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Regional Anisotropy of Airspace Orientation in the Lung as Assessed with Hyperpolarized Helium-3 Diffusion MRI

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Abstract

Purpose—To evaluate regional anisotropy of lung-airspace orientation by assessing the dependence of helium-3 (³He) apparent diffusion coefficient (ADC) values on the direction of diffusion sensitization at two field strengths.

Materials and Methods—Hyperpolarized ³He diffusion-weighted MRI of the lung was performed at 0.43T and 1.5T in 12 healthy volunteers. A gradient-echo pulse sequence was used with a bipolar diffusion-sensitization gradient applied separately along three orthogonal directions. ADC maps, median ADC values and signal-to-noise ratios were calculated from the diffusion-weighted images. Two readers scored the ADC maps for increased values at lung margins, major fissures, or within focal central regions.

Results—ADC values were found to depend on the direction of diffusion sensitization ($p < 0.01$, except for craniocaudal versus anteroposterior directions at 1.5T) and were increased at the lateral and medial surfaces for left-right diffusion sensitization (12 of 12 subjects); at the apex and base (9 of 12), and along the major fissure (8 of 12), for craniocaudal diffusion sensitization; and at the most anterior and posterior lung (10 of 12) for anteroposterior diffusion sensitization. Median ADC values at 0.43T (0.201 ± 0.017 , left-right; 0.193 ± 0.019 , craniocaudal; and 0.187 ± 0.017 cm²/s, anteroposterior) were slightly lower than those at 1.5T (0.205 ± 0.017 , 0.197 ± 0.017 and 0.194 ± 0.016 cm²/s, respectively; $p < 0.05$).

Conclusion—These findings indicate that diffusion-weighted hyperpolarized ³He MRI can detect regional anisotropy of lung-airspace orientation, including that associated with preferential orientation of terminal airways near pleural surfaces.

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Keywords

diffusion-weighted MRI; hyperpolarized gas; lung; anisotropy

INTRODUCTION

Diffusion-weighted MRI using hyperpolarized helium-3 (^3He) or xenon-129 as an inhaled gaseous contrast agent has shown great promise for assessing microstructural characteristics of the lung in a manner unmatched by other non-invasive approaches (1-7). The majority of these studies have been performed using ^3He , for which it has been shown that apparent diffusion coefficient (ADC) values reflect the microstructure of the lung, the timing and strength of the diffusion-sensitizing gradient waveforms, and also the presence of background field gradients induced by magnetic-susceptibility differences at air-tissue interfaces (1-5, 7, 8). The effects of magnetic-susceptibility differences depend upon field strength, and it has been predicted that these effects may become apparent in ^3He diffusion results at field strengths higher than 3T (9). Nonetheless, a recent study comparing the ^3He ADC values obtained in the same subjects at both 1.5T and 3T found a systematic increase in the measured ADC at 3T that was attributed to the increased susceptibility effects at the higher field strength (8).

Although multiple diffusion-sensitization directions can be used for hyperpolarized-gas acquisitions, analogous to proton MRI, relatively few studies have explored the dependence of lung ADC values on the direction of diffusion sensitization. In a previous study by Schreiber et al in which ADC data were collected along three orthogonal diffusion-sensitization directions in 15 healthy subjects, statistically significant differences in median ADC values were not observed among diffusion-sensitization directions (10). This result is not surprising, considering that the orientations of alveolar ducts are expected to exhibit an isotropic distribution within voxel sizes typically used for hyperpolarized-gas diffusion-weighted imaging. Nonetheless, it is known that lung airspaces exhibit preferential (anisotropic) orientation in at least some regions, such as near major fissures or pleural surfaces (11), although it has not been shown that these microstructural variations can be easily detected by imaging.

The goal of the present study was to evaluate the regional anisotropy of lung-airspace orientation by assessing the dependence of ^3He ADC values on the direction of the diffusion-sensitization gradient. In addition, to determine whether any observed regional variations are attributable to underlying structure versus magnetic-susceptibility effects, measurements were performed both at a standard field strength for clinical MRI (1.5T) and at a field strength 3.5 times lower (0.43T).

MATERIALS AND METHODS

The studies reported here were part of larger project aimed at characterizing hyperpolarized ^3He MRI of the lung in healthy humans at three field strengths (0.43T, 0.79T and 1.5T). All imaging was performed using a clinical whole-body scanner (Avanto, Siemens Medical Solutions, Malvern, PA), for which the magnet was ramped to the lower

field strengths and then reshimmed by a company that provides specialty services for MRI (Resonance Research, Inc., Billerica, MA). Field homogeneity of 0.9 ppm (RMS) over a 30-cm diameter spherical volume was achieved at the field strengths below 1.5T.

