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Rapid Assessment of Pulmonary Gas Transport with Hyperpolarized ^{129}Xe MRI Using a 3D Radial Double Golden Means Acquisition with Variable Flip Angles

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Abstract

Purpose—To demonstrate the feasibility of using a 3D radial, golden-means acquisition with variable flip angles to monitor pulmonary gas transport in a single breath hold with hyperpolarized xenon-129 (HXe) MRI.

Methods—HXe MRI scans with interleaved gas- (GP) and dissolved-phase (DP) excitations were performed using a 3D radial, golden-means acquisition in mechanically ventilated rabbits. The flip angle was held fixed at either 15° or 5°, or was varied linearly in ascending or descending order between 5° and 15° over a sampling interval of 1,000 spokes. DP and GP images were reconstructed at high resolution (32×32×32 matrix size) using all 1,000 spokes, or at low resolution (22×22×22 matrix size) using 400 spokes at a time in a sliding-window fashion. Based on these sliding-window images, relative change maps were obtained using the highest mean flip angle as the reference, and aggregated pixel-based changes were tracked.

Results—While the signal intensities in the DP maps were mostly constant in the fixed-flip angle acquisitions, they varied significantly as a function of average flip angle in the variable flip-angle acquisitions. The latter trend reflects the underlying changes in observed DP magnetization distribution due to pulmonary gas uptake and transport.

Conclusion—3D radial, golden-means acquisitions with variable flip angles provide a robust means for rapidly assessing lung function during a single breath hold, thereby constituting a particularly valuable tool for imaging uncooperative or pediatric patient populations.

Keywords

Hyperpolarized xenon-129; Pulmonary gas transport; 3D radial double-golden means acquisition

Introduction

Lung function can be characterized by several clinical diagnostic tools, such as computed tomography (CT), pulmonary function tests (PFTs), positron emission tomography (PET) and conventional proton MRI. Yet existing techniques are unable to provide an accurate, meaningful quantification of the overall gas transport by the lung as the culmination of all contributory processes to lung function. If any one of these processes—ventilation, gas exchange or transfer into cardiovascular circulation—goes awry, an ideal regional or global gas transport metric should appear abnormal. Developing methods to assess such metrics is therefore highly desirable in a holistic evaluation of pulmonary health, but is complicated by the limited breath hold capabilities of lung disease patients. As a step towards such an assessment, we investigated the feasibility of using a 3D radial, double golden-means acquisition to quickly extract dynamic 3D gas uptake information in a single breath hold.

Over the years, hyperpolarized noble gas MRI has offered numerous options for investigating lung physiology, morphometry and function. The modality can be coarsely divided into two categories: gas-phase (GP) and dissolved-phase (DP) imaging. GP MRI can provide information about ventilation patterns within the pulmonary airspaces (1–4), the rudimentary geometries of these airspaces as derived from apparent diffusion coefficient measurements (5–8), and regional oxygen concentration (9–11). DP MRI, on the other hand, enables the quantification of gas exchange by the lung parenchyma (12–18), as well as pulmonary circulation at the alveolar level (19–26). The transport of DP magnetization throughout the body and more distal organs has also been demonstrated using DP MRI (27–32).

Hyperpolarized xenon-129 (HXe) is a particularly powerful agent for evaluating pulmonary ventilation, gas exchange and subsequent transfer to pulmonary circulation, as it is much more soluble in water (Ostwald solubility at 37°: ~0.089) and biological tissues (Ostwald solubility at 37°: ~0.17) (33) than hyperpolarized helium. Further, due to a large chemical shift difference of about 200 ppm between the GP and DP resonances (34), it is easy to manipulate the magnetization in one compartment of the lung without affecting the magnetization in the other through the application of suitably-designed radio-frequency (RF) pulses. As a consequence, HXe can be selectively depicted in neighboring biological compartments only micrometers apart, despite a nominal spatial image resolution of several millimeters at best (35–44).

