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Dose and Pulse Sequence Considerations for Hyperpolarized ^{129}Xe Ventilation MRI

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Abstract

Purpose—The aim of this study was to evaluate the effect of hyperpolarized ^{129}Xe dose on image signal-to-noise ratio (SNR) and ventilation defect conspicuity on both multi-slice gradient echo and isotropic 3D-radially acquired ventilation MRI.

Materials and Methods—Ten non-smoking older subjects (ages 60.8 ± 7.9 years) underwent hyperpolarized (HP) ^{129}Xe ventilation MRI using both GRE and 3D-radial acquisitions, each tested using a 71 ml (high) and 24 ml (low) dose equivalent (DE) of fully polarized, fully enriched ^{129}Xe . For all images SNR and ventilation defect percentage (VDP) was calculated.

Results—Normalized SNR (SNR_n), obtained by dividing SNR by voxel volume and dose was higher for high-DE GRE acquisitions ($\text{SNR}_n = 1.9 \pm 0.8 \text{ ml}^{-2}$) than low-DE GRE scans ($\text{SNR}_n = 0.8 \pm 0.2 \text{ ml}^{-2}$). Radially acquired images exhibited a more consistent, albeit lower SNR_n (High-DE: $\text{SNR}_n = 0.5 \pm 0.1 \text{ ml}^{-2}$, low-DE: $\text{SNR}_n = 0.5 \pm 0.2 \text{ ml}^{-2}$). VDP was indistinguishable across all scans.

Conclusions—These results suggest images acquired using the high-DE GRE sequence provided the highest SNR_n , which was in agreement with previous reports in the literature. 3D-radial images had lower SNR_n , but have advantages for visual display, monitoring magnetization dynamics, and visualizing physiological gradients. By evaluating normalized SNR in the context

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of dose-equivalent formalism, it should be possible to predict ^{129}Xe dose requirements and quantify the benefits of more efficient transmit/receive coils, field strengths, and pulse sequences.

Keywords

Hyperpolarized ^{129}Xe MRI; signal-to-noise ratio; sequence

1. Introduction

Hyperpolarized (HP) ^{129}Xe has proven capable of sustaining the progress in pulmonary functional MRI, previously introduced using ^3He . ^{129}Xe ventilation images to date have used up to 1 liter of isotopically enriched ($\sim 80\%$ ^{129}Xe) gas (1-3). However, the cost of enriched gas is significant (around \$150-300/liter) and larger volumes of xenon take longer to polarize, thereby reducing exam throughput and efficiency. Although the rate at which HP ^{129}Xe can be produced continues to increase (4), the ^{129}Xe clinical exam must be made more efficient and cost-effective by employing the smallest possible ^{129}Xe volumes and extracting maximal information from each dose. However, the way in which ^{129}Xe dose affects image SNR and ability to quantify regional ventilation distribution is not yet well studied.

A second important factor impacting image quality is the pulse sequence used to acquire the data. To date, the bulk of published HP gas MR studies have employed multi-slice fast gradient recalled echo (GRE) imaging. This sequence has the advantage of being fast, robust, readily implemented, and reconstructed directly on the scanner platform. However, breath-hold imaging of HP gases faces unique challenges that may ultimately favor a different data acquisition approach. For example, radial imaging has emerged as the method of choice to image dissolved phase ^{129}Xe , since the shorter echo time overcomes the short T_2^* (~ 2 ms) of ^{129}Xe in pulmonary tissues and blood (5). Such a short TE may be advantageous even for gas-phase ^{129}Xe MRI, where susceptibility effects from the ribs can appear as ventilation defects in GRE images. Moreover, radial imaging typically samples the center of k-space immediately after each RF pulse, thereby enabling the decay of ^{129}Xe magnetization to be tracked throughout the acquisition (6). This may permit correction for the inherent signal decay that is present in all hyperpolarized MRI (7). Although 3D radial acquisition, in principle, requires π more views of k-space than Cartesian imaging, the sequence is remarkably robust to undersampling (8,9). Thus, in practice, fully isotropic 3D image data can be undersampled $10\times$ to reduce breath-hold durations or be reconstructed with retrospective accounting for premature exhalation (10). Additionally, such acquisitions are isotropic and have no artificial intensity weighting imposed by the order of slice acquisition. This may prove increasingly important for revealing the gravitational gradients inherently present in lung function (5). Thus, a truly 3D isotropic acquisition not only effectively visualizes ventilation defects, but also more faithfully represents slowly varying functional gradients versus multi-slice approaches that confer slice order-dependent artifacts due to RF and T_1 decay.

