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Assessment of Flip Angle – TR Equivalence for Standardized Dissolved-Phase Imaging of the Lung with Hyperpolarized ^{129}Xe MRI

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Abstract

Purpose—To investigate the feasibility of describing the impact of any flip angle - repetition time (TR) combination on the resulting distribution of the hyperpolarized xenon-129 (HXe) dissolved-phase magnetization in the chest using a single virtual parameter, $\text{TR}_{90^\circ, \text{equiv}}$.

Methods—HXe MRI scans with simultaneous gas- (GP) and dissolved-phase (DP) excitation were performed using 2D projection scans in mechanically ventilated rabbits. Measurements with DP flip angles ranging from 6–90° and TRs ranging from 8.3–500 ms were conducted. DP maps based on acquisitions of similar radio frequency pulse-induced relaxation rates were compared.

Results—The observed distribution of the DP magnetization was strongly affected by acquisition flip angle and TR. However, for flip angles up to 60°, measurements with the same radio frequency pulse-induced relaxation rates resulted in very similar DP images despite the presence of significant macroscopic gas transport processes. For flip angles approaching 90°, the downstream signal component decreased noticeably relative to acquisitions with lower flip angles. Nevertheless, the total DP signal continued to follow an empirically verified conversion equation over the entire investigated parameter range, which yields the equivalent TR of a hypothetical 90° measurement for any experimental flip angle - TR combination.

Conclusion—We have introduced a method for converting the flip angle and TR of a given HXe DP measurement to a standardized metric based on the virtual quantity, $\text{TR}_{90^\circ, \text{equiv}}$, using their equivalent RF relaxation rates. This conversion permits the comparison of measurements obtained with different pulse sequence types, or by different research groups using various acquisition parameters.

Keywords

Hyperpolarized xenon-129; dissolved-phase imaging; lung MRI; flip angle - TR equivalence

Introduction

Hyperpolarized xenon-129 (HXe) MR imaging and spectroscopy provides a large and growing arsenal of techniques that offer unique insights into pulmonary ventilation (1–6), gas exchange (7–13) and transport (14–17). In particular, MR measurements of xenon within the lung tissue, the so-called dissolved phase (DP), are emerging as a valuable tool for characterizing lung function at the microscopic level (18–29), complimenting conventional diagnostic tools currently in clinical use such as pulmonary function tests (PFT), computed tomography (CT) and positron-emission tomography (PET). Nevertheless, as an important step toward a more wide-spread acceptance of HXe MRI, the possibility of standardizing derived functional quantities independent of specific MR acquisition parameters needs to be addressed to allow for a better comparison of measurement results between research sites and across subject cohorts.

As xenon gas enters the alveoli, it rapidly dissolves in the lung parenchyma and blood, giving rise to multiple additional resonances (30) approximately 200 ppm removed from the xenon gas-phase (GP) resonance at 0 ppm. However, unlike GP imaging during a breath hold, DP imaging is impacted by highly dynamic processes as the DP xenon in the blood is transported by the pulmonary circulation from the gas-exchange sites to the left side of the heart (20,22) and subsequently distributed throughout the body. The rate constants of the underlying gas-exchange and transport processes are affected by numerous physiological parameters such as the alveolar surface-to-volume ratio, the composition and thickness of the septal walls, capillary blood volume and transit time, etc (15,21,31). Consequently, pathophysiological abnormalities in lung function are potentially detectable through a host of measurable HXe DP quantities.

It is important to stress that HXe DP imaging does not depict the xenon concentration in the lung tissue, but rather the distribution of xenon magnetization, which is primarily controlled by the specifics of the pulse sequence. For instance, acquisitions with a high DP flip angle or a short repetition time (TR) are weighted towards the gas exchange rate and the volume of the alveolar tissue compartments in which xenon dissolves. Pulse sequences that use low DP flip angles or long TRs, on the other hand, saturate the DP magnetization more slowly and allow for prolonged tissue accumulation, thereby adding a gas transport component to the distribution of the DP magnetization. Since the HXe signal amplitude itself is not quantitatively meaningful, it is usually reported as the ratio of a DP resonance and the GP resonance, or as the ratio of two DP resonances. However, since the DP signal is highly dependent on the flip angle and the TR of the pulse sequence employed, these measured ratios are as well. As a result, HXe DP studies conducted with different pulse sequence types or parameters are not generally comparable. Additionally, while images and spectra acquired with a 90° DP flip angle accurately represent the extent of xenon dissolution and transport in

a single TR, this intuitive quantitative interpretation is not readily available for any other flip angle – TR combination.

