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^3He Diffusion MRI in Human Lungs

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Abstract

Hyperpolarized ^3He gas allows the air spaces of the lungs to be imaged via MRI. Imaging of restricted diffusion is addressed here, which allows the microstructure of the lung to be characterized through the physical restrictions to gas diffusion presented by airway and alveolar walls in the lung. Measurements of the apparent diffusion coefficient (ADC) of ^3He at time scales of milliseconds and seconds are compared; measurement of acinar airway sizes by determination of the microscopic anisotropy of diffusion is discussed.; This is where Dr JJH Ackerman's influence was greatest in aiding the formation of the Washington University ^3He group, involving early a combination of physicists, radiologists, and surgeons, as the first applications of ^3He ADC were to COPD and its destruction/modification of lung microstructure via emphysema. The sensitivity of the method to early COPD is demonstrated, as is its validation by direct comparison to histology. More recently the method has been used broadly in adult and pediatric obstructive lung diseases, from severe asthma to cystic fibrosis to bronchopulmonary dysplasia, a result of premature birth. These applications of the technique are discussed briefly.

Keywords

Restricted diffusion; diffusion imaging; hyperpolarized; lungs; COPD; pediatric; neonatal

Introduction

The description of ^3He diffusion MRI presented here is narrowly focused on the developments at Washington University in St. Louis and at Cincinnati Children's Hospital, while trying to place these developments in the context of the larger work in the field. Of course, many researchers and many groups contributed (and continue today) to this exciting

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line of research, and this article is not intended to be a comprehensive review of the field, where many such reviews exist (1–7). While the narrow focus of this manuscript is in part due to the fact that the authors know best this part of the ^3He MRI history, the more important reason for this focus is because the work in St. Louis was aided immensely by Prof. J.J.H. (Joe) Ackerman, in honor of whom this special issue of *J. Magnetic Resonance* is written.

Professor Ackerman was instrumental in creating the initial team of Dmitriy Yablonskiy, Brian Saam, and Mark Conradi. Joe went further, connecting the team of MR physicists to the medical team of Joel Cooper (lung surgeon) and Steve Lefrak (pulmonologist) and David Gierada (radiologist). This provided true multidisciplinary, with a combination of skills and expertise that has been emulated by many groups and centers. Jason Woods quickly joined the effort, then as graduate student, and later as a postdoctoral fellow and professor, and now applies these techniques at a lung imaging center at Cincinnati Children's Hospital. This manuscript expresses our deep gratitude to Joe for helping to make this happen; his group was excellent at bridging the two cultures between medicine and basic science, and diffusion MRI was part of the daily regimen.

The early work of the multidisciplinary group at Washington University focused on chronic obstructive lung disease (COPD), because patients with COPD were expected to have much less restriction to gaseous diffusion as a result of tissue destruction in the lung, often known as emphysema (8, 9). After initial demonstration of larger ADC in COPD and of the large dynamic range of ^3He ADC in these patients (10, 11), the interest in restricted diffusion significantly increased, as it seemed possible that imaging could be more sensitive to obstructive lung disease than any other research technique, and certainly more than any standard clinical exam like pulmonary function testing (12, 13). Importantly, this led our group and others to explore this sensitivity and potential for geometric modeling in great detail (14–18). Twenty years later the collective body of work from the field includes demonstrations of exquisite sensitivity to early emphysematous changes in COPD (19–22), severity-related differences in childhood and adult asthma (23–25), a deeper understanding of alveolar recruitment in normal respiration (26), and geometric models of alveolar airspaces that match morphologic reality (16, 27). More recently, these same techniques are being applied to prematurely born infants, because of the underdeveloped and poorly-understood nature of their lung microstructure (28). Older adults and premature infants, at opposite ends of life's spectrum, have lungs that are well probed by ^3He gas diffusion MRI.

Gas Polarization, Administration and Imaging

Polarization of ^3He gas

A very practically-oriented discussion of polarizing ^3He by spin-exchange optical pumping of rubidium appeared early-on, with a “how to” slant (29). The competing method involving optical pumping of helium atoms in the 2s metastable state has not been as popular, in part because it must be performed at low pressures and requires a pump to reach useful pressures of a few bars; the pump must not de-polarize the gas (30, 31).

Linearly polarized light at 794.7 nm at the level of ~ 50–100W is obtained from a semiconductor diode laser array (32, 33). These remarkable devices have ~ 50% dc-to-light efficiencies and now significantly narrowed linewidths, due to wavelength-specific feedback (34). The rather divergent light is collimated by cylindrical, converging lenses to approximately match the 4 cm diameter glass pumping cell. The light is converted to circular polarization by a quarter-wave plate and then reaches the cell.

The glass cell contains ~10 atm of ^3He with 1–2% of N_2 added as a buffer gas for collisional de-excitation of Rb(35). A fraction of a gram of Rb metal is present in the cell; when heated to ~160°C the vapor pressure of Rb is optimum at most laser powers. The 794.7 nm photons drive the Rb transition between the $5s_{1/2}$ ground state and the $5p_{1/2}$ first-excited state. In the presence of a weak (30 Gauss) field parallel to the optical axis, the Rb transitions obey selection rules of $m = +1$ or -1 , depending on the right-vs-left hand circular polarization of the light(36).

For the $m = +1$ case, Rb atoms are driven out of the $m = -1/2$ sub-level of the ground-state. Half of these de-excite to the $m = +1/2$ sub-level, accomplishing *selective de-population*. The half that de-excite into the original $m = -1/2$ sub-level are simply returned to the excited state by subsequent resonant photons. The net result is that nearly all of the Rb atoms in the vapor are in their $m = +1/2$ sub-level of the ground state. Clearly, the electronic spins are far from thermal equilibrium.

The Rb atoms, even at the concentration of 10^{-6} (compared to ^3He atoms) *dominate* the ^3He relaxation. This is because monatomic ^3He has an extremely long T_1 in the absence of rubidium (almost always limited by wall relaxation with the walls of the glass cell), from 10–60 hours(37). Occasional Rb- ^3He collisions result in spin exchange of the Rb electron spin and the ^3He nuclear spin. With typically a 6 hour time constant, the ^3He nuclear spin polarization approaches its steady-state value of 30–55%. This is an example of the Overhauser effect, wherein electron spins far from equilibrium create a vastly enhanced nuclear spin polarization(38).

These large polarizations yield a $\sim 10^5$ increase in signal-to-noise ratio (S/N), compared with Boltzmann equilibrium in typical 1.5–3 T fields. This S/N increase more than compensates for the low density of a gas at atmospheric pressure, compared to the high density of proton spins in water in living subjects.

