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Hyperpolarized ^{129}Xe Gas Transfer MRI: The Transition from 1.5 to 3 Tesla

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Abstract

Purpose—Hyperpolarized ^{129}Xe MRI depicting 3D ventilation, interstitial barrier uptake and transfer to red blood cells (RBCs) has emerged as a powerful new means of detecting pulmonary disease. However, given the challenging susceptibility environment of the lung, such gas transfer imaging has, thus far, only been implemented at 1.5 Tesla. Here, we seek to demonstrate the feasibility of Dixon-based ^{129}Xe gas transfer MRI at 3 Tesla.

Methods—Seven healthy subjects and 6 patients with pulmonary disorders were recruited to characterize ^{129}Xe spectral structure, optimize acquisition parameters and acquire representative images. Imaging used randomized, gradient-spoiled 3D-radial encoding of 1000 gas (0.5° flip) and dissolved (20° flip) views, reconstructed into 3 mm isotropic voxels. The center of k-space was sampled when barrier and RBC compartments were 90° out of phase (TE_{90}). A single dissolved phase spectrum was appended to the sequence to measure the global RBC-to-barrier ratio for Dixon-based decomposition.

Results—A 0.69 ms sinc was found to generate minimal off-resonance gas-phase excitation ($3.0 \pm 0.3\%$ of the dissolved-phase), yielding a $\text{TE}_{90} = 0.47 \pm 0.02$ ms. The RBC and barrier resonance frequencies were shifted by 217.6 ± 0.6 ppm and 197.8 ± 0.2 ppm. The RBC T_2^* was estimated to be ~ 1.1 ms and thus each read-out was limited to 1.3 ms. ^{129}Xe gas and dissolved-phase images

have sufficient SNR to produce gas transfer maps of similar quality and sensitivity to pathology, as previously obtained at 1.5 Tesla.

Conclusions—Despite short dissolved-phase T_2^* , ^{129}Xe gas transfer MRI is feasible at 3 Tesla.

Keywords

Hyperpolarized ^{129}Xe MRI; gas transfer imaging; 3 Tesla; T_2^*

Introduction

Enabled by its solubility and large chemical shift range, hyperpolarized ^{129}Xe is increasingly used to characterize pulmonary gas transfer. Its unique properties enable 3D imaging of the ^{129}Xe distribution in the airspaces, interstitial barrier tissues and red blood cells (RBCs) in a single breath-hold scan. This capability was first applied in studying obstructive lung diseases such as asthma and chronic obstructive pulmonary diseases (COPD) [1], but more recently has been used to characterize gas transfer impairment in idiopathic pulmonary fibrosis (IPF) [2, 3], radiation therapy (RT) [4, 5] and pulmonary vascular disease [6].

The most common implementations of ^{129}Xe gas transfer MRI involve selective excitation of the gas- and dissolved-phase ^{129}Xe compartments and encoding them by using a 3D-radial scheme. Subsequently, the dissolved-phase image must be decomposed into its barrier and RBC components. This was first achieved in the pioneering work of Qing et al, by using a multi-echo hierarchical IDEAL approach [7]. However, this required obtaining at least 3 dissolved phase echo times (TE), the longest of which was 3.98 ms, nearly twice the estimated T_2^* (~2ms) of ^{129}Xe dissolved in alveolar septa [7, 8]. Thus, Kaushik et al, proposed an alternative approach to separate the barrier and RBC images using only a single acquisition with sub- millisecond TE [9]. This approach interleaves the radial encoding of the gas and dissolved-phase resonances, and adds a calibration step to ensure that the center of k-space is acquired at an echo time (TE_{90}) when the RBC and barrier resonances are 90° out of phase. A global phase shift was then applied to cast them into real and imaginary channels.