The aim of this study was to evaluate the influence of both the acquisition strategy and ^{129}Xe dose on SNR and the ability to quantify inhaled hyperpolarized ^{129}Xe lung MRI. We hypothesized that image SNR should scale with the inhaled ^{129}Xe dose (polarization,

volume, enrichment) and voxel volume. We further expected that regardless of which pulse sequence was used for acquisition, that for a given bandwidth, SNR normalized by dose and voxel volume (SNR_n) would be a constant. To test this, we acquired ^{129}Xe ventilation images in all subjects using both a multi-slice gradient recalled echo (GRE) and 3D-radial sequence, at high and low ^{129}Xe doses, differing by $3\times$ in their ^{129}Xe magnetization. For lower doses, images were acquired with commensurately larger voxel volumes in an effort to retain approximately equal SNR. As a secondary objective, we sought to evaluate the ability of each sequence and dose to detect ventilation defects in healthy non-smoking subjects over the age of 50. This population was expected to exhibit subtle ventilation defects, based on previous studies showing that ventilation defects increase with age (1, 11).

2. Materials and methods

2.1. Subject Inclusion Criteria

Studies were conducted under a protocol approved by the Institutional Review Board, and subject to an FDA Investigational New Drug application. A total of 10 non-smoking (< 5 pack-yrs) older volunteers (6 males, 4 females; mean age = 60.8 ± 7.9 yrs) were enrolled. All subjects provided written informed consent.

2.2. ^{129}Xe Polarization and Delivery

1-L and 300-ml volumes of isotopically enriched xenon (86% ^{129}Xe , Spectra Gases Inc., Alpha, NJ) were hyperpolarized by rubidium vapor spin-exchange optical pumping, cryogenically accumulated using a prototype commercial polarizer (GE Model 9800; Durham, NC), and thawed into 1-L ALTEF bags (Jensen Inert Products, Coral Springs, FL). The 300-ml volumes were diluted using 700-ml of commercial N_2 . ^{129}Xe polarization was determined using a calibrated polarization measurement station with $\pm 5\%$ relative accuracy (Polarean Inc., Durham, NC). The mean ($\pm \text{SD}$) polarization achieved for the two volumes of isotopically enriched ^{129}Xe in this study was $8.3 \pm 1.3\%$ for the 1-liter studies, and $9.3 \pm 2.4\%$ for the 300-ml studies. For convenience, we express these as dose equivalent (DE) volumes of 100% polarized, 100% isotopically enriched ^{129}Xe calculated as follows

$$DE = f_{129} \times P_{129} \times V_{Xe} \quad (1)$$

where f_{129} is the isotopic fraction of ^{129}Xe , P_{129} is the ^{129}Xe nuclear spin polarization and, V_{Xe} is the xenon volume. (Note this is similar to the concept of fully polarized spins that was introduced by Coffey et al (12). Calculated in this manner, subjects received dose-equivalent (DE) volumes of 71 ± 11 ml representing the high dose, and 24 ± 6 ml for low doses. Prior to imaging, subjects were instructed to twice inhale fully and exhale to functional residual capacity (FRC), and then to inhale the gas from the bag through a 6-mm ID Tygon tube. Subjects held their breath for the duration of the MR acquisition, which ranged from 8–15 seconds. All subjects received 4 doses of HP ^{129}Xe plus an additional 15 ml DE for transmitter gain calibration.

2.3. Image Acquisition

All MR scans were performed on a 1.5 T GE Healthcare EXCITE 15M4 MR system. Subjects were fitted with a flexible chest coil (Clinical MR Solutions, Brookfield, WI) that was tuned to the 17.66 MHz ^{129}Xe frequency and proton-blocked to permit anatomical scans to be acquired with the ^1H body coil. After the initial localizers and proton thoracic cavity scans (described below), subjects underwent ^{129}Xe ventilation MRI in the following order: GRE with DE = 71 ml, 3D radial with DE = 71 ml, GRE with DE = 24 ml, and 3D radial with DE = 24 ml. Scans were performed in the supine position and subjects were coached to inhale the gas doses from functional residual capacity (FRC).

