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Pulmonary Ventilation Imaging in Asthma and Cystic Fibrosis Using Oxygen-Enhanced 3D Radial Ultrashort Echo Time MRI

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Abstract

BACKGROUND—A previous study demonstrated the feasibility of using 3D radial ultrashort TE oxygen-enhanced MRI (UTE OE-MRI) for functional imaging of healthy human lungs. The repeatability of quantitative measures from UTE OE-MRI needs to be established prior to its application in clinical research.

PURPOSE—To evaluate repeatability of obstructive patterns in asthma and cystic fibrosis (CF) with UTE OE-MRI with isotropic spatial resolution and full chest coverage.

STUDY TYPE—Prospective.

POPULATION—Eighteen human subjects (5 asthma, 6 CF and 7 normal subjects).

FIELD STRENGTH/SEQUENCE—Respiratory-gated free-breathing 3D radial UTE (80μs) sequence at 1.5T.

ASSESSMENT—Two 3D radial UTE volumes were acquired sequentially under normoxic and hyperoxic conditions. A subset of subjects underwent repeat acquisitions on either the same day or 15 days apart. Asthma and CF subjects also underwent spirometry. A workflow including deformable registration and retrospective lung density correction was used to compute 3D isotropic percent signal enhancement (PSE) maps. Median PSE (MPSE) and ventilation defect percent (VDP) of the lung were measured from the PSE map.

STATISTICAL TESTS—The relations among MPSE, VDP and spirometric measures were assessed using Spearman correlations. The test-retest repeatability was evaluated using Bland-Altman analysis and intraclass correlation coefficients (ICC).

RESULTS—Ventilation measures in normal subjects (MPSE=8.0%, VDP=3.3%) were significantly different from those in asthma (MPSE=6.0%, $P=0.042$; VDP=21.7%, $P=0.018$) and CF group (MPSE=4.5%, $P=0.0006$; VDP=27.2%, $P=0.002$). MPSE correlated significantly with forced expiratory lung volume in 1 second % predicted ($\rho=0.72$, $P=0.017$). The ICC of the test-retest VDP and MPSE were both 0.90. In all subject groups, an anterior/posterior gradient was observed with higher MPSE and lower VDP in the posterior compared to anterior regions ($P=0.0021$ for all comparisons).

DATA CONCLUSION—3D radial UTE OE-MRI supports quantitative differentiation of diseased vs. healthy lungs using either whole lung VDP or MPSE with excellent test-retest repeatability.

Keywords

oxygen enhanced MRI; ventilation defect; asthma; cystic fibrosis; 3D radial; UTE

INTRODUCTION

Hyperpolarized (HP) noble gas MRI, using ^3He and more recently ^{129}Xe , has been validated and used in multiple clinical research studies to quantify regions of abnormal ventilation termed “ventilation defects” using the ventilation defect percent (VDP) as a measure of obstruction (1–5). However, HP gas MRI requires specialized equipment and isotopically enriched gases that add cost and limit access for multi-center clinical research studies (6). While fluorinated gases offer one alternative to hyperpolarized gases, multi-nuclear hardware and specific oxygen-fluorinated gas mixtures (6, 7) are still required adding cost and complexity compared to conventional proton MRI.

Oxygen-enhanced (OE) MRI is a potential safe and less expensive alternative, using proton MRI for ventilation imaging. OE-MRI relies on the T_1 shortening of nearby proton spins when dissolved O_2 molecules are present. Typically, two sets of T_1 -weighted proton images are acquired sequentially, one acquisition during normoxic (21% O_2) breathing and a second during hyperoxic (100% O_2) breathing. Under hyperoxia, T_1 shortening relative to normoxia is directly proportional to the local concentration of the paramagnetic O_2 delivered to the lung tissue and dissolved in blood (8, 9). OE signal enhancement images are typically obtained by subtracting normoxic from hyperoxic proton images to reveal local contrast due to the change in alveolar partial pressure of oxygen (9). The resulting difference in signal intensity is considered to be predominantly ventilation weighted, and can be visualized as contrast enhancement (8).

