Hyperpolarized $^3$He and perfluorocarbon gas diffusion MRI of lungs

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1. Introduction

A remarkable development at the interface of physics and biomedical science over the past 10 years has been the use of hyperpolarized (HP) noble gases to perform MRI of the lung
air space. Such imaging is made possible through laser-optical pumping, which can improve the magnetic resonance sensitivity of certain noble-gas isotopes having non-zero nuclear spin by several orders of magnitude. The two most important isotopes are the spin one-half nuclei \(^{3}\)He and \(^{129}\)Xe, because of their long intrinsic \(T_1\) relaxation times. We recall that the conventional thermal polarization \(P_{\text{th}}\) in an applied magnetic field \(B_0\) is given by \(P_{\text{th}}=\mu B_0/k_\text{B} T\), where \(\mu\) is the magnetic nuclear moment, \(k_\text{B}\) is the Boltzmann constant, and \(T\) is the absolute temperature in Kelvin. For fully relaxed protons in a conventional 1.5 T applied field for whole-body MRI, we have \(P_{\text{th}}=6\times10^{-6}\), which suffices for magnetic resonance (MR) imaging of protons in water. Gases delivered at pressures of \(\approx1\) atm are over 2000 times less dense than protons in water with a corresponding decrease in MR sensitivity, but hyperpolarization yields an enhancement of 4 to 5 orders of magnitude (\(P_{\text{hyp}}=10^{-50/\%}\)), more than compensating for the density difference. Indeed, highly polarized \(^{3}\)He can remain sufficiently sensitive to MRI even if it constitutes only a fraction of the inhaled gas mixture. Once introduced in vivo to the lungs, depending on the breathing maneuver and the inhaled mixture, HP gases relax with a time \(T_1=20–30\) s, where the relaxation is dominated by interaction with paramagnetic oxygen. In the glass cell used for hyperpolarization, \(T_1\) values are much longer, ranging from 20 to 40 h.

Because the function of the lung is gas exchange, it is hardly surprising that regionally specific information about inspired gas should be at least as relevant to the study of lung physiology and disease as images of the lung-tissue structure (e.g. hydrogen MRI or X-ray CT). Results from several research groups have indeed demonstrated the potential for HP-gas MRI to enhance our understanding of lung function, with further potential impact on disease treatment, surgical planning, and drug development. (Lung diseases such as chronic obstructive pulmonary disease (COPD) and asthma affect tens of millions of people in the US alone [1]). Almost immediately from the time that the first animal- and then human-lung images were demonstrated [2–5], several groups have explored pulse-sequence techniques and contrast mechanisms that go well beyond static spin-density imaging and that make use of the unique physical properties of these gases to address physiologically relevant questions.

This article deals largely with one such contrast mechanism: diffusion (i.e. Brownian motion) of gas in the lung. Rapid gas diffusion can cause problems ranging from limited image resolution to signal attenuation due to the presence of bulk susceptibility and/or imaging gradients. However, as with relaxation due to the presence of oxygen (see below), there is a flip side to the story that enables meaningful physiological information to be obtained. Indeed, an early conclusion in HP \(^{3}\)He MRI, based on the fact that diffusion does not limit signal intensity or resolution as much as might be expected, was that airway and alveolar boundaries restrict the diffusive motion of \(^{3}\)He in healthy lung [6,7]. The apparent diffusion coefficient (ADC) of the gas can thus be a powerful indicator of local airway and alveolar architecture, which is itself often profoundly affected by lung disorders, such as COPD [8].

Most of the imaging discussed here involves HP \(^{3}\)He, as it has been most widely used to date in studies of lung ADC. However, we also consider in this regard other gases that may be used as MRI signal sources. Other noble-gas isotopes (principally \(^{129}\)Xe) can be hyperpolarized and have been used for lung imaging [9]. Although \(^{129}\)Xe has only 1/3 the magnetic moment of \(^{3}\)He and has generally been more technically challenging to polarize in large quantities, it provides unique contrast in that it is taken up by the blood from the lung and exhibits a wide chemical shift range when dissolved in a variety of tissues [10]. The excitement generated by HP-gas MRI has also contributed to a renewed interest in the use of inert fluorinated gases to image the lungs [11,12]; these gases have a number of features that somewhat mitigate the disadvantage of a small (thermally generated) nuclear polarization, and they are technically easier to handle and use, particularly for in vivo studies.

Before turning exclusively to diffusion MRI, we will first briefly discuss how hyperpolarized gas is generated and imaged. We will also highlight (though by no means exhaustively), some of the developments in the last 10 years across the field of lung imaging with HP gases. More complete reviews of the field may be found in Refs. [13,14]. The subsequent sections on diffusion MRI are based largely on research done by the group at Washington University, where it has been a major effort for the past 8 years. We will start with how simple measurements of \(^{3}\)He ADC can be used to gauge the regional severity of tissue destruction due to emphysema. We then discuss a more detailed model of airway architecture that can be tested by investigating \(^{3}\)He diffusion anisotropy. The fact that gases diffuse so rapidly affords the opportunity to explore lung structure on many different length scales, and the next section discusses experiments to measure long-range \(^{3}\)He diffusion in the lung. Finally, we present some recent work involving \(^{19}\)F diffusion MRI.

### 1.1. Hyperpolarization of \(^{3}\)He

\(^{3}\)He is a stable non-radioactive isotope of helium with nuclear spin 1/2 and a gyromagnetic ratio about 25% smaller than the proton; it has \(\approx1\) ppm natural abundance but is available in pure form as the result of collection from tritium decay. The nucleus can be polarized to values approaching unity by transfer of angular momentum from circularly polarized laser light. There are two basic schemes for this transfer: metastability-exchange optical pumping (MEOP) [15,16] and spin-exchange optical pumping (SEOP) [17]. In both schemes, the \(^{3}\)He gas typically resides in a glass vessel (cell) through which the laser light is directed. In MEOP, a radio-frequency discharge is ignited in the cell to create a population of \(^{3}\)He atoms in the triplet-2S metastable electron state. Optical pumping with 1083 nm laser light, corresponding to transitions from the triplet-2S to certain triplet-2P states, leads to a large electron polarization in the metastable state, which is immediately transferred to the nucleus via hyperfine
coupling. Rapid electron-exchange collisions then produce nuclear polarized $^3$He atoms in the ground state. In SEOP, an alkali metal (usually rubidium) serves as an intermediary in the angular momentum-transfer process. Laser light is absorbed by the Rb vapor at a wavelength of 795 nm, corresponding to the first principal dipole transition ($5S_{1/2} - 5P_{1/2}$), causing the Rb valence electron to become highly polarized. A density of Rb vapor appropriate to the amount of available laser light is produced in the cell by heating it to 160–200 °C. The angular momentum is then transferred to the $^3$He nucleus via a hyperfine interaction (zero-quantum transition) that takes place during Rb–$^3$He binary collisions. In both methods, the mechanism for polarization transfer is easily turned off (in MEOP by terminating the discharge and in SEOP by cooling down the cell and condensing the Rb vapor), leaving the angular momentum stored in the form of polarized $^3$He nuclei.

The longitudinal relaxation time of the gas (usually dominated by collisions with the cell walls) can, with some attention given to how the cell is fabricated, be many 10 s of hours, allowing sufficient time for storage and transport of the hyperpolarized gas to an MRI scanner. We note that the SEOP method can also be used to hyperpolarize the other stable and abundant spin-1/2 noble-gas isotope, $^{129}$Xe.

Generally speaking, MEOP has historically had the advantage of an intrinsically faster production rate and largest maximum $^3$He polarization, routinely producing quantities $\sim$ 1 STP-liter/hour at $>$ 60% polarization [18]. However, the RF discharge requires that the gas be polarized at pressures $\sim$ 1 Torr and then compressed to atmospheric pressures without causing significant polarization loss [19]. In addition, the lasers used in MEOP have been somewhat more expensive and more difficult to maintain. Initial large-scale polarization systems have been large and expensive, but much more portable and inexpensive MEOP systems have been recently demonstrated [20]. By contrast, SEOP systems have the advantage of cheap powerful portable lasers and the ability to operate at helium pressures between 1 and 10 atm but a slower intrinsic production rate; a typical system requires many hours to produce 1 STP-liter of HP $^3$He [21]. SEOP is a photon-limited process, and the introduction in the 1990s of compact inexpensive diode-laser arrays, capable of several tens of watts at 795 nm, was a crucial technological advance that allowed the production of quantities of HP $^3$He sufficient for human-lung MRI. Recently, the simultaneous use of both rubidium and potassium metals in a SEOP cell has been shown to improve the HP $^3$He production rate by an order of magnitude [22]. Combined with ever more powerful lasers, which can now be frequency-narrowed to better match the alkali-metal absorption profile [23], this so-called ‘hybrid’ SEOP has reduced the gap in intrinsic production capacity relative to schemes employing MEOP.