Despite the increasing importance of ^{129}Xe gas transfer MRI, these techniques have only been implemented at 1.5 Tesla. However, ^{129}Xe MRI requires multinuclear imaging capabilities, which vendors are increasingly transitioning to their 3 Tesla platforms. Unfortunately, at 3 Tesla, the T_2^* of dissolved phase ^{129}Xe is expected to decrease to ~1ms, making it unclear whether RBC and barrier compartments can still be separated with sufficient SNR. Specifically, it is necessary to image at short TE, while still achieving 90° phase separation between RBC and barrier, and limiting their continued phase dispersion and T_2^* decay during read-out. Moreover, this must be done while avoiding contamination of the weak dissolved signal by off-resonance excitation from the much larger gas-phase magnetization. Therefore, the objective of this work was to develop and characterize a robust implementation for Dixon-based ^{129}Xe gas transfer MRI that could be deployed on 3 Tesla scanners.

Methods

Subject inclusion and exclusion criteria

The study was conducted under approval of the Duke University Institutional Review Board and FDA investigational new drug (IND) application #109,490. All subjects provided written informed consent prior to the scan. Healthy subjects ($n = 7$, age = 25.7 ± 4.8 y/o) were first recruited to optimize the spectroscopy and imaging parameters. Subsequently, representative images were obtained from a COPD patient (54 y/o), an IPF patient (64 y/o), a non-small cell lung cancer (NSCLC) patient who had undergone RT (66 y/o), a patient with pulmonary arterial hypertension (PAH, 42 y/o), a patient with chronic thromboembolic pulmonary hypertension (CTEPH, 66 y/o), and a heterozygote carrier of alpha-1 antitrypsin deficiency (59 y/o). The healthy subjects had no history of smoking and no diagnosed pulmonary disorders. Subjects were excluded if pregnant or lactating, had a history of cardiac arrhythmias, or had a respiratory illness within 30 days of MRI.

^{129}Xe polarization and delivery

Isotopically enriched ^{129}Xe (86%) in volumes of 700 ml were polarized via rubidium-vapor spin-exchange optical pumping [10] using a commercially available polarizer (Model 9810, Polarean, Inc., Durham, NC, USA). After hyperpolarization, ^{129}Xe was cryogenically accumulated and thawed into a Tedlar bag. The dose was then supplemented with ultra-high-purity nitrogen gas to fill the bag to its full 1 L volume and stored in the 20 Gauss holding field of a polarization measurement station (Model 2881, Polarean, Inc., Durham, NC, USA). This was also used to measure the ^{129}Xe polarization of each dose immediately prior to it being delivered to the patient.

Polarization was $20 \pm 3\%$ for this study, which in combination with 700 ml xenon volumes and 86% enrichment, yielded dose equivalents of 120 ± 18 ml [11].

Optimal RF pulse duration to limit off-resonance excitation

All spectra and images were acquired on a 3 Tesla SIEMENS MAGNETOM Trio scanner (VB19). Subjects were fitted in a quadrature ^{129}Xe vest coil (Clinical MR Solutions, Brookfield, WI, USA) that was proton-blocked to allow reference ^1H anatomical MRI scans to be acquired using the body coil, without re-positioning the subject.

Gas transfer imaging requires separate excitation of the gas-and dissolved-phase ^{129}Xe resonances. Because the dissolved magnetization is roughly 1-2% of the gas-phase signal [12], it must be selectively excited to avoid off-resonance corruption. However, since the dissolved resonances have very short T_2^* (~ 1 ms anticipated at 3 Tesla), selective excitation must be achieved using the shortest possible RF pulse to allow the read-out occur before substantial loss of transverse signal. Since the off-resonance excitation profile will inevitably be distorted by the RF power amplifier, it was evaluated empirically by acquiring gas-phase ^{129}Xe spectra from hyperpolarized ^{129}Xe in a Tedlar bag placed in a torso loader shell. The RF transmit frequency was centered +7431 Hz (218 ppm) above the gas-phase resonance, and 20° sinc pulses were applied with pulse durations varying from 0.25 to 0.80 ms. The amount of gas-phase ^{129}Xe signal was measured to identify the minimum pulse

length that yielded acceptable off-resonance signal. The off-resonance gas excitation was quantified as a percentage of signal obtained by applying a 20° excitation directly on-resonance.