GRE images were acquired with parameters (71 ml/24 ml DE): field of view (FOV) = 40/48 cm, matrix = $128 \times (90-128)/64 \times 64$, slice thickness = 12.5 mm, bandwidth (BW) = 8.3 kHz, flip angle = 7-10°, repetition time (TR)/echo time (TE) = 8.1/1.9 ms. The ^{129}Xe GRE ventilation images were analyzed in the context of a thoracic cavity image acquired using a breath-hold ^1H steady state free precession (SSFP) imaging sequence using the scanner's body coil. With subjects in the same position as for ^{129}Xe MRI, ^1H images were acquired with FOV = 40 cm, matrix = 192×192 , slice thickness = 12.5 mm, flip angle = 45°, TR/TE = 2.8/1.2 ms, and BW = 125 kHz.

For 3D-radial imaging, parameters were (71 ml/24 ml DE): FOV = 36/48 cm, matrix = 64^3 , radial views = 4601, flip angle = 1.2°, TR/TE = 3.3/0.376 ms, BW = 15.63 kHz. To facilitate analysis of the 3D radial ^{129}Xe images, a thoracic cavity image was acquired using a 4-minute, free-breathing, un-gated 3D radial ^1H scan, again using the body coil. The thoracic cavity images were acquired with parameters: FOV = 36 cm, matrix = 128^3 , TR/TE = 3/0.24 ms, radial views = 80,001, BW = 62.5 kHz, flip angle = 15°.

Ventilation images acquired using the GRE sequence were reconstructed directly on the scanner using the default Fermi filter and imported as 256×256 DICOM slices for analysis. The 3D radial acquisitions were reconstructed from the raw data using an in-house reconstruction algorithm implemented in MATLAB (The MathWorks Inc., Natick, MA) (13). For these images, no Fermi filter was applied.

2.4. Image Analysis

2.4.1. SNR Assessment—SNR of each image slice was calculated by: $(\bar{S}_{lung} - \bar{S}_{BG}) / Stdev_{BG}$ where $\bar{S}_{lung}$ was the mean signal in the ventilated lung parenchyma, $\bar{S}_{BG}$ the mean background signal and $Stdev_{BG}$ its standard deviation. The mean lung signal for each image slice was calculated from pixels constrained by applying a mask that included only the ventilated lung within the thoracic cavity (see below). Subsequently a $5 \times 5 \text{ cm}^2$ voxel region of interest (ROI) containing only background noise was manually selected for each slice and its mean signal and standard deviation were calculated. Raw SNR was plotted as a function of slice position for each acquisition and average values for the entire image were calculated. Finally, for each image its raw average SNR was divided by voxel volume V_{vox} and ^{129}Xe dose equivalent (DE) to calculate normalized SNR_n according to

$$SNR_n = \frac{SNR}{DE \times V_{vox}} \quad (1)$$

Since both DE and V_{vox} are expressed in units of volume, SNR_n has units of ml^{-2} .

2.4.2. Ventilated Volume and Ventilation Defect Percentage Calculation—All images were analyzed for ventilation defect percentage (VDP) using a corrected linear-binning approach described in (14). First, the 1H thoracic cavity images were registered to the GRE ^{129}Xe images using a multi-resolution affine transform. The free-breathing radial 1H images were registered to the radial ^{129}Xe ventilation images first using a multi-resolution affine transform, followed by a non-rigid landmark-based registration step. Then, the registered 1H thoracic cavity images were segmented to create thoracic cavity masks. These were used to confine the ^{129}Xe image analysis to regions where ventilation is expected. Prior to analysis, ^{129}Xe images were corrected for B_1 inhomogeneity using a bias field correction (15), and then rescaled by the 99th percentile of their cumulative intensity distribution, such that the intensities ranged from 0-1 (14). The rescaling permitted each ^{129}Xe voxel to be classified into one of 4 clusters (<0.2 defect, 0.2-0.4 low intensity, 0.4-0.8 medium intensity, and >0.8 high intensity). The volume of the lowest-intensity cluster (<0.2) relative to that of the thoracic cavity was used to quantify ventilation impairment, otherwise known as ventilation defect percentage (VDP). The remaining clusters within the thoracic cavity were used to calculate SNR.