In this work, the distribution of DP magnetization in the lungs of healthy rabbits was investigated as a function of DP flip angle and TR. The resulting images were studied with the goal of verifying whether different flip angle – TR combinations result in similar DP signal distributions when an equivalent RF pulse-induced relaxation rate is maintained. Finally, an empirically-verified conversion function is proposed to obtain the standardized TR value of a hypothetically-equivalent measurement with a 90° DP excitation flip angle ($TR_{90^\circ, \text{equiv}}$) for any flip angle – TR combinations.

Methods

Animal Studies

Experiments were performed using four New Zealand rabbits (3.5 – 4.5 kg each). 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. Following 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); blood pressure was stabilized by an infusion of saline, 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 during image acquisition before ventilation with room air was resumed.

HXe Data Acquisition

In each rabbit, the global RF excitation flip angle was calibrated during an initial 5 s breath hold, during which 32 xenon spectra were acquired. The TR for the first 16 acquisitions was set to 100 ms, and was extended to 200 ms for the second 16 acquisitions. Exponential decay functions were fitted to the integral of the GP amplitude in the phased, real spectra of both sets to extract the fractional signal decrease $f_{S,i}$ during each TR_i, where i signifies either the first or second set of 16 acquisitions. Although the T1 in the xenon GP slowly increases over the course of the breath hold due to continuous oxygen uptake by the lung, the effect is very small and was assumed to have negligible impact on the calibration. Therefore, the T1-corrected flip angle was calculated based on the fitted data by assuming $f_{S,i}$ to be:

$$f_{S,i} = \cos(\alpha) e^{-TR_i/T1}, \quad [1]$$

where α is the applied flip angle. Hence,

$$T1 = \frac{TR_2 - TR_1}{\ln(f_{S,1}/f_{S,2})}, \quad [2]$$

$$\alpha = \arccos \left(\frac{f_{S,1}}{e^{-TR_1/T1}} \right).$$

The ratio between the nominal and the measured flip angle was used to set the reference voltage for all subsequent studies.

At 1.5 T, all DP xenon resonances in the rabbit lung are contained in a narrow frequency region of approximately 70 Hz (~ 4 ppm) separated from the GP resonance by approximately 200 ppm. To image these two frequency bands individually, we implemented a 2D projection acquisition similar to the one previously described in detail (19). Briefly, the pulse sequence is based on a standard RF-spoiled gradient echo sequence with a non-selective 700-μs Gaussian RF excitation pulse centered 200 ppm downfield from the gas resonance that predominantly excites the DP region. However, the RF pulse was sufficiently short to excite the GP resonance as well, albeit with an effective flip angle 40 times lower than at the DP resonance. This scaling relationship was established using a 1D calibration version (i.e. without phase encoding) of the imaging pulse sequence with the parameters described below, which measured each k-space line twice in an interleaved fashion: once with a 40° excitation pulse centered at the DP resonance, and once with a 2° excitation flip angle centered at the GP resonance. The GP signal for the 2° GP excitation averaged over all k-space lines was approximately twice as large as for the 40° DP excitation.

To destroy any DP magnetization taken up prior to the data collection and thereby achieve a steady state condition for the DP signal, the sequence was first preceded by two 2-ms Gaussian RF saturation pulses. Next, a series of 700- μ s Gaussian RF excitation pulses was applied for 1.5 s using the same TR as the image acquisition. All preparatory RF pulses were also centered at 200 ppm. The sampling was 65% asymmetric with a bandwidth of 110 Hz, which at the main field strength of 1.5 T and a gyromagnetic ratio for xenon-129 of 11.78 MHz/T yielded a 32-pixel separation between the GP and DP images in the readout direction. Other sequence parameters included: matrix size 28–36 $\times$ 80 (interpolated to 112–144 $\times$ 320); TE 2.6 ms; FOV 220–238 mm. To investigate the distribution dynamics of the DP magnetization, 3 sets of studies were conducted: 1) DP flip angle 90°, TR 20–500 ms; 2) TR 100 ms, DP flip angle 12–90°; 3) DP flip angle 10–90°, TR 50–400 ms. Up to 24 images were acquired consecutively during each breath hold using identical imaging parameters.

