Published in final edited form as:

J Magn Reson Imaging. 2014 February ; 39(2): 346–359. doi:10.1002/jmri.24181.

Regional Mapping of Gas Uptake by Blood and Tissue in the Human Lung using Hyperpolarized Xenon-129 MRI

Kun Qing, Ph.D.¹, Kai Ruppert, Ph.D.², Yun Jiang, M.S.³, Jaime F. Mata, Ph.D.², G. Wilson Miller, Ph.D.², Y. Michael Shim, M.D.⁴, Chengbo Wang, Ph.D.², Iulian C. Ruset, Ph.D.^{5,6}, F. William Hersman, Ph.D.^{5,6}, Talissa A. Altes, M.D.², and John P. Mugler III, Ph.D.^{1,2}

¹Department of Biomedical Engineering, University of Virginia School of Medicine, Charlottesville, VA, USA

²Center for In-vivo Hyperpolarized Gas MR Imaging, Department of Radiology and Medical Imaging, University of Virginia School of Medicine, Charlottesville, VA, USA

⁴Department of Medicine, Pulmonary and Critical Care, University of Virginia School of Medicine, Charlottesville, VA, USA

³Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, USA

⁵Xemed LLC, Durham, NH, USA

⁶Department of Physics, University of New Hampshire, Durham, NH, USA

Abstract

Purpose—To develop a breath-hold acquisition for regional mapping of ventilation and the fractions of hyperpolarized xenon-129 (Xe129) dissolved in tissue (lung parenchyma and plasma) and red blood cells (RBCs), and to perform an exploratory study to characterize data obtained in human subjects.

Materials and Methods—A three-dimensional, multi-echo, radial-trajectory pulse sequence was developed to obtain ventilation (gaseous Xe129), tissue and RBC images in healthy subjects, smokers and asthmatics. Signal ratios (total dissolved Xe129 to gas, tissue-to-gas, RBC-to-gas and RBC-to-tissue) were calculated from the images for quantitative comparison.

Results—Healthy subjects demonstrated generally uniform values within coronal slices, and a gradient in values along the anterior-to-posterior direction. In contrast, images and associated ratio maps in smokers and asthmatics were generally heterogeneous and exhibited values mostly lower than those in healthy subjects. Whole-lung values of total dissolved Xe129 to gas, tissue-to-gas, and RBC-to-gas ratios in healthy subjects were significantly larger than those in diseased subjects.

Conclusion—Regional maps of tissue and RBC fractions of dissolved Xe129 were obtained from a short breath-hold acquisition, well tolerated by healthy volunteers and subjects with obstructive lung disease. Marked differences were observed in spatial distributions and overall amounts of Xe129 dissolved in tissue and RBCs among healthy subjects, smokers and asthmatics.

Keywords

Lung imaging; pulmonary disease; gas uptake; hyperpolarized xenon-129

The primary function of the lung is exchange of respiratory gases. Impaired gas exchange in pulmonary disease can cause symptomatic shortness of breath, and in severe disease can progress to respiratory failure and death. Although our knowledge of gas-exchange status in individual patients is derived primarily from whole-lung measurements, gas exchange can vary substantially within the lung, especially for heterogeneous conditions like chronic obstructive pulmonary disease (COPD). Thus, regional assessment of ventilation and gas uptake would permit investigation of the fundamental process of gas exchange and improve our understanding of how heterogeneous diseases such as COPD affect gas exchange. In addition, the ability to easily and non-invasively quantify regional gas uptake may prove invaluable for evaluating new therapeutics for lung diseases. Nonetheless, despite many recent advances in medical imaging technology, there is no clinical imaging method that permits quantitative regional assessment of both gas delivery to the alveolar airspaces and gas uptake into the lung parenchyma and blood.

Numerous unique approaches for evaluating the structure and function of the lung have been developed by using the hyperpolarized noble gases helium-3 (He3) and xenon-129 (Xe129) as inhaled, gaseous contrast agents for MRI (1–5). In particular, the relatively high solubility of xenon in biological tissues (6), combined with an enormous range of chemical shifts upon solution which result from the extraordinary sensitivity of xenon to its environment (7), permit gas exchange and uptake to be explored using hyperpolarized Xe129 (8–14). Following inhalation, multiple MRI spectral peaks from Xe129 , each associated with a physically different compartment, can be detected in the lung (8,15–17). Although most of the Xe129 remains in the lung airspaces (“gas-phase” xenon) and corresponds to a single large spectral peak, about 1–2% of Xe129 dissolves in the lung parenchyma and blood (“dissolved-phase” xenon) and gives rise to smaller peaks with chemical shifts of approximately 200 ppm from the gas peak (8,15–17). Driven by diffusion, dissolved-phase xenon is in dynamic equilibrium with xenon in the airspaces. The associated continual exchange of xenon atoms between the gas and dissolved compartments, which have distinctly different resonance frequencies, is key for permitting gas uptake and exchange to be assessed using hyperpolarized Xe129 MRI. The quantitative characteristics of the exchange and uptake processes are determined by physiologically relevant parameters, such as the thickness of the blood-gas barrier (12), the ratio of functional tissue volume to alveolar volume (18), and the surface-to-volume ratio (10).

Even though the fraction of xenon dissolved in the lung parenchyma and blood is quite small, early studies of the human lung demonstrated that it was possible to detect these compartments of dissolved-phase Xe129 in whole-lung spectra (16). Images of dissolved-phase Xe129 were subsequently acquired in small animals by using multiple inhalations of hyperpolarized gas (12,19,20), although with current technology such a multiple-inhalation protocol is not feasible in humans. Muradian et al (21) also demonstrated the possibility of obtaining gas-phase and dissolved-phase images in humans at low field strength (0.2T) by decomposing the total xenon signal using the 3-point Dixon method. With recent improvements in gas-polarization systems (22), however, liter quantities of hyperpolarized Xe129 can be obtained with sufficiently high polarization to permit direct imaging of the dissolved phase in humans during a single breath-hold period. In 2010, two research groups demonstrated 3D imaging of dissolved-phase Xe129 in the human lung (23,24). While these two studies represent an important step toward realizing the potential wealth of information offered by dissolved-phase imaging on the functional status of the lung, they demonstrated only the ability to assess the total dissolved-phase signal, and not its individual components including Xe129 dissolved in lung parenchyma/plasma as well as Xe129 dissolved in red blood cells (RBCs). The recent study in animals by Driehuys et al (12) has already demonstrated the substantial potential value of discriminating the individual contributions

from parenchyma/plasma and RBCs for understanding the physiological consequences of pulmonary disease.

The overall goal of this study was to advance the capability of dissolved-phase hyperpolarized Xe129 imaging in humans by developing a robust approach for regional assessment of the individual signal contributions from Xe129 dissolved in the lung parenchyma/plasma and RBCs. Specifically, we aimed to: (1) develop a pulse sequence that permits regional mapping of both ventilation (Xe129 in the alveolar airspaces) and the fractions of Xe129 dissolved in the parenchyma/plasma and RBCs from multi-echo 3D data acquired in a single breath hold with a duration tolerable for subjects with lung disease; and (2) perform an exploratory study to characterize the signal fractions obtained from parenchyma/plasma and RBCs in healthy subjects compared to those from subjects with pulmonary disease, including COPD and asthma. Acquisition of ventilation and gas-uptake images with matched spatial resolution during the same breath hold provides the necessary basis for normalizing the dissolved-phase signals (24), thus permitting quantitative comparison of the parenchyma/plasma and RBC fractions among subjects. For simplicity, the parenchyma/plasma component will be referred to using the single term “tissue” for the remainder of the paper.

