Lung protective mechanical ventilation

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PART III: Lung-Protective Mechanical Ventilation Attenuates Pulmonary Inflammation and Coagulopathy
Chapter 7

Ventilator–Induced and Ventilator–Associated Lung Injury – Inflammation and Coagulation a review

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**Introduction**

Increasing evidence from investigations in animals with experimental lung injury and studies in patients suffering from acute lung injury/acute respiratory distress syndrome (ALI/ARDS) suggest that mechanical ventilation (MV), frequently mandatory in patients with acutely injured lungs, aggravates and maybe even initiates pulmonary damage. This phenomenon is frequently referred to as “ventilator–induced lung injury” (VILI) in animals [1] and “ventilator–associated lung injury” (VALI) in humans [2]. Alveolar overdistension and/or repetitive opening and closing of atelectatic lung units are thought to play a causal role in the pathogenesis of VILI/VALI. The resulting inflammatory processes with VILI/VALI, at least in part, involve local activation of various immune cells and confined production of cytokines and chemokines [1]. Recently, it has been demonstrated that the inflammatory processes with VILI/VALI also involve alveolar coagulopathy, which is the net result of local activation of coagulation and inhibition of fibrinolysis [3].

Elevated levels of cytokines are found in plasma of patients with ALI/ARDS who are mechanically ventilated with injurious ventilator settings, suggesting MV–induced spill of these mediators from the lung into the systemic circulation [4,5]. Similarly, systemic coagulopathy has been found in mechanically ventilated ALI/ARDS–patients [6]. MV–induced loss of compartmentalization of pulmonary inflammation and coagulopathy is frequently referred to as “ventilator–associated systemic inflammation” (VASI) [7]. Worth mentioning, the systemic appearance of cytokines and systemic coagulopathy is associated with the development of multiple organ failure (MOF), thereby increasing morbidity and mortality of patients with ALI/ARDS.

In this chapter the role of inflammation and coagulation in VILI/VALI and VASI is reviewed. In addition it is discussed whether MV can cause lung injury by itself (i.e., in the absence of ALI/ARDS).

**Pulmonary inflammation and coagulation**

Pulmonary host defense consists of innate and acquired immune defense systems. Both systems consist of cellular and humoral components. The cellular components include resident alveolar macrophages, recruited polymorphonuclear cells, and epithelial/endothelial cells. These cells closely communicate in mounting an effective inflammatory response (e.g., in reaction to invading pathogens) [8].

Cytokines and chemokines, two of the humoral components of inflammation, are small glycoproteins that are produced by a large variety of cells and have effects on many different cell types. Cytokines play a crucial role in the initiation, maintenance, and finally, resolution of local inflammation. Chemokines, cytokines with chemotactic properties, attract immune cells to the site of infection.
With systemic inflammation, cytokines activate coagulation via tissue factor and attenuate fibrinolysis by stimulating the release of inhibitors of plasminogen activators [9]. Since pulmonary inflammation involves local production of cytokines, it is not surprising that pulmonary infection causes similar but local haemostatic disturbances.

**Pulmonary inflammation with ALI/ARDS and/or MV**

**ALI/ARDS**

Several studies have demonstrated high levels of cytokines in bronchoalveolar lavage fluids (BALF) and plasma of patients with ALI/ARDS [10-14]. Ratios of local to systemic cytokine concentrations are elevated, suggesting a pulmonary origin [12,13,15]. During clinical development of severe ARDS, BALF cytokine levels increase early in the course of ARDS, while they declined later on [11,13,14]. Furthermore, in patients with sustained ARDS, BALF cytokine levels correlate with survival (i.e., higher levels are found in patients who die) [10,16]. Unfavorable outcome in ARDS is also related to elevated plasma cytokine levels [16].

Like cytokines, chemokines are present in the airways of patients with ALI/ARDS [10,11,17-21]. Elevated BALF levels of interleukin 8 are found in patients with pneumonia and ARDS as compared to healthy subjects, and levels of interleukin 8 are significantly higher in patients with ARDS than in patients with pneumonia [17].

