Lung Multi-scale Model for the evaluation of the pathophysiology of Ventilator Induced Lung Injury during the treatment of Acute Respiratory Distress Syndrome

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Acute Respiratory Distress Syndrome (ARDS), a manifestation of acute pulmonary inflammation, affects nearly 200,000 critically ill patients annually, and is one of the most devastating consequences of sepsis and severe trauma. Mechanical ventilation is a mainstay in the treatment of ARDS, but is also well known to propagate pulmonary damage through ventilator induced lung injury (VILI), this despite the adoption of low tidal-volume strategies aimed at reducing the impact of ventilation on alveolar injury. The pathophysiology of VILI involves a vicious cycle consisting of forward feedback interactions between the mechanical forces of positive pressure ventilation and the inflammatory biology of the lung (primarily at the alveolar level). We hypothesize that ventilator strategies targeting more refined metrics of the delivered breath, such as the time function of airway pressure per breath, may modulate VILI more effectively. We have initiated a program of multi-scale computational modeling combined with studies in experimental animals and ARDS patients. As a component of this project, we are developing a novel modular, multiscale model of the lung, the Lung Multi-scale Model (LMSM), which encompasses the mechanical dynamics of individual alveolar units, molecular and cellular components of lung inflammation, and alveolar population dynamics within the whole lung, We present here the initial development of the basic module of the LMSM, a subcellular element method (ScEM) model of the alveolar sac. The ScEM was developed to study the spatial dynamics of individual biological cells, allowing the generation of complex geometries in an effort to account for differential adhesion, polarity, and cytoskeletal forces along a cell surface. In the LMSM, however, our “cell” is at the level of an alveolar sac, modeled as a 3-dimensional configuration of “subcellular” elements representing portions of the alveolar sac wall with different mechanical and biological properties. The LMSM also includes a force function exerted by airflow pressure on the surface normal area of the alveolar sac, and a resistance normal force representing the effect of surface tension from the amount of pulmonary surfactant and edema in the alveolus. Loss of surfactant and/or increase in edema changes in the surface tension and shifts the alveolar sac compliance function. In initial studies, we have calibrated our ScEM model of a single alveolar sac to real time *in vivo* microscopy images of alveolar mechanics in the rat lung under normal conditions and in an established Tween 20 model of ARDS (5cc/kg of 3% Tween in Saline instilled into the trachea). We will extend our single alveolar sac model into an alveolar duct consisting of multiple sacs, a whole lung represented by a heterogeneous population of alveolar ducts. The LMSM will be eventually integrated with a multi-compartment ordinary differential equation model of multi-organ and systemic inflammation. We suggest that the LMSM could be used to evaluate the biological and clinical effects of mechanical ventilation, including refined ventilation strategies intended to reduce VILI.

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