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A Hybrid Multibreath Wash-in Wash-out Lung Function Quantification Scheme in Human Subjects Using Hyperpolarized ^3He MRI for Simultaneous Assessment of Specific Ventilation, Alveolar Oxygen Tension, Oxygen Uptake and Air Trapping

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Abstract

Purpose—To present a method for simultaneous acquisition of alveolar oxygen tension ($P_{\text{A}}\text{O}_2$), specific ventilation (SV), and apparent diffusion coefficient (ADC) of hyperpolarized (HP) gas in the human lung, allowing reinterpretation of the $P_{\text{A}}\text{O}_2$ and SV maps to produce a map of oxygen uptake (R).

Method—An imaging scheme was designed with a series of identical normoxic HP gas wash-in breaths to measure ADC, SV, $P_{\text{A}}\text{O}_2$ and R in less than 2 minutes. Signal dynamics was fit to an iterative recursive model that regionally solves for these parameters. This measurement was successfully performed in twelve subjects classified in three healthy, smoker and COPD cohorts.

Results—The overall whole-lung ADC, SV, $P_{\text{A}}\text{O}_2$ and R were $(0.20 \pm 0.03 \text{ cm}^2/\text{s}, 0.39 \pm 0.06, 113 \pm 2 \text{ Torr}$ and $1.55 \pm 0.35 \text{ Torr/s})$ and $(0.21 \pm 0.03 \text{ cm}^2/\text{s}, 0.33 \pm 0.06, 115.9 \pm 4 \text{ Torr}$ and $0.97 \pm 0.2 \text{ Torr/s})$ and $(0.25 \pm 0.06 \text{ cm}^2/\text{s}, 0.23 \pm 0.08, 114.8 \pm 6.0 \text{ Torr}$ and $0.94 \pm 0.12 \text{ Torr/s})$ in healthy, smoker and COPD subjects, respectively. Maps of SV, $P_{\text{A}}\text{O}_2$ or R are indicators of both smoking-related changes and disease, and the severity of the disease correlated to the degree of this heterogeneity. Subjects with symptoms showed reduced oxygen uptake and specific ventilation.

Conclusion—High-resolution, nearly coregistered and quantitative measures of lung function and structure were obtained with less than 1 liter of HP. This promising hybrid multi-breath

technique produced measures of lung function which revealed clear differences among the cohorts and subjects, and which were confirmed by correlations with global lung measurements.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a highly prevalent, progressive set of disorders characterized by abnormally low airflow, with no effective treatment (1). COPD is typically diagnosed after patients display symptoms of cough, sputum production, or dyspnea. Although there are no established tools to determine the underlying cause of COPD in an individual subject, or to subclassify subjects in clinical studies (2), a variety of markers have been developed that are sensitive to various aspects of the disease. In addition to the quantitative measures of global airflow restriction (Forced Expiratory Volume in 1 second; FEV₁ (3) and related metrics), measurements of trans-membrane gas exchange (4) and qualitative and quantitative evaluations based on x-ray or CT imaging have become increasingly popular (5, 6). Take together, these tests probe the changes to the lung that are present to varying degrees in all COPD subjects: *restricted flow* (due to obstruction, airway wall thickening or altered tissue mechanics), *airspace enlargement* (emphysema), *altered tissue perfusion*, *alveolar membrane thickening*, and *air trapping*.

A major limitation of the current suite of measurements is that they are not comparable on a regional basis; for example, airflow restriction established in global lung function tests may or may not be related to a specific volume of emphysematous remodeling. Without more detailed, regionally-based information, it is difficult to determine the root cause of disease morbidity, and to predict which aspect (or region) of the lung is most likely to alleviate these symptoms if treated. In fact, interventions that restore ventilation to poorly perfused lung, or vice versa, are likely to further exacerbate morbidity due to increased V/Q mismatch (7). A multifaceted functional measurement is therefore necessary for developing new treatments, demonstrating utility, and effectively applying them in the clinic.

In this paper we present a method suitable for acquisition and voxel-wise analysis of a single series of hyperpolarized gas images. This analysis yields quantitative determination of four parameters describing pulmonary function as well as a qualitative depiction of air trapping in the diseased lung. Image timing and encoding is controlled throughout the sequence to highlight aspects of the lung that are altered in disease, and an iterative analysis is used to extract the corresponding maps of *oxygen concentration* and *uptake*, *airspace size*, *ventilation* and *air trapping* with acceptable accuracy. Importantly, maps are acquired on the same grid and are nearly coregistered, allowing direct comparison (8).

The acquisition scheme is closely related to three previously-published imaging methods (9–11). Each has been shown to be useful in diagnosis or staging of COPD, detecting early changes in asymptomatic smokers, or to provide a meaningful imaging surrogate for specific clinical lung function tests (12–15). The technique presented here also contains a computational technique for deriving oxygen uptake by the capillary blood in a manner that is much less sensitive to imaging noise than those previously explored (16–20). Because this measurement is expected to correspond most closely to the global Diffusing Capacity for Carbon Monoxide (DL_{CO}), we explore that relationship as a first step at validation. We also

present additional comparisons to global measurements to confirm both the computational techniques and the resulting functional maps. Finally, because the scheme relies on a device for controlled administration of gases, we discuss the ways in which monitoring of inhaled and exhaled gas composition and flow provides both a more accurate analysis and an opportunity to further confirm the results.

METHODS

Clinical Tests

Before each imaging session, spirometry, plethysmography, and diffusion capacity testing were performed in accordance with ATS/ERS 2005 guidelines (21) in the Hospital at the University of Pennsylvania Pulmonary Function Laboratory. The PFT parameters measured were: FEV₁, FVC (Forced Vital Capacity), %FEV₁ (% predicted), total lung capacity (TLC), residual volume (RV), and diffusing capacity of carbon monoxide (DL_{CO}). Subjects also filled a St. George Respiratory Questionnaire (SGRQ) and the overall score was calculated.