**Animal models of MV–induced inflammation**

Repetitive (over)–stretching of diverse pulmonary cells (as an analogue for MV with (too) large tidal volumes) induces cytokine production [22,23]. Repetitive stretching can also intensify production of cytokines by previously stimulated pulmonary cells or alveolar macrophages [22,24,25]. The effect of (too) large tidal volumes on cytokine production has also been demonstrated in several *ex vivo* studies. Low levels of cytokines are being found in rat lungs ventilated with normal volumes, while high levels are found in rat lungs ventilated with large tidal volumes [26-28]. To study more accurately the effects of MV on cytokine production, *in vivo* studies have been performed [29-31]. Similar to *ex vivo* studies MV induces local production of inflammatory mediators. Of note, pretreatment with cytokine–blocking agents (anti–tumor necrosis factor alpha–antibodies, interleukin 1 receptor antagonist, or neutralizing antibodies against chemokines) attenuates MV–induced lung damage [29,32,33].

Some animal studies have demonstrated that MV can cause loss of compartmentalization [34-36]. Indeed, in various models of lung injury with injurious ventilator settings high concentrations of cytokines are found in lung perfusates [36], and higher systemic levels of cytokines are found with injurious MV suggesting release of cytokines into the systemic
circulation [34,35]. These results are in line with those from another study, showing loss of compartmentalization due to MV in respect to bacteria [37].

**VALI and VASI in patients with ARDS**

Protective MV–strategies aim at reduction of mechanical stress through use of lower tidal volumes and/or higher PEEP–levels. Several studies have studied these concepts in patients with ARDS [38-42]. Of them, 2 demonstrated a beneficial effect of a protective MV–strategy on mortality [38,39]. In one study protective MV was found to attenuate a rise of systemic cytokine levels [38]. In another study in patients with ARDS, in contrast to patients who were ventilated with conventional MV, patients who were ventilated with protective MV showed a reduction of pulmonary as well as systemic levels of several cytokines and chemokines over time [4]. Importantly, a significant correlation was demonstrated between changes in the multi–system organ failure (MSOF) score and changes in systemic cytokine levels [5].

In conclusion, protective MV clearly reduces mortality in patients with ALI/ARDS. From the available studies it can be concluded that protective MV–strategies result in less cytokine production and reduced decompartmentalization. It is very suggestive that reduced mortality with protective MV in patients with ALI/ARDS is the result of attenuation of cytokine production and spill of cytokines into the systemic circulation.

**Pulmonary coagulopathy with ALI/ARDS and/or MV**

**ALI/ARDS**

Prominent changes in the alveolar haemostatic balance are found in alveolar pneumonia and bronchopneumonia [43]. The profile and extent of these changes in severe pneumonia demanding MV are nearly identical to those in ARDS [43,44], while less prominent alterations of fibrin turnover have been measured in spontaneously breathing patients with pneumonia [43]. Similar to pulmonary cytokine production with pulmonary inflammation [45,46], pulmonary coagulopathy is a localized process, with changes in fibrin generation being restricted to the site of infection in patients with community–acquired pneumonia [47] or ventilator–associated pneumonia [48]. In patients with ARDS increased procoagulant activity in BALF has been demonstrated. In addition, in ARDS inhibition of coagulation completely abrogates intrapulmonary fibrin deposition [49].

**Animal models of MV–induced pulmonary coagulopathy**

Presently, there is little information on the influence of MV on pulmonary fibrin turnover. Only a few animal studies suggest that pulmonary fibrin turnover is influenced by MV [50,51]. In a rat model of artificial pulmonary coagulopathy, MV with larger tidal volumes attenuated the fibrinolytic activity [50]. This appeared to be caused by increased
Inflammation

In a single-center observational cohort study, Gajic et al. reported a significant variability in the initial tidal volume settings in mechanically ventilated patients without ALI/ARDS [52]. Of patients ventilated for longer than 2 days who did not have ALI/ARDS at the onset of mechanical ventilation 25% developed ALI/ARDS within 5 days. The main risk factors associated with the development of lung injury were the use of large tidal volumes in addition to transfusion of blood products, and acidemia. Of note, female patients were mechanically ventilated with larger tidal volume (per kg predicted bodyweight [PBW]) and tended to develop lung injury more often.