Nevertheless, measuring DP magnetization transport is difficult even with rapid MR imaging techniques due to the small physiological time constants involved, which are on the order of several tens or a few hundreds of milliseconds. Dynamic acquisitions are further complicated by the fact that the DP magnetization is steadily depleted by the continuous application of RF excitation pulses, such that the further the dissolved xenon has traveled from the alveolar exchange sites, the smaller its remaining signal. Hence, for any given

repetition time (TR), acquisitions with lower flip angles will depict a steady state HXe magnetization distribution in the lung that contains a larger fraction of downstream DP magnetization than higher flip angles, as the latter results in a more rapid depolarization. As the DP magnetization is carried along by the blood stream, it becomes visible in locations more distal to the alveoli, such as the heart (45). The dynamics of pulmonary HXe gas transport can thus be revealed by obtaining multiple acquisitions with different flip angles.

3D radial sampling trajectories that fill k-space as homogeneously as possible regardless of the number of collected spokes offer a particularly efficient way of implementing this insight. One such trajectory is a 3D radial, double golden-means acquisition (46,47): this type of sampling scheme allows selection of the spatial resolution with which the 3D image data set is reconstructed after the measurement by using more or fewer of the sampled radial spokes in exchange for lower or higher effective temporal resolution, respectively. In our study, we demonstrated the capabilities of 3D double golden-means sampling order for illustrating the dynamics of HXe gas transport in rabbit lungs. This was accomplished by linear variation of the RF excitation flip angle throughout the acquisition such that the HXe magnetization distribution continuously changed during the measurement rather than remaining in steady state, allowing us to observe the pulmonary gas transport—starting at the alveolar gas exchange site and continuing all the way to the left side of the heart—from a single breath hold measurement.

Methods

Animal Studies

Experiments were performed using four New Zealand rabbits (approx. 4.5 kg each). The rabbits were sedated with 25–35 mg/kg ketamine and 5 mg/kg xylazine IM, and 1–5% isoflurane was administered through a mask to maintain deep anaesthesia throughout animal preparation. A peripheral vein was cannulated to maintain general anaesthesia during imaging. After anesthetization, a tracheotomy tube was inserted using an aseptic surgical procedure and secured using a silk ligature.

After induction of anesthesia, animals were placed in a xenon RF coil (described below) and attached to a home-built, MRI-compatible mechanical ventilator. Anesthesia was maintained throughout the imaging session by an infusion of Propofol (20–80 mg/kg/h), and body temperature was supported by a circulating warm water pad. Animals were euthanized at the end of the imaging procedures. All experiments were approved by and performed in accordance with the guidelines established by the University of Pennsylvania Institutional Animal Care and Use Committee (IACUC) and the NIH guidelines for the care and use of laboratory animals.

Imaging was performed on a 1.5-Tesla commercial whole-body scanner (Magnetom Avanto; Siemens Medical Solutions, Malvern, PA, USA) that had been modified by the addition of a broadband amplifier, permitting operation at the resonant frequency of 17.6 MHz. The RF coil was a custom xenon-129 transmit/receive birdcage design (Stark Contrast, Erlangen, Germany), positioned to cover the whole chest of the animal. Low-resolution proton MR scout images were obtained with the built-in body coil.

Gas Polarization and Administration

Enriched xenon gas (87% xenon-129) was polarized by collisional spin exchange with an optically pumped rubidium vapor using a prototype commercial system (XeBox-E10; Xemed, LLC, Durham, NH) that provided gas polarizations of 40–50%. Immediately before MR data acquisition, 1.25 L of HXe gas was dispensed into a Tedlar bag (Jensen Inert Products, Coral Springs, FL) inside a pressurizable cylinder that was subsequently connected to and controlled by the ventilator. Animals were ventilated with room air until the beginning of the imaging study, at which time the gas mix was switched to 20% oxygen and 80% HXe (6 ml/kg tidal volume). After inhalation of the gas mixture for up to 4 breaths, ventilation was suspended for up to 15 s before ventilation with room air was resumed.

