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Removal of hyperpolarized ^{129}Xe gas-phase contamination in spectroscopic imaging of the lungs

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Abstract

Purpose—A novel technique is presented for retrospective estimation and removal of gas-phase hyperpolarized Xenon-129 (HP ^{129}Xe) from images of HP ^{129}Xe dissolved in the barrier (comprised of parenchymal lung tissue and blood plasma) and red blood cell (RBC) phases. The primary aim is mitigating RF pulse performance limitations on measures of gas exchange, e.g. barrier/gas and RBC/gas ratios. Correction for gas contamination would simplify technical dissemination of HP ^{129}Xe applications across sites with varying hardware performance, scanner vendors and models.

Methods—Digital lung phantom and human subject experiments (N=8 healthy; N=1 with idiopathic pulmonary fibrosis) were acquired with 3D radial trajectory and 1-point Dixon spectroscopic imaging to assess the correction method for mitigating barrier and RBC imaging artifacts. Dependence of performance on echo time (TE), image signal-to-noise ratio (SNR), and gas contamination level were characterized. Inter- and intra-subject variation in the dissolved-phase ratios were quantified and compared to human subject experiments before and after correction.

Results—Gas contamination resulted in image artifacts similar to those in disease that were mitigated after correction in both simulated and human subject data; for simulation experiments performance varied with TE, but was independent of image SNR and the amount of gas contamination. Artifacts and variation of barrier and RBC components were reduced after correction in both simulation and healthy human lungs (barrier, $P=0.01$, RBC, $P=0.045$).

Conclusion—The proposed technique significantly reduced regional variations in barrier and RBC ratios, separated using a 1-point Dixon approach, with improved accuracy of dissolved-phase HP ^{129}Xe images confirmed in simulation experiments.

Keywords

Lung; Hyperpolarized MRI; Artifact Correction; Xenon MRI; Idiopathic Pulmonary Fibrosis; Spectroscopic Imaging

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Introduction

Hyperpolarized Xenon-129 (HP ^{129}Xe) MRI is a safe [1] and increasingly attractive technique for investigating pulmonary function [2]. One of the most attractive properties of HP ^{129}Xe is its solubility in parenchymal lung tissue and blood plasma, often referred to jointly as the diffusion barrier, and red blood cells (RBC) [3]. HP ^{129}Xe in these compartments, referred to collectively as the dissolved-phase, experience a unique chemical shift relative to the gas-phase; the barrier phase is shifted by 198 ppm, while the RBC phase is shifted by 217 ppm [4]. However, imaging the HP ^{129}Xe dissolved-phase components is challenging for two important reasons: (1) the short T_2^* (~ 2 ms at 1.5T) [5], and (2) relatively small signal (1–2% of the gas-phase HP ^{129}Xe) [6].

These challenges have been overcome in a number of ways. One approach indirectly measures cross-component diffusion transfer through selective saturation of dissolved components and allowing some time for diffusive exchange to occur prior to image acquisition [7]. Direct approaches to imaging the gas, barrier and RBC HP ^{129}Xe components have typically taken a chemical shift imaging approach with k-space trajectories that minimize echo time (TE). Spectroscopic imaging has been demonstrated with 2D imaging in rats [8], which provides high spectral but low spatial resolution. Multiple echo approaches based on IDEAL [9] have been reported using both 3D radial [10] and spiral [11] k-space trajectories to minimize TE. A 1-point Dixon based separation [12] has also been used in humans following a single echo acquisition at the appropriate TE using radial k-space trajectories in both 2D [13] and 3D [14]. Particularly in this latter case (1-point Dixon), selective excitation of the dissolved-phase is needed to isolate the barrier and RBC components from the large gas-phase reservoir [15]. In practice gas-phase contamination of the dissolved-phase signal remains a serious concern due to tradeoffs between RF pulse profile, amplifier performance, and echo time.

Any contamination by the gas-phase xenon is undesirable, particularly for 1-point Dixon approaches. In order to utilize a 1-point Dixon separation strategy, as in [16], a two-component model (i.e. barrier and RBC signal only) is required; the technique is based on imaging at a TE where components are 90° out of phase. The presence of gas contamination signal not accounted for by the model will induce errors in the dissolved-component separation and can cause severe image artifacts.

Utilizing 1-point Dixon methods for HP ^{129}Xe requires addressing a few additional problems. First, dissolved-phase and gas-phase images must clearly be acquired separately; this can be done in an interleaved fashion within a single ~ 15 sec breath hold [16]. Second, it assumes negligible B_0 field inhomogeneity. This has been mitigated in the literature [16] by assuming spatial invariance in RF phase and using the phase of the concurrently acquired gas-phase image as a surrogate for B_0 . Third, given that the exact barrier and RBC resonances may vary subject-to-subject, they must be estimated using a calibration scan (using whole lung spectroscopy) to determine the TE at which they will be 90° out of phase. A similar calibration scan is necessary in any case to calibrate flip angles, and both are performed within the same scan.

Nonetheless, using a 1-point Dixon approach may be attractive given it can be performed using a simple, single-echo, pulse sequence and requires comparably simple signal modeling for component separation.

