Combining Data-Driven and Multiscale Mechanistic Modeling to Explore Endotoxin-Induced Inflammation in Swine

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Our objective was to gain insights into the interrelation between inflammation and physiology during acute inflammation. In studies funded under R33-HL-089082, we carried out a large-animal study combined with data-driven and mathematical modeling. Four outbred juvenile swine were instrumented and subjected to endotoxemia, followed by serial plasma sampling. Plasma samples were assayed for inflammation biomarkers, followed by Principal Component Analysis (PCA) aimed at defining principal drivers of inflammation in this setting. Based on this PCA, a two-compartment Ordinary Differential Equation model was constructed, consisting of the lung and the blood (as a surrogate for the rest of the body). A key set of interactions derived from PCA and depicted in that model consisted of endotoxin inducing TNF-α in monocytes in the blood, followed by the trafficking of these cells into the lung leading to the release of HMGB1, which in turn stimulates the release of IL-1β from resident macrophages. Other components of this model included blood pressure, lung functional parameters such as PaO_2/FiO_2 ratio and lung compliance, and a damage variable that summarizes the health of the animal. This mathematical model could be fit to both inflammatory and physiologic data in the individual endotoxemic swine, which exhibited outcomes ranging from resolving inflammation

with symptoms of lung injury, to elevated inflammation and lung injury, to death prior to the conclusion of the experiment. The predicted time course of damage could be matched to the Oxygen Index ($(OI = FiO_2 * MAP / PaO_2)$) in 3 of the 4 swine. The approach described herein demonstrates how mathematical modeling - combined with a rich dataset on the dynamics of inflammation and organ function - may aid in predicting sepsis/ARDS outcomes in small cohorts of subjects with diverse phenotypes and outcomes.