HXe Data Acquisition

In a typical 3D radial acquisition, the orientation of the spokes is first modified by changing their azimuthal angles and then incrementing their polar angle such that the entirety of a spherical k-space volume corresponding to the selected FOV and image resolution has been covered at the end of the measurement. For any given FOV and spatial resolution, the step size of the azimuthal and polar angle increments can be adapted to optimize the sampling efficiency. However, the reconstruction based on these sampling schemes requires a successful completion of the measurement without intermittent gross subject motion in order to yield uncorrupted images. The spoke orientations in a 3D double golden-means acquisition are less evenly distributed (see Fig. 4b in Chan et al. (47)), but ensure relatively uniform k-space sampling regardless of the number of collected spokes. The image quality for a double golden-means acquisition is therefore slightly degraded compared to sequentially incremented orientation angles for the same number of sampled spokes. However, this acquisition permits uncorrupted image reconstructions from arbitrary segments of consecutively-acquired radial spokes at reduced spatial resolutions, and is therefore highly suitable for acquisitions with steadily varying acquisition parameters.

Images were acquired using a 3D radial, double golden-means sequence with interleaved gas- and dissolved-phase excitations. Parameters for the acquisition included TR/TE = 8.32/0.62 ms, 3,200 radial spokes with 128 sampling points, dwell time of 5 μ s, and FOV of 180 mm³. The RF pulse was an optimized low-flip-angle pulse (38) with a duration of 1 ms. The flip angle at the DP resonance was either held fixed at 5° or 15°, or varied linearly between 5° and 15° over the course of the acquisition. In the latter case, the flip angle was held constant at the starting angle of the range for the first 800 spokes so that the DP magnetization was in steady state by the time the flip angle variations began shortly after initiation of the breath hold. All spokes after the flip angle variation were acquired with the final flip angle of the variable flip angle regime. The flip angle of the GP excitation was held fixed at 0.5°.

Out of a total of 3,200 sampled spokes, radial data sets with 1,000 and 400 spokes were gridded onto 32×32×32 and 22×22×22 matrices, respectively, and Fourier transformed using the Michigan Image Reconstruction Toolbox for MatLab (Mathworks, Natick, MA, USA). A window of 400 spokes and a step size of 10 spokes were used to reconstruct the variable flip angle acquisition in a sliding-window fashion, such that the average flip angle for each

subsequent reconstructed 3D data set changed slightly from the one reconstructed before. To minimize image artifacts due to the variable signal amplitudes of the individual spokes, all spokes were normalized based on their amplitude at the center of k-space. The reconstructed DP images were subsequently normalized to their respective gas-phase images.

Data Analysis

To track the relative changes in the DP signal as a function of average flip angle in the sliding window reconstruction the 3D data set with the highest mean flip angle was used as a reference point. The data sets with a lower mean flip angle were divided by the reference data set to obtain relative-change maps. Relative changes were also calculated for each pixel and then averaged together in groups of 20 based on their relative-change value for the lowest mean flip angle for improved visualization. All data analysis was conducted using MatLab (Mathworks, Natick, MA, USA).

Results

Figure 1 shows a representative plot of the GP and DP signals from all radial spokes at the k-space center for a $15^\circ - 5^\circ$ variable flip angle measurement. Both signal curves rise quickly following the switch from room air to xenon gas, and fluctuate during the two xenon wash-in breaths. The signal decays during the breath hold, which follows an air flush after the second xenon breath. The flip angle was held constant until the start of the breath hold for all measurements. In the variable flip angle acquisitions, the flip angle of the RF excitation pulse for the sampled spokes was changed linearly from 15° to 5° , or vice versa, in 1,000 steps. The sampled range is indicated by the vertical dashed lines in Fig. 1. Over the course of the breath hold, the GP and DP signals dropped by factors of approximately 3 and 5, respectively. This decay is due to several factors: oxygen-induced T1 relaxation, the effect of GP RF excitation pulses, and GP depolarization from exchanging with the depleted DP magnetization which results from the applied DP RF excitation pulses.

Figure 2 depicts coronal, axial, and sagittal slices of three $32 \times 32 \times 32$ 3D DP data sets reconstructed from 1,000 spokes collected during the breath hold period. For the first two columns, the flip angle was set to a constant value of either 15° or 5° . In the 15° flip angle measurement, the DP signal is of high intensity and fairly homogeneous throughout the parenchyma, while the signal in the cardiac cavity is much fainter. The contrast is reversed in the 5° flip angle measurement, with the heart containing considerably higher DP signal than the parenchyma. For the third column in Fig. 2, the RF excitation flip angle for each radial spoke was decreased linearly from 15° to 5° . The resulting images therefore share characteristics with each of the fixed flip angle acquisitions in the first two columns.