The xenon DP signal S_{DP} at any given location $\mathbf{r}$ is affected by numerous physiological factors and MRI acquisition parameters. At time t_{90° , following an ideal 90° RF pulse that saturates all DP magnetization, S_{DP} can generally be written as

$$S_{DP}(\mathbf{r}, t_{90^\circ}) \propto f(c(\mathbf{r}, t_{90^\circ}), T1_{DP}) e^{-R_{RF}(\alpha, TR)t_{90^\circ}} . \quad [3]$$

The function f describes the pulse sequence-independent temporal evolution of the DP magnetization, which is dependent on the local longitudinal xenon magnetization $c(\mathbf{r}, t_{90^\circ})$ and the longitudinal xenon relaxation time constant for the DP compartment $T1_{DP}$. In addition, as the DP magnetization transits from the alveolar gas exchange sites to location $\mathbf{r}$, it is attenuated every TR by an RF pulse with flip angle α equivalent to an RF-induced T1-relaxation rate (R_{RF}). While $c(\mathbf{r}, t_{90^\circ})$ is a complicated function of pulmonary ventilation, gas exchange and transport, and contains information about how much xenon gas reaches $\mathbf{r}$ by time t_{90° , $T1_{DP}$ and R_{RF} determine how much magnetization is available for signal formation. Of these parameters, however, only R_{RF} is under direct user control. To first order, R_{RF} of a gradient-echo pulse sequence can be approximated by (32)

$$R_{RF}(\alpha, TR) = \frac{1 - \cos \alpha}{TR} . \quad [4]$$

To verify whether different flip angle – TR combinations with equal relaxation rates (according to Eq. [4]) result in similar DP magnetization distributions, two studies were conducted with relaxation rates of 0.7 s⁻¹ (DP flip angle/TR 6°/8.3 ms – 30°/192 ms) and 2.6 s⁻¹ (DP flip angle/TR 12°/8.3 ms – 60°/192 ms), respectively. Each study consisted of 9 measurements, with TRs ranging from 8.3 ms to 192 ms. Starting with one average for the longest TR, the number of averages for each measurement was adjusted such that the overall acquisition time and breath hold durations for all TRs were the same. Two of these 9 measurements were conducted with a TR of 192 ms to evaluate the variability of the magnetization distribution for identical acquisition parameters.

Finally, the behavior of the DP magnetization distribution was evaluated empirically by comparing measurements for a DP flip angle of 60° and a TR range of 20–200 ms to those for a DP flip angle of 90° and a TR range of 50–500 ms. The total masked DP signal for these measurements was plotted against TR, and a TR scaling factor that mapped the 60° DP signal to the 90° signal was extracted.

Data Analysis

All image reconstruction, post-processing and data analysis was performed using customized MatLab (Mathworks, Natick, MA, USA) scripts. The asymmetrically sampled k-space data was filled using a Homodyne algorithm (33) before Fourier transform. Each GP-DP image set was normalized by the average signal intensity in the GP image component. Since DP and GP magnetization were excited by the same RF pulse but the RF amplitude at the DP resonance was 40 times higher than at the GP resonance, this normalization factor was flip angle dependent. To correct for this effect when comparing DP maps from acquisitions with different DP flip angles α_{DP} , we re-scaled all the involved DP maps using an additional flip angle correction factor f :

$$f(\alpha_{DP}) = \frac{\sin(\alpha_{GP})}{\sin(\alpha_{DP})}, \quad [5]$$

where α_{GP} is the corresponding GP flip angle. The lung was segmented from the background noise by thresholding.