MATERIALS AND METHODS

Dissolved-phase Imaging Technique

Independent Excitation of Gas-phase and Dissolved-phase Signals—The primary peaks in a spectrum of Xe129 in the healthy human lung correspond to Xe129 in the lung airspaces (at 0 ppm, by definition), dissolved in tissue (i.e., lung parenchyma and blood plasma, at approximately 198 ppm), and bound to hemoglobin in RBCs (at approximately 218 ppm) (16,23,24). The technique proposed by Mugler et al (24) took advantage of this large chemical-shift difference between the gas-phase and dissolved-phase components to obtain both components in the same image, separated along the frequency-encoding direction due to the corresponding large difference in resonance frequency. However, a disadvantage of this method is that spatial resolution and receiver bandwidth are inherently linked, and so increasing the spatial resolution in the frequency-encoding direction requires the bandwidth to decrease, which in turn increases chemical-shift displacement along the frequency-encoding direction between the tissue and RBC components of the dissolved-phase signal, and forces a longer minimum TE unless half-echo sampling is used. A relatively long TE is problematic because T2* values for the dissolved-phase components are quite short (about 2 ms) (23,25). Another disadvantage is that this method does not depict the tissue and RBC components separately.

To overcome the echo-time and receiver-bandwidth limitations described above, we chose to perform independent excitation of the gas-phase and dissolved-phase components as described recently by Kaushik et al (26). Since, at any given instant, the gas-phase magnetization in the lung following inhalation of hyperpolarized Xe129 is roughly 100 times larger than the dissolved-phase magnetization, it is critical for the radiofrequency (RF) pulse used to excite dissolved-phase signals to provide extremely low excitation at the gas-phase frequency so that independent excitation of dissolved-phase and gas-phase signals can be achieved. Using the Shinnar-Le Roux algorithm for RF-pulse design incorporated into the open-source MATPULSE tool (version 5.1) (27), we designed an optimized low-flip-angle excitation RF pulse for this application (reject-band ripple, 0.001%; duration, 1.3 ms). A water phantom was imaged to experimentally evaluate the performance of this RF pulse using the following pulse-sequence parameters: spoiled gradient-echo pulse sequence with TR/TE = 100/0.74 msec, flip angle = 30°, voxel volume = $7.6 \times 7.6 \times 17 \text{ mm}^3$.

Multi-echo 3D-Radial Pulse Sequence—A study in rabbits by Ruppert et al (28) found a periodic variation in dissolved-phase Xe129 signal intensity with echo time, consistent with T_2^* decay superimposed on a signal variation from the evolution of the phase difference between the tissue and RBC transverse magnetizations. Successful implementation of a Dixon-based (or an optimized version such as IDEAL) method (29–32) for accelerated spectroscopic imaging of the tissue and RBC fractions requires that there are a small number (for example, two) of distinct resonances, fairly close in frequency, and that the phase difference(s) among the corresponding signals evolves linearly with time. These preliminary results from rabbits, as well as results in rats from Driehuys et al (12), indicate that a Dixon-based method provides the data necessary to separately depict the tissue and RBC components, and thus we chose this approach for our current work. Specifically, we implemented a pulse sequence based on radial k -space sampling that, to permit separation of the two dissolved-phase frequency components using an IDEAL-type method (31,32), collects three echoes for dissolved-phase Xe129 following each excitation RF pulse applied at a frequency midway between those for the tissue and RBC resonances (+3660 Hz from the gas phase at 1.5T), and, to permit calculation of a B_0 map for reference, collects two echoes for gas-phase Xe129 following each excitation RF pulse applied at the gas-phase frequency. Figure 1 shows the pulse-sequence timing diagram for one repetition of the combined gas-phase, dissolved-phase multi-echo 3D-radial acquisition.

Three-dimensional radial imaging was used because the very short T_2^* values of dissolved-phase Xe129 require short echo times to obtain adequate signal-to-noise ratios. A radial-out (half-echo) acquisition was used for the first echo of both the dissolved-phase and gas-phase portions of the pulse sequence to provide the shortest TE possible. The TR and flip-angle values can be adjusted to modify the contributions (i.e., relative amount and physical location) from the dissolved-phase compartments, yielding a total acquisition time of approximately 10 sec or greater. In this work, however, fixed TR and flip-angle values were used to permit comparison among subjects. The pulse-sequence parameters included: TR = 19 msec, TE1/TE2/TE3 = 0.74/2.36/3.98 msec for the dissolved phase and TE1/TE2 = 0.74/2.36 msec for the gas phase, flip angle = 23° for the dissolved phase and 0.4° for the gas phase, and acquisition time = 11 sec. Our current implementation provides 3D image sets covering the whole lung with a voxel volume of $7.6 \times 7.6 \times 17 \text{ mm}^3$, with the largest voxel dimension in the anterior-posterior direction. The radial readouts were oversampled by a factor of approximately 3 (corresponding, in theory, to a field-of-view of about 1 m.) Angular undersampling was used to accelerate the acquisition. The corresponding acceleration factors were 2.8 for the half echoes and 1.4 for the full (symmetric) echoes. The golden-angle method was used for arranging the undersampling scheme (33).

To provide whole-lung data for comparison with the image-based results, the pulse sequence described above also included collection of a free-induction decay (FID) for dissolved-phase Xe129 at the end of the acquisition. For healthy subjects, in particular, whole-lung values for the RBC fraction of the total dissolved-phase signal should closely match corresponding quantities calculated from the mean of values derived from 3D image sets. This data also permits estimation of the frequency difference between resonances and the average T_2^* values. The FID was acquired using the same excitation RF pulse as the imaging portion of the pulse sequence. The data-acquisition period was 54 msec, starting 0.74 msec from the center of the RF pulse.

The undersampled 3D-radial image data were reconstructed using the quadratic penalized weighted-least-squares (QPWLS) via preconditioned conjugate gradients (PCG) algorithm (34). To suppress image blurring secondary to depletion of the non-equilibrium hyperpolarized-gas magnetization during the acquisition, signal decay was compensated by

normalizing the signal intensities for each echo time by the corresponding echo data recorded midway through the acquisition.

Separation of Tissue and RBC Components using Hierarchical IDEAL—For proton MRI, the chemical-shift difference between water and fat is approximately 3.5 ppm, corresponding to a frequency separation of 220 Hz at 1.5T and 450 Hz at 3T. While the chemical-shift difference between tissue and RBCs for Xe129 is approximately 20 ppm, the corresponding frequency separation of 350 Hz at 1.5T is similar to the fat-water frequency difference due to the low gyromagnetic ratio of Xe129. Thus, it is reasonable to expect that spectral decomposition techniques optimized for fat-water separation in proton MRI should work well for separation of the tissue and RBC components of dissolved-phase Xe129. Nonetheless, an important difference between our problem and fat-water separation is that the T_2^* values in our case are much shorter than typical T_2^* values for fat and water in vivo. Thus, the method we choose should explicitly consider the effects of T_2^* decay. For this preliminary study, we have used the Hierarchical IDEAL method (35–37), which is a multiresolution approach that incorporates a T_2^* estimate into the decomposition. Reference B_0 maps obtained from the two gas-phase echoes were input as the initial field map for spectral decomposition, and compared to the final field map output by the Hierarchical IDEAL algorithm.

A possible limitation of using the Hierarchical IDEAL method is that the T_2^* value for RBCs may differ from that for tissue (as described in the Results section), while the method incorporates only a single T_2^* value for both components. Although the FID data acquired at the end of each image acquisition provides estimates of average T_2^* values for each of the two components, it is likely that local T_2^* values will vary across the lung, particularly in disease. For this case, it is challenging to both separate the components and obtain regional estimates of T_2^* for the two components, although this is the topic of ongoing research. To obtain an estimate of the impact of T_2^* variation among components on the accuracy of the predicted component fractions, we performed a theoretical calculation using the Hierarchical IDEAL algorithm to determine the difference between input and estimated RBC fractions as a function of the T_2^* value for RBCs, assuming a typical T_2^* value of 2.2 msec for tissue (determined from in-vivo data as described in the Results section).