New developments in spin-exchange optical pumping include the use of line-narrowed diode laser arrays (39). On their own, the diode laser arrays are “firehoses of infrared photons” (quote from Brian Saam) with spectra that are broad for a laser (~2–3 nm). With wavelength-selective feedback provided by an external grating or (better and more conveniently) a volumetric Bragg grating directly attached to the array, the laser runs with a much narrower optical spectrum (as small as 0.2 nm) (39). The result is that a larger fraction of the photons are “on-resonance” with the Rb absorber atoms (34). To say it differently, the typically 10 atm of ^3He gas does not provide adequate pressure broadening of the Rb absorption line, for the diode laser arrays without line-narrowing (33); most of the photons pass through, unabsorbed. A second recent development is the use of double-alkali pumping

(40). One alkali metal atom absorbs the laser light and transfers its excitation to the other alkali, which eventually transfers the polarization to ^3He nuclear spins (41). The idea is the first alkali is chosen for good optical absorption and the availability of lasers with the correct wavelength and the second alkali is selected for best transfer to the nuclear spins.

Delivery of gas to a typical patient

After sufficient polarization, the polarization cell is cooled to room temperature, where the Rb vapor condenses onto the glass cell walls. The 10 atm gas is released into a flexible bag (typically Tedlar material, for its polarization-friendly properties) and is walked to the patient (7). After a tidal exhale, the patient inhales the ^3He and holds his or her breath and imaging commences. Sometimes the ^3He (typically 0.5 liter STP) is used with added N_2 for a more comfortable breath hold (42). Oxygen can be added, but this results in more rapid T_1 relaxation and destruction of the hyperpolarized ^3He magnetization. The relaxation rate from oxygen is approximately 0.5 s^{-1} per atmosphere of oxygen partial pressure (43). Oxygen cannot be eliminated from patients' lungs of course (even after inert purge, O_2 passes back into the lungs from the blood); typically all MR imaging must be completed within about 20 s of introduction of ^3He into the lungs. On the other hand, when imaging explanted lungs, very long T_1 values can be had by excluding all oxygen (44–46).

Imaging with hyperpolarized ^3He

Imaging of the ^3He is often performed by FLASH (fast, low-angle shots), a gradient-recalled echo method (47–49). For example, use of 10° rf pulses leaves 98.5% of the spin z -magnetization after each pulse. So, after 64 pulses (64 phase encode steps), 37% of M_z remains. Thus, most (but not all) of the M_z has been used to make the image. We note that small flip-angle sequences are generally not suitable for spin echo sequences, because of the cumulative effect on M_z of the large refocusing pulses. A side benefit of small-angle pulses is the small amount of rf energy deposited into the patient. A slightly more clever use of the nonrenewable (and progressively consumed) magnetization is by increasing flip angles as the polarization is consumed, thus allowing full use of the magnetization with closer to constant signal per rf pulse (50, 51).

Others have used radial scanning of k -space, in two and three dimensions (52–54). For example, the University of Virginia group showed excellent images obtained with spiral scanning of k -space acquired in such a way that sliding-window reconstructions (reconstructions of the dataset using only a few, new spirals in k -space for an updated image) provided exquisite apparent time resolution (55). These non-Cartesian scans generally require careful adjustment, so the path through k -space matches that desired, but there clearly are benefits to the images in terms of time savings. As non-cartesian techniques gain popularity and are progressively more supported by the large MRI manufacturers, their full advantages over Cartesian acquisitions can be realized more broadly (56).

Our group was influenced early by pulmonologists and surgeons to use pixel sizes that were relevant to clinical disease and existing treatments (8). Typical dimensions were 3–4 mm in-plane and 10 mm slices for ventilation imaging, with even larger pixels for diffusion imaging, ensuring coverage of the whole lung in a single breath hold of 10 seconds or less.

More modern approaches can now achieve faster whole-lung coverage, or higher resolution at the expense of S/N (57, 58). Our experience is that regions of disease (e.g., indicated by poor ventilation or high ADC) contain many, many voxels, even at this coarse resolution (59). While ^3He ventilation MRI has been employed now for over 20 years, direct relevance to clinical care is finally being demonstrated (23, 60, 61). Indeed, there remain several applications of ventilation MRI for characterization of early disease and evaluation of new treatments (e.g. before and after surgery, as in Figure 1, or bronchial thermoplasty,) (25, 60, 62).

Diffusion of ^3He in Lungs

Short-range (typical) diffusion MRI

The lung is a bifurcating network of conducting and alveolated airways, with ~23 levels of branching (63). The smallest, called acinar airways, are levels 16–23 and transport gas primarily by diffusion (not by flow) under normal physiologic pressures of 15–25 cm H₂O. (The total length of any acinar-airway route is around 1 mm or less, so diffusion is fast compared to convection at these pressures.) The acinar airways are lined with alveoli (fully lined at the highest numbered levels), the flexible membranes through which O₂ and CO₂ are exchanged between the gas and blood. While a typical gas atom travels 98% or more of the linear distance from mouth to terminus via conducting airways, over 90% of the lung volume is acinar air space (63–65).

The mean linear intercept (a histological measure of alveolar-space size, but essentially the average distance between tissue walls) in healthy humans is ~0.2 mm(45). The membrane walls themselves are much smaller, around 0.01 mm in thickness, and contain largely diamagnetic blood, being in contact with paramagnetic O₂ in the adjacent alveoli. The sharp boundaries of these tissue-gas susceptibility interfaces result in the well-known inhomogeneous local magnetic field and line broadening of the water NMR signal in the lung-tissue, making it challenging to image the hydrogen nuclear spins of lung parenchyma except at very short echo times, via radial and spiral techniques (66, 67). This alveolated structure also restricts the diffusion (ADC) of the gas in lung (11). A gas of ~10% ^3He in air or nitrogen (the inhaled 0.5 L ^3He is diluted upon inhalation into a ~6 L lung) has a free diffusivity of 0.88 cm²/s. This is the value typically found in the trachea in the dilute limit of ^3He in air; the gas in the trachea does not generally encounter walls to collide with in an interval of 2 ms—the evolution time in typical gas diffusion pulse sequences (10).

For a typical diffusion sequence with diffusion time of 2 ms, the rms displacement along one dimension would be $\sqrt{2Dt}$, or 0.6 mm for $D = 0.88 \text{ cm}^2/\text{sec}$. This is substantially larger than the above-discussed mean linear intercept L_m of 0.2 mm. Thus, ^3He in the lung parenchyma will almost surely collide with airway and/or alveolar walls; as a result, the ADC will be reduced (or *restricted*). These straightforward measurements were the basis for initial explorations of ADC as a measure of airspace increases due to disease.

Measurement of short-range gas ADC

ADC is generally measured with gradient-recalled echoes, because of the non-renewable nature of hyperpolarization. One image is obtained in the presence of a bipolar diffusion-sensitizing gradient (after rf pulse excitation and before readout), with sensitizing parameter b that is reflective of both bipolar diffusion-sensitizing gradient strength and duration. Typically b is chosen to be $1.5\text{--}3\text{ s/cm}^2$, to give $\exp(-b \cdot \text{ADC})$ values of order 0.5. A second image is obtained without the diffusion sensitizer, to yield a reference image for ratiometric comparison. The pixel-by-pixel ratio is used to determine ADC for that pixel: $I_b/I_{b=0}$ is most often fit to $\exp(-b \cdot \text{ADC})$, where I is the image intensity for the desired pixel (10, 11, 68).