Absolute difference maps were calculated for the two studies of nine acquisitions each with constant relaxation rates using the measurement with the highest flip angle and longest TR as the reference image. The background in the difference maps was subsequently removed by multiplication with a binary mask derived from the thresholded DP signal, and a numerical difference score (DS) for each difference map was calculated as:

$$DS = \sqrt{\frac{\sum_{i=1}^N (I_i - R_i)^2}{N}}, \quad [6]$$

where i is the i -th pixel in the mask, N is the total number of mask pixels, and I is DP map that the reference DP map R is compared to.

Results

Figure 1 shows the DP signal distributions in 2D coronal projections of a rabbit lung for a DP flip angle of 90° and TRs ranging from 20 to 500 ms (Rabbit #1). The signal intensity was normalized to the average intensity of the corresponding GP maps. This measurement demonstrates how, for a fixed DP flip angle, changes in the TR control the spatial distribution of the DP magnetization in the lung parenchyma, the vasculature, the heart and

beyond. When TR was lengthened, thereby reducing the rate of the applied RF pulses, the DP signal initially increased only in the lung parenchyma. However, for TRs longer than approximately 200 ms, additional DP intensity appeared in the previously empty cardiac cavity, as the large veins and left side of the heart began to fill with xenon-saturated blood. TRs beyond 500 ms were impractical due to a resulting increase in breath hold duration beyond 15 s.

While the frequency with which RF pulses are applied has a strong effect on the DP magnetization, so does the fraction of DP magnetization that is saturated by each pulse. As illustrated in Fig. 2 (Rabbit #2), a DP signal behavior similar to that shown in Fig. 1 was observed when the TR was held constant at 100 ms but the DP flip angle was decreased from 90° to 12° . For flip angles larger than $\sim 70^\circ$ the DP signal was confined to the lung parenchyma but as the DP flip angle was decreased further the proximal veins and left side of the heart became visible. The main qualitative difference from Fig. 1 to Fig. 2 is that the DP signal intensity in the heart started to exceed that of the surrounding lung parenchyma for flip angles below 40° , reflecting a larger downstream signal component than even for the longest TR (500 ms) in Fig. 1. Although the studies were conducted in two different animals, we found the observed transport times to be typical for healthy rabbits with comparable heart rates.

The observations from Fig. 1 and 2 are expanded in Fig. 3 in the form of a flip-angle – TR matrix for Rabbit #2. The upper right-hand corner of this matrix (90° , 50 ms) is representative of the amount of xenon taken up by the lung parenchyma during 50 ms. Moving left (decreasing the flip angle for a fixed TR) or down (increasing the TR for a fixed flip angle) in the matrix is equivalent to increasing the time available for xenon gas to enter the lung tissue from the alveolar air spaces and be carried downstream towards the heart by the pulmonary circulation. The apparent symmetry in the matrix with respect to its antidiagonal indicates that DP flip angle and TR are linked, and that similar DP magnetization distributions can be achieved with different DP flip angle – TR combinations. The actual signal-to-noise ratio of the different DP maps is determined by the amount of xenon magnetization accumulating in the lung tissue during the acquisition, the DP flip angle, and the xenon T1 in the various lung compartments involved.

The axial 2D DP projection maps in Figs. 4a and 5a (Rabbit #3) demonstrate that the flip angle and TR of an acquisition can indeed be traded off according to Eq. [4] over a large parameter range by maintaining a constant, RF-induced relaxation rate. Using the acquisitions with the highest flip angles and longest TRs ($30^\circ/192$ ms and $60^\circ/192$ ms, respectively) as a reference, Figs. 4b and 5b depict the absolute differences between the corresponding DP maps in Figs. 4a and 5a and those reference images. Generally, the largest signal differences were observed near the heart and the descending aorta (yellow and red arrows in Fig. 4b, respectively). However, as indicated by the orange arrows in Fig. 5a, spurious increases in the difference amplitude were occasionally observed in the right posterior region of the lung for some acquisition parameters but not for others. The acquisitions with the reference parameters were repeated to assess overall study repeatability (red boxes in Figs. 4a and 5b). For all parameter combinations, the measured differences in the DP signal intensities relative to the reference image were small; they were also virtually

indistinguishable from the differences between the repeat-measurements of the reference acquisition.