Human Subjects

The experiments were performed under a physician's Investigational New Drug (IND) application for MR imaging with hyperpolarized Xe129 using a protocol approved by our Institutional Review Board. Written informed consent was obtained from each subject after the nature of the procedure had been fully explained.

The study group was composed of 5 healthy, nonsmoking subjects, 3 current or past smokers including 1 with mild (GOLD Stage I) COPD who had smoked for 15 years and two with severe (GOLD Stage III) smoking-related COPD, and 2 subjects with asthma (Table 1). Spirometry was performed immediately before and after the imaging session using a hand-held device (Koko; PDS Ferraris, Louisville, CO). Per IND requirements, 12-lead electrocardiography (HP Pagewriter XLi; Hewlett Packard Co., Palo Alto, CA) was performed in subjects 40 years or older immediately before and after MR imaging. Female subjects received a urine pregnancy test prior to imaging and were excluded from participation if pregnant. Before the subject was placed in the RF coil for MR imaging, a test dose of xenon (not hyperpolarized) was administered. The subject was excluded from participation if the test dose was not well tolerated. Throughout the imaging session the subject's heart rate and oxygen saturation level were monitored (3150 MRI Patient Monitor;

Invivo Research Inc., Orlando, FL), and the subject was assessed for central nervous system side (CNS) effects of the inhaled xenon. All studies were supervised by a physician.

Gas Polarization and Administration

Enriched xenon gas (87% Xe129) was polarized by collisional spin exchange with an optically-pumped rubidium vapor using a prototype commercial system (XeBox-E10; Xemed, LLC, Durham, NH), based on the flowing approach for hyperpolarized-gas production (22,38), that provided gas polarization of approximately 40%. Immediately before MR imaging, the desired volume of hyperpolarized Xe129 gas was dispensed into a Tedlar bag (Jensen Inert Products, Coral Springs, FL) and connected to one arm of a plastic Y connector. A second Tedlar bag containing medical-grade nitrogen was connected to the other arm of the Y connector. Starting from residual lung volume (maximum expiration), the subject inhaled the contents of the two bags and was then instructed to suspend respiration for the duration of data collection. For the dissolved-phase image acquisitions, the total gas volume was approximately one-third of the subject's forced vital capacity as determined by spirometry.

MR Measurements

MR acquisitions were performed using a 1.5T commercial whole-body MR scanner (Avanto; Siemens Medical Solutions, Malvern PA) equipped with the multinuclear imaging option. Two Xe129 RF coils were used for the experiments, including a flexible, circularly-polarized, vest-shaped chest RF coil (Clinical MR Solutions, Brookfield, WI) and a rigid, custom-built, linearly-polarized chest RF coil. Both RF coils were blocked at the proton resonance frequency to permit proton MRI to be performed with the Xe129 RF coil in place. The subject was positioned supine on the scanner table with the Xe129 RF coil around their chest. Breath-hold scout images were obtained using conventional proton MRI for positioning of the Xe129 acquisitions. Next, the subject inhaled a gas mixture containing approximately 200 ml of hyperpolarized Xe129 and a breath-hold acquisition was performed for calibration of the scanner center frequency and transmitter voltage. For the 3D dissolved-phase image acquisition, the subject inhaled a gas mixture containing approximately 1 L of hyperpolarized Xe129. In one of the healthy subjects, one smoker and one asthmatic (subjects H3, S2 and A1 in Table 1), the 3D dissolved-phase image acquisition was repeated, on the same day for the healthy and smoker subjects, and on different days for the asthmatic. In a subset of the subjects (two healthy, all smokers, one asthmatic), coronal Xe129 diffusion-weighting images covering the lung volume were also acquired for calculation of apparent diffusion coefficient (ADC) values using the following pulse-sequence parameters: TR/TE = 13.8/9.4 msec, flip angle = 8.5°, voxel volume = $6 \times 6 \times 25 \text{ mm}^3$, b values = 0 and 10 s/cm², diffusion-sensitization waveform = bipolar trapezoid with ramp time = 0.3 msec and flattop time = 2.6 msec, diffusion-sensitization direction = slice, diffusion time = 3.2 msec.

Data Analysis

Data were analyzed offline using custom routines programmed in MATLAB (MathWorks, Natick, MA) or PV-WAVE (Rogue Wave Software, Boulder, CO). The FID fits were performed using 1stOPT (7D Soft High Tech. Inc., Beijing China).

Image Processing—Coronal images depicting the distribution of Xe129 dissolved in tissues and RBCs were calculated for each subject from the three dissolved-phase echoes using the Hierarchical IDEAL method (35–37), programmed in MATLAB. To eliminate background regions from subsequent analysis, a mask was created from the first echo of the

dissolved-phase images using a signal-intensity-based threshold, and applied to the corresponding tissue and RBC images.

Because absolute dissolved-phase signal intensities have no physical meaning, four ratios were calculated for comparison among subjects; the ratios included total dissolved-phase signal (estimated for an echo time of zero) to gas, tissue-to-gas, RBC-to-gas, and RBC-to-tissue. For the RBC-to-tissue ratio, an additional mask, created from the tissue images using a signal-intensity-based threshold, was used to suppress isolated regions that exhibited high RBC signals but essentially no tissue signal, such as the heart. Note that these four ratios are not independent; the total dissolved-phase signal to gas and RBC-to-tissue ratios can be calculated from the tissue-to-gas and RBC-to-gas ratios. Nonetheless, the total dissolved-phase signal to gas ratio is useful for comparison to results from previous studies in which only the total dissolved-phase signal was detected (23,24). In some cases, the RBC-to-tissue ratio clearly illustrates trends that are not immediately obvious from the tissue-to-gas and RBC-to-gas ratios alone. To account for the difference between the flip-angle value used to excite the gas-phase component and that used to excite the dissolved-phase components, the three ratios involving dissolved-phase components and the gas phase were scaled by the sine of the gas-phase flip angle divided by the sine of the dissolved-phase flip angle. In this manner, each reflects the ratio of the respective dissolved-phase longitudinal magnetization to the gas-phase longitudinal magnetization. The total dissolved-phase signal to gas, tissue-to-gas and RBC-to-gas ratios are presented as percentages, and the RBC-to-tissue ratio is presented as a fractional value. For comparison to gas, tissue and RBC images, coronal tissue-to-gas, RBC-to-gas and RBC-to-tissue ratio maps are presented on scales of 0.0 to 1.8%, 0.0 to 0.9%, and 0.0 to 0.7, respectively. For one subject with asthma (A2) who exhibited elevated RBC-to-tissue ratios, corresponding maps are presented on a scale of 0.0 to 1.0.

At each coronal slice position, mean values for the four ratios described above were calculated from the corresponding values within the ventilated region of the lung. To permit comparison of the slice-by-slice ratios among subjects with different lung sizes in the anterior-to-posterior direction, the values were plotted on a normalized scale, where 0 corresponds to the most anterior slice and 1 corresponds to the most posterior slice. The mean and standard deviation of these ratios were also calculated for the lung as a whole. Similarly, whole-lung mean values for the RBC fraction of the total dissolved-phase signal were calculated for comparison to corresponding values derived from FID data.

Results from the repeated acquisitions in three subjects were compared by calculating the difference between ratio values on a slice-by-slice basis and then averaging the absolute values of these differences, and also by calculating the difference between corresponding whole-lung values.

Following application of a signal-intensity threshold to suppress background noise, ADC maps were calculated on a pixel-by-pixel basis from the $b = 0$ and 10 s/cm^2 diffusion-weighted images using the standard formula (natural logarithm of the signal ratio of the $b = 0 \text{ s/cm}^2$ image to the $b = 10 \text{ s/cm}^2$ image, divided by the difference in b values). For each subject, the mean and standard deviation of the ADC values were calculated for each slice and for the whole lung.