Human Subjects

Hyperpolarized ^3He diffusion-weighted MRI of the lung was performed at 0.43T and 1.5T in 12 healthy volunteers (4 male, 8 female, age 20-30 years). For a given subject, the time between studies at the two field strengths ranged from 3 weeks to 4 months. All experiments were performed under a physician's Investigational New Drug application (IND 57,866) for imaging with hyperpolarized ^3He using a protocol approved by our institutional review board. Informed written consent was obtained in all cases. All subjects had smoked less than 100 cigarettes in their lifetime, had no history of pulmonary disease and were not pregnant. Spirometry was performed in each subject within one hour prior to the imaging session using a hand-held device (Koko; PDS Ferraris, Louisville, CO). The subject's heart rate and oxygen saturation level were monitored (3150 MRI Patient Monitor; Invivo Research Inc., Orlando, FL) during the imaging session.

^3He Polarization and Dosing

Helium-3 gas was polarized by collisional spin exchange with optically-pumped rubidium/potassium vapor using a custom-built system (12), yielding polarizations between 40 and 60%. A gas mixture containing 500 ml of hyperpolarized ^3He and medical grade nitrogen with a total volume equal to approximately one-third of the subject's forced vital capacity, as determined by spirometry, was dispensed into a Tedlar bag (Jensen Inert Products, Coral Springs, FL). The subject was asked to exhale completely and then, after inhaling the ^3He -nitrogen mixture from the bag, the subject inhaled room air to total lung capacity.

MR Acquisitions

Flexible chest transmit/receive ^3He RF coils (Clinical MR Solutions, Brookfield, WI) of identical geometry were used at both field strengths. Diffusion-weighted data were acquired using a gradient-echo pulse sequence with application of a trapezoidal bipolar diffusion-sensitization gradient waveform (ramp times 300 μs , flat-top times 980 μs , no delay between positive and negative lobes; root-mean-square diffusion distance for helium in air of $\sim 900\ \mu\text{m}$ during one lobe of the waveform) between the excitation radiofrequency pulse and the associated spatial-encoding gradients. During a single 18-s breath-hold period, 5 or 6 (depending on lung size) coronal images (20% interslice gap) were acquired with diffusion-sensitization along three orthogonal directions (left-right [phase-encoding], craniocaudal [readout] and anteroposterior [slice-select]) and a b value of $1.6\ \text{s}/\text{cm}^2$, yielding ADC maps for the three diffusion-sensitization directions from one breath-hold. For a given line of k space, the acquisition order was $b = 0$, $1.6\ \text{s}/\text{cm}^2$ (left-right), $b = 0$, $1.6\ \text{s}/\text{cm}^2$ (craniocaudal), and then $b = 0$, $1.6\ \text{s}/\text{cm}^2$ (anteroposterior). A $b = 0$ acquisition was paired with each $b = 1.6\ \text{s}/\text{cm}^2$ acquisition to minimize bias of the ADC values from consumption of the non-equilibrium hyperpolarized magnetization by the excitation radio-frequency pulses, and to provide an identical bias for the three diffusion-sensitization directions so that the bias could be neglected when comparing values among directions. Other pulse-sequence parameters

included: TR/TE 9.8/6.4 ms, flip angle 5°, matrix 52×128 , and voxel size $6.6 \times 3.3 \times 25$ mm.

Image Analysis

Background noise was removed in the diffusion-weighted images by setting pixel values below an intensity threshold to zero. Coronal ADC maps, having the same image matrix and voxel size as the source images, were then calculated for the three diffusion-sensitization directions from the diffusion-weighted images using the standard equation ($ADC = (\ln S_{b=0} - \ln S_{b=1.6}) / b$, where S is the signal intensity for a given pixel), which assumes a mono-exponential decay due to diffusion, and routines written in MATLAB (Matworks, Natick, MA). The median ADC value for each subject was calculated for each of the diffusion-sensitization directions at both field strengths. Corresponding values in each subject were compared using a paired Student's t -test.

The signal-to-noise ratios for the $b = 0$ and $b = 1.6$ s/cm² acquisitions were calculated as the mean signal intensity within ventilated lung (i.e., the pixels remaining following application of the intensity threshold noted above) divided by the standard deviation of background noise.