Recent OE-MRI efforts (8, 10–12) typically have focused on the static and dynamic characteristics of regional oxygen delivery in normal and diseased lungs in acquisitions of one or several 2D coronal slices. With the 3D radial ultrashort echo time (UTE) sequence, Kruger et al (13) demonstrated the feasibility of static ventilation OE-MRI of the lungs with 3D isotropic resolution using 3D radial UTE sequence (UTE OE-MRI) and further reported

a preliminary qualitative comparison (14) on ventilation defect and signal intensity between UTE OE- and HP-MRI. The repeatability of quantitative measures from UTE OE-MRI has not yet been established, but is necessary prior to its use for clinical imaging of lung function.

In this work, we introduce a post-processing workflow for robust ventilation quantification for UTE OE-MRI. The purposes of our study were 1) to compare OE-MRI results in 3 distinct populations: healthy normal subjects, asthma patients, and cystic fibrosis (CF) patients and 2) to evaluate the repeatability of median percent signal enhancement (MPSE) and VDP derived from 3D UTE OE-MRI using our post-processing workflow.

MATERIALS AND METHODS

Study Population

Eighteen subjects (7 healthy normal, 5 asthmatics including 2 severe and 3 mild asthma, and 6 CF) were enrolled in two different Health Insurance Portability and Accountability Act (HIPAA) compliant studies with Internal Review Board approval. Written informed consent was obtained from each subject. Prior to each MRI scan, the asthma and CF subjects underwent spirometry to establish baseline global lung function.

Asthma subjects were recruited through exploratory MRI substudies. Subjects were excluded if there was evidence of restrictive lung disease or acute illness on the scan day, dependence on supplemental oxygen, or history of cardiac disease.

The inclusion criteria for the CF MRI protocol were an existing clinical diagnosis of CF, 10 years of age or older, and ability to return for study visits. Subjects were excluded for ventilator or oxygen dependence, history of lung transplant, contraindication to MRI, treatment with intravenous antibiotics for pulmonary exacerbation within 4 weeks of study visit, or pregnancy.

Each subject underwent UTE OE-MRI including sequential UTE scans under normoxic and hyperoxic breathing. All subjects were instructed to maintain normal tidal breathing. Mean PSE values for 7 normal subjects were reported in the earlier feasibility study (13). The repeated acquisitions were performed for a subset of 3 asthma, 6 CF and 4 normal subjects. These asthma and CF subjects were each imaged on 2 separate visits 15 days apart. The four normal subjects underwent one hyperoxic scan after two normoxic acquisitions consecutively during a single visit. A total of 2 asthma, 6 CF and 2 normal subjects were acquired consistently with the same scan parameter settings and therefore included in the repeatability analysis.

MR Pulse Sequence and Imaging

Imaging was performed with a 3D radial UTE pulse sequence optimized to minimize TE and improve the SNR and image quality of lung imaging using an axial slab-selective radiofrequency excitation with limited field of view (FOV), variable density readout gradients with eddy-current corrections, and radially oversampled projections. The flip angle was optimized to achieve the maximal contrast-to-noise ratio given expected T_1 differences.

Real-time prospective respiratory gating to end-expiration was applied with an adaptive 50% acceptance window. Additional details regarding the acquisition, reconstruction and optimization of the 3D radial UTE sequence applied to OE-MRI have been previously published (13, 15).

Acquisition parameters included: field of view (FOV) = 32 cm, repetition time (TR) = 2.9–4.2 ms, TE = 0.08 ms, flip angle = 8° , readout sampling time = 1 ms, receiver bandwidth = ± 160 kHz, approximately 38000 projections, and isotropic spatial resolution varying between 1.25, 2.5 or 3.2 mm to investigate tradeoffs in anatomic resolution and SNR ratio (not systematically explored in this study). Specifically, the isotropic resolution was 2.5 mm for two normal subjects, 3.2 mm for one asthma subject and all CF subjects, and 1.25 mm for the remaining subjects. The image resolution was down-sampled in all cases to a uniform lower 1 cm^3 resolution for PSE assessment.

All imaging was performed on a 1.5T system (Signa HDx, GE Healthcare) with an eight-channel cardiac coil (HD Cardiac, GE Healthcare). All subjects were positioned supine and breathed freely via a non-rebreather facemask at a flow rate of 15 L/min throughout the scans. Two 3.5-minute UTE scans were performed successively with the subject breathing medical grade air (21% O_2 , normoxic) for the first acquisition and 100% O_2 (hyperoxic) for the second. Each 3D UTE volume was acquired after 2 minutes of breathing the gas mixture to avoid transient effects of gas wash-in.