This method initially showed large differences in ADC between healthy volunteers and patients with emphysema, as well as spatial variations within emphysematous lungs, which led to significant interest from the larger MRI and medical communities. Regions of large ADC are regions of more severe dilatation of the lung airspaces, a hallmark of the emphysematous phenotype of COPD. The distinction between ADC values in healthy, control lungs and severely emphysematous lungs is stark – $0.2\text{ cm}^2/\text{s}$ *versus* $0.5\text{ cm}^2/\text{s}$, typically. When histogrammed, the two groups' ADC values are as different as day and night. Importantly, the ventilation patterns in many cases reflect that the areas of more severe emphysematous destruction can ventilate, therefore contributing to a mismatch between ventilation and gas exchange (Figure 2). Of course, one cannot measure ADC where there is zero ventilation (thus zero ^3He signal).

These ADC measurements have been validated in a number of human and animal studies (all with informed consent and IRB or IACUC approval)—first in mice and later in adult humans. In our own group's work, a number of lungs explanted during lung transplantation, in addition to a few donor (normal) lungs rejected at the last minute for transplantation, were imaged *ex vivo* via ^3He diffusion MRI and then frozen slowly while inflated to a similar volume as during MRI. After slicing the frozen lung on a band saw and sampling with a cork borer, the cores were processed for histology by immersions in graduated steps of ethanol and standard paraffin processing, with staining by hematoxylin and eosin. In this way regional comparisons were made between regions of interest in individual lung slices and image-slices in ADC maps (Figure 3).

While imperfect slice-matching and histological preparation provided significant biological noise in these comparisons, correlation between ^3He ADC and histological mean linear intercept was strong—providing validation of this noninvasive, non-ionizing imaging modality against the clinical gold standard of airspace enlargement (69, 70).

More recently the techniques have begun to be applied to infant and developing lungs, where airspace enlargement due to arrested development and alveolar simplification causes significant morbidities and mortality among prematurely born infants, most often in the form of bronchopulmonary dysplasia, or BPD (71). While the number of new cases each year is modest (around 10,000), advances in newborn medicine has improved premature infant survivability, which has also resulted in an increased incidence of BPD. Hospitalization costs for these infants represent 30% of newborn healthcare costs, an estimated \$13.4 billion

annually in the US(72). Long-term cardiopulmonary sequelae from BPD persist into adulthood and include asthma, increased respiratory infections, pulmonary hypertension, and sleep disorders, with repeated hospitalizations and increased mortality, so there is a compelling reason for better understanding and treating the disease. Very recently Flors et al demonstrated increased ADC in early school-age children who had been diagnosed with BPD (28). This relatively new area of scientific exploration can shed light on adolescent and adult chronic obstructive lung disease (asthma, COPD) more generally. An initial exploration in our lab demonstrated that ^3He ADC is indeed sensitive to changes in alveolar size during normal and abnormal development, which sets the stage for its use as a diagnostic tool in infancy and early childhood (Figure 4) (73).

Long-range ADC

The above-described method (gradient-echo imaging, with and without a bipolar diffusion sensitizing gradient pulse) measures displacements over times of a few milliseconds, so distances generally less than the 0.6 mm calculated above. We later became interested in measuring diffusive displacements over much longer times (seconds) and distances of 1–3 cm; such “long-range” measurements may be more relevant to the transport of gases (O_2 and CO_2) from the conducting airways to and amongst the acinar airways (46, 70).

Our version of long-range ADC measurement modulates the longitudinal magnetization with a sinusoidal variation(46). We use two 45° rf pulses separated by a gradient pulse (say along x) to yield a longitudinal spin magnetization that varies $M = M_0 (1 + \cos(2\pi x/\lambda))/2$. The modulation wavelength λ is determined by the gradient pulse amplitude G and duration τ , with $\lambda = 2\pi/(\gamma G\tau)$. The use of 45° pulses instead of 90° pulses ensures the magnetization M is never driven negative, a feature demanded by our use of FLASH with magnitude images. The two rf pulses spaced by a gradient pulse are the preparation part of the stimulated echo sequence, so this method is in fact the stimulated echo, described by other words(74). After a waiting time of order 1 s, the magnetization is read out by small-angle pulses and image acquisition. The rf read-out pulses are kept small to allow several additional read-outs at larger times (a somewhat non-destructive read-out). Alternative methods for probing longer diffusion distances include the use of stimulated echoes (74, 75).

The magnetization modulation washes out with increasing time. The peaks in M decrease and the troughs increase (or fill in). Because diffusion of M simply moves magnetization from one location to another and cannot create or destroy it, the changes due to diffusion are readily distinguished from the effects of T_1 . For uniform long-range diffusivity D , the modulation amplitude A should decay as $M \sim \exp(-Dk^2t)$, with $k = 2\pi/\lambda$, with λ the modulation wavelength and t being the time. This result is obtained from the diffusion equation, $\frac{\partial M}{\partial t} = D \nabla^2 M$. Thus, for $\lambda = 3$ cm an effective diffusion coefficient of $D = 0.11$ cm^2/sec will result in decay of the modulation by a factor of e in 2 seconds. Thus, long-range diffusion measurements as described here (over many seconds) are generally sensitive to diffusivity values smaller than the range of short-range (ms) ADC measurements.

Tissue destruction in emphysema is found to be accompanied by large increases in the long-range ADC (measured over cm lengths and time scales of seconds) (46, 70). Expressed as a

multiplicative factor relative to the ADC of healthy lungs, the increases in long-range diffusivity are generally larger than for short-range ADC (over ms times and sub-mm lengths). Figure 5 presents the modulation decay in an explanted lung from a COPD patient where the upper lobe (left side of the images) has significantly more emphysema than the lower lobe (right side), indicating rapid tagging decay that approaches the free-diffusion limit of $0.88 \text{ cm}^2/\text{s}$ —much more rapid than the $0.02 \text{ cm}^2/\text{s}$ measured in healthy lungs at this diffusion distance(70).

Curiously, the long-range ADC in healthy lungs of $\sim 0.02 \text{ cm}^2/\text{s}$ is larger than one expects from diffusion simulations using a model of the bifurcating airways (76). This discrepancy points to the existence of *collateral paths*, paths connecting points that are not represented in the 23 levels of bifurcating airways (70). The collateral paths may involve small perforations in the acinar airway walls, such as the pores of Kohn. The finding has as yet no implication for characterizing lung disease, but is of interest to anatomy and physiology.

Microscopically Anisotropic Diffusion

This subject has been focused upon by our colleague Dmitriy Yablonskiy; the present discussion is a brief overview to provide the physical principles. For a more complete discussion, the reader is referred to Dr Yablonskiy's and others' published work on the subject (16, 27, 77, 78).