These visual similarities translate into excellent numerical agreements, as shown by the difference scores in Fig. 6. Once again, no systematic bias as a function of the acquisition parameters was apparent. All difference scores were in line with the inherent measurement variability, as reflected by the right-most bar in Figs. 6a and 6b.

We hypothesized that the mathematical flip-angle – TR equivalence for constant RF-induced relaxation rate described by Eq. [4] would begin to break down for flip angles approaching 90°. Thus, each RF pulse would destroy the entire DP magnetization every TR, creating a TR-dependent barrier in space beyond which no DP signal can be measured, while the downstream accumulation continues for lower flip angles and results in detectable DP signal in more remote regions. Based on the findings presented in Figs. 4 and 5, a limit of at least 60° for the validity of Eq. [4] was assumed, such that an analytical conversion can be derived from

$$\frac{1 - \cos 60^\circ}{TR_{60^\circ, \text{equiv}}} = \frac{1 - \cos \alpha}{TR_{\alpha, \text{meas}}}, \quad [7]$$

where α and $TR_{\alpha, \text{meas}}$ are the flip angle and the TR of the actual measurement, respectively, and $TR_{60^\circ, \text{equiv}}$ is the equivalent TR of an acquisition with a flip angle of 60° and the same relaxation rate as the actual measurement. Using a comparison of the total DP signal as a function of TR for flip angles of 60° and 90° provided an empirical correction factor to scale the TR of a 60° measurement to the equivalent TR for a 90° acquisition (Rabbit #4, Fig. 7). For measurement TRs between 20 and 200 ms, the 60° acquisition was largely equivalent to a 90° acquisition at 205% of the TR of the 60° acquisition. Merging this finding with Eq. [7] allows us to turn any flip-angle – TR combination (flip angle < 60°) into an equivalent TR for a 90° measurement ($TR_{90^\circ, \text{equiv}}$):

$$\begin{aligned} TR_{90^\circ, \text{equiv}}(\alpha, TR_{\alpha, \text{meas}}) &= 2.05 \frac{1 - \cos(60^\circ)}{1 - \cos(\alpha)} TR_{\alpha, \text{meas}} \\ &= \frac{1.03 TR_{\alpha, \text{meas}}}{1 - \cos(\alpha)} \quad [8] \\ &\approx \frac{1}{R_{RF}(\alpha)}. \end{aligned}$$

At least as far as the accumulated DP magnetization is concerned, then, $TR_{90^\circ, \text{equiv}}$ is approximately equal to the inverse of the RF-induced relaxation rate over the studied range of flip angles and TRs.

Arranging the DP maps evaluated for Fig. 7 based on their $TR_{90^\circ, \text{equiv}}$ obtained with Eq. [8] illustrates the generally high agreement between the theoretically predicted and actually measured equivalence in distribution of the DP magnetization for flip angles of 60° and 90° (Figure 8). Nevertheless, the yellow and red arrows in Fig. 8 for $TR_{90^\circ, \text{equiv}} \sim 400$ ms also

highlight the anticipated, subtle differences between these measurements. Although the total DP signal for both measurements was approximately equal (see Fig. 7), the 60° measurement exhibits additional downstream magnetization in the cardiac cavity that is absent in the 90° measurement. Conversely, some regions in parenchyma appear brighter in the 90° acquisition than in the 60° acquisition.

Discussion

In this work, we investigated the connection between the flip angle and TR of an HXe DP acquisition and the observed DP magnetization distribution in the lungs of rabbits. In the past, several MR spectroscopy and imaging techniques have been developed to quantify pulmonary xenon gas uptake in an attempt to characterize the function of both healthy and diseased lungs. In these techniques, the employed acquisition parameters were mostly selected according to the requirements of the pulse sequence type, the desired spatial resolution, the maximum permissible breath hold duration, or the need for a sufficient signal-to-noise ratio. As a consequence, the results from different acquisition types, or from measurements conducted with different acquisition parameters, are generally not comparable. However, our findings indicate that it is feasible to convert any flip-angle / TR combinations over a large parameter interval into corresponding equivalent measurements with a 90° DP flip angle and equivalent repetition times $TR_{90^\circ, \text{equiv}}$. The only requirement for this conversion is that the DP magnetization be in near-steady-state throughout the measurement. This is automatically achieved during long measurements with a large number of RF pulses, but can be artificially imposed in any case by using a set of preparatory pulses. The investigator is then free to choose the imaging parameters most compatible with the desired sequence, and studies can be compared in the context of the single parameter, $TR_{90^\circ, \text{equiv}}$.

