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Improved Technique for Measurement of Regional Fractional Ventilation by Hyperpolarized ^3He MRI

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Abstract

Quantitative measurement of regional lung ventilation is of great significance in assessment of lung function in many obstructive and restrictive pulmonary diseases. A new technique for regional measurement of fractional ventilation using hyperpolarized ^3He MRI is proposed, addressing the shortcomings of an earlier approach that limited its use to small animals. The new approach allows for the acquisition of similar quantitative maps over a shortened period and requires substantially less ^3He gas. This technique is therefore a better platform for implementation in large species, including humans. The measurements using the two approaches were comparable to a great degree, as verified in a healthy rat lung, and are very reproducible. Preliminary validation is performed in a lung phantom system. Volume dependency of measurements was assessed both in vivo and in vitro. A scheme for selecting an optimum flip angle is proposed. In addition, a dead space modeling approach is proposed to yield more accurate measurements of regional fractional ventilation using either method. Finally, sensitivity of the new technique to model parameters, noise, and number of included images were assessed numerically. As a prelude to application in humans, the technique was implemented in a large animal study successfully.

Keywords

quantitative pulmonary imaging; regional lung ventilation; fractional ventilation; hyperpolarized gas MRI; mathematical models of lung

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. Noninvasive assessment of regional lung function is therefore of critical importance in quantifying the severity of the disease, evaluating response to therapy, and predicting the clinical outcome. Pulmonary function tests (such as spirometry and diffusing capacity) provide an inexpensive yet insensitive measure of lung function (1,2). These techniques only provide a global measure of lung function and, contrary to noninvasive imaging techniques, can be insensitive to regional alterations in lung function (3,4). The common clinical lung imaging technique is radio-nuclide ventilation-perfusion scintigraphy, e.g., with ^{133}Xe (5). Qualitative information about regional ventilation can also be obtained using radioactive

aerosols (6). Although noninvasive and widely available, these techniques suffer from poor spatial resolution and exposure to radioactive materials.

Regional pulmonary ventilation has also been measured from CT images using certain contrast agents, most commonly the radiodense tracer gas xenon (7). CT techniques provide high spatial resolution and a high degree of anatomic localization of the change of regional lung attenuation during the wash-in and subsequent washout of xenon (8). This technique, however, requires repeated measurements and therefore repeated exposure to ionizing radiation (9). Additionally, xenon has anesthetic and sedative properties that limit the concentration, the achievable contrast enhancement, and consequently the signal-to-noise ratio (SNR) (10).

Hyperpolarized ^3He MRI (HP ^3He MRI) has become an attractive imaging modality for regional assessment of lung function (11,12), with promising temporal and spatial resolution and a very attractive safety profile. HP ^3He MRI has opened the possibility for noninvasive visualization of ventilated lung airspaces and has recently been used in assessment of asthma, emphysema, and cystic fibrosis (13–15), as well as bronchiolitis obliterans post-lung transplantation (16). Static spin density ^3He images can be obtained during a breath hold to detect ventilation defects (17). Defect maps and deviations in dynamic ventilation patterns have been shown on HP ^3He MR images reflecting gas trapping in these conditions (13,18). Nevertheless, a more effective assessment of pulmonary diseases requires an imaging technique capable of providing quantitative gas replacement and distribution parameters. For instance, emphysema and asthma are characterized by diminished regional gas flow and exhibit an inhomogeneous gas distribution. Quantitative measurement of these pulmonary parameters is therefore the subject of ongoing research.

Deninger et al. (19) developed a technique for quantitative measurement of regional pulmonary ventilation based on signal buildup in the lung following a sequence of HP ^3He breaths. This technique, however, in its proposed form is limited to use in small animals as it requires many HP ^3He breaths and a relatively long acquisition time. These properties made the implementation of this technique impractical in large animals and in humans. In this manuscript, an improved technique for imaging quantitative regional lung ventilation is developed and described, which allows for acquisition of similar regional ventilation information over a much shorter time scale and with substantially fewer HP ^3He breaths. Furthermore, this work discusses some important issues related to dead-space modeling as relevant to regional measurements of lung ventilation.

THEORY

Fractional Ventilation Model

Airway fractional ventilation, 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 gas space of that volume element at the end of inspiration, 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 gas content at end inspiration under breath-hold pressure is assumed to be divided between r_A , consisting of the delivered fresh gas, and $q_A = 1 - r_A$, 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 HP ^3He breaths, the net magnetization of ^3He 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 (M_∞) specific to each region, which is proportional to the total airway volume present in the respective region of interest. The resulting magnetization after inhaling a ^3He breath is a function of the magnetization of the fraction r_A of the fresh ^3He and that of the fraction q_A of ^3He remaining from previous breaths. During the time interval between the two breaths, the polarization of ^3He decays according to the partial pressure of oxygen (PO_2) present in the airways (i.e., P_{AO_2} in the alveoli). The relaxation time constant is governed by $T_{1,\text{O}_2} = \zeta/\text{PO}_2$, with $\zeta \approx 2.6 \text{ bar}\cdot\text{s}$ at normal body temperature (20). Since PO_2 in the airways can vary with time, either through oxygen uptake in the alveoli or as determined by oxygen concentration in the gas delivered to the lungs, T_{1,O_2} can in general be a time-varying quantity.