A key advantage of 3D golden means sampling is that the sampled data sets can be broken into smaller subsets; these can then be reconstructed into fully consistent images, albeit at reduced resolution. Fig. 3 demonstrates this feature by comparing GP (Fig. 3A) and DP (Fig. 3B) images from a fixed flip angle measurement, either using 1,000 spokes to reconstruct a $32 \times 32 \times 32$ image matrix or a 400-spoke subset to obtain a $22 \times 22 \times 22$ image matrix with an identical field-of-view. Although the reduced resolution of the 400-spoke reconstruction

produces blurrier images than those based on the full data set, the overall contrast distribution and lung structure is equivalent.

Using only a subset of spokes sampled with continuously decreasing flip angles permits the observation of xenon gas uptake by the lung parenchyma. The increase of DP signal from subset to subset in downstream regions such as the heart is illustrated by representative relative-change maps in Figs. 4 and 5. For the former, the flip angle was varied from 5° to 15°; for the latter, the flip angle change was reversed from 15° to 5°. As the average DP excitation flip angle for the reconstructed image set decreases, the DP signal increases to varying degrees throughout the lung. For the measured flip angle range, the largest signal increase was observed in the cardiac cavity.

Acquisitions with constant 5° and 15° flip angles were also reconstructed with a sliding window, similar to the variable flip angle reconstructions. The relative DP signal intensities for 5°, 15°, 15° to 5° and 5° to 15° acquisitions in the same animal can be seen in Fig. 6, where each displayed line is the average of 20 adjacent voxels after sorting the voxels of the lowest flip angle image by intensity. In Figs. 6C and D, the signal in and near the heart (the averaged voxel with the largest amplitude) can be clearly differentiated from the signals in the lung parenchyma. This is not the case in Figs. 6A and 6B with the constant flip angles. For the 15° acquisition, the relative signal changes are fairly small across all sliding window images. In the 5° acquisition, the magnetization has a larger downstream component and the DP signal appears to increase slightly over time, possibly due to accumulation in more slowly exchanging tissue compartments such as subcutaneous fat layers.

Discussion

In this study, we demonstrated the use of a 3D radial, double golden-means HXe DP imaging sequence to observe dynamic pulmonary gas transport processes within a single breath hold in rabbits. Previously, multiple acquisitions over several breath holds would have been required to observe similar transport processes, and calculations of relative signal change between these different acquisitions would have been susceptible to physiological changes in the subject, breathing pattern variability or registration inconsistencies. By obtaining dynamic gas transport information during a single breath hold, the variable flip angle approach used here minimizes these errors and produces a series of 3D image sets with a retroactively selectable mean flip-angle increment and spatial resolution, which allows for a retroactive selection of image reconstruction parameters.

The distribution of the HXe DP magnetization within the lung parenchyma is affected by both physiological and MR imaging parameters. Some of these parameters, such as the T1 relaxation of xenon magnetization in the lung tissue, can be expected to remain fairly constant from one subject to another; others, however, such as the alveolar surface-to-volume ratio, the rate of perfusion, or the lung tissue density, can vary widely between subjects, and might in fact be of great interest in characterizing underlying disease. Finally, the MR acquisition itself imposes an additional effective T1 weighting on the DP magnetization, as the flip angle determines how much of the existing DP magnetization is used up during each RF excitation and the TR controls the rate at which this depletion

occurs. If the flip angle and TR are held constant during imaging, the DP magnetization eventually reaches a steady-state condition with the alveolar GP magnetization that is ultimately depicted in the resulting DP images. In general, the downstream xenon magnetization is depleted more rapidly the higher the flip angle or shorter the TR. For instance, with a TR of 8.3 ms and a flip angle 15° , the DP signal in our measurements predominantly originated from the immediate vicinity of the alveolar gas exchange sites (left panels in Fig. 2). Acquisitions with the same TR but a flip angle of 5° , on the other hand, showed DP signal as far downstream as the left side of the heart and the aortic arch (center panels in Fig. 2). The best values for the extremes of the flip angle range will depend on the objectives of a given study and may differ from species to species. However, if the minimum flip angle chosen is too low, the signal-to-noise ratio in the associated data sets may also become too low. On the other hand, if the maximum flip angle is too high, the GP magnetization may be depolarized too rapidly by exchange between the saturated DP compartments and the alveolar volume. In rabbits, we found the 5° – 15° flip angle range to be a good compromise.