Spirometry

Spirometry was performed in all asthma and CF subjects according to American Thoracic Society (ATS) guidelines (16). The spirometric measurements include forced expiratory lung volume in 1 second ($\text{FEV}_{1\text{s}}$), forced vital capacity (FVC). Predicted values of these measurements were calculated using the global lung function initiative (GLI) 2012 equations (17) by taking age, sex, height, and ethnicity into considerations. The spirometric measurements were missing for the last asthma subject that was enrolled two years later than the other asthma subjects.

Workflow of Computing PSE Map

Although the UTE sequence was optimized for the contrast-to-noise ratio (13), the PSE map directly calculated from high-resolution normoxic and hyperoxic volume pairs is noisy and insufficient for quantitative measurements. To improve SNR of the PSE parametric map, k-space data were low pass filtered for simultaneous low-resolution reconstruction at 1 cm isotropic resolution. The workflow (Figure 1) to generate PSE maps from the two sets (high- and low-resolution) of reconstructed normoxic (V_{21}) and hyperoxic (V_{100}) UTE volumes is summarized as follows.

1. The high-resolution normoxic and hyperoxic volume pairs (Figure 1a and 1b) were individually normalized to the range [0, 1].
2. The high-resolution normoxic volume V_{21} was then registered to the corresponding hyperoxic volume V_{100} using a two-stage multi-resolution deformable registration with the transformation denoted as T .

3. The high-resolution hyperoxic volume was segmented for a binary lung mask (Figure 1c).
4. The Jacobian determinant $\det(J_T)$ (Figure 1d) was derived from the deformation fields resulting from the registration, which equals the ratio of deformed to undeformed volumes.
5. The nonlinear transformation T from the registration in step 2 was then applied to the low-resolution normoxic volume $T(V_{2I})$.
6. The derived Jacobian determinant $\det(J_T)$ values from step 4 were applied as a voxel-wise density correction to $T(V_{2I})$, using $V_{2IC} = T(V_{2I}) \cdot \det(J_T)$.
7. PSE map (Figure 1g) was then calculated using registered and density corrected low-resolution volumes (Figure 1e and 1f) as $PSE = (V_{100} - V_{2IC}) / V_{2IC}$.

The two-stage registration in step 2 consists of a rigid transform followed by a B-spline symmetric normalization (SyN) transform (18) with a mutual information metric using Advanced Normalization Tools (<http://picsl.upenn.edu/ANTS/>). At each stage, three resolution levels were used by down sampling the undeformed and deformed volumes by factors of $4 \times 2 \times 1$ each with 200 iterations respectively. The smoothing factor was set to zero at each resolution for each stage. For the B-spline SyN stage, the B-spline knot distance was set to 80 mm such that more regularization was applied due to the small deformation nature of the problem.

Voxelwise Lung Density Correction Using the Sponge Model—The transition from normoxic to hyperoxic breathing leads to a corresponding decrease in tidal volume of respiration (19). This physiological change in lung inflation volume and consequent changes in lung tissue density are not accounted by the registration. These lung tissue density changes were adjusted using a sponge model (20), where volume correction is performed using the determinant of the Jacobian of the transformation $\det(J_T)$ as listed in step 6 assuming the mass of the lungs is preserved. Specifically, the adjustments were performed spatially using $\det(J_T)$ values, which reflect the fractional volume expansion and contraction at each voxel (21). These $\det(J_T)$ values were used to quantify the magnitude of regional volume alterations required to match the undeformed hyperoxic volume. Intuitively, on a Jacobian determinant map, $\det(J_T) < 1$ implies local contraction, $\det(J_T) = 1$ implies no volume change, and $\det(J_T) > 1$ implies local expansion.

Lung Volume Segmentation Using Deep Learning—For the quantitative analysis in the lungs, all high-resolution hyperoxic volumes were segmented for lung masks using a 3D region growing method with lungs seeds automatically detected using Euclidean distance transformation (22). To evaluate the degree of the volumetric change due to the transition from normoxic to hyperoxic breathing conditions, these 3D hyperoxic volumes with the corresponding binary lung masks were then used to train the deep learning network (23) for an objective, fully-automated segmentation of all normoxic and hyperoxic lung volumes.

Quantification in the Lungs and Oxygenated Blood—The histogram of the PSE values in the lungs generally has a nonsymmetrical distribution, particularly in the

obstructed lungs. Therefore, the median PSE (MPSE) value in the lungs was calculated and used as a global measure from UTE OE-MRI, as reported in prior OE-MRI studies (12, 24).