Serial Ventilation Sequence

The proposed approach for measuring lung fractional ventilation utilizes a series of back-to-back HP ^3He breaths with an image acquired during a short breath-hold at the end of each breath, referred to as the *serial* ventilation sequence. Each region of interest is considered a single-compartment inflatable volume element, which engages in the inhalation/exhalation process. Each compartment is assumed to have one port through which fresh polarized gas enters and leaves the volume element at end-inhale and end-exhale, respectively. Fig. 1a shows the complete serial ventilation sequence to acquire N images to form the signal buildup curve. The time interval between two consecutive breaths is τ .

The available magnetization in the airways at each step of the serial ventilation sequence can be recursively expressed as a function of the freshly arrived and the residual ^3He from the previous step:

$$M_A(j) = r_A \cdot M_S + (1 - r_A) \cdot M_A(j-1) \cdot \exp[-D_{\text{RF}} + D_{\text{O}_2}], \quad M_A(0) = 0. \quad [2]$$

M_S is the source magnetization of the HP ^3He from the reservoir that is available to the volume compartment. Even though at any given time the source polarization in the reservoir is the same for all regions of the lung, the total magnetization available to a region of interest is limited by the airway volume specific to that region, and therefore at steady state:

$M_\infty = \lim_{j \rightarrow \infty} M(j) = M_S$. This magnetization is subject to external decay of ^3He polarization in the reservoir, $D_{\text{EXT}} = -t(j)/T_{1,\text{EXT}}$, at any given time $t(j)$. The external relaxation time constant $T_{1,\text{EXT}}$ is primarily a function of the position of the HP ^3He bag in the magnetic field and the wall relaxation of ^3He molecules inside the container bag (21) and can be experimentally measured for each study. Since the time scale of this experiment ($N \cdot \tau$) is typically two orders of magnitude smaller than the external depolarization time constant ($\tau \ll T_{1,\text{EXT}}$), D_{EXT} is negligible. The oxygen-induced depolarization of ^3He during each breath is governed by $D_{\text{O}_2} = -\tau/T_{1,\text{O}_2}$.

The radiofrequency (RF) depolarization effect $D_{\text{RF}} = N_{\text{PE}} \cdot \ln(\cos\alpha)$, on the other hand, is of critical importance since the residual fraction of the gas in the airways is repeatedly exposed to RF excitations, therefore affecting the available magnetization for the following images. For each image, the signal distribution will be a function of the amplitude of the RF field, the resulting RF pulse flip angle, α , and the HP ^3He spin density distribution. For the purpose of simulations and data fitting, we approximate the signal intensity in each image with an equivalent of a point object, subject to an RF pulse train with fixed α , and N_{PE} phase encode lines:

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

with η as a proper scaling factor.

Evolution of Oxygen Tension

The oxygen-induced depolarization rate of HP ^3He , T_{1,O_2} , is a function of the oxygen tension in the airways. Neglecting the uptake of oxygen into the blood during each breath (19,22), partial pressure of oxygen in the airways, P_A , at the beginning of each ^3He breath can be recursively expressed as a function of the oxygen concentration of the freshly arrived gas, P_S , and that of the residual gas in the airways from the previous breath as:

$$P_A(j) = r_A \cdot P_S + (1 - r_A) \cdot P_A(j-1), \quad P_A(0) = P_{A,O_2} = 140 \text{ mbar}. \quad [4]$$

Cascade Ventilation Sequence

The Deninger et al. (19) method of HP ^3He magnetization buildup, referred to as the *cascade* method, consists of acquiring an image after ventilating the lung with a given number of HP ^3He breaths during a breath hold, with this procedure repeated several times with an increasing number of polarized gas breaths. Fig. 1b shows the n th step of this ventilation sequence corresponding to n HP ^3He breaths, where N_A is the number of air breaths between each step. The available magnetization in the airways at each step of this sequence can be recursively expressed for the j th breath as:

$$M_A(j) = r_A \cdot M_S \cdot \exp[D_{EXT}] + (1 - r_A) \cdot M_A(j-1) \cdot \exp[D_{O_2}], \quad M_A(0) = 0. \quad [5]$$

Since images are acquired at different breath holds, the signal intensity at each image is independent of the flip angle history. However, due to the much longer time scale of the experiment compared to the serial sequence (as a function of the number of delivered ^3He breaths, n , and air breaths, N_A , between each ventilation step), the external decay time constant $T_{1,EXT}$ is no longer negligible and has to be incorporated in ventilation measurements.

Dead Space Model

The dead space volume in the ventilation system can be divided into two main components (Fig. 2a). The first dead space component, *dynamic dead volume*, V_D , contains 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 bidirectional flow of gas during respiration. The portion of the respiratory gas residing in V_D from the previous breath is reinhaled with each new inspiration, a phenomenon known as *rebreathing* (23,24). The second compartment contains part of the ventilator system that carries the source gas toward the respirator valve's inlet, primarily containing the transmission line between the ^3He chamber and the respirator valve. Uni-directional transport of gas from the source through the transmission line will eventually fill up this dead space; hence, the *static dead volume*, V_S .

A lumped three-compartment model is proposed (Fig. 2b) to incorporate the dead volumes. The rightmost compartment comprises the acinar airways, including alveoli and small airways (with magnetization M_A). The middle compartment contains the major conductive

airways and the combination of the endotracheal tube and the respiratory valve (with magnetization M_C). Finally, the left-most compartment includes the transmission line (with magnetization M_T) that carries the HP gas from the source (M_S), and represents the magnetization of HP ^3He that enters the respirator valve at each breath.

