Ventilator-induced lung injury, cytokines, PEEP, and mortality: implications for practice and for clinical trials

Introduction

A mainstay in the supportive care of patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is mechanical ventilation. However, a number of animal and clinical studies have demonstrated that mechanical ventilation itself can worsen preexisting lung injury and produce ventilator-induced lung injury (VILI). Although the most obvious clinical abnormalities of ALI/ARDS are related to lung function, the most common cause of death is dysfunction of other organs, termed multiple organ dysfunction syndrome (MODS) [1], which is commonly accompanied by the systemic inflammatory response syndrome (SIRS). SIRS/MODS is a complex syndrome, often precipitated and intensified by a series of events rather than a single event. Recent clinical trials have demonstrated that in patients with ARDS, protective ventilatory strategies are associated with decreased serum cytokine levels [2, 3], decreased levels of organ dysfunction [3, 4], and decreased mortality [3, 5], perhaps by partially mitigating the development of MODS [6].

There are a number of factors that can precipitate the development of ALI/ARDS, including sepsis, shock, trauma, and aspiration of gastric contents. Among these sepsis is the leading cause and the major contributor to mortality in most ICUs [1, 7, 8]. Thus investigation of the impact of ventilatory strategy in the context of sepsis is of great interest. In their contribution to Intensive Care Medicine Herrera and colleagues [9] take a molecular approach to the study of VILI, systemic inflammatory cytokines, and mortality using an in vivo rat sepsis model produced by cecal ligation and perforation. They found that the application of positive end-expiratory pressure (PEEP) above the lower inflection point (LIP) of the respiratory system pressure-volume curve decreased pulmonary and systemic inflammatory cytokines [tumor necrosis factor (TNF) α and interleukin (IL) 6] as well as mortality in septic animals ventilated with low tidal volume (V_{T}: 6 ml/kg), but when higher PEEP levels were applied with high V_{T} (20 ml/kg), cytokines and mortality increased. The strengths of the study are the use of a clinically relevant injury model of sepsis and the use of multiple endpoints including mortality. However, it would have been interesting to have had data on the effect of the ventilatory strategies on hemodynamics, especially with large V_{T} and PEEP. Mechanical ventilation, in particular application of PEEP and use of large V_{T}, can have detrimental effects on systemic and regional hemodynamics as well as on global oxygen delivery and consumption, as highlighted in many excellent reviews [10, 11, 12]. It is likely that the use of high tidal volumes in conjunction with the high PEEP levels led to significant hemodynamic consequences and contributed to the mortality in this group.

Surrogate endpoints

One of the major problems facing clinical researchers in the context of trials in mechanical ventilation and ARDS is the need to enroll very large numbers of patients if mortality is used as the primary endpoint. The recent ARDSNet trial required over 800 patients to detect a 22% (relative) reduction in mortality in patients with ARDS treated with smaller tidal volumes. As therapies...
improve and as mortality decreases, studies with even more patients will be required to find a similar decrease in mortality. One approach to mitigate this serious problem is to identify appropriate surrogate (also called intermediate) endpoints that can be used instead of mortality. Cytokines/chemokines are reasonable candidates to act as surrogate endpoints since they are continuous variables and hence the sample size required to reach statistical significance would be expected to be substantially less than with a binary variable such as mortality. An important criterion for an intermediate endpoint is that it should have “biological plausibility,” i.e., there should be a plausible mechanistic link by which changes in the surrogate endpoint could lead to changes in mortality. There is a growing body of evidence suggesting biological plausibility with respect to the use of cytokines in this regard. In vitro mechanical strain has been shown to cause release of a number of mediators from a variety of lung cells including alveolar epithelial cells, endothelial cells, macrophages, fibroblasts, and smooth muscle cells [13, 14, 15, 16, 17]. Ex vivo, injurious ventilatory strategies in both isolated non-perfused rat lungs and isolated perfused mouse lungs have demonstrated an increase in release of inflammatory mediators [18, 19]. In vivo, Chiumello and colleagues [20] found increases in pulmonary and systemic inflammatory cytokines (TNF-α and macrophage inflammatory protein 2) after injurious mechanical ventilation using an in vivo rat acid aspiration model. There are also human data indicating the potential importance of cytokines. Patients with ARDS randomized to receive a conventional mechanical ventilation strategy had higher levels of a number of BAL and serum cytokines than patients who received a protective ventilatory strategy with PEEP set above the LIP [2], as in the study by Herrera et al.

Recently it has been shown that inflammatory cytokines/chemokines can modulate apoptosis in various cell types [21], and increased apoptosis has been detected in animal models of cecal ligation and perforation [22, 23] as well as in patients dying of sepsis and MODS [24]. We have recently proposed a possible mechanism to explain the decreased MODS observed with a protective ventilatory strategy [25]. Using a rabbit acid aspiration model we found increases in kidney epithelial cell apoptosis in the animals treated with a relatively injurious ventilatory strategy. This increased apoptosis appeared to be related to soluble Fas ligand, a potent pro-apoptotic factor.

The key issue, however, in relation to whether cytokine levels are good surrogate markers in ventilation trials is whether they are correlated with mortality. In this regard the current study is both encouraging and discouraging. The group of patients who had the lowest mortality also had the lowest levels of TNFα and IL-6, but the group that had the highest mortality (large V_T and high PEEP) did not have the highest cytokine levels. This is not surprising. First, animals that died before 3 h did not have cytokine serum cytokine levels measured —if cytokines are important, this would bias the results against finding high levels in the group with the highest mortality. Second, even if cytokines are important in the context of the VILI, they are certainly not the only important factor. It is very likely that the high airway pressure group in the Herrera study had the worst hemodynamics which was likely a major contributing factor to mortality in this group. The use of surrogate markers will have to take into account major physiological derangements which play a major role in outcome. Finally, the current studies were of a short duration, and the major impact of increased cytokine levels would be on a much longer timeframe.

Increased alveolar-capillary permeability

One interesting question is the source of the increased systemic proinflammatory mediators in the study by Herrera. There is evidence that VILI induces cytokine release from epithelial cells in the lung [13, 14, 15, 16, 26], although macrophages and neutrophils are also likely to be quite important. Loss of compartmentalization of local pulmonary inflammatory mediators due to mechanical ventilation has been recently proposed. The alveolar barrier restricts transport of macromolecules of a size similar to that of cytokines (15–20 kDa). After secretion in the lung, cytokines such as TNF-α remain in the alveolar space and leak into the circulation only if there is injury of the alveolar barrier. Several investigators have shown that increased permeability of the alveolar-capillary interface, as a result of lung injury leads to the release of mediators into the circulation that would normally have remained compartmentalized within the alveolar space [27, 28]. Tutor and colleagues [27] employed an isolated perfused rat lung model in which they injected TNF-α into the lung and measured its appearance in the perfusate. They found that the perfusate TNF-α concentrations were increased only when alveolar-capillary permeability was increased and not in normal lung, suggesting that loss of compartmentalization of alveolar TNF-α could occur, but only in the context of damage to the alveolar-capillary membrane. Von Bethmann and colleagues [18] reported that in an isolated perfused murine lung model, ventilation with higher transpulmonary pressure (25 cmH2O) vs. normal pressure (10 cmH2O) led to a significant increase in concentration of both TNF-α and IL6 in the perfusate. As compartmentalization of the local pulmonary response is lost, systemic release of inflammatory mediators may promote the massive inflammatory response that underlies MODS.

Recently Stuber and colleagues [29] studied patients with ALI and found that switching to conventional mechanical ventilation (V_T of 12 ml/kg, PEEP of 5 cmH2O)