The need for carefully designed and calibrated RF pulses in HP ^{129}Xe MRI applications, as well as the complications of doing so, has been addressed previously in the literature [17]. While calibration methods are technically feasible, they are often empirical, depending on the stability and linearity of a given RF amplifier. It is hard to predict precise hardware performance across sites and vendors or even between different machines at the same site. It also requires careful characterization and design of pulses for each specific application. Reducing or eliminating the significant influence of RF pulse performance and behavior would greatly simplify technical development of HP ^{129}Xe applications and allow reliable methodological dissemination across sites and hardware vendors.

In this work, we present a novel technique for retrospective estimation and removal of gas-phase xenon contamination from dissolved-phase HP ^{129}Xe data. Previously established dissolved-phase HP ^{129}Xe acquisition methodology [16] is extended by acquiring data at a second, longer echo time (relative to the first). This can be done “for free”, in the sense that the imaging acquisition sequence is otherwise unchanged (same initial TE, same TR, same total imaging time, etc.). The proposed technique leverages the signal decay due to the short T_2^* of the dissolved-phase xenon (~2 ms at 1.5T) relative to the long T_2^* of the gas-phase xenon (~40 ms at 1.5T) [5] at the second, longer TE. Thus, at a sufficiently long TE, contaminated dissolved-phase data will largely consist of *contamination only*, which allows it to be estimated and subsequently removed.

Following the detailed presentation of the theoretical basis for the correction technique, we present data generated through simulation and experiment in human subjects to justify and validate the proposed method.

Theory

Extending the work of Kaushik, et. al. [15], we employ an interleaved data acquisition at the gas and dissolved resonant frequencies for two echo times. The first TE is set such that the RBC and barrier components are 90° out of phase, facilitating a 1-point Dixon separation. The second TE is delayed and used for the estimation of the contaminant gas signal as shown in Figure 1 and described below.

The measured dissolved-phase signal at echo n is modeled as a sum of the true dissolved-phase signal, comprised of HP ^{129}Xe in both the RBC and barrier tissues, and the contaminating, off resonant gas-phase signal:

$$s_{d,raw,n}(\vec{k}) = s_{d,true,n}(\vec{k}) + \hat{s}_{g,n}(\vec{k}). \quad (1)$$

This contaminant gas signal ($\hat{s}_g$), arises from the same HP ^{129}Xe acquired during the interleaved acquisition at the gas-phase resonant frequency (s_g). However, the change in the

transmit frequency results in a change in the magnitude and phase of RF excitation of the gas-phase signal, and the change in the receive frequency induces a frequency shift in the signal. Accounting for these changes, the contaminant gas-phase signal may be related to the on-resonant gas-phase acquisition as

$$\hat{s}_{g,n}(\vec{k}) = \alpha s_{g,n}(\vec{k}) e^{2\pi i \Delta f t}, \quad (2)$$

where α is a complex-valued constant correcting for the difference in RF excitation of the gas-phase, f is the change in receive frequency and t is the readout time of the given sample. Because the frequency shift and timing of the sequence are known and the on resonance gas-phase data ($s_{g,n}$) is measured, estimation of the contaminant gas-phase signal is reduced to the estimation of the single parameter α .

As α depends only on the differences in gas-phase excitation, it will take the same value at both the first and second echo times. Exploiting the short T_2^* of the dissolved-phase signals (≈ 2 ms at 1.5 T) [5] relative to the gas-phase (≈ 25 ms at 1.5T) [18], the second echo time is chosen such that the dissolved-phase has decayed substantially, leaving a signal that is dominated by the contaminant gas-phase (Eq. 3).

$$s_{d,raw,2}(\vec{k}) = s_{d,true,2}(\vec{k}) + \alpha s_{g,2}(\vec{k}) e^{2\pi i \Delta f t} \approx \alpha s_{g,2}(\vec{k}) e^{2\pi i \Delta f t} \quad (3)$$

Using the measured second echo data at both the dissolved and gas resonant frequencies, we then estimate α as

$$\alpha = \underset{\alpha}{\operatorname{argmin}} \|s_{d,raw,2}(\vec{k}) - \alpha s_{g,2}(\vec{k}) e^{2\pi i \Delta f t}\|_2. \quad (4)$$

Finally, the gas-phase contamination is removed from the first echo dissolved-phase signal using

$$s_{d,true,1}(\vec{k}) \approx s_{d,raw,1}(\vec{k}) - \alpha s_{g,1}(\vec{k}) e^{2\pi i \Delta f t}. \quad (5)$$

The subtraction of the scaled and frequency-shifted gas images from the dissolved phase images will increase noise after correction. However, consider the case where the level of noise is equal in both the raw dissolved-phase and gas-phase data; the standard deviation of the noise in the corrected data will be increased by a factor of $\sqrt{1 + |\alpha|^2}$. Thus, we expect SNR to decrease by $< 5\%$ for typical values of $|\alpha|$ (< 0.3).

Methods

Simulated experiments

In silico experiments were performed using Matlab (The MathWorks, Inc., Natick MA) to characterize the performance of our gas estimation method under known conditions and to quantify the effect of gas contamination and correction on the separated images of the RBC and barrier components of the dissolved-phase. Simulated results were then used for comparison to experiments in human subjects.

Two digital phantoms were created based upon the geometry of the lung airspaces (for gas-phase HP ^{129}Xe) and parenchymal tissues (for the dissolved-phase components). The discrete Fourier transform (DFT) was used to sample the phantoms in k-space based upon the 3D radial image acquisition, described below, used in human subject imaging. A signal model was applied to account for the off resonant frequencies and T_2^* decay of the gas-phase, RBC, and barrier components. This model accounts for the signal dynamics both between echoes and during readout of the radial projections.

