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EDITORIAL

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Is the ventilator responsible for lung and systemic inflammation ?

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Positive pressure mechanical ventilation (MV) has proved to be very useful to support patients with acute respiratory failure. MV, however, imposes novel cyclic pressure/volume regimens on the human lung. In healthy individuals MV has no significant effect when used appropriately, but it is now accepted that MV has important effects when large volumes are applied to healthy lungs, or "reasonable" volumes are delivered to diseased lungs or lungs with impaired perfusion. In addition to air leaks due to volutrauma or barotrauma [1], it has recently been accepted that unusual mechanical forces applied to airways can induce lung cell activation (biotrauma) [2, 3]. It took a long time to recognize this effect since many of the pathways that are turned on by mechanical forces are the same as those induced by the inflammatory processes of diseased lungs [4]. Together, these complications are now termed "ventilator-induced lung injury."

During MV not only airway bronchial and alveolar epithelial cells but also other parenchymal cells, such as fibroblasts, tissue macrophages, and capillary endothelial cells, are subjected to various unusual mechanical strains [5, 6]. These include positive pressure, cell stretching, and shear forces [7]. Cell stretching is observed principally in lung regions where overdistension occurs, whereas important cyclic shear stress is typical of tidal airway recruitment. It is very likely that mechanical forces generated by positive pressure MV play an additive, if not synergistic role with the primary lung injury [8]. Supporting this are the recent studies showing that a "lung-protective approach" by lowering tidal volumes and/or recruiting collapsed lung is associated with increased survival rate [9, 10]. The cause of decreased mortality remains somewhat obscure but has to do with the lowering of the tidal volume and the subsequent lowering of airway pressures, since these were the interventions, particularly in the Acute Respiratory Distress Syndrome Network trial [10]. Patients with acute lung injury die of multiple organ system failure (MOSF) associated or not with secondary infections. It is therefore tempting to link the decrease in airway distension with the decrease in the incidence of the severity of MOSF, although the relationship may be "true-true, but unrelated."

In this issue, Stüber et al. [11] measured the effect of two ventilatory regimens on the levels of lung and circulating inflammatory mediators in patients with acute lung injury. They found that a "conventional approach" with low positive end-expiratory pressure (PEEP) and high tidal volume significantly increases plasma levels of inflammatory mediators. Returning to a "lung-protective approach" with high PEEP and low tidal volume induced a rapid decrease in these mediators in plasma. This is reminiscent of other situations in which unusual mechanical forces were applied to the lung. It has, for example, been shown that bronchoscopy with bronchoalveolar lavage (BAL) is associated with sepsis-like systemic effects [12] and with the release into the circulation of inflammatory mediators [13], particularly in patients with preexisting lung inflammation or infection. In dogs with *Escherichia coli* pneumonia an injurious ventilatory regimen induced bacteria to translocate from the alveoli to the systemic circulation [14]. In a recent study Ranieri et al. [15] showed that a "lung-protective strategy" in patients with acute respiratory distress syndrome was associated with fewer circulating and alveolar inflammatory cells and mediators after 36 h than in patients receiving conventional mechanical ventilation. Stüber et al. [11] extended these findings and studied the kinetics of mediators' elevation

in plasma and BAL samples with two different ventilatory regimens in the same patient. An important observation was that inflammatory mediators appeared very rapidly after the modification of the ventilator settings for the "low-PEEP/high-tidal volume" regimen (<1 h). This is hardly compatible with de novo protein synthesis, but rather consistent with displacement from one compartment to the other. It could therefore be postulated that injurious ventilatory regimens "push" airway mediators into the circulation through an alveolar-capillary barrier of increased permeability. Surprisingly, the half-life of all the mediators measured was very short in the circulatory compartment since a return to baseline was quick after switching to the lung-protective approach.

Stüber et al. [11] also showed in a subset of patients that the "more aggressive" ventilatory regimen induced an increase in inflammatory mediators in the BAL fluid which persisted after the return to a more protective regimen. The airway situation therefore seems different from that of the circulation. The alveolar space has been shown to be the site of an intense inflammatory reaction in patients with acute lung injury [16, 17]. The kinetics of alveolar production of inflammatory mediators seem to differ in the lung from that of other compartments [18]. In cells from the alveolar compartment mechanical forces could turn on de novo mediator production, a process that would persist even after returning to a less aggressive approach. These authors performed mini-BAL (20 ml) rather than conventional BAL (150 ml). This allowed them to repeat the procedure and did not affect systemic mediator release. Because of the small sampling size, it may be asked, however, whether the mediators measured BAL fluids originated from the alveolar or the bronchial space.