Moreover, Ventilation defects were quantified automatically from PSE map as VDP using adaptive *K*-means which was validated for VDP quantification in HP gas images (25). First, due to the wide range of PSE values, the PSE histogram of the lungs was scaled to range of $[-1\%, 15\%]$ while maintaining the whole lung MPSE unchanged. Second, the PSE maps of the first visit from 6 subjects with different levels of obstruction determined by visual inspection were used as the training set to derive the cutoff values of the percent low-intensity signal P_L in the lungs. Three options for defining the defect cluster are $P_L < 10\%$ for non-diseased, $10\% \leq P_L < 20\%$ for mild, and for $P_L \geq 20\%$ severe-diseased lungs. Third, two runs of *K*-means clustering was performed with ventilation defect cluster determined based on the P_L value. Morphometric corrections were used to account for partial volume effect to obtain the final defect mask. Additional details regarding adaptive *K*-means are presented in (25).

In addition, MPSE was measured in the left ventricular (LV) blood pool and arterial blood of the aorta. The ventricular and arterial blood pools were segmented on the high-resolution 3D radial UTE images under hyperoxic breathing by an imaging scientist (WZ) with 10-years of experience in cardiothoracic MRI. To avoid partial volume effect, regions of interest (ROIs) were placed inside the LV blood pool in consecutive slices on the axial, four-chamber views of the heart. Similarly, in consecutive sagittal slices of the aorta, ROIs were generated by manual segmentation of arterial blood. The MPSE was then measured from these ROIs on the corresponding PSE maps.

For repeatability assessment subjects were scanned on separate visits 15 days apart. The 3D rigid registration was used to register lung volumes across visits. In these studies the high-resolution hyperoxic volume at the first visit was transformed to the physical space of the hyperoxic volume from the second visit. The same transformation was applied to the PSE map in order to evaluate spatial overlap of segmented defects using the Dice coefficient.

Statistical Analysis

One-way analysis of variance (ANOVA) was used to compare the two diseased groups vs. normal for global measurements including age, MPSE and whole lung VDP. Homogeneity of variance was tested using Levene's test. Model normality assumption was checked and Welch's test was used to assess global effect if it was violated. After the global effect was confirmed to be significantly different among three subject groups, the multiple comparison test was performed using the Duennett procedure for the comparisons in the diseased groups vs. the normal group as a control to avoid type I error rate inflation. For subjects with multiple scans or visits, the repeated measurements were averaged to calculate the subject group statistics. The relationships among MPSE and spirometric measures, among VDP and spirometric measures, and between MPSE and VDP were assessed using Spearman rank correlation with 95% confidence interval (CI).

To assess the anterior/posterior (A/P) dependence, we divided the 3D lung volumes into two equal coronal volumes (anterior and posterior) along the A/P direction. We compared the

anterior vs. posterior measurements of MPSE and VDP individually using Wilcoxon signed-rank test.

In the test-retest analysis of repeatability, we used Bland-Altman plots with 95% limits of agreement (LOA) and intraclass correlation coefficient (ICC) to evaluate the agreement of repeated global measures. We used the Dice coefficient to assess the spatial overlap of the segmented ventilation defects of the same subject across scans and visits. A $P < 0.05$ was considered significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., NC, USA).

RESULTS

Effect of Normoxic and Hyperoxic Breathing

In 28 pairs of acquired normoxic and hyperoxic lung volumes, a small but significant volume decrease of up to 6.3% (mean $\pm$ standard deviation: $1.0\% \pm 2.4\%$, paired, two-sided Wilcoxon signed-rank test $P = 0.025$) was observed in hyperoxic vs. normoxic lung volumes of the same subject underscoring the need for density correction in response to the fraction of inspired oxygen (26, 27). Among these volume pairs, 19 out of 28 normoxic lung volumes were larger than the corresponding hyperoxic volumes.