Using this model, we simulated k-space data for both the on resonance gas-phase acquisition (containing isolated gas-phase signal) and the dissolved-phase acquisition (containing RBC, barrier, and off-resonant gas-phase signal). Complex Gaussian noise is then added to the simulated data such that reconstructed images have a known SNR. The process of generating simulated data is described in detail in the Appendix.

A. Estimation of Gas Contamination—Simulated data was used to determine the ability of this technique to estimate the level of gas-phase contamination in various imaging situations. We investigated the accuracy of the estimation process while varying four parameters: the delay between the first and second echo (TE), the dissolved-phase image SNR, the magnitude of the contaminant gas-phase signal, and the phase of the contaminant signal.

100 trial datasets were generated for each value of the four variables investigated with independent noise. For each dataset, the amount of gas-phase contamination was estimated and compared to the value used to generate the simulated data. The mean and standard deviation of the error over the 100 trials was recorded. The simulated RBC/Barrier ratio was set to 40% for all datasets, and the first TE was set to 0.9 ms. The remaining simulation values are specified below for each of the four *in silico* experiments performed.

Delay between echoes: The delay between echoes was varied from 1 to 6 ms. Dissolved-phase image SNR was set to 8, while the gas-phase SNR was 16. The level and phase of the gas contamination was randomly selected for each dataset between 0 to 100% of the dissolved-phase signal and 0 to 360° , respectively.

Image SNR: Dissolved-phase image SNR was varied from 1 to 20. The delay in echoes was set to 3.3 ms, yielding a TE_2 of 4.2 ms. The magnitude and phase of the contaminant gas-phase signal were randomized as above.

Magnitude of contaminant signal: The magnitude of the contaminant signal was varied from 0% to 100% of the dissolved-phase signal magnitude. TE_2 was set to 4.2

ms. The dissolved-phase image SNR was held at 8, while gas-phase SNR was 16. The phase of the contaminant signal was randomly selected for each dataset.

Phase of contaminant signal: The phase of the contaminant signal was varied from 0 to 360°. TE₂ was set to 4.2 ms. The dissolved-phase image SNR was held at 8, while gas-phase SNR was 16. The magnitude of the contaminant signal was randomly selected for each dataset between 0 and 100% of the dissolved-phase signal.

B. Estimation of RBC and Barrier Components—Simulated data were also used to analyze the impact of gas contamination and the proposed correction method on estimation of the RBC and barrier components. For these tests simulated data were generated with 100 trials, each with independent noise, for the cases of no contamination and 50% gas contamination. A total of 100 trials was found to be sufficient to show the range of variation possible. As the effects of gas contamination on the separated RBC and barrier images are strongly dependent on the initial phase, the initial phase of the gas contamination was randomized for each trial to show the range of effects contamination can have on quantitative measures of the barrier and RBC components. The remaining simulation parameters were held constant at values representative of those observed in human subject scans: dissolved-phase SNR was set to 8, gas-phase SNR to 16, and RBC/Barrier ratio to 40%.

For each trial, the data were reconstructed both with and without applying our correction technique. The RBC and barrier components were then separated using the 1-point Dixon technique [15]. We then recorded the mean and standard deviation of each component over the lung volume, and compared the results of the raw, uncorrected data to the corrected data.

Human Subject Experiments

Human subjects (8 healthy volunteers, 3 female, 5 male, ages 30–69 with mean 54.9 and standard deviation 12.5; and 1 idiopathic pulmonary fibrosis patient, male, age 64) underwent HP ¹²⁹Xe MRI on a 1.5T scanner (General Electric, Waukesha, WI) using a quadrature vest coil tuned to the xenon resonant frequency of 17.66 MHz @ 1.5T (Clinical MR Solutions, Brookfield, WI). Informed consent was obtained in accordance with approved Institutional Review Board (UW IRB 2013-0266 and UW IRB 2014-1572) and investigational new drug (FDA IND# 118077) protocols.

The ¹²⁹Xe gas (87% isotopically enriched; Linde Gases, Stewartsville NJ) was hyperpolarized via spin-exchange optical pumping [19] using a commercially available polarizer (model 9820, Polarean, Durham, NC). A total of 1 liter of HP ¹²⁹Xe gas was cryogenically accumulated and subsequently thawed into an ALTEF bag fitted with a quick-disconnect attachment. Polarization of the collected gas was measured at ~14–18% at a polarization measurement station (model 12881, Polarean, Durham NC).

Subjects were administered the HP ¹²⁹Xe gas using a non-rebreather mask with a quick-disconnect attachment fitted to the input port. Subjects were coached to exhale to FRC, during which the bag of HP ¹²⁹Xe was connected to the mask input port. The entire 1-liter bag was then inhaled followed by a breath hold of approximately 15 seconds.

