Published in final edited form as:

NMR Biomed. 2012 September ; 25(9): 1015–1025. doi:10.1002/nbm.2763.

Multi-slice Fractional Ventilation Imaging in Large Animals with Hyperpolarized Gas MRI

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Abstract

Noninvasive assessment of regional lung ventilation is of critical importance in quantifying the severity of disease and evaluating response to therapy in many pulmonary diseases. This work presents for the first time the implementation of a hyperpolarized (HP) gas MRI technique for measuring whole-lung regional fractional ventilation (r) in Yorkshire pigs ($n = 5$) through the use of a gas mixing and delivery device in supine position. The proposed technique utilizes a series of back-to-back HP gas breaths with images acquired during short end-inspiratory breath-holds. In order to decouple the RF pulse decay effect from ventilatory signal build-up in the airways, regional distribution of flip angle (α) was estimated in the imaged slices by acquiring a series of back-to-back images with no inter-scan time delay during a breath-hold at the tail-end of the ventilation sequence. Analysis was performed to assess the multi-slice ventilation model sensitivity to noise, oxygen and number of flip angle images. The optimal α value was determined based on minimizing the error in r estimation; $\alpha_{\text{opt}} = 5\text{--}6^\circ$ for the set of acquisition parameters in pigs. The mean r values for the group of pigs were 0.27 ± 0.09 , 0.35 ± 0.06 , 0.40 ± 0.04 for ventral, middle and dorsal slices, respectively, (excluding conductive airways $r > 0.9$). A positive gravitational (ventral-dorsal) ventilation gradient effect was present in all animals. The trachea and major conductive airways showed a uniform near-unity r value, with progressively smaller values corresponding to smaller diameter airways, and ultimately leading to lung parenchyma. Results demonstrate the feasibility of measurements of fractional ventilation in large species, and provides a platform to address technical challenges associated with long breathing time scales through the optimization of acquisition parameters in species with a pulmonary physiology very similar to that of human beings.

Keywords

Pulmonary ventilation; Quantitative lung imaging; Fractional ventilation; Hyperpolarized gas MRI; Mechanical ventilation

INTRODUCTION

Obstructive and restrictive lung diseases, such as emphysema, asthma, and cystic fibrosis, adversely affect gas flow in the lungs and therefore compromise regional lung ventilation. For this reason, noninvasive assessment of regional lung function is of critical importance in quantifying the severity of disease, evaluating response to therapy, and predicting clinical

outcome. Current pulmonary assessment methods, such as pulmonary function tests (including spirometry and diffusing capacity), though inexpensive, only offer a global and relatively insensitive measure of lung function. The most common clinical lung imaging technique is radionuclide ventilation-perfusion scintigraphy, e.g. with ^{133}Xe (1). Qualitative information about regional ventilation can also be obtained using radioactive aerosols (2). Although noninvasive and widely available, these techniques suffer from poor spatial resolution and expose the subject to radioactive materials.

CT imaging has been implemented to measure regional pulmonary ventilation using radiodense tracer gas xenon (3). CT techniques provide high spatial resolution and a high degree of anatomic localization of regional lung attenuation during the wash-in and subsequent wash-out of xenon (4–6). This technique however requires repeated measurements and therefore repeated exposure to ionizing radiation (7). Moreover, xenon has anesthetic properties which limit the concentration, the achievable contrast enhancement, and consequently the signal-to-noise ratio (SNR) (8). More recently ^1H MRI techniques have been developed with varying potential to measure regional ventilation from indirect contrast mechanisms. Oxygen-enhanced MRI has been used to image specific ventilation in human lungs breathing high concentrations of oxygen for a period of time (9). This approach is based on the low-cost and safe imaging contrast of oxygen gas, although long acquisition times (several minutes) and reliance on uniform perfusion distribution can be limiting factors in clinical translation, especially in diseased populations. Fourier decomposition MRI is another emerging methodology, which allows for simultaneous acquisition of perfusion- and ventilation-weighted images of lungs (10), albeit only providing qualitative information at this stage. Finally ultra-short echo time (UTE) methods have been developed to assess air trapping based on direct imaging of lung tissue (11).

Hyperpolarized (HP) gas MRI on the other hand provides a viable imaging modality for regional assessment of lung function (12,13), with promising temporal and spatial resolution and a very attractive safety profile – especially when ^3He is used. This imaging method has opened the possibility for noninvasive visualization of ventilated lung airspaces and has recently been used for investigational assessment of asthma, emphysema, and cystic fibrosis (14–16). Static spin density images can be obtained in a straight-forward manner during a breath-hold to detect gross ventilation defects (17). Likewise, defect maps and deviations in dynamic ventilation patterns can be derived from HP gas MR images reflecting disease-induced gas trapping (14,18). Nevertheless, in order to provide a more effective assessment of pulmonary diseases in human subjects, a pulmonary imaging metric is needed which can provide quantitative gas replacement and distribution parameters that are objectively comparable among different subjects. This work translates our previously developed HP gas MRI-based technique for assessing regional lung function in large species. The initial technique was prototyped and optimized in rats, but only basic feasibility (on a single-slice basis) was demonstrated in a pig lung. With the goal of eventually using this technique to obtain similar measurements in human subjects, we present for the first time the systematic translation of the proposed serial ventilation imaging technique over the entire lung volume of Yorkshire pigs through use of a dedicated HP gas mixing and delivery device.

THEORY

Fractional ventilation model

Fractional ventilation in acinar airways, r_A , is defined as the ratio of the amount of fresh gas added to a volume element in the lung during inspiration, V_f to the total end-inspiratory gas space of that volume element, V_t (comprising V_f and the residual volume V_r):

$$r_A = \frac{V_f}{V_t} = \frac{V_f}{V_f + V_r}. \quad [1]$$

A voxel's end-inspiratory gas content under breath-hold pressure is assumed to be divided between r_A , consisting of the delivered fresh gas, and $1 - r_A$, representing the residual capacity of the volume element. $r_A = 0$ indicates no gas replacement (e.g. completely occluded airways), and $r_A = 1$ indicates complete gas replacement with each breath (e.g. conductive airways).