### 1.2. Using HP $^3$He in MRI experiments

The major technical difference in the use of HP gases in MRI, as compared to conventional thermal signal sources, is that the magnetization is independent of the applied magnetic field and does not recover thermally. Rather, it continually decays towards a negligibly small thermal-equilibrium value. Even before being administered to a subject, HP gas must be handled carefully in order to avoid catastrophic relaxation due to interactions with foreign surfaces, molecular oxygen [24], magnetic-field gradients [25], and ambient fluctuating magnetic fields. The gas is usually kept in a glass cell that is known to result in a wall-relaxation time (10 s of hours) that is sufficiently long. The cell is positioned in a solenoid or similar homogeneous alignment field, preferably with external electromagnetic shielding. The gas is typically released from the cell to a flexible plastic enclosure from which the subject inhales just prior to imaging. Subjects typically breathe in an anoxic mixture containing HP $^3$He, perhaps with a subsequent inhalation of room air, in order to maximally avoid oxygen-induced relaxation [24].

An inhaled bolus of HP $^3$He possesses all of its useable magnetization from the outset, and this magnetization must be rationed appropriately over the number of images acquired and according to the $k$-space-traversal scheme employed. There is also a strong desire to use as much of the hard-won magnetization as efficiently as possible. Since there is no thermal recovery, imaging speed is limited only by gradient-switching speed and available receiver bandwidth. Spin echo sequences are generally avoided, because use of a large number of inexact 180° rf pulses would eventually tip most of the non-renewable magnetization into the transverse plane where it would dephase rapidly. The use of gradient-recalled echoes (GRE) combined with low-flip-angle excitation (e.g. the FLASH sequence [26]) was the canonical choice for early work in this field. The disadvantage of using GRE sequences is that the transverse magnetization is limited by $T_2^*$. Although $T_2^*$ is longer for $^3$He in the gas space than for protons in lung tissue [27], it is still limited to about 20 ms at 1.5 T by the magnetic susceptibility effects of the large air–tissue interface in the lung [28,29]. In addition, rapid diffusion of $^3$He through the imaging gradients themselves can also contribute to transverse-signal attenuation [30].

### 1.3. Rapid imaging of ventilation

Much of the early progress in lung imaging with HP $^3$He came in the form of improved resolution in static images of ventilation at breath-hold. A two-dimensional FLASH sequence was typically employed for human imaging, with in-plane resolution of a few millimeter and total acquisition times of about 1 s [31]. As spectacular as these early images were, it could be argued that much of the same information might be obtained with other, less technically demanding methods, e.g. the use of inert fluorinated gases or oxygen-enhanced MRI of lung parenchyma. However, the large single-shot signal intensity and the absence of any recovery-time limitation afforded by HP gas make it uniquely suitable for imaging the dynamics of gas flow. Imaging ventilation in real time during the breathing cycle requires more efficient use of the transverse magnetization through short effective echo times and/or multiple-echo sequences. Johnson and co-workers extensively developed the use of radial $k$-space acquisition
(RA) and projection reconstruction with HP $^3$He in small animals [32,33]. Although they consume somewhat larger amounts of magnetization (not as much of a problem with small animals as with humans), RA sequences have very short effective echo-times, which minimize susceptibility and diffusion losses, and they oversample near $k=0$, which tends to minimize motion artifacts (e.g., from heartbeat). Rapid repetitive imaging of the human lung [30] was first demonstrated using echo-planar imaging (EPI) [34], whereby the transverse magnetization from one excitation is repeatedly refocused by sinusoidal read-out gradients to acquire successive lines in $k$-space. Saam et al. [30] showed that in the low-flip-angle limit, an increase in linear voxel dimension leads to a sixth-power increase in the number of images that can be acquired with one bolus of inhaled HP gas. The larger voxel size also significantly reduces the signal attenuation due to diffusion through the correspondingly smaller imaging gradients. Using a coarse-grid (32×64) two-dimensional EPI sequence, they were able to acquire an image from a single rf excitation every 40 ms. These images showed gas filling the lung, the gravitational dependence of ventilation, and some washout characteristics. There were some artifacts, mostly due to susceptibility effects around the pulmonary vessels. The use of segmented EPI, where only a limited number of echoes are acquired per excitation, can reduce artifacts at the cost of using more magnetization. In spiral-acquisition scanning [35,36], a transverse magnetization from one excitation is repeatedly measured in $k$-space but spirals outward to the edge of the plane. Since a given spiral provides a more uniform sampling of $k$-space than a single radial acquisition, the entire image can be updated after each acquisition by combining it with some number of previous interleaved acquisitions ($k$-space windowing technique). Salerno et al. [36] generated images of inspiration with an effective temporal resolution of 15 ms and produced spectacular cine loops of inflowing inspired gas in both healthy subjects and patients with cystic fibrosis.

1.4. Low-field imaging

Because the magnetization in HP gases is independent of the applied field, one expects the signal-to-noise ratio (S/N) to be approximately independent of applied field in the regime where noise from the sample dominates coil noise (true for chest MRI down to fields of 0.1 T and even lower) [37]. For lung imaging, low fields should be particularly advantageous since they reduce the magnetic susceptibility gradients in the lung [38]. Durand and co-workers have imaged human lungs at 100 mT [39], taking advantage of very long transverse coherence times to use a single-shot multiple-spin-echo pulse sequence (RARE) [40], for which acquisition of the multiple CPMG echoes is limited by (the much longer) $T_2$ instead of $T_2^*$. Mair and co-workers have recently demonstrated human lung images in an open-access very low-field (<5 mT) system [41]. These systems are generally not commercially engineered, and there are some difficulties unique to low-field imaging, including low-frequency noise and undesirable gradients concomitant to the imaging gradients that can cause image artifacts [42,43]. The overall image quality is improving but has yet to rival what has been achieved at high fields.

1.5. Determination of regional oxygen partial pressure ($pO_2$) in the lung

The presence of molecular oxygen is generally considered a limitation for HP-gas MRI, because it causes rapid relaxation of the gas and is, in fact, the dominant relaxation mechanism in the lung in vivo. However, Deninger et al. [44] have demonstrated the use of this relaxation mechanism to quantify regional oxygen partial pressure ($pO_2$) in the lung, by measuring regional differences in relaxation rate of inspired $^3$He gas. Later adaptations of this technique [45] have been used to assess in porcine lung the regional ventilation-perfusion ratio ($V_i/Q$), an important physiological parameter for characterizing lung disease [46].

2. $^3$He restricted diffusion measurements

2.1. Diffusion

Any discussion of $^3$He MR measurements of restricted diffusivity in lungs necessarily involves the disease pulmonary emphysema [8]. In emphysema, the average size of the compartments which restrict the gas motion is enlarged and the restricting barriers (alveolar walls) become more porous, leading to an increase in the apparent diffusion coefficient (ADC). In the opinion of our group, $^3$He ADC measurements for mapping the extent and severity of emphysema in human lungs (in vivo) is the application of hyperpolarized gas imaging which is most likely to find widespread clinical application. It appears that this opinion is shared by a majority of the field [47].

In healthy human lungs, there are approximately 300 million alveoli, the smallest subdivisions of the air space [48]. Each alveolus is an open vessel of approximately 300 μm diameter (0.3 mm). The alveolarized space accounts for about 93% of the total gas volume. In emphysema, the compartments are enlarged by destruction of elastin, the protein responsible for the elastic tension (spring return) of the lung. Destruction of alveolar walls also results in fewer compartments. Fig. 1 presents microscope images of healthy and emphysematous lung tissue at the same scale (after excision, freezing, sampling, and slicing of thin sections), demonstrating the changes in lung microstructure in emphysema. So, at the broadest level, emphysematous lungs have fewer and larger compartments; therefore one expects (and finds) the ADC of $^3$He gas to increase in emphysema, being less restricted [49]. A more sophisticated and anatomically correct picture of lung structure is presented in the next section. It is important to remark that $^3$He ADC is sensitive to and reports upon features of sizes much smaller than the image resolution. This aspect of diffusion or $q$-space imaging has been noted previously [50].

The free diffusivity $D_0$ of $^3$He gas dilute in N2 or air has been measured to be 0.88 cm²/s [51]. Typically, a bolus of approximately 0.45 l STP $^3$He is mixed with sufficient N2
BDSG pulse at zero amplitude) are taken alternately. The bipolar diffusion sensitizing gradient pulse (BDSG) is detailed at right. The BDSG occupies a time interval in the sequence during which the imaging gradients are fully rewound (slice select) or not yet applied (phase encode and readout). Likewise, the BDSG is fully rewound to \( k=0 \) or not yet applied when the imaging gradients are applied. Thus, there are no cross terms between the BDSG and the imaging gradients and analysis of the data is simplified.

The two images, with (W) and without (WO) the BDSG, are generated simultaneously as much as possible, to avoid artifacts from bulk motion, either patient motion or incomplete breathhold. This means acquiring the same phase encode in the same slice, with and without, in immediate succession (about 11 ms apart). So the order of operations from largest to smallest is slice, phase encode, with and without BDSG.

