Lung protective mechanical ventilation
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PART IV: General Discussion
Chapter 17

General Discussion

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Introduction

Mechanical ventilation (MV) is an indispensable tool in the treatment of patients with acute respiratory failure and is mandatory during general anesthesia. However, MV induces lung injury in healthy lungs and aggravates pre–existing lung injury in patients suffering from acute lung injury (ALI) or its more severe form acute respiratory distress syndrome (ARDS). Injury caused by MV is frequently referred to as ventilator–induced lung injury (VILI) in animals or ventilator–associated lung injury (VALI) in human subjects. All mechanically ventilated patients are at risk for VALI.

One of the prevailing mechanisms thought to be responsible for causing VILI/VALI is mechanical over–distension of alveoli due to large (or too large) tidal volumes (VTs). The impact of mechanical over–distension on patient outcome is clearly demonstrated in one ARDS Network trial. Indeed, in patients suffering from ALI/ARDS mortality declines with the use of lung–protective MV using lower VT (6 ml/kg predicted body weight [PBW]) as compared to conventional MV (VT of 12 ml/kg PBW). Another mechanism which may be associated with the development of VILI/VALI is repeated recruitment and de–recruitment of unstable lung units, also called “low end–expiratory lung volume (EELV) injury”. Recruitment and de–recruitment may be avoided by application of sufficient levels of positive end–expiratory pressure (PEEP), high enough to increase the EELV to above the volume at which airway closure occurs.

During VILI/VALI biophysical forces are thought to be responsible for alteration of normal cellular physiology in the lungs, leading to a proinflammatory milieu, disturbances in alveolar fibrin turnover and changes in pulmonary repair, remodeling and mechanisms influencing programmed cell death.

Studies as described in this thesis focus on implementation of lung–protective MV with lower VT in the intensive care unit (ICU). The effects of using lung–protective MV in patients with non–injured lungs in the operation room are studied. In addition, the effects of lower VT as compared with higher VT are studied in pre–clinical models of MV in mice and rats.

Implementation of lung–protective mechanical ventilation

Initially the implementation of lung–protective MV using lower VT was severely hampered in patients with ALI/ARDS. Indeed, several studies from different centers, including those that participated in one ARDS Network trial, showed this strategy not to be routinely practiced in ALI/ARDS patients for many years. In chapter 2 several factors that hampered implementation of lower VT in patients with ALI/ARDS are discussed. One frequently heard argument against the use of lower VT was that MV in the control arm of the ARDS Network trial in fact was a harmful MV–strategy. Other concerns with the use of lower VT included
the fear that this strategy would increase the need for supportive therapies, including sedation and neuromuscular blockade. Furthermore, incorrect translation of parts of the study protocol on the use of lower $V_T$ may have obstructed, at least in part, broad implementation of lower $V_T$ for a long time. Indeed, while $V_T$ was titrated on PBW (the ideal body weight of patients as a function of height) in the ARDS Network trial, many ICU–physicians and respiratory therapists used actual body weight (ABW) instead. This incorrect translation resulted in $V_T$s becoming too large, in particular in obese patients. In chapter 3 we demonstrate that estimation of height and weight by ICU–nurses in patients admitted to the ICU is adequate in general. Height is generally better estimated than weight. Overestimation of height occurs particularly in the shortest patients, whereas overestimation of weight occurs especially in patients with a low body mass index. When measuring of height of ICU–patients is sufficient, care–givers only need to calculate PBW for correct calculation of VT. Chapter 4 and 5 describe one implementation intervention on lower $V_T$ ventilation, called “feedback and education”. In this study, feedback and education consisted of presenting the actually applied ventilator settings, the advised or suggested ventilator settings with respect to $V_T$ (as mentioned in the local guidelines on MV), followed by a discussion on potential reasons for not using lower $V_T$ and the importance of closely adjusting $V_T$ to PBW (instead of using ABW). This intervention led to a better adoption of lower $V_T$–strategy in our institution. Chapter 6 describes a secondary analysis of the intervention study as described in chapter 4. We compared the use of opioids and sedatives in patients ventilated with lower $V_T$ versus those ventilated with conventional $V_T$ in our ICU. Neither the proportion of patients receiving opioids or sedatives, nor the prescriptions at individual time points of these agents differed between before and after the implementation intervention. Thus, concerns regarding sedation requirements with the use of lower $V_T$ are unfounded and should not preclude its use.

