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Original Article

Hyperpolarized helium-3 magnetic resonance lung imaging of non-sedated infants and young children: a proof-of-concept study

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ABSTRACT

Purpose: To develop and evaluate a protocol for hyperpolarized helium-3 (HHe) ventilation magnetic resonance imaging (MRI) of the lungs of non-sedated infants and children.
Materials and methods: HHe ventilation MRI was performed on seven children ≤4 years old. Contiguous 2D–spiral helium-3 images were acquired sequentially with a scan time of ≤0.2 s/slice.
Results: Motion-artifact–free, high signal-to-noise ratio (SNR) images of lung ventilation were obtained. Gas was homogeneously distributed in healthy individuals; focal ventilation defects were found in patients with respiratory diseases.
Conclusion: HHe ventilation MRI can aid assessment of pediatric lung disease even at a young age.

1. Introduction

Lung diseases such as asthma, prematurity-associated bronchopulmonary dysplasia (BPD), and cystic fibrosis (CF) often present management challenges in childhood. However, despite being the most common method for assessing severity of lung disease, spirometry cannot be easily performed in young children [1]. Computed tomography (CT) provides information about alterations in lung structure, but its relatively high radiation dose limits its use in young children, particularly for serial assessments, due to risk of radiation-induced malignancies [2]. Chest radiographs are commonly performed in young children but are insensitive to early manifestations of many pediatric lung diseases such as asthma and CF. Improved methods for assessing the severity of lung disease in young children are critically needed so early disease progression can be better understood, and new pediatric treatments can be evaluated. Hyperpolarized helium-3 (HHe) is a nonradioactive, gaseous contrast agent that, when inhaled, provides images of lung ventilation with high spatial and temporal resolution [3–5]. This imaging technique, which has been used by several research groups in adults and older children, is typically performed during a single breath-hold following inhalation of HHe [6,7].

Focal ventilation defects are areas of reduced HHe signal intensity caused by impairment of gas flow and are frequently found in the lungs of adults and older children with obstructive lung diseases. Ventilation defects have been observed using HHe magnetic resonance imaging (MRI) in several pediatric lung diseases, including asthma, CF, and BPD [8–10]. New characteristics of lung diseases have been uncovered through HHe MRI, including the relative persistence or recurrence of ventilation defects in specific locations of the lungs of asthmatics [11,12]. Diffusion-weighted HHe MRI has also been used in healthy participants to observe aspects of the lung's structural development during childhood [6]. An overview of current literature, however, indicates that HHe MRI in children younger than 4 years of age has not been reported. Children younger than 4 years of age typically cannot hold still and are unable to perform the breath-holding maneuvers required during previously reported methods of HHe MRI.

The purpose of this study was to develop an HHe ventilation imaging protocol with magnetic resonance (MR) pulse sequences and gas-

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Table 1
Patient demographic data and helium polarization

Patient #	Age	Gender	Height (cm)	Weight (kg)	Disease	Pre pO_2 (%)	Post pO_2 (%)	Helium volume (cc)	Polarization (%)
1	13 months	F	74	10	Healthy	NR	NR	200	59
2	10 months	M	NR	8	CF	NR	97	200	62
3	14 months	M	86	11	CF	100	NR	300	38[a]
4	17 months	M	76	11	CF	NR	94	400	60
5	3 years	M	97	15	Asthma	97	96	200	36[a]
6	3 years	M	97	19	Asthma	95	96	300	53
7	2 months	M	48	2	BPD	98	99	300	63

BPD = bronchopulmonary dysplasia; CF = cystic fibrosis; NR = not recorded.
[a] MITI polarizer.

delivery methods that could be used to image lungs of non-sedated infants and children too young to cooperate with HHe MRI–related breathing instructions. A spiral-based pulse sequence was employed for this pilot study because the spiral trajectory makes more efficient use of the MR-scanner gradient system resulting in a shorter image acquisition time than that required for a conventional Cartesian acquisition with equivalent spatial resolution [13]. The spiral trajectory also has a relatively low sensitivity to motion. Therefore, the hypothesis was that, by using extremely rapid imaging, it might be possible to obtain high-quality, relatively motion-artifact–free HHe MR images in non-sedated infants and young children who are moving and breathing during the image acquisition.