FID Processing—A signal model that was comprised of two mono-exponential decays, each characterized by a frequency, phase, amplitude and rate of decay ($T2^*$), was fit to the dissolved-phase FID data from each subject using nonlinear, least-squares regression. The (whole-lung) RBC fraction of the total dissolved-phase signal for each subject was calculated from the amplitudes of the mono-exponential decays.

Statistical Comparisons—The whole-lung mean values for the ratios of total dissolved-phase signal to gas, tissue-to-gas, RBC-to-gas, and RBC-to-tissue from healthy subjects were compared to those from the smokers and asthmatics using a two-tailed unpaired *t*-test. The RBC fractions derived from FID data were compared to those calculated from image data using a two-tailed paired *t*-test. A *p*-value of 0.05 or less was considered to be statistically significant.

RESULTS

RF-pulse Performance for Dissolved-phase Excitation

The RF pulse designed for dissolved-phase excitation was used to image a water phantom. The resulting signal-to-noise ratio was 140 when the RF pulse was applied at the resonance frequency for water, and only thermal noise could be seen in the image when the frequency was shifted to +3660 Hz (the frequency difference between gas-phase and dissolved-phase Xe129 at 1.5T). This result indicates that, when applied at the dissolved-phase resonance frequency, the RF pulse should yield negligible excitation of gas-phase Xe129 in the lung.

Effect of T2* Differences on the Accuracy of Tissue/RBC Separation

Theoretical calculations indicate that a difference between the T2* for RBCs and that for tissue should yield only minor errors in the predicted amounts of RBCs and tissue comprising the total dissolved-phase signal as determined using the Hierarchical IDEAL algorithm. Figure 2 shows the theoretically predicted percentage error in the fraction of RBCs as a function of the difference between the RBC and tissue T2* values, assuming a typical T2* value of 2.2 msec for tissue. Over the range of differences expected in vivo (see table of T2* values discussed below), the maximum absolute error is approximately 5% and occurs when the RBC and tissue fractions are both about 0.5. For an RBC fraction of 0.3 or less, as typically found with our measurements in vivo, the absolute error is approximately 3% or less. This results also suggests that variations in T2* values across the lung, and within the range considered, should generate relatively small errors in the estimated amounts of RBCs and tissue comprising the total dissolved-phase signal.

Subject Demographics, Spirometry and Tolerance of Imaging Procedures

Demographics and baseline (pre-imaging) spirometry results for the 10 subjects who participated in the study are provided in Table 1. The five healthy subjects and one asthmatic (A2) had spirometry indices in the normal range; the values for smokers S2 and S3 were consistent with GOLD stage III COPD. The FEV₁/FVC ratio indicated mild COPD for smoker S1 and was well below the normal range for asthmatic A1.

All subjects tolerated the test dose of xenon well. All subjects, except one, were able to inhale the full volume of gas used for Xe129 MR imaging, and all were able to hold their breath for the 11-sec 3D dissolved-phase acquisition. Subject S3 was able to inhale only a portion (estimated to be greater than 50%) of the total gas volume. This resulted in poor signal-to-noise for the third echo of the dissolved-phase images and thus calculation of tissue and RBC images was not performed for this subject; however, total dissolved-phase results are included below. The xenon inhalations for imaging were also well tolerated by all subjects, although 6 of the 10 subjects experienced mild transient CNS side effects, such as slight tingling or lightheadedness.

Regional Mapping of Gas Uptake by Lung Tissue and RBCs

Healthy Subjects—Four of the healthy subjects (H1 through H4) demonstrated generally uniform distributions of gas-phase signal intensities throughout the lung volume, and

uniform dissolved-phase signal intensities within each coronal image slice. Healthy subject H5, who was much older than the other healthy subjects, had several ventilation defects. In all healthy subjects, the dissolved-phase signal intensities increased toward the posterior of the lung as also observed in previous studies (23,24), consistent with the well-known gravity-dependent gradient in lung tissue density from anterior to posterior in the supine position. Representative results for decomposing the signal intensities from the three dissolved-phase echoes into RBC and tissue images using Hierarchical IDEAL are illustrated in Fig. 3, which shows coronal slices for the gas-phase, tissue and RBC components from subject H2. (For all subjects, the final B_0 field map output by the Hierarchical IDEAL algorithm was, in ventilated regions of the lung, within 10 Hz of the input field map calculated from the two gas-phase echoes, which indicated that the B_0 and average $T2^*$ estimations were relatively accurate.) As seen in Fig. 3, portions of large vessels and/or part of or even the whole shape of the left heart chambers could be seen in the RBC images of some subjects. We postulate that the variation in appearance of these structures among subjects may have been associated with a variation in heart rate among subjects. Gas, tissue and RBC images for the whole lung, as well as corresponding tissue-to-gas, RBC-to-gas and RBC-to-tissue ratio maps, are shown in Fig. 4 for subject H3. Analogous to the dissolved-phase signal intensities themselves, the tissue-to-gas and RBC-to-gas ratio maps clearly show the anterior-to-posterior gradient. However, the RBC-to-tissue ratio is more uniform from anterior to posterior, and is slightly higher in the mid-coronal slices for this subject. Diffusion-weighted imaging was performed in healthy subjects H4 and H5, who had whole-lung ADC values of 0.033 ± 0.013 and 0.045 ± 0.009 cm^2/s (mean $\pm$ standard deviation), respectively, which were comparable to those for healthy subjects of similar age in the study of Kaushik et al (39), although our maximum b value (10 s/cm^2) was lower than that of Kaushik et al (12 or 18.76 s/cm^2).

The four ratios that were calculated for each coronal slice are plotted in Fig. 5 for the five healthy subjects, and the means and standard deviations of the ratios for the whole lung are plotted in Fig. 6 (all subjects). (As described in Materials and Methods, note that the total dissolved-phase signal to gas, tissue-to-gas and RBC-to-gas ratios are expressed as percentages, whereas the RBC-to-tissue ratio is expressed as a fractional value.) The tissue-to-gas and RBC-to-gas plots, and hence the total dissolved-phase to gas plot, show the general trend of increasing values from anterior to posterior, as discussed above, while the RBC-to-tissue ratio is generally flatter from anterior to posterior, but varies among subjects. The slice-by-slice and whole lung values for all ratios (except RBC-to-tissue ratios for subject H2) were similar among healthy subjects H1 through H4, while the values for subject H5 (the oldest subject) were generally lower. (When comparing whole-lung values (Fig. 7) between healthy subjects and smokers or asthmatics, it is important to note that a substantial fraction of the standard deviation for healthy subjects is attributable to the physiological anterior-to-posterior gradient, whereas for many of the diseased subjects a substantial fraction of the standard deviation is attributable to the effects of the disease process.)

Subjects with Lung Disease

Smokers: The values for the tissue-to-gas and RBC-to-gas ratios for the smokers, and thus the corresponding total dissolved-phase to gas ratios, were generally lower than those for healthy subjects as seen in Fig. 6 (whole-lung values) and Fig. 7 (slice-by-slice values for all diseased subjects compared to median values for healthy subjects). While, compared to severe COPD subject S2, mild COPD subject S1 had higher values for the total dissolved-phase to gas, RBC-to-gas, and RBC-to-tissue ratios, the tissue-to-gas ratios were similar for subjects S1 and S2. Subject S1 showed anterior-to-posterior gradients, similar to those for the healthy subjects, in tissue-to-gas and RBC-to-gas (and consequently total dissolved-

phase to gas) ratios, while the anterior-to-posterior variations for COPD subject S2 were much less. However, subject S1 also showed an anterior-to-posterior gradient in the RBC-to-tissue ratio, as well as values higher than median values for healthy subjects. In contrast, subject S2 did not show a substantial anterior-to-posterior gradient in the RBC-to-tissue ratio, and the values were well below the median values for healthy subjects.

