Imaging of Lung Ventilation and Respiratory Dynamics in a Single Ventilation Cycle Using Hyperpolarized He-3 MRI

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Purpose: To image respiratory dynamics and three-dimensional (3D) ventilation during inhalation, breath-hold, and exhalation for evaluation of obstructive lung disease using a single dose of hyperpolarized (HP) He-3 during MRI. 

Materials and Methods: A single 2D-3D projections inside Z encoding (PRIZE)-2D acquisition was performed that consisted of a rapid 2D radial acquisition phase during inhalation of the HP He-3, a 3D acquisition phase during a breath-hold interval, and finally the same 2D radial acquisition during a forced exhalation maneuver followed by tidal breathing. The 3D PRIZE acquisition was comprised of radial sampling in the coronal plane and Fourier encoding in the patient’s anterior–posterior direction. Nine patients with mild/moderate to severe asthma were studied (two individuals were studied twice) using this technique. 

Results: Breath-hold and dynamic imaging results showed physiological abnormalities and were compared with results from standard spirometry, body plethysmography, and computed tomography (CT). Dynamic images depicted regions of differential gas clearance and trapping observed during and after forced exhalation that were corroborated as regions of air trapping on CT imaging. 

Conclusion: The 2D-3D PRIZE-2D acquisition allowed for 3D depiction of ventilation during a breath-hold, as well as detection of gas trapping. Imaging results were confirmed with spirometry, body plethysmography, and CT. 

Key Words: asthma; gas trapping; hyperpolarized helium-3; lung; radial; ventilation 

these methods clinically. Specifically, there is a need to reduce costs and accommodate patients who have difficulty holding their breath due to decreased lung function.

Prior work using HP He-3 MRI has demonstrated two-dimensional (2D) dynamic imaging of respiration (14–17) and 3D breath-held imaging of ventilated regions of the lung using separate doses of HP He-3 (18). Several fast MRI k-space trajectories, including 2D spiral (17) and radial (15,16) trajectories, have been shown to provide advantages with respect to view sharing for time-resolved studies while maintaining spatial resolution for short acquisition times in HP gas MRI. These approaches are potentially advantageous for exploring the regional nature of airway obstruction and gas trapping during rapidly occurring processes, such as the forced inhalation and exhalation maneuvers commonly used in spirometry. For example, Koumellis et al (16) showed the use of a radial acquisition for detecting inhalation time constants in different regions within the lungs during a coached respiratory maneuver in CF patients. In addition, ventilation images obtained using both 2D and 3D techniques have been shown to depict regional ventilation defects that track spirometry measures in asthma (19), CF (16), and COPD (20). However, in many circumstances the breath-hold duration required for these scans can be challenging for individuals with compromised lung function.

We report a technique that captures both high-temporal-resolution 2D images depicting dynamic changes in ventilation during inhalation and exhalation, and associated static 3D ventilation data during a breath-hold. Thus the full respiratory cycle is depicted with a single dose of He-3. The technique combines concepts of view sharing (21,22), radial undersampling in high contrast-to-noise ratio (CNR) applications, and the 3D hybrid projection and Fourier acquisition method termed “projections inside Z encoding” (PRIZE) (23) to provide variable temporal apertures for dynamic 2D and breath-held 3D acquisitions without sacrificing spatial resolution. We hypothesize that this combined 2D-3D PRIZE-2D acquisition will enable both high-temporal-resolution visualization of respiratory dynamics and high-spatial-resolution static ventilation imaging within a clinically reasonable breath-hold and during a single acquisition. The key advantages of the technique over existing methods include improved depiction of lung function, robustness to motion during a breath-hold, shorter total MR exam time, and reduced He-3 dose. Previous HP gas MRI methods have relied on two separate scans to independently examine dynamic and static phases, at the cost of twice the He-3 usage and imaging time. Preliminary patient results are presented to demonstrate the imaging method in vivo.

**MATERIALS AND METHODS**

Imaging was performed using a standard clinical 1.5T MRI system with broadband capabilities (GE Healthcare, Milwaukee, WI, USA) coupled with a vest coil (IGC Medical Advances, Milwaukee, WI, USA) tuned to the resonance frequency of He-3 (48 MHz). HP He-3 of 30% to 40% polarization was produced using spin exchange from optically pumped rubidium vapor (IGI.9600.He; GE Healthcare). All of the volunteer studies were approved by our institutional review board, and informed consent was obtained from the subjects. To demonstrate the technique, nine patients were studied. Two of these individuals underwent a second exam one to two months after the first exam. All of the patients had mild/moderate to severe asthma based on the intensity of corticosteroid therapy and indicators of disease stability (24). Pulmonary function tests, including spirometry and body plethysmography, were performed prior to the MRI exams. Spirometry indicated that all volunteers exhibited ≥70% predicted forced expiratory volume at one second (FEV₁ %predicted) based on the reference tables of Hankinson et al (25). The residual volume (RV) and total lung capacity (TLC) were measured using body plethysmography. RV/TLC serves as a measure for gas trapping.