In our earliest work, we worried about the influence of bulk motion, which should be approximated well as constant velocity over the duration (2–4 ms) of the BDSG [49]. To eliminate attenuation from constant velocity motion of the spins, a gradient pulse of structure \(+--+-\) was used. For constant velocity motion (but not stochastic or diffusive motion), the phase shift generated by the first half of the gradient waveform \( (+-\) ) is cancelled by the phase shift from the second half waveform \( (-+)\). Compared to a BDSG of the simpler \(+--\) structure with the same duration of each lobe, the \(+--+\) pulse has twice the overall duration and only twice the \( b \)-value (see below). Compared to a \( +-\) pulse of the doubled duration which would have an 8\( \times \) larger value of \( b \), the \((+--+)\) pulse is inefficient. We abandoned use of the velocity compensated pulse \((+--+)\) to allow data

(0.55–1.55 l) for a breathhold; thus, in a lung of 61 total capacity, the \(^3\)He concentration is about 7%, close to the infinite dilution limit for \( D_0 \). The gradient pulses employed are typically \( t=2 \) ms in duration (we note that these are long gradient pulses, so the time interval across which the displacement is measured is not well defined) [50]. In this time interval, the root mean square free displacement in one direction is \( \sqrt{2D_0t} \) or 600 \( \mu m \) (0.6 mm). This is much larger than the alveolar size, indicating that the gas atoms will do a thorough exploration of the airway and nearby alveoli during the diffusion measurements. Thus \(^3\)He diffusive motion in healthy lungs is expected to be highly restricted: that is, the ADC will be a small fraction of \( D_0 \). For a heavier, larger gas species such as xenon or \( C_2F_6 \) or \( C_3F_8 \) (see Section 5), the BDSG is held the same, so that the only difference between the two resulting images is diffusion weighting. Typical time durations of the features of the BDSG are given in Fig. 2.

For a fixed quantity of hyperpolarized gas, the imaging time and S/N of multi-slice two-dimensional and three-dimensional acquisitions are predicted to be the same (for \( n \) partitions in three-dimensional, each spin is subjected to \( n \) times as many rf pulses as for \( n \)-slice two-dimensional acquisitions, so the notation angle must be \( 1/\sqrt{n} \) as large, in the small-angle limit; the smaller S/N of each echo is exactly compensated by the signal averaging effect of \( n \) times as many echoes). We have chosen multi-slice two-dimensional acquisitions to minimize motion effects, as each slice is acquired in about 0.7 s, for 32 phase encodes and two values of the BDSG.

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are regions of lung that ventilate poorly and receive too little gas diffusivity is highly restricted \((D/D_0 \leq 0.2)\) everywhere except in the large airways. In the trachea, \(D\) is essentially equal to \(D_0 (0.88 \text{ cm}^2/\text{s})\), with some smaller airways evident as less enhanced \(D\) through the partial volume effect (airway is thinner than image slice). The uniformity of \(D\) in the rest of the lung shows the excellent S/N here.

Ventilation (left) and restricted diffusivity (right) images from a healthy volunteer (H) and a patient with severe emphysema (E) are presented in Fig. 4. Like most of our human images, these are transverse (axial) slices to permit easy comparison with X-ray CT images, which are presently considered the gold standard radiological technique for characterizing emphysema. The ventilation or spin density image of the emphysema patient is considerably less uniform in intensity than for the healthy lungs. Some of the intensity variation in the image of the healthy volunteer is due to a spatial dependence of the sensitivity of the homebuilt rf coils. The diffusivity maps do not suffer from the rf inhomogeneity, because they use a ratiometric method as in Eq. (2). The images clearly show the restriction of diffusion in the healthy lungs, with \(D/D_0\) of about 0.22. In the emphysematous lungs, the diffusivity is substantially increased and is spatially dependent. The spatial variations in \(D\) follow the pattern one expects by comparison to X-ray CT (not shown), with regions of low

Fig. 3. Coronal \(^3\)He ventilation (gray) and restricted diffusion (color) images of a 22 kg Yorkshire pig. The slice thickness is 10 mm. The gas diffusion in the bulk of this healthy lung is much smaller than the unrestricted diffusion evident in the trachea (largest airway).

Fig. 4. Transverse-slice \(^3\)He images of a healthy volunteer (H) and a patient with severe emphysema (E). The gray-scale images show the distribution of inspired \(^3\)He at breathhold and the color images are maps of restricted diffusivity. In the emphysematous lungs, the gas distribution is less uniform and the apparent diffusion coefficient (ADC) is much larger.
X-ray attenuation (and hence low tissue density) having high $^3$He diffusion. Comprehensive quantitative comparison of CT and $^3$He diffusion, performed by identifying the same region of lung in the two image sets, finds a strong correlation between these quantities [53].

A histogram of diffusivity in 15 healthy volunteers and 33 patients with severe emphysema is presented in Fig. 5. The peak value of $D$ in healthy lungs is near 0.20 cm$^2$/s and is surprisingly narrow given the number of subjects. The peak from emphysematous subjects is greatly elevated and much broader, presumably reflecting a range of disease severity. The inescapable conclusion is that $^3$He diffusivity cleanly separates healthy and severely emphysematous lungs. An open question is how early emphysema can be detected and over how short of a time span its progress can be measured using $^3$He ADC; this last question is particularly relevant to testing the efficacy of new drugs that target emphysema.

Spin-density and diffusion images from two patients with severe emphysema appear in Fig. 6. The images demonstrate that spin-density or ventilation images and diffusivity maps report different aspects of structure and function of the lungs. That is, they deliver independent information. In general, one expects that the most diseased lung regions will have the poorest ventilation (because of air trapping) and the highest $^3$He diffusivity. Indeed, this is true in many cases. In emphysema patients with a history of cigarette smoking (but not alpha-one disease [8]), we commonly find the ventilation decreases and ADC increases from bottom to top (inferior to superior) of the lung, the usual direction of increasing extent of disease. But the upper two panels of Fig. 6 show a counter-example. There in the right lung (at left in the figure), a region of poor ventilation nevertheless shows only moderately elevated ADC (yellow). In another counter-example at bottom of Fig. 6, there is a well-ventilated region of right lung (at lower left in the figure) that has very high ADC (blue). Thus, the distribution of gas at breathhold and the ADC report on different aspects of the lung; the two kinds of images report distinct information.

Fig. 6 is a good example of non-uniform ventilation, showing that most severely emphysematous lungs contain regions that ventilate so poorly that they receive inadequate $^3$He for the diffusion measurement (i.e. inadequate S/N). To some extent, having the patient rebreathe the $^3$He–N$^2$ gas mixture in and out of a flexible vessel (plastic bag) reduces this effect. But strict limits should be placed on the total time breathing an anoxic mixture for patients with severe disease. With some patients, the distribution of inhaled $^3$He is so non-uniform that the images ‘do not look like lungs’.

Other groups and our own have examined the dependence of the measured diffusivity on several factors, including age within a pool of healthy subjects, the level of lung inflation, the direction of the BDS gradient, and the time duration of the BDS gradient pulse [54]. Studies indicate an excellent reproducibility of $^3$He diffusion results for repeated measurements on a subject [55,56]. There appears to be little or no dependence on diffusion direction (global anisotropy, quite distinct from the microscopic anisotropy discussed in Section 3) [57]. The diffusivity in healthy subjects decreases slowly with increasing diffusion time [54], from 0.22 to 0.15 cm$^2$/s for diffusion times of 1.8 to 5.8 ms (note that much longer diffusion times of order seconds give much smaller diffusion coefficients, as discussed in Section 4). While we have not carefully studied the dependence of $D$ upon the level of inflation, it appears that $D$ increases with lung volume (total volume of gas in lung), but more slowly than we expected, with the mean diffusivity increasing about 25% between a tidal inhalation (functional residual capacity plus 0.7 l) to a full inhalation (total lung volume), an approximate doubling of the lung volume.
It is not yet clear what spatial resolution is required to obtain a clear picture of the extent and severity of emphysema in each patient. Our diffusion maps generally show trends from top to bottom and/or variations between lobes, suggesting that the fairly large voxels we use in vivo (7×7×10 mm³) are still much smaller than the relevant length scales of the variation of disease severity. While one might think to always obtain images at a better resolution (smaller voxels) than needed and then simply average voxels to obtain fewer, larger cells for better S/N, this procedure (i) results in inferior S/N and (ii) requires extra imaging and breathhold time, compared to simply imaging at the desired, coarser resolution in the first place. The wasting of imaging time is obvious, with extra slices and extra phase encodes to acquire. The S/N argument can be derived from general equations [37] of the signal-to-noise in MR imaging, but we present here a quick version. We compare the S/N of the entire imaging field obtained by (a) imaging with M×N×P voxels (either in three-dimensional or multi-slice two-dimensional, because they give equal S/N here as remarked earlier) or (b) a non-imaging measurement (i.e. a single-voxel experiment). We recall that the integrated intensity of all voxels in an entire image is given by the amplitude of the k=0 datum; all other k-values do not enter into the sum across all voxels. Thus, the imaging approach (a) must use MNP rf pulses so each rf pulse is of nutation angle α, of order 1/√MNP radians, to consume most of the ³He magnetization throughout the many rf pulses. The non-imaging measurement (b) can use a single rf pulse of 90°, or approximately α=1 radian. Thus, the k=0 datum of the imaging approach has a smaller S/N by 1/√MNP; hence, for obtaining only the k=0 point which gives the spatial integral across the entire sample, the non-imaging approach is superior. The same argument can be generalized to show that higher S/N is obtained when the imaging is performed at the desired resolution, as opposed to imaging at a higher-than-needed resolution and averaging voxels afterwards. Thus, it is important to decide on an optimum spatial resolution, based on the characteristics of the disease.

Besides in vivo measurements on healthy volunteers and patients with emphysema, we have obtained images of restricted diffusion in canine lungs [58,59] (using elastase-treated dogs) and from emphysematous human lungs excised after lung transplant surgery [60]. The dogs were imaged after each of three elastase treatments; after the final treatment and ³He imaging, the dogs were sacrificed and the lungs were removed, frozen, and sliced thin for observation under the microscope. The surface area to volume ratio S/V and ³He diffusivity D showed the expected correlation, with S/V decreasing and D increasing as emphysema progressed [58]. Similar measurements on explanted human emphysematous lungs have been made but not yet published [60].