Lung structure

In a time of approximately 2 ms, ^3He atoms can readily diffuse across the diameter of typical acinar airways, but they do not diffuse far enough along the length to pass into the 'next' airway. This statement is an approximation or idealization (the very-long airway approximation); the passage to subsequent airways has been considered by simulations (27, 79, 80). Staying within this idealization, a ^3He atom's diffusion is highly restricted in the transverse directions, so it has a transverse diffusivity D_T which is much smaller than the free diffusivity D_0 . On the other hand, motion along the airway axis is *relatively* unimpeded (the airway walls are not smooth, but have alveolar walls protruding into the lumen, somewhat restricting the longitudinal diffusion) (27). Thus, the longitudinal diffusivity D_L obeys $D_T < D_L < D_0$.

It is important to note that the orientations of acinar airways are approximately isotropically distributed over macroscopic dimensions, like our imaging voxels (18, 63, 81). Thus, any diffusion measurement is *macroscopically isotropic*, meaning that the result is the same for any orientation of the diffusion sensitizing gradient. Measurements with gradients in different directions confirm this. However, for the gas in an *individual* airway, the diffusion is direction dependent, with $D_T < D_L$. This diffusion is *microscopically anisotropic*; this anisotropy is the key feature of the measurement. An analogy is a jar full of randomly-oriented, small sugar crystals. Each crystal is anisotropic (for example, in its diffraction of x-rays), while the properties of the entire jar are isotropic.

Measurement of diffusion microscopic anisotropy

In every voxel and for any direction of the gradient, there will be acinar airways perpendicular to the diffusion gradient (with diffusivity D_T), airways parallel to the gradient (with diffusivity D_L), and every value in between (18). Each group of airways will show an exponentially decaying echo amplitude dependence on the gradient b-value, $\exp(-bD_{(\theta)})$, where $D_{(\theta)} = D_L \cos^2\theta + D_T \sin^2\theta$ with θ the angle between the airway axis and the gradient direction. That is, each airway will show a weighted average diffusivity, between D_L and D_T . The sum over all airway orientations yields a non-exponential (multi-exponential) decay.

One characterizes this non-exponential decay of echo amplitude vs b to obtain D_L and D_T . Basically, the initial slope of the decay (i.e., at $b=0$) yields the average diffusivity, $\bar{D} = (D_L + 2D_T)/3$. The large-b tail of the decay yields D_T (because the components with $D_{(\theta)} > D_T$ have preferentially decayed). In this way, a fit to the echo amplitude as a function of gradient weight b yields D_L and D_T . The data are obtained with the FLASH sequence with diffusion time-scale of 2 ms and 5 to 9 values of b (27).

It is a common experience that fitting relaxation data to the sum of two exponential components requires exceedingly good S/N to yield unique values of the four parameters (amplitude and decay constant for each component) (78). The fitting of the non-exponential signal decay *versus* b is different – here there are only three parameters. These are D_L , D_T , and the initial amplitude. This reduction by one parameter means that fits with low uncertainties in the parameter values are obtained, even with only modest S/N. The assumption of an isotropic distribution of airway orientations provides the relative amplitudes of the decay components, so the relative amplitudes are not fitting parameters. Alternative approaches include diffusion kurtosis and stretched exponential models, which can relate parameters to a mean airspace size, but without a physical model (16, 82).

Physical interpretation of D_L and D_T

The transverse ADC, D_T , is a measure of the major radius, R , of the acinar airways, with larger radii corresponding to larger (less restricted) D_T . Once the radius approaches 1 mm, little restriction remains and D_T approaches the free diffusion D_o . These parameters have also been expressed in terms of acinar-airway radius, R , and alveolar depth, h , which have the advantage of relating diffusion anisotropy to physical parameters that stem from morphologic investigations of human 3D lung structure(63).

The longitudinal (axial) ADC, D_L , is reduced below D_o by alveolar walls that penetrate into the airway lumen. The protruding tissue walls form a clear passage of inner radius r . To some level of approximation, D_L is $D_o r^2/R^2$; the limit $r \rightarrow R$ corresponds to a smooth-walled tube with $D_L = D_o$. The above approximate dependence has D_L varying as the fraction of cross-sectional area that is unimpeded.

Thus, the multi-b determinations of diffusivity can reveal the average acinar major radius R and the depth h ($R-r$) to which alveolar tissue extends into the airway lumen.

In the progression of emphysema, followed from least severe disease to most severe in different patients, D_L progresses towards D_o relatively early. That is, h becomes a smaller

and smaller fraction of R , leaving nearly smooth-wall lumens. As disease progresses further, the outer radius R increases more slowly(19).

We take this opportunity to note that the above model of microscopic anisotropy of ADC attributes *all* the dispersion of ADC (within one voxel) to anisotropy. To our knowledge, this has never been well tested. Double-diffusion measurements, with two cascaded attenuation intervals (with the two gradients either parallel or perpendicular to each other), should distinguish the microscopic anisotropy case from a simple dispersion of purely isotropic diffusivities (say, arising from a distribution of sizes of restricting features (83)). A related method would be to measure the truly isotropic diffusion D_{iso} with attenuation from a G_x , then G_y , then G_z , all within one pulse sequence. The model of microscopic anisotropy would yield a sharp value for D_{iso} while the other model would not.

^3He , ^{129}Xe , and the Future

While both ^3He and ^{129}Xe can be similarly hyperpolarized by spin-exchange optical pumping, ^3He was the preferred isotope because of its larger gyromagnetic ratio, more easily achievable high polarization (near 50%), and high relative isotopic enrichment compared to ^{129}Xe . The natural abundance of ^3He is near zero (around 1 ppm), however, and the relative availability of ^3He was only facilitated by large stockpiles of global thermonuclear weapons, which often use tritium as triggering devices (^3H decays into ^3He with a half life of around 12.3 years). This makes the low-temperature and NMR uses of ^3He subject to global and market forces unrelated to science, which was demonstrated in 2008–2010 in the worldwide ^3He shortage, driven by US-interest in the use of ^3He as a neutron-sensitive agent for border security. This ^3He shortage sparked renewed interest in ^{129}Xe as a hyperpolarized gas, which coincided well with increases in ^{129}Xe polarization, due to increased understanding of ^{129}Xe spin physics at higher densities and engineering improvements in laser and polarization technologies(84–86).

Since 2010, ^{129}Xe polarizations have continuously improved, with 1-L quantities of gas at 30–40% polarization produced routinely now (87–89). Scientific interest in the use of ^{129}Xe has concomitantly increased: scholar.google.com search results for research articles with “hyperpolarized xenon MRI” increased by 59% in calendar-year 2016 compared to 2008 (170→270), while similar results for “hyperpolarized helium MRI” decreased by 25% (226→170). Thus, while there is likely a sea-change toward ^{129}Xe for in-vivo MRI, the ^3He studies mentioned above have provided the basis for both ventilation and gas-diffusion MRI as sensitive measures of early lung disease (4, 19, 90). ^{129}Xe ADC has been shown to be significantly increased in COPD, even in mild disease, and has also been validated by comparison to quantitative histology (91). Anisotropy of the acinar airways (separate measurements of D_T and D_L) is also possible to image with ^{129}Xe , and this has recently been demonstrated in a rat model and in humans (89, 92–94). The higher mass of ^{129}Xe compared to ^3He may even provide certain advantages in the detection of early lung obstruction, as ventilation to slightly obstructed regions have been shown to be poorer with a slightly heavier, more viscous gas mixture (95). Further, in situations that benefit from a smaller diffusion distance, such as ADC measurements in pediatrics, ^{129}Xe may be an advantage. Hyperpolarized ^3He has contributed significantly to the advancement of

knowledge of early lung disease, and this contribution will continue via the application of similar techniques with ^{129}Xe .

