Pulmonary Perspective

Multiple System Organ Failure
Is Mechanical Ventilation a Contributing Factor?

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Few problems facing the intensivist are as frustrating or as difficult to manage as multiple system organ failure (MSOF). While the precise etiology remains unknown, an integral feature is the development of a rampant systemic inflammatory response that persists unabated by host control mechanisms. Either a single massive insult, or a series of less intense insults (i.e., "two-hits") appear to be necessary to overwhelm the individuals innate regulatory mechanisms. Often the lung is the first organ to fail, leading to initiation (or continuation) of ventilatory support. Although in some patients a precipitating nidus of infection or inflammation is identifiable, and lung injury is simply the first clinically evident manifestation of a systemic process, there remain a large number of patients in whom the explanation for progression from respiratory failure to multiple system organ failure is unclear.

In this Perspective, we explore the hypothesis that mechanical ventilation may play a pivotal (and hereto unrecognized) role in the initiation and/or propagation of a systemic inflammatory response leading to MSOF in certain patients. We address this issue by examining the following questions: Can mechanical ventilation initiate or exacerbate lung injury/inflammation? Can lung injury/inflammation lead to systemic inflammation? Is there evidence of MSOF secondary to mechanical ventilation?

CAN MECHANICAL VENTILATION INITIATE OR EXACERBATE LUNG INJURY/INFLAMMATION?

Mechanical ventilation is an indispensable tool for providing adequate gas exchange and resting respiratory muscles in many disease states. However, in certain patients with the acute respiratory distress syndrome (ARDS) or acute lung injury (ALI), the ventilatory strategy required to maintain adequate gas exchange may exacerbate, or even initiate, significant lung injury and inflammation (1, 2). Patients with ALI/ARDS often have a number of risk factors (e.g., surfactant dysfunction, underlying lung disease, malnutrition, oxygen toxicity, infection, age) that not only increase the lungs' susceptibility to injury by mechanical ventilation, but also impair the lungs' ability to repair the damage incurred (3). Furthermore, the atelectasis of dependent lung regions and alveolar edema that is often present can markedly reduce their aerated lung capacity (e.g., to as little as 25% of normal) (4). As a result, mechanical ventilation with even modest tidal volumes (e.g., 10 to 12 ml/kg) may result in overdistention of the remaining aerated lung regions to a level equivalent to that observed if healthy lungs were ventilated with tidal volumes of 40 to 48 ml/kg.

Research in a number of species has shown that mechanical ventilation can produce lung injury that is functionally and histologically indistinguishable from that seen in ARDS (2, 5). The mechanisms of injury include structural disruption due to either lung overdistension, or to the shear forces generated during repetitive opening and collapse of atelectatic regions (1, 2). Mechanical ventilation has also been shown to have profound effects on the function of both endogenous and exogenous surfactant (6–9) resulting in an increased tendency for collapse of air spaces (distal airways and alveoli), a need for higher airway pressures to reopen (and keep open) the lung, and increased surface tension at the gas–liquid interface in the alveoli resulting in increased transmural capillary pressure gradients (favoring movement of fluid into the lung).

More recently, mechanical ventilation has also been shown to have significant effects on lung levels of inflammatory cells and soluble mediators. In saline-lavaged rabbits, manifestations of lung injury (i.e., hyaline membranes, neutrophil infiltration, and impaired gas exchange) originally attributed to mechanical disruption by conventional mechanical ventilation, were found to be almost completely abrogated in granulocyte-depleted rabbits (10). In normal rabbits subjected to saline lavage, injurious mechanical ventilation was shown to significantly increase lung neutrophil accumulation and chemiluminescence (an indicator of neutrophil priming) (11, 12), as well as bronchoalveolar lavage (BAL) levels of inflammatory mediators (platelet activating factor and thromboxane-B_2 [13]) and expression of tumor necrosis factor-alpha (TNF-α) by alveolar macrophages (14). Similarly, in rat lungs ventilated *ex vivo* increased BAL concentrations of a number of cytokines (including TNF-α and interleukin-1β [IL-1β]) were found following injurious mechanical ventilation with low end-expiratory lung volumes allowing tidal alveolar reopening and collapse with each breath (15). The superimposition of high end-inspiratory lung volume (i.e., large tidal volume) on low end-expiratory lung volume leads to a further synergistic increase in BAL cytokine concentrations (15).