Over a succession of breaths, the net magnetization of HP gas increases at a faster rate in normal regions than in poorly-ventilated regions. Theoretically, after an infinite number of ^3He breaths, the available magnetization in each region of the lung will converge to a steady state value specific to each region, which is proportional to the total airway volume present in the respective region-of-interest (ROI). The resulting magnetization after inhalation of a HP gas breath is a function of the magnetization of the fraction r_A of the fresh gas and of the fraction $1 - r_A$ of the residual gas. During the time interval between the two breaths, the polarization of HP gas decays according to the partial pressure of oxygen (PO_2) present in the airways (i.e., $\text{P}_{\text{A}}\text{O}_2$ in the alveoli). The relaxation time constant for ^3He is given by ξ / PO_2 , with $\xi \approx 2.6 \text{ bar} \cdot \text{s}$ at normal body temperature (19).

Serial ventilation sequence

The proposed approach for measuring lung fractional ventilation utilizes a series of back-to-back HP gas breaths with images acquired during short end-inspiratory breath-holds, referred to as the *serial* ventilation sequence (20). Each ROI is considered a single-compartment inflatable volume element and is assumed to have one port through which gas enters and leaves the volume element at end-inspiration and end-expiration, respectively. Figure 1(a) shows the multi-slice serial ventilation sequence acquiring N time points to form the signal buildup curve in the airways. The time interval between two consecutive images acquired at the same time in the respiratory cycle is τ .

The details of a three-compartment ventilation model were described earlier (20). The dead space volumes in the ventilation system are divided into two main components: (i) *dynamic* dead volume, V_D , containing the major conductive airways (trachea and main bronchi) and the portion of the ventilator system after the respirator valve, including endotracheal tube. V_D experiences a bi-directional gas flow during respiration; (ii) *static* dead volume, V_S , containing parts of the ventilator system that carry the source gas towards the respirator valve's inlet, primarily containing the transmission line between the HP gas chamber and the respirator valve. V_S experiences only a unidirectional gas flow from the source through the transmission line which eventually fills up this dead space. The magnetization of the gas in each of the compartments is labeled according to Figure 1(b): M_A (acinar airways, including alveoli and small airways), M_C (dynamic dead space), M_T (static dead space), and finally M_S (HP gas source reservoir).

The available magnetization in the airways at each step of the ventilation sequence can be recursively expressed as a function of the fresh and residual gas from the previous step:

$$M_A(j) = r \cdot M_T(j-1) + (1-r) \cdot M_A(j-1) \cdot \exp[N_{PE} \ln(\cos \alpha) - \tau \cdot P_A \text{O}_2 / \xi], \quad M_A(0) = 0$$

where $r = r_A \cdot (1 - V_D/V_T)$ is the apparent fractional ventilation. It is assumed that the entrance of HP gas from the source pushes the same volume of gas as that of tidal volume (V_T) out of the static dead volume, and therefore for large species with $V_T/V_S > 1$, it results

in $M_T(j) = M_S$, $M_T(0) = [1 - (V_T/V_S)^{-1}]M_S$. The RF depolarization effect – the first exponent term in Eq. [2] – is of critical importance since the residual fraction of the gas in the airways is repeatedly exposed to RF excitations, thereby affecting the available magnetization for the following images. For each image the signal distribution will be a function of B_1 field, the spatial distribution of RF pulse flip angle, α , and the HP ^3He spin density distribution. For the purpose of simulations and sensitivity analysis, we approximate the signal intensity in a single imaging pixel subject to an RF pulse train with fixed α , and N_{PE} phase encoding lines as (20):

$$S_A(j) = \eta \cdot [M_A(j) \cdot \frac{\sin \alpha}{N_{PE}} \sum_{i=0}^{N_{PE}-1} \cos^i \alpha], \quad [3]$$

with η as a proper scaling factor.

The oxygen-induced depolarization rate of HP ^3He , the second exponent term in Eq. [2], is a function of oxygen tension in the airways. By neglecting the uptake of oxygen into the blood during each breath (21,22), partial pressure of oxygen in the airways, P_A , can be recursively expressed, at the beginning of each ^3He breath, as a function of the oxygen concentration of the freshly arrived gas, P_S , and as a function of the residual gas in the airways from the previous breath:

$$P_A(j) = r_A \cdot P_S + (1 - r_A) \cdot P_A(j-1), \quad P_A(0) = P_{AO_2} = 140 \text{ mbar}. \quad [4]$$

METHODS

Model sensitivity and optimization

The signal build-up in acinar airways was simulated using Eq. [2] through [4] for a single imaging pixel. The standard deviation of the estimated parameters (α and r) was calculated as a measure of sensitivity of the respective parameter with respect to noise and other measurement uncertainties, i.e. $\Delta r = \sigma(r)$ and $\Delta \alpha = \sigma(\alpha)$. The model was constructed using *a priori* values for parameters over a range of Δr and α values, as shown in Table 1. Model sensitivity was compared in large versus small animals as a function of noise, oxygen and number of flip angle images (n). Specifically the effects were simulated for pigs (with 3 slices per breath) and rats (1 slice per breath). All sensitivity analyses combined α and r error effects in order to provide a more realistic measure of their coupled nature. If at any given trial, the α estimation failed to converge, a random value was selected in the range of nominal flip angle ($\alpha_{\text{nominal}} \pm 2^\circ$), and r was computed accordingly.

The effect of oxygen was assessed by assuming a nominal P_{AO_2} value, signal buildup was computed accordingly, and the noise-free model was used to estimate α and r values with the two common assumptions used in practice: $P_{AO_2} = 0$ mbar for α estimation, and $P_{AO_2} = 140$ mbar for r estimation, respectively. For noise analysis, the estimation accuracy was evaluated with respect to SNR of the second image in the series with magnetization $M_A(2) = r \cdot r_S \cdot M_S$ ($r_S < 1$, given that $M_A(1) = 0$ for $M_T(0) = 0$). In consideration of the effects of ventilation deficiency, this measure of SNR provides a conservative assessment (20). Normally distributed noise (23), with zero mean and a proper variance, was added to the second image to yield the desired SNR value. The same noise variance was then randomly added to all images in the sequence. Each noise level was simulated 1000 times to yield statistically plausible results. The standard deviation of successful trials corrected for sample size was then reported as the estimation error for the parameter of interest, α or r .

