Published in final edited form as:

J Thorac Imaging. 2016 September ; 31(5): 285–295. doi:10.1097/RTI.0000000000000218.

Hyperpolarized Gas MR Imaging in Children and Young Adults

Lucia Flors, MD, PhD^{1,2}, John P. Mugler III, PhD¹, Eduard E. de Lange, MD¹, G. Wilson Miller, PhD¹, Jaime F. Mata, PhD¹, Nick Tustison, PhD¹, Iulian C Ruset, PhD^{3,4}, F. William Hersman, PhD^{4,3}, and Talissa A. Altes, MD²

¹Department of Radiology, University of Virginia School of Medicine, Charlottesville, Virginia

²Department of Radiology, University of Missouri School of Medicine, Columbia, Missouri

³Xemed LLC, Durham, NH, USA

⁴Department of Physics, University of New Hampshire, Durham, New Hampshire

Summary

The assessment of early pulmonary disease and its severity can be difficult in children as they often cannot perform procedures such as spirometry. Computed tomography provides detailed structural images of the pulmonary parenchyma but its major drawback is that the patient is exposed to ionizing radiation. In this context, MRI is a promising technique for the evaluation of pediatric lung disease, especially when serial imaging is needed. Traditionally, MRI played a small role in evaluating the pulmonary parenchyma. Because of its low proton density, the lungs display low signal intensity on conventional proton-based MRI. Hyperpolarized (HP) gases are inhaled contrast agents with an excellent safety profile and provide high signal within the lung allowing for high temporal and spatial resolution imaging of the lung airspaces. Besides morphological information, HP MR images also offer valuable information about pulmonary physiology. HP gas MRI has already made new contributions to the understanding of pediatric lung diseases and may become a clinically useful tool. In this article, we discuss the HP gas MRI technique, special considerations that need to be considered when imaging children, and the role of MRI in two of the most common chronic pediatric lung diseases, asthma and cystic fibrosis. We also will discuss how HP gas MRI may be used to evaluate normal lung growth and development, and the alterations occurring in chronic lung disease of prematurity and in patients with a congenital diaphragmatic hernia.

Keywords

Hyperpolarized Gas MRI; Cystic fibrosis; Asthma

Introduction

Pulmonary function tests (PFTs) are the gold standard for the monitoring of diffuse lung disease in children aged ≥ 6 years; in younger children PFTs can usually not be obtained because they cannot perform the required forced breathing maneuvers. In a few clinical centers passive PFTs is performed in sedated children but the requirement for sedation limits the utility of this technique. Furthermore, since PFTs provide only global information of the lung function, they are relatively insensitive to detecting early lung disease. The ongoing development of new therapies to modify the course of diffuse pediatric lung diseases, such as cystic fibrosis (CF), highlights the need for sensitive outcome measures that can make global and regional assessments of disease for clinical care and interventional trials.

Modern multidetector computed tomography (CT) scanners permit submillimeter imaging of the entire chest in a single breath hold. The excellent spatial resolution images provided by CT makes this modality ideal for evaluating the pulmonary parenchyma. CT provides regional information and is more sensitive than PFTs and chest x-ray to detect early lung parenchymal abnormalities. The major disadvantage of CT is that it involves ionizing radiation. In recent years, there has been a decline in CT-related radiation exposure thanks to dose-saving strategies and improvements in scanner technology. Despite these efforts, radiation remains a very important concern in the pediatric population, because children are considerably more sensitive to the carcinogenic effects of ionizing radiation than adults and have a longer life expectancy in which to express risk (1).

In this context, the lack of ionizing radiation in Magnetic Resonance Imaging (MRI) makes the technique ideal for use in the pediatric population, especially when repeated or serial studies are required. On global (whole-lung) and regional scales, MRI can also provide functional and morphological evaluations of the pulmonary parenchyma. Traditionally, proton MR has had a small role in evaluating lung parenchyma. Because of its low proton density, the normal pulmonary parenchyma displays with low signal intensity on MR images. In addition, the signal is further degraded by the susceptibility effects induced by its many air-tissue interfaces and by cardiac and respiratory movement. MR imaging in young children is especially challenging because of motion and their inability to follow breath hold instructions. Hyperpolarized (HP) gases are inhaled contrast agents that permit imaging of the lung airspaces. HP gas MRI has become an important research tool not only for morphological and functional evaluation of normal pulmonary physiology, but also for regional quantification of pathologic changes occurring in diffuse lung diseases (2–7).

