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EDITORIAL

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Hitting new barriers in ventilator-induced lung injury

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In 2000 the hallmark study by the Acute Respiratory Distress Syndrome (ARDS) Network highlighted the risks immanent to mechanical ventilation with high tidal volumes [1]. Compared to ventilation with low tidal volumes of 6 ml/kg body weight, ventilation with tidal volumes of 12 ml/kg body weight increased mortality and prolonged ventilator use in patients with ARDS or acute lung injury [1]. It had already been recognized for years that ventilation with excessive tidal volumes may cause ultrastructural changes and stress failure of both the epithelial and endothelial barrier. This phenomenon was originally referred to as barotrauma and later, when increased tidal volume rather than peak inspiratory pressure was identified as primary trigger, as volutrauma [2]. More recently it became evident that ventilation strategies below the baro-/volutrauma safety margin may cause lung injury by activation of cellular responses at the alveolocapillary barrier.

Recently both sides of the alveolocapillary barrier, i. e., alveolar epithelial and lung endothelial cells, have been investigated intensely in cell culture models of cyclic stretch to simulate mechanical forces at the alveolocapillary barrier. These studies have yielded valuable information on mechanosensory signaling pathways in the different cell populations. However, their ready transfer to the in vivo situation is hampered by the fact that respiratory mechanics at the alveolar level, and thus the actual amount of mechanical shear and stretch acting upon these cells during the respiratory cycle are still poorly understood [3]. This situation is further complicated in lung injury when an unknown fraction of alveoli is no longer recruited, and redistribution of tidal volume to the remaining intact alveoli may cause additional overdistension.

Studies in vivo or in isolated perfused lungs, on the other hand, have primarily focused on two important aspects of mechano-induced cellular responses, i. e., the expression and release of inflammatory mediators and the regulation of endothelial responses. The notion that overventilation can cause the release of a variety of cytokines in the absence of direct cell necrosis has led to the biotrauma hypothesis according to which stretch-induced changes in gene expression and cellular metabolism cause the release of inflammatory mediators and can ultimately lead to the development of an overwhelming inflammatory response [4, 5]. Real-time microscopy or fresh isolation of microvascular cells revealed endothelial responses to overventilation in intact lungs such as increased formation of NO and focal adhesions as well as enhanced expression of P-selectin [6, 7]. Gravimetric measurements of the vascular filtration coefficient (K_f) during high volume ventilation provided insights into the regulation of endothelial permeability and underlined its role in ventilator-induced edema formation [6, 8, 9]. In contrast to these advancements in our understanding of endothelial permeability, our insights into the regulation of the alveolar epithelial barrier in ventilator-induced lung injury have been scarce. Studies in intact lungs have focused primarily on physiological functions of alveolar epithelial cells such as surfactant release [10] or alveolar fluid absorption [11]. In

a study now published in *Intensive Care Medicine* de Prost and colleagues applied an elegant double-indicator technique for simultaneous determination of the effects of high volume ventilation on both the alveolar epithelial and the microvascular endothelial barrier [12].

Low liquid conductance and permeability to small molecules normally prevent the filtration of fluid and protein into the alveoli of the intact lung [13]. Failure of the alveolar epithelial barrier promotes alveolar flooding and may simultaneously increase transendothelial fluid and protein flux by interstitial decompression. Changes in epithelial barrier properties may even influence the results of endothelial K_f measurements from whole-lung gravimetry which are based on the assumption of liquid conductance across a single, namely the endothelial barrier [14]. Several studies have previously shown that overventilation may increase lung epithelial permeability in the absence of overt structural damage. Ludwigs and coworkers [15] observed a ventilation-dependent increase in the lung clearance of inhaled technetium-99m-labeled diethylenetriaminepentaacetic acid in New Zealand rabbits from which they suggested that greater alveolar distension may increase epithelial permeability. Using a similar approach Man and colleagues [16] found an increased lung epithelial permeability in mongrel dogs after 4 h of high-frequency oscillatory ventilation with 8 or 16 Hz. Egan [17] demonstrated that lung epithelial solute permeability increases with increments in lung inflation volume and does not reverse immediately with subsequent deflation. These findings suggest that stretch-induced increases in epithelial permeability in the absence of structural barrier disruption play a critical role in the pathophysiology of ventilator-induced lung edema. However, the paucity of insights into underlying mechanosensitive signaling pathways has so far prevented the development of specific therapeutic strategies aimed at the protection or recovery of the lung epithelial barrier.

In their present study de Prost and colleagues [12] found that switching from conventional ventilation with 6 ml/kg body weight to high volume ventilation with 20–25 ml/kg body weight almost immediately increased the clearance of ^{99m}Tc-labeled albumin from the alveolar space. Importantly, intratracheal instillation of the β_2-adrenergic agonist terbutaline prior to high volume ventilation largely attenuated this increase in ^{99m}Tc-albumin clearance. This significant finding opens a new realm of research for pharmacological interventions to protect the alveolar epithelial barrier in ventilator-induced lung injury. A β_2-adrenergic agonist may be a particularly favorable choice in this context since β-sympathomimetics have been shown to strengthen the lung microvascular barrier in both inflammatory and hydrostatic stress [18, 19] and to increase alveolar fluid reabsorption during high volume ventilation [11]. Anti-inflammatory effects and stimulation of surfactant secretion by β-adrenergic agonists may yield additional benefits in lung injury [20]. Hence β_2-sympathomimetics such as terbutaline, salbutamol, and salmeterol may act independently on different targets at the alveolocapillary barrier to reduce edema formation and improve lung function.

By simultaneous analysis of ^{99m}Tc-albumin clearance from the airspace and pulmonary uptake of systemic ^{111}In-labeled transferrin de Prost and coworkers show that intratracheal instillation of terbutaline reduced both alveolar and microvascular permeability in high volume ventilation. In contrast, intraperitoneal administration of the β_2-agonist only reduced ^{111}In-labeled transferrin uptake, suggesting that its protective effect was confined to the microvascular barrier. Importantly, only the intratracheal instillation reduced pulmonary edema as demonstrated by a decrease in wet-to-dry weight ratio. Although direct comparison between both administration routes is hampered by potential differences in drug distribution and differential effects on alveolar fluid reabsorption, these findings underline the notion that therapeutic strengthening of the alveolar barrier may provide critical benefit in ventilator-induced lung injury. Pharmacological regulation of alveolar barrier properties may therefore provide a novel and promising strategy for the prevention and treatment of ventilator-induced lung injury.

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