A. Image Acquisition—Imaging data was acquired for use with a 1-point Dixon technique, as previously described by Kausik et al [16]. Briefly, data was acquired using a 3D radial pulse sequence [15] during a 15-second breath hold following inhalation of 1-L of HP ^{129}Xe . Each radial ray of k-space was acquired twice: once each with the transmit/receive frequencies set to the gas-phase and RBC resonances, respectively (3832 Hz difference). Additional acquisition parameters were: FOV = 40 cm, matrix = $64 \times 64 \times 64$, TR = 7.5 ms, BW = 31.25 kHz, flip-angles (dissolved/gas) = $22^\circ/0.5^\circ$, 1001 radial projections, 79 readout points/projection/echo. The echo time (TE_1) was adjusted based on a separate calibration scan such that the tissue and RBC components are 90° out of phase. Calibration scanning involved the acquisition of 200 whole lung spectra on the RBC resonance (512 points, $32\mu\text{s}$ sample rate, 18° – 24° flip angle, TR = 20ms, TE = 0.7ms), and the first 50 were discarded to allow the saturation of RBC magnetization downstream of the capillary beds. The latter 150 spectra were averaged and fit to 3 Lorentzian peaks: one each for the RBC, barrier and gas components. The relative areas and frequencies of these fitted peaks were used to estimate the RBC-to-barrier ratio and the precise TE_1 for Dixon imaging. The value of TE_1 was typically found to be around 0.9 ms (with a range of 0.8 – 1 ms) in this work.

Imaging in this study differed in two significant ways from the methods described by Kaushik et al [16]. First, a second echo time was acquired at $TE_2 = TE_1 + 3.3\text{ ms}$ ($TE_2 \approx 4 TE_1$) in order to estimate the gas-phase signal based on the assumption in Eq. 3. The second echo time was chosen to be as long possible to estimate gas-phase signal without requiring an increase in the imaging TR; this second echo time was acquired using flyback gradients immediately after the initial readout at TE_1 . The additional gradient readout is without additional time penalty because it occurs during the time interval allowing for exchange between gas-phase and dissolved-phase compartments. Second, a Shinnar Le Roux (SLR) RF pulse (1.2 ms, 5 kHz bandwidth) was carefully designed to have minimal stop band ripple (0.1%) in order to generally minimize off-resonance power across a range of transmit powers and off-resonant frequencies [20]. This RF pulse was used in both the calibration and imaging scan. The transmit power was adjusted for the imaging scan based on a flip angle estimate from the calibration spectra to provide the exact flip angles desired, correcting for any variations in loading of the RF coil.

A pulse sequence diagram outlining the HP ^{129}Xe imaging technique is shown in Figure 1, which also depicts the gradient spoiling (i.e. crusher gradients) applied. RF spoiling was utilized as well to minimize steady-state transverse magnetization.

Additionally, proton MRI of the chest was performed to generate of a segmented mask of the lungs for HP ^{129}Xe analysis. Subjects inhaled a volume matched bag of room air (1-liter), administered in a manner identical to the HP ^{129}Xe gas, and performed a 13-second breath hold during which a 3D radial MRI proton image was acquired (FOV = 40 cm, matrix = $64 \times 64 \times 64$, TE = 0.22 ms, TR = 2.1 ms, BW = 62.5 kHz, flip-angle = 5° , 5647 radial projections, 143 readout points/projection).

B. Processing and Analysis for Gas Correction—The raw gas-phase and dissolved-phase k-space data were separated and used to compute the gas contamination scale factor

and to correct the dissolved-phase k-space data accordingly (i.e. prior to image reconstruction) as described in further detail in the **Theory** section.

Images (both corrected and uncorrected) were reconstructed identically for both simulated and human subject data. In both cases, k-space data were interpolated onto a Cartesian grid [21] using sampling density compensation weights estimated iteratively [22] to account for the non-uniformly sampled k-space coordinates. Images were then generated by inverse Fourier transform of the resulting resampled k-space data.

The degree of gas-phase contamination was evaluated qualitatively by reconstructing dissolved-phase image data from the longer, second echo time, following demodulation of the data at the gas-phase signal resonance [14]. In these comparisons, the demodulated dissolved-phase k-space signal, $s_{d,dem}$, was

$$s_{d,dem}(\vec{k}, t) = s_d(\vec{k}, t)e^{-2\pi i \Delta f t} \quad (6)$$

where s_d is the original dissolved-phase k-space data, t is the time at which k-space coordinate $\vec{k}$ is acquired and f is the change in the receive frequency between the gas- and dissolved-phase acquisitions (3832 Hz). Note that the dissolved-phase signal has largely decayed by the second echo time.

C. Processing and Analysis for RBC and Barrier Parametric Maps—Thoracic 3D proton images were first registered to the HP ^{129}Xe ventilation images using an affine transformation. Lung regions were then segmented semi-automatically from the registered proton MRI and used to define voxels for HP ^{129}Xe analysis. Note that this was only necessary for experiments in humans, since lung regions were known for the simulation.

Static B_0 field off-resonance was estimated using the gas-phase HP ^{129}Xe images at TE_1 and TE_2 by finding the phase difference between the two and dividing by the difference in echo times, $TE_2 - TE_1$. The off-resonance estimate was subsequently used to remove associated phase accrual in the dissolved-phase HP ^{129}Xe images.

In contrast to the simulated data where the RBC-to-barrier ratio was known *a priori*, the dissolved-phase images for human subjects were separated into RBC and barrier components using a whole lung RBC-to-barrier ratio measured from a separate calibration scan [16]. Complex-valued dissolved-phase images were rotated by an increasing phase until the whole lung ratio of the real-to-imaginary image components matched the known whole lung RBC-to-barrier ratio. Following this rotation, the RBC and barrier compartments were extracted from the real and imaginary components, respectively. Note that this phase rotation and component separation was performed following gas-contamination correction where applicable.

