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Regional Alveolar Partial Pressure of Oxygen Measurement with Parallel Accelerated Hyperpolarized Gas MRI

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INTRODUCTION

Hyperpolarized (HP) ^3He MRI is an attractive method for imaging pulmonary disorders because of established contrast techniques that impose sensitivity to airway disease [1,2], alveolar integrity [3], lung perfusion [4], and the regional alveolar partial pressure of oxygen (P_{AO_2}). The latter parameter is closely related to the local ventilation-perfusion ratio [5], and the distribution of P_{AO_2} values reflects the physiological heterogeneity of the lung. Measured distributions of values, however, are also sensitive to noise, the application of radiofrequency (RF) pulses, and potentially to gas redistribution within the lung during the measurement [6]. In order to use the P_{AO_2} map as a reliable biomarker for lung disease diagnosis or assessment, the relative contribution of these confounding factors needs to be understood, and the effects on the measurement must be minimized.

Several related P_{AO_2} measurement methods using HP ^3He MRI have been introduced over the past decade [6-11]. In all of these techniques, the regional P_{AO_2} is calculated from the oxygen (O_2)-induced ^3He depolarization rate. In order to achieve an acceptable image signal-to-noise ratio (SNR), however, sufficient RF power must be applied that its depolarization effect cannot be neglected. Accurate separation of the two types of depolarization mechanism holds the key to reliable P_{AO_2} mapping. This separation can be accomplished by acquiring identical image sets, in which only the RF power is varied [7], although more efficient use of available gas and superior immunity to subject motion can be achieved by using a variable inter-scan acquisition delay scheme during a single breath-hold [8]. Optimization of the timing scheme has been undertaken, and the effect on breath-hold duration and extracted P_{AO_2} uncertainty has been well studied [8,10,11].

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Several parallel accelerated (undersampled) MRI techniques have been introduced and refined during the past two decades [12-14] along with different imaging reconstruction algorithms, and these are now widely used in clinical settings. By skipping some of the gradient phase encoding steps and sampling the k -space through spatial harmonics, parallel acceleration can greatly reduce the image acquisition time. Very few applications of parallel accelerated imaging with hyperpolarized gas have been reported [15,16], although unlike traditional MRI no signal-to-noise penalty is generally to be expected [16] as the fixed magnetization budget may be reapportioned among a smaller number of excitations, increasing the signal in each one. Because the extended breath-hold duration can limit HP gas MRI utility in human lung imaging, especially at high spatial resolution and in individuals with impaired lung function, accelerated imaging may also facilitate greater subject tolerance and image quality. With respect to P_{AO_2} imaging in particular, the shorter image duration of accelerated imaging allows greater timing flexibility to optimize the decoupling of RF pulse flip angle and oxygen-induced relaxation effects.

The purpose of this work is to further optimize the hybrid single acquisition P_{AO_2} imaging timing scheme [9,10] to include parallel accelerated acquisition. P_{AO_2} imaging utilizes signal intensity differences between successive images, and is therefore highly sensitive to noise and to RF-induced depolarization; thus, it is a particularly attractive application for parallel imaging. However, care must be taken to ensure that undersampling artifacts, which may differ between images, do not skew the derived P_{AO_2} maps in unexpected ways. We explore all of the relevant effects using computational models, phantom images in a well-defined state, and human images.

BACKGROUND

Theory

In the presence of gas phase oxygen at temperature T , the longitudinal relaxation rate ($1/T_1$) of HP ^3He gas depends linearly on the oxygen partial pressure $[O_2]$:

$$\frac{1}{T_1} = 0.45 \left(\frac{299}{T} \right)^{0.42} [O_2] \quad (1)$$

where T_1 , T , and $[O_2]$ are measured in seconds, K, and Amagat respectively [17]. At body temperature, 310K, Eq. [1] yields:

$$T_1 = \xi / pO_2 \quad (2)$$

where $\xi = 1950 \text{ Torr} \cdot \text{s}$.

We assume that there are two dominant sources of ^3He depolarization in the lungs: (i) the O_2 -induced dipole-dipole interaction of ^3He nuclei with the much larger magnetic moments associated with the unpaired electron spins of oxygen molecules, according to eq. 2, and (ii) depolarization of ^3He caused by RF pulses used in the imaging pulse sequence. All other depolarization mechanisms are considered negligible on the relevant physiological time scales during the imaging experiment. The regional values of P_{AO_2} in a given slice can therefore be extracted from the corresponding series of HP ^3He images that are acquired according to a predefined time delay sequence. Thus, the relative signal intensity loss in each successive MR image at a given voxel is taken to be the product of the relative losses due to O_2 -induced relaxation and RF depolarization. The former component depends exponentially on the time elapsed between successive MR images. The latter, on the other hand, is given by the factor $\cos^{N_{PE}}(\alpha)$, where α is the flip angle of the applied RF pulse at the location of the voxel and N_{PE} is the number of phase encoding RF pulses applied to the

voxel to acquire the images. Assuming a constant regional P_{AO_2} value during the time scale of image acquisition, the HP ^3He magnetization available to a given region-of-interest (ROI) in the n -th acquired image of the series can be expressed as (16):

$$M_n = M_0 \cos^{n \cdot N_{PE}}(\alpha) \times \exp[-P_{AO_2} \cdot t_n(k) / \xi] \quad (3)$$

where M_0 and M_n are the magnetization levels of the ROI in the initial and n -th image respectively, and $t_n(k)$ is the start time of the n -th acquisition of the k -th slice. We note that alveolar oxygen tension will decrease slowly (and approximately linearly [9]) during the breath hold due to oxygen uptake into the blood. We do not formally include this effect in eq. [3]; P_{AO_2} in this expression therefore refers to the average oxygen tension between $t = 0$ and $t = t_n$. To very good approximation, we may consider it to refer to the average P_{AO_2} during the breath hold.