Summary

Hyperpolarization of ^3He gas provides very large increases in MRI S/N, allowing the gas spaces and distribution of gas in the lung to be visualized (“ventilation images”). Here we have focused on measurement of changes in the diffusion of the gas, restricted by collisions with airway and alveolar walls. Initially these measurements were performed over milliseconds and sub-millimeter distances; very large increases were observed in patients with airspace enlargement as a result of COPD, with high sensitivity to early disease. Contrast of the ADC maps between COPD and healthy controls is large. Exhaustive work has been performed to validate the ^3He ADC against traditional (invasive, destructive) measurements of airspace expansion. The measurements were extended to long-range ADC, measured over timescales of seconds and distances of centimeters. Here the increase in ADC in COPD is even larger and may reflect the development of enlarged collateral paths, as well as airway and alveolar destruction.

The diffusion in acinar airways is microscopically anisotropic. This anisotropy results in multi-exponential decays of signal versus the diffusion-sensitizing parameter b . Fitting of the decay allows the transverse and longitudinal diffusivities to be separately obtained. From these, the average acinar airway major radius and the extent to which alveoli enter the airway lumen can be determined.

All of these techniques, first explored and developed for characterization and understanding of adult lung diseases like COPD, are now being applied to infants and young children, particularly those born prematurely. Given the central role played by lung abnormalities in neonates and infants, this application promises to be important in future care of these youngest patients.

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References

1. Altes TA, de Lange EE. Applications of hyperpolarized helium-3 gas magnetic resonance imaging in pediatric lung disease. *Topics in magnetic resonance imaging: TMRI*. 2003; 14(3):231–6. [PubMed: 12973130]
2. Fain S, Schiebler ML, McCormack DG, Parraga G. Imaging of lung function using hyperpolarized helium-3 magnetic resonance imaging: Review of current and emerging translational methods and applications. *Journal of magnetic resonance imaging: JMRI*. 2010; 32(6):1398–408. [PubMed: 21105144]

3. Heussel CP, Gast KK, Dahmen A, Morbach AE, Kauczor HU, Schreiber WG, et al. Hyperpolarized (3)helium gas for functional magnetic resonance imaging of the lung. *Medizinische Klinik*. 2005; 100(7):413–24. [PubMed: 16010478]
4. Walkup LL, Woods JC. Translational applications of hyperpolarized ³He and ¹²⁹Xe. *NMR in biomedicine*. 2014; 27(12):1429–38. [PubMed: 24953709]
5. Conradi MS, Yablonskiy DA, Woods JC, Gierada DS, Jacob RE, Chang YV, et al. ³He diffusion MRI of the lung. *Academic radiology*. 2005; 12(11):1406–13. [PubMed: 16253852]
6. Kirby M, Coxson HO, Parraga G. Pulmonary functional magnetic resonance imaging for paediatric lung disease. *Paediatr Respir Rev*. 2013; 14(3):180–9. [PubMed: 23522599]
7. van Beek EJ, Wild JM, Kauczor HU, Schreiber W, Mugler JP 3rd, de Lange EE. Functional MRI of the lung using hyperpolarized ³-helium gas. *Journal of magnetic resonance imaging: JMRI*. 2004; 20(4):540–54. [PubMed: 15390146]
8. Saam B, Yablonskiy DA, Gierada DS, Conradi MS. Rapid imaging of hyperpolarized gas using EPI. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 1999; 42(3):507–14.
9. Gierada DS, Saam B, Yablonskiy D, Cooper JD, Lefrak SS, Conradi MS. Dynamic echo planar MR imaging of lung ventilation with hyperpolarized (3)He in normal subjects and patients with severe emphysema. *NMR in biomedicine*. 2000; 13(4):176–81. [PubMed: 10867693]
10. Saam BT, Yablonskiy DA, Kodibagkar VD, Leawoods JC, Gierada DS, Cooper JD, et al. MR imaging of diffusion of (3)He gas in healthy and diseased lungs. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2000; 44(2):174–9.
11. Chen XJ, Moller HE, Chawla MS, Cofer GP, Driehuys B, Hedlund LW, et al. Spatially resolved measurements of hyperpolarized gas properties in the lung in vivo. Part I: diffusion coefficient. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 1999; 42(4):721–8.
12. Kauczor HU, Eberle B. Elucidation of structure-function relationships in the lung: contributions from hyperpolarized ³helium MRI. *Clinical physiology and functional imaging*. 2002; 22(6):361–9. [PubMed: 12464138]
13. Mayo JR, Hayden ME. Hyperpolarized helium 3 diffusion imaging of the lung. *Radiology*. 2002; 222(1):8–11. [PubMed: 11756698]
14. Yablonskiy DA, Sukstanskii AL, Leawoods JC, Gierada DS, Bretthorst GL, Lefrak SS, et al. Quantitative in vivo assessment of lung microstructure at the alveolar level with hyperpolarized ³He diffusion MRI. *Proceedings of the National Academy of Sciences of the United States of America*. 2002; 99(5):3111–6. [PubMed: 11867733]
15. Wang W, Nguyen NM, Yablonskiy DA, Sukstanskii AL, Osmanagic E, Atkinson JJ, et al. Imaging lung microstructure in mice with hyperpolarized (3)He diffusion MRI. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2010
16. Chan HF, Stewart NJ, Parra-Robles J, Collier GJ, Wild JM. Whole lung morphometry with 3D multiple b-value hyperpolarized gas MRI and compressed sensing. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2017; 77(5):1916–25.
17. Minard KR, Jacob RE, Laicher G, Einstein DR, Kuprat AP, Corley RA. MR imaging of apparent ³He gas transport in narrow pipes and rodent airways. *Journal of magnetic resonance*. 2008; 194(2):182–91. [PubMed: 18667344]
18. Wang W, Nguyen NM, Yablonskiy DA, Sukstanskii AL, Osmanagic E, Atkinson JJ, et al. Imaging lung microstructure in mice with hyperpolarized ³He diffusion MRI. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2011; 65(3):620–6.
19. Quirk JD, Lutey BA, Gierada DS, Woods JC, Senior RM, Lefrak SS, et al. In vivo detection of acinar microstructural changes in early emphysema with (3)He lung morphometry. *Radiology*. 2011; 260(3):866–74. [PubMed: 21734160]