The magnetization buildup in acinar airways (Eq. 2) is modified by replacing M_S with M_C , which is the combination of the arriving HP ^3He from the transmission line and the exhaled gas from the previous breath. Defining *rebreathing ratio* as $r_D = V_D/V_T < 1$, Eq. 2 becomes:

$$M_A(j) = r \cdot M_T(j-1) + (1-r) \cdot M_A(j-1) \cdot \exp[D_{RF} + D_{O_2}], \quad M_A(0) = 0, \quad [6]$$

where $r = r_A \cdot (1 - r_D)$ is the *apparent fractional ventilation*. It is assumed that the entrance of HP ^3He from the source pushes the same volume of gas (V_T) out of the static dead volume (Fig. 2c). Defining $r_S = V_T/V_S$, the mixing of the arriving and residual gases in V_S can be expressed as:

$$\begin{cases} r_S < 1: M_T(j) = r_S \cdot M_S + (1 - r_S) \cdot M_T(j-1), & M_T(0) = 0 \\ r_S > 1: M_T(j) = M_S, & M_T(0) = (1 - r_S^{-1}) \cdot M_S \end{cases} \quad [7]$$

For a relatively small tidal volume ($r_S < 1$, e.g., in rodents and small animals), M_T incrementally increases with each breath. However, for large tidal volumes ($r_S > 1$, e.g., in humans and large animals), the entire content of V_S is purged with the first breath, and the magnetization of the following breaths will be identical to M_S .

METHODS

Hyperpolarization of ^3He

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 h.

Mechanical Ventilation

A high-accuracy MRI-compatible mechanical ventilator prototyped in the authors' research laboratory was utilized to perform the imaging experiments. This programmable ventilator is capable of mixing up to three different types of gases (e.g., ^3He , O_2 , N_2 and air) at different ratios. 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 dead spaces. A different valve setup, suitable for the desired flow rate, is used for each range of species. For the rat setup, $V_D \approx 0.2$ mL (excluding the endotracheal tube) and $V_S \approx 3.2$ mL (between the ^3He chamber and the respirator valve), as illustrated in Fig. 2a. The same quantities for the pig valve setup are approximately 3 mL and 15 mL, respectively. Placement of the HP ^3He chamber inside the magnet bore near the RF imaging coil results in prolonged polarization relaxation times (45~60 min).

Phantom Studies

The artificial lung phantom is composed of a 10-mL Luer glass syringe (BD Yale, Franklin Lakes, NJ) with inner diameter (ID) = 1.46 cm, loaded with a nonmagnetic beryllium-copper silver-coated compression spring (Small Parts, Miramar, FL) with a 3.24-in free length and a nominal spring rate of 0.145 lb/in. A stopper was mounted on the syringe holder base to block the plunger motion beyond a certain point, enforcing a residual volume of $V_R = 4$ mL.

during mechanical ventilation. For phantom validation studies, the syringe-spring assembly was ventilated with three different tidal volumes: $V_T = 1.1, 2.5,$ and 4.5 mL, corresponding to $r_A = V_T/(V_T + V_R) = 0.22, 0.38,$ and $0.53,$ respectively. Dead space was directly measured as $V_D \approx 0.5$ mL and $V_S \approx 3.2$ mL.

Animal Studies

All animal experiments were conducted in accordance with protocols approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania. The proposed serial ventilation imaging sequence was prototyped in a healthy male Sprague-Dawley rat (350-g body weight). The applicability of the technique in large animals was assessed in a Yorkshire pig (22-kg body weight).

The rat was sedated with a 0.1 g/kg intraperitoneal ketamine and 10 mg/kg xylazine. The dose was repeated every 90 min or as necessary. The rat was then intubated with a 2-in-long, 14-gauge angiocatheter (BD Yale, Franklin Lakes, NJ) modified with a sealant (UHU Tac adhesive putty; Saunders Mfg. Co., Readfield, ME) to create a tight seal around the entrance to the trachea and was tested by ensuring a breath hold of 25 cm H_2O for 5 sec. Spontaneous respiration was then temporarily suppressed using 1 mg/kg intravenous administration of pancuronium bromide (Abbott Labs, North Chicago, IL) while under mechanical ventilation. Ventilation with air was maintained at $V_T = 1$ mL/100 g body weight for the rat at 60 breaths-per-minute (BPM). 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 rat's paw. Temperature was monitored using a rectal probe (SA Instruments, Stony Brook, NY) and maintained at $37^\circ C$ using a flow of warm air through the magnet bore. The pig was anesthetized with intravenous administration of $20\sim 25$ 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 ventilated with air at $V_T = 250$ mL at 14 BPM. As this protocol was enough to suppress the spontaneous respiratory effort, use of a paralysis agent was not necessary. Vital signs were monitored in a similar fashion as above.

Imaging Techniques

Imaging of the phantom and the rat was performed on a 50 -cm 4.7 -T MRI scanner (Varian Inc., Palo Alto, CA) equipped with 12 -cm 25 G/cm gradients and a quadrature eight-leg birdcage body coil with ID = 7 cm (Stark Contrast, Erlangen, Germany) tuned to the 3He resonance frequency of 152.95 MHz. The animal was placed supine in the RF coil. All imaging was performed using a fast gradient echo pulse sequence with field of view = 6×6 cm², slice thickness = 4 mm (projection for the syringe phantom), $\alpha = 4\sim 5^\circ$, matrix size = 64×64 pixels, pulse repetition time = 6.6 ms, and echo time = 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. Pulse width calibration was performed on the loaded RF coil to estimate the applied flip angle. The pig studies were performed on a whole-body 1.5 -T MRI system (Magnetom Sonata; Siemens Medical Solutions USA, Malvern, PA), using a quadrature eight-leg birdcage chest coil (Rapid Biomedical, Wurzburg, Germany) tuned to the 3He resonance frequency of 48.48 MHz, with an effective imaging volume of 35 cm long and 27 -cm ID. Three coronal slices were acquired using a gradient echo pulse sequence with field of view = 26×26 cm², slice thickness = 30 mm, slice spacing = 6 mm, $\alpha = 4\sim 5^\circ$, matrix size = 64×64 pixels, pulse repetition time = 6.4 ms, and echo time = 2.9 ms.

