Invited Editorial on “Dynamic properties of lung parenchyma: mechanical contributions of fiber network and interstitial cells”

MARA LUDWIG
Meakins Christie Laboratories, McGill University, Royal Victoria Hospital, Montreal, Canada H2X 2P2

DURING BREATHING, energy is required to overcome the resistance of the lung. Traditionally, the airways were thought to account for the major proportion of the energy dissipated. However, the parenchymal tissues behave as a viscoelastic material, and it has recently been recognized that much of the energy loss across the lung during breathing is occurring at the level of the lung periphery (4, 5). Moreover, after induced constriction, much of the increase in lung resistance is due to increases in the measured tissue resistance (4, 7, 9).

The lung parenchyma is a complex system consisting of alveolar walls composed of collagen, elastin, and proteoglycan macromolecules; the air-liquid interface or surfactant; and interstitial cells, which have the capacity to act in a contractile fashion. Each of these components could potentially account for the viscoelastic behavior of the pulmonary parenchyma. In addition, it is difficult to define a precise boundary where the airways end and the parenchyma begins. Airway smooth muscle exists in the terminal bronchioles and alveolar ducts, and the behavior of these structures may well influence parenchymal mechanics.

Individual collagen and elastin fibrils behave as purely elastic materials. However, when fibers are organized into a network, the behavior of the network is likely to be different from the behavior of the individual constituents (1). Recently, Mijailovic et al. (8) proposed a model based on adjacent fiber-fiber interactions that could explain the macroscopic behavior of the pulmonary parenchyma. Suki et al. (15) invoked the “reptation” or rearrangement motion of collagen and elastin fibrils to account for the viscoelastic properties. The “ground substance” of the parenchyma is made up of proteoglycans, which are complex macromolecules composed of a protein core and glycosaminoglycan side chains. These molecules are highly hydrophilic and can attract ions and fluid into the interior of the matrix, thereby altering viscoelasticity. Relatively little is known about the proteoglycan content of the extracellular matrix of the lung or the contribution of these molecules to mechanical behavior.

Other investigators have addressed the role of the surfactant layer in contributing to tissue viscoelasticity. Stamenovic and Barnes (14) concluded from experiments in which the surface layer was altered by constant surface tension test liquids that the surface film modulates tissue resistance primarily through its stabilizing effect on alveolar geometry. We, on the other hand, have shown (11) that liquid filling of excised lungs results in decreased tissue resistance, implicating the surface film as an important contributor to tissue hysteresis.

Fredberg and colleagues (2) have proposed that cross-bridge mechanics contribute to tissue viscoelasticity. They claim that the energy dissipated at the parenchymal level is related to the contractile state of the smooth muscle, with the ratio of energy dissipated to that stored (hysteresivity) being determined by the cross-bridge cycling rate. Their studies in parenchymal strips have been corroborated by similar studies in pure smooth muscle preparations (3). Whereas the contribution of this mechanism is likely to be modest during nonstimulated conditions, it becomes more important when the tissues are contracted.

Viscoelastic behavior in vivo could, in part, be attributable to interactions between these elements. For example, with changes in the surface forces, the fibrous network may be altered, and changes in the mechanical behavior of the parenchyma may result. In addition, regional heterogeneities in ventilation distribution may contribute to perceived tissue viscoelastic behavior. This mechanism is probably not important under baseline conditions but, likely, becomes more important after induced constriction.

The parenchymal strip has been used by several investigators to study the mechanical behavior of the lung periphery. The strip offers certain advantages in that the air-liquid interface is removed so that surface film does not contribute to viscoelastic behavior. However, the parenchymal strip contains small airways and vessels; the contribution of these structures to the mechanical behavior may be substantial, especially after induced constriction, depending on the size and site of the excised tissue (13).

In the study of Yuan et al. (16) in the current issue of the Journal, parenchymal strip mechanics were measured under different conditions in an attempt to delineate the role of the connective tissue matrix vs. that of the interstitial cell. The investigators measured parenchymal mechanics in excised strips. They then left the strips at room temperature for 12 h to render the tissues “nonviable.” “Nonviability” was established.

Other investigators have addressed the role of the surfactant layer in contributing to tissue viscoelasticity. Stamenovic and Barnes (14) concluded from experiments in which the surface layer was altered by constant surface tension test liquids that the surface film modulates tissue resistance primarily through its stabilizing effect on alveolar geometry. We, on the other hand, have shown (11) that liquid filling of excised lungs results in decreased tissue resistance, implicating the surface film as an important contributor to tissue hysteresis.