20. Emami K, Cadman RV, Woodburn JM, Fischer MC, Kadlecsek SJ, Zhu J, et al. Early changes of lung function and structure in an elastase model of emphysema--a hyperpolarized ^3He MRI study. *Journal of applied physiology*. 2008; 104(3):773–86. [PubMed: 18063806]
21. Ouriadov A, Lessard E, Sheikh K, Parraga G. Canadian Respiratory Research N. Pulmonary MRI morphometry modeling of airspace enlargement in chronic obstructive pulmonary disease and alpha-1 antitrypsin deficiency. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2018; 79(1):439–48.
22. Capaldi DP, Zha N, Guo F, Pike D, McCormack DG, Kirby M, et al. Pulmonary Imaging Biomarkers of Gas Trapping and Emphysema in COPD: (^3He) MR Imaging and CT Parametric Response Maps. *Radiology*. 2016; 279(2):597–608. [PubMed: 26744928]
23. Cadman RV, Lemanske RF Jr, Evans MD, Jackson DJ, Gern JE, Sorkness RL, et al. Pulmonary ^3He magnetic resonance imaging of childhood asthma. *The Journal of allergy and clinical immunology*. 2013; 131(2):369–76. e1–5. [PubMed: 23246019]
24. Horn FC, Marshall H, Collier GJ, Kay R, Siddiqui S, Brightling CE, et al. Regional Ventilation Changes in the Lung: Treatment Response Mapping by Using Hyperpolarized Gas MR Imaging as a Quantitative Biomarker. *Radiology*. 2017; 284(3):854–61. [PubMed: 28471738]
25. Trivedi A, Hall C, Hoffman EA, Woods JC, Gierada DS, Castro M. Using imaging as a biomarker for asthma. *The Journal of allergy and clinical immunology*. 2017; 139(1):1–10. [PubMed: 28065276]
26. Hajari AJ, Yablonskiy DA, Sukstanskii AL, Quirk JD, Conradi MS, Woods JC. Morphometric changes in the human pulmonary acinus during inflation. *Journal of applied physiology*. 2012; 112(6):937–43. [PubMed: 22096115]
27. Yablonskiy DA, Sukstanskii AL, Woods JC, Gierada DS, Quirk JD, Hogg JC, et al. Quantification of lung microstructure with hyperpolarized ^3He diffusion MRI. *Journal of applied physiology*. 2009; 107(4):1258–65. [PubMed: 19661452]
28. Flors L, Mugler JP 3rd, Paget-Brown A, Froh DK, de Lange EE, Patrie JT, et al. Hyperpolarized Helium-3 Diffusion-weighted Magnetic Resonance Imaging Detects Abnormalities of Lung Structure in Children With Bronchopulmonary Dysplasia. *Journal of thoracic imaging*. 2017; 32(5):323–32. [PubMed: 28221241]
29. Leawoods JC, Yablonskiy DA, Saam B, Gierada DS, Conradi MS. Hyperpolarized He-3 gas production and MR imaging of the lung. *Concept Magnetic Res*. 2001; 13(5):277–93.
30. Gentile TR, Jones GL, Thompson AK, Rizi RR, Roberts DA, Dimitrov IE, et al. Demonstration of a compact compressor for application of metastability-exchange optical pumping of He-3 to human lung imaging. *Magnet Reson Med*. 2000; 43(2):290–4.
31. Abboud M, Sinatra A, Tastevin G, Nacher PJ, Maitre X. Metastability exchange optical pumping of helium-3 at high pressures and 1.5 T: Comparison of two optical pumping transitions. *Laser Phys*. 2005; 15(4):475–9.
32. Gamblin RL, Carver TR. Polarization and Relaxation Processes in He3 Gas. *Phys Rev*. 1965; 138(4a):A946.
33. Walker TG, Happer W. Spin-exchange optical pumping of noble-gas nuclei. *Rev Mod Phys*. 1997; 69(2):629–42.
34. Chann B, Babcock E, Anderson LW, Walker TG, Chen WC, Smith TB, et al. Production of highly polarized He-3 using spectrally narrowed diode laser array bars. *J Appl Phys*. 2003; 94(10):6908–14.
35. Walker TG, Happer W. Spin-exchange optical pumping of noble-gas nuclei. *Reviews of Modern Physics*. 1997; 69(2):629–42.
36. Kadlecsek S, Walker T, Walter DK, Erickson C, Happer W. Spin-axis relaxation in spin-exchange collisions of alkali-metal atoms. *Phys Rev A*. 2001; 63(5)
37. Jacob RE, Morgan SW, Saam B, Leawoods JC. Wall relaxation of He-3 in spin-exchange cells. *Physical review letters*. 2001; 87(14)
38. Slichter, CP. *Principles of magnetic resonance*. 3. Berlin; New York: Springer; 1996. xi655updated
39. Nelson IA, Chann B, Walker TG. Spin-exchange optical pumping using a frequency-narrowed high power diode laser. *Appl Phys Lett*. 2000; 76(11):1356–8.