The whole-lung ADC values for subjects S1, S2, and S3 were 0.043 ± 0.012 , 0.056 ± 0.009 , and 0.075 ± 0.014 cm²/s, respectively. The elevated ADC values for COPD subjects S2 and S3 are consistent with emphysema (39). Subject S3, who had difficulty inhaling the total volume of gas, had a higher mean ADC in the lung parenchyma than any of those found in emphysema by Kaushik et al (39). This high value suggests substantial tissue destruction, which is consistent with the very low dissolved-phase signal intensities for this subject (Fig. 6a).

Gas, tissue and RBC images for the whole lung, as well as corresponding tissue-to-gas, RBC-to-gas and RBC-to-tissue ratio maps, are shown in Fig. 8 for COPD subject S2. The images exhibit numerous ventilation defects. Compared to a healthy subject (Fig. 4), the ratio values for subject S2 are lower and the ratio maps at each coronal position are much more inhomogeneous.

Asthmatics: The two asthmatics included in our study were quite different in age (A1, 53 years; A2, 16 years). Except for RBC-to-gas ratios (Fig. 7c), the results from the two asthmatics were markedly different; subject A1 showed higher values for total dissolved-phase to gas and tissue-to-gas ratios (Fig. 7a, b), but much lower values for RBC-to-tissue ratios (Fig. 7d). The ratio values for both asthmatics were lower than those for healthy subjects (Fig. 7), with the exception of the RBC-to-tissue ratios for subject A2, which were higher than those for all other subjects in our study (Fig. 7d). The whole-lung ADC value for subject A1 was 0.049 ± 0.014 cm²/s, which is toward the high end of normal values for the subject's age (39).

Gas, tissue and RBC images, as well as corresponding tissue-to-gas, RBC-to-gas and RBC-to-tissue ratio maps from the two asthmatics are shown in Fig. 9. Both asthmatics exhibited ventilation defects, as expected. The ratio maps illustrate how both asthmatics differ from a healthy subject (Fig. 4), but interestingly also how the two asthmatics differ substantially from one another, as discussed above. For example, while subject A2 showed relatively uniform tissue-to-gas ratios, subject A1 had elevated values in both apices in conjunction with reduced RBC-to-gas ratios (Fig. 9b).

Statistical comparison: The whole-lung mean values for the ratios of total dissolved-phase signal to gas, tissue-to-gas and RBC-to-gas for the healthy subjects were significantly larger than those for the disease group (smokers and asthmatics, $p < 0.01$ for all ratios). The RBC-to-tissue ratio for the healthy subjects was not significantly larger than that for the disease group.

Repeatability—For the three subjects in which 3D dissolved-phase acquisitions were repeated (subjects H3, S2 and A1), the percent differences in the four ratios of total dissolved-phase to gas, tissue-to-gas, RBC-to-gas and RBC-to-tissue, averaged over the 3 subjects, were 7%, 9%, 12% and 5% for slice-by-slice values (mean over slices) and 6%, 5%, 12% and 5% for whole-lung values, respectively. We believe that at least some of this variation may have been caused by differences in the level of lung inflation between studies. The asthmatic, who was imaged on different days, had the largest differences for 3 of the slice-by-slice comparisons and one of the global comparisons. However, this subject showed

a visible difference in the location and size of ventilation defects on the two days. This change in presentation of his asthma likely contributed to differences between ratio values.

Image versus FID Data—Global estimates of the $T2^*$ values for tissue and RBCs derived from FID data are shown in Table 2. The $T2^*$ values for tissue varied from 1.9 to 2.3 msec, while those for RBCs varied from 1.7 to 2.2 msec. The table also shows the values for the RBC fraction of the total dissolved-phase signal derived from FID data compared to those calculated from image data; considering all subjects (except S3), the FID and image-based RBC fractions were not significantly different. The average R^2 value for the FID fits was 0.994.

DISCUSSION

We have demonstrated a 3D radial-trajectory pulse sequence that acquires multi-echo Xe129 dissolved-phase and gas-phase images covering the whole human lung during a short breath hold of 11 sec. By using the Hierarchical IDEAL method, originally developed to separate water and fat in proton MRI, we decomposed the multi-echo dissolved-phase signals into two components: Xe129 dissolved in RBCs and Xe129 dissolved in tissue (i.e., lung parenchyma and blood plasma). Conventional chemical shift imaging provides an alternative approach for obtaining this information from the lung (19), and Reis et al (40) recently presented results for 3D chemical shift imaging of Xe129 in humans. Nonetheless, full phase-encoding of the Xe129 signals is inefficient compared to the approach demonstrated here; the implementation shown by Reis et al required a breath-hold duration of more than 20 sec while providing voxel volumes roughly 8 times larger than those presented in our work.

The pulse-sequence parameters were chosen so that sufficient signal-to-noise ratio was maintained for collection of three 3D image sets with different echo times despite the low dissolved-phase signal strength and its short $T2^*$. In addition to the effect of $T1$ and $T2^*$ relaxation, the precise signal composition for any flip angle, TR combination depends on a variety of factors including the alveolar surface-to-volume ratio and alveolar wall thickness, xenon solubility, hematocrit, pulmonary perfusion, and tissue composition (which may be altered in diseased subjects, e.g., by inflammation or fibrotic deposits), as well as any other factors that affect the diffusional processes by which the Xe129 atoms exchange between the various compartments. In general, the contribution from any given dissolved-phase Xe129 component decreases in proportion to the number of excitation RF pulses it has experienced and the associated flip angles for the pulses. Thus, because a low flip angle was used for our experiments, the resulting dissolved-phase signals reflect contributions originating from Xe129 atoms at various distances from the exchange sites. If the flip angle is sufficiently small and the TR sufficiently long for a given perfusion rate, it is feasible in humans to image Xe129 in the RBC compartment as far downstream as the left ventricle of the heart (Fig. 3). Due to the higher heart rate and the shorter distances that need to be traversed, the ascending aorta can be depicted in small animals such as rabbits (41).

Since the dissolved-phase signal reflects contributions originating from Xe129 atoms at various distances from the exchange sites, as noted above, the signal corresponds to a range of exchange times, instead of a single exchange time as in the chemical shift saturation recovery (10) and xenon polarization transfer contrast (9) techniques. This situation complicates calculation of quantitative parameters (e.g., wall thickness) from the data provided by our technique. Nonetheless, with appropriate choice of TR and flip angle values, and using models available in the literature (42–44), it may be possible in the future to derive quantitative estimates from multiple measurements.

In general, the images for the RBC component appeared less uniform than those for the tissue component or the gas phase. We believe that the primary reason for this appearance is a lower signal-to-noise ratio, secondary to the relatively low signal ratio of RBCs to tissue (typically less than 0.4, Figure 6d). However, it is possible that other effects, such as blood flow, contributed to this appearance. Considering the low flow velocities in the lung parenchyma, where the majority of dissolved Xe129 resides, together with the relatively low flip angle at the dissolved-phase (23°) and short echo times, we expect that the flow sensitivity of the technique is relatively low. Nonetheless, the potential for flow artifacts in the RBC images should be considered as the technique is further evaluated.

The total dissolved-phase to gas ratio reflects Xe129 gas-uptake efficiency by the lung parenchyma within a timeframe dictated by the selected pulse-sequence parameters. The tissue-to-gas ratio is primarily indicative of the entire alveolar wall volume, but the result from a single measurement does not reveal whether a deviation from its normal value is due to a change in alveolar size (number of walls per unit volume), a change in alveolar wall thickness, or a combination of both. (Two or more measurements using different pulse-sequence parameters may provide a means to separate these effects, although additional research is required to evaluate this possibility.) The RBC-to-gas ratio quantifies Xe129 transport from the alveolar airspaces to the bloodstream, similar to the diffusion capacity of the lung for carbon monoxide (DLCO) global lung-function test. Finally, the RBC-to-tissue ratio might reveal disease-related shifts in the relative compartment sizes. For instance, a decrease in this ratio in a subject with normal hematocrit could suggest thickening of the alveolar walls. Such thickening would also be reflected by an increased tissue-to-gas ratio, if not accompanied by concomitant tissue destruction which offsets the increase in tissue volume.