³He Imaging Markers

Specific ventilation (SV) is a non-dimensional measurement and is defined as the amount of gas added to a volume element of the lung during a single inhalation divided by the gas volume contained in that element at end exhalation (22). It is related to *fractional ventilation* (FV), which is also defined as the amount of gas added to a volume element of the lung but divided by the gas volume at the end inhalation (10). *Alveolar Oxygen Tension* (P_AO₂), measured in Torr, is the partial pressure of oxygen in the lung parenchyma (9). P_AO₂ is generally a function of time, especially as oxygen is taken up by the blood during a breath hold, but measurements here refer to the value extrapolated back to the end of inhalation. *Oxygen Uptake* (R), measured in Torr/s, is the uptake rate of oxygen in the lung (16). Apparent diffusion coefficient (ADC) is a measure of the mean diffusion distance of ³He during ~1 ms (between the application of two gradient pulses). This measurement is directly related to alveolar size and connectivity (23).

³He Hyperpolarization

We polarized the imaging gas (³He:N₂ = 99.19:0.81, Linde, Branchburg, NJ) using a commercial polarizer (IGI 9600.He, GE Healthcare, Durham, NC) through spin-exchange collisions with optically pumped rubidium atoms. Approximately 1 liter of ³He with ~30% polarization was attained after ~15 hours of optical pumping. Hyperpolarized ³He gas was diluted with a volume of medical-grade nitrogen gas based on the subject's weight or total lung capacity (TLC), stored in a Tedlar bag, and mixed with oxygen during gas administration.

Gas Delivery System

A custom-built, passively-driven respiratory gas mixing and administration device allowed delivery of HP gas over a series of breaths at a prescribed volume and fraction of inspired oxygen (FiO₂), and a breathing pattern synchronized with image acquisition. Figure 1 shows a schematic of the device and pictures of the prototype successfully tested with HP ³He MRI. Details of the design are described in (24) and (10); the general concept is to use MRI-

compatible differential pressure pneumotachometers that independently report the flow rate of each gas component, triggering the pneumatic valves and the MRI scanner when the target volume is reached. The subject then commits a voluntary breath-hold during which images are acquired, exhales freely, and the sequence is repeated as desired.

A normoxic mixture of HP ^3He - N_2 and O_2 was prepared in two separate bags administered over 7 breaths as is shown in Figure 1, while monitoring blood oxygenation, heart rate, blood pressure, and respiratory rate. The tidal volume (V_T) delivered to each subject was based on 10 mL/kg or 12% of TLC (whichever was larger), rounded to the nearest of calibrated set points that were used as V_T for the gas delivery device (650 to 1000 mL, every 50 mL). Depending on subject's V_T , the bag containing the imaging gas (^3He) was diluted with N_2 to produce the total gas mixture required ($7 \text{ breaths} \times 0.79 \times V_T$). Subjects inhaled seven times from FRC to $\text{FRC} + V_T$. The flow curves of each pathway (helium+nitrogen and oxygen) were used to measure the delivered tidal volume (V_T) and FiO_2 for each breath, and these values were incorporated in the model fit.

^3He MRI

Each subject practiced the breathing sequence with room air until he/she could perform the multi-breath protocol illustrated in Figure 1 in the supine position while conventional chest ^1H imaging was performed. After sufficient training, seven sets of back-to-back multi-slice end-inspiratory breath-hold images were acquired. Subjects were instructed to breathe at a uniform rate to complete the seven time-points of wash-in and breath-hold; then, while breathing from room air (wash-out), another series of images was acquired. The subject exhaled into a large bag, and at the end the mixed-expired gas was collected for gas analysis (to measure the mixed-expired O_2 and CO_2 and estimate global P_{AO_2}). MRI was performed in a 1.5-T Sonata scanner (Siemens Healthcare) using an 8-channel chest coil (Stark Contrast, Erlangen, Germany).

MRI Protocol

End-inspiratory slice-selective gradient-echo images were acquired for six coronal slices (thickness of 20–25 mm) spanning the entire lung with planar resolution of $6.25 \times 6.25 \text{ mm}^2$ ($\text{TR}/\text{TE} = 6.7/3.2 \text{ ms}$, $\text{FOV} = 30 \times 40 \text{ cm}^2$, flip-angle = 6° , Slice Gap = 20%) in a $\sim 1 \text{ s}$ breath-hold. Accelerated imaging was performed using the well-established GRAPPA method (25) with an undersampling factor of 4 and 16 auto-correlating reference. This scheme was repeated six times to yield the specific ventilation distribution resulting from the regional signal buildup as is illustrated in Figure 1.

Prior to the seventh breath, the subject was informed to hold his or her breath for an extended 12-sec breath-hold, during which the simultaneous P_{AO_2} -ADC imaging occurred. Because ventilation and P_{AO_2} measurements require the flip-angle maps in order to decouple the contribution of the radio-frequency pulses in depolarization, two sets of low-resolution ($25 \times 25 \text{ mm}^2$, same parameters as above with no acceleration) consecutive images were acquired for each slice in the first second of the 12-s breath-hold in order to estimate a smoothed flip-angle map (refer to Figure 1). Another slice-selective slow GRE ($\text{TR}/\text{TE} = 18.2/5.8 \text{ ms}$, same parameters as SV with no acceleration) was acquired for each slice as the

first time-point of P_{AO_2} scheme. The second P_{AO_2} time-point comes from the ADC-sequence with $b=0 \text{ cm}^2/\text{s}$ after a $\sim 5\text{-s}$ waiting time. The ADC-sequence ($TR/TE = 9.8/5.8\text{ms}$, same parameters as SV with no acceleration) was acquired for two diffusion b-values = $[0 \text{ } 1.6] \text{ cm}^2/\text{s}$ at the end of the breath-hold. The standard diffusion pulse timing parameters were $\delta=0.9\text{ms}$, $\beta = 0.2\text{ms}$, $\tau = 1.1\text{ms}$. After the last 12-second breath-hold, the subject was instructed to inhale room air and imaging was repeated (similar to the first six time-points) at end-inspiration for a minimum of five more times or until no signal could be detected.

