Mechanical Ventilation with Lower Tidal Volumes and Positive End-expiratory Pressure Prevents Alveolar Coagulation in Patients without Lung Injury

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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. The authors sought to determine the effects of mechanical ventilation on the alveolar hemostatic balance in patients without preexistent lung injury.

Methods: Patients scheduled for an elective surgical procedure (lasting ≥ 5 h) were randomly assigned to mechanical ventilation with either higher tidal volumes of 12 ml/kg ideal body weight and no positive end-expiratory pressure (PEEP) or lower tidal volumes of 6 ml/kg and 10 cm H2O PEEP. After induction of anesthesia and 5 h 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 h 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 with 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.

PULMONARY inflammation is characterized by local generation of proinflammatory mediators and a procoagulant shift of the alveolar hemostatic balance, promoting fibrin deposits within the airways.1,2 Disturbances in alveolar fibrin turnover have been demonstrated in patients with pneumonia3–6 and acute respiratory distress syndrome (ARDS).5,7 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 pathophysiologic sequelae, including local generation of inflammatory mediators, constituting a pulmonary environment that is highly proinflammatory. Another hallmark of ventilator-associated lung injury in patients with severe lung injury is the activation of bronchoalveolar coagulation.5,6 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 preexistent lung injury would benefit from mechanical ventilation with lower tidal volumes, because 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 alteration 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 per-
formed comparing two mechanical ventilation strategies in patients without preexistent lung injury who were scheduled to undergo a major surgical procedure.

Materials and Methods

Patients

The study protocol was approved by the Medical Ethics Committee of the University of Amsterdam (Amsterdam, The Netherlands), and informed consent was obtained from all patients. Adult patients were eligible if they were scheduled to undergo a surgical procedure of 5 h or more, 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 thromboembolic 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⁻¹·h⁻¹), fentanyl (2–5 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 comparing two mechanical ventilation strategies (volume-controlled 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 calculated according to the formula as described before¹⁰ and no positive end-expiratory pressure (PEEP) or 6 ml/kg and 10 cm H₂O PEEP. Anesthesiologists were allowed to change the ventilation protocol at any time point upon the surgeon’s request, or if there was any concern about patient’s safety. If the surgical procedure exceeded 5 h, anesthesiologists were allowed to change the ventilation strategy after the second sampling (blood and bronchoalveolar lavage). Patients were followed up 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, and the second performed in the contralateral lung 5 h thereafter, either perioperatively or directly postoperatively. Lavage fluid was obtained as previously described.⁴,⁶,¹⁴ In short, 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 benzamidine were added to the lavage fluids to a final concentration of 10 and 20 mm, respectively. Citrated (0.109 m) blood samples were drawn before 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.⁵,⁶ To detect differences in bronchoalveolar TATc concentrations in the study groups at a two-sided significance level of 5% with a power of 80%, the number of patients to be studied in each group was at least 19. Baseline characteristics of the randomized patient groups were compared with the Student t test or Mann–Whitney U test, where appropriate. For categorical data, the chi-square test was used. Differences within groups were analyzed with a Wilcoxon signed-rank test for paired samples comparing t = 5 versus t = 0 h, and the 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 to undergo an elective surgical procedure of 5 h or more were screened in the period December 2003 through March 2005 (fig. 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 h), 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 the two randomization groups with regard to baseline characteristics (table 1).
There were no adverse events related to the bronchoalveolar lavages. One surgeon reported hepatic congestion and requested PEEP levels to be reduced (patient ventilated with lower tidal volumes and PEEP). Aside from the mechanical ventilator settings (tidal volume, PEEP, and respiratory rate), there were no significant differences in perioperative hemodynamic parameters (table 2 and fig. 2). In particular, peak pressures were not different between the study groups during 5 h of mechanical ventilation.

**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 h of mechanical ventilation (all \( P < 0.001 \) vs. \( t \) = 0; fig. 3). In patients ventilated with lower tidal volumes and 10 cm H\(_2\)O PEEP (LV T/PEEP), only soluble tissue factor was slightly increased (\( P < 0.01 \) vs. \( t \) = 0; fig. 3B) and far less pronounced than in patients with HV T/ZEEP (\( P < 0.001 \) between groups; fig. 3B).