Percent Signal Enhancement Map

Figure 2 shows an example of the PSE maps for a normal subject. Note that the PSE map before registration (Figure 2a) has peripheral false enhancement (white arrows) due to the different chest wall position during hyperoxic breathing. The false enhancement is removed by registration and density correction (Figure 2b). The corresponding Jacobian determinant map (Figure 2c) computed from the 3D deformation field implies that slight compression occurs in some regions of the lungs between normoxic (deformed) to hyperoxic (undeformed) volumes, which is consistent with the fact that the normoxic lung volume was measured 1.0% lower relative to the corresponding hyperoxic lung volume. The image histogram of the PSE values in the lungs (Figure 2d) bears out improved conformance to a Gaussian distribution after registration (cyan dashed line, mean = 8.1 and median = 8.2) and density correction (bars in blue, mean = 6.1, median = 6.3) relative to the unregistered PSE values (red dashed line, mean = 9.5 and median = 8.8). Overall, PSE values were shifted downward relative to the unregistered PSE (red dashed line), reflecting the effect of correcting the false enhancement near the lung periphery. After subsequent density correction the PSE histogram was shifted slightly upward compared to the registered PSE histogram to compensate for the lower registered lung density (mean $\det(J_T)$ values marginally less than 1).

Figure 3 shows a somewhat different example for a mild-to-moderate asthmatic subject. Lung volumes differ more markedly between normoxic and hyperoxic conditions for this case, where the normoxic lung volume was measured 2.4% *larger* than the hyperoxic volume. Consequently, there is a more pronounced peripheral false enhancement (white arrows) and correction in the PSE map after registration and density correction (Figure 3b) vs. the unregistered PSE (Figure 3a). The Jacobian determinant map (Figure 3c) suggested

an overall expansion and corresponding adjustment of PSE values downward to compensate for the higher registered lung density.

Global Measurements

Demographic information and global measurements from UTE OE-MRI are summarized in Table 1. The arterial MPSE was significantly lower in asthma and CF subjects relative to the normal subjects. Differences in the MPSE in LV blood pool were nonsignificant between groups. Compared to the normal group, the asthmatic subjects had on average lower MPSE in the lungs ($P = 0.042$) with higher VDP ($P = 0.018$); CF subjects showed an even lower MPSE ($P = 0.0006$) and higher VDP ($P = 0.0020$). Boxplots of MPSE and VDP further demonstrate group-wise differences, reflecting the lower MPSE and greater variability in both asthma and CF (Figure 4a). Consistent with the strong, inverse correlation ($\rho = -0.91$ with $P < 0.0001$, 95% CI = $[-0.96, -0.76]$) between MPSE and VDP, the group-wise differences in VDP (Figure 4b) shows the opposite trends to MPSE with increasing VDP in both asthma and CF (Table 1).

Relating to the spirometric measurements from 4 asthma and 6 CF subjects, MPSE in the lungs correlated significantly with FEV₁ % predicted ($\rho = 0.72$ with $P = 0.017$, 95% CI = $[0.16, 0.93]$), FVC % predicted ($\rho = 0.75$ with $P = 0.011$, 95% CI = $[0.22, 0.94]$). VDP correlated significantly with FVC % predicted ($\rho = -0.67$ with $P = 0.039$, 95% CI = $[-0.91, -0.075]$), but not with FEV₁ % predicted ($\rho = -0.58$ with $P = 0.083$, 95% CI = $[-0.88, 0.085]$).

Anterior/Posterior Gradient

The posterior MPSE was 0.7% higher on average than the anterior MPSE with $P = 0.02$. Similarly, the VDP was decreased in the posterior region by 2.9% compared to the anterior VDP with $P = 0.002$. This A/P gravity dependence was observed in both MPSE (Figure 5a) and VDP (Figure 5b) for most subjects.

Intra-subject Test-retest Repeatability

The Bland-Altman plot analysis of the repeated measurements of MPSE and VDP (Table 2, Supplementary Figure 1) suggest high repeatability with substantial improvement after registration and density correction. The 95% LOA for the two repeated MPSE measurements was $[-1.7\%, 1.3\%]$ and for the VDP measurements was $[-7.9\%, 5.4\%]$. After registration and density correction, the ICC of MPSE and VDP were 0.90 and 0.98 respectively, suggesting excellent test-retest reliability.

Qualitatively, the test-retest PSE maps for the normal subject (Figure 6) showed similar enhancement variation patterns between repeated scans with few peripheral defects. The repeated PSE maps showed that the relative volume of defect regions was noticeably greater for an asthmatic subject (Figure 7) vs normal. The segmented defects were larger in size and more numerous. The spatial agreement of these defects at the two visits was modest in this case with the Dice coefficient = 0.28. For the CF subject shown in Figure 8, the PSE maps at both visits showed substantially large focal defects and notably less enhancement with

greater heterogeneity compared to the normal and asthma subjects. The segmented defects at visit #1 vs. visit #2 yielded an improved spatial overlap with the Dice coefficient = 0.48.