Our group has also performed ³He diffusion imaging of live mice [61]. Techniques for delivering ³He with each breath are used, to obtain adequate S/N. These methods were developed [62] by Hedlund and Johnson for rats and showed enhanced ³He diffusion in elastase-treated rats [63]. Likewise, the results of Dugas et al. [61] on mice show enhanced diffusivity in elastase-treated mice, but did not show elevation of D in mice that had been exposed over months to cigarette smoke. We note however, that no verification of pulmonary emphysema by other techniques was obtained for these smoking mice.

3. Fundamental measurement of ³He gas anisotropic diffusion in human lung and evaluation of lung microstructure

Here, we present a mathematical model relating the measurements of ³He gas diffusivity and lung microstructure and report in vivo measurements of airway structure at the sub-acinar level in human lung in healthy subjects and patients with emphysema.

3.1. Theory of ³He gas anisotropic diffusion

In the branching tree model [64], the hierarchy of the airway tree begins at the trachea and leads through bronchi and bronchioles to the terminal bronchiole that feeds each acinus—the major gas exchange unit in the lung. In humans there are fourteen generations of airways prior to the terminal bronchioles and another nine inside the acini [64]. Gas ventilation in the trachea, bronchi, bronchioles and terminal bronchioles occurs by convection (bulk flow), while diffusion is the primary ventilation mechanism beyond the terminal bronchioles—in the acini, where about 93% of gas resides [48]. According to Haeffeli-Bleuler and Weibel [65] essentially all airways in the acinus are decorated by alveoli forming an alveolar sleeve. Thus the structures we focus upon here are cylindrical airways covered by alveolar sleeves, as schematically represented in Fig. 7. In humans, intra-acinar airways branch dichotomously over about nine generations, and the internal airway radius r falls from 250
to 135 μm, whereas the outer radius \( R \) (including the sleeve of alveoli) remains constant at 350 μm [65].

The characteristic free diffusion length \( l_0 = \sqrt{2D_0}t \) (0.56 mm for \( t = 1.8 \) ms, as applies here) is much larger than the average alveolar radius of 0.15 mm; \(^3\text{He} \) atoms can diffuse out of alveoli and across the airways in the 1.8 ms time duration of the MR ADC measurement. During the same time, most \(^3\text{He} \) atoms will remain inside the same airway. Thus, in our model of gas diffusion in lung, we consider airways rather than alveoli as the elementary geometrical units. We approximate the airways as long cylinders-either smooth (trachea, bronchi and bronchioles) or covered with alveolar sleeves (respiratory bronchiolae, alveolar ducts and alveolar sacs). The alveolar walls as well as the walls of alveolar ducts and other branches of the airway tree serve as obstacles to the path of diffusing \(^3\text{He} \) atoms and reduce the \(^3\text{He} \) diffusivity. Crucially, these restrictions are substantially less along the airway axis than perpendicular to it. Because gas motion along the axis of an airway is less restricted than perpendicular to the axis, diffusion in the lung is anisotropic. We show that this anisotropy manifests itself in the MRI signal even though each imaging voxel contains a very large number of differently-oriented airways that cannot be resolved by direct imaging. In particular, the anisotropy of diffusion results in non-exponential MR signal decay as a function of the weight \( b \) of the diffusion-sensitizing gradients [51] (see just below Eq. (2)), allowing the diffusion rates along and across the airways to be separately determined.

If the diffusion-sensitizing gradient is applied along or perpendicular to the tube axis, the signal attenuation can be written in the form of Eq. (1) with \( D = D_L \) or \( D_T \), the longitudinal or transverse ADC, respectively. For the more general case of an airway with principal axis tilted from the field gradient direction by angle \( \theta \), the ADC can be presented as

\[
\text{ADC}(\theta) = D_L \cos^2 \theta + D_T \sin^2 \theta. \tag{3}
\]

With the spatial resolution of several millimeters currently available with \(^3\text{He} \) MRI, each voxel contains hundreds of airways with different orientations. For each individual airway with orientation \( \theta \), the signal attenuation is exponential with respect to \( b \), according to Eq. (1). Because of the ADC dependence on orientation angle \( \theta \) in Eq. (3), after summing the signals over all airways, the signal decay becomes non-mono-exponential. This problem is mathematically similar to the problem of water diffusion in randomly-oriented uniaxial layers [50]. Because of the large number of acinar airways in each imaging voxel, their orientation distribution function \( g(\theta) = \sin \theta/2 \) can be taken as uniform. Therefore, the signal \( S \) can be written as

\[
S = S_0 \int_0^\pi d\theta \frac{\sin \theta}{2} \exp[-b(D_L \cos^2 \theta + D_T \sin^2 \theta)]
= S_0 \exp(-bD_T) \left( \frac{\pi}{4bD_{AN}} \right)^{1/2} \Phi[(bD_{AN})^{1/2}] \tag{4}
\]

where \( \Phi(x) \) is the error function and we have introduced the anisotropy of ADC

\[
\text{DAN} = D_L - D_T. \tag{5}
\]

Eq. (4) assumes that all airways are similar; i.e. all airways have the same geometrical parameters and, consequently, the same values of \( D_T \) and \( D_L \). Ideally, the expression for signal \( S \) should be further averaged with respect to the different geometrical parameters of the airways. To keep the number of parameters small in the model, we assume that the diffusivities \( D_T \) and \( D_L \) already represent averaged values.

Eq. (4) describes the non-mono-exponential dependence of diffusion attenuated signal on the value of \( b \). Hence, the apparent diffusion coefficient, ADC, defined as \( \text{ADC} = -\ln(S/S_0)/b \), is a function of \( b \). It can be easily demonstrated that

\[
\text{ADC} = \begin{cases} 
\bar{D} = \frac{1}{3} D_L + \frac{2}{3} D_T, & bD_L, bD_T \ll 1, \\
\bar{D} = D_T, & bD_L \gg 1.
\end{cases} \tag{6}
\]

Apparently, in healthy lungs, \( D_T \ll D_L \). The ADC at large \( b \) values decreases to the value of \( D_T \) because the signal from airways oriented with a component along the gradient gives a much smaller contribution as compared to the signal from airways oriented perpendicular to the direction of the diffusion sensitizing gradient.

### 3.2. Relationship between \(^3\text{He} \) gas adc and airway size

Because alveoli are open polygons with openings nearly the same size as their diameters (Fig. 7), the gas diffusion perpendicular to the acinar airway direction can be approximated by the transverse diffusion in open smooth tubes. The characteristic radius \( R \) here is the major or larger radius of the airway. For the apparent diffusion coefficient in the transverse direction with respect to the tube (airway) axes and for the gradient pulse waveform and timing of Fig. 2, we [51] found the following theoretical expression:

\[
D_T = \frac{16D_0 \xi_R^4 \eta^2}{w(\eta, \varepsilon)} \sum_j \frac{\beta_{ij}^4}{(\beta_{ij}^4 - 1)} \frac{Q\left(\frac{\beta_{ij}^4}{2\eta^2}, \eta, \varepsilon\right)}{Q\left(\frac{\beta_{ij}^4}{2\eta^2}, \eta, \varepsilon\right)}, \tag{7}
\]

Here we have introduced dimensionless parameters \( \xi_R, \eta, \) and \( \varepsilon \) for the tube radius and gradient pulse timing (see Fig. 2)

\[
\xi_R = \frac{R}{l_0}, \quad \eta = \frac{\Delta}{\delta}, \quad \varepsilon = \frac{\tau}{\delta}, \tag{8}
\]

and the function \( w \) is defined as

\[
w(\eta, \varepsilon) = \eta - \frac{1}{3} + \varepsilon \left(1 - 2\eta + \eta^2 - \frac{7}{6} \varepsilon + \frac{8}{15} \varepsilon^2\right). \tag{9}
\]

Here, \( \beta_{ij} \) is the \( j \)th (non-zero) root of the equation \( J'_1(x) = 0 \), where \( J'_1 \) is the first derivative of the first order
Bessel function and the function \( Q(a, \eta, \epsilon) \) is given by

\[
Q(a, \eta, \epsilon) = 1 - \frac{4}{3} \epsilon - \frac{2}{a \epsilon^2} \left[ \exp(-a \epsilon) + a \epsilon - 1 \right] 
+ \frac{4}{a^3 \epsilon^2} \sin h^2 \left( \frac{a \epsilon}{2} \right) 
\times \left[ \exp(-a(1-\epsilon)) - 2 \sin h^2 \left( \frac{a(1-\epsilon)}{2} \right) \exp(-a\eta) \right].
\]

(10)

where \( a = D_0 \beta^2 \gamma^2 b l / R^2 \).