In this article, we discuss the HP gas MRI technique and special considerations that need to be taken into account when imaging the pediatric population. We review the role in the technique in two of the most common chronic pediatric lung diseases, asthma and cystic fibrosis. Further, we will discuss its role in the evaluation of normal lung growth, and in assessing the development of the structural alterations that occur in children with chronic lung disease of prematurity and in patients with congenital diaphragmatic hernia.

HP Gas MRI Technique

HP gases are prepared using a laser-based system called a polarizer, separate from the MR scanner, wherein the nuclear spins of the gas atoms are brought into preferential alignment with a weak magnetic field. This achieves a signal strength many times higher than that which would be obtained if the subject were to inhale the gas without this preparation. After polarization, the gas is transferred to a plastic bag, transported to the MR scanner, and inhaled by the subject through a small plastic tube or using a gas-administration apparatus.

HP Gases: Helium-3 and Xenon-129

Helium-3 and xenon-129 are two non-radioactive isotopes of noble gases that can be hyperpolarized and have different physiologic properties (Table 1). They are classified as investigational drugs by the US Food and Drug Administration (FDA). Owing to its very low solubility in blood and tissue, helium is relatively biologically inert, and remains almost entirely within the airspaces when inhaled. Conversely, xenon is weakly soluble in lipids and in blood and tissue. This weak solubility makes xenon biologically active and gives it anesthetic properties at high doses. For imaging, the solubility of xenon in tissues allows detection of the regional gas transfer between the alveoli and the tissue in the lung (8,9). Although most research in humans has used HP helium-3, a reduction in the world supply of helium-3 and consequent increases in price turned attention to HP xenon-129. Compared to helium-3, xenon-129 provides intrinsically lower signal due to its smaller magnetic moment. Recent advances in gas-polarization technology for xenon-129 have enabled studies that found ventilation, diffusion, and partial pressure of oxygen imaging with HP xenon-129 is comparable to HP helium-3 (10–13)(Fig.1).

MR Sequences

1. Ventilation Imaging—Images of lung ventilation are obtained using spin density imaging during a breath hold following the inhalation of HP gas. When the HP gas is inhaled the airspaces are filled, and when subsequently MR images are obtained, the changes in the regional ventilation resulting from airflow obstruction are depicted. In healthy subjects the gas distributes uniformly throughout the airspaces producing uniformly high signal throughout the pulmonary parenchyma. When there is disease that leads to reduction of local airflow, the airspaces distal to that area are poorly ventilated and appear dark on ventilation images, resulting in so-called ventilation defects (Fig.2). This is conceptually similar to nuclear medicine lung ventilation imaging, albeit with better temporal and spatial resolution. Modern computational processing methods permit automated quantification of ventilation defects on HP gas MRI (Fig. 3) (14,15).

Dynamic ventilation MRI is performed using ultrafast spin density imaging while the subject inhales or exhales the gas. The technique is used to show the distribution of the gas in the lung parenchyma over time with sub-second time resolution.

2. Diffusion Imaging—Proton-based diffusion-weighted (DW) MR imaging studies the random Brownian motion of water molecules within a voxel of tissue. A similar principle can be applied to HP gas MR to assess the motion of HP gas atoms within the alveolar

spaces and the degree of restriction by alveolar walls as measured by an apparent diffusion coefficient (ADC) (16). The ADC provides a noninvasive quantitative measure that correlates with alveolar dimensions (17–22). Precise correlations between the global and regional ADC measured by HP gas MRI and alveolar size as measured histologically have been reported (17,23–25).

DW HP gas MRI is one of the most extensively developed HP-gas methods for studying emphysema (21,24,26–28). Enlarged airspaces have been detected using DW HP helium-3 and xenon-129 MR imaging in animal models and humans with emphysema (21–24,26,27,29). The technique has also applications in pediatric lung diseases as we will further discuss below.

3. Oxygen Sensitive Imaging—The rate of loss of the polarization of the gas is strongly influenced by the local environment. In the presence of oxygen, due to its paramagnetic effect, the longitudinal relaxation of HP gas is accelerated. By assessing the rate of decay of polarization (measuring the T1) of HP helium-3 or xenon-129 within the lung, it is possible to obtain an indirect measurement of the alveolar partial pressure of oxygen (30,31).