Gas Dynamic Models

To compute specific ventilation, signal buildup in N back-to-back identical wash-in HP images (here $N = 6$, images 1–6 in Figure 1) was acquired in a voxel-wise manner. Available magnetization after each inhalation, $M_A(j)$, is a combination of magnetization in the fresh HP gas reaching the lung (with source magnetization M_S) and magnetization left from the last breath (10). This can be written as:

$$M_A(j) = FV \cdot M_S + (1 - FV) \cdot M_A(j-1) \cdot \exp(D_A), \quad M_A(0) = 0 \quad (1)$$

where FV represents fractional ventilation (26) and is related to specific ventilation as $SV = FV/(1-FV)$, and D_A accounts for all localized relaxation mechanisms, including oxygen-induced relaxation, radiofrequency (RF) depolarization, and less significant factors such as magnetization decay due to collisions with alveolar surfaces (9). *Ex vivo* relaxation in the ^3He reservoir is negligible due to the large factor by which the reservoir relaxation time exceeds the scan time. The above equation can be rewritten in a closed form as:

$$M_A(n) = M'_S \left(1 - \left(\frac{1}{1+SV} \right)^n \times \exp^n(D_A) \right), \quad M'_S = \frac{SV}{1+SV - \exp(D_A)} \cdot M_S \quad (2)$$

Right after the seventh time-point of the multi-breath maneuver, when ^3He signal is at its peak, a longer end-inspiratory MR image (breath-hold ~ 12 seconds) is acquired to obtain the voxel-by-voxel signal drop of individual images (images 7–11 in Figure 1). While the analysis is performed using a simultaneous fit of all signal intensities from each voxel, imaging conditions were chosen to best separate the effects of RF depolarization (images 7–8), P_{AO_2} (images 9–10), and ADC (images 10–11). Regional SV, ADC and P_{AO_2} were then derived by fitting each voxel's time-series to the coupled equations describing magnetization (M_A) and alveolar oxygen (P_{AO_2}) evolution as:

$$M_A(t_i) = \left[\frac{1}{1+SV} \times M_A(t_{i-1}) \times \cos(\alpha)^{n_{PE}} + \frac{SV}{1+SV} \times M_S \right] \times \exp \left[-\frac{\overline{P_{AO_2}}(t_{i-1}, t_i) \times (t_i - t_{i-1})}{\xi} \right], \quad (3)$$

$$P_A O_2(t_i) = \frac{1}{1+SV} P_A O_2(t_{i-1}) + \frac{SV}{1+SV} \times F_I O_2 - R \times (t_i - t_{i-1}), \quad (4)$$

$$ADC = \frac{1}{b_0} \times \log \frac{S_0}{S_1}, \quad (5)$$

where SV, initial $P_A O_2$, flip angle α , HP gas magnetization M_S and R are allowed to vary in the fit (10). The O_2 -relaxivity was $\xi = 1.95 \times 10^3$ Torr.s (27) and the number of phase-encodes was $nPE = 48$. S_0 and S_1 are the signals in the back-to-back diffusion-sensitizing interleaved images.

The $\overline{P_A O_2}$ value used in the exponent of Equation 3 refers to the $P_A O_2$ mid-way through acquisition of oxygen-encoding images during the 12s breath-hold (between t_{i-1} and t_i), as described previously (10, 28). The SV in Equation 3, and the R and $P_A O_2(t_i)$ in equation 4 are updated iteratively until the change in the average regional values ($P_A O_2$, SV and R) in consecutive iterations is less than 0.1%.

The unavoidable dead space in the gas delivery device and the upper airways makes the regional SV calculations more complicated (10). The dead space was modeled before (26) using two components: *dynamic volume* (V_D , upper airways and the portion of the gas delivery system after the respirator valve) and *static volume* (V_S , the portion of the device that carries the source gas to the respirator valve). Some of the gas from the previous breath remains in the dynamic volume and is re-inhaled with each new inspiration. This effect known as *rebreathing* (26) was accounted for by replacing M_S with the combination of the HP ^3He arriving from the transmission line and the residual exhaled gas from the previous

breath. Defining $r_s = V_T / V_S$, where V_T is the tidal volume and V_S is the static volume, the *apparent specific ventilation*, SV_a , can be defined as:

$$M_A(j) = \frac{SV_a}{1+SV_a} \times M_T(j-1) + \frac{M_A(j-1) \times \exp(D)}{1+SV_a}, \quad M_T(0) = (1-r_s^{-1}) \times M_S \quad \& \quad M_T(j) = M_S \quad (6)$$

As a first step, the global fit to SV was performed for the sum of signals in the whole-lung as was explained before (10):

$$M_A(n) = M_S \times \frac{SV}{1+SV} \times \left[\frac{1 - \left(\frac{1}{1+SV}\right)^n \times e^{-n \cdot \Delta t / T_1}}{1 - \left(\frac{1}{1+SV}\right) \times e^{-\Delta t / T_1}} - \frac{V_{\text{Device}}}{V_T} \cdot \left(\frac{1}{1+SV}\right)^{n-1} \right] \quad (7)$$

where V_{Device} is the gas delivery dead space, and $t = t_j - t_{j-1}$, and T_1 is the total oxygen relaxation and RF depolarization rate. The voxel-by-voxel apparent specific ventilation was then computed from Equation 6 using the offset concept introduced in the dead space model, such that the overall mean of all the voxel SV_a agrees with the global whole-lung value from Equation 7.