The subjects inhaled a 3.4–5.4-mM dose of HP He-3 and nitrogen gas mixture. Nitrogen was mixed with the He-3 to produce a total volume equivalent to 14% of TLC (0.7–1.1 liters). This lung volume gives a position comparable to end-inspiration of one tidal volume from the functional reserve capacity (FRC). Thus, the inhaled volume was normalized to lung size among patients.

During the imaging studies the patients were coached to inhale the gas mixture, pause respiration for a short while, perform a forced exhalation maneuver, and finally resume tidal breathing. The sequence switched among three separate imaging phases (Fig. 1a): 1) a rapid 2D radial acquisition was performed during inhalation, 2) a 3D PRIZE acquisition was performed twice during a breath-hold, and 3) the sequence was switched back to the 2D radial acquisition to capture dynamics during forced exhalation followed by tidal breathing. Vocal cues were given to the patient to synchronize their efforts with the data acquisition. If the subject was able to complete the full 14.2-second breath-hold, the two separate 3D PRIZE interleaved radial datasets were combined for improved radial sampling. If the patient was unable to complete the entire breath-hold, a single 3D PRIZE dataset with diagnostic quality was still acquired within the first 7.1 seconds of the breath-hold.

Imaging for the dynamic phase (2D radial acquisition) was performed over a 48 cm × 48 cm FOV in the coronal plane with 128 points sampled along each radial line. A small flip angle of ~1° was employed to preserve magnetization during the dynamic phase (~15% polarization loss during the inspiratory phase). Seventy-two “bent” projections (26) were acquired. The second half of each projection was bent by half of the angle spacing (1.5° in this instance), resulting in a total of 144 unique projection angles. Two different acquisitions using either ±125 kHz or ±15.63 kHz receiver bandwidth were performed. Additional acquisition parameters are listed in Table 1. Two patients were studied using the ±15.63 kHz receiver bandwidth acquisition and the others were studied using the ±125 kHz receiver bandwidth. The use of a ±125 kHz receiver bandwidth allowed much shorter TR times (4 msec for ±125 kHz vs. 7 msec for ±15.63 kHz); however, this shorter time can lead to a higher time rate of RF depletion. To lessen the rate of RF
depletion for the faster receiver bandwidth acquisition and retain magnetization for later time frames, the TR time for the faster receiver bandwidth acquisition was increased from 4 msec to 7 msec during the dynamic phase to mitigate RF depletion compared to that of the 15.63 kHz receiver bandwidth acquisition, while decreasing blurring due to off-resonance.

The 3D PRIZE method performs projection acquisition in one plane ($k_x-k_y$) and conventional phase encoding in the perpendicular direction ($k_z$), and has been shown to yield high-temporal and -spatial-resolution 3D imaging for angiographic applications (23). This technique has also been applied to HP gas imaging of small animals and humans for applications that require centric encoding and high spatial resolution, and employ rapid readout times (27,28). For the present application, the phase-encoding direction was oriented along the short axis of the lungs (anterior–posterior) to limit the number of phase-encoding values required to achieve sufficient spatial resolution. Asymmetric phase encoding was used with 14 of the 24 total linear phase-encoding values acquired beginning at $-k_y$ (Fig. 1b). During the 3D acquisition the acquired resolution was 3.75 mm × 3.75 mm × 8 mm, and the flip angle was also increased to $\sim1.5^\circ$ to improve the signal. The remaining imaging parameters for each phase-encoding value for the 3D PRIZE breath-hold were the same as for the inhalation and exhalation 2D phases of the acquisition. Unique sets of interleaved projection angles covering a range of 180° of k-space were acquired during each of the two separate 3D PRIZE datasets, allowing the potential to combine volumes to reduce undersampling artifact.