Coupled sensitivity of r and α was simultaneously assessed for a range of r and n (number of images acquired for flip angle estimation), in presence of noise. The optimal α value was then determined based on minimizing the r error. Since the acquired signal intensity is, in general, a function of the number of applied RF pulses and magnitude of the flip angle, comparisons were normalized with respect to the SNR as a function of α and N_{PE} values, as follows. The available polarization in the airways was determined by fractional ventilation magnetization buildup. An arbitrary SNR value was assigned to a nominal set of parameters (α , r , n and N_{PE}), from which the corresponding noise variance was derived and added to the signal amplitude for all other cases as determined by Eq. [3] for a single imaging pixel.

Animal preparation and mechanical ventilation

All animal experiments were conducted in accordance with protocols approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Pennsylvania. The multi-slice serial ventilation imaging technique was implemented on five healthy Yorkshire pigs ($n = 5$, 20–26 kg body weight). Pigs were anesthetized with intravenous administration of 20–25 mg/kg ketamine and 4 mg/kg xylazine, intubated with a 6.5-mm cuffed endotracheal tube (Teleflex Medical - Rusch, Research Triangle Park, NC), and placed inside the MRI scanner in supine position. A high precision MRI-compatible mechanical ventilator, prototyped in the authors' laboratory and capable of mixing up to three different types of gases (e.g. ^3He , O_2 , N_2 and air) at different ratios, was utilized to perform the imaging experiments (Figure 2(a)). The ventilator gas-handling unit is composed entirely of pneumatic and nonmagnetic delivery valves, placed in the proximity of the RF imaging coil as close as possible to the animal in order to minimize the ventilatory dead spaces (Figure 2(b)). The HP gas was stored in a 2-L Tedlar plastic bag (Jensen Inert Products, Coral Springs, FL) and mounted inside a hard plastic chamber, which was pressurized up to 8–10 psi with nitrogen (regulated by the ventilator) for controlled delivery to the animal. As shown in Figure 2(c) a secondary chamber was connected in series to the main one in order to reduce the fluctuation of internal pressure as the HP gas was depleted during the imaging process. For the pig valve setup: $V_D \approx 15$ mL (excluding the endotracheal tube), and $V_S \approx 15$ mL (between the ^3He chamber and the respirator valve). For normal breathing, animals were ventilated with air at $V_T = 7$ –9 mL/kg, 14–18 breaths per minute (BPM), and inspiratory-to-expiratory ratio (I:E) = 1:2. Details of variation in ventilatory parameters are provided in Table 2. Since the anesthesia protocol was effective enough to suppress the spontaneous respiratory effort, use of a paralysis agent was not necessary. Heart rate and blood oxygen saturation level were monitored using a portable veterinary pulse-oximeter (Nonin Medical, Inc. Plymouth, MN) with the optical probe attached to the pig's tongue. Body temperature was monitored using a hand-held rectal probe, and maintained at around 37°C using a hot water heating pad placed under the animal.

Imaging techniques

The imaging helium gas (Spectra Gases, Branchburg, NJ) has a nominal concentration of 99.19% ^3He and 0.81% N_2 . This mixture was hyperpolarized through spin exchange collisions with optically pumped rubidium (Rb) atoms, using a commercial polarizer (IGI. 9600.He, GE Healthcare, Durham, NC), to a level of 30~35% over approximately 14–16 hours. All imaging experiments were performed in a whole body 1.5-T MRI system (MAGNETOM Sonata, Siemens Medical Solutions USA, Malvern, PA) using a flexible 8-channel (2×4 phased array) chest coil (Stark Contrast, Erlangen, Germany) tuned to the nominal ^3He resonance frequency of 48.48 MHz, with an approximate imaging volume of 35 cm long and 27 cm ID. Three ^3He coronal images ($NS = 3$) were acquired using a 2D multi-slice gradient echo pulse sequence at a planar resolution of 3.75×3.75 mm² using the following parameters: FOV = 24×18 cm², slice thickness (ST) = 30 mm, slice spacing = 6

mm, $\alpha = 3\sim 4^\circ$, matrix size (MS) = 64×48 pixels, TR = 7.0 ms, and TE = 3.3 ms. The middle coronal slice was selected by performing preliminary scout ^3He images to determine position in the three major planes, assuring that the trachea was included in the middle slice. Proton images were acquired in an identical manner with the exception of the following: $\alpha = 20^\circ$, TR = 20.0 ms, and TE = 3.4 ms.

Ventilation images were acquired using the multi-slice serial ventilation sequence (Figure 1(a)), during an approximately 1.5-sec end-inspiratory breath-hold following each HP ^3He breath ($N = 6$). A 500-msec end-inspiratory pre-acquisition delay was incorporated to allow the lung tissue reach a steady state volume prior to acquiring the images. For imaging, the concentration of the administered HP gas was controlled with the ventilator at $^3\text{He}:\text{N}_2:\text{O}_2 \approx 2:2:1$. A total amount of 2.0 L of HP gas mixture was prepared for each study by mixing 500 mL of ^3He , 400–500 mL of N_2 in a Tedlar bag inside the gas delivery chamber and placed inside the bore of the MRI scanner. The mixture was then delivered to the intubated animal using the MR-compatible ventilator. Each measurement of fractional ventilation was completed in approximately 2.0 min.

Regional distribution of flip angle α was measured by acquiring a series of back-to-back images ($n = 5$, unless otherwise stated in Table 1) with no inter-scan time and imaging parameters identical to the ventilation imaging sequence (24). In order to minimize coregistration errors between α and r maps, flip angle images were acquired at the tail-end of the ventilation sequence while holding the last HP ^3He breath for approximately 5 sec. This ensured identical lung position and inflation level with ventilation images. For this purpose the slice ordering was switched to the sequential mode, and each slice was imaged five times, as shown in Figure 1(a). The RF-induced polarization decay of HP ^3He was then calculated from:

$$M_A(j) = M_A(N) \cdot \exp [j \cdot N_{PE} \cdot (\ln(\cos \alpha) - TR \cdot P_A \cdot O_2 / \xi)], \quad [7]$$

where $M_A(j)$ is the magnetization in acinar airways after acquiring j images in the final end-inspiratory breath-hold. N indicates the final image acquired in the preceding serial ventilation sequence. This calculation is based on the assumption that RF-induced depolarization is the dominant decay mechanism in the time scale of image acquisition compared to oxygen-induced decay.

