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In Vivo Lung Morphometry with Accelerated Hyperpolarized ^3He Diffusion MRI: A Preliminary Study

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Abstract

Purpose—Parallel imaging can be used to reduce imaging time and to increase the spatial coverage in hyperpolarized gas MRI of the lung. In this proof-of-concept study we investigate the effects of parallel imaging on the morphometric measurement of lung microstructure using diffusion MRI with hyperpolarized ^3He .

Methods—Fully sampled and under-sampled multi- b diffusion data were acquired from human subjects using an 8-channel ^3He receive coil. A parallel imaging reconstruction technique (GRAPPA) was used to reconstruct under-sampled k -space data. The morphometric results of the GRAPPA-reconstructed data were compared with the results of fully sampled data for three types of subjects: healthy volunteers, mild, and moderate COPD patients.

Results—Morphometric measurements varied only slightly at mild acceleration factors. The results were largely well preserved compared to fully sampled data for different lung conditions.

Conclusion—Parallel imaging, given sufficient signal-to-noise ratio, provides a reliable means to accelerate hyperpolarized-gas MRI with no significant difference in the measurement of lung morphometry from the fully sampled images. GRAPPA is a promising technique to significantly reduce imaging time and/or to improve the spatial coverage for the morphometric measurement with hyperpolarized gases.

Keywords

lung morphometry; hyperpolarized gas MRI; parallel imaging; GRAPPA; g -factor

Introduction

Direct imaging of lung tissue using magnetic resonance is challenging for various reasons, including the low tissue density in the lung and the short T_2^* of lung tissue. Hyperpolarized gas (HPG) MRI has been widely used as an alternate approach of lung MRI. Among the various imaging techniques with HPG, diffusion MRI, which studies the random motions of the gas molecules restricted by lung tissue (1,2), was demonstrated to be a powerful probe for the microstructure of the lung (3–5). Specifically, using the Weibel geometrical model

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(6) of the acinar airways as shown in Fig. 1, one can determine the acinar duct radius R , alveolar depth h , and then evaluate standard morphometric parameters such as the mean linear intercept (L_m), surface-area-to-volume ratio (S/V), and alveolar density (N_v) (3,4). Such *in vivo* measurement of lung microstructure, or morphometry, is promising as a tool to study lung function in health and disease including the early detection of chronic obstructive pulmonary disease (COPD) (7–9), the understanding of formation of new alveoli after pneumonectomy (10), and the mechanics of lung inflation (11). In practice, however, diffusion lung imaging with HPG is usually restricted to partial lung coverage, mainly because the acquisition of every line of k -space must be repeated with multiple values of the magnetic field gradients used for diffusion measurements (3). The echo-planar imaging (EPI)-based diffusion sequence, commonly used to greatly speed up diffusion acquisition in the brain, is not readily available for our purposes because of the strong field inhomogeneities induced by magnetic susceptibility gradients at the air-tissue interfaces in the lung. Thus, in order to keep scan time within a breath-hold, the coverage and/or the spatial resolution must be compromised. The partial coverage of the lung also results in waste of HPG. In our typical 6- b measurements, 3 transverse slices of 30 mm thickness are acquired within a 10 second breath-hold, which cover only a portion of the total lung volume.

Parallel imaging (PI) with multiple receive channels can be used to reduce scan time in MRI, leading to shorter breath-holds which makes our study accessible to more patients. Two main approaches for PI based on image space (SENSitivity Encoding, or SENSE) (12) and k -space (generalized autocalibrating partially parallel acquisitions, or GRAPPA) (13,14) reconstructions are now widely available in clinical scanners. Compared to SENSE, GRAPPA has the advantage of not requiring explicit coil sensitivity maps, which is especially advantageous for COPD patients that may not have uniform ventilation across the lungs. In addition, PI is particularly suitable for HPG MRI from the point of view of signal-to-noise ratio (SNR). For traditional proton MRI, the partially sampled images using PI are generally noisier than the fully sampled images because of two factors: the smaller number of sampling points and a coil-geometry-dependent factor, referred to as the g -factor (12,15). For PI of HPG, however, the first factor can be considerably reduced or even removed; with the total gas magnetization available for imaging fixed by pre-polarization, the reduced number of total excitations allows for a higher flip angle in each RF excitation, which results in a higher SNR in each individual k -space acquisition (16). Thus, the SNR loss of HPG MRI can be much smaller than that of proton MRI in the context of PI (16–18). However, the g -factor still can play a significant role in determining the SNR of the under-sampled images. It is *a priori* unclear how these PI-related factors affect the quantitative diffusion measurement of HPG in the lung, and consequently the morphometric measurement of the lung microstructure.