Two human readers (PK and TAA, with 4 and 17 years of experience, respectively) scored by consensus the ADC maps for conspicuity of ADC values that were increased at the lung margins corresponding to the direction of diffusion sensitization compared to ADC values interior to the lung margins, and for the conspicuity of the major fissures. The readers also assessed the maps for focal regions in which the ADC values for a given direction of diffusion sensitization were increased compared to those for a different direction of diffusion sensitization. Increased ADC values at lung margins were scored using a 3-point scale: score 1: increased ADC values at the margin are not recognizable; score 2: marginal zone of increased ADC values is seen, however its thickness is difficult to assess; score 3: distinct marginal layer of increased ADC values is present. Major-fissure conspicuity was also scored using a 3-point scale: score 1: major fissure is not seen; score 2: major fissure is seen on at least one side; score 3: major fissure is clearly seen on both sides.

RESULTS

Median ADC values of the lungs, averaged over all subjects, were 0.201 ± 0.017 (left-right, phase-encoding direction), 0.193 ± 0.019 (craniocaudal, readout direction) and 0.187 ± 0.017 cm²/s (anteroposterior, slice-select direction) at a field strength of 0.43T, and 0.205 ± 0.017 , 0.197 ± 0.017 and 0.194 ± 0.016 cm²/s, respectively, at 1.5T. Median ADC values obtained at 0.43T were typically a few percent lower than those obtained at 1.5T ($p < 0.05$) for each sensitization direction (Fig. 1). The 95% confidence intervals for 0.43T values minus those for 1.5T were -0.002 to -0.007 (left-right), -0.001 to -0.006 (craniocaudal) and -0.004 to -0.009 cm²/s (anteroposterior). In addition, at each field strength, median ADC values were significantly different among directions ($p < 0.01$), except for the craniocaudal versus anteroposterior directions at 1.5T ($p = 0.07$). The corresponding 95% confidence intervals were 0.003 to 0.012 and 0.005 to 0.012 (left-right minus craniocaudal), 0.010 to 0.017 and 0.009 to 0.014 (left-right minus anteroposterior), and 0.002 to 0.010 and 0.000 to

0.006 cm²/s (craniocaudal minus anteroposterior) for 0.43T and 1.5T, respectively. The signal-to-noise ratios, averaged over all subjects, were 104 ± 30 and 76 ± 22 at 0.43T for the $b = 0$ and $b = 1.6$ s/cm² acquisitions, respectively, and 110 ± 29 and 80 ± 21 at 1.5T, respectively.

As seen in the representative examples shown in Figures 2 and 3, ADC maps obtained at both 0.43T and 1.5T were inhomogeneous. (Note that the range of ADC values used for the maps [0.2 cm²/s] is approximately five times less than that often used to display ³He ADC maps.) For example, compared to the central region of the lung, a marginal area of increased ADC values was typically seen at the lateral and medial surfaces for left-right diffusion sensitization (e.g., white arrowheads in Fig. 2); at the apex and base for craniocaudal diffusion sensitization; and at the most anterior and posterior lung for anteroposterior diffusion sensitization. This pattern was seen on the ADC maps from the majority of subjects (12 of 12 for left-right, 9 of 12 for craniocaudal, and 10 of 12 for anteroposterior; Table 1). The sensitization direction-dependent pattern of increased ADC values appeared essentially identical in distribution, thickness and relative intensity for both 0.43T and 1.5T, as illustrated by Figure 2a compared to 2b.

The ADC maps also showed focal but generally ill-defined areas of relatively higher or lower ADC values in the central lungs. Whether these foci demonstrated relatively increased or decreased ADC values was dependent upon the direction of diffusion sensitization, i.e., areas that demonstrated relatively higher ADC values with the diffusion-sensitization gradient applied in one particular direction showed relatively lower ADC values when the diffusion-sensitization gradient was applied in another direction (Table 1; blue circles in Fig. 2). It was not uncommon that, for a given diffusion-sensitization direction compared to another, areas of relatively higher ADC values were observed in some regions of the lung while areas of relatively lower ADC values were observed in other regions. Furthermore, linear foci of higher ADC values were evident on the maps for the majority of subjects, corresponding to the expected locations of the major fissures when diffusion sensitization was applied along the craniocaudal direction (8 of 12, Table 1; arrow in Fig. 3). Analogous to the behavior discussed above, the sensitization direction-dependent pattern of ADC-value variations appeared essentially identical at 0.43T and 1.5T (Fig. 2a vs. 2b).