Data analysis

Data analysis was performed using custom MATLAB (Mathworks, Natick, MA) programs developed in authors' laboratory. Analysis was performed on a voxel-by-voxel basis at a planar isotropic resolution of 3.75 mm. Voxels with an SNR below a certain threshold (varying between 3:1 and 5:1) were excluded from analysis. The last image in the ventilation sequence ($j = N$, equivalent to the first image in the flip angle sequence) is typically expected to have the highest signal intensity and was therefore used as the basis for SNR threshold. In order to assure a continuous B_1 map over the length scale of imaging voxels, the resulting α map was smoothed using a moving average filter by replacing each valid (SNR > threshold) voxel's α with the average α value of valid voxels in the surrounding 3×3 grid within each slice. This smoothed α map was then used to simultaneously fit Eq. [2] through [4], yielding M_S and r as free parameters for each voxel. In reporting the mean fractional ventilation value, voxels with a near unity r value were excluded from the analysis, since they represent major conductive airways.

RESULTS

Sensitivity analysis and optimization

Figure 1(c) shows a representative combined r and α measurement experiment with noise added to the nominal signal with parameters typical to a pig study (Table 1). Also shown is the best fit to the noisy data. The plateau signal of the ventilation sequence ($N = 7$) serves as the initial signal for the flip angle measurement sequence. In the absence of noise, the systematic error in r estimation as a function of oxygen concentration misassumption in the airways is shown in Figure 3. The actual $P_{A}O_2$ value is shown on the abscissa versus the nominal 140 mbar assumed everywhere. An actual $P_{A}O_2$ lower than the nominal value leads to an underestimated r . The PO_2 -induced error in pigs ($NS = 3$ per breath) is substantially larger than rats ($NS = 1$ per breath), over $r = 0.2$ – 0.4 . The error bars represent the Δr variation as a function of $N_{PE} = 24$ – 64 . Assuming a perfect knowledge of α , the error in r is shown in Figure 4 as a function of SNR in the second image of the ventilation sequence, using $N = 10$ breaths. The r estimation accuracy in pigs is up to three times more sensitive to noise than it is in rats.

A representative set of α sensitivity assessment as a function of number of images, n (acquired during the final breath-hold in the ventilation sequence) is shown in Figure 5 for a single voxel with $N_{PE} = 48$ and $SNR = 22$. For small flip angles ($\alpha \sim 3^\circ$), the estimation accuracy improves almost uniformly with larger n values. Larger flip angles ($\alpha \sim 6^\circ$), however, lead to a local minimum in estimation error as a function of number of images, beyond which acquiring more images adversely affects the α accuracy. For smaller number of images ($n = 5$), α accuracy is always better for larger α values. Acquiring more than 6 images however only marginally improves α estimation accuracy. The estimation error in r as a function of the applied α value was used to determine the optimal flip angle over a range of $r = 0.1$ – 0.3 for the same imaging pixel, as shown in Figure 6 (using $N_{PE} = 48$ and $n = 4$). The optimal neighborhood of α gets narrower for smaller r values as a result of a slower signal buildup in the airways. Variation of Δr versus α was fit to a second order function in order to assist in estimating the optimal flip angle, $\alpha_{opt} = 5.0$ – 6.0° for the respective range of r values.

Measurements of fractional ventilation in pig lungs

Measurements of fractional ventilation were performed using the multi-slice r - α imaging technique in all animals over three coronal slices. The flip angle maps were measured using $n = 5$ images during the tail-end breath-hold of the ventilation sequence (with the exception of pig #1, $n = 2$). Representative images from the middle slice of pig lung #4 are shown in Figure 7 corresponding to the ventilation sequence (Figure 1(a)). Images 1–6 represent the respiratory signal buildup as a function of serial inspiration of HP gas, and images 6–10 indicate the signal decline in the tail-end breath-hold dominated by RF decay. The corresponding flip angle map is shown in Figure 8 before and after smoothing, along with the pixel-by-pixel correlation between the two maps. The r maps for the five healthy pig lungs are shown in Figure 9 overlaid on chest proton images, and summary of measurement results are shown in Table 2 for each of the ventral, middle and dorsal slices. The mean r values for the entire group were as follows: 0.27 ± 0.09 , 0.35 ± 0.06 , 0.40 ± 0.04 for ventral, middle and dorsal slices, respectively, (excluding conductive airways by masking $r > 0.9$ voxels). Gravitational dependence of ventilation (a positive ventral–dorsal gradient) distribution was unanimously present in all measurements.

DISCUSSION

Estimation model sensitivity to noise and other parameters

Compared to rats (60 BPM and $NS = 1$ per breath), the P_{AO_2} -induced error in pigs (16 BPM and $NS = 3$ per breath) was substantially larger over the range of $r = 0.2$ – 0.4 (Figure 3). The increased sensitivity to P_{AO_2} misassumption largely stems from the 3–4 times slower breathing rate in pigs. This rate yields a greater oxygen-induced signal decay, resulting in an overestimated α and, consequently, an underestimated r value. The mismatch between the actual P_{AO_2} and the nominal 140 mbar value in the airways may be explained by regional or time-dependent variations of oxygen concentration or lung diseases, such as air trapping or gas exchange deficiencies, which affect the oxygen uptake rate and its steady state value. In addition to the systematic error associated with P_{AO_2} misassumption, the larger effect of oxygen-induced signal decay in presence of noise adversely affects the r estimation accuracy in pigs up to three times more than in rats (Figure 4). As shown earlier (20), the relative error in r drops almost exponentially with an increased number of ventilation images, N . Including a larger number of images (achieved for instance by diluting the HP ^3He mixture with N_2 gas) can therefore offset the SNR impact. In regards to α estimation using a series of n back-to-back images, acquiring more than 6 images, in general, appears to improve α estimation accuracy only marginally (Figure 5). For this reason, the final breath-hold need not be more than what is typically used in other breath-hold imaging techniques, e.g. 10–12 sec for P_{AO_2} imaging (25,26), and is expected to be tolerable by most individuals, even with severe lung diseases.