Ventilation images were acquired using the serial ventilation sequence (Fig. 1a) using $N = 10$ HP 3He breaths ($N = 8$ for the pig) during a 350 -ms breath hold (1 sec for the pig) at end-inhale of HP 3He breaths. The concentration of the administered HP gas was controlled with

the ventilator at $^3\text{He}:\text{O}_2 \approx 4:1$ ($^3\text{He}:\text{N}_2:\text{O}_2 \approx 3:5:2$ for the pig). Reproducibility studies in rat were performed using $V_T = 3$ mL, whereas for volume-dependency studies four different V_T values were used: 2, 3, 4, and 5 mL. For comparison, one extra set of ventilation measurements was performed in the rat, using the cascade ventilation sequence (Fig. 1b) with the same number of HP ^3He and 30 normal air breaths before each cycle of HP gas breaths, in order to wash out the residual ^3He gas from the lung parenchyma and adequately oxygenate the animal. Both measurements were performed using pure ^3He . For the pig study, a total amount of 2.0 L of HP gas mixture was prepared by mixing 0.6 L of ^3He , 1 L of N_2 , and 0.4 L of O_2 , delivered over $N = 8$ breaths at a concentration of $^3\text{He}:\text{N}_2:\text{O}_2 \approx 3:5:2$ at a $V_T = 250$ mL.

Regional distribution of flip angle, α , was estimated in the imaged body by acquiring a series of back-to-back images with identical imaging parameters to the ventilation imaging sequence, with no interscan time delay. In order to avoid misregistration between α and r_A maps, flip angle images were acquired at the tail end of the ventilation sequence while holding the last HP ^3He breath for 2~3 sec, ensuring identical lung position and inflation level with ventilation images. The RF-induced polarization decay of HP ^3He was then calculated from $S(j)/S(0) = (\cos \alpha)^{j \cdot N_{\text{PE}}}$, where $S(j)$ is the observed signal in the j th image after applying j RF pulses of equal α . 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 or in vivo T_1 relaxation.

Data Analysis

Data analysis was performed using custom MATLAB (Mathworks, Natick, MA) programs developed in the authors' laboratory. Analysis was performed on a voxel-by-voxel basis at a planar isometric resolution of $\sim 940 \mu\text{m}$ in rats. Bins with an SNR below a certain threshold (varying between 3:1 and 7:1) were excluded from analysis. Time evolution of signal intensity of valid voxels was then fit simultaneously to Eqs. 3, 4, 6, and 7, yielding M_S and r_A as free parameters for each voxel. In reporting the mean fractional ventilation value, voxels with a near-unity r_A value were excluded from the analysis since they represent major conductive airways. The intrasubject reproducibility of fractional ventilation measurement was assessed by calculating intravoxel variation of the calculated r_A value across three consecutive measurements. The mean coefficient of variation $\hat{r}_A = \sigma(r_A)/\mu(r_A)$ was then calculated as a measure of reproducibility over the entire lung. Pairwise comparison between different conditions was performed using a voxel-by-voxel linear regression analysis between the two r_A maps.

Model Sensitivity

The signal buildup in acinar airways was simulated for various model parameters, using fixed values shown in Table 1 and initial conditions of Eqs. 4, 6, and 7. The relative error $\Delta r_A = \delta r_A / r_A$, was calculated as a measure of sensitivity of r_A estimation to uncertainty in model parameters and to the value of r_A itself. The model was constructed using a priori values for parameters (r_D , r_S , α , $P_S = P_A \text{O}_2$) and their respective variations shown in Table 1. An additional analysis was performed to evaluate model sensitivity to ignoring V_S by building the model using $r_S \in [0.1, 10]$ and solving for r_A by setting $r_S \rightarrow \infty$.

The accuracy of r_A estimation was also evaluated with respect to SNR of the second image with magnetization $M_A(2) = r \cdot r_S \cdot M_S$ ($r_S < 1$, given that $M_A(1) = 0$ for $M_T(0) = 0$) for the range of SNR values shown in Table 1. We note that in poorly ventilated regions, a smaller quantity of HP gas arrives with one breath compared to normal regions, and therefore the reported SNR value reflects both the available polarization level and ventilation deficiency. Consequently, these regions are more "signal-demanding" than normal regions in regard to

measurement accuracy. In consideration of the effects of ventilation deficiency, this measure of SNR provides a conservative assessment of sensitivity to noise. Noise was introduced in the noise-free simulated model by adding a normally distributed noise (25) to the second image, with zero mean and a proper variance 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 a statistically plausible result. Finally, a similar analysis was performed using a partial number of ventilation images to assess the robustness of the model to the number of included images in the presence of noise.

Optimal Flip Angle

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 to acquire the image. As it is demonstrated by simulation in Fig. 3c and d, the flip angle value has a significant nonlinear effect on the rate of HP gas signal buildup in the airways. As is evident by Eq. 3, using a too small value for α (e.g., less than 1°) results in a diminished MR signal, which in turn adversely affects the reliability of parameter estimation from the model. A too large value for α (e.g., larger than 10°) causes an excessive RF signal decay of the residual magnetization at each step (i.e., the $M_A(j-1)$ term in Eq. 2). This results in a significant decrease of signal buildup and makes it impractical to extract the fractional ventilation information from the sequence of images. Therefore, α value has to be selected such that both criteria are satisfied.