It is important to note that apparent specific ventilation was assumed to be zero for non-ventilated voxels; i.e., the voxels not exceeding the ^3He signal-to-noise during the entire imaging session:

$$SV_a = 0, \quad \text{for ventilation defects} \quad (8)$$

Image Analysis

Image analysis was performed using custom software developed in the MATLAB environment (MathWorks, Inc., Natick, MA). The signal in the acquired images were bias-corrected for the background noise according to $\hat{S} = \sqrt{S^2 - \sigma^2}$, where $\sigma = \bar{B} \sqrt{2/\pi}$ and $\bar{B}$ was the average background noise of a 10×10 -pixel region far away from the lung in the acquired image (29, 30). Automatic contrast-limited adaptive histogram equalization (CLAHE (31)) with a gray-scale threshold was then applied to mask the background noise and segment the lung (10). For each voxel's signal intensity build-up in six consecutive images, a recursive model was fit to compute M_S and global SV and the initial SV_a (10). Each voxel's signal intensity drop for the last breath-hold was fit to a $P_A\text{O}_2$ model as described in (10) to calculate M_0 (initial magnetization), α , and $\overline{P_A\text{O}_2}$. An iterative fit to both Equations 3 and 4 at the same time was performed to compute updated SV_a , $P_A\text{O}_2$, and R while accounting for all the relaxation mechanisms.

While subject is not moving during the complete sequence and the images are acquired at the same exact inflation volume starting from FRC (precisely controlled by gas delivery device), still some differences in the lung position may affect the results. To account for these minor position changes during the sequence, a non-rigid affine-based co-registration was performed on spin density maps from all seven time points before the fitting process (32). Translation, rotation, and scaling were used for the 2D maps of each slice; shearing was set to zero. To account for the ventilation defects, the SV_a was assumed to be zero for non-ventilated voxels. The abovementioned segmentation technique (CLAHE) was used for both ^1H and ^3He images, followed by a morphology-based co-registration (33) between the ^1H and ^3He in the manner described by Kirby et al (34) to compute the ventilation defect percentages (VDP).

For B1 map corrections, two back-to-back low-resolution images were acquired (images 7–8 in Figure 1). The B1 maps computed from the pixel-by-pixel ratio of the two images were further smoothed based on *a priori* knowledge of the spatial smoothness of the flip angle distribution by analyzing the corresponding image pairs separately, fitting the map to a low-order polynomial, and removing it as an independent fit parameter as was described before (9).

Global Calculations

Global ADC, $P_{A}O_2$ and SV values are calculated by fitting Equation 3–5 and 7 to the signal summed over the subject's whole lung at each time point. This reduces the limitations due to co-registration error or diffusion / slow filling [8] among the individual voxels and increases the SNR.

Global values for SV and $P_{A}O_2$ can be estimated from other alternative methods as a means of confirming the hyperpolarized gas metrics. The administered V_T (average gas delivery volume in seven breaths) and the total end-inspiratory volume (EIV, measured from the volume of the last time-point of ventilation maps) can be used to globally estimate specific ventilation and analysis of collected mixed-expired gas of O_2 and CO_2 can be used to globally estimate $P_{A}O_2$ (28).

Error Analysis

A detailed optimization and error analysis of the presented scheme is presented as a supplementary appendix (Figures S1–S7).

Statistical Analysis

All statistical analyses were performed using the R software; an open-source project that is distributed under the GNU General Public License (Copyright 2007 Free Software Foundation, Inc). All the validation/confirmation tests were performed in the global level (whole-lung sum of signal), while all the other statistical comparisons were performed at the voxel, slice or ROI (region of interest) level to maintain the regionality of the data. ANOVA tests were performed to assess the differences between the three cohorts. Data is presented in the form of 'mean $\pm$ standard deviation' throughout the text. An experiment-wide Type I error level of 0.05 was used.

RESULTS

Subject demographics and clinical tests

The study included 12 subjects: four healthy nonsmokers (HN: 2F, 2M, 53 $\pm$ 10 years old), four asymptomatic smokers (AS: 1F, 3M, 51 $\pm$ 7 years old, 25 $\pm$ 9 pack-years), and four COPD subjects (COPD: 2F, 2M, 57 $\pm$ 10 years old, 37 $\pm$ 12 pack-years, all GOLD stage II). Table 1 displays subject demographics, St. George Respiratory Questionnaire (SGRQ) results, and a subset of Pulmonary Function Test (PFT) results.

Gas Delivery Results

Figure 2 summarizes the breathing volumes, inspired fraction of oxygen (FiO_2), and respiration time for all seven time points of the imaging protocol (refer to Figure 1) for each subject in a boxplot format. The top part of Figure 2 shows the breathing curves for a representative case obtained from the gas delivery device for the $^3He-N_2$ and O_2 pathways. The overall deviation of tidal volume (V_T) from the set point was 27 $\pm$ 32mL in all subjects, and overall deviation from the normoxic FiO_2 was 1.29 $\pm$ 0.90%. The overall variability of V_T (standard deviation) in one experiment between the breaths for all subjects was 31 $\pm$ 21mL and the variability was 0.63 $\pm$ 0.27% for FiO_2 .

Global SV, P_{AO_2} and R

Global ADC, SV and P_{AO_2} values are listed in Table 2. The global ADC, SV and P_{AO_2} distributions across all subjects were $0.213 \pm 0.043 \text{ cm}^2/\text{s}$, 0.315 ± 0.088 and 111.9 ± 5.0 Torr, respectively. The administered tidal volume (V_T) and the total end-inspiratory volume (EIV) as well as mixed-expired gas measurements are also listed in Table 2. The ratio of V_T to EIV was compared to the whole lung SV in Figure 3A, and shows the precision of the globally-imaged fractional ventilation (a slope of 0.81 with negligible bias) despite the attempt to standardize SV to subjects' lung volumes. Moreover, the two methods have an excellent correlation ($R^2 = 0.96$). Figure 3B shows the association between the estimated global P_{AO_2} from collected mixed-expired gases and imaged global oxygen tension (whole-lung P_{AO_2}) for all of the subjects. The average oxygen tension estimated from all voxels for each subject is significantly correlated to the amount of collected exhaled oxygen exhaled back into the bag after the 12-second breath-hold. The oxygen uptake for the whole-lung was estimated from Equation 4 and is listed in Table 2. The distribution across all subjects was $1.179 \pm 0.394 \text{ Torr/s}$.