Finally, we note an inherent limitation of the proposed three-compartment ventilation model. Both dead space components are defined for the entire lung and used as a global first-order correction term applied to all voxels. The distribution and value of the dynamic dead space compartment is undoubtedly different among the airway units. This is the subject of ongoing research and more realistic models for independent treatment of the conductive path to each collection of airway units (e.g. enclosed within each voxel) is under development. Even so, the value reported for each voxel will inherently represent the average effect of the conductive dead space effect to that particular region of interest and needs to be interpreted accordingly.

Optimality and tradeoffs

Regardless of the actual magnetization buildup in the airways, the apparent MRI signal observed at the end of each breath is a function of the applied flip angle α used to acquire the images. As exemplified by Eq. [3], the flip angle value has a significant nonlinear effect on the rate of HP gas signal buildup in the airways. Using a too small flip angle results in a diminished MR signal, and a too large flip angle causes an excessive RF signal decay of the residual magnetization at each step and a subsequent information loss. Proper selection of α value therefore should ensure a balance between these two counteracting processes. Signal buildup, on the other hand, is tightly related to r , which also affects the choice of α . Due to r variation in different regions of the lung, as well as among different subjects, it is fundamentally impossible to find a globally optimal α value (α_{opt}) for all conditions.

Combined error analysis of r and α shows that, in general, there exists a neighborhood of flip angle values that simultaneously minimizes the uncertainty in both parameters (Figure 6). This minimum value corresponds to the optimal condition where the signal gain achieved by applying the RF pulses is balanced by the irrecoverable loss of magnetization as a function of applying the same pulses. The α_{opt} value to minimize r error in the case of pigs was around 5.0° , with minimal dependence on r value; the analysis for the single imaging pixel shows that α_{opt} is confined within $\pm 0.5^\circ$ of the optimal value over $r = 0.2$ – 0.4 . This

range of fractional ventilation is wide enough to cover the majority of a healthy lung parenchyma.

Implementation in large species

Multi-slice measurement of fractional ventilation was successfully implemented in five healthy pig lungs. As shown in Figure 8, the effective α was around $3.7 \pm 0.3^\circ$ throughout the lungs. This flip angle was selected rather conservatively prior to the complete investigation of optimality conditions discussed above. It is therefore expected that the achievable SNR, and subsequently the measurement accuracy, would benefit by increasing the α value to the vicinity of $5.0\text{--}6.0^\circ$. All pigs depict a qualitatively similar distribution of fractional ventilation throughout their lungs, as shown in Figure 9. Trachea and major conductive airways show a near unity r value, with progressively smaller values as the airways transition towards smaller diameters and eventually reaching lung parenchyma. It is expected that regions near the diaphragm and the heart to be affected by motion artifacts compared to other regions. The gravitational dependence of ventilation distribution from ventral to dorsal position was evident in all pigs, a phenomenon established by earlier HP gas MR studies in mechanically ventilated rodents (27).

The overall r values measured in five pigs across the three slices was 0.34 ± 0.06 (with $r > 0.9$ pixels masked). This value is significantly similar to the corresponding value in the middle slice, as is the case in each individual animal (Table 2). The intersubject variation of r value among different pigs is likely due to two primary factors. Firstly, with the exception of the first animal, all others were ventilated at a fixed $V_T = 200$ mL. The weight of the animals however varied between 20 and 26 kg, and therefore it is expected that their lung volumes, as well as their functional residual capacity (FRC) would vary accordingly, and in turn result in a different overall fractional ventilation value, $V_T/(V_T + \text{FRC})$. Secondly, the duration of stay of pigs inside the MRI scanner before the ventilation measurements were actually performed varied between 1 to 3 hours, mainly as a function of the time required for each animal to reach a stable physiological condition under anesthesia and to synchronize their respiratory pattern with mechanical ventilation. It is an established fact in critical care medicine (also shown recently with HP gas diffusion MRI in rats (28)), that both humans and animals develop atelectasis under mechanical ventilation in an unperturbed posture. This is mainly driven by the alveolar collapse of dependent regions of the lung due to gravity. The atelectatic regions of a healthy lung can be re-opened through various alveolar recruitment maneuvers, e.g. by applying positive end-expiratory pressure (PEEP) for a short period of time. Such a recruitment maneuver was not utilized in this study and therefore it is expected that animals developed atelectasis with varying degree, which in turn affected their FRC and subsequently the measured r values. This factor may not be significant for conscious human subjects due to their substantially shorter duration of stay in the MRI scanner, but is arguably a necessary normalization step in mechanically ventilated subjects immediately before acquiring ventilation images or performing any pulmonary functional imaging.

Diffusion effect

Among all experimental factors, respiratory gas diffusion between different airway compartments – both within and out of the imaging slices – has arguably the largest effect on the measurement accuracy. As shown in Figure 8, the majority of voxels enclosed by the trachea and major bronchi exhibit an elevated α value compared to lung parenchyma. This observation is most likely a function of the relatively higher (i.e. nearly free) diffusion of gas particles in these regions, which in turn leads to a more rapid dephasing and subsequent diffusion-induced signal decay during the breath-hold and a proportionally higher apparent α value. Inter-slice diffusion effects on the other hand can affect both flip angle

measurement accuracy during the tail-end breath-hold, and signal buildup in the airways during the ventilation maneuver. In either case, while a given slice is being excited by a slice-selective pulse, spins from neighboring slices can diffuse into the slice of interest and contaminate the RF-induced signal attenuation history. These effects can potentially lead to an overestimation of r value due to the possibility of diffusion of polarized spins from adjacent slices and can be more substantial especially in presence of a non-uniform B_1 field. These systematic errors need to be investigated in a similar fashion described previously in (29,30), especially when a larger number of slices or a higher spatial resolution is employed. Even though the suggested inter-slice gap in the multi-slice 2D acquisition provides some protection against this mechanism, utilization of a 3D acquisition scheme may address this problem to some degree, although in-plane diffusion may remain a source of error whether multi-slice or 3D imaging is used.