Raw RBC and barrier component images were converted to absolute RBC-to-gas and barrier-to-gas ratio images, similar to [23]. Specifically, RBC and barrier images were divided by the concurrently acquired gas image and then scaled to account for the

differences in flip angles (dissolved/gas = $0.5^\circ/22^\circ$) and T_2^* decay. Flip angles were calibrated to the specified values as described above and the scaling correction was computed globally for the entire lung volume as the ratio of the sines of the (assumedly spatially invariant/globally) applied flip angles. Corrections for T_2^* decay rates (again, under the simplifying assumption of spatial invariance) were performed using decay rates measured from the calibration spectra, with unique T_2^* decay rates estimated independently for the barrier and RBC components, and applied globally to the lung volume for each component.

Parametric maps of RBC-to-gas and barrier-to-gas ratios were also created in a similar manner to [23]. Reference normal RBC-to-gas and barrier-to-gas ratio distributions were generated from the images acquired in the 8 healthy normal volunteers. These reference distributions were used to classify the human subject maps by color based on the number of standard deviations from the reference normal mean. These parametric maps were compared in a subset of healthy subjects with and without using the proposed correction to show the presence of likely artifacts due to gas contamination and the ability of the correction to provide normal results. Parametric maps for a patient with IPF were included to verify that defects related to disease were retained after correction. Voxel-wise RBC-to-gas and barrier-to-gas ratios throughout the entire lung were converted to histograms, which were also compared before and after gas contamination correction. Qualitative comparisons to simulation results were made to establish whether simulated and human data trends were in agreement.

Statistical Analysis

Quantitative comparisons were made in the healthy normal cohort by comparing: 1) dispersions (variances) of the whole lung means using the Ansari Bradley test [24] and 2) means of the whole lung variances before and after the proposed correction using a paired t-test. Differences were considered statistically significant when $P < 0.05$.

Results

Typical coronal dissolved-phase images covering the lung volume for both simulation and healthy human subject (63 year old male, average RBC/Barrier ratio of 0.3) experiments are compared for identical acquisition parameters in Figure 2 (also see Supporting Figures S1 and S2). Notably, artifacts and erroneous estimations are found in the uncorrected images for both simulation (Figure 2A,C) and human subject (Figures 2G,I) experiments. Due to the large off-resonance of the gas-phase signal (3.8 kHz at 1.5 T) acquired with the 3D radial trajectory, the contaminant signal experiences severe blurring and complex phase behavior creating artifacts interior to and around the lung periphery. These artifacts can manifest as homogeneous erroneous estimation, as shown in the barrier images (Figure 2A,G) or additional, false, heterogeneity within the lungs, as shown in RBC images (Figure 2C,I). Applying the proposed correction apparently resolves both these issues in both simulated (Figure 2B,D) and human subject (Figure 2H,J) data. The reconstruction of the second dissolved-phase echo modulated such that the gas component is on-resonance depicts the

magnitude of the underlying gas contamination signal as an image (Figure 2E,K) that is largely removed after correction (Figure 2F,L). In the human subject, we measure a ~30% reduction in SNR after correction in both barrier (from 15.0 to 10.9) and RBC (3.9 to 3.0) images. However, the background noise of both barrier and RBC images is reduced overall by 1%, suggesting that the reduction in SNR comes from removing the contaminating signals and not noise amplification.

Estimation of Gas Contamination

Quantitative comparisons in the simulation experiments show the method is highly dependent on the delay between echoes (Figure 3A). As this delay increases, the correction technique performs increasingly well due to the decay of the dissolved relative to the gas-phase signals. As described in *Theory*, this technique is predicated on the assumption that the dissolved-phase signal is negligible in the second echo. The error in the estimate of gas contamination therefore increases with the amount of dissolved-phase signal residual in the second echo. Based on the delay used in the human subject scans (3.3 ms), our simulated data predicts a residual error of 9% relative to the first echo dissolved-phase magnitude. Importantly, simulation results also indicate that the proposed method is robust to both dissolved-phase SNR and the magnitude and phase of the gas contamination (Figure 3B–D).

Estimation of RBC and Barrier components

Both RBC-to-gas and barrier-to-gas ratios followed a similar pattern for human subject and simulation experiments as shown in Figure 4. For the simulation experiments, whole lung ratio measures are more tightly grouped following correction, indicated by a smaller standard deviation of the mean values at the cost of a small bias of ~5% (Figure 4a). Comparable measures in human subjects (Figure 4c) indicate similar behavior, although the differences before and after correction did not reach statistical significance (barrier-to-gas: 0.351 raw, 0.2218 corrected, $P=0.057$; RBC-to-gas: 0.180 raw, 0.134, $P=0.303$). The spatial heterogeneity introduced by the gas-phase contamination (Figure 2) is quantitatively estimated by the standard deviation of the respective ratios over the lung volume. For the simulation, the standard deviation of both the barrier-to-gas and RBC-to-gas across the lung volume are reduced to approximately ~10% higher standard deviation than the background noise level (Figure 4b). For the human subjects the reduction in standard deviation is less pronounced (Figure 4d) but reaches statistical significance (barrier to gas: 0.355 raw, 0.306 corrected, $P=0.010$; RBC-to-gas: 0.353 raw, 0.291 corrected, $P=0.045$). The numerical measures of RBC and barrier values for all experiments are further summarized in Table 1.