Timing Scheme of P_{AO_2} Acquisition

The choice of time delays separating the images acquired during a breath-hold is crucial for distinguishing the depolarization effect of the oxygen from that of the RF pulses, and therefore directly impacts the accuracy of P_{AO_2} estimation. As can be seen in eq. 3, longer time delays between successive images of the same voxel will enhance the effect of oxygen on signal dynamics. Due to the high sensitivity of P_{AO_2} measurement errors to the accuracy of α estimates, and significant flaws in independent measurements and registrations of α maps (especially in flexible human chest coils), the timing has to be designed to permit effective and simultaneous decoupling of P_{AO_2} and α . The general approach is therefore to utilize a combination of both short and long time delays during the breath hold, to maintain sensitivity to both effects. A minimum of three images with different inter-scan time delays is theoretically necessary to make the decoupling of the two effects possible.

The acquisition schemes depicted in Figure 1 forms the basis for the P_{AO_2} measurements presented here. Like other successful schemes, inter-scan delay is varied as much as possible within the constraint of a fixed number of images acquirable within one breath-hold (in this case, four fully sampled or eight accelerated). In all cases, two consecutive images of each slice are acquired at the beginning of the breath hold with no inter-scan delay followed by a period of waiting time (during which other slices may be acquired). At least one additional image of each slice (and as many as three additional pairs) are then acquired subsequently. The signal intensity of corresponding voxels among all of the acquired images is extracted and fit to eq. 3, the signal decay function, to solve for α and P_{AO_2} simultaneously using a least squares fit.

Parallel Accelerated Imaging for Hyperpolarized Gas

The k -space sampling process with a phased array coil system can be expressed as:

$$S_n(k_x, k_y) = \iint dx dy C_n(x, y) M_0(x, y) \exp(-jk_x x - jk_y y) \quad (4)$$

in which M_0 represents the initial longitudinal magnetization, C_n and S_n are the coil sensitivity profile and sampled k -space signal of the n -th coil, respectively, and $k_x = \gamma G_x t_x$ and $k_y = \gamma G_y t_y$ are the phase encoding steps achieved by applying magnetic field gradient G for time t . The number of gradient phase encoding steps can be reduced by simultaneous acquisition of spatial harmonics with a sinusoidal coil sensitivity profile which is approximated by a linearly combined surface coil array. In such a case, as shown in eq. 5 and 6, the spatially varying coil sensitivity causes shifts in k -space, and is used as an alternate way of phase encoding which is otherwise produced only by magnetic field gradients.

$$C(x, y) = C_0 \cos(\Delta k_x x) + j C_0 \sin(\Delta k_x x) = C_0 \exp(j \Delta k_x x) \quad (5)$$

$$\begin{aligned} S_n(k_x, k_y) &= \iint dx dy C_n(x, y) M_0(x, y) \exp(-j k_x x - j k_y y) \\ &= \iint dx dy C_{n0} M_0(x, y) \exp(-j(k_x - \Delta k_x)x - j k_y y). \end{aligned} \quad (6)$$

When compared to other k -space acquisition schemes [12-13], Generalized Autocalibrating Partially Parallel Acquisitions (GRAPPA) [14] is noteworthy in that it minimizes SNR loss arising from partial cancellation of the individual coils' signal. For each of the m coils in the receive array, k -space sampling is specified by an acceleration factor and number of autocalibration lines, chosen from the fully sampled set near $k=0$. The full k -space and its corresponding uncombined image are then generated and the final image is reconstructed by combining all of the m individual images.

For HP ^3He imaging, the k -space signal intensity of the parallel coil system can be written as:

$$S_n(k_x, k_y) = \sum_{x=1}^N \sum_{y=1}^N M_0(x, y) \sin(\alpha) C_n(x, y) \exp\left(\frac{-(k_x-1)TR}{T_1}\right) \times \cos^{k_x-1}(\alpha) \exp\left(\frac{j2\pi(k_x+k_y)}{N}\right) \quad (7)$$

where $M_0(x, y)$ is the initial total magnetization, $C_n(x, y)$ is the coil sensitivity, α is the flip angle, $e^{-(k_x-1)TR/T_1}$ is the non-recoverable T_1 relaxation by oxygen, $\cos^{k_x-1}(\alpha)$ is the non-recoverable decay by RF pulses, $e^{j2\pi(k_x+k_y)/N}$ is the phase encoding term, and N is the total phase encoding steps.