Translation to human subjects

The results obtained in Yorkshire pigs demonstrate the feasibility of robust measurements of fractional ventilation in large species, and a stepping-stone towards implementation in human subjects. It also provides a platform to address the technical challenges associated with long breathing time scales and to optimize acquisition parameters in a species with pulmonary physiology very similar to human beings. The major unresolved factor in translation of the technique to humans is repeatable and accurate mixing and simultaneous delivery of HP gas and oxygen to voluntarily breathing subjects. This objective will most likely require some level of supervision, possibly by using a passive gas delivery device, coaching during the MRI session, providing audio-visual feedback to the subject, or a combination thereof. The major advantage is that, as long as the amount of inhaled gas per breath is monitored or regulated by a device, the breathing pattern can be autonomously controlled by the human subject or with minimal supervision in a similar fashion to spirometry maneuvers or those utilized in delivering radio-labeled aerosols.

The primary factor determining the number of images acquirable in one session is the HP gas production capacity (2 L of ^3He per session in this study). This volume can be a limiting factor if measurements need to be repeated (either by design or due to a measurement failure). The available amount of HP gas is typically diluted with ultra-high-purity N_2 to achieve larger quantities of imaging gas, provided that the polarization level is adequate to meet the SNR requirements (Figure 4). Almost all HP ^3He -based MRI techniques are, in principle, translatable (or have been proven to be comparable) to HP ^{129}Xe as a means of overcoming the limited supply of the former isotope. With the advent of high capacity and continuous ^{129}Xe hyperpolarizing technology (31,32), the quantity of polarized gas available for use may no longer be a limiting factor in a single imaging session. The anesthetic properties of xenon, however, remain a challenge for implementation in humans. Human xenon inhalation is limited by anesthetic considerations to $< 35\%$ alveolar concentration (33). Therefore, depending on the available polarization, the concentration of the inhaled gas and the number of breaths should be optimally selected to limit the alveolar concentration of this gas while still providing a reasonable measurement of accuracy. Due to the relatively short time span of these studies, however, the period of the breath-holds and the likelihood of substantial uptake are smaller than in anesthetic applications (34).

Acknowledgments

This work was supported by NIH grant R01-HL089064.

ABBREVIATIONS

He	helium
Xe	xenon
Rb	rubidium
HP	hyperpolarized
CT	computed tomography
IACUC	Institutional Animal Care and Use Committee
$P_{A}O_2$	alveolar partial pressure of oxygen
P_A	partial pressure of oxygen in the airways
P_S	partial pressure of oxygen in the source reservoir
V_T	tidal volume
V_D	dynamic dead space volume
V_S	static dead space volume
V_f	fresh inspired volume
V_t	total end-inspiratory volume
V_r	airway residual volume
r	apparent fractional ventilation
Δr	relative error in r
r_A	acinar fractional ventilation
M_A	magnetization in acinar airways
M_C	magnetization in conductive airways (V_D)
M_T	magnetization in transport line (V_S)
M_S	magnetization in source reservoir
τ	respiratory time interval
N	number of ventilation images
n	number of flip angle images
BPM	breaths per minute
I:E	inhale-to-exhale ratio
j	image index
SNR	signal-to-noise ratio
RF	radiofrequency
ROI	region of interest
α	RF pulse flip angle
$\Delta\alpha$	relative error in relative error in r
N_{PE}	number of phase encoding RF pulses
NS	number of slices

FOV	field of view
ST	slice thickness
MS	matrix size

REFERENCES

1. Ball WC Jr, Stewart PB, Newsham LG, Bates DV. Regional pulmonary function studied with xenon 133. *J Clin Invest.* 1962; 41:519–531. [PubMed: 13864417]
2. Fazio F, Wollmer P, Lavender JP, Barr MM. Clinical ventilation imaging with In-113m aerosol: a comparison with Kr-81m. *J Nucl Med.* 1982; 23(4):306–314. [PubMed: 7069494]
3. Kreck TC, Krueger MA, Altemeier WA, Sinclair SE, Robertson HT, Shade ED, Hildebrandt J, Lamm WJE, Frazer DA, Polissar NL, Hlastala MP. Determination of regional ventilation and perfusion in the lung using xenon and computed tomography. *J Appl Physiol.* 2001; 91(4):1741–1749. [PubMed: 11568158]
4. Marcucci C, Nyhan D, Simon BA. Distribution of pulmonary ventilation using Xe-enhanced computed tomography in prone and supine dogs. *J Appl Physiol.* 2001; 90(2):421–430. [PubMed: 11160037]
5. Reinhardt JM, Ding K, Cao K, Christensen GE, Hoffman EA, Bodas SV. Registration-based estimates of local lung tissue expansion compared to xenon CT measures of specific ventilation. *Med Image Anal.* 2008; 12(6):752–763. [PubMed: 18501665]
6. Simon BA. Regional ventilation and lung mechanics using X-Ray CT. *Acad Radiol.* 2005; 12(11):1414–1422. [PubMed: 16253853]
7. Kalra MK, Maher MM, Toth TL, Hamberg LM, Blake MA, Shepard JA, Saini S. Strategies for CT radiation dose optimization. *Radiology.* 2004; 230(3):619–628. [PubMed: 14739312]
8. Lachmann B, Armbruster S, Schairer W, Landstra M, Trouwborst A, Van Daal GJ, Kusuma A, Erdmann W. Safety and efficacy of xenon in routine use as an inhalational anaesthetic. *Lancet.* 1990; 335(8703):1413–1415. [PubMed: 1972207]
9. Sa RC, Cronin MV, Henderson AC, Holverda S, Theilmann RJ, Arai TJ, Dubowitz DJ, Hopkins SR, Buxton RB, Prisk GK. Vertical distribution of specific ventilation in normal supine humans measured by oxygen-enhanced proton MRI. *J Appl Physiol.* 2010; 109(6):1950–1959. [PubMed: 20930129]
10. Bauman G, Lutzen U, Ullrich M, Gaass T, Dinkel J, Elke G, Meybohm P, Frerichs I, Hoffmann B, Borggreffe J, Knuth HC, Schupp J, Prum H, Eichinger M, Puderbach M, Biederer J, Hintze C. Pulmonary functional imaging: qualitative comparison of Fourier decomposition MR imaging with SPECT/CT in porcine lung. *Radiology.* 2011; 260(2):551–559. [PubMed: 21586678]
11. Togao O, Ohno Y, Dimitrov I, Hsia CC, Takahashi M. Ventilation/perfusion imaging of the lung using ultra-short echo time (UTE) MRI in an animal model of pulmonary embolism. *J Magn Reson Imaging.* 2011 In Press([Epub ahead of print]).
12. Wang C, Altes TA, Mugler JP 3rd, Miller GW, Ruppert K, Mata JF, Cates GD Jr, Borish L, de Lange EE. Assessment of the lung microstructure in patients with asthma using hyperpolarized ³He diffusion MRI at two time scales: comparison with healthy subjects and patients with COPD. *J Magn Reson Imaging.* 2008; 28(1):80–88. [PubMed: 18581381]
13. Holmes JH, O'Halloran RL, Brodsky EK, Jung Y, Block WF, Fain SB. 3D hyperpolarized He-3 MRI of ventilation using a multi-echo projection acquisition. *Magn Reson Med.* 2008; 59(5):1062–1071. [PubMed: 18429034]
14. Altes TA, Powers PL, Knight-Scott J, Rakes G, Platts-Mills TAE, de Lange EE, Alford BA, Mugler JP, Brookeman JR. Hyperpolarized ³He MR lung ventilation imaging in asthmatics: preliminary findings. *Journal of Magnetic Resonance Imaging.* 2001; 13(3):378–384. [PubMed: 11241810]
15. Fain SB, Panth SR, Evans MD, Wentland AL, Holmes JH, Korosec FR, O'Brien MJ, Fountaine H, Grist TM. Early Emphysematous Changes in Asymptomatic Smokers: Detection with ³He MR Imaging. *Radiology.* 2006; 239(3):875–883. [PubMed: 16714465]