2. Methods and materials

HHe MRI was performed on seven non-sedated children younger than 4 years of age (five male, two female), including one healthy infant (13-month-old), three infants with CF (10-month-old, 14-month-old, and 17-month-old), two young children with asthma (both 3-years-old), and one infant who was born prematurely at 28 3/7 weeks' gestational age (age at imaging approximately 2 months old) (Table 1). The study was prospective, HIPAA-compliant, and approved by the local institutional review board. Both parents of each child gave written informed consent.

HHe was administered under an FDA-approved physician's investigational new drug application (IND #57,866). Patients were recruited from the pediatric pulmonary and CF outpatient clinics and the neonatal intensive care unit. The helium-3 gas was polarized using an optical-pumping and spin-exchange system (home-built, University of Virginia, Charlottesville, VA, USA and a prototype commercial system, MITI, Durham, NC). The home-built polarizer achieved polarizations between 50% and 65% [14] and the prototype commercial polarizer achieved polarizations between 35% and 40%. When available the home built polarizer was used due to the higher polarization (Table 1).

Imaging was performed by an MR technologist or physicist on a 1.5 T whole-body MRI system (Avanto, Siemens Healthcare, Malvern, Penn) using specially designed radio-frequency (RF) coils tuned to helium frequency. Different helium frequency RF coils were used with different patients based on coil availability and the size of the individual (Table 2). The four RF coils used in this study were: 1) a flexible wrap, circularly polarized, transmit/receive coil (IGC-Medical Advances, Milwaukee, WI, USA; 30-cm by 110-cm); 2) a multichannel array receive and rigid, linearly polarized transmit/coil (Rapid Biomedical, Rimpar, Germany; anterior and posterior arrays each measuring 22-cm by 40-cm and containing 16 coil elements); 3) a rigid, linearly polarized, transmit/receive RF coil (Rapid Biomedical, Rimpar, Germany, 50-cm length with an oval cross-section measuring 34-cm by 44-cm); and 4) a purpose-built, infant-sized birdcage RF coil (19-cm inner diameter and 18-cm length) (Fig. 1).

During HHe administration, contiguous coronal 2D interleaved-spiral helium-3 images covering the whole lung were acquired sequentially. The acquisition parameters provided excess coverage in both the spatial and temporal domains to account for patient motion and variability in the timing of the HHe inhalation. Because we could not predict when the child would inhale a sufficient volume of HHe, we acquired at least five full sets of coronal slices repeatedly with no time gap between them. No attempt was made to control the lung inflation level during imaging. A field of view ≤40 cm ensured that the child would be within the field of view even if he or she moved during acquisition. Further, to ensure the entire anterior-to-posterior lung volume was within the imaging volume, the number of slices acquired per whole-lung imaging set more than covered the patient's chest size and varied by individual (Table 2). During the course of this project, the spiral sequence parameters were modified to optimize imaging of young children, and the parameters for each individual are given in Table 2. The image reconstruction included semiautomatic correction for magnetic field inhomogeneity and concomitant gradients [15]. The pulse sequence was started just before gas administration. The total acquisition time varied slightly depending upon the acquisition parameters but in all individuals was <15 s. Of note, the total acquisition time is less important in this application than the acquisition time per slice, which ranged from 0.12 to 0.19 s (Table 2). A very short acquisition time per slice enabled the acquisition of nearly motion-free images in a moving child.

