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Original Research

Hyperpolarized ^{3}He MR Lung Ventilation Imaging in Asthmatics: Preliminary Findings

Talissa A. Altes, MD,[1,2]* Patrick L. Powers, MD,[4] Jack Knight-Scott, PhD,[1] Gary Rakes, MD,[3] Thomas A.E. Platts-Mills, MD,[4] Eduard E. de Lange, MD,[1] Bennett A. Alford, MD,[1] John P. Mugler III, PhD,[1,2] and James R. Brookeman, PhD[1,2]

Asthma is a disease characterized by chronic inflammation and reversible obstruction of the small airways resulting in impaired pulmonary ventilation. Hyperpolarized ^{3}He magnetic resonance (MR) lung imaging is a new technology that provides a detailed image of lung ventilation. Hyperpolarized ^{3}He lung imaging was performed in 10 asthmatics and 10 healthy subjects. Seven asthmatics had ventilation defects distributed throughout the lungs compared with none of the normal subjects. These ventilation defects were more numerous and larger in the two symptomatic asthmatics who had abnormal spirometry. Ventilation defects studied over time demonstrated no change in appearance over 30–60 minutes. One asthmatic subject was studied twice in a three-week period and had ventilation defects which resolved and appeared in that time. This same subject was studied before and after bronchodilator therapy, and all ventilation defects resolved after therapy. Hyperpolarized ^{3}He lung imaging can detect the small, reversible ventilation defects that characterize asthma. The ability to visualize lung ventilation offers a direct method of assessing asthmatics and their response to therapy. J. Magn. Reson. Imaging 2001;13: 378–384. © **2001 Wiley-Liss, Inc.**

Index terms: clinical applications of MR; chest; hyperpolarized gas; asthma; contrast agents

ASTHMA IS A CHRONIC DISEASE affecting more than 14 million people in the United States alone. It is defined by reversible obstruction of the small airways, inflammation, and increased airway responsiveness to a variety of stimuli, a process that disrupts adequate ventilation of the alveoli causing dyspnea and hypoxia. Asymptomatic asthmatics with normal pulmonary function testing can have airway inflammation detectable through bronchoscopy (1), but it is not known whether this degree of asthma activity results in ventilation defects. Our understanding of regional ventilation impairment in asthmatics is incomplete. Existing methods of assessing ventilation are indirect or imprecise. The dynamics of airflow at the mouth can be measured objectively by spirometry and monitored by peak flow measurements. However, these are global measures which are not capable of characterizing the existence or extent of regional ventilation abnormalities.

Current radiological techniques for assessing pulmonary ventilation are of limited value in asthma. Chest radiographs offer only gross evaluation of aeration and are not routinely employed in asthma management. Indirect, but more detailed, assessments of ventilation can be made from high resolution CT. Air trapping has been demonstrated by CT even in mild asthmatics, but it is not clear whether these indirect assessments of aeration correlate with asthma severity (2–5). Pulmonary radionuclide studies can be used to evaluate regional lung ventilation and perfusion. In the early 1980's, there was initial enthusiasm for the evaluation of asthmatics with the nuclear medicine ventilation/perfusion (V/Q) scan (6–8). The V/Q scan has demonstrated an uneven distribution of ventilation even in mild asthmatics (8). However, the nuclear medicine V/Q scan never enjoyed application in the clinical management of asthmatics, most likely due to its inherent radiation exposure and low resolution.

MR imaging of the lung is difficult because of the low proton density and significant susceptibility artifacts. The low proton density results in a weak MR signal, but this limitation can be overcome with a new class of contrast agent, the hyperpolarized gases. Using specialized laser polarizers, two non-radioactive isotopes of noble gases can be polarized, ^{3}He and ^{129}Xe. The resulting large non-equilibrium polarization of the nuclei provides sufficient signal to image air spaces despite the low physical density of a gas.

With hyperpolarized gas, high-resolution MR images of lung ventilation have been obtained (9–14). Hyperpolarized gas imaging has the potential to increase our understanding of lung ventilation disturbances in a variety of lung diseases, and has been used to image

[1]Department of Radiology, University of Virginia, Charlottesville, Virginia.

[2]Department of Biomedical Engineering, University of Virginia, Charlottesville, Virginia.

[3]Department of Pediatrics, University of Virginia, Charlottesville, Virginia.

[4]Department of Internal Medicine, University of Virginia, Charlottesville, Virginia.

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*Address reprint requests to: T.A., Box 800170, Department of Radiology, University of Virginia Health Services, Charlottesville, VA 22908. E-mail: taa2c@virginia.edu

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lung ventilation in emphysema (12,13), lung cancer (12) and cystic fibrosis (14). To our knowledge, hyperpolarized gas MR lung imaging has not been previously evaluated in asthmatics.

The objective of this study was to determine whether hyperpolarized ^{3}He lung ventilation imaging can detect the reversible ventilation defects that characterize asthma, and whether the imaging findings in asthmatics differ from healthy subjects.