16. Donnelly LF, MacFall JR, McAdams HP, Majure JM, Smith J, Frush DP, Bogonad P, Charles HC, Ravin CE. Cystic fibrosis: combined hyperpolarized ^3He -enhanced and conventional proton MR imaging in the lung--preliminary observations. *Radiology*. 1999; 212(3):885–889. [PubMed: 10478261]
17. Salerno M, de Lange EE, Altes TA, Truwit JD, Brookeman JR, Mugler JP. Emphysema: hyperpolarized ^3He diffusion MR imaging of the lungs compared with spirometric indexes- initial experience. *Radiology*. 2002; 222(1):252–260. [PubMed: 11756734]
18. McMahon CJ, Dodd JD, Hill C, Woodhouse N, Wild JM, Fischele S, Gallagher CG, Skehan SJ, van Beek EJ, Masterson JB. Hyperpolarized ^3He magnetic resonance ventilation imaging of the lung in cystic fibrosis: comparison with high resolution CT and spirometry. *Eur Radiol*. 2006; 16(11):2483–2490. [PubMed: 16871384]
19. Saam B, Happer W, Middleton H. Nuclear relaxation of ^3He in the presence of O_2 . *Phys Rev A*. 1995; 52(1):862–865. [PubMed: 9912313]
20. Emami K, Kadlecsek S, Woodburn JM, Zhu J, Yu J, Vahdat V, Pickup S, Ishii M, Rizi RR. Improved Technique for Measurement of Regional Fractional Ventilation by Hyperpolarized ^3He MRI. *Magn Reson Med*. 2010; 63(1):13.
21. Deninger AJ, Mansson S, Petersson JS, Pettersson G, Magnusson P, Svensson J, Fridlund B, Hansson G, Erjefeldt I, Wollmer P, Golman K. Quantitative measurement of regional lung ventilation using ^3He MRI. *Magn Reson Med*. 2002; 48(2):223–232. [PubMed: 12210930]
22. Moller HE, Hedlund LW, Chen XJ, Carey MR, Chawla MS, Wheeler CT, Johnson GA. Measurements of hyperpolarized gas properties in the lung. Part III: ^3He T_1 . *Magn Reson Med*. 2001; 45(3):421–430. [PubMed: 11241699]
23. Gudbjartsson H, Patz S. The Rician distribution of noisy MRI data. *Magn Reson Med*. 1995; 34:910–914. [PubMed: 8598820]
24. Dupuich D, Berthezene Y, Clouet PL, Stupar V, Canet E, Cremillieux Y. Dynamic ^3He imaging for quantification of regional lung ventilation parameters. *Magn Reson Med*. 2003; 50(4):777–783. [PubMed: 14523964]
25. Fischer MC, Spector ZZ, Ishii M, Yu J, Emami K, Itkin M, Rizi RR. Single-acquisition sequence for the measurement of oxygen partial pressure by hyperpolarized gas MRI. *Magn Reson Med*. 2004; 52(4):766–773. [PubMed: 15389934]
26. Yu J, Law M, Kadlecsek S, Emami K, Ishii M, Woodburn JM, Vahdat V, Rizi RR. Simultaneous measurement of pulmonary partial pressure oxygen and apparent diffusion coefficient by hyperpolarized ^3He MRI. *Magn Reson Med*. 2009; 61(5):1015–1021. [PubMed: 19230017]
27. Mansson S, Deninger AJ, Magnusson P, Pettersson G, Olsson LE, Hansson G, Wollmer P, Golman K. ^3He MRI-based assessment of posture-dependent regional ventilation gradients in rats. *J Appl Physiol*. 2005; 98(6):2259–2267. [PubMed: 15640396]
28. Cereda M, Emami K, Kadlecsek S, Xin Y, Mongkolwisetwara P, Profka H, Barulic A, Pickup S, Mansson S, Wollmer P, Ishii M, Deutschman CS, Rizi RR. Quantitative imaging of alveolar recruitment with hyperpolarized gas MRI during mechanical ventilation. *J Appl Physiol*. 2011; 110(2):499–511. [PubMed: 21127207]
29. Wild JM, Woodhouse N, Paley MN, Fischele S, Said Z, Kasuboski L, van Beek EJ. Comparison between 2D and 3D gradient-echo sequences for MRI of human lung ventilation with hyperpolarized ^3He . *Magn Reson Med*. 2004; 52(3):673–678. [PubMed: 15334590]
30. Wild JM, Fischele S, Woodhouse N, Paley MNJ, Kasuboski L, van Beek EJ. 3D Volume-Localized pO_2 Measurement in the Human Lung with ^3He MRI. *Magn Res Med*. 2005; 53(5):1055–1064.
31. Hersman FW, Ruset IC, Ketel S, Muradian I, Covrig SD, Distelbrink J, Porter W, Watt D, Ketel J, Brackett J, Hope A, Patz S. Large production system for hyperpolarized ^{129}Xe for human lung imaging studies. *Acad Radiol*. 2008; 15(6):683–692. [PubMed: 18486005]
32. Driehuys B, Pollaro J, Cofer GP. In vivo MRI using real-time production of hyperpolarized ^{129}Xe . *Magn Reson Med*. 2008; 60(1):14–20. [PubMed: 18581406]
33. Muradian, I.; Butler, J.; Hrovat, M.; Topulos, G.; Hersman, E.; Frederick, S.; Covrig, S.; Ruset, I.; Ketel, S.; Hersman, F.; Patz, S. Human regional pulmonary gas exchange with xenon polarization transfer (XTC). 15th Annual Scientific Meeting of ISMRM; Berlin. 2007. p. 454

34. Abdeen N, Cross A, Cron G, White S, Rand T, Miller D, Santyr G. 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]

Figure 1.