By selectively blocking interleukin-1 (IL-1) through use of an IL-1 receptor antagonist (IL-1ra), Narimanbekov and Rozycki were able to reduce lung lavage concentrations of a number of markers of lung injury (i.e., albumin, elastase, neutrophils), as well as reduce histologic evidence of lung injury in a rabbit surfactant deficient, hyperoxic lung injury model (16). However, as would be expected given the complexity and redundancy of the stress/injury response, lung injury was not completely abrogated. No significant improvement in either lung compliance or oxygenation was found, supporting the involvement of other factors (e.g., other cytokines, arachidonic

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acid derivatives, complement, reactive oxygen species, cationic proteins, gelatinases and other proteolytic enzymes, inflammatory cells, fibrin deposition, and physical forces) in the pathogenesis of lung injury (17–22).

Because mechanical ventilation alters both the periodicity and magnitude of forces on the lung, it has also been suggested that mechanotransduction (the conversion of physical forces on the cell membrane/receptors into activation of intracellular signal transduction pathways [23, 24]) may play a role in the ventilator-induced lung inflammatory response. Certainly, the importance of lung volume and movement in fetal lung development is well established (25, 26). Recently, significantly greater production of interleukin-8, a chemokine involved in granulocyte recruitment, was observed when transformed human type II alveolar cells (A549) were subjected to 24 to 48 hours of cyclic stretch with a larger versus a smaller strain pattern (27). In a number of other organ systems, such as the heart and vasculature, an association between aberrant cell stretch/loading patterns and cell dysfunction/organ injury has been shown experimentally (28–30).

CAN LUNG INJURY/INFLAMMATION LEAD TO SYSTEMIC INFLAMMATION?

From an anatomic and physiologic perspective, the lungs are uniquely poised to affect distal organs. The pulmonary vasculature not only receives the entire cardiac output, but also harbors a large reservoir of marginated neutrophils (up to a third of all neutrophils outside the bone marrow). Thus, significant potential exists for the lungs to interact with, and contribute to, the circulating pool of inflammatory cells. In rabbits, mechanical ventilation strategy was found to affect both neutrophils within the lung, as well as neutrophils taken from peripheral blood specimens (11, 31).

In addition to effects on circulating cells, injury to the alveolar–capillary interface may cause release, or allow efflux of inflammatory mediators from the alveolar space into the general circulation. Given the vast surface area of the lung in contact with the blood, a stimulus resulting in release of even small quantities of inflammatory mediators per cell, could result in a significant influx of these mediators into the vascular space. Several investigators have also 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 (32, 33). Von Bethman and colleagues recently reported that in an isolated perfused murine lung model, ventilation with higher transpulmonary pressures (-25 cm H_2O) versus "normal" pressures (-10 cm H_2O) leads to a significant increase in concentrations of both TNF-α and IL-6 in the perfusate (34).

As the presence of inflammatory mediators in the circulation has been shown to play a critical role in the pathophysiology of multiple system organ failure and shock (35–37), to the extent that mechanical ventilation leads to spillover of inflammatory mediators from the lung into the circulation, it could contribute to the initiation or propagation of a systemic inflammatory response. There is evidence in humans with MSOF, that the highest levels of cytokines and lactate in the blood are found downstream from the most affected organ (38). In patients with ARDS, concentrations of IL-1β and IL-6 were higher in the arterialized blood (obtained via a wedged Swan-Ganz catheter), as compared with the mixed venous blood, suggesting that the lungs in these patients were contributing cytokines to the systemic circulation. Meduri and coworkers found persistent elevation of BAL and blood levels of TNF-α, IL-1β, IL-6, and IL-8 in 10 nonsurvivors of early ARDS (39). Although far from conclusive, these findings lend support to the postulate that spillover of an ongoing lung inflammatory response (which may occur due to the recurrent trauma of mechanical ventilation, as well as secondary to infection, aspiration, etc.) might affect patient outcome.