The gas administration technique was tailored to each individual child's ability to cooperate. The 3-year-old patients voluntarily lay within the RF coil and, with coaching, were able to inhale the non-diluted

Table 2
Helium MRI acquisition parameters and image SNR

Patient #	RF coil	TR/TE (ms)	Flip angle (degrees)	Voxel volume (mm)	Spiral interleaves[a]	Acquisition time per slice (s)	Single series acquisition time	Central slice SNR
1	Wrap	8.1/0.9	20	3.3 × 3.3 × 10	13 + 2	0.12	1.46 s for 12 slices	61
2	Wrap	8.1/0.9	20	3.3 × 3.3 × 10	13 + 2	0.12	1.46 s for 12 slices	40
3	Array	8.69/0.9	20	1.8 × 1.8 × 10	20 + 2	0.19	2.87 s for 15 slices	20
4	Rigid	8.1/0.9	20	3.3 × 3.3 × 10	13 + 2	0.12	2.19 s for 18 slices	71
5	Wrap	8.67/0.9	20	2.0 × 2.0 × 10	20 + 2	0.19	2.29 s for 12 slices	26
6	Rigid	8.67/0.9	20	2.0 × 2.0 × 10	20 + 2	0.19	2.86 s for 15 slices	33
7	Purpose-built	9.0/0.98	20	2.2 × 2.2 × 10	15 + 2	0.15	2.91 s for 19 slices	47

MRI = magnetic resonance imaging; RF = radio-frequency; SNR = signal-to-noise ratio; TR/TE = Repetition Time/Echo Time.
[a] Values are stated as X + 2. X denotes the number of spiral interleaves used to acquire data for one image. 2 denotes the number of spiral interleaves used to create a field map for each image for off-resonance correction during image reconstruction.

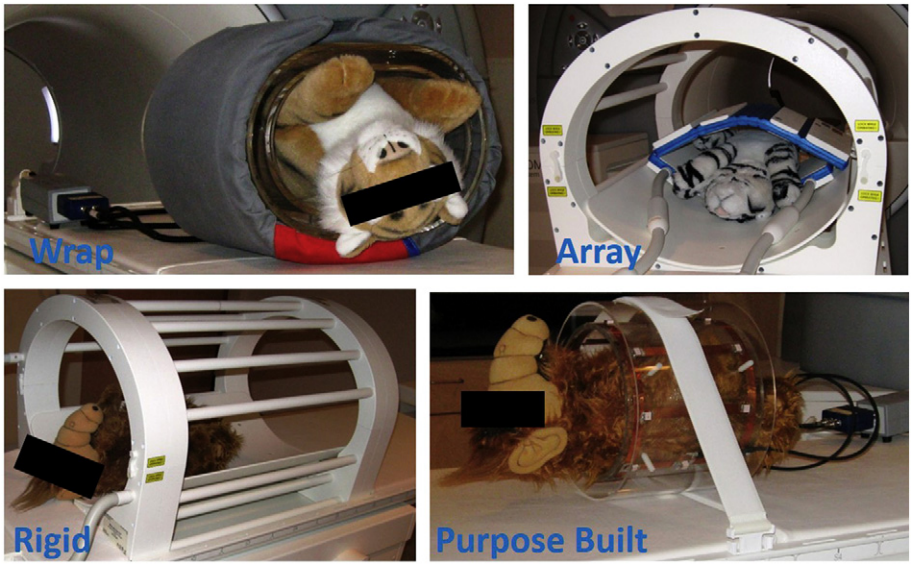

Fig. 1. The four RF coils used in this study.

HHe gas from a small plastic straw attached to the bag (Fig. 2). When the patient inhaled the HHe from the bag, the bag deflated. These two individuals were, however, unable to hold their breath and breathed in and out through the straw into the bag, re-inflating and deflating it, throughout the MRI acquisition process.

For patients younger than 2 years of age, we filled a 500-mL plastic bag (Jensen Inert Products, Coral Springs, Fla) with non-diluted HHe gas and attached it to the medication port of a pediatric-sized bag valve mask (Ambu bag) via a small straw (Fig. 2). Immediately before imaging, the non-sedated infant was placed supine within the RF coil. The spiral acquisition was started and a pediatric facemask, attached to the bag valve mask, was placed over the infant's nose and mouth. A physician administered the HHe by squeezing the HHe bag, which deflated it. This introduced the HHe into the face mask where it mixed with the room air in the face mask. The physician then gently squeezed the Ambu bag a few times, which administered this mixture to the subject. The infant was then removed from the scanner.