DISCUSSION

Previous studies using diffusion-sensitization gradients applied in one direction demonstrated heterogeneity of ADC values in healthy lungs, most notably a gradual increase in ADC in the craniocaudal and (subject posture-dependent) anteroposterior directions (3, 6, 13, 14), likely reflecting gravity-dependent variations in alveolar size. Nonetheless, Halaweish et al (14) demonstrated that the anteroposterior ADC gradient essentially disappears at total lung capacity, as used for all images collected in our study.

We observed significant differences in median ADC values among diffusion-sensitization directions, which was not the case for the earlier study by Schreiber et al (10). Perhaps, significant differences were not found in the previous study due to signal-to-noise limitations (110 ± 29 for our $b = 0$ acquisition at 1.5T versus 15.4 ± 10.9 reported in Fig 10a

of ref. 10), because the authors did not collect the data at total lung capacity to suppress the effects of gravity-dependent ADC gradients, or due to differences between the diffusion times and b values (diffusion time and b value of 1.58 ms and 1.6 s/cm² for the current study versus 2.3 ms and 3.89 s/cm² for the studies of ref. 10). In all subjects, we also observed focal regions within the central portion of the lung where ADC values varied markedly depending on the direction of diffusion sensitization. We do not currently understand the specific source or possible structural significance of these variations, but studies in an ex-vivo lung preparation or in an appropriate structural phantom may be useful in understanding the mechanism behind these focal changes. Nonetheless, these patterns of ADC differences were essentially identical at 0.43T and 1.5T, suggesting that they are due to underlying regional variations in microstructure rather than being caused by magnetic-susceptibility effects.

The median ADC values were generally highest for left-right diffusion sensitization, which corresponds to the direction of major deformation of lung tissue by the heart. Although equivalent lines of k space for $b = 0$ and $b = 1.6$ s/cm² were separated by only one repetition time (9.8 ms), which is much shorter than the cardiac cycle, it is possible that heart motion resulted in increased signal attenuation for the $b = 1.6$ s/cm² acquisition, manifesting as a slightly higher ADC value for left-right diffusion sensitization. Acquisition of data using ECG triggering could be used to evaluate this possibility.

For each of three orthogonal diffusion-sensitization directions, ADC values for the healthy human lung based on 2 b -value measurements were, on average, a few percent smaller at 0.43T than at 1.5T. Although the differences were small, they were significant. The trend of higher ADC values with higher field strength is consistent with that previously observed by Parra-Robles et al (8), although the magnitude of the difference between 0.43T and 1.5T is several times smaller than that between 1.5T and 3T, which is not surprising since susceptibility effects on the ADC vanish as the field decreases toward zero and likely have a higher-order than linear dependence on field strength.

The pattern of increased ADC values adjacent to the visceral pleural surfaces observed in our study can be explained by the preferential alignment of the alveolar ducts found in prior histological studies of the lung; alveolar ducts emanating from respiratory bronchioles near the visceral pleural surface show a preferential orientation perpendicular to the surface, in contrast to deeper regions in which the orientation is more evenly distributed (11). Such a preferential alignment would be expected to result in an ADC value higher than that for randomly oriented alveolar ducts when the direction of diffusion sensitization is perpendicular to the surface, because the ADC value corresponding to ³He gas within a relatively thin tube varies with the angle between the direction of diffusion sensitization and the long axis of the tube, and is largest when the diffusion direction and tube axis are parallel. The finding that the observed variations of ADC values near the pleural surfaces were independent of field strength supports the notion that these variations, analogous to those observed in the central portion of the lung, are due to regional differences in microstructure rather than being caused by magnetic-susceptibility effects. This study demonstrates that diffusion-weighted hyperpolarized ³He MRI is sensitive to detecting these differences. In the study of Schreiber et al, the authors also collected diffusion tensor data

using six diffusion-sensitization directions (10). Anisotropy analysis of this data (see Fig. 12b in ref. 10) indicated the presence of markedly increased anisotropy of the airways at the surface of the lung. The authors dismissed this finding as likely being artifactual. Our results suggest, however, that their findings could actually reflect the preferential alignment of alveolar ducts near pleural surfaces.

It has previously been shown that hyperpolarized ^3He diffusion MRI is a sensitive method for detecting the gross alterations in lung structure that occur in patients with emphysema (1, 2, 7). With this disease the walls of the lung airspaces break down, causing the airspaces to enlarge, and hence the ADC values in regions of lung destruction are increased compared to those in regions with normal lung airspaces. Our study showed that hyperpolarized ^3He ADC is also sensitive to detect anisotropic orientation of alveolar ducts in the healthy lung as the ADC values of lung airspaces bordering the visceral pleura were consistently greater than the values in nearby lung regions when the diffusion-sensitization gradient was applied in the direction perpendicular to the surface.