40. Babcock E, Nelson I, Kadlecsek S, Driehuys B, Anderson LW, Hersman FW, et al. Hybrid spin-exchange optical pumping of He-3. *Physical review letters*. 2003; 91(12)
41. Baranga ABA, Appelt S, Romalis MV, Erickson CJ, Young AR, Cates GD, et al. Polarization of He-3 by spin exchange with optically pumped Rb and K vapors. *Physical review letters*. 1998; 80(13):2801–4.
42. Gierada DS, Woods JC, Bierhals AJ, Bartel ST, Ritter JH, Choong CK, et al. Effects of diffusion time on short-range hyperpolarized (3)He diffusivity measurements in emphysema. *Journal of magnetic resonance imaging: JMRI*. 2009; 30(4):801–8. [PubMed: 19787725]
43. Deninger AJ, Eberle B, Ebert M, Grossmann T, Heil W, Kauczor HU, et al. Quantification of regional intrapulmonary oxygen partial pressure evolution during apnea by He-3 MRI. *Journal of magnetic resonance*. 1999; 141(2):207–16. [PubMed: 10579944]
44. Conradi MS, Yablonskiy DA, Woods JC, Gierada DS, Bartel SE, Haywood SE, et al. The role of collateral paths in long-range diffusion of 3He in lungs. *Academic radiology*. 2008; 15(6):675–82. [PubMed: 18486004]
45. Woods JC, Choong CK, Yablonskiy DA, Bentley J, Wong J, Pierce JA, et al. Hyperpolarized He-3 diffusion MRI and histology in pulmonary emphysema. *Magnet Reson Med*. 2006; 56(6):1293–300.
46. Woods JC, Yablonskiy DA, Chino K, Tanoli TS, Cooper JD, Conradi MS. Magnetization tagging decay to measure long-range (3)He diffusion in healthy and emphysematous canine lungs. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2004; 51(5):1002–8.
47. de Lange EE, Mugler JP 3rd, Brookeman JR, Knight-Scott J, Truitt JD, Teates CD, et al. Lung air spaces: MR imaging evaluation with hyperpolarized 3He gas. *Radiology*. 1999; 210(3):851–7. [PubMed: 10207491]
48. Fain SB, Korosec FR, Holmes JH, O'Halloran R, Sorkness RL, Grist TM. Functional lung imaging using hyperpolarized gas MRI. *Journal of magnetic resonance imaging: JMRI*. 2007; 25(5):910–23. [PubMed: 17410561]
49. Wild JM, Woodhouse N, Paley MN, Fichelle S, Said Z, Kasuboski L, et al. Comparison between 2D and 3D gradient-echo sequences for MRI of human lung ventilation with hyperpolarized 3He. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2004; 52(3):673–8.
50. Ouriadov AV, Lam WW, Santyr GE. Rapid 3-D mapping of hyperpolarized He-3 spin-lattice relaxation times using variable flip angle gradient echo imaging with application to alveolar oxygen partial pressure measurement in rat lungs. *Magn Reson Mater Phy*. 2009; 22(5):309–18.
51. Deppe MH, Wild JM. Variable flip angle schedules in bSSFP imaging of hyperpolarized noble gases. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2012; 67(6):1656–64.
52. Wild JM, Paley MNJ, Kasuboski L, Swift A, Fichelle S, Woodhouse N, et al. Dynamic radial projection MRI of inhaled hyperpolarized He-3 gas. *Magnet Reson Med*. 2003; 49(6):991–7.
53. Bell LC, Johnson KM, Fain SB, Wentland A, Drees R, Johnson RA, et al. Simultaneous MRI of lung structure and perfusion in a single breathhold. *Journal of magnetic resonance imaging: JMRI*. 2013
54. Kruger SJ, Nagle SK, Couch MJ, Ohno Y, Albert M, Fain SB. Functional imaging of the lungs with gas agents. *Journal of magnetic resonance imaging: JMRI*. 2016; 43(2):295–315. [PubMed: 26218920]
55. Salerno M, Altes TA, Brookeman JR, de Lange EE, Mugler JP. Dynamic spiral MRI of pulmonary gas flow using hyperpolarized He-3: Preliminary studies in healthy and diseased lungs. *Magnet Reson Med*. 2001; 46(4):667–77.
56. Kaushik SS, Robertson SH, Freeman MS, He M, Kelly KT, Roos JE, et al. Single-breath clinical imaging of hyperpolarized (129)Xe in the airspaces, barrier, and red blood cells using an interleaved 3D radial 1-point Dixon acquisition. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2016; 75(4):1434–43.

57. Rizi RR, Baumgardner JE, Ishii M, Spector ZZ, Edvinsson JM, Jalali A, et al. Determination of regional V-A/Q by hyperpolarized He-3 MRI. *Magnet Reson Med*. 2004; 52(1):65–72.
58. Lee RF, Johnson G, Grossman RI, Stoeckel B, Trampel R, McGuinness G. Advantages of parallel imaging in conjunction with hyperpolarized helium- A new approach to MRI of the lung. *Magnet Reson Med*. 2006; 55(5):1132–41.
59. Altes TA, Eichinger M, Puderbach M. Magnetic resonance imaging of the lung in cystic fibrosis. *Proceedings of the American Thoracic Society*. 2007; 4(4):321–7. [PubMed: 17652494]
60. Thomen RP, Sheshadri A, Quirk JD, Kozlowski J, Ellison HD, Szczesniak RD, et al. Regional Ventilation Changes in Severe Asthma after Bronchial Thermoplasty with (3)He MR Imaging and CT. *Radiology*. 2015; 274(1):250–9. [PubMed: 25144646]
61. Kirby M, Pike D, Coxson HO, McCormack DG, Parraga G. Hyperpolarized (3)he ventilation defects used to predict pulmonary exacerbations in mild to moderate chronic obstructive pulmonary disease. *Radiology*. 2014; 273(3):887–96. [PubMed: 24960283]
62. Svenningsen S, Eddy RL, Lim HF, Cox PG, Nair P, Parraga G. Sputum Eosinophilia and MRI Ventilation Heterogeneity in Severe Asthma. *American journal of respiratory and critical care medicine*. 2018
63. Haefelibleuer B, Weibel ER. Morphometry of the Human Pulmonary Acinus. *Anat Rec*. 1988; 220(4):401–14. [PubMed: 3382030]
64. Vasilescu DM, Gao ZY, Saha PK, Yin LL, Wang G, Haefeli-Bleuer B, et al. Assessment of morphometry of pulmonary acini in mouse lungs by nondestructive imaging using multiscale microcomputed tomography. *Proceedings of the National Academy of Sciences of the United States of America*. 2012; 109(42):17105–10. [PubMed: 23027935]
65. Rodriguez M, Bur S, Favre A, Weibel ER. Pulmonary Acinus - Geometry and Morphometry of the Peripheral Airway System in Rat and Rabbit. *Am J Anat*. 1987; 180(2):143–55. [PubMed: 3673919]
66. Higano NS, Hahn A, Walkup LL, Thomen R, Merhar S, Kingma PS, et al. Imaging-Based Pulmonary Functional Measurements From Self-Gated Neonatal Ultra-Short Echo-Time (ute) Magnetic Resonance Imaging (mri). *American journal of respiratory and critical care medicine*. 2016:193.
67. Shioya S, Christman R, Ailion DC. An in vivo NMR imaging determination of multiexponential Hahn T2 of normal lung. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 1990; 16(1):49–56.
68. Chen XJ, Hedlund LW, Moller HE, Chawla MS, Maronpot RR, Johnson GA. Detection of emphysema in rat lungs by using magnetic resonance measurements of 3He diffusion. *Proceedings of the National Academy of Sciences of the United States of America*. 2000; 97(21):11478–81. [PubMed: 11027348]
69. Woods JC, Choong CK, Yablonskiy DA, Bentley J, Wong J, Pierce JA, et al. Hyperpolarized 3He diffusion MRI and histology in pulmonary emphysema. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2006; 56(6):1293–300.
70. Woods JC, Yablonskiy DA, Choong CK, Chino K, Pierce JA, Hogg JC, et al. Long-range diffusion of hyperpolarized 3He in explanted normal and emphysematous human lungs via magnetization tagging. *Journal of applied physiology*. 2005; 99(5):1992–7. [PubMed: 16024528]
71. Walkup LL, Woods JC. Newer Imaging Techniques for Bronchopulmonary Dysplasia. *Clinics in Perinatology*. 2015; 42(4):871. [PubMed: 26593084]
72. Johnson TJ, Patel AL, Jegier BJ, Engstrom JL, Meier PP. Cost of Morbidities in Very Low Birth Weight Infants. *J Pediatr-Us*. 2013; 162(2):243.
73. Higano NS, Thomen R, Parks K, Huyck H, Hahn A, Fain SB, et al. Hyperpolarized 3he Gas Mri In Infant Lungs: Investigating Airspace Size. *American journal of respiratory and critical care medicine*. 2017:195.
74. Wang C, Miller GW, Altes TA, de Lange EE, Cates GD Jr, Mugler JP 3rd. Time dependence of 3He diffusion in the human lung: measurement in the long-time regime using stimulated echoes. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2006; 56(2):296–309.