The observed distribution of HXe DP magnetization in the lung is dependent on a number of physiological (e.g., ventilation-perfusion patterns, cardiac output, alveolar surface-to-volume ratio, etc.) and MR acquisition parameters—particularly the DP flip angle and the TR. In the theoretical case of perfect 90° DP RF pulses, the DP magnetization is completely consumed by each excitation and the only manner by which it can be replenished is through additional alveolar gas exchange and transport. All else being equal, the TR of the measurement would entirely determine how much time is available for HXe magnetization to accumulate within the DP compartments of the lung before the next RF pulse resets the DP magnetization to zero. As shown in Fig. 1, it is thereby possible to fine tune the depicted DP magnetization from predominantly exchange-weighted (short TRs) to heavily transport-weighted (long TRs) simply by adjusting the TR of the acquisition. Nevertheless, although 90° excitations yield DP images that are easily interpreted, high excitation flip angles are rarely used due to the resulting rapid GP depolarization (7,34) and the low signal-to-noise ratios of DP images acquired with short TRs, or the impractically long acquisition times associated with long TRs. Note that in this context numerical values for the terms “short TR” and “long TR” are likely to be species dependent. For instance, pulmonary xenon gas exchange times in humans have been consistently reported to be on the order of several tens of milliseconds, while capillary transit times were found to be around 1.5s (15,21,35).

For DP excitation flip angles less than 90° , the DP magnetization is not completely saturated by a single RF pulse, but instead accumulates across multiple TRs to reach a parameter-dependent steady state. Under these conditions, the direct correspondence between the TR and the distribution of the DP magnetization dissipates. Nonetheless, for any fixed TR, the dependence of the steady-state DP magnetization distribution as a function of the DP flip angle (Fig. 2) exhibits a striking similarity to its TR-dependence for a fixed flip angle (Fig. 1). In fact, Fig. 3 emphasizes that a change in flip angle can be compensated for by an appropriate change in TR (or vice versa), thereby yielding a comparable DP map. This finding would come as no surprise under static conditions, as the RF-induced relaxation rate of a pulse sequence depends on both the flip angle and the TR as described by Eq. [4]. However, in the presence of macroscopic pulsatile (28,36) transport processes, the applicability of Eq. [4] is less obvious because, unlike the inherent continuous T1 relaxation, the relaxation rate induced by RF pulses is discrete and impacts the DP magnetization only once every TR. Nevertheless, for the studied flip angle and TR intervals ranging from $6^\circ - 60^\circ$ and 8.3 ms – 192 ms, respectively, no large deviations from the theoretical predictions in Eq. [4] could be detected (Figs. 4–6). In general, the difference scores for small RF-induced relaxation rates are lower than for high relaxation rates. This effect is due to the fact that the highest DP amplitudes are concentrated in the heart and the descending aorta, the part of the depicted anatomy that is most affected by motion artifacts. The difference scores in these regions of the DP maps are therefore at their extremes and contribute disproportionately to the total difference score. With increasing relaxation rates, the overall DP signal in the heart and the aorta is reduced, lowering the total difference score in the process. Also, as most of the regions with difference amplitudes above the noise level colocalize with heavily vascularized lung volumes, we speculate that they are likely due to fluctuations in heart rate over the course of the study.