4. Alveolar-Capillary Gas Transfer—Upon inhalation, HP xenon-129 follows the functional pathway of gas exchange in the lung by diffusing from the alveolar airspaces into the alveolar septa (blood and tissue) (32). Since the spectral peaks associated with xenon-129 magnetization in the different pulmonary compartments are at different chemically shifted frequencies, it is possible to monitor the kinetics of xenon-129 magnetization diffusion from one compartment to another and to distinguish the xenon gas- and dissolved-phases.

Several image acquisition methods have been developed to obtain information of gas exchange and alveolar-capillary gas uptake. In chemical shift saturation recovery (CSSR), a frequency-selective radio frequency (RF) pulse is initially employed to destroy the xenon-129 magnetization in the dissolved phase. Recovery of the dissolved phase xenon-129 magnetization, by diffusion of HP xenon-129 from the alveolar gas space to septal tissue, is then observed (33). Compared to CSSR, which directly measures the dissolved-phase xenon magnetization, the xenon polarization transfer contrast (XTC) method measures the diffusion into the dissolved phase indirectly by looking at the attenuation in the gas phase signal after multiple opportunities for interphase diffusion (8,33). Parenchymal tissue to alveolar-volume ratio, surface-to-volume ratio and blood–gas barrier thickness can be determined (32).

Since little work has been done with oxygen sensitive and alveolar gas transfer imaging in children, we will not further discussed it and we will focus on the applications of ventilation and diffusion imaging in the pediatric population.

Considerations for MR Imaging in Infants and Young Children

Children are difficult to evaluate with MR imaging because they often cannot remain motionless or comply with breathing instructions. Clear explanation and coaching on breathing maneuvers are essential. In infants, it is necessary to restrain motion similarly to

other clinical imaging procedures. Parents are also usually asked not to feed the infant for 2 hours before the MR appointment. Children may be fed immediately prior to being placed in the MR scanner, and parents are encouraged to be in the scanner room with their child during the MR scanning. If tolerated, skull-caps with noise attenuating material over the ears may prevent the child from being startled by the noise of brief MRI acquisitions. Helium-3 gas delivery methods have been developed based on clinical methods for delivering oxygen and inhaled medications to infants and young children. Stuffed animals and other toys are usually used to distract infants during the short MRI acquisition times.

In adults, HP gas MR imaging of the entire lung volume requires a 4- to 20-second breath-hold. Because children have smaller lungs, the duration of the breath-hold is usually shorter, but still beyond the ability of infants and young children. The acquisition time can be reduced by a factor of ten with spiral-sampling-based strategies, thus making possible imaging of free breathing infants and young children (Fig.4). The helium-3 MR acquisition time for a set of images covering the whole lung is less than 1 second, and the total time the subject is in the MR scanner less than 10 minutes. The acquisition time is comparable to or shorter than that of a CT scan. The extremely short acquisition time allows helium-3 MRI in non-sedated infants. Helium-3 MRI has been successfully performed in children as young as 10 months. Specially designed infant-sized helium-3 MRI RF coils must be used to obtain high spatial resolution imaging in small children (Fig.5). Since the gas is polarized outside the scanner, it is possible to image HP gases with a very low magnetic field strength scanner that could easily be located in an NICU.

The primary safety advantage of HP gas MRI is the absence of ionizing radiation, and helium-3 itself is not radioactive. Its chemical properties are not altered by polarization such that it retains low solubility in blood or tissue and is thus biologically inert. Inhaled helium-3 remains within the airspaces and is exhaled in subsequent breaths. To date, HP gas MRI has been well tolerated and used safely (34,35). In a review of the safety data of HP helium-3 MRI performed at our institution during three consecutive years in 313 subjects, we found mild respiratory adverse events in 7% of the patients with spontaneous resolution in all cases (36). Children were not more likely to have an adverse event than adults, and patients with lung disease were not more likely to have an adverse event than healthy volunteers. Thus inhaled helium-3 has the outstanding safety profile required for use in infants.

Although there are concerns about the anesthetic properties of xenon-129 and experience with this gas is more limited, its safety and tolerability have also been recently demonstrated in adult healthy subjects and patients with pulmonary disease (11,37). In our institution, we have safely performed HP xenon-129 MR imaging in healthy children and children with pulmonary diseases.