Signal buildup, on the other hand, is tightly related to r_A , which in turn affects the choice of α . Since r_A varies in different regions of the lung, and possibly among different subjects, it is fundamentally impossible to find a globally optimal α value to meet the SNR and signal buildup requirements for all conditions. We therefore define a simple cost function of the form $f = \max_{\alpha} [S_A(p) - S_A(1)]$ to serve as a guideline for determining a range of optimal α values as function of the number of breaths included in the analysis. In this function, $S_A(p)$ represents the signal corresponding to 80% of steady state signal S_∞ in a given region of interest, and p is the (nearest) breath number at which this 80% S_∞ signal is achieved. The underlying idea is to find the α value that maximizes the change in signal amplitude for a given number of images. Therefore, the α value that maximizes this cost function can provide a conservative balance between the achievable SNR and the signal buildup dynamic range. Assuming that all system parameters are fixed, p th breath (corresponding to 80% S_∞ signal) can hold a different value for any given r_A , and therefore the optimal flip angle α_{opt} will be a function of r_A , as discussed earlier. Simulations were performed using parameters in Table 1 to find the range of α_{opt} value for a range of given breath numbers.

RESULTS

Simulation of Model Parameters

Figures 3a and b illustrate the effect of dead space on magnetization and signal buildup, respectively. Introduction of the two types of dead space affects the magnetization and signal buildup characteristics of the ventilation system in very different ways. Adding V_D to a no-dead-space system ($r_D = 0$ and $r_S = \infty$) is depicted as a lower steady-state magnetization, M_∞ , and a lower apparent fractional ventilation, $r = r_A \cdot (1 - r_D)$. Introduction of V_S to a no-dead-space system, on the other hand, increases the rise time of magnetization buildup curve. Nonetheless, this curve eventually reaches the same M_∞ as that of the no-dead-space system. Another important property of introducing the static dead volume (for $r_S < 1$) is that the magnetization in the first image vanishes as a result of delayed gas delivery through the transmission line. This property was embedded in Eq. 6

through direct dependence of $M_A(j)$ on $M_T(j-1)$. MR signal buildup behaves in a similar fashion to magnetization buildup for all these conditions (Fig. 3b).

Figures 3c and d illustrate the effect of flip angle on magnetization and signal buildup, respectively. Since a larger α implies a higher RF-induced depolarization of residual HP ^3He in the airways, the steady-state magnetization in the airways, M_∞ , is smaller compared to that of a smaller α . A larger flip angle, however, results in a greater MR signal for a given concentration of HP ^3He . Therefore, the rise time of signal buildup and the steady-state signal, S_∞ , will be a nonlinear function of α history. For instance, $\alpha = 2^\circ$ results in a larger steady-state magnetization due to accumulation of HP ^3He in the residual volume compared to that of $\alpha = 5^\circ$ (Fig. 3c). The resulting steady-state signal, however, will be larger for $\alpha = 5^\circ$, whereas $\alpha = 8^\circ$ results in a faster rising airway signal than either of the former two cases, with a plateau signal falling between the two.

Sensitivity Analysis

The relative error in r_A as a function of uncertainty in r_D is governed by $\Delta r_A = \delta r_A / r_A = \delta r_D$. Figure 4a illustrates a monotonic dependence of Δr_A on r_S variation. It is also evident that the relative error is larger for smaller r_A values. For instance, an error of +0.05 in r_S results in 80% overestimation of $r_A = 0.15$, whereas it only affects $r_A = 0.45$ by 45%. The net result of entirely ignoring V_S is underestimation of the r_A value, again with a larger relative error for smaller fractional ventilation values. However, as the actual r_S value grows beyond ~ 6 (e.g., in large species) the model quickly becomes less sensitive, as shown in Fig. 4b.

The sensitivity of the model to variations in the two primary decay mechanisms, α and P_{AO_2} , was assessed in a similar fashion. As shown in Fig. 4c, over/underestimating the α value results in a monotonic over/underestimation of r_A . Small r_A values are affected to a larger extent by α assumption. For the same example as above, overestimating α by 1° results in more than 80% overestimation of $r_A = 0.15$, whereas it only affects $r_A = 0.45$ by 20%. The effect of P_{AO_2} value assumption is illustrated in Fig. 4d, showing a much smaller effect on relative error compared to α . For the same example, overestimating P_{AO_2} at 200 mbar results in about 4% underestimation of $r_A = 0.15$, whereas the effect on $r_A = 0.45$ is almost negligible.

Noise Analysis and Number of Images

Figure 5a shows the evolution of Δr_A as a function of the SNR in the second image for different r_A values over 20 breaths. An SNR > 20 limits the relative error to 10% for all the selected r_A values between 0.15 and 0.55. However, smaller r_A values in general show better robustness against added noise. For SNR < 10 , the significance of Δr_A becomes large and undermines the reliability of measurements. In general, including a larger number of images by using a larger quantity of gas (achieved, for example, by diluting the HP ^3He mixture with N_2 gas) can offset the SNR impact. Figure 5b shows the variation of Δr_A (for $r_A = 0.3$) with respect to the number of included images in the curve fit procedure for a given SNR < 20 . Relative error in r_A drops exponentially with increasing number of images in the analysis and shows a very similar performance for SNR ≥ 10 . Similar characteristic curves can serve as a guide in designing the experiment in terms of available HP ^3He and polarization level. For instance, the same level of Δr_A can be retained as SNR = 20 with five images, when acquiring eight images at an SNR = 10.