For visualization, dynamic data were reconstructed using regridding in k-space followed by zero-filling to provide a 256×256 matrix in the x-y plane after inverse 2D Fourier transformation. The two separate 3D datasets acquired during the breath-hold could be combined to create a single 288 projection angle k-space data volume to satisfy the Nyquist criterion in the projection reconstruction plane. Each 3D dataset was reconstructed to a 256×256×120 matrix using homodyne and zero-filling in the phase-encoding direction to achieve a nearly isotropic reconstructed resolution of $\sim2$ mm for display. At higher receiver bandwidths, gradient timing errors can become sufficiently large in non-Cartesian acquisitions that k-space trajectory corrections are required (29). Therefore, k-space data were corrected during regridding to account for deviations from the ideal k-space trajectory due to time delays between gradient and data acquisition boards. Errors due to eddy currents were not directly corrected in this study. Instead, eddy currents were mitigated by using a

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**Table 1**

<table>
<thead>
<tr>
<th>Summary of Acquisition Parameters</th>
<th>15.63 kHz</th>
<th>125 kHz</th>
</tr>
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<tbody>
<tr>
<td><strong>Receiver bandwidth</strong></td>
<td>2 × 7.1 seconds</td>
<td>2 × 7.1 seconds</td>
</tr>
<tr>
<td><strong>Sampled points</strong></td>
<td>128</td>
<td>128</td>
</tr>
<tr>
<td><strong>TR/TE</strong></td>
<td>7.0/3.0 msec</td>
<td>7.0/1.6 msec</td>
</tr>
<tr>
<td><strong>Effective temporal resolution during the dynamic phases</strong></td>
<td>504 msec</td>
<td>504 msec</td>
</tr>
<tr>
<td><strong>FOV</strong></td>
<td>48 cm × 48 cm × 24 cm</td>
<td>48 cm × 48 cm × 24 cm</td>
</tr>
<tr>
<td><strong>Acquired resolution</strong></td>
<td>3.75 mm × 3.75 mm × 10 mm</td>
<td>3.75 mm × 3.75 mm × 10 mm</td>
</tr>
<tr>
<td><strong>Phase encodes</strong></td>
<td>14 acquired (of 24 total)</td>
<td>14 acquired (of 24 total)</td>
</tr>
<tr>
<td><strong>Projections</strong></td>
<td>72 (144 unique angles covering 360°)</td>
<td>72 (144 unique angles covering 360°)</td>
</tr>
<tr>
<td><strong>Flip angle</strong></td>
<td>$\sim1^\circ$ dynamic/$\sim1.5^\circ$ breath-hold</td>
<td>$\sim1^\circ$ dynamic/$\sim1.5^\circ$ breath-hold</td>
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*aTotal of 144 unique angles using bent projections (25).
large FOV to reduce the deviations from the expected k-space trajectory.

A whole-lung defect score was used to quantify the extent of ventilation anomalies for each subject, as described previously (30). Briefly, each lung was divided into three regions in the coronal plane (apical, middle, and basal) and the percent of ventilation defect was assessed for each region. A weighted score was assigned for each region as follows: 0 = no defects, 1 = 0–25%, 2 = 25–50%, 3 = 50–75%, and 4 = 75–100%. The total defect score was the sum of all regions for all slices. Gas trapping was evaluated based on the percent decrease in SNR between images acquired immediately pre and post forced expiration during the exhalation phase. Figure 3 shows the percent decrease in SNR plotted against the RV/TLC (a measure of gas trapping determined from body plethysmography) for 10 of 11 exams. One dataset was excluded because the patient lost her breath-hold prior to the beginning of the final 2D dynamic imaging phase. More residual signal (i.e., a smaller decrease in SNR) was found with compromised RV/TLC. Of the individuals who showed a small percent decrease in SNR following forced exhalation, two were found to have focal regions of residual signal. An example of this focal signal is depicted in the dynamic exhalation series shown in Fig. 4a (arrow). Figure 4b shows signals as a function of time from three ROIs taken at points in the left lung (trachea, upper-middle, and basal). The curves show a dramatic temporal change in gas signal with a rapid drop in signal in the trachea, as expected due to clearance of HP gas from exhalation and the inhalation of a new breath of room air. The two ROIs placed in the parenchyma of the lung show a longer clearance time for the residual gas signal compared to the signal in the trachea. The ROI in the base of the left lung depicting the longest signal decay time from the MR images correlates to a region of

**Figure 2.** Dynamic 2D ventilation images depicting inhalation acquired over a 48 cm × 48 cm FOV using 144 unique projection angles at a temporal aperture of 504 msec for a patient with mild/moderate asthma, FEV1 %predicted of 103, and a defect score of 8 determined from 3D imaging during a breath-hold (see Fig. 4).