In Vivo Spectroscopic calibration of Frequency, Transmit and Echo Time

A spectroscopic ^{129}Xe calibration scan was first obtained to determine frequency, transmitter reference voltage, and the TE_{90} . This spectrum used a 0.69 ms 1-lobe sinc pulse, with a target flip angle of 20°, acquired at $\text{TE} = 0.45$ ms. Here, TE was defined from the center of RF excitation pulse to the start of ADC sampling and represented the minimum value at which T/R switching was complete. The spectrum consisted of 2 parts: 200 spectra acquired with excitation on the RBC resonance (shifted +7431 Hz from gas-phase), and 20 spectra on the gas resonance (0 Hz shift). All spectra were acquired at $\text{TR} = 73$ ms, with 512 samples, 10 kHz bandwidth, and were followed by a gradient crusher. The first 100 dissolved-phase spectra were discarded and the remaining 100 were averaged and fit in the time domain to determine the frequency and phase separation between the barrier and RBC resonances [13]. These values were used to calculate the TE_{90} . The final twenty spectra of the gas-phase resonance were used to establish its frequency and the necessary transmitter reference voltage for subsequent ^{129}Xe images. In a subset of participants, calibration spectra were acquired with pulse durations ranging from 0.5-1ms to characterize off-resonance gas-phase excitation *in vivo*.

Acquisition of Dixon-Based ^{129}Xe Gas Transfer Images—Gas transfer images were acquired during a 16-sec breath-hold, as depicted in Figure 1(a). Both gas- and dissolved-phase compartments were encoded by 3D radial imaging, with 1000 radial projections each, 64 samples per projection, $\text{TE/TR} = \text{TE}_{90}/7.5$ ms, $\text{FOV} = 36\text{-}40$ cm, bandwidth = 800 Hz/pixel (dwell time = 9.8 μs), flip angles = $\sim 0.5/20^\circ$; the frequency offset for dissolved-phase excitation was +7431 Hz. The radial rays are deployed such that their end-points are distributed in 3-D k-space, following an Archimedean spiral pattern. However, their order of acquisition was randomized by their polar angle according to a Halton random sequence [14, 15] to confer robustness against exhalation or motion. This in turn also randomizes the azimuthal angle and, as shown in Figure 1(b), this semi-random trajectory converges to a homogenous distribution upon completion. The readout gradients were delayed slightly (24 μs) beyond their intrinsic delay times to ensure that $k = 0$ was fully sampled before gradient encoding started. Each radial read-out was followed with an x-gradient crusher to de-phase residual gas-phase magnetization. Immediately after image encoding a single dissolved-phase ^{129}Xe spectrum, consisting of 256 samples, was acquired using the same 20° flip angle. This spectrum, obtained during the same breath-hold, could be used to derive the global, steady-state RBC:barrier ratio, exactly corresponding to the TR and flip angle used for imaging.

To facilitate analysis of the ^{129}Xe gas transfer images, a ^1H breath-hold 3D radial scan was acquired to delineate the thoracic cavity. For this scan, the subjects inhaled 1 L room air to match the lung inflation level from ^{129}Xe MRI. This acquisition consisted of 4601 radial projections, 64 samples per projection, $\text{TE/TR} = 0.52/3.54$ ms, readout bandwidth = 562 Hz/pixel, flip angle = 5° .

Image reconstruction and quantification— ^{129}Xe gas transfer images were reconstructed offline and decomposed into gas, barrier and RBC images [9], with several refinements. All radial free induction decays (FIDs) first underwent a third-order 1-D median filter to suppress noise. The dissolved-phase views were reconstructed with a kernel sharpness of 0.14 [16]. The gas-phase views were reconstructed using the same kernel to match resolution, as well as being reconstructed a second time with a sharper kernel (0.32) to generate a higher resolution ventilation image. The dissolved-phase image was then further decomposed by phase-shifting to align the RBC and barrier signals to the real and imaginary image channels. The phase shift was applied such that the ratio of real to imaginary image intensities within the thoracic cavity matched the RBC:barrier ratio derived from the spectrum. These two channels were then further corrected for B_0 inhomogeneity using a phase map derived from the gas-phase ^{129}Xe image. All images were reconstructed onto $128 \times 128 \times 128$ matrices.

