

Mechanical Ventilation

Taking Its Toll on the Lung

MECHANICAL ventilation—although necessary to support respiration during anesthesia for surgical procedures and to sustain life in patients with acute lung injury (ALI)—may directly or indirectly damage the lung. This is termed ventilation-induced lung injury. The demonstration that low-tidal volume protective ventilation strategies can improve patient survival in ALI/acute respiratory distress syndrome (ARDS)¹ has been hailed as a key therapeutic advance of the past decade. Furthermore, the pathogenic mechanisms contributing to ventilation-induced lung injury are increasingly well understood. For the anesthesia and critical care communities, however, a troubling body of evidence is emerging to suggest that mechanical ventilation at even clinically relevant low tidal volumes and for relatively short periods of time may activate an inflammatory response in the lung. This raises the possibility that mechanical ventilation of our patients in the operating room as well as in the critical care unit may increase susceptibility to subsequent lung and systemic organ injury. A better understanding of the mechanisms by which this occurs is essential to minimize the potential for harm to patients. In this regard, the findings by Vaneker *et al.*² that the Toll/interleukin-1 receptor domain-containing adapter protein inducing interferon- β (TRIF) plays a key role in ventilator-induced pulmonary inflammation represent an important step forward.

Toll-like receptors (TLR) have long been recognized to play a role in the immune response to pathogens.³ This nine-member family of receptors activates a series of complex and highly conserved signaling pathways. These ultimately lead to the activation of nuclear factor- κ B (NF- κ B), a transcription factor that is central to the initiation of inflammation, innate immunity, and repair. Specific TLR's include TLR4, which is the receptor for endotoxin, and TLR3, which senses viral DNA. Recently, the potential for TLRs to be activated after a nonseptic insult, such as acid aspiration⁴ and mechanical ventilation,⁵ has been demonstrated. Most closely implicated in the pathogenesis of this nonseptic immune

response is TLR4. In a previous paper in *ANESTHESIOLOGY*, Vaneker *et al.*⁵ reported that TLR4-deficient animals have a reduced, although not abolished, inflammatory response to mechanical ventilation. The specific endogenous activators of TLR's remain to be determined, but potential candidates include modified matrix components, hyaluronan, high-mobility group box chromosomal protein 1,⁶ and oxidized phospholipids⁴ (fig. 1).

The signaling pathways activated by TLRs are complex and tightly regulated. After activation of TLR4, two separate intracellular signaling pathways may be activated (fig. 1). The best characterized is the classic MyD88 (myeloid differentiation primary-response gene 88) pathway, which causes rapid activation of NF- κ B.³ This pathway is the signaling adaptor for most TLRs, with the exception of TLR3 and certain TLR4 signals.³ The other signaling pathway involves TRIF, the focus of the paper by Vaneker *et al.*² In a recent publication, Imai *et al.*⁴ demonstrated that the TRIF pathway, and not the MyD88 pathway, was the key pathway that controlled the inflammatory response to acid aspiration and viral pathogen-induced lung injury. Vaneker *et al.*,² therefore, hypothesized that the TRIF pathway was likely implicated in the inflammatory response to mechanical ventilation.

For these studies, they randomized wild-type and TRIF knockout mice to undergo mechanical ventilation by using a clinically relevant strategy (tidal volume 8 ml/kg, positive end expiratory pressure of 4 cm H₂O and F_{IO}₂ 0.4) for 4 h. Two separate experimental series were conducted. In the first series, the mice were instrumented for hemodynamic measurement. In the second series, cytokine and histologic analyses were performed. Endotoxin contamination was carefully excluded—an important issue when conducting studies on the TLR4 pathway.

