Systemic Effects of Mechanical Ventilation

Y. Imai and A. S. Slutsky

Introduction

The acute respiratory distress syndrome (ARDS) is a serious form of acute lung injury (ALI) that has a mortality rate of at least 30%. A mainstay in the supportive care of patients with ARDS/ALI is mechanical ventilation. However, a number of animal and clinical studies have shown that mechanical ventilation itself can worsen preexisting lung injury and produce ventilator-induced lung injury (VILI). Although the most obvious clinical abnormalities of ARDS are related to lung function, the most common cause of death is dysfunction of other organs, termed multiple organ dysfunction syndrome (MODS) [1]. One hypothesis that has recently been advanced to explain this observation is that mechanical ventilation *per se* may be responsible not only for worsening the preexisting lung injury but, by a number of mechanisms including development of systemic inflammatory response, may contribute to MODS [2] (Fig. 1).

Supportive evidence for this hypothesis comes from both *in vitro* and *in vivo* experimental studies as well as clinical studies. *In vitro*, using cell stretch devices, 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 [3–7]. Injurious ventilatory strategies in both isolated non-perfused rat lungs and isolated perfused mouse lungs have also demonstrated an increase in release of inflammatory mediators [8, 9]. *In vivo*, studies in 'two-hit' models have also found increases in pulmonary and systemic inflammatory cytokines after injurious mechanical ventilation [10]. Recently clinical trials have demonstrated that protective ventilatory strategies are associated with decreased serum cytokine levels [11, 12], decreased levels of organ dysfunction [12, 13], and decreased mortality [12, 14] in patients with ARDS. The concept of loss of the compartmentalization of local pulmonary inflammatory mediators caused by mechanical ventilation has been proposed to explain translocation of inflammatory mediators from the lung into the systemic circulation, promoting the massive inflammatory response that underlies MODS [2]. Mechanical ventilation with injurious ventilatory strategies can also induce bacterial translocation from lung to the systemic circulation, which may promote development of MODS [15]. In addition, it is well known that mechanical ventilation can affect the systemic and regional circulation as well as oxygen delivery and oxygen consumption in critically ill, which may affect the development of MODS.

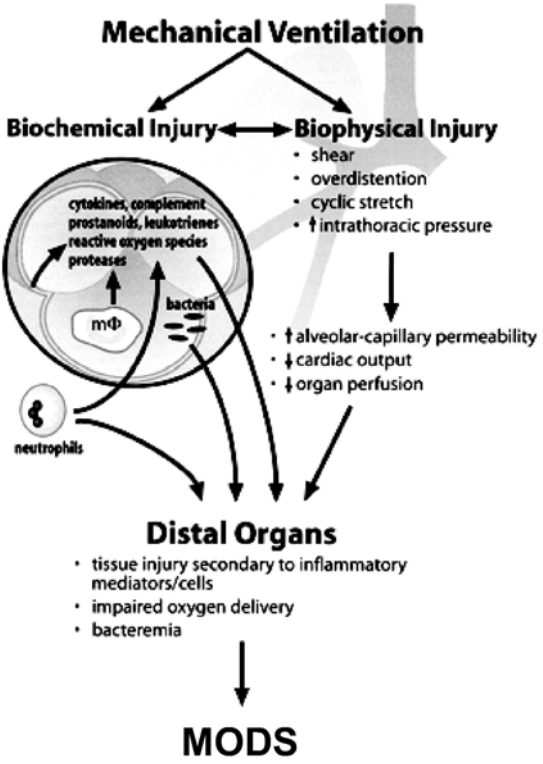

Fig. 1. Postulated mechanisms whereby mechanical ventilation contributes to MODS. From [2] with permission

This chapter is motivated by the clinical question of how mechanical ventilation might contribute to the development of MODS. We will extract and integrate information from several different fields of investigation, and wish to highlight some of the most recent and pertinent findings that have contributed to our understanding of the mechanisms by which mechanical ventilation contributes to MODS. MODS is often irreversible, with mortality ranging from 60 to 98% [16]. To date, there is neither an effective treatment for MODS nor an effective means for preventing its onset. By understanding the mechanisms by which mechanical ventilation contributes to MODS, this new conceptualization of VILI could lead to a paradigm shift for therapies to prevent ventilated ARDS patients from developing MODS.

Physiological Effects of Mechanical Ventilation

It has been known for decades that mechanical ventilation can have important effects on systemic and regional hemodynamics, as well as global oxygen delivery and consumption, as highlighted in many excellent reviews [17–19]. The application of positive end-expiratory pressure (PEEP) is one of the key components of the ventilatory management of ARDS. PEEP decreases cardiac output by decreasing

venous return and by an increase in right ventricular afterload [20–22]; as a result, global oxygen delivery falls. This effect can usually be reversed by volume loading and inotropic agents. PEEP may also induce regional hemodynamic alterations due to the combined effects of decreases in cardiac output and blood flow redistribution [17]. In addition, intraabdominal pressure may increase in response to diaphragmatic swings, so that the splanchnic organs may be compressed [23].