Spatially, the test-retest comparisons found only modest agreement of the segmented defects. The average Dice coefficients of the defects segmented from repeated PSE maps of the same subject were 0.20, 0.26, and 0.35 for the normal (N=2), asthma (N=2), and CF (N=6) subjects.

DISCUSSION

This study demonstrates the capability of 3D UTE OE-MRI to characterize and quantify differences in whole lung ventilation deficits on PSE parametric maps in diseased vs. healthy lungs. The method leverages advantages of the 3D radial UTE technique to provide T_1 -weighted contrast without substantial T_2^* decay to obtain OE contrast with isotropic spatial resolution and full chest coverage. Despite the small sample size, MPSE reported from OE-MRI was significantly correlated with the spirometric measurements. Similarly, whole lung VDP was measured and shown to correlate with FVC % predicted. We also demonstrate repeatability of both MPSE and VDP to quantify obstructive patterns in a subset of enrolled subjects. Simple post-processing corrections including deformable registration and density corrections improved repeatability of both MPSE and VDP as image biomarkers. The regional characterization of obstruction using the gravity dependent anterior to posterior signal gradients for both MPSE and VDP are also consistent with the expected gravity dependence of the supine lung and are similar to that measured with HP gas MRI (28).

Several studies have used 2D OE-MRI with T_1 -weighting obtained from inversion-recovery fast spin echo and Look-Locker GRE pulse sequences for patients with various pulmonary diseases (10–12, 29) and have observed differences in relative enhancement associated with disease and disease severity. These studies examined small volume measurements or ROIs that often covered only a modest portion of the lungs due to the extended scan times required for 3D coverage using these pulse sequences. It is therefore unclear whether the T_1 values or mean signal enhancement observed are representative of the entire pulmonary parenchyma. These 2D methods are not conducive to targeted evaluation of specific regions of local lung disease that may be valuable to guide treatments. The 3D radial UTE OE-MRI method, however, discriminates asthma and CF subjects from the normal group using full lung volumes to be assessed with isotropic spatial resolution that supports more accurate volumetric measurements of MPSE and VDP.

The high degree of repeatability in global measures shown for our UTE OE-MRI methodologies suggests robust implementation is feasible. In studies of regional repeatability using HP gas MRI, the ICC for ventilation defect volumes assessed from breath-held images on two separate days were 0.77–0.89 (30). Other recent repeatability studies of lung T_1 quantification found significant inter-day variability of T_1 , the relative reduction between normoxic and hyperoxic breathing, to be on the order of 23% for asthmatic lungs (24). Our study suggests that the known volumetric dependence of the lungs while breathing normoxic vs. hyperoxic conditions (19) is a factor; subjects may become

more relaxed during the several minute time course of the typical UTE OE-MRI acquisition affecting consistency of the tidal-breathing volume. Without accounting for associated lung density changes, such variability in tidal volume would not be accounted for purely by deformable registration. Based on our results variability in tidal volume biases the PSE measurement when calculated under the assumption of equal spin density. We found that retrospective density correction based on the Jacobian determinant improved the repeatability in the global measurements and enabled defect quantification in our data.

Despite these advances, we acknowledge that comparatively low-to-moderate Dice coefficients suggest that either there is remaining work to be done or areas of defect are changing location or filling while imaging under the steady-state condition between scans. Two issues may further improve repeatability of UTE OE-MRI. First, CF subjects can have irregular tidal breathing patterns due to their disease in addition to the physiological response to normoxic vs. hyperoxic breathing. Inconsistencies in tidal volume from breath to breath lead to data inconsistencies in respiratory gating over the 3.5-minute scan time that contribute to local blurring. Using adaptive motion compensation or improving consistency of respiratory gating may mitigate this source of variation. Second, the 15-day time interval between repeated scans may allow for genuine ventilation differences between visits, especially in asthma but possibly also in CF.