Slice Comparisons and Anatomical Distribution

Figure 4 shows the ADC, SV, and P_{AO_2} maps in a representative subjects from each cohort. Figure 5 compares the ADC, SV, R and P_{AO_2} slice mean and SD (heterogeneity) values between the cohorts, and Table 3 shows the results of the statistical tests to assess whether the markers are significantly different among groups. A more detailed comparison between the cohorts is presented in Table S1 as an online supporting document. Figure 6 displays the slice SV and R in all subjects in the anterior to posterior (A–P) direction. The vertical slopes of slice SV from A–P were 0.058, 0.016 and 0.009 in healthy, smoker and COPD subjects, respectively. The vertical slopes of slice R from A–P were 0.327, 0.127 and 0.067 in healthy, smoker and COPD subjects, respectively. It can be seen that the healthy subjects have a greater increase in ventilation and oxygen uptake in their dependent regions compared to the other cohorts.

Correlations between MRI and non-imaging metrics

The global oxygen uptake (R) correlated with DL_{CO}/VA ($r_p = 0.76$), and both SV and R heterogeneity associated well with %FEV₁ lung obstruction ($r_p = 0.56$ and $r_p = 0.45$) and SGRQ overall score ($r_p = -0.63$ and $r_p = 0.45$).

DISCUSSION

The multi-breath hybrid scheme presented in this study has clear technical, cost, and subject compliance advantages over the previously published methods. In part, these advantages stem from the use of a series of breaths to better approximate gas exchange during normal tidal breathing. The technique allows us to generate essentially all of the regional measurements of lung structure and function (ADC, P_{AO_2} , SV and R) made possible by HP gas imaging technology whilst using a maximum of 1L of HP gas. Because the entire imaging sequence is less than 2 minutes long, there is limited or no patient movement, allowing direct comparisons of interconnected parameters regionally without the need for advanced post-processing co-registration techniques between the acquired images.

To the extent possible, we attempted to simulate real respiratory physiology by using tidal breathing and very short breath-holds (~1 sec) to obtain more physiologically relevant values. By necessity, the available HP gas was diluted and divided between imaging breaths. The scheme represents a balance between the need to use less HP gas and the need to accurately measure regionally variable physiological values both simultaneously and in the same small spatial region. The latter consideration is important for a full characterization of the diseased lung; it is also critical if an *accurate* map of even a single parameter is sought. Although the acquisition timing and type have been previously optimized for maximum sensitivity to a particular aspect of lung function (e.g., the serial imaging for ventilation (10) or the time-separated images for P_{AO_2} (9)), a complete separation between parametric maps has proved impossible. In translating the multi-parametric imaging techniques from small animals (26, 35) to the slower breathing rate of humans, coupling between extracted parameters becomes more significant primarily due to the increased effect of oxygen-induced relaxation during tidal breathing. The presented scheme addresses this problem by using each map to iteratively correct the others, leading to the most accurate values possible. In acquiring a near-simultaneous measurement of both ventilation (SV) and oxygen tension (P_{AO_2}), the analysis also provides a high-resolution estimate of oxygen uptake (R). This value has not been accurately derived in humans using hyperpolarized gas previously, and as shown here, is related to the clinical measure of trans-membrane gas exchange, the Diffusing Capacity for Carbon Monoxide (DL_{CO}).

In a comparison of single- versus multi-breath P_{AO_2} imaging (36), it was previously shown that the series of wash-in ^3He breaths achieves a more homogeneous signal throughout the lung than is seen after even a large single breath. As published elsewhere (10, 36–38), it is common to observe—especially in the symptomatic subjects—apparently non-ventilated regions of parenchyma in the first breath or two (or in the beginning of the breath-hold) that are gradually filled by the imaging gas through collateral pathways or other mechanisms (9).

This has three somewhat related effects in our measurement. First, lung regions with poor or collateral ventilation will show some signal after the series, allowing quantitative distinction between abnormally low ventilation and that which is entirely absent. Second, signal-to-noise buildup is complete at the end of the series, allowing the best estimate of the (SNR-sensitive) regional P_{AO_2} . This estimate is possible even in regions that, after a single breath, would be impossible to characterize due to lack of signal. Third, the signal uniformity achieved after the ventilation series minimizes the chance that gas flow or diffusion between regions with differing HP gas concentration may mimic the effect of abnormal oxygen concentration, thereby causing error in the P_{AO_2} measurement. This bias has been discussed before (9, 15, 36, 39), and is most noticeable in diseased regions. In the most extreme case, HP gas arrives at a voxel after the first set of images due to slow filling or an extremely long ventilation time constant. This leads to very low or even negative apparent P_{AO_2} values; because flow is not explicitly included in the modeled signal dynamics, increasing signal is interpreted as the ‘repolarization’ arising from a negative oxygen tension. While multi-breath imaging cannot address this shortcoming completely, we have shown that it mitigates the problem to a large extent by homogenization of the gas signal in the diseased lung before P_{AO_2} MR imaging (36).

The relatively homogeneous gas distribution is achieved after six breaths of approximately 8 seconds each (3s inhalation, 4s exhalation, 1s scan time). As noted above, this extended period of signal buildup allows the imaging agent to permeate all but the most isolated regions of the lung, but requires careful accounting for oxygen effects during the ventilation sequence. We made these adjustments using a high-resolution T_1 map, which accounts for the heterogeneous oxygen tension in diseased subjects. To further correct for the error caused by oxygen-induced T_1 relaxation, we sought to ensure that the P_{AO_2} values factored into calculation of SV were reflective of the P_{AO_2} during the times at which ventilation images were actually acquired. Assuming the well-established approximation of linear oxygen uptake (8, 16, 17, 20), our first-order P_{AO_2} estimate reflects oxygen tension midway through imaging of each slice (approximately six seconds into the breath-hold) (28, 40, 41). Applying this P_{AO_2} value for correction of the T_1 relaxation that occurs during the 1-second breath-hold in which ventilation images were acquired would induce a bias. The rate of oxygen uptake (R , in Equation 4) is incorporated to extrapolate P_{AO_2} to each point during the breathing cycle and during the 12-second breath-hold. The local mass balance requirement (that the difference between inhaled and exhaled oxygen tension be accounted for by uptake) constrains the iterative correction such that convergence on all parameters is achieved in nearly all circumstances.

