Pathogenesis of ventilator-induced lung injury: trials and tribulations

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Research into ventilator-induced lung injury (VILI) spans the decades since this life-sustaining technology was introduced into widespread clinical use in the mid-twentieth century (24). Early on, it was recognized that lungs ventilated with high ventilatory pressures have a propensity to develop air leaks (barotrauma). However, investigators soon realized that it was excessive lung volume (volutrauma) rather than the ventilatory airway pressure per se that produced lung injury (8). At the other end of the spectrum, ventilation using low end-expiratory lung volumes that allowed repetitive alveolar opening and collapse was also injurious (atelectrauma) (34). Over the past few years there has been a realization that injury due to mechanical ventilation represents not only structural disruption of the lung but can also have an inflammatory component associated with mediator release (biotrauma), which can worsen lung injury and potentially cause systemic organ dysfunction (25, 27, 35, 41).

One of the earliest studies to suggest an inflammatory mechanism for VILI was that of Kawano et al. (14). Having noticed an association between the development of VILI and the presence of increased numbers of neutrophils within surfactant-depleted lungs, they repeated experiments in neutrophil-depleted rabbits and found only minimal lung injury. Numerous studies followed exploring the role of various inflammatory mediators in a variety of live animal and ex vivo models. In the hunt for a key putative mediator, it was not surprising that TNF-α, one of the first cytokines to be characterized and a pivotal mediator of the inflammatory cascade, received a great deal of attention.

These early studies, however, produced a debate as to the role of TNF-α in VILI (31, 42, 46). In the presence of a preexisting stimulus such as LPS or surfactant depletion, lungs subjected to injurious mechanical ventilation often had elevated levels of lung TNF-α detected (13, 15, 17–19, 29, 31, 37–39), but not always (43). Similarly, in lungs injured purely by mechanical ventilation, elevated TNF-α levels were detected in many studies (3, 4, 6, 20, 26, 30, 32, 36, 39, 40, 45, 46), but not all (11, 31). Were these conflicting results due to inherent differences in the studies (e.g., different species/strains, in vivo vs. ex vivo models, different time points, varying severity in lung injury, contamination by endotoxin) or problems with the assays (e.g., mRNA vs. protein, different reagents/sensitivities, sample degradation by endogenous proteases, presence of inhibitors)? And, perhaps more importantly, what role (if any) were the inflammatory mediators such as TNF-α playing in the pathogenesis of VILI and systemic injury?

The report from Wilson et al., one of the current articles in focus (Ref. 46, see p. L599 in this issue), presents a novel approach using transgenic mice to further elucidate the role of TNF-α in ventilator-induced lung inflammation. This study builds on the results of two earlier studies in which Wilson and colleagues used a mouse model and demonstrated that 1) high-volume ventilation produces an early but transient increase in bronchoalveolar lavage TNF-α (as detected by ELISA and bioactivity) (45); and 2) high-volume ventilation produces early changes in deformability of circulating polymorphonuclear leukocytes (PMN) and increases PMN sequestration mediated by l-selectin within the pulmonary vasculature (5, 45). In their latest study, Wilson et al. (46) examined the effect of high-volume ventilation on the lung inflammatory response (as assessed by lung neutrophil infiltration) in either wild-type mice or double knockout (DKO) mice lacking TNF receptors (46). They also examined the effect on neutrophil infiltration of administering anti-TNF-α antibody, either intravenously or intratracheally. The three salient findings were 1) in the absence of functional TNF-α signaling (DKO mice or intra-alveolar anti-TNF-α antibody), neutrophil influx into lungs of mice subjected to an injurious ventilation strategy was significantly reduced; 2) reduced neutrophil infiltration occurred despite no reduction in alveolar CXC chemokines [macrophage inflammatory protein-2 (MIP-2) or keratinocyte-devoid chemokine]; and 3) in contrast to intratracheal anti-TNF-α antibody, intravenous anti-TNF-α antibody had no apparent effect on PMN influx into the lungs. As such, Wilson et al. concluded that TNF-α signaling mediates, in part, the pulmonary inflammation induced by high-stretch ventilation in mice (46).

Will this study definitively lay to rest the debate about the role of TNF-α in the pathogenesis of VILI? No, particularly if this study is looked at in isolation. As the authors clearly point out, the end point of the current study was inflammation (not injury) as assessed by neutrophils in lung lavage at the end of a 4-h ventilation protocol, and the mere presence of increased neutrophils is not synonymous with subsequent lung injury (16). Furthermore, as the authors concede, there are model- and species-specific limitations that prevent direct extrapolation of their findings to other species (1). However, if viewed in the context of the literature, the study by Wilson et al. (46) does identify a novel role for TNF-α signaling in mediating high-volume, ventilation-induced neutrophil lung infiltration in mice, and it further strengthens the argument that the release of inflammatory mediators with injurious ventilation is an early event that precedes neutrophil infiltration and the development of histological signs of lung injury. Indeed, a couple of previous studies have demonstrated that the use of antibodies to TNF-α decreased VILI or its systemic sequelae. For example, Imai and colleagues (13) demonstrated that administration of intratracheal anti-TNF-α antibody in an in vivo surfactant-
depleted rabbit lung model minimized VILI (as assessed by oxygenation, compliance, leukocyte infiltration, and histology). Guery et al. (10) demonstrated that intravenous delivery of a TNF-α antibody mitigated pulmonary (capillary-pulmonary permeability) and systemic effects (gut permeability) of VILI.