The primary limitation of the study design is the inconsistency of the time interval between two visits, which is varied from 7 to 15 days. A future prospective study that includes test-retest consistently on the same visit, followed by a second exam to investigate inter-visit repeatability would better refine our understanding of whether variations in the location of regional defects is physiologic or due to unaccounted errors. Improvement of spatial defect repeatability is therefore a goal of future work. Another, more technical, limitation is the assumption of mass conservation. Although the normoxic and hyperoxic UTE acquisitions were prospectively gated to end expiration—the same point during the breathing cycle, there were measureable differences in lung volume that here are attributed primarily to the respiratory physiological response (1.0% higher in normoxic lung volume). However, irregular breathing patterns may also lead to variations in blood volume that can be an additional confounding factor. As shown previously in phantom experiments (20), it is worth investigating whether the adapted slope model could provide more accurate density correction for cases of large lung volume differences (>200 mL) between normoxic and hyperoxic acquisitions.

An extension of this 3D UTE OE-MRI technique from steady-state to dynamic imaging may reveal regional variations in physiology that are specific to asthma vs. CF. The ability to monitor dynamic changes in gas uptake is an important potential advantage of OE-MRI over other MRI approaches to imaging of lung ventilation. The 3D evaluations of delivery, uptake and washout of O₂ using our approach, similar to that developed for 2D (12), is therefore an important area of future work.

In this work, we found that the T₁ contrast of the arterial blood demonstrated higher MPSE compared to that of the lung tissues for all subjects. The arterial MPSE was significantly lower in asthma and CF subjects compared to that of the normal subjects. These results

reveal that subtle changes in lung function may reflect reduced efficiency of gas exchange that leads to overall poorer blood oxygenation, in agreement with literature findings (12, 31). Also found in our study, the MPSE of LV blood pool showed a consistently lower value for asthmatic subjects but a nonsignificant increase in CF compared to normal subjects. We speculate that the observed discordance of MPSE in the LV blood pool vs aorta of CF subjects may be primarily due to cardiac pulsation and intermittent bulk motion artifacts during free breathing but this possible discrepancy warrants further study.

In conclusion, we have demonstrated that UTE OE-MRI with 3D whole lung coverage can depict functional deficits in the lungs of subjects with asthma and CF relative to normative lungs. We have also demonstrated repeatable whole lung defect quantification using VDP derived from the PSE map when the proposed post-processing workflow was applied. However, regional repeatability of ventilation defects is not well supported by the current study, suggesting the need for a controlled prospective study of test-retest and inter-visit repeatability in larger sample sizes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Workflow of computing percent signal enhancement (PSE) map from UTE OE-MRI. High-resolution normoxic (a) and hyperoxic (b) UTE volumes were used to align the two volumes using deformable registration and segmented to produce the 3D binary lung mask (c). The resultant deformation field and its corresponding Jacobian determinant (d) along with the lung mask were applied on the low-resolution volume pairs (e and f) to compute PSE (g).

Figure 2.

Example of the percent signal enhancement (PSE) map for a normal subject in a coronal slice computed before registration (a) and after registration and density correction (b) with the corresponding Jacobian determinant map (c). Histograms of the PSE values in the lungs (d) were shown before registration (red dashed line), after registration only (cyan dashed line), and after density correction (blue bars). The slight shift of the PSE histogram after registration and density correction implies a slightly higher lung volume acquired at hyperoxic vs. normoxic breathing. The white arrows indicate the false high PSE values at the lung periphery caused by the misalignment of the hyperoxic and normoxic volumes. The PSE and Jacobian determinant values outside the lungs were disregarded.

Figure 3.

Example of the percent signal enhancement (PSE) map for a mild-to-moderate asthmatic subject in a coronal slice computed before registration (a) and after registration and density correction (b) with the corresponding Jacobian determinant map (c). Histograms of the PSE values in the lungs (d) were shown before registration (red dashed line), after registration only (cyan dashed line), and after density correction (blue bars). The PSE histogram after registration and density correction was shifted to the left, implying a higher lung volume acquired at normoxic vs. hyperoxic breathing. The PSE and Jacobian determinant values outside the lungs were disregarded.

Figure 4.

Boxplots of a) median percent signal enhancement (MPSE) and b) whole lung ventilation defect percent (VDP) in normal, asthma, and cystic fibrosis (CF) groups respectively. Each Box extends vertically between the minimum and maximum values, the central line of the box represents the median and all values of a group are plotted with the cross markers. The stars represent statistically significant differences relative to the normal. [Median, interquartile range] of MPSE for normal, asthma, and CF was [7.6%, 1.8%], [6.8%, 0.9%], [4.7%, 2.6%] respectively. For VDP, the median and interquartile ranges are [3.3%, 1.3%] for normal, [21.7%, 21.0%] for asthma, and [27.1%, 20.5%] for CF.