In experimental conditions, a number of authors have reported that PEEP decreases splanchnic blood flow [24, 25], although splanchnic oxygen consumption can usually be maintained by a compensatory increase in oxygen extraction [26]. A similar response to PEEP has been observed in patients during abdominal surgery [27]. Trager and colleagues [28] progressively increased the PEEP level up to 15 cmH_2O in patients with septic shock. Cardiac output decreased in all patients, and hepatic vein oxygen saturation and hepatic vein oxygen saturation decreased more at PEEP 15 than at 10 cmH_2O. Kiefer and colleagues [29] reported that in patients with ALI, moderate levels of PEEP did not significantly alter splanchnic blood flow as well as indices of tissue hypoxia such as gastric mucosal PO_2 and the blood lactate to pyruvate ratio, provided fluid resuscitation was able to maintain cardiac output. Fournell and colleagues [30] found in anesthetized dogs that gastric mucosal oxygen saturation decreased at PEEP 15 cmH_2O despite the maintenance of cardiac output by fluid infusion. The effect of PEEP on gastric mucosal oxygenation may be dissociated from the effect on cardiac output and splanchnic blood flow. Seeman-Lodding and colleagues [31] measured arterio-venous concentration gradients of tissue-type plasminogen activator (t-PA) and the respective blood flow across the pulmonary, coronary, hepatic and preportal vascular beds in pigs after the application of PEEP up to 10 cmH_2O. They found that with PEEP, the magnitude of the preportal net release of t-PA was markedly enhanced, with a concomitant decrease in liver blood flow, suggesting that clinically used levels of PEEP induce increases in net release of t-PA within preportal organs.

Reduction of tidal volume (V_T) is another key component of the ventilatory management of ALI/ARDS. V_T reduction may exert systemic and regional circulatory effects. The increase in cardiac output resulting in oxygen delivery during V_T reduction has been observed in several studies of patients with ARDS [32, 33]. There are two mechanisms that could be responsible for the increased cardiac output with reduced V_T: First, the decrease in airway pressure, by inducing a reduction in pleural pressure, will lead to an increase in venous return. In addition, a decrease in transpulmonary pressure could decrease overdistension of the lung, leading to a decrease in the resistance of alveolar microvessels, hence imposing a relatively reduced transient resistance to right ventiricular output. Another mechanism leading to an increase in cardiac output during V_T reduction is the resulting hypercapnia. A number of studies have demonstrated that hypercapnia induces an increase in sympathetic activity, which may enhance cardiac output [34, 35]. In addition to the central hemodynamic effects, V_T reduction may also induce regional hemodynamic alterations such as effects on the gut circulation. The effect of V_T reduction on gut regional blood flow is controversial. Cardenas and colleagues [36] reported a parallel increase in cardiac output and mesenteric blood flow after V_T reduction in animals. In contrast, despite an increase in cardiac output, Sitbon and colleagues [37] observed no increase in gastric mucosal blood

flow after V_T reduction resulting in hypercapnia in ARDS patients. They speculated that the heterogeneity in the individual response of gastric mucosal blood low during V_T reduction resulting in hypercapnia could be due to opposing direct (i.e., local vasodilatory effect) and indirect (i.e., global sympathetic stimulation) effects of hypercapnia on gut vessels.

Relatively little is known with regards to changes in regional circulation and global oxygen delivery due to mechanical ventilation in relation to protective ventilatory strategies (small V_T and higher PEEP) versus conventional ventilatory strategies (large V_T and low PEEP) in patients with ARDS.

Mechanical Strain-induced Release of Inflammatory Mediators *in vitro*

Because of the complexity of lung structure, the variety of cell types, and the variety of mechanical forces to which these cells are exposed, there are a number of mechanisms by which mechanical stimulation may alter cellular responses. There are several excellent recent reviews of this topic [38–42]. Dos Santos and Slutsky [38] have detailed putative mechanoreceptive mechanisms leading to proinflammatory signaling by lung cells in VILI. In this review, the authors emphasized both stretch-activated ion channels and plasma membrane disruption. Grembowicz and colleagues demonstrated in a series of studies that calcium influx accompanying plasma membrane disruption is associated with translocation of nuclear factor kappa B (NF-κB) and upregulation of stress response genes [3]. These, in turn, could represent up-stream events leading to pro-inflammatory signaling. In a recent review, Vlahakis and Hubmayr [43] emphasized that plasma membrane stress failure is a central event in the pathophysiology of injury from alveolar overdistension.