Although oxygen uptake was originally incorporated into the model in order to make the values of the coupled parameters P_{AO_2} and SV more accurate, it is itself of physiological and potentially diagnostic interest. R was significantly different between the nonsmokers and both smokers and COPD subjects. Whole-lung R significantly correlated with the alveolar volume corrected DL_{CO} (DL/VA). Because both tests are expected to highlight decreased gas transfer between the inhaled air and pulmonary capillaries, the significant positive correlation suggests that HP-derived oxygen uptake carries the physiological interpretation suggested in its derivation.

Global estimates for the whole-lung

Specific ventilation (SV) and alveolar oxygen tension (P_{AO_2}) were also partially confirmed by comparisons between experimental groups and by alternative measurements provided by the gas delivery device (T_V/EIV (9) and mixed-expired gas analysis (24)). Whole-lung global means and ROI standard deviations (heterogeneity) of SV, P_{AO_2} , and R were significantly different between cohorts with the exception of heterogeneity of R and mean P_{AO_2} . The failure of the latter parameter to distinguish among cohorts suggests that changes to functional regions of the smoking or diseased lung are largely balanced between regions of higher and lower oxygen tensions and ventilation.

Gravitational gradients and lung physiology

Healthy subjects typically show a vertical gradient of ventilation caused by higher pleural pressure in dependent lung (42). This has usually been explained by the nondependent lung being already stretched such that the change in volume with inspiration, and thus specific ventilation, is not as great as in the relatively compressed dependent lung (the “slinky” effect (43)). The observed gradient in SV values shown in Figure 6 is consistent with this effect

and is seen in all subjects. The observed ADC gradient for all subjects may also be attributable to this effect.

Perfusion is also relatively low in the nondependent lung due to hydrostatic effects as described in the zone model by West (44). As a result, under normal circumstances, the nondependent lung is poorly ventilated and even more poorly perfused. The net effect of the decreased perfusion is greater than that of ventilation, leading to elevated P_{AO_2} in the nondependent lung (45). This can be observed in all of the healthy subjects imaged in this study. However, the ventilation and oxygen tension gravity gradients of COPD subjects were markedly reduced from those of normal subjects. As shown in Figure 6, this reduction is notable, and of such an extent that one COPD subject actually displayed a reverse gradient. As we have posited with respect to the loss of imaged oxygen tension, gravity gradients in asymptomatic smokers (28) and COPD subjects (41), we hypothesize here that the loss of SV vertical gradients in the COPD patients is linked to the associated increase in ventilation heterogeneity. This notion is supported by the fact that the asymptomatic smokers who displayed lowered gradients also had significantly more ventilation heterogeneity than normal subjects, while the smoker who had a normal gradient was more homogeneous. In COPD subjects, we speculate that the observation of lower P_{AO_2} and SV in the nondependent lung may be associated with generalized loss of elastic recoil and that the relatively larger effect observed in nondependent regions may be due to the greater importance of tissue recoil in determining ventilation of the gravitationally-stretched tissue. However, it is also possible that systematic errors arising from flow and diffusion within the lung that are not explicitly modeled may partly or wholly contribute to the observed reduction in gravitational gradients in the symptomatic subjects.

Air trapping and qualitative interpretation of signal dynamics

Comparison of the raw signal dynamics of the six time-points of the ^3He wash-in build-up signal and the ^3He wash-out signal decay showed obvious visual differences among the cohorts. Higher variability between subjects in the COPD cohort and higher intra-organ variability in the symptomatic subjects' ROIs was observed, which resulted in more heterogeneity in the diseased lungs.

The wash-out images were used to qualitatively study the existence of abnormal air trapping in COPD subjects. A quantitative wash-out technique was described previously by Horn et al. (46) to estimate fractional ventilation. In another preliminary study (47) the two techniques were compared (wash-in and wash-out), but quantification of SV using the wash-out images is beyond the scope of this study, as their SNR is not sufficiently high for this purpose (mainly because of the 12 second breath hold and the RF depolarization during the P_{AO_2} -ADC imaging). On the other hand, adding wash-out imaging to the multibreath technique proved to be very successful in identifying air trapping in severely diseased lungs by highlighting regions in which the signal can be detected even in the last wash-out breath. Although most subjects in this study displayed very little signal after the first washout image set, some of the COPD subjects had detectable signal even after five wash-out breaths; this highlights the presence and extent of regional trapped air with low alveolar oxygen tension (refer to the representative example of a COPD subject in Figure 1).

Gas delivery device

An important breakthrough that made this multi-breath wash-in wash-out imaging scheme possible is the design of a precise passive-driven gas delivery device which delivers a constant volume of a normoxic gas mixture. However, because the device is entirely under subject control, we still saw a small bias and variability in the inhaled volume (31 ± 21 mL) despite the training that subjects underwent to assure breath-to-breath reproducibility. Subjects inevitably inhaled the gas at varying speeds and quantities, and their breathing patterns were not absolutely consistent. As it can be seen in Figure 2, accuracy was related to the inhalation time; subjects who inhaled more variably (in time), had less reproducible desired V_T and FiO_2 . Nevertheless, the real volumes and durations of individual subject breaths were measured, as were the separate volumes inhaled from each bag. Each breath's length, V_T and FiO_2 were therefore incorporated into the fitting model (Equations 3–5 and 7) to correct for variability to the extent possible. The first breath of the imaging scheme—when the subject initiated the protocol—showed a particularly high level of variability. One way to address this issue would be to allow the subject to first inhale two or three breaths of room air before switching to the imaging gas. There may be cases in which variability is larger than observed here, particularly in diseased subjects for whom breathing control is difficult, but the gas delivery device measurements and the collected exhaled gas can be used to confirm the experimental precision or indicate the need for a repeat measurement if the error is unacceptably large.

While we showed the validity of our measurement in a global level, it should be noted that since the polarizer produces 1 liter of imaging gas, which is the minimum requirement for hybrid imaging, we were not able to perform a systematic comparison of the multi-breath washing technique with the conventional single-breath technique in the same manner that was performed for alveolar oxygen tension (36). A further work is required to show the regional reproducibility of the single- and multi-breath scheme in measuring the other parameters.