The results from the wild-type mice support earlier findings from experimental^{2,5} and clinical^{7,8} studies that even relatively low stretch mechanical ventilation activates a pulmonary and systemic inflammatory response in the absence of prior injury. Pulmonary levels of interleukin-1 α , interleukin-1 β , and keratinocyte-derived chemokine were all increased. Most interestingly, however, they found that mechanical ventilation of TRIF knockouts elicited only a modest increase in interleukin-1 β and keratinocyte-derived chemokine. Consistent with these findings, the activation of NF- κ B in the lung was reduced in the TRIF-deficient mice. This ventilation strategy also generated a *systemic* cytokine response in the wild-type compared to the knockouts, increasing plasma concentrations of interleukin-6 and keratinocyte-derived chemokine. Not surprisingly, given the mechanical ventilation

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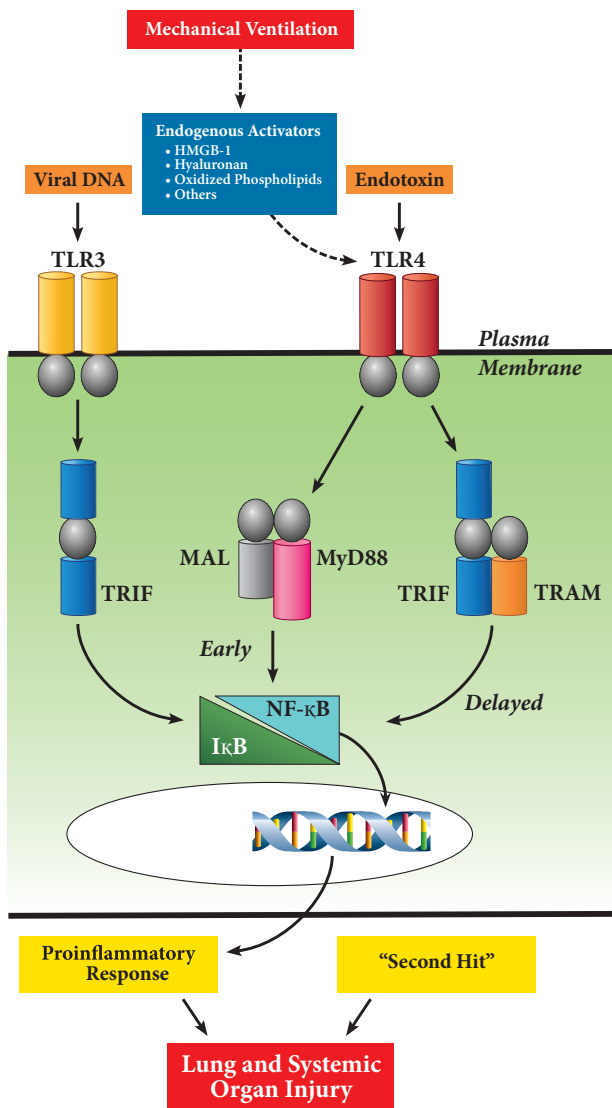


Fig. 1. Mechanical ventilation induces a TLR-TRIF-mediated inflammatory response that may cause or predispose to lung and systemic organ injury. Mechanical ventilation may activate TLR receptors, particularly TLR4, via the production of putative endogenous activators such as oxidized phospholipids. Activation of the TLR4 receptor, by endotoxin or endogenous activators, leads to activation of the MyD88-MAL and/or TRIF-TRAM pathways. TRIF may also be activated after activation of the TLR3 receptor, e.g., by viral DNA. MyD88 and TRIF activate complex kinase cascades leading to the phosphorylation and inactivation of the I κ B α subunit, which binds and inactivates NF- κ B in the cytoplasm. I κ B dissociates, and the activated NF- κ B translocates to the nucleus and activates the transcription of a host of cytokines and other factors important in inflammation and repair. After a second hit such as sepsis, a generalized inflammatory response, leading to lung and systemic organ injury, may result. HMGB-1 = high-mobility group box chromosomal protein 1; MAL = MyD88 adaptor-like protein; MyD88 = myeloid differentiation primary-response gene 88; TLR = Toll-like receptor; TRAM = TRIF-related adaptor molecule; TRIF = Toll/interleukin-1 receptor domain-containing adapter protein inducing interferon- β .

strategy used, there was no evidence that either the wild-type or the TRIF knockouts sustained a lung injury.