2.5. Statistical Methods

All statistical analysis was performed using JMP 11 (SAS Institute Inc., Cary, NC). The dependence of SNR on acquisition sequence and ^{129}Xe dose equivalent was determined using linear regression analysis and the Pearson's correlation coefficient (r). The same approach was used to test the dependence of VDP on acquisition sequence and dose. Any systematic deviation between sequences or volumes was further evaluated using Bland-Altman analysis.

3. Results

Ventilation images were successfully acquired using both xenon doses and both pulse sequences in all subjects. A sample dataset from a 65-year-old volunteer with $FEV_1\% = 124\%$ is shown in Figure 1. For this subject, numerous small ventilation defects are clearly visible in all scans as shown by the arrows. Of these scans, the high-DE GRE image exhibited an SNR of 22.5, low-DE GRE had SNR = 18.0, high-DE radial had SNR = 8.1, and low-DE radial had SNR = 7.0. After dividing by voxel volume and DE, the high-DE GRE image exhibited a normalized SNR_n of $2.3\ ml^{-2}$, the low-DE GRE had $SNR_n = 1.2\ ml^{-2}$, high-DE radial had $SNR_n = 0.5\ ml^{-2}$, and low-DE radial had $SNR_n = 0.7\ ml^{-2}$.

3.1. SNR Comparisons

The mean, uncorrected SNR for all subjects obtained at high and low dose for each sequence is plotted in Figure 2a. For high-DE GRE images, mean SNR was 14.7 ± 5.6 , versus 11.3 ± 4.3 for low-DE GRE. For high-DE radial images, mean SNR was 6.9 ± 1.9 versus 6.2 ± 3.2 for the

low-DE radial scans. Similarly, Figure 2b shows SNR_n values that have been normalized by voxel volume and dose equivalent. As was the case for the individual subject shown previously, the high-DE GRE images exhibited the highest SNR_n of $1.9 \pm 0.8 \text{ ml}^{-2}$ compared to $0.8 \pm 0.2 \text{ ml}^{-2}$ for low-DE GRE. Similarly, the high-DE radial images had $\text{SNR}_n = 0.5 \pm 0.1 \text{ ml}^{-2}$ versus $0.5 \pm 0.2 \text{ ml}^{-2}$ for low-DE radial MRI.

3.2. Ventilation Defect Percentage Validation

Additionally, all ventilation images were segmented using linear binning to map each voxel into one of four distinct intensity clusters. Such maps are shown in Figure 3, which were generated using the ^{129}Xe images of the same subject shown in Figure 1. The maps highlight several ventilation defects that are present in this older volunteer. These appear to be similar in extent and location across all binning maps.

The VDP derived from all sequences and doses across groups are shown in Figure 4. The mean VDP was greatest for the high-DE GRE images ($6.4 \pm 2.8\%$), and lowest for the low-DE radial acquisitions ($4.6 \pm 3.2\%$). However, these differences in VDP were not statistically significant. There was a trend towards higher VDP being observed from high-DE compared to low-DE images.

Figure 5 shows the correlations and Bland-Altman plots for VDP derived from the different acquisition sequences and ^{129}Xe DEs. VDP was well-correlated across all acquisitions and doses. Correlations were strongest between different doses within a given acquisition sequence. For the GRE acquisitions, VDP exhibited a correlation of $r = 0.85$ between low- and high-DEs. For the 3D-radial acquisitions VDP exhibited a correlation of $r = 0.97$. For a given dose, the VDP derived via GRE vs. radial acquisition, was somewhat less strongly correlated with $r = 0.80$ and $r = 0.74$ for the high- and low-dose cases, respectively. Testing this further with Bland-Altman analysis showed that neither GRE nor radial images exhibited a significant bias between high- and low-DE scans (0.16 and 0.60 higher defect percentage points respectively). However, some bias was evident in comparing the two acquisition sequences. At high-DE, VDP derived from the GRE acquisition was 1.3 points higher than for the 3D-radial acquisition. Similarly at low-DE, VDP was 1.7 points higher for the GRE vs. 3D-radial acquisition.