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 (somewhat analogous to the gut bacterial translocation hypothesis of multiple organ failure [MOF] [40]). Following instillation of *Escherichia coli* into the lungs of dogs, Nahum and coworkers found a higher incidence of bacteremia when a ventilatory strategy with low positive end-expiratory pressure (PEEP) (3 cm H_2O) and a high transpulmonary pressure (35 cm H_2O) was used, as compared with less injurious strategies using either similar transpulmonary pressures with 10 cm H_2O of PEEP, or lower transpulmonary pressures (15 cm H_2O) (41).

Finally, mechanical ventilation may also affect distal organ function via effects on cardiac output, as well as the level of oxygenation and the distribution of blood to the various organ systems (e.g., mesenteric, renal, and hepatic perfusion) (1, 42, 43). For example, although fluid resuscitation of rats ventilated with PEEP returned cardiac output to normal values, mesenteric blood flow remained significantly reduced (approximately 50% normal) (43). An increase in distal ileal permeability has also been reported in rats ventilated with larger (20 ml/kg) versus smaller (10 ml/kg) tidal volumes (44).

IS THERE EVIDENCE OF MSOF SECONDARY TO VENTILATION?

Although no study has addressed the specific question—whether mechanical ventilation leads to MSOF—ventilation strategy has been shown in a variety of animal species to have a significant effect on mortality (10–13, 45, 46). Because the majority of these studies were designed to look only at the early effects of ventilation (within a few hours), most deaths occurred as a result of a progressive deterioration in gas exchange and hypoxia. However, in one study examining the effects of mild or severe ventilator-induced lung injury in otherwise normal sheep, mechanical ventilation was continued until either successful weaning or death. The cause of death in the group with severe lung injury (and 8 of 11 sheep with mild lung injury) was progressive hypotension unresponsive to intravenous fluids and multiple system organ failure occurring within 27 h, the pathophysiology of which was unclear (47).

In humans, of four recent prospective randomized trials comparing the effect on survival of a less injurious ("protective") strategy to a control ventilatory strategy, a significant difference was found in one study—the study in which the greatest attention was paid to minimizing low end-expiratory lung volumes in the "protective" strategy arm (48). Further confirmation of this finding in a larger multicenter trial is needed, especially in light of the high mortality in the control group (higher than that of the other, negative studies).

It is important to emphasize that MSOF is a complex syndrome, often precipitated by a series of events rather than a single event, whose pathophysiology is not as yet fully understood. An ongoing inflammatory response as a result of persistence of the initiating/aggravating factors, and/or failure of host regulatory mechanisms to bring about resolution and repair, appears to be involved. As has been discussed, mechanical ventilation can cause lung injury and inflammation, and mechanical ventilation is often a persistent "aggravating" fac-