As expected, in healthy subjects, we found that the ventilation, tissue and RBC images, as well as their associated ratios discussed above, were uniform within coronal slices of the lung. We also observed an anterior-posterior gradient in the ratio maps and ratio plots that reflects the well-documented tissue compression in dependent areas of the lung. On the other hand, the 3D image sets acquired from subjects with obstructive lung disease (COPD and asthma) revealed inhomogeneous distributions in the images as well as in the ratio maps, and slice-by-slice and whole-lung ratio values which differed from those for healthy subjects. Nonetheless, one of the limitations of this exploratory study was that the majority of the healthy subjects were much younger than the COPD subjects.

The two COPD GOLD Stage III subjects showed low total dissolved-phase to gas ratios, which is consistent with the high ADC values found with diffusion-weighted imaging, indicating an increase of the average distance between alveolar walls due to tissue destruction. The RBC-to-tissue ratio was also low in one of these subjects, which might indicate thickening of the alveolar walls secondary to inflammation, which would reduce the amount of Xe129 diffusing to the RBCs while increasing the volume of the tissue compartment. This indication of septal wall thickening in COPD is consistent with that found by Dregely et al (18) using the multiple-exchange-time xenon polarization transfer contrast technique, and also with that detected using morphometric techniques in human lung specimens from subjects with emphysema (45). Alternatively, decreased pulmonary capillary perfusion could also cause a low RBC-to-tissue ratio, and patients with COPD are known to have pulmonary vascular pruning apparent on pulmonary angiography. Interestingly, the smoker with mild COPD exhibited a lower than normal tissue-to-gas ratio, while the RBC-to-gas ratio was similar to those for healthy subjects and the RBC-to-tissue ratio was somewhat elevated. This could indicate normal alveolar wall thickness, but the onset of emphysematous tissue destruction.

The two asthmatics showed markedly different patterns. The changes in subject A1, a 53-year old who exhibited numerous ventilation defects, were qualitatively similar to those in COPD subject S2. These changes suggest increased alveolar wall thickness in conjunction with hyperexpansion, or possibly with mild emphysema-like tissue destruction as indicated by the ADC value found in this asthmatic, which was at the high end of the normal range for the subject's age. By decreasing the amount of dissolved Xe129 per unit volume, either hyperexpansion or tissue destruction would be expected to decrease the ratios of dissolved-Xe129 components to gas compared to those for healthy subjects. In the 16-year old asthmatic A2, we found a very high RBC-to tissue ratio, which, overall, was even higher than those in healthy subjects. However, the total dissolved-phase to gas and tissue-to-gas ratios were very low compared to those in healthy subjects, possibly due to lung hyperexpansion. A frequent finding in asthmatics is an elevated residual volume, which indicates lung hyperexpansion. Perhaps the young asthmatic (A2) had an increased cardiac output to compensate for his lung disease, resulting in the high RBC-to-tissue ratio.

In three subjects we tested the repeatability of the acquisition method introduced in this study. While the results for repeated acquisitions were reasonably consistent, we believe, as mentioned above, that differences in the level of lung inflation were a major source of the observed variability. We are currently investigating approaches for measuring the level of lung inflation using proton image sets acquired during the same breath-hold period, and assessing whether the various ratio values can be corrected or normalized based on the level of lung inflation.

The FID data acquired during the same breath hold as the imaging data permitted a preliminary validation of the relative signals obtained from RBCs and tissue using our 3D method. The whole-lung RBC fractions calculated from image data were comparable to those from FID data (Table 2), although exact correspondence is not expected considering fundamental differences between the two acquisitions. Further validation, including the ratios of dissolved-Xe129 components to gas, will be important to perform. In future studies, we plan to validate the results from the method presented here against those obtained using conventional 3D chemical shift imaging (40).

In conclusion, we have demonstrated an imaging method that permits regional mapping of the tissue and RBC fractions of Xe129 dissolved in the human lung, as well as quantitative comparison of tissue- and RBC-based ratios among subjects. The 11-sec breath-hold acquisition was well tolerated by both healthy volunteers and subjects with obstructive lung disease. Our preliminary results, although obtained from a small number of subjects in this exploratory study, suggest marked differences in the spatial distributions and overall amounts of Xe129 dissolved in tissue and RBCs among healthy subjects, smokers with COPD, and asthmatics. Additional studies, including more subjects and appropriate age matching, are clearly warranted to fully assess the potential of this technique.

Acknowledgments

Grant support: Supported by NIH grant R01 HL109618 from the National Heart, Lung, and Blood Institute, and by Siemens Medical Solutions. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

Author Y. Jiang thanks Drs. Mark A. Griswold and Jeffrey Tsao for their support and guidance. The authors thank John M. Christopher, RT(R) (MR) and Joanne C Gersbach, RN for their invaluable assistance with the human studies.

References

1. Salerno M, Altes TA, Mugler JP 3rd, Nakatsu M, Hatabu H, de Lange EE. Hyperpolarized noble gas MR imaging of the lung: potential clinical applications. *Eur J Radiol.* 2001; 40(1):33–44. [PubMed: 11673006]
2. Moller HE, Chen XJ, Saam B, et al. MRI of the lungs using hyperpolarized noble gases. *Magn Reson Med.* 2002; 47(6):1029–1051. [PubMed: 12111949]
3. van Beek EJ, Wild JM, Kauczor HU, Schreiber W, Mugler JP 3rd, de Lange EE. Functional MRI of the lung using hyperpolarized 3-helium gas. *J Magn Reson Imaging.* 2004; 20(4):540–554. [PubMed: 15390146]
4. Matsuoka S, Patz S, Albert MS, et al. Hyperpolarized gas MR imaging of the lung: current status as a research tool. *J Thorac Imaging.* 2009; 24(3):181–188. [PubMed: 19704321]
5. Fain S, Schiebeler ML, McCormack DG, Parraga G. Imaging of lung function using hyperpolarized helium-3 magnetic resonance imaging: review of current and emerging translational methods and applications. *J Magn Reson Imaging.* 2010; 32(6):1398–1408. [PubMed: 21105144]
6. Abraham MH, Kamlet MJ, Taft RW, Doherty RM, Weathersby PK. Solubility properties in polymers and biological media. 2. The correlation and prediction of the solubilities of nonelectrolytes in biological tissues and fluids. *J Med Chem.* 1985; 28(7):865–870. [PubMed: 4009609]
7. Miller KW, Reo NV, Schoot Uiterkamp AJ, Stengle DP, Stengle TR, Williamson KL. Xenon NMR: chemical shifts of a general anesthetic in common solvents, proteins, and membranes. *Proc Natl Acad Sci USA.* 1981; 78(8):4946–4949. [PubMed: 6946442]
8. Sakai K, Bilek AM, Oteiza E, et al. Temporal dynamics of hyperpolarized ^{129}Xe resonances in living rats. *J Magn Reson B.* 1996; 111(3):300–304. [PubMed: 8661297]
9. Ruppert K, Brookeman JR, Hagspiel KD, Mugler JP 3rd. Probing lung physiology with xenon polarization transfer contrast (XTC). *Magn Reson Med.* 2000; 44(3):349–357. [PubMed: 10975884]
10. Butler JP, Mair RW, Hoffmann D, et al. Measuring surface-area-to-volume ratios in soft porous materials using laser-polarized xenon interphase exchange nuclear magnetic resonance. *J Phys Condens Matter.* 2002; 14(13):L297–304. [PubMed: 12741395]
11. Mansson S, Wolber J, Driehuys B, Wollmer P, Golman K. Characterization of diffusing capacity and perfusion of the rat lung in a lipopolysaccharide disease model using hyperpolarized ^{129}Xe . *Magn Reson Med.* 2003; 50(6):1170–1179. [PubMed: 14648564]
12. Driehuys B, Cofer GP, Pollaro J, Mackel JB, Hedlund LW, Johnson GA. Imaging alveolar-capillary gas transfer using hyperpolarized ^{129}Xe MRI. *Proc Natl Acad Sci USA.* 2006; 103(48):18278–18283. [PubMed: 17101964]
13. Abdeen N, Cross A, Cron G, et al. Measurement of xenon diffusing capacity in the rat lung by hyperpolarized ^{129}Xe MRI and dynamic spectroscopy in a single breath-hold. *Magn Reson Med.* 2006; 56(2):255–264. [PubMed: 16767751]
14. Patz S, Hersman FW, Muradian I, et al. Hyperpolarized ^{129}Xe MRI: a viable functional lung imaging modality? *Eur J Radiol.* 2007; 64(3):335–344. [PubMed: 17890035]
15. Wagshul ME, Button TM, Li HF, et al. In vivo MR imaging and spectroscopy using hyperpolarized ^{129}Xe . *Magn Reson Med.* 1996; 36(2):183–191. [PubMed: 8843370]
16. Mugler JP 3rd, Driehuys B, Brookeman JR, et al. MR imaging and spectroscopy using hyperpolarized ^{129}Xe gas: preliminary human results. *Magn Reson Med.* 1997; 37(6):809–815. [PubMed: 9178229]
17. Ruppert K, Brookeman JR, Hagspiel KD, Driehuys B, Mugler JP 3rd. NMR of hyperpolarized ^{129}Xe in the canine chest: spectral dynamics during a breath-hold. *NMR Biomed.* 2000; 13(4):220–228. [PubMed: 10867700]
18. Dregely I, Mugler JP 3rd, Ruset IC, et al. Hyperpolarized xenon-129 gas-exchange imaging of lung microstructure: first case studies in subjects with obstructive lung disease. *J Magn Reson Imaging.* 2011; 33(5):1052–1062.
19. Swanson SD, Rosen MS, Coulter KP, Welsh RC, Chupp TE. Distribution and dynamics of laser-polarized ^{129}Xe magnetization in vivo. *Magn Reson Med.* 1999; 42(6):1137–1145. [PubMed: 10571936]