Vlahakis and colleagues [7] found that in cultured A549 cells, mRNA for interleukin (IL)-8 increased 4-fold after four hours of cyclic strain sufficient to change the cell surface area by 30%. Continued strain for up to 48 hours resulted in a nearly 50% increase in IL-8 secretion compared with non-strained controls. This finding was confirmed by Quinn and colleagues [6], who also found that the increase in IL-8 secretion was associated with activation of the JNK family of mitogen activated protein kinases (MAPKs). Mourgeon et al. [4] found that in cultured fetal rat lung cell, macrophage inflammatory protein-2 (MIP-2), a rodent analog of human IL-8, was liberated into supernatant after four hours of cyclic strain.

Pugin and colleagues [5] cultured human alveolar macrophages on flexible silastic membranes and exposed the cells to cyclic stretch for up to 32 hours. They found that cyclic strain increased secretion of IL-8 and MMP-9 (gelatinase b – a type IV collagenase), but not tumor necrosis factor (TNF)-α or IL-6. When the macrophages were pretreated with lipopolysaccharide (LPS), TNF-α and IL-6 secretion increased to a greater extent in strained cells compared with static cultures. Mechanical strain also activated NF-κB in macrophages after 30 minutes. In another study, these same authors found that a bronchial epithelial cell line, an endothelial cell line, and primary lung fibroblasts exposed to the same cyclic strain, did not secrete IL-8, but macrophages and A549 cells secreted IL-8 in response to

mechanical distention. The relative amount of IL-8 secreted from macrophages was much greater than that from A549 cells [44].

Pulmonary endothelial cells form a continuous monolayer on the luminal surface of the lung vasculature. During mechanical ventilation, pulmonary endothelial cells are exposed to shear stress, in particular repetitive opening and collapse of atelectatic regions of the lung, as well as changes in transluminal pressure during alveolar inflation. Changes in shear stress could be sensed directly by cell membrane components such as membrane proteins, ion channels, or caveolae or by alterations of the cellular cytoskeleton; subsequent cellular signaling cascades through phosphorylation events can lead to diverse effects such as the release of cytokines and other mediators, activation of transcription factors, altered gene expression and protein expression, and cell division or death [39]. Gan and colleagues [45, 46] found that various combinations of shear and intraluminal pressures in human umbilical veins caused gene and protein expression of vascular endothelial growth factor as well as c-jun and c-fos.

Pulmonary and Systemic Release of Inflammatory Mediators in VILI *ex vivo* and *in vivo*

Under experimental conditions, high V_T and/or low PEEP induces release of pro-inflammatory cytokines into the airspaces and bloodstream, increased neutrophil infiltration into the lung, and activation of alveolar macrophages. There is considerable evidence supporting a role for the release of inflammatory mediators in VILI *ex vivo* and *in vivo*.

Tremblay and colleagues [9] found that ventilation of isolated, non-perfused rat lungs with V_T of 40 ml/kg and zero PEEP for 2 hrs resulted in large increases in lavage concentrations of TNF-α, IL-1β, IL-6, and MIP-2. The increase in these cytokines was greater if rats were pretreated with LPS. Northern blot analysis of whole lung homogenates revealed increased expression of c-fos mRNA, with both high and moderate V_T and/or zero PEEP ventilation.

Chiumello and colleagues [10] demonstrated that mechanical ventilation for 4 hrs with a V_T of 16 ml/kg, zero PEEP versus V_T of 9 ml/kg, PEEP of 5 cmH_2O produced an increased release of pro-inflammatory cytokines (TNF-α and MIP-2) in the lung as well as in the systemic circulation in an *in vivo* acid aspiration model in rats. Haitsma and colleagues [47] found that mechanical ventilation for 20 min with peak inspiratory pressure/PEEP ratio 45/0 versus 45/10 increased release of TNF-α into the systemic circulation in rats pretreated with LPS intratracheally, while increased bronchoalveolar lavage (BAL) TNF-α in rats pretreated with intraperitoneal LPS, suggested loss of alveolar and systemic compartmentalization of TNF-αrespectively.

Evidence for the importance of these inflammatory mediators in the development of VILI comes from experimental studies of the effects of an anti-TNF antibody and an IL-1 receptor antagonist on lung injury following saline-lavage. Imai and colleagues [48] employed anti-TNF-α antibodies and observed improvements in oxygenation and respiratory compliance, decreased lavage neutrophil

counts, as well as reduced histological evidence of lung injury. Narimanbekov and colleagues [49] used an IL-1β receptor antagonist and found reduced lung lavage concentrations of a number of markers of lung injury (i.e., albumin, elastase, and neutrophils) in a saline-lavaged rabbit model.