In this study, we investigate the effects of PI on the morphometric measurement of the human lung using HPG diffusion MRI. Partial k -spaces were acquired or mimicked by decimating the fully sampled k -space data, followed by reconstruction using GRAPPA (13). The morphometric results were compared to those of fully sampled images for different subjects varying from healthy to moderate COPD. We found that GRAPPA provides a

reliable means to accelerate data acquisition with no significant difference in lung morphometry from the fully sampled images.

Methods

This study was approved by the FDA (IND 59,269) and local IRB, and written consent was obtained from all subjects. All data were acquired on a 1.5 T whole body scanner (Avanto, Siemens Medical Solutions, Iselin, NJ) using a rigid volume transmitter coil and a flexible 8-channel receive array (Stark Contrast, Germany) around the chest that was tuned for ^3He (48.5 MHz). The arrangement of the array is illustrated in Fig. 2(a). Helium-3 gas was hyperpolarized to approximately 40% using a commercial Nycomed Amersham Imaging IGI.9600. He polarizer (GE Healthcare, Durham, NC). Subjects inhaled 1 liter of a 40/60 mixture of hyperpolarized ^3He gas in nitrogen from functional residual capacity (FRC) and held their breath. During ^3He imaging, each subject's ECG and oxygen saturation were monitored for potential adverse effects.

Fully Sampled (FS) MRI Acquisition

Diffusion data were obtained from nine subjects: five healthy non-smokers (ages 38 ± 16 , range 19–57) and four long-term smokers of varying disease severity (> 30 pack year history, ages 67 ± 1.8 , range 64–69, GOLD status: U, 1, 2, 3 (19)). Some details of data acquisition include: 2D spoiled gradient-echoes (FLASH) sequence, TR/TE = 13.0/8.3 ms, bandwidth = 260 Hz/pixel; 3 sequentially acquired slices, 40 centric ordered phase-encoding (PE) lines, 64 readout (RO) points, $7 \times 7 \text{ mm}^2$ in-plane resolution, 30 mm slice thickness; PE is from anterior to posterior, RO is from left to right, as shown in Fig. 2(b). Diffusion sensitizing gradients of 6 b values (0, 2, 4, 6, 8, 10 s/cm^2) were used for diffusion measurement; the gradient waveform consists of a pair of bipolar, anti-symmetric trapezoidal field gradient pulses; pulse duration (δ) = 1.8 ms, ramp-up and ramp-down times = 0.3 ms, and separation (Δ) = 1.8 ms (no gap) (3); the loop of b values was inside the loop of PE steps. To maintain a fair distribution of the signals throughout the k -space, an efficient use of gas polarization, and to avoid local magnetization overconsumption due to the RF inhomogeneities across the lung (20), we aimed to consume 70% of the total polarization for imaging. This results in a calibrated flip angle of 5.5° . RF power was computed based on the body-coil calibration for proton MRI (21).

Retrospective GRAPPA (rGRAPPA) Reconstruction

The fully sampled data were decimated by removing the phase-encoding lines in the k -space for GRAPPA reconstruction. We refer to this procedure as rGRAPPA. An acceleration factor (AF) of 2 was mimicked on all 9 subjects. Different numbers of PE lines near the center of k -space were used for GRAPPA kernel calibration (auto-calibrating lines, or ACLs). These ACLs were plugged back into the reconstructed k -spaces of each channel, resulting in different effective acceleration factors (eAF). The directions of PE and RO relative to the orientation of the receive array are shown in Fig. 2(b); the under-sampling pattern and the GRAPPA kernel geometry for AF=2 are shown in Fig. 2(c). The procedure was repeated for all 3 slices and all 6 b values in each subject, followed by calculations of lung morphometry parameters (4,7).