Conclusion

In this paper, we have presented a method for near-simultaneous and nearly co-registered acquisition of alveolar oxygen tension, specific ventilation, and apparent diffusion coefficient of hyperpolarized gas in the human lung. Further, mass-balance considerations allow reinterpretation of the P_{AO_2} and SV maps as a map of oxygen uptake. The latter parameter is directly related to both fundamental aspects of lung function and the DL_{CO} test of alveolar-capillary membrane permeability. Inclusion in the model also allows for an iterative refinement of the other lung function parameters such that an accurate imaging analog of the common pulmonary function tests can be achieved.

Although alternative methods to map both ventilation and oxygen tension exist (22, 48–56), as well as the aforementioned DL_{CO} as an analog of oxygen uptake, direct comparisons are difficult because the methods are either qualitative (“weighting”) techniques, are quantitative but sensitive to slightly different aspects of the lung, or are susceptible to known but different sources of error than these HP methods. Notably, all methods for measuring ventilation regionally suffer from a definitional ambiguity with respect to the source of the

gas arriving at the region after inhalation. In the case of HP measurements, magnetized gas originating from other areas of the lung or dead space is indistinguishable from that originating from outside the trachea. Registration-based CT methods, for example, can therefore be expected to yield differing results, especially in disease.

For this reason, we have taken the first steps toward measurement validation through comparison to global lung function measurements, physiologically expected gradients, and mixed exhaled gas analysis. Additional comparisons are used to justify the functional map resolution by showing that negligible bias is introduced with respect to the same analysis performed on the whole-lung sum of signals. Evidence for each measurement's utility comes from its ability to distinguish among experimental groups, including the "asymptomatic" smokers. We conclude that ventilation-based maps (SV and R) are the most sensitive markers of disease, and ADC-based metrics are clearly but less well correlated to diseased state; while P_{AO_2} heterogeneity was significantly increased with disease severity, mean P_{AO_2} across the lung does not appear to be a useful parameter for studying lung disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A) Multi-breath sequence designed to yield lung fractional ventilation, alveolar O₂ tension, and gas diffusion. The series begins with a repeated slow inhale/ exhale maneuver with a ~1s multi-slice image (denoted 'SV') acquired after each full inhale. Arrows on top of each breath shows the order of acquisition of each slice (3 slices is shown). After the signal buildup is complete (6 breaths), the steady-state gas distribution is used to estimate flip-angle using two rapid low-resolution images (denoted ' α ' and requiring ~650ms) followed by three images, two of which are acquired without diffusion-sensitizing gradients and a long (~6s) inter-image delay and one of which is acquired using bipolar gradients and sensitizing strength of $b = 1.6 \text{ cm}^2/\text{s}$. The latter pair is acquired with k-space-interleaved ordering to minimize any effect of RF depolarization on the reconstructed image pair. The former pair is acquired such that the corresponding k-space lines are separated by the same time delay; thus the single image ('Slow GRE') is acquired in twice the time that is necessary—needed for faithful determination of PAO₂. After the long breath-hold subject lung will be imaged again during the wash-out (3–5 breaths). B) The gas delivery device piping and instrumentation schematic diagram and prototype used in this study.

Figure 2.

(**Top**) The prescribed volumes inhaled by each subject chosen based on weight (10mL/kg) rounded to the nearest calibrated volumes of 600, to 1000mL (50 mL precision) shown in boxplot format. (**Bottom**) The measured inspired partial pressure of oxygen (FiO₂) for each subject. Each small dot shows one of the seven breaths in the multibreath protocol and the line in the middle of the boxplot shows the median in each subject.

Figure 3.

Mean fractional ventilation and $P_A O_2$ derived from imaging compared to an alternative measurement with correlation and Bland-Altman plots. **(Left)** A comparison between the whole-lung imaged fractional ventilation and the ratio of tidal volume (measured by a gas delivery system) to the end-inhale inspired volume (computed from 3He spin density maps). **(Right)** A comparison between the global $P_A O_2$ derived from imaging and the mixed-expired partial pressure of oxygen collected from the lung after the 12 second breath-hold.

Figure 4. Representative subject's ADC, SV and $P_{A}O_2$ maps from each cohort and their selected clinical test results.

Figure 5.

Cohort distribution of SV, $P_{A}O_2$ and ADC calculated for each of the six slices in all the subjects. The mean (left) and standard deviation (right, a marker of heterogeneity) are plotted in boxplot format for each cohort. Each small marker shows one of the six slices' values in each subject and the line in the middle of the boxplot shows the median in each subject. The solid circle in the middle of the box plot is the mean value in each cohort. Note that as shown in Figure 6, some of the observed spread in parameter values arises from within-subject gravitational gradients rather than variability among same-cohort subjects.

Figure 6. Summary plots of oxygen uptake and specific ventilation from anterior to posterior in all the subjects of the three cohorts from top to bottom for six slices.