Recently Held and colleagues [50] demonstrated in isolated perfused mouse lungs that both LPS and overventilation caused translocation of NF-κB to the nucleus, leading to release of MIP-2. However, there were major differences in response to the two different stimuli when they used LPS-resistant C3H/HeJ mice, which have abnormalities in Toll like receptor (TLR)-4. In LPS-resistant C3H/HeJ mice overventilation, but not LPS, caused translocation of NF-κB and release of MIP-2, suggesting that initial signaling steps between LPS and ventilation differ and that the NF-κB translocation elicited by overventilation is independent of TLR4.

Passage of Mediators from Lung to Bloodstream

One important question is where the increased systemic pro-inflammatory mediators originate from. Loss of compartmentalization of local pulmonary inflammatory mediators due to mechanical ventilation has been recently proposed. The alveolar barrier restricts transport of macro-molecules 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 circulation that would normally have remained compartmentalized within the alveolar space [51, 52]. Tutor and colleagues [51] 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 Bethman and colleagues [8] reported that in an isolated perfused murine lung model, ventilation with higher transpulmonary pressure (25 cmH_2O) versus normal pressure (10 cmH_2O) led to a significant increase in concentration of both TNF-α and IL-6 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.

ARDS is characterized by a loss of integrity of the alveolar capillary barrier due to severe diffuse alveolar damage, leading to bidirectional protein flux. Therefore, not only pro-inflammatory cytokines but also locally secreted proteins, particularly the surfactant-associated protein (SP) may pass into the systemic circulation. SP-A, SP-B and SP-D, which have anti-inflammatory properties, have been detected in serum of ARDS patients, and have been associated with outcome of patients with ARDS [53, 54]. The balance between the pro- and anti-inflammatory cytokines passing from the lung to the bloodstream may be more important in determining the subsequent effect than the absolute values of any single mediators.

Bacterial Translocation in Mechanical Ventilation

Another mechanism whereby mechanical ventilation may contribute to the development of a systemic inflammatory response is by promoting bacterial translocation from the air spaces into the circulation. Two recent studies evaluated the influence of mechanical ventilatory strategy on the translocation of bacteria from the lung into the bloodstream in dogs and rats[55, 56]. After intratracheal instillation of bacteria, these animals were ventilated with a high transpulmonary pressure (–30 cmH_2O) and minimal (0 to 3 cmH_2O) or 10 cmH_2O PEEP. Bacteremia seldom occurred in control animals ventilated with low airway pressure, whereas it was found in nearly all animals ventilated with high V_T and a low PEEP. In contrast, ventilation with the same transpulmonary pressure but with 10 cmH_2O PEEP resulted in rates of bacteremia as low as in controls. In a saline-lavaged rabbit lung injury model, mechanical ventilation with a V_T of 12 ml/kg and without PEEP resulted in translocation of intratracheally instilled endotoxin into the systemic circulation, but ventilation with a V_T of 5 ml/kg and a PEEP of 10 cm H_2O did not. The appearance of endotoxin in the blood stream was associated with an increase in plasma TNF-α [57]. Since the gut could be a "motor" of MODS, bacterial and endotoxin translocation caused by mechanical ventilation may play a role in development of MODS [15].

Pulmonary and Systemic Inflammatory Mediators in VILI in Clinical Studies

Elevated levels of pro-inflammatory mediators have been measured in airspace lavage fluid and in the plasma of patients with ARDS. Ranieri and colleagues [11] measured BAL and plasma levels of several pro-inflammatory cytokines in 44 patients with ARDS. At study entry, patients were randomized to receive mechanical ventilation with a conventional strategy (mean V_T of 11.1 ml/kg, mean plateau airway pressure 31 cmH_2O, and mean PEEP of 6.5 cmH_2O), or a protective ventilatory strategy with V_T (7.6 ml/kg) and higher PEEP (14.8 cmH_2O) with a mean plateau airway pressure of 24.6 cmH_2O. PEEP in the latter group was set above the lower inflection point of the respiratory system pressure volume curve. Baseline measurements of cytokines were made at the time of admission (study entry), and were then measured serially for three days. By 36 hours, BAL fluid from patients in the protective ventilation group had significantly fewer polymorphonuclear cells and lower concentrations of TNF-α, IL-1β, IL-6, and IL-8. Plasma levels of IL-6 were also significantly lower in the patients receiving protective ventilation. The NIH ARDS Network study found lower levels of plasma IL-6 at three days in patients ventilated with low V_T compared with conventional V_T [12].