The importance of these findings stems from the potential for mechanical ventilation to harm our patients. It

is clear from multiple studies in patients with ARDS that high stretch ventilation can exacerbate damage to the lungs and increase mortality.¹ The impact of lung stretch for patients with healthy lungs is less clear. It is reported that high stretch ventilation can predispose patients who are ventilated for other reasons, such as after major surgical procedures, to develop ALI/ARDS. However, several days of mechanical ventilation appear to be required.⁹ In a recent clinical study of patients with healthy lungs ventilated for at least 5 h, serum markers sensitive for lung injury revealed no indication that high (12 ml/kg) tidal volumes were any more injurious than low (6 ml/kg) tidal volumes.¹⁰ Similarly, when we look at measures of inflammation in otherwise healthy patients who receive mechanical ventilation, the evidence does not point to a flagrant response. Indeed, Wrigge *et al.* found no effect at all on levels of cytokines, irrespective of whether mechanical ventilation was applied with high (15 ml/kg) or low (6 ml/kg) tidal volumes.¹¹ In a more recent study, Wolthuis *et al.*⁷ found modest elevations in levels of interleukin-6 and interleukin-8 with mechanical ventilation, but there were no significant differences between the high (12 ml/kg) and low (6 ml/kg) tidal volume groups.

In common with several other forms of organ injury, therefore, a two-hit process may be required for the development of ventilator-induced lung injury. If this is the case, is there a scientific rationale to support an involvement of TLR4 and TRIF in this process? Interestingly, the potential for activation of TLR4 by other stimuli, such as endotoxin, to cause priming for a later insult, has recently been demonstrated.¹² Perhaps most intriguing of all, is the possibility, yet to be directly investigated, that anesthetic agents might interact with this pathway to modulate the response of lung tissue to stress-induced injury. In a recent report, inhibition of complex I of the mitochondrial respiratory chain in lung tissue was found to abrogate TLR4-mediated inflammatory activation and to attenuate lung injury in a murine model.¹³ Halogenated anesthetics are known inhibitors of complex I.¹⁴ Others, investigating the effects of propofol, found downregulation of TLR4-mediated responses to endotoxin in cultured cells.¹⁵ Have we been unknowingly intervening on this process all along?

The study from Vaneker *et al.*² has some limitations. First, it is important to consider that the animals received a tidal volume of 8 ml/kg, which is at the high end of the range that would be acceptable in current clinical practice.¹ Even at this degree of lung stretch, there was no evidence of lung injury or circulatory compromise, and the significance of the cytokine generation recorded is therefore questionable. Second, the 4-h duration of mechanical ventilation in these studies was relatively short. TRIF causes delayed activation of NF- κ B, raising the possibility that the findings might differ when mechanical ventilation is more prolonged. Lastly, and perhaps

most crucially, further studies are needed to determine whether this inflammation is exclusively mediated *via* the TLR4-TRIF pathway; TLR3 may also signal through TRIF (fig. 1). Although the authors' previous work does point to the importance of TLR4,⁵ the current study does not exclude other TLRs in the ventilator-inflammatory response. Moreover, MyD88 knockout mice have also been shown to have defective production of cytokines in response to TLR ligands.¹⁶ The role of MyD88-signaling in ventilation-induced lung injury deserves more study. Finally, the ligand responsible for receptor activation can only be guessed at. A Pandora's box has clearly been opened!

Notwithstanding these issues, Vaneker *et al.*² make an important contribution to our understanding of the mechanisms by which mechanical ventilation, even at relatively modest degrees of tidal stretch, may cause a pulmonary and systemic inflammatory response. The potential for mechanical ventilation to prime the lung for subsequent injury is clear. We await with interest further developments in the elucidation of the role of the TRIF pathway in the pathogenesis of mechanical ventilation-induced lung injury.

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