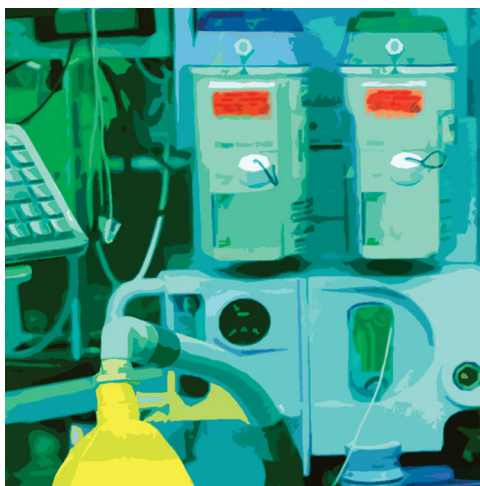


Ventilator-induced Lung Injury in Healthy and Diseased Lungs

Better to Prevent than Cure!

IN this issue of ANESTHESIOLOGY, Curley *et al.*¹ report on the time course and mechanisms of resolution and repair after ventilator-induced lung injury (VILI) in previously healthy rats. Few previous studies have reported on the time course of lung remodeling and repair in normal² and injured^{3,4} lungs. The current study established a relevant experimental model to better identify the healing and remodeling processes in VILI. Understanding these processes will help develop new potential strategies for VILI. Furthermore, the experimental data provided suggest that nonprotective ventilation in healthy lungs makes the lungs weaker. This information has clinical relevance in the context of mechanical ventilation-induced damage (as often occurs during surgery) in patients with healthy lungs, recovery in intensive care units after brain injury, as well as in donors, or other clinical conditions in which the lungs are not primarily affected.

Two ventilatory strategies were used: tidal volume to reach inspiratory pressure of 35 cm H₂O and positive end-expiratory pressure of 0 cm H₂O; and tidal volume = 6 ml/kg and positive end-expiratory pressure = 2 cm H₂O. Animals not subjected to anesthesia or mechanical ventilation were used as a sham group. Inflammation and repair were analyzed in VILI animals at different time points (6, 24, 48, and 96 h; 7 and 14 days). VILI led to early neutrophil infiltration associated with release of proinflammatory (tumor necrosis factor- α and interleukin-1 β) and antiinflammatory (interleukin-10) cytokines. Furthermore, an early increase in transforming growth factor- β and a transient fibroproliferative response were observed. Both inflammation and fibrogenesis decreased late



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in the course of VILI, and normal lung architecture was restored.

VILI is the result of a complex interplay among various mechanical forces acting on lung structures during mechanical ventilation.⁵ Critical physical forces contributing to VILI have been defined as stress (force per unit of area) or strain (force along longitudinal axis), and their primary possible targets include epithelial and endothelial cells, extracellular matrix (ECM), and peripheral airways. Curley *et al.*¹ investigated four specific mechanisms of lung repair: regulation of apoptosis by lymphocytes; the balance and time kinetics between transforming growth factor- β and keratinocyte growth factor; fibrogenic response and collagen deposition; and the balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). Alveolar lymphocytes and monocytes/macrophages modulate innate immune responses and also induce neutrophil apoptosis and phagocytosis of inflammatory cells participating in the repair process. Therefore, in the absence of apoptosis and cleavage of alveolar lymphocytes and monocytes/macrophages, the repair process may not occur.

Transforming growth factor- β has been reported to stimulate fibrogenesis, whereas keratinocyte growth factor is an epithelial-specific growth factor that suppresses fibroproliferation after stretch injury. Interestingly, in the study by Curley *et al.*, stretch-induced lung injury triggered a pronounced early profibrotic stimulus, with an increase in procollagen I messenger RNA and myofibroblasts followed by progressive decrease. Conversely, procollagen III messenger RNA as well as lung tissue collagen were unaffected by VILI and did not change with time. Collagen fibers are the main ECM component, with type III collagen fiber a precursor of

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type I collagen. The turnover of collagen fibers is a dynamic process that is necessary to maintain the normal lung architecture. In short: messenger RNA collagen response in lung tissue does not always reflect the actual production of collagen; the degree of inflammation is dissociated from lung tissue collagen deposition⁴; despite stimulating the production of procollagen I messenger RNA, transforming growth factor- β did not yield collagen deposition in lung tissue; and keratinocyte growth factor plays a pivotal role in inhibiting fibrogenesis. These observations may open new perspectives in the pharmacologic management of the fibrogenic process.