Table 1

Demographics and Clinical Test Results

Subject	Sex	Age Years	Weight kg	Height cm	BMI Kg/m ²	Smoking pack-years	Cough / Phlegm*	SGRQ %	FEV ₁ /FVC %	FEV ₁ L [***]	TLC L	RV L [%]	DL _{co} ml/min/mmHg [%]	DL/VA ml/min/mmHg/L
HN1	M	47	102	189	28.1	0	0/0	0	83	5.08 [110]	8.2	2.14 [94]	40.6 [112]	4.94
HN2	M	63	80	177	25.6	0	0/0	4	77	2.50 [83]	5.9	2.34 [102]	22.1 [80]	4.44
HN3	F	58	69	171	23.2	0	0/0	0	88	3.21 [109]	5.9	2.00 [99]	27.8 [119]	4.63
HN4	F	42	49	160	19.2	0	0/0	0	84	2.80 [97]	5.1	1.57 [100]	25.2 [108]	5.34
M (SD)**	2M, 2F	53 (10)	76 (22)	175 (13)	24.1 (3.9)	0(0)	0/0	1 (2)	83 (5)	[100 (13)]	6.3 (1.4)	[99 (4)]	[1.05 (18)]	4.9 (0.4)
AS1	M	41	79	188	22.1	23	2/2	2	73	4.56 [97]	8.8	2.85 [134]	30.9 [107]	3.76
AS2	M	57	82	182	24.6	36	1/2	5	80	3.08 [79]	6.6	2.34 [98]	32.1 [117]	4.75
AS3	M	54	90	175	32.7	16	0/0	6	79	3.86 [105]	7.0	1.95 [87]	33.8 [141]	4.86
AS4	F	51	46	163	17.2	25	2/2	1	77	2.20 [96]	4.5	1.64 [100]	14.7 [77]	3.64
M (SD)	3M, 1F	51 (7)	75 (20)	177 (11)	24.2 (6.5)	25 (9)	1/2	4 (3)	78 (4)	[95 (11)]	6.8 (1.8)	[1.05 (21)]	[111 (27)]	4.3 (0.7)
COPD1	M	67	64	178	20.2	50	4/4	26	49	2.25 [67]	8.4	3.69 [144]	21.6 [101]	3.15
COPD2	M	63	91	170	31.1	22	4/4	11	49	1.58 [58]	7.4	2.84 [128]	14.2 [67]	2.59
COPD3	F	51	55	157	21.9	40	4/4	53	62	1.75 [74]	4.4	1.55 [112]	-	0
COPD4	F	46	73	165	26.6	33	1/1	2	67	2.21 [74]	5.2	1.94 [113]	20.6 [87]	4.13
M (SD)	2M, 2F	57 (10)	71 (16)	168 (39)	25.0 (4.9)	37 (12)	3/3	23 (23)	57 (10)	[69 (8)]	6.4 (1.9)	[1.25 (16)]	[85 (18)]	2.5 (1.8)

*The numbers are 0: never, 1: when have a cold or flu, 2: once a week, 3: more than a day in a week 4: everyday

**Numbers in barenthesis are the standard deviations

***Numbers in brakets are the percent predicted values

Table 2

Whole-lung Imaging Results and Gas Delivery Device Measurements

Subject	Whole-lung Global Hybrid parameters					Global parameters Measured from Gas Delivery Device and Mixed Expired Gases							
	ADC cm ² /s	SV -	P _A O ₂ Torr	R Torr/s	VDP %	VT mL	EIV L	SV _G -	ETO ₂ %	ETCO ₂ %	FIO ₂ %	Dead Space mL	Est. _i P _A O ₂ Torr
HN1	0.198	0.452	107.5	1.86	0.2	984	3.31	0.422	14.4	4.4	20.7	165	108.3
HN2	0.197	0.364	113.2	1.46	1.1	825	3.19	0.349	15.5	3.9	21.7	136	116.7
HN3	0.198	0.327	104.0	1.24	0.0	734	3.08	0.313	13.9	4.2	20.7	110	104.5
HN4	0.162	0.409	108.8	1.96	0.8	647	2.26	0.400	14.2	4.5	21.1	85	106.9
M (SD) *	0.20 (0.03)	0.39 (0.06)	113.1 (2.4)	1.55 (0.35)	0.6 (0.5)	798 (145)	2.97 (0.48)	0.38 (0.05)	15.0 (0.5)	4.3 (0.3)	21.1 (0.5)	124 (35)	112.6 (3.6)
AS1	0.205	0.281	110.1	0.83	9.0	884	4.63	0.236	14.3	4.7	18.9	142	107.9
AS2	0.206	0.380	111.4	1.16	10.1	809	3.15	0.346	14.8	4.1	20.1	142	111.4
AS3	0.164	0.345	111.2	1.09	7.5	851	3.24	0.356	15.3	4.3	23.6	144	114.7
AS4	0.223	0.317	117.7	0.79	1.4	683	2.99	0.297	16.1	3.7	20.6	83	121.8
M (SD) *	0.21 (0.03)	0.33 (0.06)	115.9 (3.7)	0.97 (0.19)	7.1 (3.9)	807 (89)	3.51 (0.77)	0.31 (0.06)	15.2 (0.8)	4.2 (0.5)	20.8 (2.0)	128 (30)	114.0 (6.0)
COPD1	0.314	0.143	111.9	0.83	24.0	834	5.45	0.181	15.2	4.6	22.4	119	114.4
COPD2	0.267	0.190	108.3	0.92	32.9	933	5.24	0.217	14.6	4.3	22.1	140	109.7
COPD3	0.230	0.312	122.1	0.90	14.5	726	3.03	0.315	15.9	3.5	23.2	99	119.7
COPD4	0.188	0.257	116.8	1.11	11.2	717	3.42	0.265	15.4	4.2	23.1	122	115.6
M (SD) *	0.25 (0.06)	0.23 (0.08)	114.8 (6.0)	0.94 (0.12)	20.7 (9.9)	803 (102)	4.29 (1.24)	0.25 (0.06)	15.3 (0.6.0)	4.2 (0.5)	22.7 (0.6)	120 (17)	114.9 (4.2)

* Numbers in parenthesis are standard deviations

Table 3

Comparison among cohorts

Imaging Parameter*	Mean**	SE of Residuals	F(2,9)	Pr(>F)	Significance
ADC	0.209	0.0249	3.40	0.080	.
ADC ^H	0.056	0.0265	0.16	0.853	
SV	0.360	0.0516	14.11	0.002	**
SV ^H	0.280	0.0809	9.00	0.007	**
P _A O ₂	110.97	12.61	0.59	0.576	
P _A O ₂ ^H	30.8	5.49	11.85	0.003	**
R	1.263	0.254	12.77	0.002	**
R ^H	1.319	0.644	3.47	0.077	.

* The superscript H stands for heterogeneity measure as the standard deviation of each ROI

** Mean values are for all the subject and all the ROIs, in this case for each Slice. They are reported for comparison with standard errors of residuals.