

Is mechanical ventilation an inflammatory insult?

Recent experimental work supports the concept of ventilator-induced lung injury (VILI) precipitating multiple organ dysfunction either through direct transmission of bacteria from the lung or decompartmentalization of locally produced mediators of inflammation (1). In a canine study of mechanical ventilation following *E. coli* instillation, Nahum, et al demonstrated an increased rate of bacterial transmission into the blood stream with a high tidal volume, low Positive End-Expiratory Pressure (PEEP) ventilator strategy (2). Pulmonary translocation of endotoxin has also been related to ventilator strategy employed (3). Subsequent reports suggest that a shift in cytokines between the vascular and alveolar compartments may occur (4).

In rats injured by hydrochloric acid installation, a high tidal volume, low PEEP strategy increased levels of Tumor Necrosis Factor (TNF)- α and MIP-2 in the circulation (5). Another small animal study demonstrated that at high peak ventilator pressures TNF- α appeared to move between alveolar and vascular compartments (4). Elevating the level of PEEP appeared to reduce systemic spread (decompartmentalization) of TNF- α produced in the lung. While much has recently been written relating management of mechanical ventilation to pulmonary and systemic inflammation, we will briefly examine the quality of evidence surrounding this link.

Proinflammatory cytokines are potential candidates for initiation or potentiation of VILI and may drive some of the outcome effects attributed to inappropriate patterns of mechanical ventilation (6). Nonetheless, cellular and molecular mechanisms accounting for the biotrauma of VILI are unknown. In vitro and in vivo studies imply that cellular stretch may be a part of the transduction of mechanical injury to the lung to biotrauma. Matthay, in a recent editorial, hypothesizes that pulmonary epithelium is an important modulator of VILI (7). Taylor and Lausch suggest that the lung may help regulate systemic inflammation through responses to inflammatory mediators and cell populations passing through the pulmonary vascular bed (8). It seems obvious that modulating inflammatory response could favorably affect the response to mechanical injury to the lung caused by mechanical ventilation.

One approach to evaluating available data on the role of inflammatory mediators in VILI is an analogy to Koch's postulates (9,10). Filkins, in a recent publication, similarly suggests the type of evidence required to ascribe an etiological

role to any given cytokine in the pathogenesis of a post-traumatic syndrome such as VILI. Three types of experimental evidence must be present:

1. When the clinical syndrome prevails, then cytokines are present.
2. When steps are taken to nullify the cytokine signal, then the clinical syndrome is alleviated.
3. When a purified cytokine is administered to a test subject, then the syndrome ensues.

First, we must assess the relationship between injurious patterns of ventilation and cytokine release. Isolated perfused (blood free) and ventilated murine lungs (with no influence of extrapulmonary organs) release cytokines with hyperventilation (11). During low tidal volume ventilation, reduced amounts of proinflammatory cytokines may be detected in the perfusate circuit. In these experiments, no physical damage was noted on gross examination and light microscopy. Thus, mechanisms other than tissue destruction may account for release of cytokines. Mediator release could be caused by stretch or over distention of the lung (12). In vitro examination of cellular deformation suggests that stretching may trigger inflammatory response at the level of alveolar epithelial cells.

In further studies in rat lungs, an association was found between high tidal volume, low PEEP, high frequency and proinflammatory cytokine release. Again, in an ex vivo rat lung study, a significant relationship was found between respiratory system pressure time characteristics, lung injury score and elevated proinflammatory cytokine levels (13). In another isolated rat lung model, a low tidal volume, low PEEP strategy yielded reduced levels of proinflammatory cytokines whereas a high tidal volume administered without PEEP produced the highest levels of cytokines including TNF- α , MIP-2, interleukin (IL)-1 β , interferon gamma and IL-6 (14).

These isolated organ experiments are supported by a small amount of clinical data. A recent study using bronchoalveolar lavage material suggests that polymorphonuclear leukocytes (PMNs) are activated by mechanical ventilation. Subsequent release of neutrophil elastase correlated with the degree of systemic inflammatory response and multiple organ failure (15). Where patients were treated with conventional (high tidal volume, low PEEP) ventilatory strategy, a greater amount of elastase was recovered from bronchoalveolar lavage as

well as a higher number of activated neutrophils. Where a low tidal volume, high PEEP strategy was employed, neutrophil and elastase levels were reduced. Increased plasma concentrations of IL-6 appeared to correspond with increased release of neutrophil elastase. A second recent clinical study divided 37 patients into experimental groups (16). One group received standard mechanical ventilation while the second received a lung protective strategy. Patients receiving conventional ventilation had increased bronchoalveolar lavage concentrations of IL-1b and IL-6 with plasma levels of TNF and IL-6 increased over 36 hours. Lung protective ventilation was associated with reduced detection of inflammatory mediators. The authors concluded that mechanical ventilation may affect cytokine response and that this response may be attenuated by a strategy designed to minimize over distention and injurious inflation/deflation cycles during ventilation.

While the above work suggests a correspondence between injurious ventilation and proinflammatory cytokine release, two studies do not confirm these results. First, in a carefully executed rat study, high versus low tidal volume ventilation did not affect cytokine release (17). A subsequent clinical study compared patients receiving high or moderate tidal volumes. No differences were identified between groups in plasma cytokines which remained low in all settings. Notably, the duration of mechanical ventilation in these patients was only one hour and no previous priming insult was present (18).

The second component of evidence supporting inflammatory mediators as participants in ventilator-induced lung injury comes from studies where blockade of these agents reduces evidence of VILI. Only two preclinical studies address this issue. First, Imai and coworkers pretreated rabbits with intratracheal installation of anti-TNF- α antibody (19). Rabbits were then ventilated aggressively for 4 hours in a pattern thought to cause VILI. Compared to control rabbits, animals receiving anti-TNF- α antibody displayed improved oxygenation and respiratory compliance, reduced infiltration of leukocytes and decreased changes on pathologic examination. An IL-10 activator has also been examined as an antiinflammatory strategy in a rabbit model of lung injury secondary to pancreatitis. Injection of this material resulted in significant reduction in blood levels of TNF- α and IL-8 from 3 to 6 hours after onset of mechanical ventilation (20). In addition to reduction in proinflammatory cytokines, IL-10 activation reduced the amount of ascitic fluid and inhibited neutrophil infiltration and margination. Edema and microvascular thrombosis was reduced in pulmonary tissue specimens with IL-10 activation.

The third component in the case regarding a role for inflammatory mediators in ventilator-induced lung injury addresses the impact of combined administration of injurious ventilation and triggers of inflammation. In an insult, which combines inflammatory and mechanical components, the contribution of each must be dissected to best understand their

interaction and relative contribution. To our knowledge, no studies have adequately addressed this issue.

While we are seeing exciting developments with respect to critical care interventions and patient outcomes, the biologic aspects of VILI remain a laboratory phenomenon and our understanding insufficient to permit effective clinical application. Dreyfuss and coworkers provide a more detailed review of this issue (21). We provide a standard approach to categorization of this evidence on VILI.

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