A favorable balance between MMPs and TIMPs is believed to be necessary to facilitate cell detachment from the basement membrane and cell migration during lung parenchyma remodeling and healing. Alveolar concentrations of MMPs and TIMPs increased rapidly after VILI, but decreased to preinjury concentrations by 96 h. Because MMPs may cause significant host damage, their proteolytic activity is tightly regulated at multiple levels, such as the activation of proenzymes and *via* suppression by TIMPs. Any imbalance between MMPs and TIMPs determines matrix turnover, and either an excess of MMPs or a deficit of TIMPs may result in excess extracellular matrix degradation.

We hypothesize the following sequence of events during VILI in healthy lungs: first, excess stress and strain promote a fragmentation of the ECM that results in progressive loosening of proteoglycan intermolecular connections with other ECM components as well as epithelial-endothelial cells. The loss of proteoglycan regulatory functions compromises the protective role of the ECM, leading to interstitial and eventually severe lung edema. Second, inflammatory and anti-inflammatory processes are activated by the presence of epithelial and endothelial cells as well as released fragments of proteoglycans. Third, collagen synthesis is activated to stimulate the repair process. Fourth, if the VILI stimulus persists, type III collagen fiber and subsequently type I are synthesized and mediated by different biochemical factors. Thus, collagen matrix deposition would be expected to decrease interstitial compliance and make the ECM stronger. This process is essential for the correct cross-talk between ECM, cells, and biochemical response. If the VILI stimulus does not persist, the collagen is not synthesized and inflammation decreases over time. Therefore, collagen synthesis might be an effective process to protect the lung if a VILI stimulus is maintained over time.

Thus, VILI might be a continuous phenomenon that depends on the level and time of stress and strain application, and not an “on-off” process, as previously suggested.⁶

It is important to consider therapeutic maneuvers that minimize injury and reduce lung volume during general anesthesia and in the early postoperative period. The reduction in lung volume during surgery and in the early postoperative period is associated not only with detrimental effects on re-

spiratory mechanics and gas exchange but also with increased risk of lung injury and infection.

It is the authors' expert opinion that important strategies include protective ventilation with tidal volume lower than 10 ml/kg ideal body weight and plateau pressure of the respiratory system equal to or lower than 20–25 cm H₂O⁷; moderate levels of positive end-expiratory pressure equal to or higher than 5 cm H₂O⁷; induction of anesthesia with noninvasive respiratory support⁸ as well as recruitment maneuver at 35–40 cm H₂O immediately after intubation and before extubation,⁹ an alternative that might be considered in clinical conditions where a marked reduction in lung volume is expected (*e.g.*, obese patients or those with increased intraabdominal pressure); and optimized fluid balance, respiratory therapy, and pain management,¹⁰ which should always be considered in the early postoperative period in patients identified as being at risk to develop postoperative pulmonary complications.

In conclusion, the study by Curley *et al.* in the current issue of ANESTHESIOLOGY provides novel information on the lung remodeling process in healthy lungs undergoing mechanical ventilation, as well as allows the formulation of new hypotheses for the diagnosis and treatment of lung repair and remodeling in healthy lungs. However, because the best approach is still prevention, gentle treatment of the lung when mechanical ventilatory support is required is foremost.

“It is easier to prevent bad habits than to break them.” Benjamin Franklin (January 17, 1706 [O.S. January 6, 1705]–April 17, 1790), scientist and one of the Founding Fathers of the United States.

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