The limit of strongly restricted diffusion corresponds to the case when the free atom root mean square displacement \( \xi_0 \) during the time \( \Delta \) is much larger than \( R \), i.e. \( \xi_0 \ll 1 \). In this limit, \( Q(a, \eta, \epsilon) \approx (1 - 4 \epsilon / 3) \), the sums in Eq. (7) can be calculated exactly, and the transverse ADC turns out to be inversely proportional to \( D_0 \) (motional narrowing).

\[
D_T \cong D_0 \frac{7(1-4\epsilon)\eta^2}{12\pi(\eta, \epsilon)} \xi_R^2 - \frac{R^4}{D_0}, \quad \xi_R \ll 1.
\]

(11)

In the case \( \xi_R \gg 1 \), the free atom displacement during the time \( \Delta \) is much smaller than \( R \), and therefore only the atoms residing in the cylindrical shell within the distance \( \xi_0 \) from the cylindrical surface ‘sense’ the boundaries. Hence, in this limit, \( D_T \) can be approximated as

\[
D_T \cong D_0 \left[ 1 - \frac{c_1(\eta, \epsilon)}{\xi_R^2} \right],
\]

(12)

where \( c_1(\eta, \epsilon) \) is a numerical coefficient depending on the waveform parameters. For the waveform parameters given in Fig. 2, \( c_1 \approx 0.65 \). Naturally, when \( \xi_R \to \infty \), the value of \( D_T \) approaches that for the free-diffusion coefficient \( D_0 \), as expected.

To derive the relationship in Eq. (7) between transverse diffusivity and tube radius for given parameters of gradient waveform, we used a theoretical approach that relies on the assumption of a Gaussian distribution of the phases accumulated by the precessing spins [66,67]. This approach is based on the assumption of a random character of the phase accumulated by the nuclei and, in fact, is identical to the random walk approximation used in the pioneering papers [68,69]. Since, then it has been applied to describing NMR signal behavior under the constant or pulsed field gradient in some restricted geometries (between two parallel barriers, in a cylinder and in a sphere) in numerous papers (see, for example [50] and references therein). To test the applicability of the Gaussian approximation in our case, we have verified our theoretical result against computer Monte Carlo random walk simulations. The ratio \( D_T / D_0 \) versus the reduced radius \( \xi_R \), calculated by means of Eq. (7), is plotted in Fig. 8 along with the results of computer simulations for the present gradient waveform parameters listed in Fig. 2. This figure shows that for \( \xi_R < 0.5 \) (\( R < l_0 / 2 = 0.28 \) mm), \( D_T \), the transverse ADC, is very small—less than 5% of the free diffusion coefficient \( D_0 \). Qualitatively, the very small value of \( D_T \) results from a motional averaging effect during each half (±) of the gradient pulse. In the physiologically most relevant interval \( l_0 / 2 < R < 2l_0 \) (0.28 mm < \( R < 1.1 \) mm), the transverse diffusivity \( D_T \) grows sharply to about 65% of \( D_0 \). With further increase in the tube radius \( R \), the value of \( D_T \) increases very slowly and approaches the \( ^3 \)He free diffusion coefficient \( D_0 \) as 1/R. This means that for all airways with radius less than 1.1 mm, \( ^3 \)He diffusivity is substantially restricted (\( D_T < 0.65 D_0 \)).

The main feature restricting diffusion along the acinar airways leading to a reduction in the value of \( D_L \), the longitudinal ADC, compared to the free diffusion coefficient \( D_0 \) is the presence of alveolar sleeves as in Fig. 7. Longitudinal diffusion of particles (\( ^3 \)He atoms) located in the open area of the tube can be considered as unrestricted, whereas diffusion of particles within the external cylinder are significantly restricted due to the alveolar structure. In fact, from the point of view of longitudinal diffusion, the alveolar sleeves play the role of ‘traps’, effectively reducing the longitudinal diffusion coefficient.

If the trapped atoms in the alveolar sleeves cannot exchange (or can exchange only slowly) with the ‘free’ atoms in the center of the tube, the average longitudinal diffusion \( D_L \) becomes equal to \( D_0 (r/R)^2 \), based on averaging over the numbers of atoms in each region and their long-time limit diffusivities (0 and \( D_0 \)). So, with exchange occurring, one has

\[
D_0 (r/R)^2 < D_L < D_0.
\]

(13)

Simulations of longitudinal diffusion confirm this expression. For realistic dimensions, the simulations indicate that \( D_L \) is about mid-way between the limits expressed in Eq. (13).

### 3.3. Methods

Eq. (4) is the basis for separation of longitudinal and transverse ADC values. Indeed, by collecting a series of MR images with different \( b \) and fitting Eq. (4) to the data on a pixel-
by-pixel basis, we can create maps of the values of the transverse and anisotropic ADC, $D_T$ and $D_{AN}$. The mean $\bar{D}$ and longitudinal $D_L$ are then obtained from Eqs. (6) and (5), and the mean airway radius $R$ is obtained from Eq. (7). We use an imaging technique for $^3$He diffusion measurement with six two-dimensional gradient echo sequences as in Fig. 2, combined together so that each has its own identical small-angle RF pulse, and its own identical slice selection, phase encode, and read-out gradients. Data are collected in an interleaved manner by collecting the same line in $k$-space for all six images prior to stepping to the next line, ensuring reduced sensitivity to motion artifacts. The standard central reordering of phase encoding is used to reduce the possible influence of signal decay during acquisition. All six sequences except the first one include diffusion-sensitizing gradients with increasing amplitudes, $G_m$, and consisting of one bipolar pulse pair as in Fig. 2. The corresponding values of $b$ are 0, 1.5, 3, 4.5, 6 and 7.5 s/cm$^2$. The diffusion gradient is applied perpendicular to the long axis of the body. For a typical experiment, we use a slice thickness of 20 mm and an in-plane resolution of $7 \times 7$ mm ($225 \times 450$ mm field of view with 32 $\times$ 64 $k$-space samples). Each of the 32 lines in $k$-space uses an RF excitation of about 7$^\circ$, allowing for repeated acquisition from the same hyperpolarized spins. The gradient echo time in all sequences is $TE = 7.2$ ms.

All images were acquired with a 1.5 T whole body Siemens Magnetom Vision scanner. Homemade double-tuned RF Helmholtz coils were used to transmit and receive the MRI signal at the $^1$H and $^3$He resonance frequencies. Switching of the operating frequency was performed without moving the subject, allowing for better registry and comparison between $^3$He and $^1$H scout images. After the RF coils were placed above and below the chest, the subject was positioned supine in the MR magnet. First, scout images were obtained using conventional proton MRI. These proton images were used to select the slices and orientations for the $^3$He images, and for anatomic reference to the $^3$He images. Then, the hyperpolarized $^3$He gas mixed with nitrogen was delivered to the subject through a plastic ventilator tubing connected to a mouthpiece. Imaging was performed during breathhold at the end of full inhalation. Four slices were obtained from each subject in less then 10 s, except for one normal volunteer with only three slices because of inadequate S/N. Diffusivity maps were obtained by fitting Eq. (4) to the experimental data on a pixel-by-pixel basis using Bayesian probability theory with uninformative prior probabilities. Normal volunteers and patients with severe emphysema and selected for lung volume reduction surgery were studied.

### 3.4. Preliminary findings

In all of the subjects, both normal and emphysema patients, gas diffusivity is anisotropic with the mean longitudinal ADC being usually two to three times as large as the mean transverse ADC. Representative maps of ADCs and the mean radii of acinar airways are shown in Fig. 9 for one normal subject and two patients with severe emphysema.

![Fig. 9. Single-slice maps of diffusivities for a normal subject (N1) and two patients with severe emphysema (P1 and P2). From left to right the columns display the orientationally-averaged diffusivity $\bar{D}$, the longitudinal ADC value $D_L$, the transverse ADC value $D_T$, and the mean airway radius $R$. The color scale on the right represents diffusivity coefficients in centimeter$^2/$second and airway radii in millimeter. Each color corresponds to 0.05 unit. Brown arrows point to an area of emphysematous lung with minor airway destruction, pink arrows to an area with moderate airway destruction, and green arrows to a lung area with severe emphysema. The small high-diffusivity regions in N1 are the two bronchi below their branching from the trachea.](image_url)

The following points are evident from our results. In healthy subjects, the transverse diffusivity is strongly restricted, with the mean value of $D_T$ almost eight times smaller than the $^3$He free diffusion coefficient in air ($D_0 = 0.88$ cm$^2$/s). The maps defining $D_T$ and the resulting external radii $R$ of the acinar airways (including the alveolar sleeves as depicted in Fig. 7) are highly homogeneous. The mean $R$ is about 0.36–0.37 mm in normal subjects. Given that our in vivo measurements were made during full inhalation, this result is in remarkable agreement with measurements on normal, excised lungs of mean $R = 0.35$ mm [65]. In these subjects, the mean values of $D_L$, the longitudinal ADC, are less than half of the $^3$He free diffusion coefficient. This is mainly the result of the restrictions to diffusion imposed by the walls separating neighboring alveoli along the same airway, as depicted in Fig. 7. In the healthy subjects, both $D_T$ and $D_L$ decrease slightly from apices to base; similar variation is present in some patients. As our subjects are supine, gravity effects do not explain this variation.

In patients with severe emphysema, nearly all transverse ADC maps show increased $D_T$ as compared to normal subjects, but the diffusion is still restricted ($D_T < D_0$). The increase in $D_T$ is consistent with an increase in the mean airway radius $R$. The value of $D_L$ is also substantially elevated, becoming practically unrestricted in some parts of the lungs ($D_L \approx D_0$). This effect is consistent with the limits in Eq. (13) discussed above and with an inflation of the airways which results in $r$ approaching the value of $R$ (see inset of Fig. 7).