MATERIALS AND METHODS

$\text{P}_{\text{A}}\text{O}_2$ Acquisition Simulations and Error Estimation

The parallel accelerated $\text{P}_{\text{A}}\text{O}_2$ mapping process was first simulated, and its precision and accuracy was compared to that of the full k -space sampling based on voxel-wise $\text{P}_{\text{A}}\text{O}_2$ mapping using eq. 1. The simulation was implemented on a personal computer in the Matlab (MathWorks, Natick, MA) environment and consisted of four parts: 1) assembly of an image series using an assumed 'ground truth' and Rician noise at a specified signal-to-noise ratio, 2) k -space sampling, 3) image reconstruction, and finally 4) voxel-wise $\text{P}_{\text{A}}\text{O}_2$ mapping using eq. 3 and the reconstructed images. Based on eq. 4, accelerated image series were simulated in k -space for each of 4 phased array coils, individual images were reconstructed for each coil with GRAPPA, and the summed magnitudes of the individual images were used for $\text{P}_{\text{A}}\text{O}_2$ mapping. Phase-encoding factors (e.g., in eq. 4) were calculated using the built-in Fast Fourier Transform (FFT) function of Matlab. The $\text{P}_{\text{A}}\text{O}_2$ mapping process then proceeded in a manner identical to that used for acquired images; the signal intensity of a single voxel was extracted from the simulated image series and fit to the magnetization decay function (eq. 3) allowing the initial magnetization, flip-angle, and $\text{P}_{\text{A}}\text{O}_2$ to vary independently. Oxygen uptake was not simulated, although its effect on the measurement appears in the discussion section.

Because of the shorter duration of each individual image acquisition, several accelerated schemes could be formulated and used for both simulation and imaging studies. Each scheme was subject to the requirement that its total duration not exceed that of the continuously acquiring, fully-sampled, 12-slice scheme employed in ref. [18] and pictured schematically in Figure 1a. At under 11 seconds, we have found this duration to be tolerable

by nearly all human subjects. Schemes utilizing three (the minimum theoretically needed) and four images were simulated for both fully sampled and accelerated imaging, and three, four, five, six and eight-image series were simulated for accelerated imaging. In each case, the schemes utilized a mixture of short and long delays, in order to best separate RF and oxygen-induced depolarization

The timing of each scheme is depicted schematically in Figure 1. Each scheme was simulated using a variety of signal-to-noise values and flip-angle covering all experimentally common situations. The mean error ($\mu - \mu_{actual}$) and variation coefficient (VC) were used as metrics to evaluate each P_{AO_2} mapping scheme. In simulation and phantom studies, both metrics were calculated with respect to simulated or measured pO_2 values of the N voxels exceeding the SNR threshold, as:

$$\mu - \mu_{actual} = \frac{1}{N} \sum_{i=1}^N pO_{2i,measured} - pO_{2i,actual} \quad (8)$$

$$VC = \sqrt{\frac{1}{N} \sum_{i=1}^N \frac{(pO_{2i,measured} - pO_{2i,actual} - (\mu - \mu_{actual}))^2}{pO_{2i,actual}^2}} \quad (9)$$

The latter metric is equivalent to the commonly used coefficient of variation (COV) in the case of uniform pO_2 whose true mean is estimated correctly, but tends toward zero as the reconstruction approaches the same spatial distribution as the assumed ground truth; thus, any uniform bias or offset of the estimation may be studied separately from the distortive effect of spatial artifacts or noise. A ‘lung-like’ model was chosen for simulation in which the true (noise-free) signal level was assumed to be that of the first measured image in a previous, fully-sampled human imaging experiment, and the P_{AO_2} was assumed to be the P_{AO_2} extracted the same experiment. Despite the imperfect correspondence to the true P_{AO_2} , we believe that it represents the best approximation available of the human lung and that its complex geometry and spatially varying pO_2 levels provide a more realistic milieu for testing the effect of acceleration-induced artifacts on the derived P_{AO_2} accuracy.

Phantom Experiments

Phantom experiments were conducted to verify the trends uncovered in the simulation results. All experiments were conducted on a Siemens Sonata 1.5T MRI system. A commercial volume transmit/8-channel receive phased array RF coil (Stark Contrast, Germany) was used for imaging. The transmit coil was saddle-shaped, 45cm long and 35cm wide, and both transmit and receive coils were tuned to the ^3He resonance frequency of 48.48 MHz. A $17 \times 7 \text{ cm}^2$ Tedlar bag was filled with a gas mixture of 40ml helium (^3He) and 160ml nitrogen (N_2). After injection of 50ml oxygen (O_2), the bag was tightly sealed and imaged using a Cartesian gradient echo pulse sequence with the following parameters: FOV of 300 mm, TR of 6.8ms, TE of 3.25ms, and $\text{MS} = 64 \times 64$. For the timing mode that requires acceleration, GRAPPA with an acceleration factor of 4 and 16 auto-calibration lines was used. The mixed gas was loosely contained in the bag such that the internal pressure was balanced with the atmospheric pressure in the room. The resulting oxygen concentration in the mixed gas was measured with an oxygen analyzer (Gemini Respiratory Monitor, CWE Inc., Ardmore, PA, USA), and actual oxygen partial pressure of the mixed gas was assumed to be uniform and calculated as: $\text{Actual } pO_2 = \text{O}_2 \% \times 760\text{Torr}$.