As the DP excitation flip angle approaches 90° , the validity of Eq. [4] should eventually break down due to inherent constraints that cannot be overcome. First, a perfect 90° RF pulse represents a temporal discontinuity in the DP magnetization that cannot be approximated with DP flip angles significantly less than 90° . As illustrated by Fig. 8, we observed this phenomenon in the form of visible downstream DP signal outside the parenchyma for a 60° acquisition that is entirely absent in an equivalent 90° acquisition. Nevertheless, the effect seems to be surprisingly small, and Eq. [8] appears to serve as a good approximation for the determination of $TR_{90^\circ, \text{equiv}}$ even close to the theoretical limit. The second constraining factor is based on hardware limitations, as the relaxation rate of high flip-angle pulses combined with short TRs becomes too large to emulate via the ever-shorter TRs required to maintain a constant relaxation rate at lower flip angles. However, we anticipate that hardware limitations will be of little relevance in practice.

Importantly, although the studies presented here were conducted in rabbits using a 2D MR projection acquisition, all findings are directly transferable to human subjects, independent of the imaging pulse sequence used. Since the human heart beats approximately 3 times slower than that of a rabbit, the physiological conditions are actually much closer to static in humans than in small animals. We therefore anticipate that the presented results are in fact more applicable in humans than they might be in much smaller animals such as rats and mice. Nevertheless, our studies did reveal one critical limitation for the validity of the

$TR_{90^{\circ},equiv}$ conversion—namely, the requirement that the DP magnetization be in steady state everywhere within the imaged lung parenchyma (or the heart, if it is part of the quantification) at the moment of image acquisition. The lower the flip angle of the RF pulses and the larger the fraction of downstream vessels in any given pixel, the longer until steady state conditions are achieved. For instance, we anecdotally observed that the DP signal peak in the heart was not reached until 1.5 – 2 s after beginning gas inhalation in healthy rabbits, so we would expect to find even longer delays in humans. In general, the impact of such physiological transport delays on the measurement of a given DP parameter would strongly depend on the temporal averaging characteristics of the pulse sequence used. We anticipate multi-second 3D radial acquisitions to be less sensitive than rapid 2D Cartesian acquisitions.

One possible limitation of our findings is that the $TR_{90^{\circ},equiv}$ conversion might fail outside the tested flip angle – TR parameter interval, in particular for acquisitions with very low DP flip angles. It is also conceivable that the empirical scaling factor of ~ 2.05 for transforming $TR_{60^{\circ},meas}$ into $TR_{90^{\circ},equiv}$ is itself TR-dependent. As discussed above and shown in Fig. 8, the agreement in the distribution of the DP magnetization for a fixed relaxation rate decreases in the 60° – 90° DP flip angle interval as the flip angle approaches 90° , although Eq. [8] seems to hold as far as the total DP signal amplitude is concerned. Future studies will therefore be required to stake out the boundaries of validity for Eq. [8].

Global flip angle calibrations are generally highly accurate and result in flip angles that are, in aggregate over the sensitive RF coil volume, close to the desired value. However, the regional flip angle distribution is dependent on the imaged subject and the B1-inhomogeneity of the RF coil. Since the RF-induced relaxation of the DP magnetization is flip angle-dependent, it will vary in a time-dependent manner as the magnetization flows through inhomogeneous coil regions over the course of the acquisition. Unfortunately, the spatial and temporal parameters of the pulmonary gas transport are not known, which makes retroactive B1 corrections infeasible. Although we did not observe a flip-angle dependent drift in the magnetization distribution with our birdcage coil (see Figures 4 – 6), it is conceivable that more inhomogeneous RF coil configurations are susceptible to such systematic errors. Nevertheless, coil homogeneity is a general concern for standardized quantitative DP measurements and not a particular weakness in our approach.

Finally, we anticipate the observed distribution of the DP magnetization to be dependent on the duration of the measurement, especially for sequences with high DP relaxation rates. Although the GP magnetization is approximately 50 times larger than the DP magnetization, it is eventually depleted by exchange with the depolarized xenon from the DP compartments. What is more, this depletion is not homogeneous, but rather a function of the local gas exchange rates. In lung volumes with high gas exchange, the GP magnetization will decrease more rapidly than in those with lower gas exchange, such that the measurement begins to accumulate a bias due to higher residual GP magnetization in low-exchanging regions of the lung. However, again this potential concern is not limited to the presented work but affects all DP imaging in general.