**Figure 3.** Plot of percent decrease of SNR in the lungs from images obtained before and after forced exhalation (averaged for both lungs) vs. RV/TLC determined from body plethysmography.
hyperlucency and air trapping on the CT image acquired at FRC (Fig. 4d). Moreover, a ventilation defect on the MR image in this same area (arrow in Fig. 4c) correlates with a region showing ground-glass opacity on the CT images.

Coronal and axial images reconstructed from the first acquired dataset and a combination of both acquired 3D datasets are shown in Fig. 5 for a subject with severe asthma. The in-plane (coronal) and through-plane (axial) resolutions are demonstrated for a single 3D dataset acquired in 7.1 seconds (Fig. 5a and b), and for the combination of two 3D datasets acquired in 14.2 seconds (Fig. 5c and d). The improved spatial resolution achieved during the 3D PRIZE phase allows detection of ventilation defects (arrows in Fig. 5). Images from an individual with compromised lung function who was unable to perform the complete 14.2-second breath-hold are shown in Fig. 6. An image reconstructed from the 3D data acquired during the first 7.1 seconds of the breath-hold (Fig. 6a) depicts large ventilation defects and is compared with an image reconstructed from the 3D data acquired during the second 7.1-second phase of the breath-hold (Fig. 6b). Motion is evident as indicated by the change in the diaphragm position in the difference image (arrows in Fig. 6c) when the subject began to breathe during the scan.

In Fig. 7 the defect score is plotted vs. the whole-lung spirometry measure of FEV$_1$ %predicted. As in previous studies of lung disease (30), higher defect scores were associated with compromised lung function (FEV$_1$ $<$ 80% predicted). Note, however, that subjects with confirmed air trapping based on RV/TLC (triangles) did not always have an increased defect score or reduced FEV$_1$ %predicted.

**DISCUSSION**

The technique presented allows depiction of the airways and parenchyma during respiratory dynamics and a breath-hold. Furthermore, this approach reduces both the required dose of costly HP He-3 and exam time. Offsetting the PR angles between 3D acquisitions allows the datasets to be combined to decrease in-plane arti-

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**Figure 4.** a: Images from the exhalation phase (acquired using the 2D radial acquisition) from a subject with FEV$_1$ %predicted of 103, and ventilation defect score of 8 (the same subject represented in Fig. 2). Note that a region of signal is still visible in the last time frame (arrow). b: Signals as a function of time from three ROIs during the 2D exhalation and tidal breathing phase. c: Locations of the ROIs are depicted as black circles on a single coronal image acquired during the breath-hold interval using the 3D PRIZE acquisition. Ventilation abnormalities, including a ventilation defect (arrow), are visible superior to the apparent site of regional gas trapping. d: A CT slice acquired during expiration, which corresponds to the MR slice depicted in part c, showing a region of ground glass opacity near the location of the ventilation defect (upper arrow) and air trapping (lower arrow).

**Figure 5.** (a) Coronal and (b) axial images reconstructed from the first 3D dataset acquired during the breath-hold. (c) Coronal and (d) axial images reconstructed from the combined data of the first and second 3D datasets acquired during the same breath-hold, showing decreased radial undersampling artifacts. Note that ventilation defects are visible in both planes (arrows). The FEV$_1$ %predicted was 81 and the defect score was 9 for this subject with severe asthma.

**Figure 6.** An example of a patient with severe asthma and highly compromised ventilation (FEV$_1$ %predicted of 77, defect score of 32). a: Coronal image from the first 3D dataset acquired. b: Coronal image from the second 3D dataset acquired. c: Difference image obtained by subtracting b from a, showing diaphragm motion (arrows) due to loss of the breath-hold.
facts and improve image quality in patients capable of achieving longer breath-holds. Therefore, the acquisition of consecutive datasets using 3D PRIZE during the breath-hold ensures diagnostic image quality in as little as 7.1 seconds, with improved image quality if the subject is capable of longer breath-holds.

Using the same TR and flip angle during all studies results in a relatively consistent rate of RF depletion among subjects. This allows quantitative comparisons of signal changes associated with gas trapping between patients. Moreover, because ventilation defects and gas trapping are both imaged with a single scan acquired during a single respiratory cycle, the two abnormalities can be readily compared. By providing a means to assess regional severity of airway obstruction and respiratory dynamics, the proposed technique can assess disease heterogeneity, a central characteristic of obstructive lung diseases such as asthma, COPD, CF, and bronchiolitis obliterans syndrome in lung-transplant patients.