Neither mechanical ventilation strategies were associated with changes in bronchoalveolar plasminogen activator activity (both within groups and between groups), despite a slight up-regulation of PAI-1 with HV T/ZEEP (\( P < 0.05 \) vs. \( t \) = 0; fig. 4). tPA was increased in both groups (both \( P < 0.001 \) vs. \( t \) = 0; fig. 4C), slightly more in HV T/ZEEP ventilation (\( P < 0.05 \) between groups).

There was a trend toward lower levels of bronchoalveolar APC with HV T/ZEEP as opposed to a trend toward higher APC with LV T/PEEP (fig. 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; fig. 5B), which was not with LV T/PEEP.

**Table 1. Baseline Characteristics of Patients**

<table>
<thead>
<tr>
<th></th>
<th>LV T/PEEP (n = 21)</th>
<th>HV T/ZEEP (n = 19)</th>
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<tbody>
<tr>
<td>Age, mean ± SD, yr</td>
<td>62 ± 9.8</td>
<td>61 ± 9.5</td>
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<tr>
<td>Male, n (%)</td>
<td>14 (67)</td>
<td>14 (74)</td>
</tr>
<tr>
<td>ASA, median (range)</td>
<td>2 (1–4)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>Height, mean ± SD, cm</td>
<td>176 ± 8.7</td>
<td>174 ± 10.0</td>
</tr>
<tr>
<td>Weight, mean ± SD, kg</td>
<td>79 ± 14.4</td>
<td>76 ± 13.7</td>
</tr>
<tr>
<td>IBW, mean ± SD, kg</td>
<td>70 ± 9.5</td>
<td>69 ± 10.6</td>
</tr>
<tr>
<td>Tobacco use, n (%)</td>
<td>9 (43)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Whipple procedure*</td>
<td>5 Laparoscopic radical prostatectomy</td>
<td>8 Whipple procedure*</td>
</tr>
<tr>
<td>6 Hemihepatectomy</td>
<td>2 Retroperitoneal tumor resection</td>
<td>3 Hemihepatectomy</td>
</tr>
<tr>
<td>2 Total pancreatectomy</td>
<td>1 Open prostatectomy†</td>
<td>1</td>
</tr>
</tbody>
</table>

* Whipple procedure is a pancreatoduodenectomy. † The open prostatectomy was performed after an initial laparoscopic approach.

ASA = American Society of Anesthesiologists (physical status classification); HV T/ZEEP = higher tidal volumes/zero positive end-expiratory pressure; IBW = ideal body weight; LV T/PEEP = lower tidal volumes/positive end-expiratory pressure.
Systemic Hemostasis
During surgery, both systemic procoagulant and fibrinolytic activity were increased. In patients ventilated with HVT/ZEEP, there was an increase in TATc (6.1 ± 0.76 vs. 5.78 ± 1.10 ng/ml; P < 0.05) and plasminogen activator activity (5.9 vs. 6.5%; P < 0.01); in patients ventilated with LV T/PEEP, there was also an increase in TATc (5.63 ± 1.13 vs. 4.86 ± 1.09 ng/ml; P < 0.01), but only a trend toward higher plasminogen activator activity (8.7 vs. 6.6%). The changes over time were not different between the two mechanical ventilation strategies.

Postoperative Course
In the postoperative recovery, 28 patients had follow-up chest radiographs. There were no differences in postoperative arterial blood gas analyses (HVT/ZEEP vs. LV T/PEEP): partial pressure of oxygen 117 ± 42 versus 123 ± 53 mmHg, partial pressure of carbon dioxide 43 ± 5 versus 42 ± 5 mmHg, and pH 7.36 ± 0.053 versus 7.34 ± 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 hemi-hepatectomy. 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 preexistent lung injury. We here demonstrated that mechanical ventilation has significant effects on bronchoalveolar hemostasis: Although the duration of mechanical ventilation was only 5 h 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 noninjured 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 up-regulation of plasminogen activation, which is not immedi-