Human Subject Parametric Maps

Whole lung histograms and parametric maps from RBC-to-gas and barrier-to-gas ratio estimates in 3 example healthy subjects are shown in Figure 5 and Figure 6, respectively, before and after the proposed correction. After correction, the distributions of the ratios are narrower and more similar with respect to mean and overall shape. The histogram results are mirrored in the parametric maps indicating before correction numerous regions of both abnormally low and abnormally high barrier-to-gas (Figure 5) and RBC-to-gas that resolve after correction (Figure 6).

A similar presentation is provided in the IPF patient in Figure 7. Importantly, the histograms are clearly different from the healthy subjects, showing areas of abnormally high barrier-to-gas (pink color) and low RBC-gas (red color) ratios that are maintained following correction. While the underlying disease makes it more difficult to characterize the impact of the gas contamination, correction generally elevates regional barrier-to-gas and RBC-to-gas ratios while preserving their histogram distributions.

Discussion and Conclusion

We present numerical simulation and human subject results for dissolved-phase HP ^{129}Xe MRI data that demonstrate the problem of contamination by undesirable excitation of the more abundant gas-phase component even when using a carefully designed RF pulse with a narrow passband and minimal side lobes in the stopband. The impact of gas-phase contamination error includes increased variability in estimated barrier- and RBC-to-gas ratios both across subjects and over the regions of the lungs. We explore the impact of such gas contamination signal on image quality and both propose and implement a method to recover image quality and improve consistency and accuracy of quantitative barrier- and RBC-gas ratios in realistic simulations. The simulations indicate that the performance of the correction is independent of both the initial degree of contamination and image SNR. The method was then shown to reduce dissolved-phase signal heterogeneity in healthy human lungs using a 1-point Dixon acquisition sequence with parameters commonly used in the literature [16]. Based on simulation results, we can expect the correction to reduce errors due to gas-phase contamination to less than 10% of the dissolved-phase signal.

Corresponding experiments in human subjects are consistent with increased individual and regional variation of barrier- and RBC-to-gas ratios as predicted by the simulation experiments. Using the proposed correction, both mean and regional variation is reduced across the healthy normal subject population, suggesting more consistent quantitative measures following removal of the contamination. Unlike the simulated data, the human data is expected to present some degree of real physiologic variability such that the difference in the whole lung mean ratios following correction still reflect patient-specific differences (Figure 4). Importantly, regional standard deviation across the lung volume was significantly reduced after correction to reflect more homogeneous values as would be expected in a healthy normal population. In the IPF patient investigated, the expected regional variability due to disease was maintained after correction indicating the method does not affect disease-related heterogeneity.

The reduction in image SNR seen in the human subject images after correction seems to be attributed to reductions in the signal due to correction, rather than substantial increases in the noise. By removing the contaminant gas-phase signal from the images, the average signal intensity throughout the lung is obviously reduced. The increase in data noise expected due to the subtraction of gas-phase data in this method was not observed; a decrease in the background noise of both the barrier and RBC images was instead observed after applying the correction. We hypothesize that this reduction in “noise” arises from deterministic artifacts that are mitigated by the reduction of the signal amplitude in k-space after removing

the estimated gas-phase data, likely due to decreased intensity of radial undersampling and off-resonance artifacts.

A significant advantage of the proposed correction is that it can be implemented as a part of the standard 1-point Dixon HP ^{129}Xe imaging methodology reported in previous work [16] without changing important parameters, most notably TR, which is sufficiently long to allow both compartmental exchange of HP ^{129}Xe to occur and acquisition at a second TE.

In current practice a handful of clinical research sites have achieved good performance with well-designed and calibrated RF pulses for *specific* HP ^{129}Xe MRI applications using site-*specific* vendor hardware and careful tuning of flip angle excitation to minimize the side lobe at the gas-phase resonance [15,17]. However, the method proposed enables robust dissolved-phase HP ^{129}Xe data despite known variabilities in RF amplifier hardware and potentially suboptimal RF pulse stop band performance with different excitation flip angles [15,17]. The proposed method, therefore, provides practical flexibility to translate methods across sites, hardware manufacturer, and application, facilitating the methodological dissemination of dissolved-phase HP ^{129}Xe MRI. Moreover, reducing the constraints on RF pulse performance opens up potential opportunities to optimize other acquisition design elements such as TE.

An additional advantage of this approach is that it may eliminate the requirement for relatively long (~ 1 ms) RF pulses. These longer pulses are generally necessary to achieve sufficient spectral selectivity (i.e. minimize gas-phase excitation), but are detrimental to signal-to-noise ratio (SNR) of the short T_2^* dissolved-phase components. Using the proposed correction, suppression of gas-phase excitation could be relaxed (and undesirable signal removed retrospectively) in exchange for shorter RF pulses that increase dissolved-phase SNR.

Given that the parameter of interest in this technique, α , represents a combination of the differences in frequencies and flip angles at the gas-phase resonance between dissolved- and gas-phase “selective” excitations, it seems plausible that the global spectroscopy acquired during the calibration could be used to make the measurement of α . The reason this does not work in practice is that power amplifier settings for the calibration and the imaging are different, and the stop-band pulse performance varies non-linearly with RF amplifier power [15]. Therefore, the α measured from the calibration will be different from that used for imaging, and there is no straightforward way to relate the two beyond extensive empirical calibration (similar to the original problem we wish to avoid).