20. Wakayama T, Narazaki M, Kimura A, Fujiwara H. Hyperpolarized ^{129}Xe phase-selective imaging of mouse lung at 9.4T using a continuous-flow hyperpolarizing system. *Magn Reson Med Sci*. 2008; 7(2):65–72. [PubMed: 18603837]
21. Muradian, I.; Patz, S.; Butler, JP., et al. Hyperpolarized ^{129}Xe human pulmonary gas exchange with 3-point Dixon technique (abstract). Proceedings of the 14th Annual Meeting of ISMRM; Seattle. 2006. p. 1297
22. Hersman FW, Ruset IC, Ketel S, et al. Large production system for hyperpolarized ^{129}Xe for human lung imaging studies. *Acad Radiol*. 2008; 15(6):683–692. [PubMed: 18486005]
23. Cleveland ZI, Cofer GP, Metz G, et al. Hyperpolarized ^{129}Xe MR imaging of alveolar gas uptake in humans. *PLoS ONE*. 2010; 5(8):e12192. [PubMed: 20808950]
24. Mugler JP 3rd, Altes TA, Ruset IC, et al. Simultaneous magnetic resonance imaging of ventilation distribution and gas uptake in the human lung using hyperpolarized xenon-129. *Proc Natl Acad Sci U S A*. 2010; 107(50):21707–21712. [PubMed: 21098267]
25. Mugler, JP., 3rd; Altes, TA.; Ruset, IC., et al. Image-based measurement of T_2^* for dissolved-phase Xe^{129} in the human lung (abstract). Proceedings of the 20th Annual Meeting of ISMRM; Melbourne. 2012. p. 1347
26. Kaushik, SS.; Cofer, GP.; Freeman, MS.; Cleveland, ZI.; Driehuys, B. Single-acquisition imaging of hyperpolarized ^{129}Xe in the gas and dissolved phases using an interleaved 3D-radial sequence (abstract). Proceedings of the 19th Annual Meeting of ISMRM; Montreal. 2011. p. 878
27. Matson GB. An integrated program for amplitude-modulated RF pulse generation and re-mapping with shaped gradients. *Magn Reson Imaging*. 1994; 12(8):1205–1225. [PubMed: 7854027]
28. Ruppert, K.; Mata, JF.; Dregely, IM., et al. Hyperpolarized xenon-129 dissolved-phase signal dependence on the echo time (abstract). Proceedings of the 18th Annual Meeting of ISMRM; Stockholm. 2010. p. 2552
29. Dixon WT. Simple proton spectroscopic imaging. *Radiology*. 1984; 153(1):189–194. [PubMed: 6089263]
30. Glover GH, Schneider E. Three-point Dixon technique for true water/fat decomposition with B0 inhomogeneity correction. *Magn Reson Med*. 1991; 18(2):371–383. [PubMed: 2046518]
31. Reeder SB, McKenzie CA, Pineda AR, et al. Water-fat separation with IDEAL gradient-echo imaging. *J Magn Reson Imaging*. 2007; 25(3):644–652. [PubMed: 17326087]
32. Yu H, McKenzie CA, Shimakawa A, et al. Multiecho reconstruction for simultaneous water-fat decomposition and T_2^* estimation. *J Magn Reson Imaging*. 2007; 26(4):1153–1161. [PubMed: 17896369]
33. Chan RW, Ramsay EA, Cheung EY, Plewes DB. The influence of radial undersampling schemes on compressed sensing reconstruction in breast MRI. *Magn Reson Med*. 2012; 67(2):363–377. [PubMed: 21656558]
34. Sutton BP, Noll DC, Fessler JA. Fast, iterative image reconstruction for MRI in the presence of field inhomogeneities. *IEEE Trans Med Imaging*. 2003; 22(2):178–188. [PubMed: 12715994]
35. Tsao, J.; Jiang, Y. Hierarchical IDEAL robust water-fat separation at high field by multiresolution field map estimation (abstract). Proceedings of the 16th Annual Meeting of ISMRM; Toronto. 2008. p. 653
36. Jiang, Y.; Griswold, M.; Tsao, J. Fast and robust separation of multiple chemical species from arbitrary echo times with complete immunity to phase wrapping. Proceedings of the 20th Annual Meeting of ISMRM; Melbourne. 2012. p. 2484
37. Tsao J, Jiang Y. Hierarchical IDEAL: Fast, robust, and multiresolution separation of multiple chemical species from multiple echo times. *Magn Reson Med*. 2012; 1002/mrm.24441
38. Driehuys B, Cates GD, Miron E, Sauer K, Walter DK, Happer W. High-volume production of laser-polarized ^{129}Xe . *Appl Phys Lett*. 1996; 69(12):1668–1670.
39. Kaushik SS, Cleveland ZI, Cofer GP, et al. Diffusion-weighted hyperpolarized ^{129}Xe MRI in healthy volunteers and subjects with chronic obstructive pulmonary disease. *Magn Reson Med*. 2011; 65(4):1154–1165. [PubMed: 21413080]
40. Reis, S.; Ruppert, K.; Altes, T., et al. Hyperpolarized Xe -129 CSI of the human lung: Preliminary results from healthy, second-hand smoker and cystic-fibrosis subjects (abstract). Proceedings of the 20th Annual Meeting of ISMRM; Melbourne. 2012. p. 629

41. Ruppert, K.; Mata, JF.; Dregely, IM., et al. Hyperpolarized xenon-129 dissolved-phase signal dependence on flip angle and TR (abstract). Proceedings of the 18th Annual Meeting of ISMRM; Stockholm. 2010. p. 2551
42. Ruppert K, Mata JF, Brookeman JR, Hagspiel KD, Mugler JP 3rd. Exploring lung function with hyperpolarized ^{129}Xe nuclear magnetic resonance. *Magn Reson Med*. 2004; 51(4):676–687. [PubMed: 15065239]
43. Patz S, Muradyan I, Hrovat MI, et al. Diffusion of hyperpolarized ^{129}Xe in the lung: a simplified model of ^{129}Xe septal uptake and experimental results. *New J Phys*. 2011; 13:015009.
44. Chang YV. MOXE: A model of gas exchange for hyperpolarized ^{129}Xe magnetic resonance of the lung. *Magn Reson Med*. 2012;10.1002/mrm.24304
45. Vlahovic G, Russell ML, Mercer RR, Crapo JD. Cellular and connective tissue changes in alveolar septal walls in emphysema. *Am J Resp Crit Care Med*. 1999; 160(6):2086–2092. [PubMed: 10588633]

Figure 1.