For each group of experiments using a given timing scheme, one additional image series was acquired with no added oxygen for comparison to the derived flip angle values when oxygen

was included. In order to eliminate the effect of inter-slice diffusion on P_{AO_2} mapping, which would otherwise be non-negligible in the freely-diffusing gas [18], a single slice with 250 mm thickness was positioned to cover the entire volume of the bag, and delays were inserted in lieu of the additional eleven slice acquisitions. Two groups of phantom experiments were conducted; one utilized a nominal flip angle of 5 degrees for all timing modes and the second utilized an 8-degree flip-angle for both the four-point and eight-point accelerated modes. These values were chosen to represent the range of optimal values as determined by simulation. To get a measure of reproducibility and to increase the sample size, each pO_2 mapping experiment was repeated 4 times. After injection, the bags were manually mixed and imaging began 4 seconds after oxygen injection.

Human Experiments

All experiments were conducted under a protocol approved by the Institutional Review Board at the University of Pennsylvania, and with informed subject consent. The subjects' vital signs (saturation of peripheral oxygen (SpO_2), heart rate, blood pressure and respiratory rate) were continuously monitored and a physician supervised the entire procedure. Prior to each P_{AO_2} imaging session, 1H MRI was performed using the 3He breath-hold protocol described below, with the HP gas mixture substituted by air.

Two different P_{AO_2} timing schemes, the four-point fully-sampled and four-point accelerated mode, were tested and compared on five human subjects: a healthy nonsmoker 57YO female, a healthy smoker 42YO male, healthy smoker 43YO male, COPD smoker 57YO male, COPD smoker 48YO male. All smokers had >35 pack-years smoking history, and the 48YO male COPD smoker was diagnosed during his imaging visit.

The accelerated scheme was selected as representative of the class on the basis of its superior performance in simulation and phantom studies. The two P_{AO_2} measurements were performed 5 minutes apart, using the same batch of HP 3He gas; in two instances the comparison experiment was repeated with another batch of HP 3He gas and the measurement order reversed, for a total of seven comparisons under near-identical conditions. During human lung imaging, the following imaging parameters were used, FOV=400×400mm, six or eight slices with anterior-to-posterior ordering, ST=20mm, TR/TE=6.8/3.25ms, and MS=64×64. For the four-point accelerated mode, GRAPPA acceleration with an acceleration factor of 4 and 16 auto-calibration lines was used. This resulted in an acquisition time reduction of approximately 56% per slice (28 phase-encodes as compared to 64).

3He imaging was performed at breath-hold after inhalation of a mixture of HP 3He , N_2 , and O_2 at a prescribed ratio, with the partial pressure of oxygen at ~ 21%. The volume of administered gas was adjusted to functional residual capacity (FRC) + 12% total lung capacity (TLC), measured prior to the MRI session by whole-body plethysmography. The mixture of HP 3He and N_2 was initially dispensed into a Tedlar bag, transferred to the bore of the MRI scanner, and connected to a three-way pneumatic valve, already connected to the bag with O_2 gas. Prior to inhalation of the HP gas mixture, the subject was instructed to breathe normally over three or four breath cycles (inhale:exhale~3:4) at a uniform rate of approximately 1 breath per 7 seconds. The three-way valve was then actuated and the subject was allowed to inhale the entire contents of both bags simultaneously. In order to ensure adequate post-inspiratory mixing of the gases and to minimize gas distribution and flow artifacts on the measurements, the imaging started approximately three seconds after the onset of the breath-hold, resulting in a breath-hold time of 13 seconds. In two instances, the protocol was slightly modified such that the hyperpolarized gas sample was diluted in nitrogen and inhaled over six breaths prior to the breath-hold.

Since independent confirmation of localized P_{AO_2} in a human lung is not feasible, comparison of the two techniques is limited to the coefficient of variation of the P_{AO_2} maps. During analysis, a signal mask was employed in order to restrict measurements to voxels which met the SNR threshold in the corresponding slices for both methods. This facilitated a more straightforward interpretation, though at the cost of rejecting approximately 2% of the total number of voxels that would otherwise have been included. No coregistration was performed.

RESULTS

Simulation

Figure 2 shows an example set of simulation results that is representative of the conditions encountered in a human experiment. Figure 2a,b depicts the ‘ground truth’ model (a previously acquired, fully-sampled intensity image (**2a**) and P_{AO_2} map (**2b**)) and is accompanied by a simulated acquisition and reconstruction of the image series using full k -space sampling (**2c**) and one using four-point accelerated sampling (**2d**). Both simulations began with identical initial magnetization, chosen such that the signal-to-noise ratio of the fully sampled case was twenty. As representative of their optimal conditions, the fully-sampled and accelerated examples employ 5° and 8° flip-angles, respectively.