Image quantification and visualization

Ventilation, barrier uptake and RBC transfer images were quantified using color binning as previously described [2]. Each bin encompassed one standard deviation of the corresponding distribution derived from a healthy reference population [2, 17]. Briefly, the high-resolution gas phase image was normalized by its top percentile and divided into 6 equal bins to create a ventilation map [18]. The barrier and RBC images were each divided, on a voxel-by-voxel basis, by the resolution-matched gas image to create barrier:gas and RBC:gas ratio maps. The barrier:gas and RBC:gas maps were then cast into discrete color bins (8 for barrier and 6 for RBC). All three maps (ventilation, barrier uptake, and RBC transfer) were quantified according to the fraction of voxels falling into the lowest bin (defect), the second lowest bin (low) and the two highest bins (high). Each fraction was reported relative to the thoracic cavity volume.

Results

Image SNR for the ventilation (high resolution), barrier and RBC images were 11.7 ± 4.5 , 9.2 ± 4.5 , and 2.9 ± 1.5 .

On-resonance FIDs and off-resonance excitation

Figure 2 shows how sinc pulse duration affects the degree of off-resonance gas-phase excitation. When probing the gas-phase ^{129}Xe in the bag, with the transmit frequency +7431 Hz above the gas resonance, the off-resonance excitation exhibited several local minima. However, a pulse duration of 0.69 ms generated the lowest gas excitation (0.03%). Testing these pulse durations in healthy subjects confirmed that 0.69 ms also minimized off-resonance excitation in vivo. Over a cohort of 17 scans with 0.69 ms pulse duration, the average off-resonance gas-phase signal was $3.0 \pm 0.3\%$ that of the dissolved-phase signal.

^{129}Xe Dissolved-Phase Spectroscopic Line Shapes at 3T

A representative dissolved-phase ^{129}Xe spectrum from a healthy subject and associated curve-fit [13] to extract its spectral profile is shown in Figure 3(a). The line-shape parameters derived from the entire cohort of healthy volunteers are shown in Figure 3(b).

Relative to the gas-phase resonance, the RBC and barrier frequencies were shifted by 217.6 ± 0.6 ppm and 197.8 ± 0.2 ppm, with linewidths 8.3 ± 0.2 ppm and 7.6 ± 0.2 ppm respectively. The RBC linewidth suggests a lower bound of $T_2^* \sim 1.1$ ms. The gas-phase linewidth was found to be 1.31 ± 0.03 ppm, implying a lower limit on its T_2^* of ~ 8.0 ms.

Representative Magnetization Dynamics and Raw Separated Images

Figure 4(a)(b) shows the raw, interleaved gas and dissolved FIDs as well as their dynamics during the acquisition. In steady-state, the gas FIDs have amplitudes roughly $3\times$ larger than the dissolved FIDs, despite being acquired with $\sim 40\times$ smaller flip angles. After the first 50 FIDs, the magnetization in the two pools decays in synchrony down to $\sim 1/3$ of the starting value.

Figure 4(c) shows the reconstruction of the ventilation (gas), and Dixon-decomposed barrier and RBC images for a healthy subject prior to B_0 inhomogeneity correction. These initial barrier and RBC images are then further corrected by small local phase shifts estimated from a phase map generated from the gas image. These corrections are typically modest (standard deviation = 9.8° across the lung); in this example the correction is most prominent in the left lower lung.