Optimal Flip Angle

The combined effect of flip angle and number of images on maximizing the signal buildup range was assessed according to the proposed cost function, f . Figure 6 shows the range of optimal α for a series of given r_A values as a function of the minimum number of breaths, p

corresponding to 80% S_{∞} . The individual curves are slightly offset horizontally to avoid masking each other. For any given number of breaths p , a range of α_{opt} is returned that maximizes the cost function. This is due to the discrete nature of number of breaths, and therefore the largest α in each range can be selected as the candidate α_{opt} for a given p . It is interesting to note that this optimization criterion is inclusive in the sense that for any given r_A , the α_{opt} meets the optimality requirement, as well as for any other larger r_A values. For example, if the target number of breaths is 10, then $\alpha_{\text{opt}} \approx 5^\circ$ meets the criterion of $r_A > 0.1$, whereas an $\alpha_{\text{opt}} \approx 4^\circ$ only meets the requirement for $r_A > 0.2$.

Validation in Syringe Phantom

Fractional ventilation was measured in the spring-syringe setup with three tidal volumes, $V_T = 1.1, 2.5$, and 4.5 mL (corresponding to $r_A = 0.22, 0.38$, and 0.53). Each measurement was repeated three times. Since ^3He molecules can freely diffuse inside the syringe volume ($D \approx 2.0 \text{ cm}^2/\text{sec}$), the region in the image containing the syringe body was manually segmented and the sum of signal intensity for all the enclosed voxels was used as the representative signal value corresponding to each breath in the sequence. A typical SNR of 30~40 in the second image was achieved in the phantom. Figure 7 shows example MR images of the syringe displaced with the respective tidal volume, along with experimental data points and fit results. The individual points on each curve represent the average summed signal value for the three runs, and the error bars represent the SD of this quantity. The results (reported on top of Fig. 7a–c) show good agreement with a priori r_A values. In addition, r_A value for each individual run was calculated and compared to the corresponding nominal r_A value. As shown in Fig. 7d, the measurements for each tidal volume also agree with the corresponding nominal r_A values.

Reproducibility and Volume Dependency in Small Animal

Figure 8a shows the voxel-by-voxel $\hat{r}_{A,i} = \sigma(r_{A,i})/\mu(r_{A,i})$ across the three measurements, with an average $\hat{r}_A = 8.9 \pm 8.0\%$. In addition, the pairwise spatial correlation of every two sets of measurements was evaluated. Shown in Fig. 8b is the voxel-by-voxel correlation assessment of the first and second measurements, with a relatively linear regression coefficient of $R^2 = 0.94$. As evident from the scatter plot, the dispersion of data points becomes larger for higher r_A values.

A larger tidal volume yields a distribution with an elevated mean r_A value. Figure 9 shows example MR images of the rat lung, along with the corresponding r_A map and the distribution histogram. SNR values in the second images in the sequence varied between 15 and 25. For comparing r_A mean and SD values in each measurement, voxels with a near-unity r_A value (corresponding to conductive airways) were excluded from the distribution and calculated as follows: 0.42 ± 0.21 , 0.49 ± 0.16 , 0.63 ± 0.16 , and 0.69 ± 0.15 for the listed V_T values, respectively. Histograms also move to the right with increasing tidal volumes. Fractional ventilation in regions closer to major bronchi increase to a larger degree with increased tidal volume compared to distal regions of lung parenchyma.

Comparison of Techniques

Fractional ventilation measurement was also performed in the same rat, using the cascade ventilation sequence at $V_T = 3$ mL. The required amount of time and HP ^3He gas to perform this measurement was 405 sec and 180 mL, respectively (using a $^3\text{He}:\text{O}_2 = 4:1$, 30 air breaths between each ^3He step, and two 10-breath normalization images at the beginning and at the end of the ventilation sequence) compared to 13 sec and 24 mL, respectively, for the same measurement performed using serial ventilation sequence. Measurements were also performed using pure ^3He gas, as proposed in the original work by Deninger et al. (19). In accordance with this work, no dead-space effects were considered in the analysis. Figure 8c

and d shows the voxel-by-voxel correlation analysis of the two techniques. Results of the two methods are virtually identical, as evident by linear regression coefficient $R^2 = 0.93$, and were the same for both gas mixtures. The scatter plots comprise two clusters, one grouped around $r_A = 0.8$ (corresponding to conductive airways) and a larger group spanning $0.0 < r_A < 0.4$, corresponding to acinar airways. We note that the lower r_A values in acinar airways compared to Fig. 8b are primarily due to the underestimation of this quantity as a result of ignoring the dead-space volumes.

Feasibility in Large Animal

The serial ventilation imaging sequence was implemented on a Yorkshire pig to test the feasibility of r_A measurements in large species with a comparable lung volume to humans. Figure 10 shows the resulting fractional ventilation map overlaid on top of an MR image, along with the distribution frequency histogram. SNR value in the second image of the ventilation sequence was approximately 24. The histogram depicts two distinct peaks as corresponding to acinar airways ($r_A \approx 0.2$), and trachea and major conductive airways ($r_A \approx 0.8$).