Signal-to-noise ratio (SNR) measurements for each patient were obtained by calculating the average of signal intensities from two regions of interest (one in the middle of the right lung and one in the middle of the left lung) in a central image slice section (slice containing the trachea) from the series with the highest signal in the lungs. The average signal intensity was then divided by the standard deviation of noise determined from a region outside the lung in the image background of the same slice. A board certified pediatric radiologist reader assessed whether diagnostic quality images were obtained.

3. Results

Five infants cried during the procedure but otherwise tolerated the imaging well (smiling once removed from scanner). One 3-year-old, who played while in the scanner, apparently enjoyed the experience; the other 3-year-old appeared frightened but cooperated with instructions.

We successfully acquired HHe MRI scans from all seven patients, all of which were of diagnostic quality. The SNR in central slices ranged from 20 to 71, with a mean value of 43, a value that was quite high given the large size of the RF coil used for six of the seven patients (Table 2). The HHe signal was homogeneously distributed throughout the lungs of the healthy 13-month-old infant, indicating good ventilation. Among the babies with CF, a tiny potential ventilation defect was present in the images from the 17-month-old (Fig. 3), whereas distinct small defects were seen in the images from both the 10-month-old and 14-month-old (Fig. 4). Focal ventilation defects were present in the images from both 3-year-olds with asthma (Figs. 5 and 6), with evidence of large defects in one of these children (Fig. 6). The images obtained

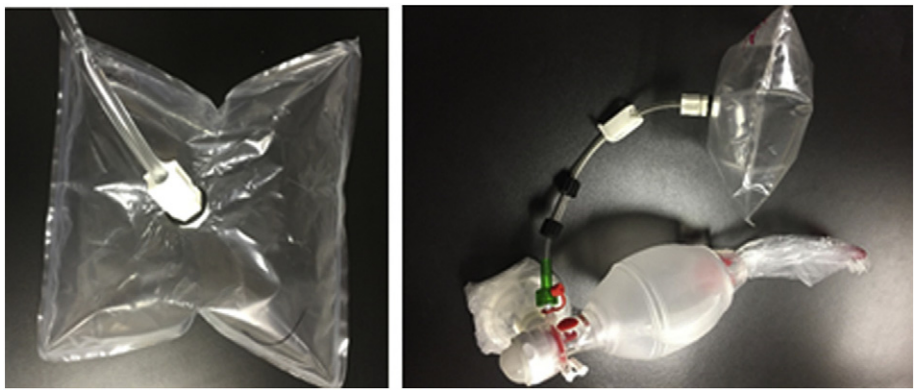

Fig. 2. The dosing bag used for administration of the HHe to older children (A) and dosing bag attached to the bag valve mask used for administration of the HHe to infants (B).