Representative ratio maps at 3T for various pulmonary disorders

Figure 5 shows representative, quantitative color maps of regional ventilation, barrier uptake and RBC transfer for patients with different pulmonary disorders. The healthy subject exhibits ventilation, barrier uptake, and RBC transfer confined largely to the normal (green) range, without substantial defects. The COPD patient shows distinct ventilation defects (red), with relatively normal barrier and RBC values, in the remaining ventilated lung. The IPF patient exhibits increased barrier uptake (pink/purple), with focal RBC transfer defects (red) near the lung bases. The RT patient exhibits high barrier uptake in the left lung that received the majority of the dose, as well as some RBC defects at the bases of both lungs. The PAH patient exhibits relatively normal barrier uptake, but striking RBC transfer defect in the posterior lung. Similarly, the CTEPH patient shows a major RBC defect in the right lung base, but also significantly increased barrier uptake.

Discussion

^{129}Xe Spectral Structure at 3 Tesla is Capable of Dixon-Based Decomposition

As expected, the dissolved ^{129}Xe resonances at 3 Tesla are broader than at 1.5 Tesla. However, in relative terms, the barrier and RBC resonances were found to be narrower at 3 Tesla, than at 1.5 Tesla (7.7 ± 0.3 ppm vs 8.6 ± 0.5 ppm for barrier, and 8.5 ± 0.4 ppm vs 10.0 ± 0.4 ppm for RBC). The barrier and RBC linewidths provide a lower limit on their T_2^* of 1.2 ms and 1.1 ms, respectively. These values are slightly better than what might be expected by halving the T_2^* at 1.5 Tesla measured by Qing et al (barrier: 2.2~2.3 ms, RBC: 1.8~1.9 ms) [7], and may be the result of less exchange occurring during the 0.45 ms before sampling. On the other hand, the gas-phase linewidth of 1.31 ± 0.03 ppm, suggests a lower limit of $T_2^* \sim 8.0$ ms, which is considerably shorter than the 18 ± 6 ms reported by Xu from multi-echo imaging in 2 healthy males [19]. This suggests that for the longer-lived gas phase

transverse magnetization, it is likely necessary to map T_2^* regionally to improve accuracy [20].

Frequency-selective Excitation and Short TE are Feasible

Selective excitation of dissolved-phase ^{129}Xe was achieved with a simple 0.69 ms 1-lobe sinc pulse, while generating only 0.03% off-resonance gas-phase signal in vitro. In human subjects, off-resonance contamination led to gas-phase signals that were $3.0 \pm 0.3\%$ of the dissolved phase. Given that the gas-phase pool is $\sim 50\times$ larger [12], this suggests the excitation was limited to $\sim 0.06\%$. This surpassed the suppression achieved in our previous 1.5 Tesla implementation ($10.3 \pm 1.6\%$ gas/dissolved or $\sim 0.20\%$ excitation), and is likely attributable to the larger frequency separation between the resonances. We note that off-resonance excitation could be greater in patients who load the coil more significantly, and therefore require higher transmit power. However, no such trend was observed in this small cohort. Importantly, the short, frequency-selective pulse duration enabled the read out to commence at TE as short as 0.45 ms. This is slightly earlier than the window at which RBC and barrier are 90° out of phase, which was found to be $\text{TE}_{90} = 0.47 \pm 0.02$ ms across the cohort. This represents a smaller variability than seen in our 1.5 T work [2] ($\text{TE}_{90} = 1.00 \pm 0.06$ ms in healthy volunteers) and may again be attributable to less exchange occurring prior to the short echo time. However, since TE_{90} plays a critical role in decomposing barrier and RBC compartment, it remains important to develop a fundamental understanding of why it varies across subjects and why it deviates from 0.37 ms that would be predicted from a simple calculation based on the RBC-barrier frequency difference[21].