Visual inspection of the simulated image reconstructions is instructive when considering the effect of acceleration on signal-to-noise and imaging artifacts. The raw image series from the example simulation are included as Figures 2e (fully sampled) and 2f (accelerated). Notably, the initial signal-to-noise of the fully sampled and accelerated images are approximately equivalent, but the late-time images show greater signal-to-noise in the accelerated case due to reduced RF depolarization. The image series are shown in false color to highlight the pattern of noise in each case; as expected, there is no spatial pattern to the background noise in the fully sampled images. However, the background noise shows a distinct spatial pattern in the accelerated image. This is due to the reconstruction technique’s estimation of missing k -space data, and highlights the need to test the fidelity of P_{AO_2} maps generated from these images.

A summary of all simulated cases is presented in Figure 3. Mean error and variation coefficient are shown for a variety of initial signal-to-noise values (representative of typical human imaging conditions) and flip-angle. The results in the figure are then used to select optimal imaging parameters, for comparison of the imaging schemes, and for comparison to the experimental results of the next section.

Three general features are apparent in all of the summarized results of Figure 3; first, the four-point schemes (depicted in Figures 1b and 1d) yields the most accurate results for either fully sampled or accelerated imaging. Second, at the optimal flip-angle, the accelerated case yields superior results in every case (although the difference between the two diminishes at high signal-to-noise ratio). Third, the accelerated techniques display a much wider range of acceptable flip-angles than the fully sampled techniques.

Phantom Experiment Results

Tedlar bag phantom experiment results are summarized in Figure 4. Figure 4a summarizes the comparison of three pO_2 mapping techniques chosen to be representative of the simulation results, and **4b** shows the corresponding comparison of flip angle estimation of the same experiments. Error bars represent the coefficient of variation of each pO_2 and α map respectively. The 4-point, fully-sampled pO_2 maps averaged a 5.0% estimation error and a 10.1% variation coefficient. The four-point accelerated scheme, which performed the

best, was characterized by an average estimation error of 0.1% and a coefficient of variation of 7.1%. A more comprehensive summary of the results and details of the individual trials appear as Table 1.

Human Experiments Results

Figures 5a and 5c show the P_{AO_2} maps of a human lung (57YO healthy female) using two different acquisition schemes; a four-point, full k -space acquisition with nominal flip-angle of 5° (**5a**) and the four-point, accelerated acquisition using a nominal flip-angle of 8° (**5c**). The corresponding histograms appear in the rows below for the fully sampled (**5b**) and accelerated (**5d**) cases. Only one of the two comparisons between the imaging techniques is summarized graphically in Figure 5 but a direct slice-by-slice comparison of the coefficients of variation using the two techniques across all seven imaging sessions appear in Figure 6. All image sets demonstrated a whole-image average P_{AO_2} near 100 Torr and an easily distinguishable posterior to anterior P_{AO_2} gradient. In-slice variation coefficients varied considerably based on the subject, ranging from approximately 0.2 in a healthy subject to nearly 0.5 in the COPD subject, but in each case most or all slices demonstrated a smaller coefficient of variation when the accelerated acquisition was used to generate the P_{AO_2} maps.

DISCUSSION

The overall finding of this study is that the use of accelerated imaging in determining alveolar oxygen tension by hyperpolarized ^3He is always beneficial, although the benefits become less pronounced at high signal-to-noise. In addition, the fidelity of the results is less sensitive to an accurate or uniform flip-angle when using the accelerated scheme. We see no evidence that the spatial distortion of the noise field, apparent in the simulation results of Figure 2 and in the raw human images acquired with acceleration, leads to detectable distortion of the P_{AO_2} map.

Timing Scheme Optimization

Based on the results of both simulation and the set of phantom experiments, the four-point P_{AO_2} mapping proved to be the best timing scheme in reducing the inherent uncertainty in the measurement, minimizing both the bias of the mean and the deviation from the true spatial pattern of P_{AO_2} . Notably, there is additional uncertainty in the estimate of the flip angle in the four-point accelerated scheme, due to fewer overall excitations, but this parameter is not in itself of interest except insofar as its estimation is required for accurate P_{AO_2} estimation. The inclusion of additional acquisitions during the waiting period made possible by accelerated imaging did not increase the accuracy of P_{AO_2} estimation in either simulation or phantom studies, although the additional excitations provided a more accurate estimate of the flip-angle.

One of the intriguing aspects of accelerated imaging of hyperpolarized gases is that the familiar relationship between the number of excitations and the SNR does not hold, and the expected SNR penalty for acceleration is not observed [16]. This is because of the fixed magnetization budget, which an accelerated acquisition can apportion between a smaller number of excitations. In the context of P_{AO_2} mapping, there is no apparent disadvantage to acceleration, while there is a distinct advantage, albeit one which differs from other applications in which higher resolution or shorter imaging times are desired. In this use, the benefit is largely from the longer delay time between image pairs, which enhances the effect of oxygen on the signal intensity. Specifically, the delay between image pairs is 5.22 seconds in the fully sampled acquisition, and this increases by 56% to 8.16 seconds in the

accelerated case. This additional flexibility in timing translates directly into a larger imprint of the oxygen concentration on the signal intensity, and hence to a greater P_{AO_2} accuracy.