In patients with ARDS, concentration of TNF-α, IL-1β and IL-6 were higher in the arterialized blood (obtained via a wedged Swan-Ganz catheter), as compared with mixed venous blood, suggesting that the lungs in these patients were contributing cytokines to the systemic circulation [58]. Recently, Stuber and colleagues [59] studied patients with ALI and found that switching to conventional mechanical ventilation (V_T of 12 ml/kg, PEEP of 5 cmH_2O) from a lung protective strategy (V_T

of 5 ml/kg, PEEP of 15 cmH_2O) was associated with a marked increase in plasma cytokine levels within 1 h, while plasma cytokine levels returned to baseline when lung protective settings was reestablished. In contrast, in 39 patients with normal lungs, without ARDS, Wrigge and colleagues [60] found that ventilation with a high V_T (15 ml/kg) and zero PEEP did not affect plasma levels of either IL-6, TNF-α, IL-1 receptor antagonist, or IL-10. These data suggest that if the lung is normal, mechanical ventilation, even with relatively large V_T, is unlikely to increase alveolar capillary permeability and augment the pulmonary inflammatory response, leading to increased production of inflammatory mediators.

Multiple Organ Dysfunction and VILI in Clinical Studies

There are now prospective data in the literature examining the hypothesis that a protective ventilatory strategy can have an impact on the development of MODS. As previously mentioned, Ranieri and colleagues reported that the use of a lung-protective strategy in patients with ARDS attenuated an increase in pulmonary and systemic cytokine levels including TNF-α and IL-6 [11]. In a subsequent *post hoc* analysis (Fig. 2), they found a higher incidence of renal failure in ARDS patients ventilated with conventional ventilation compared with a lung protective strategy. Furthermore, they found a significant correlation between overall MODS score with changes in plasma concentration of a number of inflammatory mediators (IL6, TNF-α, IL-1β and IL-8), which are involved in MODS [13]. Similarly, the NIH ARDS Network reported the results of a randomized, clinical trial comparing a V_T of 12 ml/kg with 6 ml/kg (predicted body weight). They found lower levels of plasma IL-6 in the 6 ml/kg tidal volume group, associated with a greater number of organ failure-free days and a 22% reduction in mortality rate [12]. These data suggest that mechanical ventilation, which is invariably used in the care of patients with ARDS, can increase alveolar capillary permeability and augment the pulmonary inflammatory response, leading to increased production of inflammatory mediators. If these mediators (e.g., cytokines) enter the circulation, they could contribute to the development of MODS. It is important to emphasize that MODS is a complex syndrome, often precipitated and intensified by a series of events rather than a single event. A likely scenario is that there is an ongoing inflammatory response as a result of the persistence of the factors that either initiated or exacerbated the response, and/or failure of intrinsic regulatory mechanisms. Conversely, patients with normal lungs who receive prolonged ventilation (e.g., neuromuscular disease with respiratory failure) would not develop VILI nor MODS.

Implications

In this review, we have focused mainly on the effects of mechanical ventilation on hemodynamics and systemic inflammation, but how might these lead to end organ dysfunction? Recently, it has been shown that inflammatory cytokines/chemokines can modulate apoptosis in various cell types [61] and increased apoptosis has been detected in animal model of CLP [62, 63] as well as in patients dying of sepsis and