4. Discussion

This study sought to evaluate the effects of both dose and acquisition strategy on image SNR and ventilation defect conspicuity. To do so, we have introduced the notion of a dose equivalent that incorporates ^{129}Xe polarization, volume, and enrichment into a single, relatively intuitive metric that can simply be expressed as a volume of 100% polarized, isotopically pure ^{129}Xe . This dose definition, in conjunction with the target voxel volume, allows us to estimate the expected image SNR.

4.1. SNR Assessment

In our study, we found that the conventional spoiled gradient echo image, with centric encoding, obtained at 8 kHz acquisition bandwidth and high DE, provided the highest normalized SNR of all scans ($\text{SNR}_n = 1.9 \pm 0.8 \text{ ml}^{-2}$). It was interesting to note that the low-

DE GRE scan, which was acquired using a 64×64 matrix size to increase voxel volume by 4-fold, nevertheless yielded a more than 2-fold lower normalized SNR_n of $0.8 \pm 0.2 \text{ ml}^{-2}$. It appears that the high degree of interpolation applied by scanner's reconstruction algorithm caused a significant degradation of SNR. Thus, at least for our particular scanner, it would have been preferable to either prescribe a larger FOV and 128×128 matrix, or to have reconstructed the raw data offline using our own algorithms (see below).

The radially acquired images had a more consistent normalized SNR ($\text{SNR}_n = 0.5 \pm 0.1 \text{ ml}^{-2}$ and $0.5 \pm 0.2 \text{ ml}^{-2}$ for high and low-dose acquisitions, respectively), although still significantly lower than for GRE. This is partially attributable to having acquired these scans at twice the bandwidth of the GRE scans to allow more frames to be acquired in the breath-hold. Thus scaling these SNR values by 2 to remove bandwidth differences brings them in line with the low-dose GRE scan, but they remain well below the high-dose GRE value. This partially reflects the challenge of defining true SNR and resolution for radially acquired images. Specifically, when radial images are reconstructed, SNR and resolution are strongly impacted by the convolution kernel sharpness parameter (13). For our reconstructions, kernel parameters were manually tuned by a trained observer to optimize perceived image quality. However, if a sharper kernel had been used, image SNR would have increased, but structural detail would have been lost. We further note that the radial images employed no additional Fermi filter, whereas a Fermi filter with Fermi radius equal to half the matrix size and Fermi width equal to 10 (matrix unit) is applied for the standard GRE image reconstructed on our scanner. Thus, while the radially acquired images have lower SNR, it is interesting to note that they are approaching that of multi-slice GRE.

It is interesting to compare our normalized SNR notion to those that can be calculated from previous literature reports (see Table 1). For example, Xu et al. (16) reported mean SNR of 36, and 44 for ^{129}Xe ventilation MRI at 1.5 T and 3.0 T. They employed a voxel volume of 0.24 ml and an estimated DE ~ 0.36 ml. This suggests that they achieved an SNR_n of 4.2 ml^{-2} at 1.5 T, and 5.0 ml^{-2} at 3.0 T. Even after accounting for their use of a lower 4 kHz bandwidth, their normalized SNR values are 50-86% higher than those we report here. One possible difference may be that Xu et al. reconstructed their images offline, and therefore may have employed a stronger Fermi filter, or suffered less interpolation noise. Similarly, Svenningsen et al. (17) reported a mean SNR of 22 for ^{129}Xe images scanned with a three-dimensional fast gradient echo sequence with centric phase-encoding ordering at 3.0 T. Their images were acquired with a voxel volume of 0.15 ml, and assuming a mean polarization of 35% employed an estimated DE = 150 ml. This suggests they achieved a voxel- and dose-normalized $\text{SNR}_n = 1.0 \text{ ml}^{-2}$, accounting for their higher bandwidth results in $\text{SNR}_n = 1.3 \text{ ml}^{-2}$, which is reasonably close to our observed value. Thus, although these comparisons of voxel size and DE-normalized SNR were done using only literature-reported values, it is interesting that all values (scaled to 8kHz bandwidth) are within a factor of 2 of what we report, ranging from approximately $1.3 - 3.6 \text{ ml}^{-2}$. This suggests that normalized SNR is a fairly fundamental value and in conjunction with the dose equivalent concept can be used to predict achievable SNR for a given target image resolution. Moreover, such a normalized SNR value may represent a useful benchmark for evaluating image quality (18,19) at lower field strengths (20,21), or more efficient hardware and pulse sequences,

such as interleaved spiral (22) and steady-state free-precession methods (23,24) that may extract more SNR from a given dose.