As a consequence of the dynamic nature of gas transport by the lung, the spatial distribution of the DP magnetization is poorly controlled as HXe gas is inhaled and subsequently absorbed by the lung tissue. To rapidly imprint a well-defined steady-state condition necessary for extracting meaningful information, it is therefore crucial to start the train of DP RF excitation pulses before the gas has even entered the lung; the variable flip angle acquisition should begin only after steady has been reached. In practice, we achieved this objective by holding the flip angle constant for the first several hundred excitations. The number of these preparatory RF pulses ahead of the actual data acquisition averaged 700 – 1,000 in our experiments, and was dependent on the ventilation rate, the TR and the number of wash-ins used.

When the flip angle of the RF excitation pulses is slowly modified throughout the image acquisition, the associated steady-state distribution of the DP magnetization gradually changes as well. It is thereby feasible to move through an entire interval of near-continuous steady-state conditions of interest within a single breath hold study, where the extreme values of the selected flip angle range effectively control the assessed time frame of the underlying gas transport processes. However, much of the dynamical information obtained in this manner would be lost in sequential k-space ordering schemes. On the other hand, a 3D radial, double golden-means sampling order allows temporal and spatial resolutions to be traded off against each other retroactively during image reconstruction, instead of being predetermined at the time of measurement. Since the image sets reconstructed from each consecutive subset of the sampled radial spokes were obtained with a different excitation flip angle, this advantage was particularly relevant to the current study. When the reconstruction process is repeated by removing some spokes from the beginning of the prior subset and adding the same number of new spokes in a sliding-window fashion, the resulting 4D DP data set reflects the response of the spatial DP distribution to incremental changes in the average flip angle. In our study, we linearly varied the flip angle between 5° and 15° over the course of 1,000 radial spokes. The image set reconstructed from the 400 spokes with the highest mean excitation flip angle corresponds to the DP magnetization distribution most proximal to the gas exchange sites, while the image set obtained from the 400 spokes with

the lowest average excitation flip angle shows the furthest downstream distribution of DP magnetization. All reconstructed intermediary image sets fall in between these two extremes and, when processed in sequential order, permit a visualization of the xenon gas transport over time. Naturally, the perceived temporal resolution of these measurements can be adjusted by changing the number of spokes used for each reconstruction, as well as the number of spokes added and removed for each incremental step in the sliding-window reconstruction.

Ideally, an acquisition with increasing flip angles (Fig. 4) would be equivalent to one with decreasing flip angles (Fig. 5), while the former would be the preferred implementation because the images obtained with low flip angles would be based on data collected when the overall polarization is still near its maximum value (see Fig. 1). As demonstrated in Fig. 6, however, we observed noticeable differences in the relative-change plots for measurements obtained with reversed acquisition order—most likely because the flip angle varies too quickly for the spatial magnetization distribution to remain in steady state. In our experience, the best results are achieved when progressing from high flip angles to lower ones for maximum flip angles of 10° or less, as it takes more low flip-angle RF pulses to reach steady state than high-flip angle pulses. It is therefore more effective to increase downstream magnetization by decreasing flip angles than to decrease downstream magnetization by increasing flip angles. For maximum flip angles larger than 10° , on the other hand, it appears advantageous to start with the lowest flip angle. We also observed occasional fluctuations in the relative-change plots (see Fig. 6c), which we attribute to signal oscillations in the GP signal distribution and pulmonary gas uptake throughout the cardiac cycle (11,25).

The absolute quantification of the regional gas transport rate, requires additional insights into the link between the average excitation flip angle and the TR, and will be the subject of future research. For the time being, however, an accurate time scale cannot be attached to the visualized gas transport. Another challenge to be addressed is that how far the observed magnetization distribution is removed from its steady-state is not inherently accessible, although this parameter can be controlled in principle by modifying the slope of the flip angle variation as well as the flip angle interval. It is also important to note that changes in TR affect the measured magnetization distribution similarly to changes in flip angle. However, due to the large number of excitations in a 3D radial acquisition, any significant TR increase is likely to result in undesirably long measurement times. If it was indeed feasible to maintain steady state throughout the variable flip-angle regime of the measurement, additional information that is collected as a byproduct of our acquisition technique, such as the GP depolarization rate or the DP wash-in rate, could be quantitatively analyzed using existing theoretical models. In the future, we will investigate whether our approach could greatly improve the efficiency of these measurements. Nevertheless, the available qualitative regional GP depolarization and DP wash-in data may already be of interest.