In conclusion, implementation of a lower $V_T$ MV–strategy is rather simple. The need for correct calculation of $V_T$, by using PBW and not ABW, must be emphasized. Commonly heard concerns about increased use of sedation does not apply for MV with lower $V_T$.

Lung–protective mechanical ventilation in patients with non–injured lungs

Currently, there are guidelines that strongly support the use of lower $V_T$ in patients with ALI/ARDS. Widely–agreed upon guidelines for setting $V_T$ in patients who do not meet the ALI/ARDS consensus criteria are lacking, partly because there is a paucity of randomized controlled trial evidence on the best way to ventilate these patients. Moreover, it is unclear whether MV per se can induce VALI in patients with non–injured lungs. However, retrospective clinical studies suggest that the use of large $V_T$ favors the development of lung injury. Chapter 8 – 10 describe the results of a randomized controlled trial in which surgical patients with non–injured lungs and expected to be ventilated for at least 5 hours were either ventilated with $V_T$ of 12 ml/kg PBW and no PEEP or a lung–protective MV–
strategy with \( V_T \) of 6 ml/kg PBW and 10 cmH\(_2\)O PEEP. In contrast to MV with lower \( V_T \) and PEEP, the use of conventional \( V_T \) and zero PEEP causes activation of pulmonary coagulation, as reflected by a marked increase in thrombin–antithrombin complexes, soluble tissue factor, and factor VIIa. In addition, MV with conventional VT and no PEEP causes an increase in soluble thrombomodulin levels, which is generally believed to represent epithelial or endothelial damage and lower levels of activated protein C in comparison with lower \( V_T \) and PEEP (chapter 8). MV with lower \( V_T \) and PEEP attenuates the increase of pulmonary levels of interleukin 8, myeloperoxidase and elastase as seen with higher VT and no PEEP (chapter 9).

It can be hypothesized that MV affects epithelial integrity of the lungs even with short–term MV. Several biological markers such as Clara cell protein (CC16), soluble receptor for advanced glycation end products (sRAGE), surfactant protein (SP)–A and SP–D have been shown to be increased in sera of patients with ALI/ARDS. However, CC16, sRAGE, SP–A and SP–D are not different with the two different MV–strategies. Systemic levels of CC16 and sRAGE increase significantly in both groups, while systemic levels of SP–A and SP–D remain unchanged (chapter 10).

The high–mobility group box (HMGB)–1 is a recently discovered mediator of pro-inflammatory responses that contributes to ALI. In chapter 11 we demonstrate that long–term MV (days) is associated with increased pulmonary (HMGB)–1 levels in contrast to short–term MV (hours) in patients with non–injured lungs. In addition, HMGB–1 levels during ventilator–associated pneumonia are increased compared with healthy volunteers; however, pulmonary (HMGB)–1 levels are not different from those found in patients intubated and mechanically ventilated for a similar period of time.

In conclusion, conventional MV with high \( V_T \) (12 ml/kg PBW) and zero PEEP for as short as 5 hours in patients with non–injured lungs already can cause lung injury, as seen by an increase in pulmonary inflammation and coagulation.

**Mechanical ventilation in pre–clinical studies**

In most models of VILI unphysiological large \( V_T \) s are being used. Too large \( V_T \) s potentially lead to hemodynamic instability and as such may hamper extrapolation of study results to the clinical setting. Indeed, such models may be merely seen as “shock”–models than models of VILI. In addition, mice frequently develop metabolic acidosis which may influence frequently used endpoints of VILI. For this reason we aimed at setting up a more realistic VILI model in mice, using more physiological \( V_T \) s.

In chapter 12 we describe a more physiological model of VILI in two commonly used mice strain (C57Bl/6 and BALBc). The settings of the ventilator in this model resulted in lower \( V_T \) ~ 7.5 ml/kg and higher \( V_T \) ~ 15 ml/kg. We obtained baseline acid–base parameters from
spontaneously breathing mice and used these as a reference. To correct for hypovolemia during 5 hours of MV, saline or sodium bicarbonate was used: infusion of sodium bicarbonate completely compensated for the metabolic acidosis seen with saline infusion. With high Vr, VILI developed in both mice strain. This model was used for the testing of several hypothesis in the pathogenesis of VILI.