To gauge the practicality of these imaging studies with the dose ranges we report here, it is further useful to consider the DE production rates for ^{129}Xe hyperpolarizers that have been reported in the literature. These are shown in Table 2 and range from approximately 40 ml/hr to 240 ml/hr. It is clear that all systems are capable of producing one or more low dose volumes per hour, and many are capable of producing one or more high-dose volumes per hour. Furthermore, the more recently reported systems are exhibiting an ever-increasing trend towards higher polarization levels, which allow smaller volumes of xenon or even potentially naturally abundant xenon to be used (25).

4.2. Effects on Ventilation Defect Percentage Calculations

In this study of older, healthy non-smoking volunteers, subtle ventilation defects appeared to be effectively visualized using both GRE and isotropic 3D-radial acquisitions at both high and low ^{129}Xe dose equivalents. As illustrated in Figure 1, most of the subtle defects could be visualized on all 4 scans. While all images in this study were successfully quantified using a linear-binning-derived VDP metric, no statistically significant differences were found between scans or DEs. Moreover, within a given acquisition strategy, the VDP derived from low-DE vs. high-DE ^{129}Xe MRI was extremely well correlated ($r=0.85$ for GRE and $r=0.97$ for 3D-radial). This suggests that it may be possible to adequately resolve ventilation defects in these older subjects using the lower ^{129}Xe dose.

4.3. Potential Advantages of Radial vs. GRE MRI

Although to date, SNR achieved by radial imaging lags behind that achieved by conventional GRE, there continue to be reasons to pursue this approach. The first is seen in the way the 3D-radial acquisition exhibits SNR that increases in the anterior to posterior directions. Such variation is attributable to physiological factors that drive greater ventilation in the gravitationally dependent lung (5,34,35). However, this slope was much smaller or even presented as a descending trend in the GRE acquisition (Figure 6). This is likely because GRE images were acquired from the anterior-to-posterior slice order, which attenuates the true signal enhancement in the better-ventilated posterior slices because they experience greater T1 and RF decay before being encoded (16,34). By contrast the 3D-radial acquisition is a truly 3D scan that preserves the physiologically dictated SNR distribution. Hence, if fundamental physiology is of interest, a truly 3-dimensional acquisition is preferred to a multi-slice one.

Perhaps the most relevant advantage of a 3D-radial vs. a Cartesian acquisition is illustrated in Figure 7. In a high-DE 3D-radial acquisition of one subject, the reconstructed image appeared to show two diaphragm borders near the right basal lung. We hypothesized that the artifact was caused by partial exhalation during the scan. Because the radial image was acquired with randomized views, it was possible to reconstruct the images in arbitrary time and k-space increments. By reconstructing multiple subsets of data, it was revealed that the lung position changed at approximately 1400 frames (4.6 seconds) into the scan (Figure 7c). Thus, by discarding the first 1400 frames and reconstructing only the frames obtained after

the change in diaphragm position, the artifact was removed, and the image quality became suitable for quantitative analysis.

4.4. Study Limitations

The study did have some limitations. First, we note that the GRE images were reconstructed directly on the scanner. Those acquired at low DE, used only a 64×64 matrix size for the acquisition, which appeared to introduce significant interpolation artifacts that reduced the normalized SNR relative to expectations. A more ideal comparison might have been made if the images had been reconstructed offline. Second, a more ideal way to test the effect of dose equivalent could have been to acquire the identical scan at a broad range of doses and establish the SNR to DE correlation by linear regression. Here, instead, each image was acquired with fairly equivalent ^{129}Xe doses, thus preventing meaningful linear regression. We further note that our notion of normalized SNR assumes that it depends only on dose equivalent and voxel volume. Clearly, there must also be some dependence on subject lung volume and maneuver of inhalation. Subjects with a larger lung volume might be expected to dilute the available dose to a greater extent than those with smaller lung volumes. However, we were unable to uncover any systematic relationship between the subject's lung capacity and SNR. Finally, in comparing SNR from different scans, we also point out that the scan order was not randomized. Hence, it is conceivable that some systematic bias was introduced by acquiring all data for each subject in the same order.