In this work, we have demonstrated the feasibility of using a 3D radial, double golden-means acquisition with linearly-varying flip angles to rapidly assess pulmonary function during a single breath hold. Modifying the flip angle interval offers control over the gas

transport regime for which the acquisition is optimized, as higher flip angles emphasize alveolar gas exchange while lower flip angles enhance the gas transport component of the measurement. Further, the proposed technique is particularly robust with regard to common causes of study failure with HXe MRI: since temporal and spatial image resolutions can be controlled retroactively during reconstruction instead of being predetermined at the beginning of the study, it is possible to obtain salvageable GP and DP data sets even for low polarization levels or in uncooperative, claustrophobic or severely ill subjects. This type of pulse sequence might therefore be particularly valuable as an initial screening tool, which can be used as the basis for selecting more specialized pulse sequences for additional, targeted measurements.

Conclusions

In this preliminary study, we have demonstrated the feasibility of using a 3D radial, double golden-means acquisition to quickly extract dynamic 3D gas transport information in a single breath hold. By linearly decreasing the flip angle during acquisition, a series of reduced-resolution sliding window images can be reconstructed to characterize the uptake and transport of xenon gas. This type of sequence might be particularly suitable as an initial screening tool for abnormal lung function or to image uncooperative patient populations.

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Figure 1.

GP (dashed) and DP (solid) signal at the k-space center for each radial spoke during a typical variable flip angle acquisition. Since the measurement is started before the xenon gas is administered, the first several hundred spokes trace the initial HXe wash-in and absorption by the lung parenchyma. Shortly after the breath hold period begins (around spoke 800, 7 s after acquisition start), the excitation flip angle for the variable flip angle acquisitions is varied linearly for 1,000 spokes over the course of 8.3 s (demarcated by the vertical dashed lines).

Figure 2.

Full-resolution DP maps for fixed flip angles of 15° (1st column) and 5° (2nd column), as well as for flip angles linearly decreasing from 15° to 5° (3rd column), all reconstructed using 1,000 spokes. The fixed flip-angle acquisitions illustrate the differences in the steady-state distribution of DP magnetization for higher and lower flip angles. The DP maps reconstructed from the variable flip angle acquisition exhibits features from both fixed flip angle DP maps.

Figure 3. Differences in the appearance of GP (a) and DP (b) maps using 1,000 spokes for reconstruction onto a $32 \times 32 \times 32$ matrix versus using a subset of 400 spokes for reconstruction onto a $22 \times 22 \times 22$ matrix. While the lower resolution maps appear blurrier, the image contrast remains largely unchanged.

Figure 4. Low-resolution DP maps with different average flip angle overlaid on GP maps (gray) based on a single variable flip angle acquisition increasing from 5° to 15°. As the RF excitation flip angle is rising throughout the measurement, the observed DP magnetization distribution shifts from downstream, pulmonary gas-transport dominated to upstream, alveolar exchange-site centered.

Figure 5. Low-resolution DP maps with different average flip angle overlaid on GP maps (gray) based on a single variable flip angle acquisition decreasing from 15° to 5°. Similar to Fig. 4, the DP contrast changes in response to the prevailing average flip angle for each map.

Figure 6.

Averaged relative changes of pixel amplitudes in the DP maps for fixed flip-angle (top row) and variable flip-angle acquisitions in a sliding window reconstruction normalized by the respective GP maps. To improve visualization, data from 20 pixels of similar relative change over the course of the measurement were averaged together for each line. While the normalized DP signal remains largely unchanged for all reconstructed image subsets, it increases by up to a factor of 5 in the variable flip angle acquisitions. The highest relative changes are usually observed in the left ventricle of the heart and the surrounding major blood vessels at the lowest flip angles.