Figure 5.

Median percent signal enhancement (MPSE) in a) and ventilation defect percent (VDP) in b) of anterior and posterior regions of 7 normal subjects (blue solid lines), 5 asthma (green dashed lines) and 6 cystic fibrosis (red dotted lines). In each subject group, the markers representing the anterior and posterior data points varied by subject. The repeated measurements for the same subject were averaged when available. In all 18 subjects, the posterior regions yielded significantly higher MPSE and lower VDP relative to the anterior regions.

Figure 6.

Example of test-retest percent signal enhancement (PSE) maps with segmented defects outlined in green for a normal subject at scan #1 and scan #2 on the same day. After registration and density correction, the PSE maps at scan #1 and #2 showed similar PSE variations. The global measures for scan #1 and scan#2 were 8.3% vs 7.5% for median PSE and 3.6% vs. 2.3% for VDP respectively. Dice coefficient of ventilation defects between scans was 0.31. The PSE values outside the lungs were disregarded.

Figure 7.

Example of test-retest percent signal enhancement (PSE) maps after registration and density correction with segmented defects outlined in green for a mild-to-moderate asthma at two visits separated by 9 days. The PSE map at visit #1 was transformed to the physical space of visit #2 via 3D rigid registration of the two high-resolution hyperoxic volumes. The global measures for visit #1 and #2 were 7.1% vs 6.3% for median PSE and 5.3% vs. 6.6% for VDP respectively. Dice coefficient of ventilation defects between visits was 0.28. The PSE values outside the lungs were disregarded.

Figure 8.

Example of test-retest percent signal enhancement (PSE) maps after registration and density correction with segmented defects outlined in green for a cystic fibrosis (CF) subject at two visits separated by 7 days. The PSE map at visit #1 was transformed to the physical space of visit #2 via 3D rigid registration of the two high-resolution hyperoxic volumes. The PSE maps at both visits showed large regional defects with modest spatial alignment between visits. The global measures for visit #1 and visit #2 were 3.4% vs 2.9% for median PSE and 31.5% vs. 31.7% for VDP respectively. Dice coefficient of ventilation defects between visits was 0.48. The PSE values outside the lungs were disregarded.

Table 1

Demographic information and global measurements from UTE OE-MRI

	Normal (N = 7)	Diseased groups		P values	
		Asthma (N = 5)	Cystic Fibrosis (N=6)	Asthma vs. Normal	Cystic Fibrosis vs. Normal
Age (year)	30.4±9.7	43.2±16.7	31.2±13.0	-	-
Male/Female	5/2	4/1	2/4	-	-
MPSE _{LV} (%)	8.5±1.3	6.0±0.6	9.6±3.3	0.10	0.54
MPSE _{aorta} (%)	9.1±1.2	6.6±1.7	6.5±1.8	0.028	0.016
MPSE _{lung} (%)	8.0±0.9	6.0±0.6	4.5±2.1	0.042	0.0006
Ventilation defect percent (%)	3.3±1.8	21.7±11.9	27.2±14.7	0.018	0.0020
FEV ₁ (% predicted)	-	94.7±12.6	66.7±25.2	-	-
FVC (% predicted)	-	100.0±8.5	83.9±26.6	-	-

Values are expressed as mean ± standard deviation. MPSE_{LV}: median percent signal enhancement in the left ventricle; MPSE_{aorta}: median percent signal enhancement in the aorta; MPSE_{lung}: median percent signal enhancement in the lungs; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; A $P < 0.05$ was considered significant.

Table 2

Test-retest mean bias with 95% limits of agreement (LOA) and intraclass correlation coefficient (ICC) for global measurements in the lungs

	Mean bias (%)	95% LOA (%); <i>P</i> value	ICC; <i>P</i> value
Unregistered MPSE	0.28	[-6.36, 6.92]; 1.00	0.56; 0.045
Registered MPSE	0.21	[-6.03, 6.45]; 0.92	0.46; 0.090
Corrected (registration and density) MPSE	-0.42	[-2.15, 1.31]; 0.19	0.90; <0.0001
Corrected (registration and density) VDP	-1.23	[-7.87, 5.40]; 0.63	0.98; <0.0001

MPSE: median percent signal enhancement in the lungs; VDP: ventilation defect percent. A $P < 0.05$ was considered significant.