Similarly, while our data seem to suggest that lower ^{129}Xe dose equivalents may be equally useful for detecting subtle age-related defects, this is also subject to limitations. The most significant is the assumption that ventilation distribution was identical over each dose the subject inhaled. This assumption may not be entirely valid, as shown in the example of Figure 1 where one defect is only visible on the initial high-DE GRE scan, but not on subsequent scans. This could have been the result of a small region of atelectasis that opened up after subsequent inhalations. However, this was a rather subtle change, and prior studies of short-term reproducibility indicate that ventilation defects are relatively stable during a given MRI session (36,37). Second, while ventilation defect percentage (VDP) has become the most widely used metric of regional ventilation, it does not capture all elements of pulmonary ventilation. Hence, it is possible that if these scans were compared with different metrics than the ones used here, the differences could be more significant. Third, the thoracic cavity and ventilation images were obtained during different breath-holds, or in the case of radial images, during free breathing. This introduces the necessary step of image registration, which can introduce error into the analysis. In this work, we found it especially challenging to register the free-breathing UTE images to the breath-held ^{129}Xe MR images. We have since transitioned to using a lower-resolution, breath-held radial image to delineate the thoracic cavity. However, recent work by Johnson et al. (38), suggests improved free-breathing UTE sequences are on the horizon. We note that even breath-held images pose challenges in registration, as diaphragm position can be significantly different during a self-directed breath-hold of room air vs. inhalation from a 1-liter bag. We have since found it beneficial to collect breath-hold anatomical images after subjects inhale air from a 1-liter bag rather than a self-directed breath-hold. Alternatively, there may be benefit to simultaneously acquiring the ^1H thoracic cavity image and the HP gas ventilation image

within a single breath-hold, as described by Wild et al.(39). Such an approach should largely obviate the need for registration, or at least greatly reduce the degree of image warping required.

5. Conclusion

We have tested the effect of both acquisition strategy and ^{129}Xe dose on image SNR and ventilation defect calculations. To do so, we have introduced the notion of a ^{129}Xe dose equivalent that incorporates volume, polarization, and isotopic enrichment into a single metric expressed simply as the equivalent volume of 100% enriched, 100% polarized ^{129}Xe . This approach has allowed us to estimate that for our scanner configuration and similar ones from the literature, the SNR one can expect from a conventional spoiled gradient echo ventilation scan is on order $\sim 2 \text{ ml}^{-2}$. Thus, for example, to obtain an image SNR of 15 for a voxel volume of 0.25 ml, an equivalent ^{129}Xe dose of approximately 30 ml is required. Such a dose can be produced, for example using 250 ml of 86% enriched ^{129}Xe , polarized to 14%. Alternatively, one could employ 500 ml of xenon at natural abundance (26% ^{129}Xe) polarized to 23%. Both are well within reach of emerging polarizer technology (40). Of course, as pulse sequences and transmit/receive coil technology improves, dose efficiency will increase, and smaller volumes of xenon can be used. It would not be unreasonable to expect that normalized SNR_n could increase from 2 ml^{-2} today to values of 5 ml^{-2} with further development.

Finally, even though 3D-radial scans exhibited a lower image quality compared to GRE scans, they provide isotropic resolution that allows any slice plane to be visualized, the ability to monitor magnetization dynamics, better visualization of physiological gradients, and the ability to reconstruct different temporal windows of the same acquisition. However, in spite of the advantages afforded by 3D-radial acquisition, further work is required to improve SNR performance. In short, the future looks promising for developing an efficient and integrated ^1H and ^{129}Xe radial imaging exam that can readily yield quantitative maps of regional ventilation. When complemented with emerging images of ^{129}Xe gas exchange (41), this moves us towards a fully isotropic and comprehensive exam of regional pulmonary function.

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Figure 1. Representative ^1H SSFP and free-breathing 3D-radial ^1H anatomical images as well as ^{129}Xe ventilation images acquired with low and high ^{129}Xe dose equivalents using both multi-slice GRE and 3D radial sequences. Features that appear similar across different images are indicated by arrows.

Figure 2.

a) SNR for ventilation images acquired using GRE and radial sequences at high and low dose. b) SNR normalized by voxel volume and dose equivalent polarization.