Actual GRAPPA Data Acquisition and Reconstruction

In under-sampled (US) acquisitions of HPG MRI, the flip angles should be increased to optimize polarization consumption (16). If the FS and US images were acquired by N_f pulses of flip angle α_f and N_u pulses of flip angle α_u , respectively, in order for both schemes to consume the same fraction (i.e., 70%) of the total polarization, these values must satisfy

$$(\cos\alpha_f)^{N_f} = (\cos\alpha_u)^{N_u} \quad [1]$$

For small α_f and α_u ,

$$\left(1 - \frac{\alpha_f^2}{2}\right)^{N_f} = \left(1 - \frac{\alpha_u^2}{2}\right)^{N_u} \Rightarrow 1 - N_f \frac{\alpha_f^2}{2} = 1 - N_u \frac{\alpha_u^2}{2}$$

Using $N_f/N_u = eAF$, the relation between α_u and α_f is

$$\frac{\alpha_u}{\alpha_f} = \sqrt{eAF} \quad [2]$$

From the SNR ratio established between the US (SNR_u) and the FS (SNR_f) proton images (12)

$$\left(\frac{SNR_u}{SNR_f}\right)_{1_H} = \frac{1}{g \sqrt{eAF}} \quad [3]$$

we estimate that the ratio for HPG is

$$\left(\frac{SNR_u}{SNR_f}\right)_{HPG} = \sqrt{eAF} \left(\frac{SNR_u}{SNR_f}\right)_{1_H} = \sqrt{eAF} \frac{1}{g \sqrt{eAF}} = \frac{1}{g} \quad [4]$$

This result indicates that by setting the appropriate flip angle the SNR loss for an under-sampled HPG MR image is only related to the g -factor.

Three subjects (healthy #5, GOLD 1, and 3) were also imaged with US acquisitions at $AF = 2$ and $ACLs = 4$, resulting in $eAF = 1.74$ ($=40/23$). Accordingly, the flip angle α_u was increased to 7.3° (from $\alpha_f = 5.5^\circ$) and the imaging time was reduced from 9.4 s to 5.4 s. Other parameters remained the same as in the full acquisition.

Data Analysis

For all reconstruction algorithms (FS, rGRAPPA, and GRAPPA) images from all channels were jointly analyzed using Bayesian probability theory (22–24) and a mathematical model of ^3He diffusion in lung acinar airways (4). All morphometry maps were masked based on their respective $b=0$ images to remove pixels outside of the lung and the low-signal pixels

within the lung. In addition, to quantify the accuracy of the estimated morphometry, the uncertainties from the Bayesian parameter estimation routines (4), which were shown to be inversely proportional to the SNR of the images (Eq. [9] in (25)), were also compared. Using the acinar duct radius R as an example, if we denote the uncertainty of parameter R by δR , then δR of the FS and US images, δR_f and δR_u , are proportional to $1/\text{SNR}_f$ and $1/\text{SNR}_u$, respectively (with the same ratio constant). Thus, using Eq. [3] and [4], the relative uncertainty, $(\delta R)_{\text{rel}} = \delta R_u / \delta R_f$, is given by

$$(\delta R)_{\text{rel}} = g \sqrt{eAF} \quad [5]$$

for rGRAPPA (without flip angle adjustment) and

$$(\delta R)_{\text{rel}} = g \quad [6]$$

for GRAPPA with appropriate flip angle ($\alpha_u = 7.3^\circ$) adjustment (Eq. [2]).

To estimate the g -factors, coil sensitivity maps were first generated for the $b=0$ images of a healthy subject using the method of McKenzie et al. (26), then the g -factors were estimated pixel-by-pixel for a given AF (12). The noise correlation matrix was assumed to be identity (i.e., no noise correlation between channels).

Results

For simplicity, we only present the results related to the acinar duct radius R . The results for other parameters are similar (available upon request). An example slice corresponding to $b=0$ of the FS, GRAPPA, and rGRAPPA of a normal subject from all channels are shown in Fig. 3. No obvious artifacts were seen in the under-sampled images. The GRAPPA images appear slightly brighter because of the increased flip angle (7.3° , Eq. [2]).