The relationship Eq. (7) depicted in Fig. 8 between transverse ADC and airway radius $R$ was derived under the assumption that the diffusing $^3$He atoms cannot penetrate through the alveolar walls. However, alveolar walls always have pores. In normal lung the number of pores (known as pores of Kohn) is very small and they are generally smaller than 10 $\mu$m in diameter [70]; hence, their effect on $D_L$ and $D_T$ and Eq. (7) is negligible. However, in emphysematous lung many more pores (known as fenestrae) of variable sizes occur...
in alveolar walls [71]. The destruction of alveolar walls in emphysema will contribute to the above-discussed increases in the longitudinal and transverse ADC values. Thus, in the light of tissue destruction in emphysema, Eq. (7) should be considered as an approximation and the calculated values of $R$ should be regarded as an apparent radius of the airways.

The orientationally averaged ADC values $\bar{D}$ from Eq. (6) are similar to two-$b$-value ADC measurements for healthy subjects and patients with severe emphysema [49,72,73]. However, the previous work employed only two-$b$ values and effectively assumed exponential signal decay as a function of $b$ through the diffusion-sensitizing gradient strength. As is evident from the present results and analysis, the ADC in lungs determined from the two-$b$ method depends on $b$-value and approaches the true orientation-average value $\bar{D}$ from below only in the limit of vanishing $b$. That is, the true $\bar{D}$ is the slope of the curve (ln of signal as a function of $b$) at $b=0$, while the two-$b$-value of ADC is the slope taken between two points. The $\bar{D}$ values reported herein provide a more objective result because they do not depend on the diffusion-sensitizing gradient strength.

The above analysis allows us to draw some general conclusions about gas diffusivity in normal and emphysematous lungs and to develop some notions about emphysema progression. Our patient pool has been selected for lung volume reduction surgery and therefore has very heterogeneous presentations of the disease. As a result, most of the $D_T$ and $D_L$ maps in the patients are highly inhomogeneous, showing regions of nearly normal as well as very abnormal lung tissue. This provides an opportunity to follow the dynamics of lung destruction through the progression of emphysema by examining the variations within each patient, as well as between patients. For example, the brown arrows in Fig. 9 point to a quasi-normal area of lung in Patient 1. Here, transverse diffusivity is only 30% increased as compared to a normal lung (see similar area in the image above). This corresponds to a mean airway external radius of $R=0.42$ mm, according to Eq. (7) and Fig. 8. However, the longitudinal diffusivity in this area of the lung is increased by about 60%. Pink arrows point to an area of lung that has an intermediate level of emphysema (Patient 2)—here $D_T$ is increased by almost 100% (corresponding to $R=0.52$ mm) while $D_L$ is elevated by about 80%, nearly equal to the unrestricted value. Up to this stage we can envision that emphysema progresses by expansion of airways without substantial destruction of alveolar walls; this picture is entirely consistent with recent findings [74]. Green arrows point to a highly emphysematous lung region in Patient 2 where the transverse ADC value is 0.62 cm$^2$/s—more than four times as large as in normal lung while the longitudinal ADC is only 90% elevated. This indicates that according to Eq. (7) and Fig. 8 the mean external airway radius has become larger than 1 mm. The large increase in apparent radius $R$ and the concomitant decrease in anisotropy ($D_L/D_T$) are consistent with substantial tissue destruction in this region. These data indicate that the value of $D_L$ is the more sensitive parameter for identifying early stages of emphysema, while $D_T$ is the more sensitive parameter for identifying lung tissue destruction as emphysema progresses (because $D_L$ cannot increase beyond $D_0$).

In summary, in this section we have described a further refinement to the technique of $^3$He diffusion MRI that incorporates a model for the lung airway architecture and allows the measurement of ADC anisotropy. Analysis of the non-exponential signal decay on a pixel-by-pixel basis yields separate values for the ADC along and across the acinar airways, despite the fact that individual airways are too small to be resolved directly. A mathematical model links the transverse ADC and the mean airway radius $R$. Our in vivo measurements of $R$ in normal lungs are in excellent agreement with previous ex vivo results. The results demonstrate substantial differences between healthy and emphysematous lung at the acinar level and may provide new insights into emphysema progression.

4. Magnetization tagging and long-range diffusivity of $^3$He

The methods of Sections 2 and 3 follow the diffusive decay of transverse spin magnetization over times of a few milliseconds, corresponding to diffusion distances of a few tenths of a millimeter. While these methods are quite successful, the diffusion times are limited by $T_2^*$, making it impossible to probe the lung structure at longer distances with transverse magnetization. An important reason to study diffusion at longer length scales is to understand the interconnections of the airways in health and disease. In particular, collateral ventilation pathways (direct connections between generationally distant parts of the lung tree) can best be assessed by long-distance diffusion measurements.

There are two strategies for studying diffusion across longer distances: (1) reduce the external field $B_0$ to a point where $T_2^*$ is much longer, since the decay time of transverse magnetization, $T_2^*$, is predicted to be inversely proportional to $B_0$ (or even to $B_0^2$ in the motional averaging regime), or (2) tag the longitudinal magnetization, which decays with a relatively long time constant $T_1$ (approximately 25 s for $^3$He in healthy lungs in vivo). The problems associated with low-field imaging were discussed in Section 1; preliminary images have been of more modest signal-to-noise than expected [41]. Here, we focus on tagging the longitudinal magnetization of $^3$He as a method for measuring long-range diffusivity. Because of the bifurcating nature of airways in lung (Fig. 10), the measured diffusivity is dependent on the length-scale of the measurement and thus on the time-scale. The long-range diffusivity may be altered differently with different types of lung-tissue destruction and is a significantly different measure of lung structure [8] than the short-range diffusivity [49,75]. The ADC measured over times of seconds and distances of centimeters is denoted $D_{sec}$ to distinguish it from the ADC over milliseconds and fractions of a millimeter, $D_{msec}$, discussed in the two sections above. We emphasize that the different time and distance scales make these ADC values different, not the use of transverse versus longitudinal spin magnetization. Further, for $D_{msec}$ measurements, the gradient produces modulation of the magnetization with a (minimum) wavelength smaller than the
4.1. Lung structure

Healthy lungs are composed of approximately 24 levels of bifurcating airways (Fig. 10); these are singly connected, meaning that only one path along the airways exists between any two points in the lung [48]. Some collateral, bypass channels exist in human lungs via the pores of Kohn and channels of Lambert, but these pathways have high resistance and are not considered to be important in normal respiration [76,77]. The conducting airways (approximately the first 15 levels) are essential but only represent about 7% of the total gas volume. The last 9–10 levels are short in length and comprise a conducting airway node at level 14 (or lower-numbered) in the tree. Thus to travel between alveolar sacs at the 24th level in different acini, atoms must travel up at least 10 levels of branching airways and then back down [48]. The apparent diffusion measured over such distances is thus much more restricted and occurs over times of several seconds. We and others have determined that this diffusion coefficient $D_{\text{sec}}$ is about 0.02 cm$^2$/s for explanted healthy human lungs and in vivo dog lungs [75,79,95].

In emphysematous lungs, tissue destruction is known to create progressively more alternate (collateral) routes for gas motion between arbitrary points [80]. Diffusion over centimeter distances thus can proceed through the airways and the collateral paths in parallel, so that $D_{\text{sec}}$ is increased by the collateral paths. The existence of these collateral pathways is the basis for a new idea for minimal surgery that relieves dyspnea by relieving trapped gas in patients with severe emphysema [81]. Characterization of the collateral pathways by long-range gas diffusion measurements would potentially be very useful in planning for such a procedure. Magnetization tagging with hyperpolarized gas is the only currently available method capable of imaging diffusive gas motion and collateral pathways at these distances, and is due to the long relaxation time constant $T_1$.

4.2. Diffusion at long distances in lung

The branching nature of airways in lung, in particular that arbitrary points are singly connected by unique airway paths, necessitates that atoms must travel from one acinar airway to the next for diffusion distances greater than 1 mm; over centimeter distances, the change in direction at each airway branch results in a tortuous path. Diffusion between arbitrary points one or more centimeters apart requires that atoms must travel from one acinus to another, connecting via a common conducting airway node at level 14 (or lower-numbered) in the tree. Thus to travel between alveolar sacs at the 24th level in different acini, atoms must travel up at least 10 levels of branching airways and then back down [48]. The apparent diffusion measured over such distances is thus much more restricted and occurs over times of several seconds. We and others have determined that this diffusion coefficient $D_{\text{sec}}$ is about 0.02 cm$^2$/s for explanted healthy human lungs and in vivo dog lungs [75,79,95].

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4.3. Spatial modulation of longitudinal magnetization

Spatial modulation of the longitudinal spin magnetization $M_z$, was originally used to track cardiac or thoracic motion by establishing a coordinate grid locked into the tissue [82,83]. The primary advantage of this type of imaging is that encoding or labeling of position is in the longitudinal magnetization, which is characterized by the longest relaxation time constant in the spin system, $T_1$. Magnetization tagging of gases uses the same imaging techniques as those used for cardiac tagging, but here the motion of tagged magnetization in lungs at breathhold is diffusive. The random (diffusive) motion of the $^3$He gas atoms results in attenuation of the spatial modulation, allowing measurements of diffusion over times limited only by $T_1$, approximately 25 s in vivo in human lungs and many minutes ex vivo where $O_2$ is excluded [75,79].