While this work focused exclusively on 1-point Dixon based chemical species separation approaches, gas-contamination will still be of concern for IDEAL based approaches. Theoretically, the acquisition of an additional echo to estimate gas-phase amplitude is all that is necessary, but practical problems remain, because (1) the gas-phase is so far off-resonance from the dissolved-phase components (3832 Hz at 1.5T) and (2) non-Cartesian trajectories are being used. In IDEAL, a single estimate of the complex-valued field modulation due to the combined effects of B_0 and T_2^* is assumed in each voxel. However, a single image voxel will contain gas-phase signal aliased from a wide range of positions, and

thus potentially a wide range of field modulations. In essence, if the spatial variations in the field modulation occur on the scale of the gas-phase point spread function, the gas phase amplitude is challenging to accurately model with IDEAL without additional constraints. Extending the gas-contamination correction to IDEAL-based approaches for HP ^{129}Xe imaging is therefore an important avenue of future research.

This work has several limitations. First, the digital phantom used makes several simplifying assumptions, specifically related to the regional distribution of the gas, barrier and RBC components. The quantitative evaluation of residual contamination error was performed under the assumption of uniform (within the lung) distributions of each component. This is clearly not representative of the lungs of our human subject cohort, yet it is unclear how this might bias the results. Given the similarity between simulated and human subject results, it seems reasonable to assume that the impact of dissolved-phase gas contamination and correction are well characterized through simulation.

A second limitation is the necessary assumption that a negligible (technically zero) dissolved-phase signal is present in the data at TE_2 . At $TE_2 \approx 4.2 \text{ ms}$, gas contamination signal (in simulations) was reduced to approximately 10% of the dissolved-phase signal, which is generally below the noise floor for a typical human subject experiment (SNR typically > 5). However, this amount of error could be problematic in some applications. To improve performance, either longer values of TE_2 are required, or an extension of the model to allow simultaneous estimation of the correction scale factor in the presence of dissolved-phase signal components. These improvements are left to future work.

Third, the scale factor corrections required for barrier-to-gas and RBC-to-gas ratio maps to account for flip angle differences between dissolved- and gas-phase excitations as well as component-specific T_2^* are necessarily over-simplified. Most notably, given that flip angles and T_2^* values are estimated from global spectroscopy, we are assuming spatial invariance, which is only valid for gross effects and ignores regional variations. Furthermore, the effect of applying different flip angles on the gas- and dissolved- phase compartments is not straightforward, given that these compartments are coupled through diffusive exchange. Despite delay times inserted into the design of the acquisition to facilitate mixing of these compartments, regional variations in this dynamic equilibrium may still exist, especially in disease. Excitation related attenuation in one is reflected in the other, possibly leading to bias. Developing robust methodology in the future to quantify and account for these potential sources of variation is a challenging, but important avenue of future research.

Finally, only 8 healthy subjects and 1 IPF patient were enrolled for this study, which limits statistical power and generality of the results, especially in disease. While the normal subjects were without clinical diagnosis of lung disease, many were older with potential variation in lung function. This likely contributes to inter-subject differences in quantitative measures after correction. A repeatability study would be a more effective means to demonstrate reduced variability in quantitative measures but is left to future work.

In conclusion, we have presented a novel method for removing gas-phase contamination of dissolved-phase HP ^{129}Xe MRI using a 2-echo acquisition. This technique is shown to

significantly improve the reliability, consistency and accuracy of 1-point Dixon based dissolved-phase HP ^{129}Xe images in simulation experiments with similar behavior in human subject experiments. The method is designed to mitigate the influence of suboptimal RF pulse behavior that will contribute to gas-phase excitation for multi-spectral acquisitions using HP ^{129}Xe .

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix: Generation of simulated data

Two three-dimensional digital phantoms were created, based upon the geometry of the lung. The first, based upon the airspaces of the lung and including the large airways, was used for the generation of gas-phase data (ρ_g). The second phantom was based on the parenchymal tissues and used for creating dissolved-phase data (ρ_d). The digital phantoms were created with dimensions of $64 \times 64 \times 64$ voxels, matching the image reconstruction matrix used in human subject scans. Both phantoms were designed to have uniform signal intensity across the lung volume and large airways.

From the digital phantoms, gas and dissolved-phase signal was generated based upon a signal model that accounts for the dynamics of the signal due to the T_2^* decay and off resonance frequencies of the components, as described by Eqs. 7a and 7b. Parameters of the

model include the chemical shift frequencies (f), transverse relaxation (T_2^*), and relative magnitudes of the barrier and RBC components (a_B and a_{RBC} , respectively). Complex, Gaussian random noise was added to evaluate the dependence of the method on the SNR of the on resonance gas and dissolved-phase images.

$$s_g(\vec{k}, n) = \mathcal{F}_{\vec{k}} \left[\rho_g e^{-\frac{TE_n + t_k}{T_2^*}} \right] \quad (7a)$$

$$s_{d,raw}(\vec{k}, n) = \mathcal{F}_{\vec{k}} \left[a_B \rho_d e^{\left(2\pi i f_B - \frac{1}{T_2^*}\right)(TE_n + t_k)} + a_{RBC} \rho_d e^{\left(2\pi i f_{RBC} - \frac{1}{T_2^*}\right)(TE_n + t_k)} + \alpha \rho_g e^{\left(2\pi i f_g - \frac{1}{T_2^*}\right)(TE_n + t_k)} \right] \quad (7b)$$

In this model, $\mathcal{F}_{\vec{k}}$ represents the discrete Fourier transform evaluated at the specified k-space vector, α is the intensity of the contaminant gas-phase signal, TE_n is the echo time of echo n , and t_k is the readout time of the sample k . For the 31.25 kHz bandwidth used in the human subject imaging and 79 points acquired in each radial projection, t_k will take values from the set $[0, 8 \mu\text{s}, 16 \mu\text{s}, \dots, 684 \mu\text{s}]$. The relative magnitudes of the barrier and RBC components were chosen such that they summed to 1 and had the specified RBC/Barrier ratio. Simulated signals were generated along the same 3-dimensional radial trajectory used in the human subject studies. Simulated values for the transverse relaxation and frequency shifts of each species during the dissolved-phase readout (Table 2) were based upon whole lung spectroscopy performed on the healthy normal volunteers included in this study.