Example maps of R for the FS, GRAPPA, and rGRAPPA images, along with their ventilation images, are shown in Fig. 4(a) for three subjects ranging from healthy to moderate COPD. As shown, the distributions as well as the magnitudes of R are highly consistent across these images. The median R values and the standard deviations are listed in Table 1 for all subjects. The median uncertainty δR for each subject obtained from the Bayesian parameter estimation for the rGRAPPA images was first normalized by the δR of the corresponding FS images and the resulting $(\delta R)_{\text{rel}}$ was plotted in Fig. 4(b) against $g \sqrt{eAF}$, along with the theoretically predicted trend line for $(\delta R)_{\text{rel}}$ (black line, Eq. [5]). For our data, the g -factor varied very slightly (from 1 to 1.01) and we used the average g -factor (1.005) across all three slices in the plot. For the GRAPPA images, the relative uncertainty is independent of eAF (Eq. [6]). All uncertainties δR are listed in Table 1.

Discussion

Our results indicate that the lung morphometry measurement can be accelerated using PI with no significant difference from the fully sampled images: the average difference is only

1% (Table 1). The changes in these parameters caused by under-sampling in k -space (columns of Fig. 4(a)) are very small compared to the heterogeneity across the lung and the pathological changes in COPD (rows in Fig. 4(a)) (4,7). One common concern for PI is the reduced SNR of the accelerated images, which naturally leads to higher deviations of morphometry measurement from the true values. For example, the reduced SNR may result in slightly higher R values because the signals at high b values decay more quickly into noise. This effect plays a more significant role for the COPD lungs, where regions of poor ventilation have lower SNR for $b=0$, and consequently the signals decay faster into noise. Therefore, for patients with moderate to severe COPD, moderate or low AF's should be used. Overall, as a rule of thumb, to obtain a reasonably accurate estimation of lung morphometry, the SNR of the $b=0$ images should be around 100 (25), which can be used as a reference to estimate the upper limit of acceleration in practice by using Eq. [3] or Eq. [4] (with appropriate flip angle adjustment).

For the rGRAPPA images, as shown in Fig. 4(b), the relative uncertainty $(\delta R)_{\text{rel}}$ increases as the number of PE steps decreases, as expected from the general theory of SNR in MRI. However, we note that the $(\delta R)_{\text{rel}}$ of the rGRAPPA images (open symbols) appear to be lower than the theoretically predicted values (dark line). One possible explanation is the implicit numerical regularization effect in the procedures of GRAPPA, which improves the SNR of the reconstructed images, especially at low AF's (27). For the actual GRAPPA images, however, the δR in theory should be similar to the δR of the FS images, according to Eq. [6]. The small differences in δR between the FS and the real GRAPPA data sets listed in Table 1 could be due to any variations between the repeated measurements such as gas polarization and lung inflation. We notice that for two out of the three subjects (Healthy 5 and GOLD 1) the GRAPPA δR is lower than the FS δR . In addition to the numerical regularization mentioned above, we speculate that two factors could have contributed to this difference. First, the reduced total imaging time has likely helped mitigate the motion artifacts of the images. It is known that all HPG images of the lung, even at breath-holds, contain physiological noise (e.g., the cardiac motion and the pulsatile motion of the blood (28)); such noise increases as the imaging time gets longer. By under-sampling the k -space we reduced the total imaging time from 9.4 s to 5.4 s, thereby reducing the motion-induced incoherence between the lines in k -space. Such different δR values between the fully and under-sampled images may potentially be used to quantify physiological noise. Second, the shorter scan time reduced the ^3He gas polarization loss due to T_1 relaxation, which would boost the signal strengths of the GRAPPA images relative to the FS images. Such T_1 effect was not considered in our approximated treatment (Eq. [1]). A more detailed approach taking T_1 into account was presented in Ref (16). In addition to the reduced number of acquisitions, images acquired and reconstructed by the PI techniques are also known to have uneven distributions of noise related to the g -factor variations across the image. Essentially, the g -factors amplify the noise of an image in a non-uniform fashion, modifying the SNR distribution of the image. The modified SNR distribution will in turn propagate to the uncertainty of the lung morphometry (25). Therefore, at higher acceleration factors the g -factor maps should be used to monitor the accuracy of morphometry estimation, especially in regions of high g -factors. Overall, the exact relation between the relative morphometry

uncertainty and the AF, taking into account all the factors mentioned above, requires further investigation.