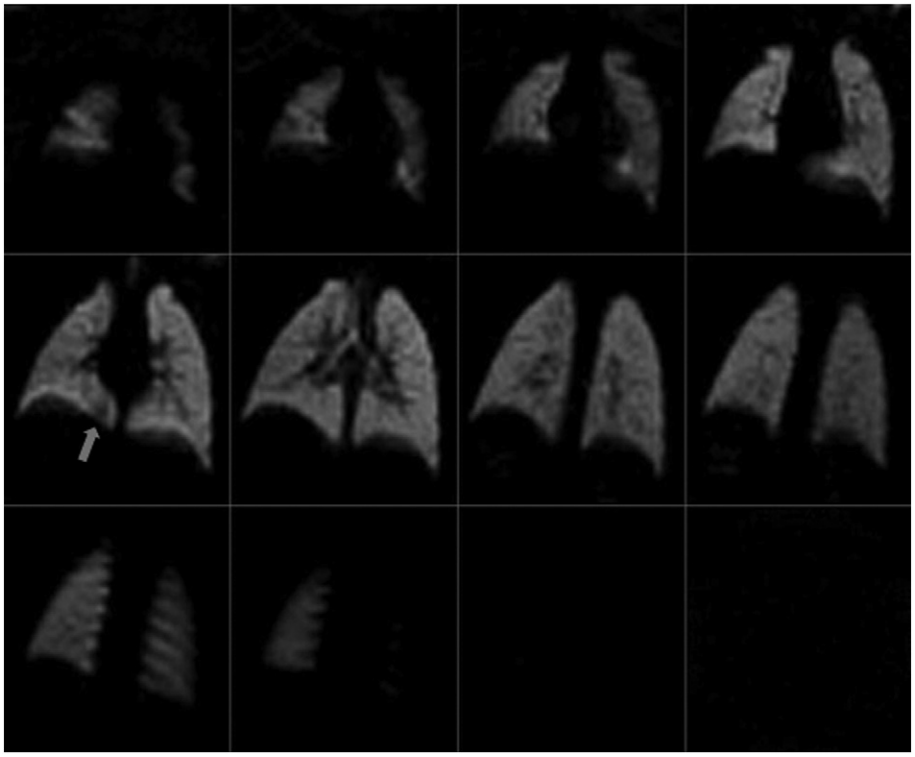

Fig. 3. HHe coronal MR images of a 17-month-old non-sedated, unrestrained infant with CF. Homogeneous ventilation is seen throughout the lungs. A possible tiny ventilation defect is seen at the right base (arrow). No noticeable motion artifacts are noticeable.

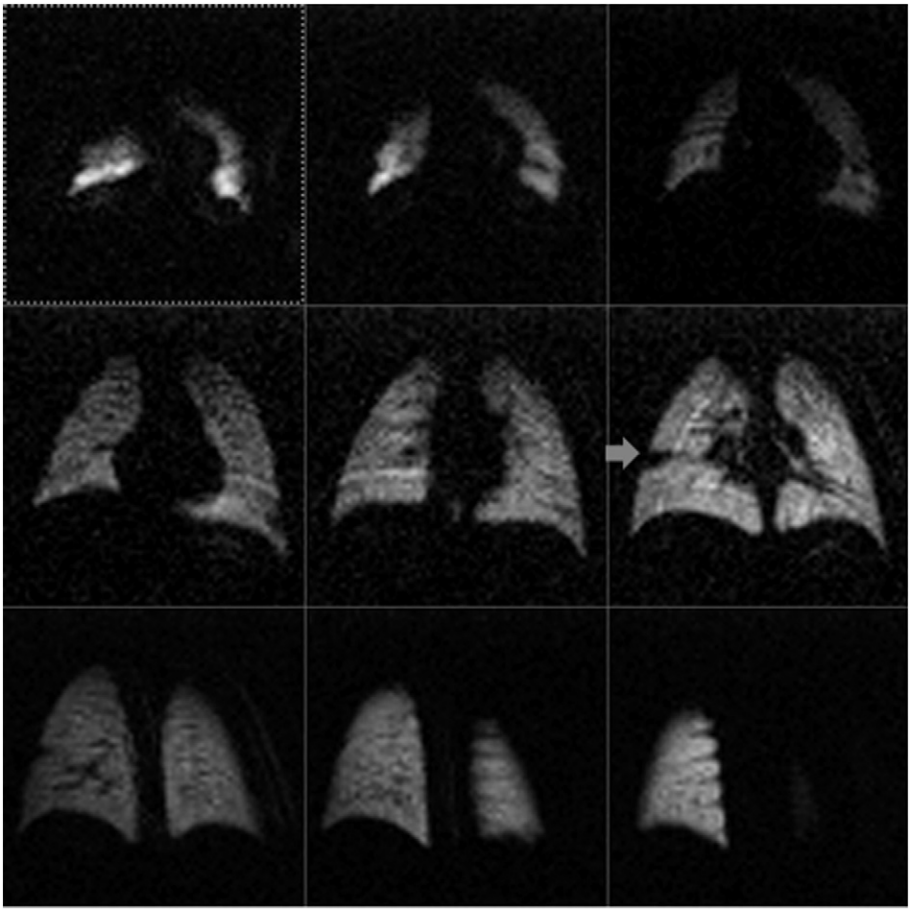

Fig. 4. HHe coronal MR images of a 14-month-old non-sedated, unrestrained infant with CF. A small focal ventilation defect is seen in the right lung (arrow). Homogeneous ventilation is seen throughout the remainder of the lungs.