Key Refinements – Rapid Read-out, Single-axis Crushers, View Randomization, and Integrated Gas Transfer Spectrum—

Analysis of the RBC line-shape suggests $T_2^* \sim 1.1$ ms, which requires a rapid read-out. In our case, the read-out was 1.25ms [22]. However, the dissolved phase signal was driven to the noise floor after encoding ~ 32 points (within $\sim 0.3\text{ms}$). During this period the continued additional phase accumulation between RBC and barrier was limited to $<100^\circ$, similar to what was achieved in our prior 1.5 Tesla work. Although the dissolved signal was captured within 32 points, the longer readout was beneficial for encoding the higher spatial frequencies of the stronger gas-phase signal. This allowed ventilation images to be reconstructed at higher resolution. However, the longer T_2^* of the gas-phase signal also required its residual transverse magnetization to be spoiled, lest it contaminate the ensuing dissolved phase view 7.5 ms later. This was done by applying gradient crushers along a single fixed axis, rather than along the read-out direction. This was important because the view randomization caused opposite hemispheres of k-space to be alternately sampled, which has the potential to unwind much of the previous crusher. The effectiveness of this crushing strategy was evidenced by the monotonic decay of magnetization seen in the raw FIDs.

An important refinement to the initial published method was to integrate the whole-lung ^{129}Xe gas transfer spectrum for RBC:barrier ratio determination into the imaging sequence. This ensured that the RBC:barrier ratio used for Dixon decomposition reflected not only the same breath-hold maneuver, but also the same steady-state TR and flip angle conditions of imaging.

Consistency from 1.5 to 3 Tesla

Figure 6 shows ventilation and gas transfer maps from a single patient who was evaluated both on our 1.5 Tesla GE system and 3 Tesla. In this patient, who carries a single copy of the alpha-1 antitrypsin deficiency mutation (a heterozygote), the maps, although obtained 21 months apart, show good consistency across the two field strengths. Specifically, on both scans the patient exhibits distinct RBC transfer defects at the lung bases, providing encouragement that ^{129}Xe gas transfer MRI is portable across field strengths and vendor platforms. The patient also exhibited somewhat elevated barrier uptake, which increased in right lung at 3 Tesla. Given that 21 months elapsed between scans, this could indicate a progressing inflammatory process[3].

Study Limitations and Opportunities for Refinement

This initial study of transitioning ^{129}Xe gas transfer MRI to 3 Tesla reveals several limitations and opportunities for improvement. For one patient, the TE_{90} indicated by spectroscopy was slightly shorter (~ 0.05 ms) than the minimum achievable TE of 0.45 ms; hence Dixon decomposition would be imperfect for this case. It is possible to decrease the minimum TE to 0.38 ms, by decreasing the sinc pulse duration to its next local minimum ~ 0.55 ms, at the cost of modestly increased gas-phase excitation. Alternatively, a more sophisticated RF profile could be used to shorten TE without increasing gas-phase excitation [23]. In addition, the gas-phase excitation problem could be obviated by instead using a multiple-echo scheme to image all the compartments with each radial view as suggested by Kammerman [24]. This approach uses the fact that at longer echo time, only off-resonance gas-phase signal will remain, owing to its longer T_2^* . In fact, given the short dissolved-phase T_2^* , this method may perform even better at 3 Tesla.

One limitation of this one-point Dixon-based decomposition is that the RBC and barrier compartments continue to accumulate phase during the readout. Thus, the compartments are only truly separable at $k = 0$. In our work, the continued phase accumulation is $\sim 100^\circ$ over the time of meaningful dissolved-phase encoding, which is similar to our 1.5 Tesla work. It is possible that Dixon separation could be improved by encoding even more rapidly, although the required bandwidths would degrade the already modest SNR. Methods such as IDEAL could address this issue, however, their requirement for multiple echoes is difficult to meet at 3 Tesla.

Finally, it should be noted that the quantitative maps (such as seen in Figures 5 and 6) were generated using reference distributions derived from our 1.5 Tesla healthy cohort. To first order, these distributions should depend primarily on the number of views and relative flip angles between gas and dissolved compartments, and these were kept identical. However, it is conceivable that different effects of T_2^* and read-out bandwidth could somewhat alter these distributions. It will clearly be valuable to obtain a new reference distribution in a healthy cohort at 3 Tesla. Ultimately, such data must also be combined with tests of reproducibility and the effect of lung inflation.