It is tempting to associate the release of proinflammatory mediators with deleterious systemic effects induced by the ventilator [19]. However, these results should be taken with caution. The mediators released into the circulation described by Stüber et al. [11] are principally "anti-inflammatory" cytokines, such as interleukin 1 receptor antagonist, interleukin 10, and interleukin 6 [20], whereas tumor necrosis factor-α showed only a modest elevation, and interleukin 1β remained undetectable. The net inflammatory activity (bioactivity) of plasma was not assessed in this study [16, 17]. It is possible that the systemic response to the injurious ventilation is predominantly "anti-inflammatory" and inducing secondary immune suppression, as recently proposed for various types of injury [20]. The proof of an involvement of ventilator-induced mediators translocation in the development of MOSF and MOSF-related mortality should come from a trial aimed at blocking the activity of the mediator(s). Nevertheless, this study strongly suggests that unusual mechanical forces applied to diseased lungs induce local (lung) production of inflammatory mediators and their translocation from the airways to the circulation. Additional experimental work is needed to address whether "ventilator-induced lung injury" translates into "ventilator-induced MOSF" or "ventilator-induced death."

References

1. Dreyfuss D, Saumon G (1998) Ventilator-induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med 157:294–323
2. Tremblay LN, Slutsky AS (1998) Ventilator-induced injury: from barotrauma to biotrauma. Proc Assoc Am Physicians 110:482–488
3. Pugin J, Jolliet P (1998) Ventilator-induced lung injury: an inflammatory disease? Clin Pulm Med 5:290–299
4. Ware LB, Matthay MA (2000) The acute respiratory distress syndrome. N Engl J Med 342:1334–1349
5. 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
6. Pugin J, Dunn I, Jolliet P, Tassaux D, Magnenat JL, Nicod LP, Chevrolet JC (1998) Activation of human macrophages by mechanical ventilation in vitro. Am J Physiol 275:L1040–1050
7. Dos Santos CC, Slutsky AS (2000) Mechanisms of ventilator-induced lung injury: a perspective. J Appl Physiol 89:1645–1655
8. Dreyfuss D, Soler P, Saumon G (1995) Mechanical ventilation-induced pulmonary edema. Interaction with previous lung alterations. Am J Respir Crit Care Med 151:1568–1575
9. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CR (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338:347–354
10. Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308
11. Stüber F, Wrigge H, Schroeder S, Wetegrove S, Zinserling J, Hoeft A, Putensen C (2002) kinetic and reversibility of mechanical ventilation associated and systemic inflammatory response in patients with acute lung injury. Intensive Care Med doi.org/10.1007/s00134-002-1321-7
12. Pugin J, Suter PM (1992) Diagnostic bronchoalveolar lavage in patients with pneumonia produces sepsis-like systemic effects. Intensive Care Med 18:6–10
13. Krause A, Hohberg B, Heine F, John M, Burmester GR, Witt C (1997) Cytokines derived from alveolar macrophages induce fever after bronchoscopy and bronchoalveolar lavage. Am J Respir Crit Care Med 155:1793–1797

14. 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
15. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:54–61
16. Pugin J, Ricou B, Steinberg KP, Suter PM, Martin TR (1996) Proinflammatory activity in bronchoalveolar lavage fluids from patients with ARDS, a prominent role for interleukin-1. Am J Respir Crit Care Med 153:1850–1856
17. Pugin J, Verghese G, Widmer MC, Matthay MA (1999) The alveolar space is the site of intense inflammatory and profibrotic reactions in the early phase of acute respiratory distress syndrome. Crit Care Med 27:304–312
18. O'Grady NP, Preas HL, Pugin J, Fiuza C, Tropea M, Reda D, Banks SM, Suffredini AF (2001) Local inflammatory responses following bronchial endotoxin instillation in humans. Am J Respir Crit Care Med 163:1591–1598
19. Slutsky AS, Tremblay LN (1998) Multiple system organ failure. Is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 157:1721–1725
20. Munford RS, Pugin J (2001) Normal responses to injury prevent systemic inflammation and can be immunosuppressive. Am J Respir Crit Care Med 163:316–321