![Table 2. Perioperative Parameters](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LV T/PEEP (n = 21)</th>
<th>HVT/ZEEP (n = 19)</th>
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<tbody>
<tr>
<td>MV duration, mean ± SD, min</td>
<td>304 ± 35</td>
<td>308 ± 52</td>
</tr>
<tr>
<td>Blood loss, median (IQR), ml</td>
<td>1,550 (800–2,325)</td>
<td>1,000 (463–1,675)</td>
</tr>
<tr>
<td>Transfused erythrocytes, median (IQR), units</td>
<td>0 (0–1.5)</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>Transfused plasma, median (IQR), units</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Colloids, median (IQR), l</td>
<td>0.5 (0.5–1.5)</td>
<td>0.5 (0.5–1.5)</td>
</tr>
<tr>
<td>Crystalloids, median (IQR), l</td>
<td>4.5 (2.75–5.75)</td>
<td>4.0 (2.5–5.5)</td>
</tr>
<tr>
<td>Lowest Hb, mean ± SD, mm*</td>
<td>6.0 ± 1.2</td>
<td>6.2 ± 1.0</td>
</tr>
<tr>
<td>Highest SBP, mean ± SD, mmHg</td>
<td>122 ± 17</td>
<td>135 ± 21†</td>
</tr>
<tr>
<td>Lowest SBP, mean ± SD, mmHg</td>
<td>82 ± 9.6</td>
<td>87 ± 14.9</td>
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* Hemoglobin (Hb), 1 mm = 1.61 g/dl. † Difference from LV T/PEEP (P < 0.05).

HVT/ZEEP = higher tidal volumes/zero positive end-expiratory pressure; IQR = interquartile range; LV T/PEEP = lower tidal volumes/positive end-expiratory pressure; MV = mechanical ventilation; SBP = systolic blood pressure.

![Fig. 2. Perioperative parameters. Tidal volumes (VT), respiratory rate (respir. rate), and maximal pressures (Pmax) 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). There are no significant differences in arterial blood gas analyses at any time point. Data are mean ± SD. Note 1 kPa = 7.5 mmHg. MV = mechanical ventilation; PacO₂ = partial pressure of alveolar carbon dioxide; PacO₂ = partial pressure of alveolar oxygen.](image)
Fig. 3. Thrombin-antithrombin complexes (TATC, A), soluble tissue factor (tTF, B), and factor Vila (FVila, C) in bronchoalveolar lavage fluid recovered at baseline (t = 0) and after 5 h (t = 5) from patients mechanically ventilated with 6 ml/kg and 10 cm H2O positive end-expiratory pressure (LVr/PEEP, n = 21) or with 12 ml/kg and zero positive end-expiratory pressure (HVr/ZEPP, n = 19). * Difference from t = 0 in LVr/ZEPP (P < 0.001). † Difference from t = 0 in LVr/PEEP (P < 0.01). ‡ Intergroup difference (P < 0.001). Data are mean ± SD.

Fig. 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 h (t = 5) from patients mechanically ventilated with 6 ml/kg and 10 cm H2O positive end-expiratory pressure (LVr/PEEP, n = 21) or with 12 ml/kg and zero positive end-expiratory pressure (HVr/ZEPP, n = 19). * Difference from t = 0 in HVr/ZEPP (P < 0.05). † Difference from t = 0 in LVr/PEEP (P < 0.001). ‡ Difference from t = 0 in HVr/ZEPP (P < 0.001). § Intergroup difference (P < 0.05). Data are mean ± SD.
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. Mechanical ventilation with high tidal volumes induced shedding of soluble thrombomodulin into the airspaces, which is generally believed to represent endothelial or epithelial damage. On the other hand, there was a trend toward lower levels of APC, which was not statistically significant. The question is whether pulmonary effects of rhAPC may contribute to patient survival. 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.

All of the described effects shift the hemostatic balance toward a procoagulant side, promoting fibrin deposition 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, these patients were critically ill patients in an intensive care unit, developing ARDS after 48 h or more. Wrigge et al. recently showed that in patients undergoing major surgery with up to 3 h 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 h by selecting patients undergoing cardiac surgery. Again, no systemic effects were observed, but postoperative levels of tumor necrosis factor α 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 h thereafter; this way, every patient would be his or 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 relation between alveolar procoagulant activity and patient outcome.

References

COAGULATION IN MECHANICALLY VENTILATED LUNGS


19. Ranieri VM, Giunta F, Suter PM, Sluiter AS. Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA 2000; 284:43–4