Use of HP Gas MRI in Children

Asthma

Asthma is the most common chronic disorder of childhood. It is a chronic inflammatory disorder of the lung that predominantly involves the small and medium-sized airways. Symptoms are usually associated with variable airway obstruction and impaired ventilation

caused by such changes as airway hyper-responsiveness and bronchoconstriction, airway wall edema, mucus hypersecretion, and airway remodeling with smooth muscle hypertrophy and subepithelial fibrosis.

Spirometry measurements of airflow obstruction tend to overestimate large airway constriction and underestimate small airways disease and, moreover, cannot identify specific airways responsible for regional airflow obstruction (38). Current imaging techniques are of limited value in asthma. CT provides detailed images of the bronchial walls and air trapping, but it is not clear whether these indirect assessments of aeration correlate with asthma severity. CT provides only indirect functional information about lung ventilation. HP gas MRI can evaluate functional alterations of airflow within the lung caused by structural changes of the airways. Because no radiation is involved, serial imaging permits the safe assessment of temporal changes within the lungs of asthmatics.

Most studies with HP gas MRI have been performed on adult asthmatic patients. These studies have found ventilation defects in asthmatics, even when asymptomatic (39). There is correlation between the number and size of ventilation defects detected by HP helium-3 MRI and disease severity as measured by spirometry or the frequency of symptoms (4).

Recently, lung defect volume percentage was found to correlate with several clinical features of asthma such as severity, symptom score, medication requirement, airway physiology, and atopic markers in children with mild and severe asthma (40). Another recent study (41) using helium-3 MR in a subset of 44 children participating in the Childhood Origins of Asthma (COAST) study (42) found that children with asthma had more and larger ventilation defects and a greater degree of restricted gas diffusion (lower average root-mean-square diffusion length) than non-asthmatic children in this cohort, without correlation between the two measures. The authors hypothesized that the dimensions of the small airways and alveolar spaces are smaller in children with asthma. Results in adults contradict those in children (43) and suggest that there may be age-related or duration of disease related differences in structural features of asthma. Thus, further investigation is needed.

Ventilation defects can be induced medically with methacholine (an inhaled direct bronchoconstrictor) (44,45) and with exercise, and can be reversed by albuterol (an inhaled bronchodilator) (Fig.6). The percent increase in defects from premethacholine to postmethacholine administration was much greater than the percent decrease in spirometric values (45)

HP gas MRI has given new insight in the of regional airflow variability within the lungs of patients with asthma in that ventilation can defects persist or recur in the same location with time (45) regardless of disease severity or treatment (46) (Fig.7). This suggests that the severity of the disease within the lung varies regionally. The use of HP gas MRI may have important implications for regional treatments such as local aerosolized anti-inflammatory agents or bronchial thermoplasty, where the airway wall smooth muscle is RF ablated during bronchoscopy. In fact, in a study of 10 patients with severe asthma who received treatment with bronchial thermoplasty (47), quantification of regional ventilation changes indicated

that ventilation defects decrease as a function of time after treatment. In particular, ventilation defects first increased early post-treatment but then decreased with time.

Dynamic ventilation images permit analysis of the kinetics of air trapping in asthmatic patients with good concordance between the areas of air trapping depicted by HP gas MRI and CT (48).

Cystic Fibrosis

Cystic fibrosis (CF), is an autosomal recessive disorder caused by mutations on the CF transmembrane conductance regulator (CFTR) gene. Impaired function of the CFTR protein causes abnormal chloride transport and increased viscosity of exocrine secretions in the pulmonary airways and GI tract. Abnormal airways in the lung are prone to infection and exhibit a marked and prolonged inflammatory response. The cycle of infection and inflammation along with obstruction due to abnormal mucous produces progressive structural damage causing bronchiectasis and fibrosis. Progressive lung disease remains the primary cause of death in CF (49) and imaging monitoring is usually necessary. With an estimated incidence of one in 2500 live births (50), CF is the most common fatal genetic disease in Caucasians.

Proton-based or conventional MRI may be an imaging alternative to study structural abnormalities in patients with CF. Spatial resolution of MRI is lower than that of CT, however MRI can detect bronchial wall thickening, mucus plugging, bronchiectasis, air-fluid level, and airspace consolidations (51,52). New ultrashort TE techniques hold promise for greatly improving image quality in MRI of the pulmonary parenchyma (53). A detailed description of proton-based MR in CF patients is beyond the scope of this article.