Fredberg and colleagues (2) have proposed that cross-bridge mechanics contribute to tissue viscoelasticity. They claim that the energy dissipated at the parenchymal level is related to the contractile state of the smooth muscle, with the ratio of energy dissipated to that stored (hysteresivity) being determined by the cross-bridge cycling rate. Their studies in parenchymal strips have been corroborated by similar studies in pure smooth muscle preparations (3). Whereas the contribution of this mechanism is likely to be modest during nonstimulated conditions, it becomes more important when the tissues are contracted.

Viscoelastic behavior in vivo could, in part, be attributable to interactions between these elements. For example, with changes in the surface forces, the fibrous network may be altered, and changes in the mechanical behavior of the parenchyma may result. In addition, regional heterogeneities in ventilation distribution may contribute to perceived tissue viscoelastic behavior. This mechanism is probably not important under baseline conditions but, likely, becomes more important after induced constriction.

The parenchymal strip has been used by several investigators to study the mechanical behavior of the lung periphery. The strip offers certain advantages in that the air-liquid interface is removed so that surface film does not contribute to viscoelastic behavior. However, the parenchymal strip contains small airways and vessels; the contribution of these structures to the mechanical behavior may be substantial, especially after induced constriction, depending on the size and site of the excised tissue (13).

In the study of Yuan et al. (16) in the current issue of the Journal, parenchymal strip mechanics were measured under different conditions in an attempt to delineate the role of the connective tissue matrix vs. that of the interstitial cell. The investigators measured parenchymal mechanics in excised strips. They then left the strips at room temperature for 12 h to render the tissues “nonviable.” “Nonviability” was established.
by documenting a lack of response to $10^{-5}$ M methacholine (MCh). The investigators compared a number of different mechanical moduli (storage and loss moduli, tissue stiffness and damping, "Newtonian" resistance, hysteresivity, and a nonlinearity index $k_d$) under viable and nonviable conditions. Their results in viable tissues largely agree with those previously documented in the literature. Nonviable tissues demonstrated very similar mechanical behavior. The authors interpret this as evidence that interstitial cells contribute minimally to parenchymal mechanics. However, while the tissues left at room temperature for 12 h may not have responded to the low concentration of MCh employed, this does not indicate that the tissues were no longer viable. The tissues might well have responded to a higher concentration of MCh. The remainder of the molecular machinery in the interstitial cells may be intact. The cell membrane and organelles and intracellular matrix may all be undisturbed, and these components of the cell may all contribute to the viscoelasticity of the parenchymal strip. The question of the contribution of the different components of the parenchymal strip to parenchymal mechanics is an important one and deserving attention, but the current protocol cannot separate out the contribution of the matrix from the contribution of the interstitial cell per se. These data can address, in part, the contribution of the smooth muscle contractile apparatus to mechanical behavior under baseline conditions. Assuming that the contractile machinery is, indeed, completely disabled, then the lack of a significant difference in mechanical behavior in viable vs. nonviable tissues suggests that, at baseline, cycling of cross bridges contributes minimally to parenchymal hysteresis.

The authors also examine parenchymal mechanics after exposure to MCh. They document modest increases in tissue damping and stiffness. Furthermore, they show that, while changes in tissue stiffness are similar whether induced by active contraction or passive stretch, changes in tissue damping depend on the mode of stimulus delivered. This argues that contractile stimulation has a specific effect on tissue damping, reflecting changes in energy dissipation related to alterations in the state of the contractile machinery, as proposed by Fredberg and colleagues (2). The role of the parenchymal tissues in contributing to increases in tissue resistance after induced constriction in vivo has generated some recent controversy. Lutchen et al. (6) have suggested that much of the increase in tissue resistance after induced constriction is due to airway inhomogeneities and not to constriction at the parenchymal level per se. However, similarly to Yuan et al. (16), we have shown differences in tissue damping dependent on whether tissues were stimulated with passive inflation or contractile agonists (12). We have also reported morphological data in animals showing substantial distortion of parenchymal tissues after induced constriction, of a degree that would invariably lead to altered mechanical behavior (10). The precise site of the contractile response may reside in the interstitial cell and/or the smooth muscle cell in the terminal airway or alveolar duct. Furthermore, the increases in tissue resistance seen in vivo may require the amplification of the signal provided by the distortion of the adjacent collagen-elastin-proteoglycan matrix. Nonetheless, these data and the data of Yuan et al. (16) point to a specific change in mechanics related to stimulation of the contractile machinery in cells at the extreme periphery of the lung.

REFERENCES