Timing diagram showing one repetition of the multi-echo 3D radial pulse sequence for acquiring dissolved-phase and gas-phase Xe129 images. During each TR, three echoes (a half-echo and two symmetric echoes) of dissolved-phase data are collected for calculation of tissue and RBC images, followed by two echoes (a half-echo and a symmetric echo) of gas-phase data for calculation of ventilation images and a field map. The frequency offset of the RF pulses from resonance is indicated by Δf .

Figure 2.

Theoretical prediction of the effect of a difference between the $T2^*$ for RBCs and that for tissue on the accuracy of tissue/RBC separation using the Hierarchical IDEAL algorithm. The predicted percentage error is shown as a function of the true (input value for the calculation) RBC fraction and the difference in $T2^*$ values, assuming a typical $T2^*$ value of 2.2 msec for tissue. For typical in-vivo values for $T2^*$ differences and RBC fractions (Table 2), the expected error is approximately 3% or less.

Figure 3.

Representative coronal gas, tissue and RBC images from a healthy subject (H2). The RBC signal from the left ventricle of the heart (right image) was clearly seen in this subject.

Figure 4.

(a) Coronal gas, tissue and RBC images covering the whole lung, and (b) corresponding tissue-to-gas, RBC-to-gas and RBC-to-tissue ratio maps from a healthy subject (H3). While dissolved-phase signal intensities and ratio values were generally uniform within each coronal slice, the tissue and RBC images, as well as tissue-to-gas and RBC-to-gas ratio maps, showed an anterior-to-posterior gradient associated with the gravity-dependent gradient in lung tissue density in the supine position.

Figure 5.

Calculated slice-by-slice ratios for all healthy subjects. Plots are shown of the mean values for (a) total dissolved-phase to gas, (b) tissue-to-gas, (c) RBC-to-gas, and (d) RBC-to-tissue ratios for each coronal slice as a function of position along the anterior-posterior (A-P) direction. A value of 0 for A-P position corresponds to the most anterior slice and 1 corresponds to the most posterior slice. Subject H3 was imaged twice on the same day; H3* denotes repeat imaging for this subject. The values for this subject are plotted using dashed lines. The values of all ratios for subject H5, who was much older than subjects H1-H4 (Table 1), were generally lower than those for the other healthy subjects.

Figure 6.

Whole-lung ratio values for all subjects. Means (denoted by plotting symbols) and standard deviations (vertical bars denote ± 1 standard deviation) are shown for (a) total dissolved-phase to gas, (b) tissue-to-gas, (c) RBC-to-gas, and (d) RBC-to-tissue ratios. Healthy subjects, asthmatics and smokers are shown in black, blue and red, respectively. Except for the RBC-to-tissue ratio, the mean ratios for asthmatics and smokers were generally lower than those in healthy subjects. These differences were statistically significant (see text). Only the total dissolved-phase to gas ratio is shown for subject S3 because the dissolved-phase signal intensities for this subject were too low to permit accurate separation of the tissue and RBC components (see text for additional explanation).

Figure 7.

Calculated slice-by-slice ratios for smokers and asthmatics. Plots are shown of the mean values for (a) total dissolved-phase to gas, (b) tissue-to-gas, (c) RBC-to-gas, and (d) RBC-to-tissue ratios for each coronal slice as a function of position along the anterior-posterior (A-P) direction. A value of 0 for A-P position corresponds to the most anterior slice and 1 corresponds to the most posterior slice. Smokers are plotted in red and asthmatics are plotted in blue. For comparison, the solid black line shows the median of the respective ratio values for healthy subjects (Fig. 5). Subject S2 was imaged twice on the same day and subject A1 was imaged twice on different days; S2* and A1* denote repeat imaging for these subjects. The values for these subjects are plotted using dashed lines. Values for smoker S3 are not shown because the dissolved-phase signal intensities for this subject were too low to permit accurate separation of the tissue and RBC components (see text for additional explanation).

Figure 8.

(a) Coronal gas, tissue and RBC images covering the whole lung, and (b) corresponding tissue-to-gas, RBC-to-gas and RBC-to-tissue ratio maps from subject S2 with COPD GOLD stage III. This subject showed numerous ventilation defects, as well as markedly inhomogeneous tissue and RBC images and ratio maps. The anterior-to-posterior gradient seen in healthy subjects was also absent.

Figure 9.

(a) Coronal gas, tissue and RBC images, and (b) corresponding tissue-to-gas, RBC-to-gas and RBC-to-tissue ratio maps from asthmatic subjects A1 (age 53, left side of each panel) and A2 (age 16, right side of each panel). The homogeneity and overall values for the ratio maps for subject A1 were much different than those for subject A2, as seen by comparing the tissue-to-gas and RBC-to-tissue maps for the two subjects. Because the RBC-to-tissue ratios in subject A2 were higher than those in all other subjects, the corresponding ratio maps are presented on a scale of 0.0 to 1.0 (versus 0.0 to 0.7) so that features of the maps can be visualized.

Table 1

Subject demographics and baseline spirometry results.

Subject ^a	Age	Sex	FEV ₁ %pred ^b	FEV ₁ /FVC ^c
H1	18	F	119	0.87
H2	21	F	105	0.86
H3	21	F	108	0.90
H4	21	F	91	0.81
H5	54	M	128	0.75
S1	40	M	86	0.69
S2	55	F	39	0.57
S3	58	M	46	0.42
A1	53	M	95 (81) ^d	0.56 (0.52) ^d
A2	16	M	100	0.73

^aH, S and A denote healthy, smoker and asthmatic subjects, respectively.

^bPercent-predicted value for forced expiratory volume in 1 second (FEV₁).

^cRatio of FEV₁ to forced vital capacity (FVC).

^dValues in parentheses are for the second day of imaging.

Table 2

T2* values for RBCs and tissue derived from FID data, and comparison of RBC fractions calculated from FID and image data.

Subject	RBC T2* [msec]	Tissue T2* [msec]	RBC fraction from FID	RBC fraction from images
H1	1.8	2.2	0.27	0.24
H2	1.8	2.2	0.29	0.28
H3	1.8	2.2	0.29	0.23
H3*	1.8	2.2	0.28	0.23
H4	1.9	2.3	0.27	0.23
H5	1.9	2.2	0.21	0.20
S1	1.9	2.1	0.28	0.27
S2	2.2	2.0	0.13	0.14
S2*	2.2	2.0	0.13	0.15
S3	2.2	2.1	0.11	†
A1	2.2	2.2	0.14	0.16
A1*	2.0	2.2	0.18	0.19
A2	1.7	1.9	0.33	0.32

* Repeated acquisition, on same day for H3 and S2, and different days for A1.

† Value not calculated due to low signal-to-noise ratio.