CALL FOR PAPERS

“Real-time visualization of lung function: from micro to macro”

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STUDIES ON NORMAL PHYSIOLOGICAL and pathological processes that take place in the lung are hampered by the architecture and behavior of a living, breathing lung with a very complex three-dimensional structure that is constantly in motion. Not only do the airways and vasculature constrict and relax, but the alveolar air spaces regularly and rapidly expand and retract, appreciably changing the size and volume of the lung at regular intervals during normal lung function. The development and function of the lung are dependent on the intactness and coordinated movement of the lung, making in vitro studies on intact lungs difficult. Although the proximal regions of the intact, breathing lung are relatively accessible for imaging studies via the trachea, the most distal regions of the lung, the alveolar units, are relatively inaccessible (in terms of visualization of lung function), being reachable only through the tiny alveolar ducts that provide passage into the alveolar sacs. Recently, there has been an explosion of interest in imaging physiological processes in the lung in real time, and several notable advances have been made, which have been facilitated by new methodological approaches, novel microscopic and radiological imaging technologies, as well as the development of genetically modified animal models.

One example of where real-time imaging of lung function has led to unexpected and paradigm-shifting observations is the field of ion transport. Previously, physiological studies on intact animals and isolated perfused lungs, as well as patch-clamp and Ussing chamber studies on isolated alveolar epithelial cells and lung slices, have demonstrated the presence of amiloride-sensitive cation as well as anion channels. However, vectorial Na+ transport has been regarded as the predominant form of ion transport, with chloride transport by the cystic fibrosis transmembrane conductance regulator playing an important role in enhancing Na+ transport. Recent work published in the pages of the Journal continues to underscore the importance of patch-clamp and Ussing chamber studies to investigate fluid clearance (7, 8, 16, 21, 23). However, elegant imaging studies have clearly demonstrated the presence of chloride secretion in air-filled lungs (17). The isolated, ventilated, and perfused lung model has also been adapted to follow, in real time, the transport of radioactive tracers (22Na and [3H]mannitol for example), applied by ultrasonic nebulization to the alveolar air spaces, into the vascular perfusate (10). Such technology has tremendous scope for extension to chloride and other ions, as well as radioactive protein tracers. The isolated lung technology has also lent itself to studies on the real-time assessment of channel function in lung permeability (12) and, indeed, real-time assessment of ventilator-induced lung damage (13). Isolated lung studies are, by their nature, terminal experiments, which yield indirect (although real-time) data about lung function. Most of the studies referred to above have focused on ion transport in the lung epithelium. Studies on other lung cell types that actively transport ions, such as vascular and airway smooth muscle, are sorely lacking. Accordingly, manuscripts dealing with the real-time visualization of ion transport in cell types other than the epithelium are particularly encouraged in this Call for Papers.

In contrast to isolated lung studies, radiological assessment of lung function both permits the direct visualization of processes taking place within a live, working lung and also allows for the repetitive determinations to be made on the same animal, which represent two important advances over isolated lung studies. Furthermore, radiological imaging will also allow for lung measurements to be made at fixed levels of expansion, facilitating standardization and comparison. The increasing use of radiological monitoring employing magnetic resonance imaging (MRI) (20), positron emission tomography (PET) (4), and computed axial tomography (CAT) (18) technologies has revealed the potential of these approaches in the study of lung structure and function. The beauty of these techniques includes the noninvasive and nonterminal nature of these assessments. Whereas most analyses of lung tissue rely on the extraction of the lung and subsequent processing for microscopic or biochemical analysis, radiological analysis of lung structure and function permits repetitive in vivo assessment of the living, breathing lung. The number of repeat measurements is limited only by exposure to radiation, which applies largely to CAT studies. Indeed, studies have reported the monitoring of postnatal pulmonary artery growth at regular intervals for up to 160 days by phase-contrast MRI (22), highlighting the usefulness of noninvasive, nonterminal radiological approaches to study lung structure and function. In terms of airway function, synchrotron radiation computed tomography (CT) imaging has recently been very elegantly used to differentiate central vs. peripheral airway and lung parenchymal components of the response to airway provocation by cigarette smoke (19), and single proton emission computed tomography (SPECT) to quantify clearance of intratracheally delivered 99mTc-diethylene triamine pentaacetic acid has been used to assess airway barrier function (26). Optical coherence tomography is another elegant approach that has been very successfully used to define (in real time) neo-plastic morphological changes in bronchial microstructure
cytoskeletal dynamics and actin remodeling, as recently demonstrated in the Journal for alveolar epithelial type I cell wound healing (11) and hypoxia-induced contractile events in the pulmonary endothelium (2).