Sinusoidal spatial modulation of the longitudinal magnetization, as opposed to a more nearly square-wave modulation, offers advantages in that attenuation of sinusoidal contrast can be easily interpreted in terms of a single diffusion length and because it can be easily prepared with two rf pulses separated by a gradient pulse. The result of this preparation is sinusoidally modulated magnetization with wavelength $\lambda$ (Figs. 11 and 12). For a gradient pulse of amplitude $G$ and effective duration $t$, the value of $\lambda$ is given by $\lambda = 2\pi/\gamma G t$, with $\gamma$ being the spin magnetogyric ratio. If the two rf pulses are
where the decay rate constant $R$ is determined by $R = D_{sec} k^2 = 4\pi^2 D_{sec}/\lambda^2$. Thus, the long-range diffusivity $D_{sec}$ can be calculated from measurements of $R$, since $\lambda$ is known. Both the decay rate $R$ and resulting $D_{sec}$ are independent of the initial modulation depth $B(0)$, so exact calibration of the rf tagging pulses is not essential. The effect of both $T_1$ relaxation and the consumption of longitudinal magnetization $M_z$ by subsequent rf imaging pulses (used to inspect the decaying modulated magnetization and ignored in Eqs. (16) and (17)) is to drive $M_z$ uniformly toward zero (recall the equilibrium $M_z$ is virtually zero compared to hyperpolarized values), independent of position $x$ as in Fig. 11. We define the fractional sinusoidal modulation $FM(x)$, as $B(t)/A$ from Eq. (17); this ratio is unaffected by $T_1$ and rf pulses, allowing long-range diffusion to be measured without corruption from these effects. This is valid provided that $T_1$ and rf pulses are uniform over the length scale $\lambda$. The rf field amplitude $B_1$ is a slowly-varying function of position in the rf coil, so $B_1$ inhomogeneity is not expected to distort the decaying sinusoidal magnetization over the relevant scale of $\lambda$ (2–3 cm in our measurements).

The details of the data analysis of the successive images showing the decay of tagged magnetization as in Figs. 11 and 12 has been published [75]. Essentially, the relative stripe amplitude $FM$ is determined at each voxel using a Fourier integral over a single wavelength. The values of $FM$ are fitted to $\exp(-Rt)$ separately for each voxel.

### 4.4. Long-range diffusion in lungs

The first magnetization tagging measurements with hyperpolarized $^3$He in lung were reported by Owers-Bradley et al. [79]. The tagging was also used to image respiratory motion, and a global, lung-average diffusion was measured from the decay of tagged magnetization across the entire lungs, without imaging [83]. Their method calculated $D_{sec}$ from decay rates at several different tagging wavelengths. They found $R = A + D k^2$ with a constant $D$ (which we call $D_{sec}$) for values of $\lambda$ from 1 to 4.5 cm. The constant decay rate $A$ accounts for $T_1$ relaxation. Their result of $D_{sec} = 0.02$ cm$^2$/s in a healthy human subject in this range of wavelengths is one tenth of typical values of restricted diffusivity measured over milliseconds (denoted $D_{msec}$ here). This dramatic decrease in diffusivity over larger distances is consistent with the idea that gas atoms must travel from one acinus to another through the maze of airways via a common node on the airway tree. We show below in several
show that our technique for measuring different than typical smokers’ emphysema, the canine images capacity, the lungs were repeatedly ventilated with 300-mL similarly. With the lungs at approximately functional residual studies of healthy lung that $D_{sec}$ is typically about a factor of 10 smaller than $D_{msec}$. We note that an alternative method for measuring long-range diffusion involves observing the non-exponential decay of magnetization within a single slice that is repeatedly imaged; one can extract the rate of diffusion of spin magnetization from neighboring regions into the imaged slice [85]. One could also monitor the ‘washout’ of a slice into adjacent slices with zero magnetization or the modulation of slice-to-slice contrast. The method described here appears to be a more direct measurement of $D_{sec}$.

4.5. In vivo Imaging of $D_{sec}$ in dogs with unilateral emphysema

Our group has acquired images of $D_{sec}$ via magnetization tagging in live dogs with elastase-induced emphysema in one lung only [75,86]. This unilateral emphysema model allowed simultaneous control experiments in the left lungs of each animal. Restriction to diffusion of $^3$He gas was significant in the control lungs, as expected, and the measured long-range diffusivity was about $12 \times$ smaller than short-range diffusivity in the same lungs (0.015 versus 0.19 cm$^2$/s). Fig. 12 demonstrates an obviously faster decay of magnetization tagging in the emphysematous lung over the control lung; there were marked increases (300%) of $D_{sec}$ in the emphysematous lungs compared to control lungs. More modest increases in $D_{msec}$ (160%) were observed in the same animals (Fig. 12).

This increase in $D_{sec}$ for canine, elastase-induced emphysema is strikingly smaller than that observed in several human patients with severe emphysema (Fig. 14 and Ref. [75]). We have demonstrated that this canine model reflects diffuse panacinar emphysema, similar to that often encountered in patients with $\alpha-1$ antitrypsin deficiency. Although this is different than typical smokers’ emphysema, the canine images show that our technique for measuring $D_{sec}$ can be utilized in vivo and reflects a significant increase in collateral pathways in emphysema via an increase in long-range $^3$He diffusion over control lungs.

4.6. Imaging $D_{sec}$ in explanted human lungs with emphysema

Explanted lungs offer distinct advantages for $^3$He imaging and functional lung research: they can be held at inspiration for several minutes, and the lack of saline (with attendant rf loss) provides for the use of high-sensitivity coils for multiple measurements on one bolus of gas. We imaged $D_{sec}$ in explanted human lungs from transplant recipients with advanced COPD and in healthy donor lungs that were rejected for transplant due to recipient mismatch [95].

The lungs with advanced COPD were removed at transplant, fitted with a bronchial connection to laboratory tubing, sealed of leaks, and purged of O$_2$ (the paramagnetic effects of which depolarize $^3$He) with N$_2$. The donor lungs were prepared similarly. With the lungs at approximately functional residual capacity, the lungs were repeatedly ventilated with 300-mL tidal volumes of hyperpolarized $^3$He to mix the gas for diffusion imaging. After there was sufficient gas in all areas of the lung, $D_{sec}$ was measured by preparing sinusoidally modulated magnetization and then repeatedly imaging with FLASH.

Fig. 13 clearly demonstrates the small decay of modulation in a normal donor (control) lung. A value of 0.017 cm$^2$/s was measured for $D_{sec}$ nearly uniformly in the 20-mm, approximately sagittal slice; this value is a factor of ten smaller than $D_{msec}$ measured in the same lung. In stark contrast, Fig. 14 shows similar images in an emphysematous lung. Decay of the sinusoidal modulation is apparent already at the second image, taken 0.33 s after the first. In particular the upper lobe (at left in each image) shows marked decay, as reflected in the map of $D_{sec}$ (0.6 cm$^2$/s in this region, an increase by a factor of 30 over the control lung).

4.7. In vivo Imaging of $D_{sec}$ in humans

Measurement of the diffusivity from inspection of magnetization-tagged images is significantly affected by bulk flow, so complete breath hold during the entire experiment time is essential. We note that proper breath hold for other diffusion imaging modalities is also important, but small amounts of flow will affect $D_{msec}$ much less than $D_{sec}$, because $D_{sec}$ measures displacements over such long times (see discussion in Section 2). Since tagging decay must be measurable after the approximately 10 s of breath hold, we have not increased in vivo tagging wavelengths beyond 3 cm. Shown in Fig. 15 are inspection images of tagged magnetization in a healthy volunteer. In these images we see slow decay of the tagging contrast and some heterogeneity—the apex decays more quickly than the base. We suspect that this may be mixing driven by cardiac motion.

In summary, measurements of the ADC over centimeter length-scales ($D_{sec}$) is reduced in healthy lungs by a factor of about 50 from the free diffusivity $D_o$. This large restriction is attributed to the tortuous network of airways. In some regions of severely emphysematous lungs, $D_{sec}$ values approaching $D_o$ have been measured, demonstrating the large range of increase possible for this measure of lung microstructure. The increase in $D_{sec}$ in emphysema is due to increases in collateral

![Fig. 13. Decay of sinusoidal modulation (grayscale) and resultant long-range diffusion map (color) in a nominally healthy, excised donor lung. Even after 6 s, there is little attenuation of the modulation; $D_{sec}$ is measured to be 0.017 cm$^2$/s nearly uniformly.](image-url)
ventilation pathways, so $D_{sec}$ may be useful in distinguishing different phenotypes of emphysema.

5. Fluorine-19 ADC measurements

5.1. Rationale

This review is focused on the diffusion of hyperpolarized $^3$He gas in lungs. Nevertheless, recent results on the diffusion of perfluorinated gases in lungs are relevant. Imaging of these inert gases, primarily C$_2$F$_6$, C$_3$F$_8$, and possibly SF$_6$ and CF$_4$, offers advantages over $^3$He: laser-driven polarizing apparatus is not involved, resulting in a simpler and less expensive technique; such gases gain S/N by having as many as six equivalent $^{19}$F spins per molecule and a short $T_1$ to allow rapid signal averaging; and the gases may be mixed with oxygen to allow continuous breathing (as opposed to breath hold of a single bolus). The major drawback is that the perfluorinated gases offer much less image S/N in a given acquisition time compared to hyperpolarized $^3$He. In addition, long-distance diffusion measurements as described in Section 4 for $^3$He, are impossible for gases with nuclei of short $T_1$. It remains to be seen whether the perfluorinated gases will enter into widespread use.