75. Rodriguez I, Perez-Sanchez JM, Peces-Barba G, Kaulisch T, Stiller D, Ruiz-Cabello J. Long-range diffusion of hyperpolarized ^3He in rats. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2009; 61(1):54–8.
76. Bartel SE, Haywood SE, Woods JC, Chang YV, Menard C, Yablonskiy DA, et al. Role of collateral paths in long-range diffusion in lungs. *Journal of applied physiology*. 2008; 104(5):1495–503. [PubMed: 18292298]
77. Yablonskiy DA, Sukstanskii AL, Leawoods JC, Gierada DS, Bretthorst GL, Lefrak SS, et al. Quantitative in vivo assessment of lung microstructure at the alveolar level with hyperpolarized He-3 diffusion MRI. *Proceedings of the National Academy of Sciences of the United States of America*. 2002; 99(5):3111–6. [PubMed: 11867733]
78. Sukstanskii AL, Yablonskiy DA. In vivo lung morphometry with hyperpolarized ^3He diffusion MRI: theoretical background. *Journal of magnetic resonance*. 2008; 190(2):200–10. [PubMed: 18037313]
79. Parra-Robles J, Wild JM. The influence of lung airways branching structure and diffusion time on measurements and models of short-range ^3He gas MR diffusion. *Journal of magnetic resonance*. 2012; 225:102–13. [PubMed: 23159820]
80. Yablonskiy DA, Sukstanskii AL, Conradi MS. Commentary on “The influence of lung airways branching structure and diffusion time on measurements and models of short-range ^3He gas MR diffusion”. *Journal of magnetic resonance*. 2014; 239:139–42. [PubMed: 24314822]
81. Wang W, Nguyen NM, Guo J, Woods JC. Longitudinal, Noninvasive Monitoring of Compensatory Lung Growth in Mice after Pneumonectomy via (^3He) and (^1H) Magnetic Resonance Imaging. *American journal of respiratory cell and molecular biology*. 2013; 49(5):697–703. [PubMed: 23763461]
82. Trampel R, Jensen JH, Lee RF, Kamenetskiy I, McGuinness G, Johnson G. Diffusional kurtosis imaging in the lung using hyperpolarized ^3He . *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2006; 56(4):733–7.
83. Shemesh N, Jespersen SN, Alexander DC, Cohen Y, Drobnjak I, Dyrby TB, et al. Conventions and nomenclature for double diffusion encoding NMR and MRI. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2016; 75(1):82–7.
84. Nikolaou P, Coffey AM, Walkup LL, Gust BM, Whiting N, Newton H, et al. XeNA: an automated ‘open-source’ (^{129}Xe) hyperpolarizer for clinical use. *Magnetic resonance imaging*. 2014; 32(5): 541–50. [PubMed: 24631715]
85. Stewart NJ, Norquay G, Griffiths PD, Wild JM. Feasibility of human lung ventilation imaging using highly polarized naturally abundant xenon and optimized three-dimensional steady-state free precession. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2015; 74(2):346–52.
86. Korchak SE, Kilian W, Mitschang L. Configuration and Performance of a Mobile (^{129}Xe) Polarizer. *Appl Magn Reson*. 2013; 44(1–2):65–80. [PubMed: 23349565]
87. Thomen RP, Walkup LL, Roach DJ, Cleveland ZI, Clancy JP, Woods JC. Hyperpolarized ^{129}Xe for investigation of mild cystic fibrosis lung disease in pediatric patients. *Journal of cystic fibrosis: official journal of the European Cystic Fibrosis Society*. 2016
88. Mugler JP 3rd, Altes TA. Hyperpolarized ^{129}Xe MRI of the human lung. *Journal of magnetic resonance imaging: JMIR*. 2013; 37(2):313–31. [PubMed: 23355432]
89. Chan HF, Stewart NJ, Norquay G, Collier GJ, Wild JM. 3D diffusion-weighted (^{129}Xe) MRI for whole lung morphometry. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2017
90. Smith L, Marshall H, Aldag I, Horn F, Collier G, Hughes D, et al. Longitudinal Assessment of Children with Mild CF Using Hyperpolarised Gas Lung MRI and LCI. *American journal of respiratory and critical care medicine*. 2017
91. Thomen RP, Quirk JD, Roach D, Egan-Rojas T, Ruppert K, Yusem RD, et al. Direct comparison of (^{129}Xe) Xe diffusion measurements with quantitative histology in human lungs. *Magnetic resonance*

in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 2017; 77(1):265–72.

92. Sukstanskii AL, Yablonskiy DA. Lung morphometry with hyperpolarized ^{129}Xe : theoretical background. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 2012; 67(3):856–66.
93. Ouriadov A, Farag A, Kirby M, McCormack DG, Parraga G, Santyr GE. Lung morphometry using hyperpolarized (^{129}Xe) apparent diffusion coefficient anisotropy in chronic obstructive pulmonary disease. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 2013; 70(6):1699–706.
94. Ouriadov A, Farag A, Kirby M, McCormack DG, Parraga G, Santyr GE. Pulmonary hyperpolarized Xe morphometry for mapping xenon gas concentrations and alveolar oxygen partial pressure: Proof-of-concept demonstration in healthy and COPD subjects. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 2014
95. Kirby M, Svenningsen S, Kanhere N, Owringi A, Wheatley A, Coxson HO, et al. Pulmonary ventilation visualized using hyperpolarized helium-3 and xenon-129 magnetic resonance imaging: differences in COPD and relationship to emphysema. Journal of applied physiology. 2013; 114(6): 707–15. [PubMed: 23239874]

Figure 1. ^3He ventilation MRI to depict and quantify treatment response pre- and post-lung volume reduction surgery (a), a treatment for severe heterogenous COPD, and pre- and post-bronchial thermoplasty (b), an emerging treatment for severe refractory asthma.

Figure 2.

Comparison of ³He ventilation and ADC in an adult healthy volunteer (left) and a patient with severe COPD (right). While the COPD patient has areas of poor ventilation and very high ADC, there is relatively poor correspondence between the low ventilation and high ADC, in contrast to a medical canonical view of obstructive lung disease.

Figure 3. Images of a frozen lung illustrating approximate physical slice locations, frozen lung slice with samples, matching ADC map, and examples of histological slides after processing and staining.

Figure 4.

Ventilation and ADC map in an explanted infant control lung, with accompanying histological slide. The lung-average ADC was $0.13 \text{ cm}^2/\text{s}$ —significantly lower than in older children and adults and reflective of smaller and less developed alveolar spaces.

Figure 5. Modulated magnetization in an explanted lung from a patient with COPD after initial modulation (left) and after 2 seconds (right). The modulation decays more quickly in the upper lobe with higher tissue destruction (left in the images).

Figure 6.

Representation of the geometry used for model-based fits to D_T and D_L , often called in-vivo lung morphometry. Here, changes in D_L primarily relate to changes in alveolar depth, h , and changes in D_T primarily relate to changes in R . Figure reproduced with permission, from (26).