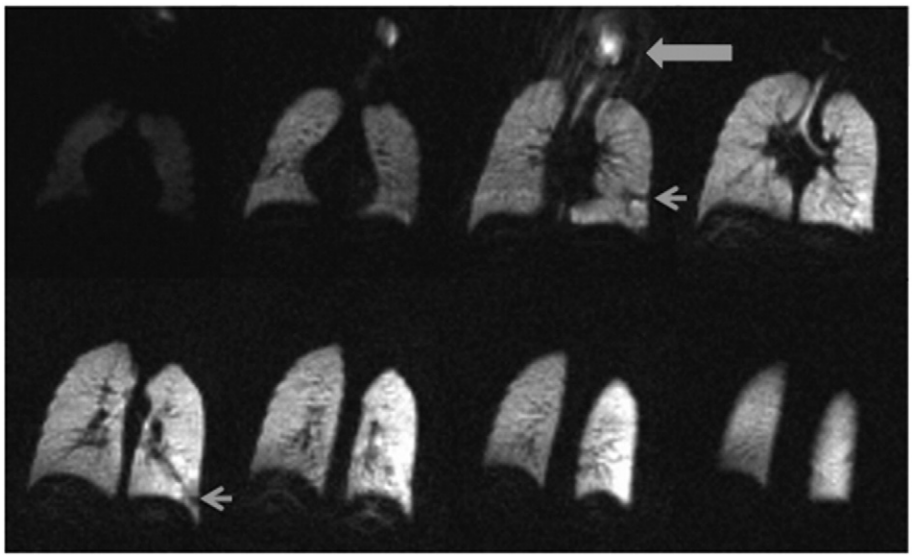

Fig. 5. HHe coronal MR images of a 3-year-old non-sedated, unrestrained child with asthma. Small focal ventilation defects are present in the left lower lobe (arrows). Motion artifacts are seen adjacent (inferior) to the diaphragm and surrounding the HHe in the pharynx and hypopharynx (long arrow).

from the premature infant also demonstrated a focal ventilation defect (Fig. 7). Although all patients were breathing during the acquisitions, appreciable motion artifacts were noticeable only in images from one asthmatic child (Fig. 5).

The two 3-year-old asthmatic patients rebreathed HHe and air during multiple sequential acquisitions. In one of these patients, ventilation defects present on the first acquisition filled in on successive acquisitions, while others did not (Fig. 6).

4. Discussion

This proof-of-concept study demonstrates the feasibility of using HHe MRI to assess the lung air spaces in non-sedated infants and in children too young to cooperate with breathing instructions. Through a simple gas delivery system, non-sedated infants inhaled HHe sufficiently to provide adequate MR signals for imaging. We noted that the lungs of the healthy infant filled homogeneously with HHe, consistent with previous observations in healthy children and young adults [8,9]. The mean SNR in central slices was 43, a value that was high considering that an adult-sized helium-3 RF coil was used for six of the seven patients and that the amount of HHe inhaled by each individual likely varied. The infant-sized RF coil, used for the premature infant, should generally increase SNR by a factor of 2–4; this increased SNR could then be leveraged for increased spatial resolution when needed. Although the infants were in motion during acquisition, minimal motion and breathing artifacts were observed, supporting the utility of short acquisition times enabled by the spiral trajectory pulse sequences used.

We also found ventilation defects in the lungs of an otherwise healthy 10-month-old and a 14-month-old infant with CF, confirming the suspicion that obstructive pulmonary pathology is manifest even at a young age [16,17]. Studies of older children and adults with CF found focal ventilation defects when imaged using HHe MRI, despite normal spirometry [9,18–22]. Prior studies with CT have also found focal areas of trapped air in the lungs of infants with CF [17]. The ventilation defects seen in the HHe MRI images from patients with CF may correspond to areas where air is trapped, although this could not be confirmed in this study because CT images were not obtained [16]. In any case, our results lend additional support for the hypothesis that changes in the lungs of young children with CF occur before they can be detected through clinical measures of lung function.