DISCUSSION AND CONCLUSIONS

Dead Space Considerations

Simulation and experimental results both indicate that inclusion of dead-space volume in the ventilation model allows for a better fit to the data by providing additional degrees of freedom to the signal buildup model. As was shown in simulations (Fig. 3) and the syringe phantom experiment (Fig. 7), in presence of static dead volume, the signal buildup curve starts resembling an S-shaped curve. In the absence of the static dead-space model, the signal buildup curve is mathematically incapable of exhibiting such a behavior and therefore adversely affects the estimation of r_A value. This model has a greater significance in small animals and rodents, where the tidal volume is of the same order of magnitude as dynamic and static dead-space volumes. On the other hand, it is important to note that inaccurate estimation of system dead volumes can lead to error in r_A calculation (Fig. 4), and therefore it is necessary to balance the tradeoff between the two factors through accurate measurement of system dead spaces.

Number of Images

The determining factor in the number of images acquirable in one session is the HP ^3He production capacity (1 L per day in the authors' laboratory). This volume can provide several tens to hundreds of HP ^3He breaths in rodents and small animals but can be a limiting factor in large animals and humans. Nevertheless, the gas mixture for large species can be diluted with ultrahigh-purity N_2 gas to achieve larger quantities of imaging gas, provided that the polarization level of ^3He is adequate to meet the final magnetization necessary to perform the study, as determined by the SNR requirements (Fig. 5b).

Optimal Flip Angle

The optimality of the flip-angle value is a multivariable problem that must take into account several factors, including the available amount of HP ^3He for imaging, sensitivity within a desired range of r_A values, and the available ^3He polarization level. Ultimately, a suitable cost function has to be devised to meet the study requirements. The proposed cost function, f (the maximum flip angle that yields 80% of steady-state signal at a desired number of breaths), was based on the idea that reaching S_{80} provides a reasonable signal buildup to allow for an accurate estimation of r_A . As shown in Fig. 6, this choice can widely vary, depending on the r_A value. As a general rule, a larger number of breaths provides increased

accuracy in measurements and therefore should be the determining factor in selecting an optimal flip angle.

Validation

Preliminary validation of the serial ventilation imaging technique was performed in a syringe-spring phantom. The measurements were reproducible and in good agreement with theory using three different tidal volumes. It is, however, important to validate the measurements in vivo to assess the model accuracy in calculating fractional ventilation in a multipath airway system. The validation of this technique is a subject for ongoing and future research. As a gold standard, inhaled microspheres in the form of aerosols have been traditionally used to assess regional ventilation (26). The number of deposited microspheres in each region of the lung over a known period of time, determined by postmortem analysis, is correlated to the corresponding regional ventilation value. However, this method is inherently flawed by coregistration artifacts and the limit on number of specimens acquirable from the lung with reasonable effort and accuracy. Alternatively, a xenon-enhanced CT ventilation scan can serve as a more compatible imaging modality for a cross-correlation study, with already demonstrated performance level (8).

Reproducibility and Volume Dependency

The repeatability of in vivo measurements was assessed in a healthy rat lung with a voxel-by-voxel variation of less than 10%. In addition, results were shown to tightly correlate ($R^2 = 0.94$) across different measurements. This level of precision is a function of highly reproducible tidal volume, as controlled by the mechanical ventilator. In fact, as shown in Fig. 9, the actual V_T value can have a drastic effect on the measured r_A value. This observation signifies the importance of normalizing and accurately titrating tidal volumes, especially when using this technique to compare different subjects and to noninvasively assess lung ventilation abnormalities.

Pros and Cons

In the cascade ventilation sequence, each point on the signal buildup curve for a given region of interest is acquired separately. The j th point is acquired during a breath hold after

inhaling j HP ^3He breaths, therefore requiring $\sum_{j=1}^N j$ HP ^3He breaths for N data points. In contrast, the serial ventilation sequence acquires an image at the end of each inhaled breath and therefore only requires N HP ^3He breaths for the same number of data points. The acquisition time of N images in the serial technique is approximately $N\tau$, which is roughly a factor of N shorter than the cascade technique. These features are specifically desirable for performing the measurements on large species and humans, where the total quantity of available HP ^3He per imaging session is typically a limiting factor. Even in rodents this benefit can be utilized for performing a higher number of acquisitions under different conditions, more slices, and a larger number of animals per imaging session. In addition, the shorter acquisition time can benefit the physiologic stability of the animal during the imaging session.

From a technical standpoint, thanks to its short acquisition time, the serial ventilation imaging sequence is practically independent of the external relaxation of HP ^3He in the reservoir. The external relaxation time constant, $T_{1,\text{EXT}}$, was shown (19) to have a profound effect on the cascade ventilation sequence signal buildup. On the other hand, since images in the cascade ventilation sequence are acquired at separate breath holds, the signal buildup model is independent of the regional α value, and therefore a larger α can be used to benefit from a higher SNR. In addition to the inherent cap on the maximum α value in the serial

ventilation sequence, the inaccuracy in estimating α can adversely affect the r_A measurements, rendering the homogeneity of amplitude of the RF field an important factor. Utilization of a homogeneous RF coil (e.g., a volume birdcage coil versus a jacket coil) not only reduces the amplitude of the RF field heterogeneity but also allows for subject-independent mapping of the amplitude of the RF field, which can then be scaled for each specific loading condition, using an overall RF pulse power calibration (27).