The proposed computation of the virtual quantity $TR_{90^{\circ},equiv}$ has at least two important implications. First, the parameter $TR_{90^{\circ},equiv}$ greatly facilitates the interpretation of any DP

measurement by condensing two independent acquisition parameters—the flip angle and the TR—into a single one that uniquely characterizes the underlying distribution of the assessed DP magnetization within the lung. Second, it makes DP measurements obtained by the various pulse sequence tools currently in use compatible with each other. This is particularly exciting, as standardized metrics of lung function would make it feasible to merge the results from the various research groups that employ hyperpolarized gas MRI, and to pool the findings from the different patient cohorts studied.

Conclusions

In this work, we have introduced and preliminarily verified a method for the conversion of the flip angle and TR of a given HXe DP measurement to a standardized metric based on the virtual quantity $TR_{90^{\circ}, \text{equiv}}$ linked through their equivalent RF relaxation rates. Such a conversion permits measurement results obtained with different pulse sequence types, or by different research groups using various acquisition parameters, to be compared to each other.

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Figure 1.

2D coronal projections of the normalized HXe DP signal in the lung of a healthy rabbit for a flip angle of 90° as a function of measurement TR. Since each RF pulse saturates the DP magnetization, the TR controls the time available for xenon magnetization to exchange in the alveolar volume and be transported downstream by the pulmonary circulation. In a healthy rabbit, it takes ~ 200 ms for the first DP magnetization to reach the central vessels and left ventricle of the heart (green ellipse).

Figure 2.

2D coronal projections of the normalized HXe DP signal in the lung of a rabbit for a TR of 100 ms as a function of measurement flip angle. Similar to an increase in TR for a constant flip angle, a reduction in the flip angle for a fixed TR increases the accumulation of DP magnetization in the lung.

Figure 3.

Matrix of the distribution maps of the DP magnetization in a rabbit lung as a function of flip angle and TR. For high flip angles and short TRs, no significant amount of DP magnetization can accumulate in the lung parenchyma, so the resulting maps only depict DP xenon in the vicinity of the alveolar gas exchange sites. An increase in TR or a decrease in the flip angle reduces the relaxation rate of the acquisition and allows visualization of xenon gas transport by the pulmonary circulation.

Figure 4.

2D axial measurements with similar RF-induced relaxation rates of 0.7 s^{-1} but different flip angle – TR combinations. (a) Maps of the distribution of the DP magnetization. (b) Difference maps of the reference acquisition (upper left-hand corner in (a)) and all other measurements. The arrows identify pulsatile signal oscillations in the heart (yellow arrow) and the descending aorta (red arrow) as the regions with the largest signal differences between acquisitions. The red box highlights the differences between two measurements obtained with identical imaging parameters.

Figure 5.

2D axial measurements with similar RF-induced relaxation rates of 2.6 s^{-1} but different flip angle – TR combinations. (a) Maps of the distribution of the DP magnetization. (b) Difference maps of the reference acquisition (upper left-hand corner in (a)) and all other measurements. The orange arrows point out regions with sporadically elevated difference amplitudes that appear for some parameter combinations but not for others. The red box highlights the differences between two measurements obtained with identical imaging parameters.

Figure 6.

Bar charts of the quantitative differences within the masked lung volume for (a) Fig. 4b, relaxation rate 0.7 s^{-1} , and (b) Fig. 5b, relaxation rate 2.6 s^{-1} . Similar to the difference maps in Fig. 4b and Fig. 5b, no quantitative biases were observed between DP maps acquired with different flip angles and TRs but equivalent RF-induced relaxation rate.

Figure 7. Plots of the total normalized DP signal as a function of TR for flip angles of 60° (red) and 90° (blue). The green squares illustrate that the 60° acquisition matches up with the 90° acquisition if the TR of the former is stretched by 205%.

Figure 8.

2D axial DP projection maps underlying Fig. 7 arranged according to the $TR_{90^\circ, \text{equiv}}$ of their acquisition. The arrows point out subtle differences in the DP magnetization distribution in the cardiac cavity (yellow arrow) and within the parenchymal volume (red arrow) between measurements of similar relaxation rate but a flip angle of 90° versus 60° .