The pressing need for further advances in the development or refinement of experimental approaches for the real-time assessment of lung structure and function, together with an explosion of interest in this area of preclinical and clinical pulmonary research, has prompted this Special Call for Papers on “Real-time Visualization of Lung Function: from Micro to Macro” from the *American Journal of Physiology Lung Cellular and Molecular Physiology*. This Special Call for Papers aims to highlight novel methodological advances that address how lung function may be visualized in real time, both in the laboratory and in a clinical setting, as well as the application of these methodologies in studies on lung pathophysiology. Basic, translational and clinical research papers, as well as methodological reports and reviews will be considered, particularly those focusing on the following specific themes.

**Real-Time Visualization of Ion, Protein, and Water Transport**

The contribution of transepithelial ion and protein transport to alveolar fluid dynamics remains controversial and poorly understood. The development of new, or refinement of existing, techniques that permit the real-time visualization of ion, protein, and water transport in vivo, ex vivo, or in vitro, would do much to further our understanding of these processes. Similarly, new methodologies to assess the function and indeed monitor the efficiency of the mucociliary escalator would contribute much to studies on the epithelial function in the conducting airways. Studies addressing the refinement of methodology to quantify airway surface liquid volume and mucus transport rates by simple light refraction and confocal microscopy would also be welcome.

**Real-Time Radiological Assessment of Pulmonary Structure and Function**

Novel or refined radiological approaches such as CAT, MRI, PET, including microCT and dynamic contrast-enhanced MRI, approaches to study and quantify lung structure and pathological processes, including normal and aberrant lung vascularization, are encouraged. This theme also spans the use of high-resolution synchrotron radiation X-ray tomographic microscopy to assess lung microstructure, for example, three-dimensional visualization of the alveolar capillary network, as well as the use of MRI and nuclear magnetic resonance (NMR) to monitor inflammation, vascular remodeling, and metabolism in the lung. Manuscripts reporting the development and use of hyperpolarized gas MRI for the quantitative imaging of alveolar recruitment during mechanical ventilation, and the quantitative assessment of alveolar edema, would be very welcome, particularly comparative studies that evaluate radiological approaches as alternatives to currently employed, more classical (but perhaps more precise) assessments of extravascular lung water. Additionally, manuscripts reporting the radiological monitoring of the delivery of genes and pharmacological agents to the distal lung are also sought after.
Real-Time Microscopic Imaging of Pulmonary Structure and Function

Manuscripts reporting novel or refined intravital microscopic approaches to study lung function in vivo, as well as functional fluorescence-based approaches to address signaling in situ in living, breathing lungs, are particularly encouraged. The latter might include photolytic uncaging to study cation signaling, optical-sectioning microscopy to study cytoskeletal dynamics, and fluorescence energy transfer approaches to reveal protein-protein interactions in situ. Manuscripts reporting the novel use of high-speed video and multiphoton microscopy to study large airway and cilia function as well as live-cell imaging in whole-lung sections and dark-field and fluorescence microscopy to study protein trafficking and secretion are encouraged. Quantum dot single particle tracking studies would also be most welcome, addressing, for example, nanoparticle distribution in the distal lung in vivo, as well as membrane protein complex formation and trafficking within and on the surface of isolated cells in vitro.

Manuscripts that are submitted in this area, in response to this call, will receive expedited review. Submitting authors should indicate in their covering letter, as well as in the online submission system under “Manuscript Type,” that the submission is in response to a Special Call for Papers. Submitted papers will be reviewed very promptly by members of the Editorial Board as well as selected guest reviewers who are acknowledged experts in the relevant areas of expertise. Accepted manuscripts will be published under a distinct headline. Please direct any enquiries to Dr. Sadis Matalon, the Editor-in-Chief, via email at sadis@uab.edu.

REFERENCES