In serial ventilation sequence, the lung oxygenation and image acquisition take place simultaneously, and it is desirable to minimize the deviation from normal ventilation pattern. This is a less important concern in the cascade ventilation technique, where the breath hold occurs only once per cycle of the ventilation sequence. Serial ventilation sequence adds a short breath hold at the end of each HP ^3He breath (~350 ms in rats and 1 sec in pigs) for image acquisition. In practice, it would be desirable to acquire multiple slices from the entire lung, especially in presence of a heterogeneous diseases such as emphysema. It will therefore be necessary to prolong the breath hold to accommodate the additional number of slices. This change is most tolerable by large species with a relatively slower breathing rate compared to image acquisition times. However, in rodents and other small animals it may be necessary to acquire each slice in a different ventilation sequence or alternatively use fast acquisition schemes currently under development (12,28).

Application in Humans

Preliminary results in a Yorkshire pig demonstrated the potential for implementation in large species. Concerns with inadequate gas supply and long acquisition times are largely addressed by the proposed serial ventilation sequence. Additionally, almost all ventilation-based HP ^3He MRI techniques are directly translatable to HP ^{129}Xe as a means of overcoming the limited supply. With the advent of high-capacity and continuous ^{129}Xe hyperpolarizing technology (29,30), eliminating the limit on the quantity of polarized gas available in one imaging session is getting closer to reality. 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 (31), and 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 providing a reasonable measurement accuracy. Due to the relatively short time course of these studies, however, the period of breath holds and the likelihood of substantial uptake are smaller than anesthetic applications (32).

Another practical concern entails accurate delivery of the HP gas over a series of breaths to human subjects. This will require some level of supervision, possibly by using a passive gas delivery device and coaching during the MRI session. The major advantage is that, as long as the amount of inhaled gas per breath is monitored by the device (either through real-time gas volume measurement or by simple monitoring of peak inspiration pressure), the breathing pattern can be autonomously controlled by the human subject. By eliminating the need for active mechanical ventilation, the individual will be able to breathe at a comfortable rate that best suits the instantaneous physiologic conditions.

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FIG. 1.

Schematic diagram of (a) the complete *serial* ventilation sequence, during which one image is acquired after each HP ${}^3\text{He}$ breath (for a total of N images); and (b) the n th step of *cascade* ventilation sequence, during which one image is acquired at the end of the n th HP ${}^3\text{He}$ breath. Acquiring a complete series of ventilation images requires repeating this sequence N times.

FIG. 2.

a: Schematic diagram of the MR-compatible ventilator system depicting the static and dynamic dead space volumes. **b:** Three-compartment lumped model of ventilator system dead space volumes. **c:** The details of the gas replacement model in the static dead space compartment.

FIG. 3. Simulation results for magnetization and signal buildup dynamics in the serial ventilation sequence with $\alpha = 5.0^\circ$ in (a) and (b), and $r_D = 0.3$ and $r_S = 0.3$ in (c) and (d).

FIG. 4.

The sensitivity of the serial ventilation sequence in predicting airway fractional ventilation value (r_A) to model parameters, including (a) incorrect assumption of static dead space value, (b) ignoring static dead space, (c) incorrect assumption of flip angle value, and (d) incorrect assumption of oxygen tension.

FIG. 5.

The sensitivity of the serial ventilation sequence in predicting airway fractional ventilation value (r_A) to (a) SNR in the first image, and (b) number of images included in the analysis.

FIG. 6.
The estimation of optimal flip angle for serial ventilation imaging sequence in order to maximize the dynamic range of 80% of steady-state signal.

FIG. 7.

Signal buildup curves for the spring-syringe phantom for three different tidal volumes, along with the respective predicted fractional ventilation values. The error bars in (a–c) represent the SD of signal for three sequential runs in each condition. Also shown are example MR images of the syringe at each tidal volume. **d:** The comparison of nominal values (solid line) to the estimated fractional ventilation values for each tidal volume. The error bars represent the SD of the predicted fractional ventilation for the three trials.

FIG. 8.

Assessment of regional reproducibility of measurements of fractional ventilation in a healthy rat lung. Shown are (a) the pixel-by-pixel variation of the estimated r_A values over three consecutive measurements and (b) correlation analysis for two separate measurements. Comparison of the serial and cascade ventilation sequences for measuring r_A in a healthy rat lung is shown as a pixel-by-pixel correlation analysis for the two separate measurements (c), with and (d) without oxygen.

FIG. 9.

Volume dependency of regional fractional ventilation in a healthy rat lung, for four different tidal volumes as shown on top of each map. The corresponding frequency distribution histograms are also shown.

FIG. 10. Regional fractional measurement in the lung of a healthy Yorkshire pig as a demonstration for applicability in large species.

Model Parameters for Simulation of Sensitivity of Fractional Ventilation to Model Uncertainty, Noise, and Number of Images

Table 1

Fixed model parameters			Nominal model parameters		
Quantity	Value	Units	Quantity	Value	Units
M_S	1	arbitrary units	r_D	0.3	—
N	30	Breaths	r_S	0.3	—
τ	1.0	sec	α	5.0	deg
N_{PE}	64	Lines	$P_S = P_A O_2$	140	mbar
P_S	140	mbar	r_A	0.15~0.55	—
V_T	2.0	mL			
V_R	6.0	mL			
Sensitivity to model parameters					
Effect of dead space volume					
V_D	0.0 or 1.0	mL	r_D	0.0~0.9	—
r_D	0.0 or 0.5	—	r_S	0.0~0.9	—
V_S	0.0 or 10.0	mL	α	3.0~7.0	deg
r_S	∞ or 0.2	—	$P_A O_2$	0~200	mbar
Sensitivity to noise and number of images					
Optimal flip angle					
α	0.0~90.0	deg	SNR	5~60	—
r_A	0~1	—	N	3~10	Images

Also shown are parameters for optimizing flip angle value.

“—” represents a non-dimensional quantity.