The flexibility of this 2D-3D PRIZE-2D acquisition enables further optimization of the 3D breath-hold acquisition phase. In the current implementation, the RF depletion was limited by acquiring only two 3D datasets, with each dataset requiring ~1000 RF excitations. Limiting the number of RF pulses during the 3D breath-hold phase preserves magnetization for improved image quality during the later 2D dynamic phase for imaging of exhalation and tidal breathing. By decreasing the number of projections and/or slice-encoding values, sufficient magnetization can be preserved to allow the acquisition of additional consecutive 3D datasets. These additional 3D datasets may be used to provide flip angle and T1 maps to enable 3D regional mapping of PO2 and the ventilation-perfusion ratio (31–33).

This study focused on applying the 2D-3D PRIZE-2D technique to analyze the forced expiratory component of the respiratory cycle for detection of gas trapping in asthmatics. Koumellis et al (16) demonstrated the use of a 2D PR acquisition for rapid imaging during a coached inhalation and exhalation maneuver in CF patients. Inhalation data acquired using this 2D-3D PRIZE-2D technique could be similarly analyzed for detection of inspiratory abnormalities in other lung diseases.

There are, however, several limitations to the present technique. In order to observe the entire lung at high temporal resolution, the dynamic data were collected using a thick imaging slice, which can obscure small regions of gas trapping and ventilation defects. Alternatively a thin 2D slice could be imaged for increased anterior–posterior resolution, or 3D imaging could be performed at a decreased temporal resolution.

For projection acquisition methods, it is desirable to acquire data at faster receiver bandwidths (such as ±125 kHz) to decrease TE and mitigate off-resonance blurring. However, data acquisition at accelerated TE and TR can lead to errors due to eddy currents and system-dependent differences in the timing of the gradients relative to each other and to the timing of the receiver. These effects have been well documented with a variety of techniques being utilized to correct both gradient delay and eddy current issues (29,34,35). Gradient system calibration methods can be difficult to perform using HP gas contrast agents due to signal decay and gas availability. In the present study, timing differences existed between the gradients in the projection acquisition plane (X and Z gradient systems) that resulted in a deviation of the actual k-space trajectory compared to the expected result. While trajectory deviations due to system timing differences were accounted for during the regridding process, errors due to eddy currents were not directly corrected in this study. Instead, eddy currents were mitigated by using a large FOV to reduce the deviations from the expected k-space trajectory.

Spiral acquisition is another rapid non-Cartesian technique that has been demonstrated for high-spatial and -temporal-resolution dynamic HP gas imaging of the lungs (17). Projection acquisition has advantages over spiral acquisition with respect to T2*-related signal loss and off-resonance sensitivity in applications involving the lungs (36).

The use of a larger data acquisition receive bandwidth (±125 kHz vs. ±15.63 kHz) provides a shorter TE time (1.6 msec vs. 3 msec) for these two projection acquisitions. While there is negligible diffusion weighting due to the readout gradients for the ±15.63 kHz bandwidth acquisition at the center of the data readout window (b = 0.06 s/cm² at the center of k-space), the larger gradients of the ±125 kHz bandwidth acquisition result in a minor diffusion weighting (b = 0.1 s/cm²).

The current implementation of the 2D-3D PRIZE-2D scheme uses fixed time durations for the different imaging phases that could result in loss of data if the subjects lose their breath-hold. An attractive solution to this problem would be to synchronize the scan to the respiratory cycle via a subject-controlled breath-hold trigger to control the scanner transition between breath-held and dynamic imaging phases. The current study demonstrated this technique in a limited number of subjects, all of whom had mild/moderate to severe asthma. Future work will look at a larger number of subjects, including normal subjects, to further explore the sensitivity of the acquisition.

Figure 7. Graph depicting the whole-lung spirometry measure of FEV1 %predicted vs. defect score. Cases of gas trapping (one of which is depicted in Fig. 4) are represented by triangles, while the remaining data points are represented by diamonds.
In summary, we have demonstrated the 2D-3D PRIZE-2D acquisition method for collecting both high-temporal-resolution data during dynamic phases and high-spatial-resolution 3D data during breath-hold. This enables imaging of ventilation defects during a static breath-hold, regional depiction of gas trapping during the forced exhalation dynamic phase, and spatial correlation of the results captured within a single breath of gas.

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