Nonetheless, these preliminary results indicate that ^{129}Xe gas transfer MRI is not only feasible at 3 Tesla, but that its exquisite sensitivity to a wide range of pathology has been

preserved. Although this work would benefit from imaging a larger cohort of patients at both field strengths, ^{129}Xe gas transfer MRI should prove to be a powerful addition to the functional imaging arsenal that is now poised for dissemination across field strengths and vendor platforms.

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References

1. Mugler JP 3rd, et al. Simultaneous magnetic resonance imaging of ventilation distribution and gas uptake in the human lung using hyperpolarized xenon-129. *Proc Natl Acad Sci U S A*. 2010; 107(50):21707–12. [PubMed: 21098267]
2. Wang Z, et al. Quantitative analysis of hyperpolarized ^{129}Xe gas transfer MRI. *Med Phys*. 2017; 44(6):2415–2428. [PubMed: 28382694]
3. Wang JM, et al. Using hyperpolarized (^{129}Xe) MRI to quantify regional gas transfer in idiopathic pulmonary fibrosis. *Thorax*. 2018; 73(1):21–28. [PubMed: 28860333]
4. Rankine LJ, et al. Is Lung Ventilation Imaging a Reasonable Surrogate for Gas Exchange? Implications for Functionally Guided Radiation Therapy Planning. *International Journal of Radiation Oncology Biology Physics*. 2017; 99(2):S109–S109.
5. Zanette B, et al. Detection of regional radiation-induced lung injury using hyperpolarized (^{129}Xe) chemical shift imaging in a rat model involving partial lung irradiation: Proof-of-concept demonstration. *Adv Radiat Oncol*. 2017; 2(3):475–484. [PubMed: 29114616]
6. Kreitner KF, et al. Chronic thromboembolic pulmonary hypertension - assessment by magnetic resonance imaging. *European Radiology*. 2007; 17(1):11–21. [PubMed: 16838142]
7. Qing K, et al. Regional Mapping of Gas Uptake by Blood and Tissue in the Human Lung Using Hyperpolarized Xenon-129 MRI. *Journal of Magnetic Resonance Imaging*. 2014; 39(2):346–359. [PubMed: 23681559]
8. Mugler, JP, , et al. *Proc Intl Soc Mag Reson Med*. Honolulu, HI: 2009. T2* for Hyperpolarized Xe129 in the Healthy Human Lung at 1.5T and 3T.
9. Kaushik SS, et al. Single-breath clinical imaging of hyperpolarized (^{129}Xe) in the airspaces, barrier, and red blood cells using an interleaved 3D radial 1-point Dixon acquisition. *Magn Reson Med*. 2016; 75(4):1434–43. [PubMed: 25980630]
10. Driehuys B, et al. High-volume production of laser-polarized Xe-129. *Applied Physics Letters*. 1996; 69(12):1668–1670.
11. He M, et al. Dose and pulse sequence considerations for hyperpolarized (^{129}Xe) ventilation MRI. *Magn Reson Imaging*. 2015; 33(7):877–85. [PubMed: 25936684]
12. Kaushik SS, et al. Measuring diffusion limitation with a perfusion-limited gas--hyperpolarized ^{129}Xe gas-transfer spectroscopy in patients with idiopathic pulmonary fibrosis. *J Appl Physiol* (1985). 2014; 117(6):577–85. [PubMed: 25038105]
13. Robertson SH, et al. Uncovering a third dissolved-phase (^{129}Xe) resonance in the human lung: Quantifying spectroscopic features in healthy subjects and patients with idiopathic pulmonary fibrosis. *Magn Reson Med*. 2017; 78(4):1306–1315. [PubMed: 28940334]
14. Lerner EE. Uniform distribution of sequences generated by iterated polynomials. *Doklady Mathematics*. 2015; 92(3):704–706.
15. Kuipers L, Uchiyama S. Notes on Uniform Distribution of Sequences of Integers. *Proceedings of the Japan Academy*. 1968; 44(7):608–&.
16. Robertson SH, et al. Optimizing 3D noncartesian gridding reconstruction for hyperpolarized ^{129}Xe MRI—focus on preclinical applications. *Concepts Magn Reson Part A*. 2015; 44(4):190–202.
17. He M, et al. Using Hyperpolarized ^{129}Xe MRI to Quantify the Pulmonary Ventilation Distribution. *Acad Radiol*. 2016; 23(12):1521–1531. [PubMed: 27617823]