Functional information can be obtained by using HP gases. Studies investigating HP gas in CF patients were mostly performed using ventilation imaging. HP helium-3 MR uncovered ventilation defects in young adults with CF (6), and children with CF (54). CF patients had more defects than age-matched healthy subjects (50). Defects were also present in CF patients with normal pulmonary function tests (50,55) (Fig.8).

HP gas ventilation MRI correlates strongly with structural CT abnormalities (Bhalla score) (56) and spirometry (50,56), but correlation between the MRI findings and those of chest radiograph (Swachman and Chrispin-Norman scores) is poor (54). Conversely, the correlation between HP gas MRI and spirometry is stronger than that of CT (56). The abnormalities depicted with HP helium-3 MRI are more extensive than those seen with conventional proton MRI (6).

Ventilation defects in CF patients change with treatment including bronchodilator (Fig.9) and mechanical airway clearance (50,57,55). HP helium-3 MRI findings are reproducible over time (58). Hence, HP gas MRI can be a sensitive test for depicting early disease and has the potential to become a biomarker of pulmonary CF.

The life expectancy of CF patients increased substantially from 14 to 40 years during 1969 to 2013 (49) and is expected to continue to improve. Many different mutations have been identified in the CFTR gene, prompting development of drugs specific to a mutated gene

product. In this context, sensitive outcome measurements are needed. Ivacaftor (Kalydeco®, Vertex Pharmaceuticals) is the first of these drugs and targets patients with the G551D (glycine to aspartate change in nucleotide 1784 in exon 11) mutation. The drug is a CFTR potentiator since it is responsible for improved chloride transport via the G551D-CFTR protein (59). Ivacaftor is approved for the treatment of CF in patients aged ≥ 6 years with G551D mutation of CFTR. HP gas MRI recently detected changes in ventilation in CF patients after Ivacaftor therapy (60). Thirty days of treatment with Ivacaftor led to a substantial reduction in total ventilation defects and total defect volume as assessed by HP gas MRI.

Lung growth

Knowledge of human lung development is based upon a few autopsy studies with a small number of subjects (61–63). Alveolar development starts 25 to 40 weeks post-conception and continues during the first few years of life (64,65). Approximately 20 million alveoli are thought to be present at birth and progressively increase to 200 million by the age of three years (61–63). Beyond approximately 8 years of age, most lung growth has been thought to be secondary to enlargement of preexisting alveoli (66,67). Interestingly, recent data in mammals (68–70) from studies using modern morphometric techniques suggest that alveolarization continues throughout lung growth. Since DW HP helium-3 MRI has demonstrated that the ADC provides information about the alveolar size and morphology (20–22) that correlates with histology (17,23–25), HP gas MRI may be able to non-invasively evaluate normal lung growth and development.

In a group of 29 normal subjects, DW HP helium-3 MRI demonstrated an increase in ADC with increasing subject age, with a 55% increase in mean ADC from the youngest (4 years of age) to the oldest (30 years of age) subject. This ADC pattern likely reflects increasing alveolar size as the lung grows during childhood (71). Another study using DW HP helium-3 MRI in 109 subjects with an age 7–21 years (median 12.8 yr) suggested that alveolarization also continues during childhood and adolescence (72). The alveolar dimensions increased with age and lung size, at a rate much less than would be expected if lung growth occurred only by expansion of the existing airspaces. The explanation for these results was that the lung grows largely by neoalveolarization through childhood and adolescence.

Chronic lung disease of prematurity

As noted above, formation of alveoli occurs late in gestation and during the first years of life (64,65). At 24–26 weeks' gestation infant lungs are in the canalicular phase of development, a time when alveolar and distal vascular development commences (64). Chronic lung disease of prematurity, also known bronchopulmonary dysplasia (BPD), is thought to be at least partially due to an alteration in normal lung development. When an infant is born prematurely, its lungs must act as a gas exchange organ despite being at a time when alveoli are still forming (65). At least in some premature infants this appears to result in alveoli that are abnormally large and fewer in number (64,65,73,74). Surfactant deficiency, perinatal insults such infection and damage from the ventilation supportive care, and alterations in lung development interact to impair lung function (65). Unfortunately, morphological alterations of lung structure in children with BPD are not well characterized, since lung

tissue from living children is not readily available and lung autopsy specimens have rarely been studied (75). Alveolar size and data on normal lung growth and development may be gleaned from DW HP gas MRI. Alterations in the normal lung growth and development caused by prematurity and childhood lung diseases may therefore be amenable to study with MR imaging.