A number of limitations of this study deserve discussion. Most importantly, there was no direct means to confirm or quantify the degree of regional changes in the distribution of alveolar-duct orientations in our subjects. For example, although our findings are consistent with previous histological studies (11), increased ADC values at the lung margins or major fissures were generally less pronounced in certain subjects compared to others (e.g., subject 9 versus subject 2, Table 1), and we do not know whether this was due to limitations of the measurement (e.g., signal-to-noise ratio or spatial resolution), or if it instead reflected actual microstructural differences among subjects. In this regard, increased ADC values which appeared to be associated with the major fissures were identified based on the typical shape, orientation and location of the fissures, although no independent imaging data were available to confirm that a given feature was indeed at the location of a major fissure. Because the spatial resolution in the anteroposterior direction was several times less than that in the left-right or craniocaudal directions, identification of increased ADC values in the anteroposterior direction was hampered by the correspondingly larger partial-volume effects. Another limitation of the current study is that the measurement protocol included only three diffusion-sensitization directions, as compared to six diffusion-sensitization directions used by Schreiber et al (10) or many sensitization directions commonly used in proton MRI. In addition, the effect on the ADC results of varying the diffusion time was not evaluated. A limitation of the reader evaluation is that the scoring decisions were made by consensus instead of by the individual readers.

In summary, ^3He ADC MR imaging is a sensitive technique for assessing subtle variations of the lung microstructure, and our findings suggest that with this technique anisotropic orientation of lung airspaces near the pleural surfaces can also be detected. Median ADC values were found to be significantly different among diffusion-sensitization directions, and focal regions within the central portion of the lung were seen where ADC values varied markedly depending on the direction of diffusion sensitization. The observed variations of ADC values with diffusion-sensitization direction, occurring near pleural surfaces and in the central portion of the lung, were very similar at 0.43T and 1.5T, supporting that these

variations result from regional differences in microstructure rather than being caused by magnetic-susceptibility effects.

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Figure 1.

Median ADC values from each subject (open circles) and the mean $\pm$ standard deviation of median ADC values (closed circles) at 0.43T and 1.5T with the diffusion-sensitization gradient applied in the left-right (LR), craniocaudal (CC) or anteroposterior (AP) direction. Median ADC values were significantly different between the two field strengths for each of the three diffusion-sensitization directions (* $p < 0.05$). (The lines connecting open circles indicate median ADC values for the same subject.)

Figure 2.

Representative coronal ^3He ADC maps obtained at 0.43T (a) and 1.5T (b) with the diffusion-sensitization gradient applied in the left-right (LR, phase-encoding), craniocaudal (CC, readout) or anteroposterior (AP, slice-select) direction. The white arrowheads indicate increased ADC values at the lateral surfaces for left-right sensitization. The blue circles indicate a region with relatively higher ADC values for left-right sensitization and relatively lower ADC values for craniocaudal sensitization.

Figure 3. Magnified sections of the right lung from representative coronal ^3He ADC maps obtained at 0.43T with the diffusion-sensitization gradient applied in the left-right (LR), craniocaudal (CC) or anteroposterior (AP) direction. The linear structure indicated by the arrow corresponds to the major fissure of the right lung. (See Fig. 2 for colorbar.)

Table 1

Morphologic assessment of the ADC maps

Subject	Score for increased ADC values at lung margins			Direction dependence of heterogeneity [†]	Score for major fissure conspicuity
	LR	CC	AP		
1	3	3	3	LR, CC	2
2	3	3	3	CC, AP	3
3	3	2	3	LR, CC	1
4	2	2	2	CC, AP	2
5	3	2	1	CC, AP	2
6	2	1	2	LR, CC	1
7	3	2	2	LR, CC, AP	1
8	3	2	2	CC, AP	3
9	2	1	1	LR, AP	1
10	3	2	2	LR, CC, AP	2
11	3	3	2	LR, CC, AP	3
12	3	1	2	LR, CC	3
Median	3	2	2		2

LR, left-right; CC, craniocaudal; AP, anteroposterior.

[†]For the ADC maps corresponding to each direction specified, there was at least one region for which the ADC values were relatively higher while those in the associated region for at least one of the other diffusion-sensitization directions were relatively lower.