Building a theoretical framework to quantify alveolar injury

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Submitted 17 June 2014; accepted in final form 24 June 2014

RESPIRATORY SUPPORT by mechanical ventilation is central to the therapeutic strategy for acute lung injury (ALI) and the adult respiratory distress syndrome (ARDS), conditions associated with high mortality and morbidity. However, mechanical ventilation can also worsen ALI and promote ARDS by inducing proinflammatory mediators that lead to multiple organ failure (12). Although trials indicate that low-tidal-volume mechanical ventilation reduces mortality (3), mechanisms underlying ventilator-induced ALI (VILI) remain unclear (1). In this regard, the patchy lung pathology in VILI (6, 12) suggests that the micromechanics of localized alveolar injury must be better understood.

Using real-time optical section microscopy (OSM) and the single-alveolar model of pulmonary edema, Perlman et al. (5) quantified the micromechanics of an air-filled alveolus that shares a septum with a liquid-filled alveolus. They found that the liquid-filled alveolus shrinks and its compliance remains unaffected, while the neighboring air-filled alveolus overdistends and its compliance is reduced. Another insightful observation by these authors was that liquid filling of one alveolus is sufficient to cause preexpansion of the neighboring air-filled alveolus (5). These observations provide a mechanism for patchy hyperinflation in aerated parts of the edematous lung, and they suggest that liquid-filled alveoli might render neighboring air-filled alveoli susceptible to overdistension injury (8). This study sets the stage to identify how micromechanical events might induce a proinflammatory alveolar phenotype, and it raises the question of how mechanical strain (ratio of change in length to original length) in alveoli might relate to concurrent mechanical stress (force per unit area).

Considering the complexity of lung structure, stress-strain relationships in lung tissue might be best understood by suitable mathematical modeling (7). Often simple models turn out to be quite insightful. In the current issue of the Journal of Applied Physiology, Chen et al. (2) present such a simple static, two-dimensional model of a septum between an air-filled alveolus and a liquid-filled alveolus. In their model, the authors consider the alveolar septum to be purely elastic with compliance and thickness to be spatially homogeneous. This model shows that, when surfactant layer is completely replaced by edema fluid, even at functional residual capacity, the septum remains under strain and protrudes into the liquid-filled alveolus. This study not only supports the observations of Perlman et al. but also provides a simple framework, which upon further development can be immensely useful in predicting alveolar shape changes in ALI.

To establish the model, Chen et al. (2) extract a relationship between septal thickness (t) and change in alveolar radius (ε) from published experimental images (4). However, these experiments demonstrate that in the alveolar wall, the stretch ratio (λ) is spatially heterogeneous, implying that change in septal thickness might also be heterogeneous. As such, the expected direct relationship between t and ε may not be statistically significant, diminishing the model’s validity. An alternative approach would be to use the direct local relationship between λ and t as provided by the Poisson’s ratio for alveolar tissue. This approach would also enable an assessment of the heterogeneity in λ.

Chen et al. (2) found that in the case of a septum separating two air-filled alveoli, the relationship between ε and λ is indeed linear. By contrast, in the case of a septum separating an air-filled alveolus from a liquid-filled alveolus, the relationship is highly nonlinear. This nonlinearity implies intriguing alveolar strain patterns, which require further investigation, particularly in the context of deformation-induced alveolar injury (9).

Safe mechanical ventilation requires control over two key pathogenic responses: production of proinflammatory mediators (12), and disruption of the alveolar-capillary barrier (10). Physical mechanisms underlying these responses remain unclear (1), but are potentially accessible to study through further development of the model of Chen et al. (2). One possibility is to include 1) dynamic mechanical properties of the tissue such as power-law rheology and tissue remodeling (7), and 2) force-dependent responses of the cells such as molecular signaling and cytoskeletal reorganization (11). Taken together, modeling studies such as that of Chen et al. can help in quantifying local alveolar injury associated with ventilation of edematous lung. Predictive capabilities of such models might promote better understanding of the micromechanics of VILI.

ACKNOWLEDGMENTS

Dr. Jahar Bhattacharya (Columbia University, New York) read the manuscript.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: D.T.T. drafted manuscript; D.T.T. edited and revised manuscript; D.T.T. approved final version of manuscript.

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