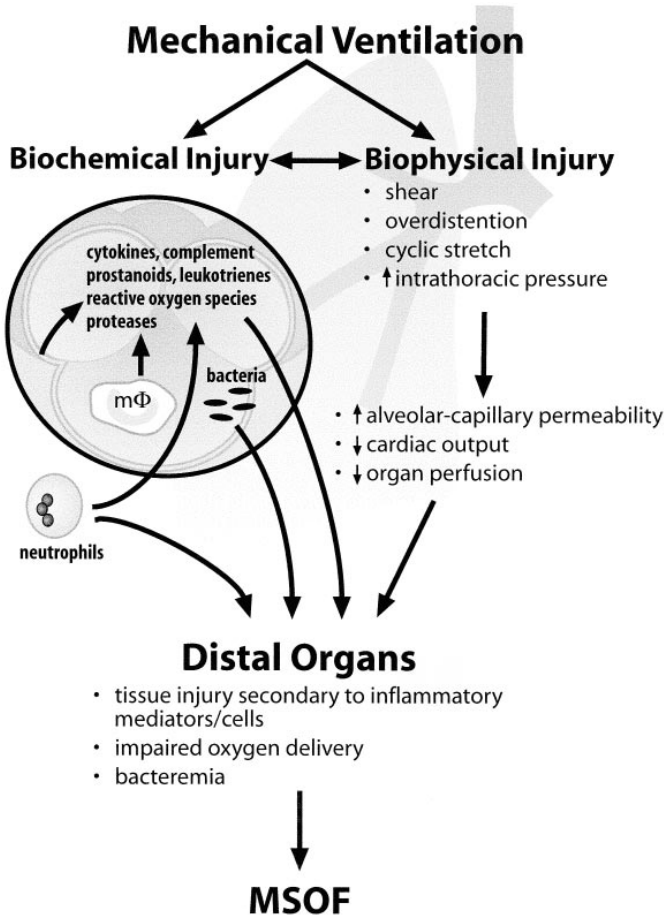

Figure 1. Postulated mechanisms whereby mechanical ventilation may contribute to MSOF.

tor in the critically ill patient "hitting" the 70 m^2 surface area of the lung 10 or more times a minute. The experimental evidence, albeit largely from animals, does lend credence that injurious mechanical ventilation, via the mechanisms depicted in Figure 1, may contribute to the development of MSOF.

But, why then would only some and not the vast majority of ventilated patients succumb to MSOF? After all, mechanical ventilation is ubiquitous in most intensive care units. And, why do some individuals receive ventilatory support for years without adverse sequelae? Within the context of the present hypothesis, we suggest that the major factor is the particular ventilatory strategy used. Experimental data suggest that those ventilatory strategies that cause overstretching of lung regions, or ventilation strategies that cause repetitive opening/closing of lung units, are most "injurious". Thus, patients with diseases in which functional lung volume is decreased (secondary to atelectasis, edema, consolidation) and/or in which there is repetitive recruitment/collapse of lung units (surfactant dysfunction, increased weight of overlying lung tissue) would be at risk of ventilation-induced development of MSOF. Conversely, patients with normal lungs who receive prolonged ventilation (e.g., patients with ALS or acute spinal cord injury) with "noninjurious" ventilation strategies, would not develop ventilator-induced lung injury leading to MSOF. In addition, factors such as age, nutritional status, and inspired oxygen concentration can all have effects on the susceptibility of a patient to lung injury (2, 3, 49–51). Finally, there are biologic and genetic factors that affect the sensitivity of a particular individual to injury or disease. For example, in 40 patients with severe sepsis, homozygotes for a genomic polymorphism (TNF-B2) within the TNF locus were found to have significantly higher circulating plasma TNF-α concentrations, as well as higher mortality compared with either heterozygotes (TNF-B1/TNF-B2) or homozygotes for TNF-B1 (52).

IMPLICATIONS

Despite advances in intensive care medicine, the mortality of ARDS remains about 50% (53). Because most patients die of MSOF rather than hypoxia (54), it has been suggested that modifications of ventilatory strategies will not have a significant impact on mortality even though they might improve gas exchange and reduce lung injury. However, if injurious mechanical ventilation does indeed play a pivotal role in initiating or propagating a systemic inflammatory response, then improvements in ventilatory management might also reduce MSOF.

The difficulty is ensuring, in heterogeneously injured lungs, that all lung regions receive a noninjurious ventilatory pattern. Take, for example, the lung in ARDS. The optimal PEEP to keep open a dependent region of lung, may lead to overdistention of other less dependent lung regions (55). Among the approaches that are currently being investigated to improve gas exchange and distribution of ventilation are: prone positioning, liquid ventilation, and inhaled nitric oxide (53, 56–58). Based on the paradigm developed in this Perspective, we believe that use of such protective ventilatory strategies, in concert with novel therapies aimed at mitigating the cellular and molecular sequelae of mechanical ventilation, *and* treatment of comorbid conditions such infection, should reduce the development of multisystem organ failure and decrease mortality in mechanically ventilated patients.

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