Multiscale Modeling of Ventilator Effects on Lung Inflammation and the propagation to Multiple Organ Dysfunction Syndrome

Gary Nieman[1], Scott Christley[2], Gary An[2], and Yoram Vodovotz[3]

[1]Department of Surgery, Upstate University of New York
[2]Deptartment of Surgery, University of Chicago
[3]Department of Surgery, University of Pittsburgh

Trauma/hemorrhagic shock (T/HS) is the most common cause of death for young people in the U.S., costing over $400 billion annually. T/HS induces an acute inflammatory response that drives – and in turn is driven by – cascading physiologic system failure termed the Multiple Organ Dysfunction Syndrome (MODS). Acute Respiratory Distress Syndrome (ARDS), driven by lung inflammation, is one of the most devastating components of MODS, affecting nearly 200,000 critically ill patients annually. ARDS is managed via organ-level support, using mechanical ventilation. However, mechanical ventilation itself is known to induce lung injury (Ventilator Induced Lung Injury – VILI), and can therefore hasten the progression to ARDS. Unfortunately, the vast increase in knowledge regarding the inflammatory processes involved in the pathogenesis of ARDS and MODS has not translated into any therapy that can halt the progression of these syndromes. Based on a decade of systems and computational approaches to acute inflammation, we propose that ARDS/MODS evolves due to a multiscale, feed-forward cycle of inflammation → damage → inflammation. We have developed a Biological Scale/Compartment hypothesis suggesting that inflammation proceeds at a given, 'nested' level or scale until positive feedback exceeds a 'tipping point'. Below this tipping point, inflammation is contained and manageable; when this threshold is crossed, inflammation becomes disordered, and dysfunction propagates to a higher biological scale. In support of this hypothesis, we have shown that appropriate ventilation strategies can therapeutically alter the mechanistic pathophysiology of ARDS, and in so doing attenuate the progression of MODS. We propose to characterize and model the multiscale intra-pulmonary dynamics of, and the effects of diverse ventilatory strategies on, the pathogenesis of ARDS in hemorrhaged rats. We are developing a novel multiscale model of the lung that incorporates the mechanical dynamics of individual alveolar units, alveolar population dynamics within the whole lung, molecular and cellular components of lung inflammation induced by T/HS, and clinically relevant whole-lung physiology. We propose to integrate this model with existing, multi-compartment models of whole-animal inflammatory and cardiovascular physiology. Using an experimental workflow involving iterative model development and *in vivo* experiments we will characterize specific ventilator strategies' ability to limit VILI and attenuate ARDS. We will further determine if such effective containment of pulmonary inflammation will avoid breeching scale/compartment molecularly-defined inflammatory tipping points, and thus preventing propagation to MODS. The proposed studies would define the multiscale aspects of inflammation progression in T/HS, and outline a rational strategy that combines in vivo and in silico tools to suggest and test therapeutic strategies for the treatments of ARDS/MODS resulting from T/HS.

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