In a large sample of patients prospectively enrolled in a multi-center international study on mechanical ventilation of intensive care unit patients [53] the same investigators confirmed these findings [54]. Indeed, development of ALI/ARDS was associated with large tidal volumes.

Deleterious clinical effects of large tidal volumes have also been suggested in patients that were ventilated for only several hours. Fernandez et al. collected intraoperative tidal volumes of pneumonectomy patients [55]. Of these patients, 18% developed postoperative respiratory failure; in half of the cases these patients developed ALI/ARDS, according to the consensus criteria. Patients who developed respiratory failure had been ventilated with larger intraoperative tidal volumes than those who did not. Multivariate
logistic regression analysis demonstrated larger intraoperative tidal volumes in addition to larger volumes of intraoperative fluid were identified as a risk factor of postoperative respiratory failure.

Several investigators have prospectively tested the hypothesis that mechanical ventilation settings could be deleterious and induce or alter pulmonary inflammation in patients without lung injury at the onset of mechanical ventilation. Unfortunately, until now studies have only been performed in patients who were ventilated for a short time (i.e., in the operating rooms or for a short period in the postoperative phase).

In one study in a surgical intensive care unit patients were randomly assigned to mechanical ventilation with tidal volumes of 12 ml/kg or lower tidal volumes of 6 ml/kg [56]. Duration of intubation and length of stay tended to be shorter and the incidence of pulmonary infection tended to be lower for patients randomized to the lower tidal volume strategy, suggesting that morbidity may be decreased. Although use of lower tidal volumes was associated with a statistically significant decrease in oxygenation, this was clinically irrelevant. In a recent study, patients undergoing planned oesophagectomy for cancer were randomly assigned to a conventional ventilation strategy (tidal volumes of 9 ml/kg during two–lung and one–lung ventilation) or a protective ventilation strategy (tidal volumes of 9 ml/kg during two-lung ventilation, reduced to 5 ml/kg during one-lung ventilation) [57]. The protective strategy resulted in higher PaO2/FiO2 ratio during one–lung ventilation and 1 hour after surgery and in a reduction of postoperative mechanical ventilation duration.

Other studies investigated the production of inflammatory mediators with different tidal volumes, either in the operating room or in the postoperative period. Opposite to some reports that did not show any effect of larger tidal volumes in patients with non–injured lungs [58-60], several articles did display injurious effects of large tidal volumes. In one study on postoperative mechanical ventilation after cardiopulmonary bypass surgery, mechanical ventilation with tidal volumes of 6 ml/kg PBW resulted in significantly lower bronchoalveolar lavage fluid tumor necrosis factor alpha levels as compared to tidal volumes of 12 ml/kg PBW [61]. These results were confirmed by others, who showed that the use of large tidal volumes of 10–12 ml/kg resulted in an increase of bronchoalveolar lavage fluid and plasma interleukin 6 and interleukin 8 levels as compared to lower tidal volumes of 8 ml/kg [62].

Coagulopathy

At present, no studies have been performed on the effects of MV on pulmonary coagulopathy in humans without lung injury.
Conclusion

From numerous *in vitro* –, *ex vivo* – and *in vivo* experiments we conclude that repetitive (over)–stretching and opening and closing of atelectatic lung parts induce local production of inflammatory mediators, such as cytokines and chemokines, and coagulopathy.

Unfortunately, many of the injurious MV–modes used in *ex vivo* models of MV are rapidly fatal in real life. Furthermore, interpreting the results from *in vitro*– and *ex vivo* experiments is difficult because cardiopulmonary interactions are not taken into account.

Several studies suggest that MV can induce lung injury by itself, i.e., also in patients without ALI/ARDS. Additional studies are needed to determine whether protective MV–strategies, as applied in patients with ALI/ARDS, should be used in patients with healthy lungs as well.
References

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