It should be noted that increased accuracy is expected only in so far as measurement noise is a significant contributor to the observed P_{AO_2} map dispersion. In the limit of very high SNR, the expected benefit of the accelerated technique disappears, as can be observed in the trends of Figure 3b. However, this situation is not expected in practice; if it were routinely encountered, acceleration could still be used to shorten the breath-hold, increase spatial resolution, or impose direct sensitivity to oxygen uptake as per ref. [19].

Qualitative discussion of human imaging results

In a visual inspection of Figure 5, three features are immediately apparent; first a strong gravity-induced gradient is observed, averaging approximately 2.3 Torr/cm, with P_{AO_2} decreasing in the posterior direction. This gradient is expected physiologically, largely due to increased perfusion in the dependent regions, and is consistent with the previously measured 1.65 ± 1.01 Torr/cm in a reproducibility study of twelve volunteers [18]. Second, visual features are clearly consistent between the two image sets; for example, an increased apparent P_{AO_2} in the anterior, basal lung is observed in both image sets, as are elevated values near the heart. The apparent magnitude of these features is consistent between imaging techniques. Third, the P_{AO_2} maps derived from the accelerated images appear qualitatively smoother (less grainy) than those derived from the fully sampled images. This is consistent with an interpretation in which the additional variation in the fully sampled maps arises from spatially unstructured noise rather than a more faithful depiction of spatially structured true variability in P_{AO_2} .

Experimentally, this is seen as an additional ~ 0.05 in the coefficient of variation of each slice of the fully sampled P_{AO_2} maps (Figure 6). We have chosen to depict it this way because the whole-subject coefficient of variation is significantly larger than that of each slice due to gravitational effects, and the relative improvement of accelerated imaging is correspondingly smaller. Nonetheless, the improvement is statistically significant whether the slices are considered as 46 independent measurements ($p < 0.001$, Figure 6), or grouped as seven independent imaging sessions ($p < 0.01$).

Diffusion and the distribution of observed P_{AO_2} values

The effect of diffusion and gas flow was not included in the simulation model, and was minimized in the phantom experiment by imaging in projection and taking care to ensure uniform ^3He and oxygen concentrations. In the human or animal lung, however, gas redistribution during the measurement is likely not ignorable. Other published work has treated this subject in detail, and its effect can be minimized by a suitable choice of slice profile and interslice gap [18], or by using 3D imaging [20]. Residual effects can be further minimized by imaging at relatively coarse resolution, or by including several hyperpolarized wash-in breaths before imaging to equalize the gas distribution in slow-filling areas, as was done here. However, the effects cannot be entirely eliminated [18].

Despite the likely presence of these inaccuracies, other work has demonstrated that physiological effects, including gravitational P_{AO_2} gradients, are apparent using this technique [18]; this accounts for some of the coefficient of variation observed in the oxygen maps. In this work, we have presented evidence that some of the remaining variance originates in measurement noise, which can be minimized by extending the time base of the measurement (most conveniently by using an accelerated imaging technique) or by increasing ^3He polarization or imaging system sensitivity.

Routine or clinical use

This work suggests that when hardware allows, parallel accelerated imaging should be adopted for $P_{A}O_2$ mapping and will provide better precision than the use of full k -space sampling. Here, the acceleration was used to extend the separation between measurements and thereby to increase accuracy. Alternately, the timing flexibility of accelerated imaging could be used to delay the beginning of the first breath-hold and consequently minimize the confounding effect of true gas flow (as opposed to diffusion) should this cause significant error in $P_{A}O_2$ estimation of flow-compromised subjects. Still another approach would be to shorten the total duration of the breath-hold if the 10.8-second imaging duration proves difficult for some severely diseased patients.

Conclusion

We have presented and tested the use of a straightforward acceleration scheme to increase the accuracy of $P_{A}O_2$ mapping in the human lung using HP gas MRI. Despite the potential for imaging artifacts due to undersampling, any degradation of the $P_{A}O_2$ map accuracy is more than compensated by the increased $P_{A}O_2$ -dependent signal.