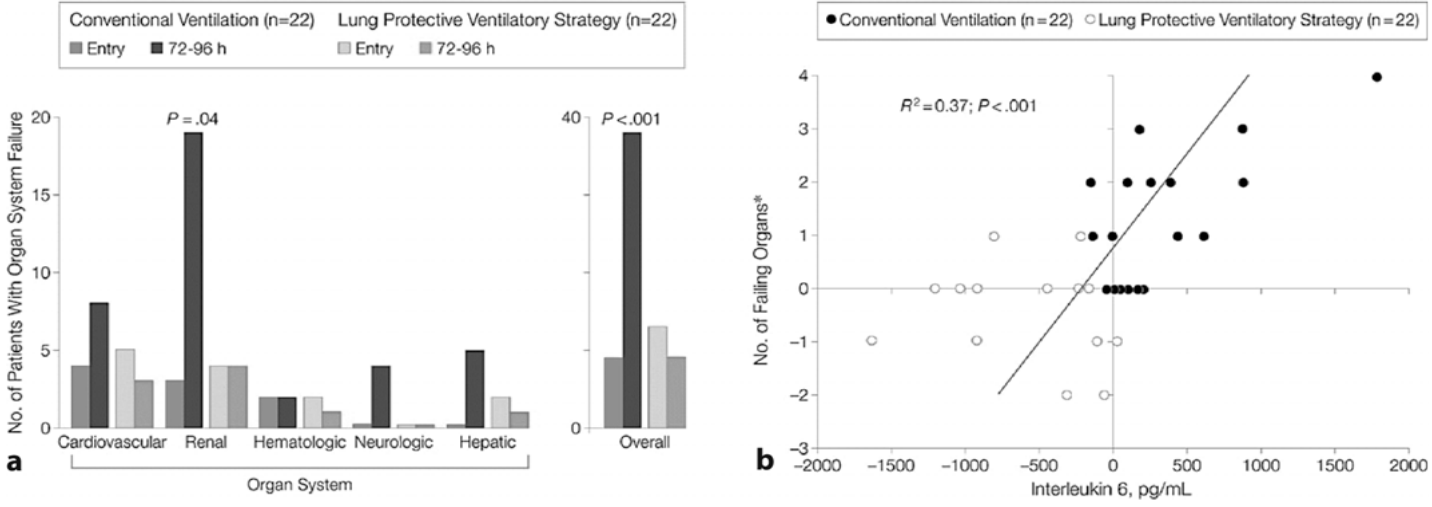

Fig. 2. a. Number of patients with organ system failure in the 2 groups of patients on entry and within 72 hours of mechanical ventilation. Patients may have failure of more than 1 organ system. **b.** Changes in total number of failing organs and in plasma concentration of interleukin 6. Asterisk indicates number of failing organ systems at 72 hours minus number on entry. Dagger indicates change in interleukin 6 derived from value at 36 hours minus entry value. From [13] with permission.

MODS [64]. Imai and colleagues have demonstrated increases in end organ epithelial cell apoptosis after injurious mechanical ventilation in an *in vivo* rabbit ARDS model [65]. Apoptosis might thus be an important down-stream effect in the development of systemic inflammatory response syndrome (SIRS)/MODS caused by VILI in ALI/ARDS, although there are insufficient data to confirm this hypothesis at present.

Conclusion

Based on the paradigm developed in this chapter, it is suggested that in patients with ARDS, VILI plays a crucial role in initiating and/or propagating a systemic inflammatory response leading to MODS. As such, protective ventilatory strategies in concert with other novel therapies could reduce the development of MODS and decrease mortality in mechanically ventilated patients. Furthermore, pharmacological modulation of cellular and molecular sequelae may reduce VILI and/or development of MODS.

References

1. Esteban A, Anzueto A, Frutos F, et al (2002) Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 287:345–355
2. Slutsky AS, Tremblay LN (1998) Multiple system organ failure. Is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 157:1721–1725
3. Grembowicz KP, Sprague D, McNeil PL (1999) Temporary disruption of the plasma membrane is required for c-fos expression in response to mechanical stress. Mol Biol Cell 10:1247–1257
4. Mourgeon E, Isowa N, Keshavjee S, Zhang X, Slutsky AS, Liu M (2000) Mechanical stretch stimulates macrophage inflammatory protein-2 secretion from fetal rat lung cells. Am J Physiol 279:L699–L706
5. Pugin J, Dunn I, Jolliet P, et al (1998) Activation of human macrophages by mechanical ventilation in vitro. Am J Physiol 275:L1040–L1050
6. Quinn D, Tager A, Joseph PM, Bonventre JV, Force T, Hales CA (1999) Stretch-induced mitogen-activated protein kinase activation and interleukin-8 production in type II alveolar cells. Chest 116:89S–90S
7. Vlahakis NE, Schroeder MA, Limper AH, Hubmayr RD (1999) Stretch induces cytokine release by alveolar epithelial cells in vitro. Am J Physiol 277:L167-L173
8. von Bethmann AN, Brasch F, Nusing R, et al (1998) Hyperventilation induces release of cytokines from perfused mouse lung. Am J Respir Crit Care Med 157:263–272
9. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS (1997) Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest 99:944–952
10. Chiumello D, Pristine G, Slutsky AS (1999) Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. Am J Respir Crit Care Med 160:109–116
11. Ranieri VM, Suter PM, Tortorella C, et al (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:54–61

12. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared wit1h traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308
13. Ranieri VM, Giunta F, Suter PM, Slutsky AS (2000) Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA 284:43–44
14. Amato MB, Barbas CS, Medeiros DM, et al (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338:347–354
15. Carrico CJ, Meakins JL, Marshall JC, Fry D, Maier RV (1986) Multiple-organ-failure syndrome. Arch Surg 121:196–208
16. Le Gall JR, Klar J, Lemeshow S, et al (1996) The Logistic Organ Dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. JAMA 276:802–810
17. De Backer D (2000) The effects of positive end-expiratory pressure on the splanchnic circulation. Intensive Care Med 26:361–363
18. Pinsky MR (2002) Recent advances in the clinical application of heart-lung interactions. Curr Opin Crit Care 8:26–31
19. Russell JA, Phang PT (1994) The oxygen delivery/consumption controversy. Approaches to management of the critically ill. Am J Respir Crit Care Med 149:533–537
20. Fessler HE, Brower RG, Wise RA, Permutt S (1991) Effects of positive end-expiratory pressure on the gradient for venous return. Am Rev Respir Dis 143:19–24
21. Jardin F, Farcot JC, Boisante L, Curien N, Margairaz A, Bourdarias JP (1981) Influence of positive end-expiratory pressure on left ventricular performance. N Engl J Med 304:387–392
22. Robotham JL, Lixfeld W, Holland L, et al (1980) The effects of positive end-expiratory pressure on right and left ventricular performance. Am Rev Respir Dis 121:677–683
23. Brienza N, Revelly JP, Ayuse T, Robotham JL (1995) Effects of PEEP on liver arterial and venous blood flows. Am J Respir Crit Care Med 152:504–510
24. Dorinsky PM, Hamlin RL, Gadek JE (1987) Alterations in regional blood flow during positive end-expiratory pressure ventilation. Crit Care Med 15:106–113
25. Matuschak GM, Pinsky MR, Rogers RM (1987) Effects of positive end-expiratory pressure on hepatic blood flow and performance. J Appl Physiol 62:1377–1383
26. Sha M, Saito Y, Yokoyama K, Sawa T, Amaha K (1987) Effects of continuous positive-pressure ventilation on hepatic blood flow and intrahepatic oxygen delivery in dogs. Crit Care Med 15:1040–1043
27. Aneman A, Eisenhofer G, Fandriks L, et al (1999) Splanchnic circulation and regional sympathetic outflow during peroperative PEEP ventilation in humans. Br J Anaesth 82:838–842
28. Trager K, Radermacher P, Georgieff M (1996) PEEP and hepatic metabolic performance in septic shock. Intensive Care Med 22:1274–1275
29. Kiefer P, Nunes S, Kosonen P, Takala J (2000) Effect of positive end-expiratory pressure on splanchnic perfusion in acute lung injury. Intensive Care Med 26:376–383
30. Fournell A, Scheeren TW, Schwarte LA (1997) Oxygenation of the intestinal mucosa in anaesthetized dogs is attenuated by intermittent positive pressure ventilation (IPPV) with positive end-expiratory pressure (PEEP). Adv Exp Med Biol 428:385–389
31. Seeman-Lodding H, Haggmark S, Jern C, et al (1999) Systemic levels and preportal organ release of tissue-type plasminogen activator are enhanced by PEEP in the pig. Acta Anaesthesiol Scand 43:623–633
32. Kiiski R, Takala J, Kari A, Milic-Emili J (1992) Effect of tidal volume on gas exchange and oxygen transport in the adult respiratory distress syndrome. Am Rev Respir Dis 146:1131–1135
33. Thorens JB, Jolliet P, Ritz M, Chevrolet JC (1996) Effects of rapid permissive hypercapnia on hemodynamics, gas exchange, and oxygen transport and consumption during mechanical ventilation for the acute respiratory distress syndrome. Intensive Care Med 22:182–191
34. Brofman JD, Leff AR, Munoz NM, Kirchhoff C, White SR (1990) Sympathetic secretory response to hypercapnic acidosis in swine. J Appl Physiol 69:710–717