Likewise, HHe MRI scans obtained in this study from the premature infant and from the two 3-year-old children with asthma indicated several ventilation defects, consistent with HHe MRI results from older children and adults with asthma [7,8,23]. In adults, a moderate correlation between disease severity and the number of HHe MRI ventilation defects has been demonstrated [24]. Further, the regional location of ventilation defects within the lungs of adult asthmatics has been shown to persist or recur over time and with provocation such as exercise or administration of methacholine [11,12]. Whether ventilation defects in young children are similarly fixed or variable in location is an interesting question that could be further investigated using HHe MRI.

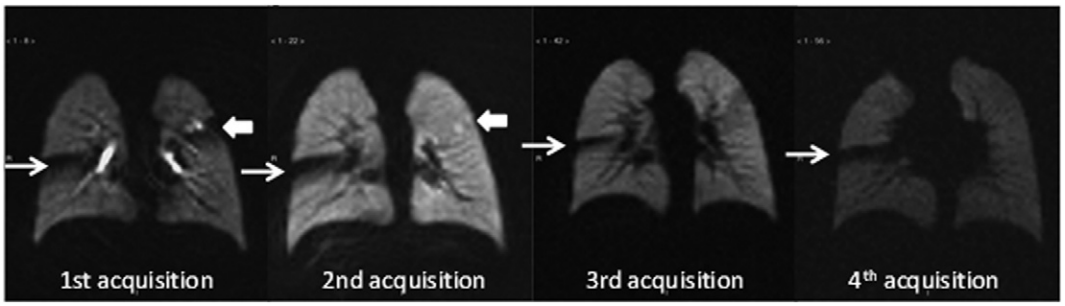

Fig. 6. Coronal HHe MRI slice sections obtained at the same anatomic level in a non-sedated, unrestrained 3-year-old child with asthma breathing gas from a bag containing HHe. On the first acquisition, ventilation defects are present in the right lower lobe (thin arrows) and the left upper lobe (thick arrows). With successive breaths, the left upper lobe defect fills in (thick arrows), but the right lower lobe defect does not (thin arrows).

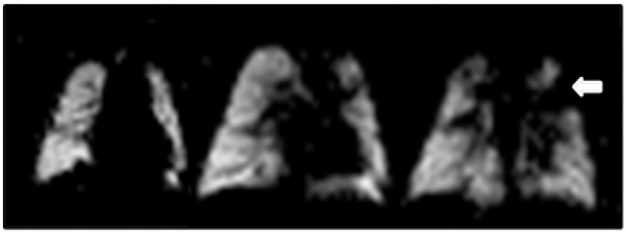

Fig. 7. HHe coronal MR images of a 2-month-old premature infant. A focal ventilation defect is present in the left upper lobe (arrow). Other smaller defects are also present. For this patient, HHe gas was administered via the medication port on a pediatric bag valve mask.

Because HHe is biologically inert and because the risks associated with MRI scanning are considered minimal, children may safely undergo repeated HHe MRI scans [25]. Thus HHe MRI may also be suitable for longitudinal studies to evaluate changes in lung function and structure throughout development.

While the quality of images obtained in these young children was good, it could be improved by development of pediatric-sized HHe MRI RF coils. Further, a multichannel receive coil could decrease acquisition time by enabling parallel imaging. Interestingly, the loss of SNR in conventional-proton MRI associated with the decreased time required for parallel imaging does not occur with HHe MRI, supporting the utility of HHe MRI for use in parallel imaging [26].

We acknowledge that the small sample size is a limitation of this study. Further corroborative studies with infants and young children should solidify evidence in favor of HHe MRI as a means of obtaining high-quality images from these patients.

5. Conclusion

This pilot study demonstrated that HHe MR imaging is feasible and potentially useful for assessing lung disease in non-sedated infants and young children.

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