Several groups have reported spin-density or ventilation images from $^{19}$F MRI using SF$_6$ [11,12]. This gas has an exceptionally short $T_1$ and $T_2$ of about 1.8 ms at room temperature and 1 atm pressure [87]. We note that the first images of the air-spaces of lungs used CF$_4$ in dogs, by Lauterbur et al. [88]; CF$_4$ has a similar short relaxation time as SF$_6$ [87].

However, diffusion measurements to determine the local severity of emphysema in lungs impose further requirements. First, the $T_2$ must be sufficiently long to allow the diffusivity $D$ to be measured with the available gradient strengths. As the goal of all this work is clinical implementation, this means gradients of no more than 40 mT/m, for today’s whole body MRI instrument. Second, the diffusion must be measured using a sufficiently long diffusion time, $t$, so that the diffusive motions of the gas molecules are substantially restricted by the lung microstructure. Diffusion measurements on gases of very short $T_2$ necessarily use short diffusion times $t$ and will report a value very close to the free diffusivity $D_0$ of the gas (see below). For both reasons, the gases C$_2$F$_6$ and C$_3$F$_8$ (with $T_1 = T_2$ of 10 and 20 ms, respectively) are more suitable for measurements of diffusion in human lungs. We note recent measurements of $D$ in rat lungs using SF$_6$ gas [89].

The reduced diffusivity, $D_{10}/D_0$, is sketched in Fig. 16 as a function of $\sqrt{t}$ (after scaling of this variable to dimensionless units) [90]. The ratio of surface area to gas-phase volume of the porous structure or lung, $S/V$, can be used to define the reciprocal of the characteristic length or feature size. Thus, the dimensionless variable along the horizontal axis, $x \equiv (S/V)\sqrt{D_0t}$, is approximately the ratio of the free (unrestricted) root mean square displacement in time $t$ to the feature size, $(S/V)^{-1}$. In healthy human lungs [74], $S/V$ is approximately 200 cm$^{-1}$, the reciprocal of 50 $\mu$m. For $x \ll 1$, essentially no gas molecules contact a restricting wall in time $t$, so $D = D_0$. For $x \gg 1$ molecules make many collisions with walls during the measurement duration $t$ and $D$ approaches $D_0/\alpha$, where $\alpha$ is the tortuosity as defined in the standard theory of porous structures. (An interesting issue is that lungs with their bifurcating branches do not truly have a characteristic length, so they do not strictly possess a unique value of tortuosity $\alpha$, as would a sponge for example.) For intermediate values of diffusion time (that is, $x$ less than or of order unity), a famous approximation [91] exists between the diffusivity and $t$,

$$D_{10}/D_0 \cong 1 - (4/9)\sqrt{\pi}(S/V)\sqrt{D_0t}. \quad (18)$$

Fig. 14. Decay of sinusoidal modulation (grayscale) and resultant long-range diffusion map (color) in an emphysematous, explanted human lung. The rate of diffusion of $^3$He is very high compared to normal lungs, especially in the upper lobe (at left in the images). Each grayscale image advances by 0.33 s.

Fig. 15. Tagging decay in a healthy volunteer, in vivo; each grayscale image progresses in time by 2.9 s. The rate of decay is low, and the extracted average diffusion coefficient is consistent with ex vivo studies by us and in vivo studies in Nottingham [79]. Some heterogeneity is visually apparent; gas in the apex mixes more quickly than at the base of the lungs. This may be due to cardiogenic mixing at breath hold.
This expression describes the linear portion of the graph in Fig. 16. Aside from the numerical factors, this relationship has a simple physical explanation [92]. For $^{3}$He, the very large $D_0$ of 0.88 cm$^2$/s (dilute in N$_2$ or air) results in typical $x$ values of 25, for typical $t$ values of 1–5 ms as is common (see above); this places $^{3}$He measurements well into the tortuosity limit and well outside the realm of applicability of Eq. (18). For C$_2$F$_6$ or C$_3$F$_8$ ($D_0 = 0.035$ or 0.022 cm$^2$/s, respectively [90]), the $x$ values are approximately 3–4 (see Fig. 16). Thus, imaging measurements of restricted diffusion using these heavy, large gas molecules should allow the surface-to-volume ratio to be determined on a voxel-by-voxel basis, provided $D_0$ is known. Measurement of the local $S/V$ should be a particularly valuable characterization of lung microstructure in emphysema; we know of no competing non-invasive method for measuring $S/V$ in lungs with spatial resolution. We note that the approximate relationship of Eq. (18) is model-free; thus the interpretation in terms of $S/V$ is comparatively unambiguous.

5.2. Methods

The images and results presented here used 100% concentration of perfluorinated gas in excised lungs, to avoid regulatory issues. It is our opinion that explanted emphysema-tous human lungs are superior models of the disease in live humans, compared to animal models. A high $Q$ solenoidal rf coil oriented sideways in the magnet bore (1.5 T) was used. Three-dimensional data acquisition results in much more efficient (faster) signal averaging than sequential-slice two-dimensional acquisition. Typically, voxels were 5.5×5.5×32 mm$^3$. For C$_3$F$_8$, only the 6 equiv. perfluoromethyl spins were excited. The two center $^{19}$F spins are chemically shifted by 42 ppm, about 2380 Hz at 59.85 MHz, and were placed in a null of the rf spectrum of the pulses [90].

5.3. Results

The excised lungs were exhausted of air and very uniformly refilled with 100% C$_2$F$_6$ or C$_3$F$_8$ gas using a bell jar apparatus, designed to function with the same pressure inside and outside the lung. Thus, there should be essentially the same amount of gas in each image voxel. Indeed, spin-echo images (formed using an rf $\pi$-pulse) obtained without diffusion attenuation are strikingly uniform in signal intensity [90]. However, gradient-echo images show intensity variations, most notably as regions of low intensity due to dephasing effects across the large voxels employed. These artifacts become larger at longer gradient echo times (typical values are 4–10 ms), as expected for susceptibility/dephasing effects. However, as remarked below, the use of spin echoes in human subjects will involve a substantial increase in deposited rf energy (SAR).

Restricted diffusivity results for C$_3$F$_8$ are presented in Fig. 17, comparing a normal donor lung to an explanted severely emphysematous lung. Both panels show individual partitions (three-dimensional equivalent of slices); outside the chest cavity, lungs take on quite different shapes. Judging from the color bar, the diffusion of C$_3$F$_8$ is distinctly smaller (more restricted) in the healthy lung than in the emphysematous lung. This result shows the potential of $^{19}$F MR to characterize emphysematous lung changes.

The histogram of Fig. 18 displays the data from C$_2$F$_6$ on two normal donor lungs (nominally healthy) and eight explanted lungs with severe emphysema. The data from the two groups are well resolved with relatively little overlap. The average ADC is 0.017 cm$^2$/s for the normal lungs and 0.032 cm$^2$/s for the emphysematous group. Analysis of the raw data indicates that a significant component of the standard deviation (see figure caption) is from measurement noise. The factor of nearly two change in the mean diffusivity between healthy and emphysematous lungs is promising.
5.4. Transition to human imaging

The primary issues for in vivo human imaging are S/N, rf energy deposition in the chest (SAR), and safety of the gaseous agent. This last question is outside the scope of this review, but the perfluorinated gases are exceptionally inert, appear to have no toxicity, and have only small anesthetic activity (e.g. C2F6 is similar to argon and only twice as active as nitrogen [93]). We note that C3F8 is currently used to inflate microspheres in the standard deviation are 0.017 (0.0037) for healthy and 0.032 (0.0094) for emphysema.

The (S/N)2 accumulated in a given averaging time is proportional to the fraction of real time that the spin signal is present. Approximately, each signal persists for time T2 and can be repeated every T1; thus (S/N)2 is proportional to T2/T1. Since each of the gases considered here has nearly equal values of T2, T2, and T1, all should yield the same S/N in a given time, for equal numbers of equivalent spins per molecule. There is no advantage to the very fast T1 and T2 of SF6 and CF4; in fact, these gases would have to be used with very high pulse repetition rates to compete with C2F6 and C3F8 because of their short T2 values, leading to excessive rf power dissipation. As noted earlier, the short T1 gases are also not suitable for measuring restricted diffusion. We note that gases with even longer T1 T2 than C3F8 would suffer from T2 becoming smaller than T2, yielding less efficient accumulation of (S/N)2.

The present results demonstrate that the restricted diffusivity of C2F6 and C3F8 can distinguish healthy and emphysematous lung tissue and may be able to provide a spatially resolved measurement of the surface area to volume ratio, S/V [94]. This method would not require hyperpolarization apparatus and would be more readily adoptable at medical sites. Based on the imaging times used here with the high sensitivity rf solenoid coil and the expected factor of 20 increase in averaging time, it appears that additional improvements in S/N will be needed for this technique to be practical. The available avenues for improvement include use of a higher static field strength than the present 1.5 T and use of a superior rf coil such as a phased array.

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References


[38] D.G. Norris, J.M.S. Hutchison, Concomitant magnetic field gradients and their effects on imaging at low magnetic field strength, Magn. Reson. Imaging 8 (1990) 33–34.