18. He M, et al. Extending semiautomatic ventilation defect analysis for hyperpolarized (129)Xe ventilation MRI. *Acad Radiol.* 2014; 21(12):1530–41. [PubMed: 25262951]
19. Xu X, et al. Hyperpolarized 129Xe gas lung MRI-SNR and T2* comparisons at 1.5 T and 3 T. *Magn Reson Med.* 2012; 68(6):1900–4. [PubMed: 22294386]
20. Theilmann RJ, et al. Quantitative MRI measurement of lung density must account for the change in T(2) (*) with lung inflation. *J Magn Reson Imaging.* 2009; 30(3):527–34. [PubMed: 19630079]
21. Cleveland ZI, et al. 3D MRI of impaired hyperpolarized 129Xe uptake in a rat model of pulmonary fibrosis. *NMR Biomed.* 2014; 27(12):1502–14. [PubMed: 24816478]
22. Glover GH, Pauly JM, Bradshaw KM. Boron-11 imaging with a three-dimensional reconstruction method. *J Magn Reson Imaging.* 1992; 2(1):47–52. [PubMed: 1623280]
23. Leung G, et al. Radiofrequency pulse design for the selective excitation of dissolved 129Xe. *Magn Reson Med.* 2015; 73(1):21–30. [PubMed: 24395490]
24. Kammerman, J, , et al. *Proc Intl Soc Mag Reson Med.* Honolulu, HI: 2017. Dissolved Phase Hyperpolarized Xenon-129 Pulmonary Imaging in the Presence of Gaseous Xenon Signal.

Figure 1.

(a). The 3D radial sequence consists of 1000 interleaved radial acquisitions each of the gas and dissolved distributions, followed by a single dissolved-phase spectrum. (b). The radial rays are deployed in temporally random order, with end-points that follow an Archimedean spiral distribution upon completion of the acquisition.

Figure 2.

(a). Off-resonance gas excitation vs. pulse duration from gas-phase ^{129}Xe in a bag. (b). *In-vivo* off-resonance gas excitation vs. pulse duration. (c). Representative dissolved-phase spectra of one healthy subject with optimum 0.69 ms pulse duration and one healthy subject with non-optimal 0.64 ms pulse duration.

Figure 3.
(a). The representative ^{129}Xe spectrum for a healthy subject at 3 Tesla (Magnitude View).
(b). The average dissolved-phase spectroscopic line-shape parameters with phase shift removed for the 7 healthy volunteers.

Figure 4.

(a). Interleaved dissolved and gas FIDs (starting from the 50th gas FID). (b). Magnetization decay over course of acquiring the 1000 gas and dissolved FIDs. (c). Dixon-based dissolved signal decomposition and representative raw ventilation(gas), barrier and RBC images from a healthy subject before and after B₀ correction

Figure 5.

Representative ventilation, barrier uptake and RBC transfer maps of a healthy subject as well as patients with COPD, IPF, NSCLC having undergone RT, PAH and CTEPH. The fractions of voxels falling in the lowest bin (defect/red), second lowest bin (low/orange), and the highest 2 bins (high) are reported for each map for each patient.

Figure 6. Representative ratio maps of the alpha-1 antitrypsin mutation carrier (heterozygote) acquired 21 months apart on both a 1.5 Tesla GE scanner and a 3 Tesla Siemens system, show good consistency across platforms and field strengths.