A study of children with history of preterm birth and BPD and of corresponding normal children detected alterations of lung structure in children with BPD as shown by DW HP helium-3 MR (76). Elevated ADC values (Fig.10), suggestive of enlarged alveoli, occurred in children with a history of BPD who had the same lung volumes as age-matched healthy control children. Although limited, histological data support the observation that children with BPD have larger but fewer alveoli than healthy children. The elucidation of the disease process of BPD and its pulmonary consequences require more study for optimal treatment (65), and HP gas MRI may be a critical tool.

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a developmental defect of the diaphragm with associated pulmonary hypoplasia and abnormal pulmonary vasculature. A recent study used HP helium-3 DW MRI to evaluate 9 young adults with a history of repaired congenital diaphragmatic hernia (CDH) and noted higher ADC values for the ipsilateral lung than the contralateral lung in 8 of 9 subjects (Fig. 11) (77). Ventilation defects and smaller ventilation volume was also found in the ipsilateral lung in six patients. Enlarged alveolar dimension and decreased alveolar number in the ipsilateral lung support post-mortem findings of larger and fewer alveoli in both lungs with the ipsilateral side affected more than the contralateral in young children after repair of CDH (78,89), suggesting an arrest in normal alveolar development.

Current limitations and future directions

HP gas MRI has opened a new window into pulmonary imaging. It has demonstrated to be a valuable research tool that provides meaningful functional and morphological information of a full range of lung diseases providing a new insight in our understanding of their pathophysiology. Nonetheless, further technological development is still required to turn this promising imaging technique into an established clinical tool.

Most of the initial human research with HP gas MRI has been performed using helium-3. Xenon-129 could become widely used due ongoing advances in xenon polarization which permit higher polarization rates and recent contraction in helium-3 supply leading to increasing costs of the gas. The excellent safety and tolerability of xenon-129 has been proven in adult subjects (10).

Continuous research and development of novel therapies with the potential of cure or delay the progression of pediatric respiratory diseases make obvious the need for a non-invasive method to monitor the start and the progression of early lung damage in infants and young children as well as to closely track and quantify early changes after treatment to assess the effectiveness. The lack of ionizing radiation and the capability to perform free-breathing

imaging make HP Gas MRI the ideal imaging method for these purposes. HP gas MRI-based endpoints or scores have the potential to become surrogate markers of disease, ideally using quantitative segmentation methods but further validation is needed.

Conclusion

HP gas MRI has two main advantages over CT: lack of ionizing radiation and the ability to directly provide functional information of the lung. Its imaging capabilities have already uncovered new information about pediatric lung disease. HP gas MR found ventilation defects in patients with asthma and CF even when patients had normal PFTs. A good correlation exists between HP gas MRI findings, and structural CT abnormalities and spirometry, and HP gas MR has detected changes after treatment and persistence over time. The technique also demonstrated the heterogeneity of asthma which may have important implications for regional treatments. Early results in BPD and congenital diaphragmatic hernia suggest that HP DW MRI can detect abnormal alveolar development. For all these reasons, HP gas MRI can be a sensitive test for assessing early pulmonary disease and may become an excellent biomarker. Despite the current limited availability of the technique, if clinical applications for HP gas MR increase, regulatory and adoptive barriers will likely decline.

Acknowledgments

HP Gas MRI in Pediatric Respiratory Diseases

Funding for this work was provided by NIH (R01-HL66479, 1R43 HL117337-01, 1R43 HL108452-01A1), The Hartwell Foundation, and Vertex Pharmaceuticals Incorporated. General research support was provided by Siemens Healthcare.

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Fig. 1. Ventilation imaging: comparison of Helium-3 and Xenon-129 imaging

Twenty-eight year-old male with CF (FEV1 57%). Coronal Helium-3 (a) and Xenon-129 (b) MR ventilation images performed on the same day show similar appearing upper lobe predominant ventilation defects (arrows).

Fig. 2. Helium-3 MR ventilation images

Coronal images show homogenous distribution of signal throughout the lung parenchyma in a subject without lung disease (a) and multiple ventilation defects in a patient with cystic fibrosis (b).

