Alveolo-capillary diffusion of hyperpolarized $^{129}$Xe as a marker of pulmonary fibrosis

Connie C. W. Hsia
Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas
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Quantifying the lung’s capacity for O$_2$ uptake by diffusion across the alveolo-capillary tissue-plasma barrier followed by binding to hemoglobin is not straightforward, owing to the nonlinearity of the oxyhemoglobin dissociation curve. Direct assessment of lung diffusing capacity for O$_2$ (DL$_{O2}$) is possible only by employing invasive methods under hypoxic conditions, i.e., when alveolar capillary partial pressure of O$_2$ is within the linear portion of the dissociation curve. Instead, carbon monoxide (CO) is commonly used as a tracer gas for assessing lung diffusing capacity (DL$_{CO}$), a noninvasive approach that takes advantage of its simpler hemoglobin binding kinetics. Like DL$_{O2}$, DL$_{CO}$ is sensitive to changes in the conductance both of the tissue-plasma barrier and inside the red blood cells (RBCs). The classic Roughton-Forster model (6) attempts to decompose DL$_{CO}$ into two serial steps—diffusion across tissue-plasma barrier, and the combined diffusion into the red blood cell (RBC) interior plus reaction with hemoglobin—by measuring DL$_{CO}$ at two alveolar O$_2$ tensions. Later, diffusing capacity for nitric oxide (DL$_{NO}$) was employed as another measure (1). Because of its extremely high binding affinity for hemoglobin, NO conductance within RBCs greatly exceeds that across the tissue-plasma barrier, making DL$_{NO}$ a more sensitive indicator of barrier conductance than DL$_{CO}$. Despite the differences in their physical properties and reaction kinetics, both DL$_{CO}$ and DL$_{NO}$ empirically correlate with DL$_{O2}$. It remains debated whether CO and NO in the context of the Roughton-Forster model sufficiently resolve the tissue-plasma from the RBC components, especially in pathological conditions.

Another approach to assess the lung’s capacity for O$_2$ transfer, suitable only at postmortem in fixed lungs, is to estimate the maximum O$_2$ flux that could be supported by alveolar structure, whereby the key determinants (surface area, harmonic mean barrier thickness, capillary blood volume, and capillary hematocrit) are measured using stereological techniques (4). Because basal O$_2$ flux amounts to only a fraction of maximum flux, the structure-based estimates of diffusing capacity far exceed physiological measurements obtained at rest, but the differences diminish when compared with physiological measurements obtained at peak exercise.

The physiological measurements of diffusing capacity vary with lung volume, blood flow, and hemoglobin concentration, are subject to errors caused by ventilation-perfusion and perfusion-diffusion heterogeneity, and yield no anatomical information. The structure-based estimates are subject to errors due to the nonphysiological conditions of preparation, sampling variability, and the neglect of physiological inhomogeneity. Both approaches assume a number of constants for permeability and hemoglobin binding. While these approaches continue to be useful and complementary, there is a need for indexes of alveolar gas diffusion that directly probe the anatomical compartments of the transfer process.

In the last decade, hyperpolarized $^{129}$Xe magnetic resonance (MR) imaging has been used to map gas distribution within air spaces and diffusion in lung tissue and blood, including transient binding to hemoglobin. Because $^{129}$Xe is highly soluble in tissue and blood and exhibits distinct resonance frequencies in the gas, tissue-plasma, and RBC compartments, it has shown sensitivity in detecting compartmental changes of gas transfer in experimental lung injury and fibrosis (3). In this issue of the Journal of Applied Physiology, Kaushik et al. (5) applied this technique to normal subjects and patients with idiopathic pulmonary fibrosis (IPF). They analyzed hyperpolarized $^{129}$Xe MR spectra, obtained as part of the calibration sequence of MR imaging, to separate whole lung $^{129}$Xe resonance signals in tissue barrier from that in RBCs during breath-hold. As lucidly explained in their article, separation is based on the fact that the applied radiofrequency pulses both excite and deplete magnetized $^{129}$Xe, which is replenished by diffusion of fresh magnetized $^{129}$Xe atoms from air spaces first into the barrier and then into RBCs, resulting in a temporal delay of resonance signals between compartments. In IPF, the thickened barrier delays replenishment in RBCs by a factor proportional to the square of the thickness while changes in the quantity or properties of tissue barrier by inflammation and fibrosis are thought to enhance replenishment in the barrier relative to the alveolar gas compartment. The result is a reduced RBC:gas signal ratio, an elevated barrier:gas ratio, and a net reduction in the RBC: barrier ratio in IPF compared with normal subjects; the latter ratio correlates significantly with resting DL$_{CO}$.

This novel noninvasive radiation-free approach of separating serial diffusion steps across the air space, barrier, and RBCs has potentially important applications in probing pathophysiology as well as in clinical diagnosis, monitoring, and therapeutic assessment. Whether this potential will be fulfilled depends on gaining a fuller understanding of the sources of spectral variability (frequency, amplitude, and width), and on the successful validation of the interpretative frame of the spectral ratios. The physiological variables that differentially influence compartmental $^{129}$Xe resonance signals should be similar to those that influence DL$_{CO}$, including lung inflation, pulmonary microvascular recruitment, and capillary hematocrit, as well as ventilation, perfusion, and diffusion heterogeneities. The effects of these variables on barrier:gas, RBC:gas, and RBC:barrier ratios need to be systematically investigated to ensure that accurate conclusions are drawn regarding compartmental diffusion limitation. The authors (5) report inflation- and pressure-related changes in compartmental $^{129}$Xe...
signal ratios that could account for the dynamic range of ratios observed in healthy subjects and that were attributed to changes in capillary blood volume. There may be direct relationships between the resonance ratios and alveolar microvascular recruitment similar to that observed for DL\textsubscript{CO} and DL\textsubscript{O2}. Delineation of these relationships should strengthen their results. Further studies should clarify the effects of hemoglobin mass and hematocrit; one expects polycythemia to increase, and anemia to decrease, the RBC:gas and RBC:barrier signal ratios without altering the barrier:gas ratio. Ventilatory heterogeneity reduces the quantity of magnetized \textsuperscript{129}Xe bolus delivered to poorly ventilated regions, which would proportionally reduce signal amplitude in air, barrier, and RBC compartments, i.e., RBC:barrier ratio is not expected to change. In contrast, perfusion heterogeneity should reduce RBC signals in poorly perfused regions where the RBC:barrier ratio would be selectively reduced.

The analysis of whole lung MR spectra lacks spatial discrimination. It could be combined with 3D MR imaging to generate spatial maps of compartmental \textsuperscript{129}Xe transfer and define regional abnormalities (2). The effect of oxygenation on \textsuperscript{129}Xe MR frequency is another interesting feature that might be exploited to characterize global and regional RBC oxygenation in the lung. Several important technical aspects need to be optimized as discussed by Kaushik et al. (5). The sensitivity in detecting early interstitial lung disease needs to be established. A practical limitation is the availability of the equipment and the cost of measurement compared with the inexpensive, widely available measurement of DL\textsubscript{CO}, especially for serial measurements needed to monitor the evolution of pathology or treatment response. More work remains to be done before realizing the potential of this powerful tool in bridging the structure-function gap and providing a comprehensive picture of gas transfer in the lung. The rapid pace of progress in this field promises many new and exciting developments in the near future.

DISCLOSURES

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