The current results of Wilson et al. (46) do raise a number of interesting questions and dilemmas. First, why did TNF receptor−/− mice develop the same level of lung injury (as assessed by gas exchange and lavage protein levels) following the same duration of high-volume ventilation as the wild-type mice? Were compensatory pathways in the DKO mice responsible? Or, does this mean that TNF signaling has no role in the initiation of VILI? Certainly we know that when Debs et al. (7) administered aerosolized TNF-α to normal lungs, they found only a mild pulmonary inflammatory response consisting of increased margination of leukocytes and a few small foci of pulmonary hemorrhage, with no evidence of lung edema or significant pulmonary infiltrates. Second, it is notable that the wild-type mice given anti-TNF-α antibody an hour after initiation of injurious ventilation still had an ~70% reduction in neutrophil infiltration (a greater reduction than that seen in DKO mice−/− for TNF receptors). Although this raises the question again as to the importance of TNF signaling in the earliest stages of VILI, it does have an important therapeutic implication, i.e., that interventions to reduce ventilator-induced inflammation do not necessarily have to precede the period of injurious ventilation. Clinically, this is important, as the initiation of mechanical ventilation in normal lungs is not necessarily synonymous with initiation of VILI (assuming injurious ventilation settings are not inadvertently used). Rather, as patients develop progressive and/or heterogeneous lung disease, the risk of VILI due to regional disparities in ventilation (e.g., regional alveolar overdistension and/or repetitive opening and collapse) becomes a greater concern.

Third, the finding that ventilation-associated neutrophil infiltration could be attenuated by intratracheal administration of an anti-TNF-α antibody supports the concept that it may be possible to selectively target the lung in future clinical studies to mitigate ventilation-induced changes (thereby avoiding systemic toxicity). Unfortunately, at present, the specific cells responsible for initiating the earliest events in VILI/inflammation are as yet unknown, although there are data implicating the pulmonary epithelium (40). Thus it also remains unknown whether an endothelial rather than an epithelial approach (or both) will be needed if the goal is to prevent initiation of the inflammatory cascade. Also, as Wilson et al. (46) concede, lack of TNF signaling only reduced but did not abolish neutrophil infiltration. Thus, analogous to the role of TNF-α in sepsis (1), other mediators/mechanisms appear to be involved in ventilator-induced lung inflammation. Indeed, it is quite interesting that similar reductions in VILI/inflammation have been achieved in various animal models using a wide array of agents targeting different pathways. For example, agents that have been shown to reduce VILI/inflammation include anti-chemokine antibodies [e.g., anti-MIP-2 (28) and anti-CXCR2 (2)], matrix metalloproteinase inhibitors (9), steroids (12), pentoxifylline (20), inhibitors of neutrophil adhesion (33), ion channel inhibitors [e.g., gadolinium (23)], tyrosine kinase inhibitors [e.g., genistin (21)], myosin light chain kinase inhibitors (21, 44), and isoproterenol (21, 22). Fourth, what are the pathways whereby TNF signaling alters neutrophil infiltration despite similar levels of chemokines? Fifth, given the incidence of infectious complications in patients with acute respiratory distress syndrome requiring ventilation, would the risks of blocking a pivotal inflammatory mediator such as TNF-α to reduce ventilator-induced inflammation outweigh the benefits?

Finally, the study by Wilson et al. (46) also serves as an example of the complexities and difficulties involved in dissecting out mechanisms of VILI. For example, to balance the goal of producing a uniform level of early “pure mechanical lung stretch” injury in vivo in otherwise normal mice (with the goal of being able to assess neutrophil infiltration in live mice several hours later), only an hour of high-volume ventilation was used followed by 3 h of a less-injurious strategy (i.e., 2 ventilation strategies/subject). In addition, the high-volume strategy consisted of both high tidal volume ventilation (43–44 ml/kg) and zero positive end-expiratory pressure (i.e., both overdistension and potential repetitive opening/collapse). If one also considers the multiple systemic sequelae of high-volume ventilation in vivo, it becomes impossible to pinpoint the particular stimulus or component of the ventilation strategy that led to the TNF-α-mediated changes in neutrophil infiltration. If one then considers species-specific differences as well individual genetic determinants of each of the various components of the inflammatory response to a given stimulus, the only firm conclusion becomes that many more trials and tribulations will come to pass before the precise role of TNF-α (and other inflammatory mediators) in the pathogenesis of VILI is defined.

In summary, our understanding of VILI has increased due to the efforts of numerous investigations such as the one in the current issue of AJP-Lung Cellular and Molecular Physiology. However, additional studies in a variety of models are needed to confirm and further dissect out the intricate interactions of ventilation strategies with the lung and the host immune/inflammatory response, particularly if novel molecular interventions to mitigate VILI are to be developed. And, with each new study, investigators will continue to face the age-old challenge described by Epictetus in the second century AD: Things either are what they appear to be; or they neither are, nor appear to be; or they are, and do not appear to be; or they are not, yet appear to be. Rightly to aim in all these cases is the wise man’s task.

REFERENCES
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