients with normal lungs induces a procoagulant shift in the alveolar hemostatic balance. Mechanical ventilation with lower tidal volumes and PEEP largely attenuates these changes in procoagulant activity within the airways. Clinical studies are warranted to establish the effects of prolonged mechanical ventilation (i.e., in an intensive care unit) on bronchoalveolar hemostasis, and the relationship between alveolar procoagulant activity and patient outcome.

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