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REFERENCES

- [1]. Santyr GE, Lam WW, Parra-Robles JM, Taves TM, Ouriadov AV. Hyperpolarized noble gas magnetic resonance imaging of the animal lung: Approaches and applications. *J. Appl. Phys.* 2009; 105(10):102004.
- [2]. Emami K, Kadlecsek SJ, 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):137–150. [PubMed: 19877277]
- [3]. Yablonskiy DA, Sukstanskii AL, Woods JC, Gierada DS, Quirk JD, Hogg JC, Cooper JD, Conradi MS. Quantification of lung microstructure with hyperpolarized ^3He diffusion MRI. *J. Appl. Physiol.* 2009; 107(4):1258–1265. [PubMed: 19661452]
- [4]. van Beek EJR, Wild JM, Kauczor H-U, Schreiber W, Mugler JP, de Lange EE. Functional MRI of the lung using hyperpolarized 3-helium gas. *J. MRI.* 2004; 20(4):540–554.
- [5]. Rizi RR, Baumgardner JE, Ishii M, Spector ZZ, Edvinsson JM, Jalali A, Yu J, Itkin M, Lipson DA, Geftter W. Determination of regional V_A/Q by hyperpolarized ^3He MRI. *Magn. Reson. Med.* 2004; 52(1):65–72. [PubMed: 15236368]
- [6]. Kadlecsek S, Mongkolwisetwara P, Xin Y, Ishii M, Profka H, Emami K, Rizi R. Regional determination of oxygen uptake in rodent lungs using hyperpolarized gas and an analytical treatment of intrapulmonary gas redistribution. *NMR Biomed.* 2011 Epub before press, DOI: 10.1002/nbm.1685.
- [7]. Deninger AJ, Eberle B, Ebert M, Großmann T, Heil W, Kauczor H-U, Lauer L, Markstaller K, Otten E, Schmiedeskamp J, Schreiber W, Surkau R, Thelen M, Weiler N. Quantification of regional intrapulmonary oxygen partial pressure evolution during apnea by ^3He MRI. *J. Magn. Res.* 1999; 141:207–216.
- [8]. Fischer MC, Spector ZZ, Ishii M, Yu J, Emami K, Itkin M, Rizi R. Single-acquisition sequence for the measurement of oxygen partial pressure by hyperpolarized gas MRI. *Magn. Reson. Med.* 2004; 52(4):766–773. [PubMed: 15389934]
- [9]. Fischer MC, Kadlecsek S, Yu JS, Ishii M, Emami K, Vahdat V, Lipson DA, Rizi RR. Measurements of regional alveolar oxygen pressure using hyperpolarized ^3He MRI. *Acad. Radiol.* 2005; 12(11):1430–1439. [PubMed: 16253855]

- [10]. Yu J, Ishii M, Law M, Woodburn JM, Emami K, Kadlecek S, Vahdat V, Guyer RA, Rizi RR. Optimization of scan parameters in pulmonary partial pressure oxygen measurement by hyperpolarized ^3He MRI. *Magn. Reson. Med.* 2008; 59(1):124–131. [PubMed: 18050348]
- [11]. Miller GW, Mugler JP III, Altes TA, Cai J, Mata JF, de Lange EE, Tobias WA, Cates GD, Brookeman JR. A Short-Breath-Hold Technique for Lung pO_2 Mapping With ^3He MRI. *Magn. Reson. Med.* 2010; 63(1):127–136. [PubMed: 19918891]
- [12]. Sodickson DK, Manning WJ. Simultaneous acquisition of spatial harmonics (SMASH): fast imaging with radiofrequency coil arrays. *Magn. Reson. Med.* 1997; 38(4):591–603. [PubMed: 9324327]
- [13]. Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P. SENSE: Sensitivity Encoding for Fast MRI. *Magn. Reson. Med.* 1999; 42:952–962. [PubMed: 10542355]
- [14]. Griswold MA, Jakob PM, Heidemann RM, et al. Generalized autocalibrating partially parallel acquisitions (GRAPPA). *Magn. Reson. Med.* 2002; 47:1202–1210. [PubMed: 12111967]
- [15]. Vasanawala SS, Yu H, Shimakawa A, Brittain JH. A flexible 32-channel receive array combined with a homogeneous transmit coil for human lung imaging with hyperpolarized (^3He) at 1.5 T. *Magn. Reson. Med.* 2011 Epub before print PMID 21574180.
- [16]. Lee RF, Johnson G, Grossman RI, Stoeckel B, Trampel R, McGuinness G. Advantages of Parallel Imaging in Conjunction With Hyperpolarized Helium—A New Approach to MRI of the Lung. *Magn. Reson. Med.* 2006; 55:1132–1141. [PubMed: 16586457]
- [17]. Saam B, Happer W, Middleton H. Nuclear relaxation of ^3He in the presence of O_2 . *Phys. Rev. A.* 1995; 52:862–865. [PubMed: 9912313]
- [18]. Hamedani H, Kadlecek SJ, Emami K, Kuzma NN, Xu Y, Xin Y, Mongkolwisetwara P, Barulic A, Rossman M, Ishii M, Miller GW, Rizi RR. A Robust High-Resolution Technique for Imaging Alveolar Oxygen Tension in Humans. *Magn. Reson. Med.* 2011 In Press.
- [19]. Yu J, Rajaei S, Ishii M, Law M, Emami K, Woodburn JM, Kadlecek S, Vahdat V, Rizi RR. Measurement of pulmonary partial pressure of oxygen and oxygen depletion rate with hyperpolarized helium-3 MRI: a preliminary reproducibility study on pig model. *Acad. Radiol.* 2008; 15(6):702–12. [PubMed: 18486007]
- [20]. Wild JM, Fischele S, Woodhouse N, Paley MNJ, Kasuboski L, van Beek JR. 3D volume-localized pO_2 measurement in the human lung with ^3He MRI. *Magn. Reson. Med.* 2005; 53(5):1055–1064. [PubMed: 15844148]

Figure 1.