Figure 1.

Pulse sequence diagram (A) of the 3D interleaved gas and dissolved-phase image acquisition shows the analog-to-digital converter (ADC) readout of two echoes following each of a spectrally selective dissolved-phase and then gas-phase RF excitation. The magnitude of the total gradient along the direction of a 3D radial projection is depicted, including readout and spoiler gradients at the end of each half of the TR. Flyback gradients are positioned after the readout at echo time, $TE_1 = 0.9$ ms, in preparation for the second echo at $TE_2 = 4.2$ ms. Gradients are identical in the dissolved-phase and gas-phase portions of each TR, and arrows indicate the echo and component acquired during each readout. A flow chart (B) depicts the steps taken by the proposed correction algorithm. The corresponding equations to each processing step are listed.

Figure 2.

Views in a single central slice of raw and corrected images from (A–F) simulated data and (G–L) data acquired in a healthy normal human subject (63 year old male, average RBC/Barrier ratio of 0.3). The lung boundary is drawn in white. Note the homogeneously elevated barrier signal (A,G) relative to corrected data (B,H), as well heterogeneous artifacts in the RBC (C,I) largely resolved following correction (D,J). Dissolved-phase data from TE₂ were reconstructed on the gas resonance (Eq. 6) to depict residual gas contamination images before (E,K) and after (F,L) correction, respectively.

Figure 3.

Quantitative simulation results depicting the expected theoretical performance of the proposed correction. The residual gas contamination error (as a % of dissolved-phase signal at TE_1), is approximately proportional to dissolved-phase signal remaining at TE_2 (**A**). However, the error is influenced by the relative phase between the RBC and tissue components of the dissolved-phase signal, evidenced by the local minimum in the residual contamination error near 3.7ms in (**A**). The image SNR also has no effect on the residual contamination error (**B**). The confidence intervals of the measures are smaller than the width of the line for $SNR > 2$. Similarly, residual error appears independent of both the (**C**) magnitude and (**D**) phase of the gas contamination itself.

Figure 4.

Distributions of the whole lung mean (A,C) and standard deviations (B,D) of barrier and RBC values in the simulated (top row) and human subject (bottom row) data with gas contamination and after correction. The large dispersion in the global mean values caused by the contaminant gas signal is removed in the simulation experiments, and for the Barrier/Gas ratio in the human subject experiments. The regional standard deviation after correction reflects reduced regional heterogeneity in both simulation and human subject results (* indicate $P < 0.05$).

Figure 5.

Whole lung histograms and parametric maps of barrier-to-gas ratio from 3 healthy normal human subjects (1 per row). Histograms show whole lung parameter distributions that are narrower and more similar across subjects following the gas contamination correction. Uncorrected parametric maps show numerous regions of defect and hyper-intensity that largely resolve post-correction.

Figure 6.

Whole lung histograms and parametric maps of barrier-to-gas ratio from 3 healthy normal human subjects (1 per row). Histograms show whole lung parameter distributions that are narrower and more similar across subjects following the gas contamination correction. Uncorrected parametric maps show numerous regions of defect and hyper-intensity that largely resolve post-correction.

Figure 7.

Whole lung histograms (A, B) and parametric maps (C, D) of barrier-to-gas ratio (A, C) and RBC-to-gas ratio (B, D), respectively, from a subject diagnosed with idiopathic pulmonary fibrosis. Regions of defect, which are expected to be present in this disease population, remain but in some cases enhanced, following correction with average values increased overall.

Table 1

Results summarizing impact of gas contaminant removal on quantitative measures of the dissolved-phases.

Simulation Data		
	Raw	Corrected
Mean Barrier	1.099 ± 0.453	1.048 ± 0.002
Mean RBC	0.447 ± 0.195	0.421 ± 0.001
St. Dev. of Barrier	0.348 ± 0.028	0.192 ± 0.003
St. Dev. of RBC	0.355 ± 0.049	0.182 ± 0.002
Human Subject Imaging		
	Raw (%)	Corrected (%)
Mean Barrier/Gas	1.13 ± 0.35	1.16 ± 0.22
Mean RBC/Gas	0.41 ± 0.18	0.42 ± 0.13
St. Dev. of Barrier/Gas	0.35 ± 0.07	0.31 ± 0.08
St. Dev. of RBC/Gas	0.35 ± 0.07	0.29 ± 0.07

Table 2Properties of gas and dissolved-phase HP ^{129}Xe at 1.5T

Species	T2* (ms)	Chemical Shift (PPM)	Frequency relative to RBC resonance (Hz)
Gas	25	0	3832
Barrier	2.4	198	347
RBC	2.1	217	0