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Low tidal mechanical ventilation is the most effective treatment to reduce mortality of patients suffering from acute respiratory distress syndrome (ARDS) and acute lung injury (ALI). However, it is now well recognized that mechanical ventilation can result in additional injury, known as ventilator-induced lung injury (VILI). The mechanisms of VILI are related to altered and extreme stresses in the micromechanical environment of the alveoli. Despite decades of research – and notable progress - mortality rates for ARDS/ALI patients remains at between 40-60% and is thus still a major health concern. Numerous mathematical models of alveolar mechanics have been developed over the years and have been instrumental in increasing our understanding of the relationship between alveolar dynamics, alveolar septal mechanics and cell damage. Typically, these models are either phenomenological or address simple subsystems of isolated respiratory units. However, both the macro- and micromechanics of the normal parenchyma are spatially heterogeneous and become markedly more so in the presence of disease. Thus, ventilation protocols that are appropriate for some regions of the lung may produce damaging stresses in other regions. Moreover, the lung is inherently multiscale, with significantly different behavior at the scale of the organ and at the scale of the alveoli, where the majority of VILI occurs. The very notion of alveolar recruitment - a discrete event - reveals the difficulty of a simple mapping between a continuum representation of a unit of parenchyma and its perhaps thousands of constituent alveoli. The result is that the clinician is at a loss to determine which – if any – ventilation protocols are appropriate for the whole lung. This is especially important when one considers that small, localized events can produce a cascade of inflammation-related events that spread far beyond the site of original insult.To investigate whether regionally heterogeneous alveolar stresses related to VILI can be predicted and thereby avoided, we are developing and experimentally validating imaging-based multiscale computational models of the entire rat respiratory tract that connect airway transport and mechanics with coupled macro- and microscale mechanics of parenchyma. Continuum scale parenchymal mechanics is based on a novel implicit framework for soft-tissues that telescopes from the continuum scale to the microstructural scale of respiratory alveoli. This framework is to be further extended to account for alveolar recruitment with a novel fractional-order viscoelastic kernel, informed by hyperpolarized helium (3He) MRI. Model predictions will be compared against micro-CT (μCT) and 3He measurements of regional ventilation. Because alveolar mechanics are complex, model predictions of acute stress will also be compared against regionally specific expression of inflammatory cytokines that signal epithelial cell damage, as measured by 2D nano-DESI mass spectrometry. The long term goals of this program are twofold: 1) to determine whether the clinically available metrics, including time-dependent CT can be used determine patient vulnerability, and 2) to bring a predictive multiscale model to the bedside to provide the clinician with in-silico information with regard to otherwise unseen spatially-heterogonous microstructural consequences of ever-evolving ventilation protocols.