Figure 3.

Representative ^{129}Xe ventilation images and associated linear-binning maps for high- and low-dose equivalent images acquired with each acquisition. Note, the 3D-radial acquisition is isotropic and can be reformatted in any view plane. Features that appear similar across different images and binning maps are indicated by arrows.

Figure 4.

Comparison of ventilation defect percentage (VDP) derived from both sequences at both high and low ^{129}Xe dose equivalents. No statistically significant differences were observed across any acquisitions. The GRE images, however, tended to exhibit higher VDP than 3D-radial, and high-dose equivalent images tended to have higher VDP than low-dose equivalent. Error bars represent standard error about the mean.

Figure 5. Correlations and Bland-Altman plots of the VDP generated with different acquisition sequences and with different ^{129}Xe dose-equivalents.

Figure 6.

Comparison of the SNR variation from the anterior-to-posterior slice positions for both GRE and 3D-radial acquisitions.

Figure 7.

Possible benefits of 3D-radial acquisition illustrated in subject with changing right-lung volume. (a) Multi-slice GRE reference image showing homogeneous distribution. (b) 3D-radial ^{129}Xe ventilation image shows a false lung border caused by probable motion in the right basal lung during acquisition. (c) 3D-radial image reconstructed 700 frames (2.3 seconds) at a time showing that the right lung position changed around frame 1400 (4.6 seconds). (d) This artifact of diaphragm movement was corrected by reconstructing only frames 1401 to 4601 (4.6-15.2 seconds).

Table 1
Parameters and SNR summary for hyperpolarized ^{129}Xe MRI at different sites

	Current Work	Xu (16)	Xu (16)	Svenningsen (17)
<i>Scanner</i>	GE	GE	GE	GE
<i>Field strength (T)</i>	1.5	1.5	3	3
<i>Coil</i>	Chest coil	Twin Helmh transmit-receive coil	oltz quadrature receive coil	Quadrature asymmetric birdcage coil
<i>Voxel volume (ml)</i>	0.12	0.24	0.24	0.15
<i>BW (kHz)</i>	8.25	4	4	15.63
<i>Phase encoding</i>	Centric	Centric	Centric	Centric
<i>Flip angle</i>	7-10	9	9	Variable
<i>Xenon volume (ml)</i>	1000	300	300	500
<i>Polarization (%)</i>	8	14	14	10-60
<i>Enrichment</i>	86%	86%	86%	86%
<i>DE (ml)</i>	71	36	36	150
<i>SNR</i>	14	36	44	22
<i>Offline Recon (Y/N)</i>	N	Y	Y	N
<i>SNR (ml⁻²)</i>	1.9	4.2	5.0	1.0
<i>SNR_n (8.25kHz) (ml⁻²)</i>	1.9	2.9	3.5	1.3

Table 2
Polarization, xenon flow rate and maximum DE production rate for polarizer designs as reported in the literature

Polarizer	Laser Power	Polarization	Xe Flow Rate (ml/hr)	DE Rate (ml/hr)**
Driehuys, 1996 (26)	140 W	5%	1000 ml/hr	50
Rosen, 1999 (27)	30 W	7.5%	1884 ml/hr	141
Zook, 2002 (28)	>150 W	67%	150 ml/hr	111
Zook, 2002 (28)	210 W	12%	1000 ml/hr	40
Ruset, 2006 (29)	90 W	64%	300 ml/hr	192
Hersman 2008 (4)	90W	64%	300 ml/hr	192
Schrank, 2009 (30)	60W	84%	60 ml/hr	50
Schrank, 2009 (30)	30 W	20%	600 ml/hr	120
Norquay, 2013 (31)	25 W	12%	540 ml/hr	65
Korchak, 2013 (32)	75 W	40%	97 ml/hr	39
Korchak, 2013 (32)	75 W	25%	390 ml/hr	98
Nikolaou, 2014 (33)	170W	83%	130 ml/hr	108
Nikolaou, 2014 (33)	170W	64%	230 ml/hr	147
GE 9800 (this work)	100 W	8%	1000 ml/hr	80
Polarean 9800	60 W	12%	1000 ml/hr	120
Polarean 9810	60 W	24%	1000 ml/hr	240

** DE rate assuming 100% isotopically enriched ^{129}Xe .