Additional strategies to attenuate pulmonary inflammation and/or coagulation may be useful to further reduce VILI/VALI. In a series of studies we tested different strategies in our murine VILI model (chapter 13 – 15): we investigated one anti-inflammatory strategy (tumor necrosis factor–alpha (TNF) inactivation), one anticoagulant strategy and one pro-fibrinolytic strategy.

VILI possesses a significant TNF–dependent component. We therefore studied the effect of recombinant human soluble TNF receptor fusion protein (etanercept) on VILI in our mice model (chapter 13). Inhibition of TNF activity by etanercept attenuates VILI–associated inflammatory changes (less pulmonary neutrophils and lower pulmonary cytokine levels) as well as ventilator–induced coagulopathy. Wet to dry ratio, histopathology score, local protein level in bronchoalveolar lavage fluid (BALF), other frequently used endpoints of VILI, are not influenced by etanercept treatment, however.

Coagulopathy is a feature of VILI and tissue factor (TF) seems to play an important role in the pathogenesis of disturbed alveolar fibrin turnover. Pharmacologically targeting pulmonary coagulopathy may be of benefit to patients with lung injury. We therefore investigated the role of TF in our VILI–model in mice by using heterozygous TF knockout mice (TF+/-) (chapter 14). MV results in pulmonary coagulopathy in wild type animals, as reflected by increased thrombin–antithrombin complexes. This procoagulant response is largely attenuated in TF+/- mice. However, relative TF deficiency does not reduce VILI. Indeed, relative TF deficiency even seems to induce more pulmonary inflammation.

Plasminogen activator inhibitor (PAI)–1, the main inhibitor of fibrinolysis, is upregulated during pulmonary inflammation. In patients with ALI/ARDS elevated plasma levels of PAI–1 are associated with mortality and adverse clinical outcomes. We determined the role of PAI–1 in the pathogenesis of ventilator–induced coagulopathy (chapter 15). For this we used PAI–1 gene deficient mice (PAI–1-/-) in our VILI model. PAI–1 gene deficiency attenuates neutrophil recruitment into the lung, while pulmonary levels of cytokines and chemokines are increased. No differences are seen for wet to dry ratio, total protein level in BALF and histopathology between wild type and PAI-1-/- mice. These results suggest PAI–1 to play a stimulatory role of neutrophil migration into the alveoli, which is independent of local production of chemokines.
Finally, in a model of LPS–induced lung injury in rats we demonstrated that MV creates an alveolar anti–fibrinolytic milieu, at least in part, due to an increase in PAI activity (chapter 16).

In conclusion, different interventions in our murine model on mechanical ventilation showed us more insight into the pathogenesis of VILI. We have intervened with inflammation, coagulation and fibrinolysis in the course of VILI.

Conclusions
Adoption of a lower V₁ MV–strategy has been rather slow. One of the hampering factors in our institution was the difficulty with the interpretation of the lower V₁–protocol, as described by the ARDS Network. We emphasize the importance of titrating V₁ on PBW as a function of height, instead of ABW.

The results of our randomized controlled trial have clinical implications for ventilating patients with non–injured lungs, not only in the operation room but maybe also in the intensive care unit. We propose lung injury to be a “multiple–hit” entity, wherein predisposing conditions, such as injurious MV or major surgery may result in pulmonary inflammation. Possible second hits, such as transfusion of blood products which may cause transfusion–related acute lung injury, prolonged (injurious) MV, aspiration, shock, sepsis, and pulmonary infection, may all cause additional lung injury. Based on our findings we propose to use lower V₁ and sufficient levels of PEEP in all mechanically ventilated patients: VALI can and should be limited.

We demonstrate that MV can induce pulmonary coagulopathy, with activation of coagulation, inhibition of fibrinolysis and natural anticoagulant activity. Coagulopathy plays a role in VILI/VALI. Local changes in alveolar coagulation and fibrinolysis resemble those found systemically in patients with sepsis. Recent studies have demonstrated the beneficial effect of anticoagulant therapy in sepsis. The potential role of anticoagulant and pro–fibrinolytic therapy in the treatment of VALI remains to be established in future experimental and clinical studies.