Although our work is based on HP ^3He with our 8-channel receive coil, the results can be easily generalized to HP ^{129}Xe (8) or any receive array with a different number of channels. As discussed above, the main concern for PI in the context of lung morphometry is the decrease of SNR. Thus the SNR of the reconstructed images should be monitored and maintained for accurate parameter estimations. Specifically, for instance, given the same number of receive channels for ^3He and ^{129}Xe , the AF used for ^{129}Xe should be less than the AF for ^3He in order to compensate for the generally lower SNR of ^{129}Xe images. Obviously, receive arrays with higher number of channels generally perform better than those with lower number of channels because of the better g -factor performance, and therefore higher AF's should only be used when sufficient number of receivers are available. Further, volumetric (3D) imaging with accelerations in two dimensions take advantage of the spatial arrangement of the receive channels in more than one dimension, which can be used to significantly increase the eAF with relatively little loss in SNR (i.e., small increase in the g -factor).

Conclusions

In this proof-of-concept work, we demonstrate that GRAPPA is a promising technique to significantly reduce imaging time and/or to improve the coverage for measurements of lung morphometric parameters with HP ^3He diffusion MRI. Our results show that the reduction of k -space lines used in PI, compensated by a corresponding increase in the flip angle, provides results with no significant difference in the measurement of lung morphometry from the fully sampled images.

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Figure 1.
(Adopted from (25)) Acinar duct radius R , alveolar depth h and alveolar diameter L are illustrated in a simplified model of alveolar geometry in acinar airways.

Figure 2.

(a) Approximate positions of the 8-channel receive coil relative to the lungs of a subject in the transverse view; (b) the phase-encoding (PE) and read-out (RO) directions relative to the coil geometry in (a); (c) shows the under-sampling pattern and the data synthesizing scheme used in this study, where solid circles represent acquired data, and open circles represent skipped data.

Figure 3.

An example slice ($b=0$) of the fully sampled (FS), prospectively under-sampled (GRAPPA), and retrospective GRAPPA (rGRAPPA) image sets of a healthy subject from all 8 channels. The GRAPPA images appear slightly brighter because of the increased flip angle (7.3°).

Figure 4.

(a) Ventilation images and maps of the acinar duct radius R of fully sampled (FS), GRAPPA, and retrospective GRAPPA (rGRAPPA) of normal and diseased subjects (healthy non-smoker, smoker (GOLD 1), and smoker with moderate COPD (GOLD 3)). No obvious difference was observed between the R maps of fully-sampled and under-sampled images, and regional features were all well preserved.

(b) Plot of the relative uncertainties of R ($(\delta R)_{\text{rel}}$) of the retrospectively under-sampled (rGRAPPA) images against $g\sqrt{eAF}$. Each $(\delta R)_{\text{rel}}$ is calculated from the median of R

uncertainties of the under-sampled images in each subject normalized by that of the FS images. The trend line is predicted by Eq. [5]. Each shape (or color) corresponds to a single subject. Average g -factors across all three slices were used to compute $g \sqrt{eAF}$, where $g = 1.005$ and eAF is the effective acceleration factor.

Table 1

Median R values, the standard deviations (in parentheses) across the lung, and the median δR for all subjects, fully sampled (FS) and under-sampled. Under-sampled data that are decimated from the fully sampled data are labeled as rGRAPPA (for “retrospective GRAPPA”). eAF stands for effective acceleration factor.

Subject	Age	R median (μm)			δR median (μm)		
		FS	eAF=1.74 (rGRAPPA)	eAF=1.74 (GRAPPA)	FS	eAF=1.74 (rGRAPPA)	eAF=1.74 (GRAPPA)
Healthy 1	26	305 (31)	305 (37)		11	13	
Healthy 2	52	320 (34)	320 (37)		8	10	
Healthy 3	57	329 (34)	333 (33)		7	8	
Healthy 4	19	312 (33)	313 (39)		14	18	
Healthy 5	35	331 (26)	336 (28)	334 (33)	9	11	7
GOLD 3	68	372 (96)	385 (102)	375 (95)	11	13	13
GOLD 2	68	399 (67)	404 (68)		15	18	
GOLD 1	69	328 (36)	332 (36)	331 (41)	16	19	11
GOLD U	65	334 (36)	340 (42)		14	17	