(a) Multi-slice fractional ventilation imaging sequence. NS images are acquired during each end-inspiratory HP gas breath-hold to cover the entire lung volume (NS = 3 in the shown example). A long breath-hold is performed after inhaling the last HP gas breath, during which the flip angle mapping imaging sequence is performed ($n = 4$ in the shown example). Arrows ($\Downarrow$) indicate image acquisition per slice with slice numbers shown on top. The dashed and blank boxes represent air and hyperpolarized gas breaths (N in the shown example), respectively. **(b)** The three-compartment fractional ventilation model consisting of the static and dynamic dead space volumes, V_S and V_D . These quantities are normalized with respect to tidal volume, V_T , to yield the non-dimensional quantities, r_S and r_D respectively. **(c)** Simulated signal buildup for a representative voxel with nominal $r = 0.2$ and $\alpha = 3^\circ$. Image numbers 1 through 7 represent the signal buildup during the serial breathing of HP gas breaths, whereas image numbers during the sequential acquisition during the final breath-hold. The noisy data points are generated with a normal noise distribution corresponding to SNR = 20.5, and 24 RF pulses are assumed to be applied per image. Estimations for r and α (indicated with an asterisk) are shown on top of the panel.

Figure 2. The programmable ventilator setup used to implement the fractional ventilation imaging technique in pigs, consisting of: **(a)** the remote controller, actuating and respiratory gas analysis components, **(b)** respiratory and gas mixing valves connected directly to the animal, and **(c)** pressurizing chambers for holding and dispensing HP gas.

Figure 3.

The systematic error in r estimation as a function of oxygen concentration misassumption in the absence of noise. A nominal $P_{AO_2} = 140$ mbar is assumed everywhere. The abscissa reflects the actual P_{AO_2} which may be different from the nominal value. Data points corresponding to the same P_{AO_2} values are slightly offset horizontally for better visibility.

Figure 4. The relative error in r estimation as a function of SNR in the second image of the ventilation sequence, assuming a perfect knowledge of α . Error bars represent the Δr variation as a function of $r = 0.1-0.5$.

Figure 5.

The relative error in α estimation as a function number of sequential images, n , acquired during an end-inspiratory breath-hold in the ventilation sequence, for a typical voxel with an initial $SNR = 22$ and $N_{PE} = 48$. The line segments are drawn between datapoints to aid visualizing the trends.

Figure 6. The relative error in r and α estimation as a function of the applied α value for a range of RF pulses to a single imaging pixel. The SNR effect is implicitly incorporated in this analysis as a function of the applied α and polarization buildup as a result of the fractional ventilation.

Figure 7.

Representative HP gas spin density images of the middle slice of a pig lung acquired using the serial ventilation imaging sequence shown in Figure 1(a). Images 1–6 represent the ventilatory signal buildup in the airways, whereas images 6–10 correspond to the RF pulse decay during the tail-end breath-hold.

Figure 8.

A representative flip angle map acquired in the middle slice of a pig lung at the tail-end of the ventilation sequence, pre- and post-smoothing.

Figure 9.
Three-slice fractional ventilation maps measured in lungs of five healthy Yorkshire pigs.

Table 1

The numerical values of ventilation model parameters used for simulation, sensitivity and optimization analysis.

Parameter	Description	Units	Rat	Pig
NS	Number of slices	-	1	3
MS	Matrix Size	-	64	48
TR	Repetition time	ms	7	7
PAD	Pre-acquisition delay	ms	500	500
N	Ventilation image	-	10	7
BR	Breathing rate	breaths/min	60	16
FRC	Functional residual capacity	mL	4	800
V _D	Dynamic dead space	mL	0.5	15
V _S	Static dead space	mL	3.5	15
I:E	Inhale-to-exhale ratio	-	1:2	
V _T	Tidal volume	mL	FRC ^{2/3} /r(1-r)	
P _S	Source oxygen concentration	mbar	140	

Parameter	Description	Units	Value
r	Fractional ventilation	-	0.1–0.4
P _A O ₂	Alveolar partial pressure of oxygen	mbar	0–200
α	Flip angle	deg	3–8
SNR	Signal-to-noise ratio in image #2	-	5–60

Table 2

Ventilatory parameters used for fractional ventilation and flip angle measurement studies in pigs, along with mean and standard deviation of r measured in all three slices of the pig lungs along with the corresponding peak SNR values.

Pig No.	Weight [kg]	Respiratory Rate [breaths/min]	VT [mL]	n	r				Overall r
					Peak SNR	Ventral Slice	Middle Slice	Dorsal Slice	
1	20.5	14	150	2	45	0.27 ± 0.15	0.38 ± 0.16	0.40 ± 0.15	0.36 ± 0.16
2	25.0	16	200	5	42	0.15 ± 0.13	0.29 ± 0.16	0.38 ± 0.14	0.30 ± 0.17
3	22.0	16	200	5	54	0.35 ± 0.14	0.40 ± 0.12	0.45 ± 0.13	0.41 ± 0.13
4	23.0	16	200	5	57	0.17 ± 0.13	0.26 ± 0.17	0.34 ± 0.15	0.27 ± 0.17
5	26.0	18	200	5	47	0.32 ± 0.15	0.39 ± 0.18	0.43 ± 0.15	0.38 ± 0.17
						0.25 ± 0.09	0.34 ± 0.06	0.40 ± 0.04	0.34 ± 0.06

* r > 0.9 masked