A schematic depiction of all of the timing schemes explored in this study. In each case, two images of a single slice are acquired back-to-back at the beginning (dark blue) and additional $n-1$ slices are acquired similarly immediately thereafter (light blue) in order to determine a flip-angle map with minimal contamination by oxygen-induced relaxation. Additional images are acquired as breath-hold timing allows (up to two in the case of fully sampled imaging, or six in the case of accelerated imaging) such that a combination of short and long delays are included. Based on simulation results, sequences b) and d) are particularly favorable and are typically used for our imaging studies.

Figure 2.

An experimentally-derived P_{AO_2} map (**2a**, signal intensity, and **2b**, oxygen tension) is used as the ‘ground truth’ for simulation of a fully sampled image series (**2e**) and a four-point, accelerated image series (**2f**). Subsequent reconstruction of the P_{AO_2} maps (**2c**, fully-sampled, and **2d**, accelerated) are summarized by the inset histograms, which show the frequency of deviations from the actual map values (extending from -100 Torr to $+100$ Torr). In the simulation, identical Rician noise is added to each acquisition. The undersampling of **2e** results in a more spatially structured noise/artifact background, but the larger optimal flip-angle and longer delay results in a more faithful P_{AO_2} reconstruction (histograms).

Figure 3.

A summary of the P_{AO_2} map mean errors (left) and variation coefficients (right) derived from the full set of simulations exemplified by Figure 2. Fully-sampled and accelerated simulations are depicted by solid and dashed lines, respectively. Three, four, five, six, and eight-time-point simulations are depicted by red, dark green, blue, light green, and purple lines, respectively. The seven inset figures, top to bottom, correspond to an initial magnetization which corresponds to a signal-to-noise of 10, 20, 30, 40, 50, 70 and 100, if averaged across the voxels of the first acquisition under reference conditions of a 5° flip-angle in the fully sampled case. Features of note include: a reduced variation coefficient in all cases when using the accelerated approach (a 13% reduction for standard signal-to-noise=10 falls to a <1% reduction as signal-to-noise approaches 100), a higher optimal flip-angle when acceleration (undersampling) is used, and a tendency toward a slight underestimation of the mean P_{AO_2} which is reduced in the accelerated case.

Figure 4.

Experimentally measured mean estimation error (**4a**) and variation coefficient of different pO₂ sampling techniques in a Tedlar bag phantom. As predicted in the simulation, the mean estimation error and variation coefficients of the pO₂ map are reduced by accelerated imaging, at the expense of poorer flip-angle estimation, and the four-point accelerated scheme displays the best performance.

Figure 5. Extracted $P_{A}O_2$ maps from one comparison of a human subject using the four-point full k -space sampling timing scheme (5a) and the four-point GRAPPA accelerated timing scheme (5c). Histograms of the corresponding maps from the fully sampled (5b) and accelerated (5d) schemes. The numbers inset in the histograms indicate the mean and coefficient of variation (standard deviation divided by the mean) of each slice. Visual features in both the maps and the histograms are preserved by undersampling, and the variation coefficient is in all cases reduced.

Figure 6.

Summary of human imaging experiments comparing variation coefficient of fully sampled and accelerated techniques. The points compare the coefficient of variation (COV) of the accelerated (x coordinate) and fully sampled (y coordinate) $P_{A}O_2$ maps from each slice in each individual. If the COVs from the two techniques were equal, the points would lie on the diagonal line shown; notably, all but five of the 46 same-slice comparisons lie above the line, indicating a smaller COV in the accelerated dataset. Markers indicate COPD (triangle), healthy smoker (square) and healthy nonsmoker (circle) subjects. Filled markers indicate imaging sessions following multiple, hyperpolarized gas washing breaths, open markers indicate imaging session following a single hyperpolarized gas breath.

Table 1

Complete summary of Tedlar bag phantom studies. Shaded columns correspond to metrics derived from fully sampled images; unshaded columns correspond to accelerated images.

	Mean pO ₂ Estimation Error (%)			pO ₂ Map Variation Coefficient (%)		
$\alpha=5$	Fully sampled	Accelerated 4-point	Accelerated 8-point	Fully sampled	Accelerated 4-point	Accelerated 8-point
<i>Trial 1</i>	-5.28	-0.31	-5.55	10.18	7.18	14.57
<i>Trial 2</i>	-4.58	-0.48	-4.94	11.73	6.33	16.37
<i>Trial 3</i>	-4.62	0.58	-5.07	9.17	7.44	14.71
<i>Trial 4</i>	-5.50	0.70	-5.62	9.35	7.58	14.51
<i>Group Mean</i>	-5.00	0.12	-5.23	10.11	7.13	15.04
$\alpha=8$	Fully sampled	Accelerated 4-point	Accelerated 8-point	Fully sampled	Accelerated 4-point	Accelerated 8-point
<i>Trial 1</i>	-3.86	-0.44	-4.39	13.37	12.54	23.50
<i>Trial 2</i>	-3.30	0.04	-4.96	11.36	10.91	21.81
<i>Trial 3</i>	-3.38	2.05	-6.17	12.36	10.86	26.53
<i>Trial 4</i>	-3.94	0.25	-5.94	11.30	8.71	22.07
<i>Group Mean</i>	-3.62	0.48	-5.37	12.10	10.76	23.48