Fig. 3. Automatic segmentation of ventilated lung volume

HP helium-3 ventilation MRI (left) in a pediatric patient shows multiple bilateral ventilation defects (arrows). Segmentation using an automatic ventilation-based segmentation algorithm (14) (b) allows precise quantification of the ventilated lung volume. The color legend in b is as follows: red-ventilation defect, green-hypoventilation, blue/yellow-normal ventilation.

Fig. 4. Free-breathing ventilation helium-3 MRI

MR images obtained during free breathing show homogeneous distribution of signal throughout the lung parenchyma in a 4-year-old healthy child (a) and several ventilation defects in a 5-year-old child with cystic fibrosis (arrows) (b).

Fig. 5.
Infant sized coil tuned to the RF frequency to the HP gas enables fast, high-resolution head and smaller field-of-view imaging.

Fig. 6. Ventilation changes after inhalation of albuterol in 10 year old male with asthma
Coronal helium-3 ventilation images at baseline (a) (FEV₁ 53%) show extensive bilateral ventilation defects which decreased after treatment with albuterol (b) (FEV₁ 86%)

Fig. 7. Recurrence of ventilation defects in 19 year old female with asthma

HP Helium-3 MR images performed at 3 different time points (a: baseline, b: 55 days later, c: 93 days after a) show three ventilation defects at baseline (arrowheads) (a) that resolved at 55 days (b) and recurred at 93 days with exam location and size as at baseline (arrowheads) (c) (Adapted with permission from: de Lange EE, Altes TA, Patrie JT, Battiston JJ, Juersivich AP, Mugler JP 3rd, Platts-Mills TA. *Radiology* 2009, 250, 567–575. DOI: 10.1148/radiol.2502080188).

Fig. 8. Ventilation defects in cystic fibrosis

Coronal helium-3 MR ventilation images in three patients with cystic fibrosis reveal multiple bilateral ventilation defects regardless the spirometry results.

Fig. 9. Ventilation changes after inhalation of albuterol in 16-year old female with cystic fibrosis
Coronal helium-3 ventilation images show extensive bilateral ventilation defects before treatment (arrows) (a) which decreased after treatment with albuterol (b). FEV 1 increased from 74% to 75% with treatment.

Fig. 10. Diffusion weighted HP helium-3 MRI: Detection of alveolar enlargement in Bronchopulmonary Displasia (BPD)

Coronal HP helium-3 ADC map in 10-year-old healthy child (a) and 12-old patient with BPD (c). ADC maps show diffusely elevated values in the BPD patient (b) compared to the healthy child (a) (0.33 cm²/s vs 0.15 cm²/s respectively).

Fig. 11. Diffusion weighted HP helium-3 MRI in congenital diaphragmatic hernia

Coronal proton MR image (a) and HP helium-3 ADC map (b) in a patient with left-sided congenital diaphragmatic hernia. Left diaphragmatic elevation (white arrow) is seen on the proton images. Black brackets on the sides of the proton image (a) show the extent of diaphragm movement ipsilateral and contralateral measured from the proton dynamic images (not shown). HP helium-3 ADC map (b) shows elevated values in the left lung when compared to the right lung. In the graph, ADC values of the ipsilateral lung (blue) and contralateral lung (red) are plotted for all slices, error bars show the standard deviation of the mean. (Adapted with permission from: Spoel M, Marshall H, IJsselstijn H, et al. Pulmonary ventilation and micro-structural findings in congenital diaphragmatic hernia. *Pediatr Pulmonol.* 2015 Oct 9. doi: 10.1002/ppul.23325 [Epub ahead of print])

Table 1**Hyperpolarized Gases**

Comparison of physical and physiologic properties of hyperpolarized Helium-3 and Xenon-129.

	Helium-3	Xenon-129
Gyromagnetic ratio [MHz/T]	32.4	11.8
Blood Solubility (%)	1	17
Side effects	No known side effects	CNS (euphoric and anesthetic) side effects
Atomic mass (u)	3.016	128.904
Free diffusion coefficient in air (cm²/s)	0.86	0.06
Supply	Tritium decay (1.3×10 ⁻⁴ % on Earth) Shortage of supply	Earth's atmosphere (26.44% on Earth) Readily available
Price (approx. \$/L)	900	200

CNS: Central Nervous System