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Mechanisms of ventilator-induced lung injury in healthy lungs

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Mechanical ventilation is an essential method of patient support, but it may induce lung damage, leading to ventilator-induced lung injury (VILI). VILI is the result of a complex interplay among various mechanical forces that act on lung structures, such as type I and II epithelial cells, endothelial cells, macrophages, peripheral airways, and the extracellular matrix (ECM), during mechanical ventilation. This article discusses ongoing research focusing on mechanisms of VILI in previously healthy lungs, such as in the perioperative period, and the development of new ventilator strategies for surgical patients. Several experimental and clinical studies have been conducted to evaluate the mechanisms of mechanotransduction in each cell type and in the ECM, as well as the role of different ventilator parameters in inducing or preventing VILI. VILI may be attenuated by reducing the tidal volume; however, the use of higher or lower levels of positive end-expiratory pressure (PEEP) and recruitment maneuvers during the perioperative period is a matter of debate. Many questions concerning the mechanisms of VILI in surgical patients remain unanswered. The optimal threshold value of each ventilator parameter to reduce VILI is also unclear. Further experimental and clinical studies are necessary to better evaluate ventilator settings during the perioperative period in different types of surgery.

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Introduction

Mechanical ventilation is a supportive therapy used to maintain respiratory function and to minimize the task of breathing in several clinical and surgical scenarios [1]. Much research has focused on the development of ventilator strategies for reducing ventilator-induced lung injury (VILI) in different respiratory diseases [2]; however, the rationale for using protective ventilator strategies in healthy lungs, such as in the perioperative period, requires elucidation. During the perioperative period, general anesthesia, either combined or not with neuromuscular blockade, may affect the alveolar capillary membrane [3], reducing surfactant and functional residual capacity, leading to alveolar collapse, and thus impairing lung mechanics and gas exchange.

VILI is the result of a complex interplay among various mechanical forces that act on lung structures, such as type I and II epithelial cells, endothelial cells, macrophages, peripheral airways, and the extracellular matrix (ECM), during mechanical ventilation [4]. The critical physical forces contributing to VILI have been defined as stress (force per unit of area) and strain (force along the longitudinal axis). Two main mechanisms can lead to VILI: direct damage to the alveolar capillary membrane and ECM; or mechanotransduction, which is the conversion of a mechanical stimulus into intracellular biochemical and molecular signals.

The development of VILI can be triggered by a complex interplay of the following potentially injurious factors: (a) regional overdistension of the alveoli caused by application of high volumes and/or alveolar pressures; (b) modifications of local stress, which deforms cells and their supporting matrix into abnormal shapes and dimensions compared with normal spontaneous breathing; (c) abrasion of the epithelial airspace, observed in particular with ventilation at low tidal volumes (V_T) and caused by the repeated recruitment and derecruitment of unstable lung units; (d) conversion of surfactant molecules into inactive surfactant aggregates as a consequence of large alveolar surface area oscillations; and (e) increased stresses between neighboring cells and between cells and the surrounding tissue caused by the interdependence phenomenon.

In this review article, we focus on the mechanisms of mechanical stretch in each cell type (Fig. 1) and in the ECM (Fig. 2), and we seek to elucidate their contribution to VILI in previously healthy lungs (during the perioperative period).

Type I epithelial cells

Type I epithelial cells comprise >95% of the surface area of the alveolus. These cells can respond to cyclic stretch through genomic alterations, depending on the magnitude and duration of stress [5]. Several genes are upregulated during type I epithelial cell stretch, such as the epidermal growth factor receptor ligand amphiregulin; genes involved in maintaining glutathione homeostasis; and Ppp1r10, an inhibitory protein of protein phosphatase 1. Type I cells display a duration-dependent microRNA (miRNA) expression profile in response to cyclic stretch [6], with loss of tight junction integrity and increased paracellular permeability. Specific inhibition of miRNAs (miR-466d-5p and miR-466f-3p) has been shown to result in the preservation of barrier permeability closer to that observed under unstretched conditions, thus enabling the recognition of relevant miRNA:messenger RNA (mRNA) interactions during cyclic stretch. The generation of reactive oxygen species (ROS), superoxide, and nitric oxide is also increased after different ranges of type I epithelial cell stretch (12%, 25%, and 37% change in surface area (ΔSA)) [7]. In addition, these ROS increments are associated with cell monolayer permeability via nuclear factor kappa B (NF-κB) activation and extracellular-signal-regulated kinase (ERK) phosphorylation. Administration of inhibitors of the Rac1 pathway (one of the Rho family of small guanosine triphosphatases (GTPases)) led to attenuation of the stretch-induced increase in permeability and signs of tight junction recovery through occludin expression [8]. Another pathway possibly associated with the recovery of tight junctions is Wnt signaling. This pathway comprises a family of highly conserved secreted growth factors that activate multiple signaling pathways controlling epithelial cell proliferation, differentiation, and migration [9]. The canonical Wnt pathway blocks the degradation of cytosolic β-catenin by translocating to the nucleus and binding to nuclear