35. Rose CE Jr, Althaus JA, Kaiser DL, Miller ED, Carey RM (1983) Acute hypoxemia and hypercapnia: increase in plasma catecholamines in conscious dogs. Am J Physiol 245:H924–H929
36. Cardenas VJ Jr, Zwischenberger JB, Tao W, et al (1996) Correction of blood pH attenuates changes in hemodynamics and organ blood flow during permissive hypercapnia. Crit Care Med 24:827–834
37. Sitbon P, Teboul JL, Duranteau J, Anguel N, Richard C, Samii K (2001) Effects of tidal volume reduction in acute respiratory distress syndrome on gastric mucosal perfusion. Intensive Care Med 27:911–915
38. Dos Santos CC, Slutsky AS (2000) Invited review: mechanisms of ventilator-induced lung injury: a perspective. J Appl Physiol 89:1645–1655
39. Fisher AB, Chien S, Barakat AI, Nerem RM (2001) Endothelial cellular response to altered shear stress. Am J Physiol 281:L529–L533
40. Liu M, Post M (2000) Invited review: mechanochemical signal transduction in the fetal lung. J Appl Physiol 89:2078–2084
41. Uhlig S (2002) Ventilation-induced lung injury and mechanotransduction: stretching it too far? Am J Physiol 282:L892–L896
42. Waters CM, Sporn PH, Liu M, Fredberg JJ (2002) Cellular biomechanics in the lung. Am J Physiol 283:L503–L509
43. Vlahakis NE, Hubmayr RD (2000) Invited review: plasma membrane stress failure in alveolar epithelial cells. J Appl Physiol 89:2490–2496
44. Dunn I, Pugin J (1999) Mechanical ventilation of various human lung cells in vitro: identification of the macrophage as the main producer of inflammatory mediators. Chest 116:95S–97S
45. Gan L, Doroudi R, Hagg U, Johansson A, Selin-Sjogren L, Jern S (2000) Differential immediate-early gene responses to shear stress and intraluminal pressure in intact human conduit vessels. FEBS Lett 477:89–94
46. Gan L, Miocic M, Doroudi R, Selin-Sjogren L, Jern S (2000) Distinct regulation of vascular endothelial growth factor in intact human conduit vessels exposed to laminar fluid shear stress and pressure. Biochem Biophys Res Commun 272:490–496
47. Haitsma JJ, Uhlig S, Goggel R, Verbrugge SJ, Lachmann U, Lachmann B (2000) Ventilator-induced lung injury leads to loss of alveolar and systemic compartmentalization of tumor necrosis factor-alpha. Intensive Care Med 26:1515–1522
48. Imai Y, Kawano T, Iwamoto S, Nakagawa S, Takata M, Miyasaka K (1999) Intratracheal anti-tumor necrosis factor-alpha antibody attenuates ventilator-induced lung injury in rabbits. J Appl Physiol 87:510–515
49. Narimanbekov IO, Rozycki HJ (1995) Effect of IL-1 blockade on inflammatory manifestations of acute ventilator-induced lung injury in a rabbit model. Exp Lung Res 21:239–254
50. Held HD, Boettcher S, Hamann L, Uhlig S (2001) Ventilation-induced chemokine and cytokine release is associated with activation of nuclear factor-kappa B and is blocked by steroids. Am J Respir Crit Care Med 163:711–716
51. Tutor JD, Mason CM, Dobard E, Beckerman RC, Summer WR, Nelson S (1994) Loss of compartmentalization of alveolar tumor necrosis factor after lung injury. Am J Respir Crit Care Med 149:1107–1111
52. Kurahashi K, Kajikawa O, Sawa T, et al (1999) Pathogenesis of septic shock in Pseudomonas aeruginosa pneumonia. J Clin Invest 104:743–750
53. Greene KE, Wright JR, Steinberg KP, et al (1999) Serial changes in surfactant-associated proteins in lung and serum before and after onset of ARDS. Am J Respir Crit Care Med 160:1843–1850
54. Doyle IR, Bersten AD, Nicholas TE (1997) Surfactant proteins-A and -B are elevated in plasma of patients with acute respiratory failure. Am J Respir Crit Care Med 156:1217–1229
55. Nahum A, Hoyt J, Schmitz L, Moody J, Shapiro R, Marini JJ (1997) Effect of mechanical ventilation strategy on dissemination of intratracheally instilled Escherichia coli in dogs. Crit Care Med 25:1733–1743

56. Verbrugge SJ, Sorm V, van't Vee A, Mouton JW, Gommers D, Lachmann B (1998) Lung overinflation without positive end-expiratory pressure promotes bacteremia after experimental Klebsiella pneumoniae inoculation. Intensive Care Med. 24:172–177.
57. Murphy DB, Cregg N, Tremblay L, et al (2000) Adverse ventilatory strategy causes pulmonary-to-systemic translocation of endotoxin. Am J Respir Crit Care Med 162:27–33
58. Douzinas EE, Tsidemiadou PD, Pitaridis MT, et al (1997) The regional production of cytokines and lactate in sepsis-related multiple organ failure. Am J Respir Crit Care Med 155:53–59
59. Stuber F, Wrigge H, Schroeder S, et al (2002) Kinetic and reversibility of mechanical ventilation-associated pulmonary and systemic inflammatory response in patients with acute lung injury. Intensive Care Med 28:834–841
60. Wrigge H, Zinserling J, Stuber F, et al (2000) Effects of mechanical ventilation on release of cytokines into systemic circulation in patients with normal pulmonary function. Anesthesiology 93:1413–1417
61. Papathanassoglou ED, Moynihan JA, Ackerman MH (2000) Does programmed cell death (apoptosis) play a role in the development of multiple organ dysfunction in critically ill patients? a review and a theoretical framework. Crit Care Med 28:537–549
62. Hiramatsu M, Hotchkiss RS, Karl IE, Buchman TG (1997) Cecal ligation and puncture (CLP) induces apoptosis in thymus, spleen, lung, and gut by an endotoxin and TNF-independent pathway. Shock 7:247–253
63. Hotchkiss RS, Swanson PE, Cobb JP, Jacobson A, Buchman TG, Karl IE (1997) Apoptosis in lymphoid and parenchymal cells during sepsis: findings in normal and T- and B-cel-deficient mice. Crit Care Med 25:1298–1307
64. Hotchkiss RS, Swanson PE, Freeman BD, et al (1999) Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. Crit Care Med 27:1230–1251
65. Imai Y, Parodo J, Kajikawa O, et al (2003) Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of ARDS. JAMA 289:2104–2112

ARDS/VILI: Assessment