MATERIALS AND METHODS

Twenty subjects, including 10 asthmatics (7 women and 3 men; age range 20–35 years; mean age 25 years) and 10 healthy volunteers (6 women and 4 men; age range 21–32 years; mean age 25 years), underwent hyperpolarized ^{3}He MR lung ventilation imaging. This study was performed under a protocol approved by our local institutional review board, and under a Food and Drug Administration (FDA) approved physician's Investigational New Drug (IND) application for the use of hyperpolarized ^{3}He. To evaluate repeatability, 6 of the 10 asthmatics and 4 of the 10 control subjects were imaged twice in a single session, 30–60 minutes apart. The remaining subjects were imaged once in the imaging session. A single asthmatic subject was imaged again, 3 weeks after the first imaging session, to assess the time course of the ventilation defects. In the second session, this subject was evaluated twice: prior to, and approximately 20 minutes after, inhaled bronchodilator therapy (albuterol, 2 puffs).

The asthmatic subjects had physician-diagnosed asthma as defined and classified by the NIH Expert Panel (15). Using the NIH classification scheme, only mild intermittent or mild persistent asthmatics were recruited. At the time of imaging, the asthmatic subjects were free of any additional respiratory illnesses such as infection. The healthy volunteers had no history of asthma, allergy, or chronic lung disease, and were free of current respiratory tract symptoms. Present and prior smokers were excluded from both arms of the trial. Spirometry was performed in the asthmatics immediately prior to imaging.

Hyperpolarized ^{3}He

The ^{3}He gas was polarized using a prototype commercial system (Nycomed Amersham-Magnetic Imaging Technologies, Durham, North Carolina). The details of the polarization process have been described previously (13). Briefly, ^{3}He is polarized by collisional spin exchange with optically pumped rubidium vapor. This process occurs at 8 atmospheres in a glass bulb containing approximately 1 ppm of rubidium vapor. The bulb is heated to 200°C in a 23G magnetic field. A high-power diode array laser, tuned to the 795 nm D1 resonance of rubidium, illuminates the bulb with circular polarized light. Absorption of the laser light produces a high electronic polarization in the rubidium atoms, which is then transferred by collisional exchange to the nuclear spin polarization of the ^{3}He atoms. The collisional spin exchange process is very slow; but after polarizing for several hours, ^{3}He polarizations of up to 35% can be achieved. The glass bulb is then cooled to room temperature, causing the rubidium to condense onto the wall of the glass bulb. To minimize the possibility of contaminating the ^{3}He gas with any remaining rubidium droplets, the gas was passed through a 0.2 μm filter (Gelman Sciences, Ann Arbor, Michigan). ^{3}He polarizations between 15% and 35% were achieved.

For each experiment, a 1 liter plastic bag (Jensen Inert Products, Coral Springs, Florida) was filled with between 300 and 500 cc of hyperpolarized ^{3}He and enough ^{4}He to total approximately 1 liter. The bag was taken to the subject, who was positioned supine in the MR scanner. The subject was asked to exhale completely and then inhale the hyperpolarized ^{3}He through a small plastic tube attached to the bag containing the gas. Imaging was performed during a breath hold, typically 9–16 seconds, depending upon the number of slices required to cover the subject's lungs.

Image Acqusition

Imaging was performed on a 1.5T Magnetom Vision whole body MRI system (Siemens Medical Systems, Iselin, New Jersey) which was modified to operate at the helium frequency, 48 MHz. Two transmit/receive coils were used for the helium imaging experiments: a tunable Helmholtz pair, and a quadrature flexible wrap coil (Medical Advances, Milwaukee, Wisconsin). The choice of coil for a particular experiment was determined largely by coil availability at the time of the experiment. The Helmholtz coil had an element diameter of 28.5 cm, and was sufficiently geometrically decoupled from the body coil to allow acquisition of proton scout images using the body coil. The flexible wrap coil was 30 × 100 cm, and it could not be used in conjunction with the body coil. Thus, low resolution coronal and transverse helium scout images were obtained with a small amount of inhaled polarized ^{3}He (< 50 cc) mixed with ^{4}He (~950 cc). Imaging parameters for the helium scout images were repetition time = 15 msec, echo time = 4 msec, flip angle = 20°, rectangular field of view = 30 × 50 cm, slice thickness = 5 cm, and matrix size=16 × 32.

Coronal hyperpolarized ^{3}He lung images were obtained using a gradient-echo, two-dimensional, fast low-angle shot (FLASH) sequence. Typical parameters were repetition time = 9 msec, echo time = 4 msec, flip angle = 14°, field of view = 30 × 50–55 cm, slice thickness = 1–1.5 cm, and matrix 80—96 × 256. A single slice was acquired in 0.6 seconds, and the entire lung was imaged during a 9–16 second breath hold. Subjects were monitored for blood oxygen saturation, and with a 3-lead EKG during ^{3}He inhalation and scanning. A physician supervised all experiments.

Following the hyperpolarized ^{3}He lung ventilation imaging, the helium coil was removed, and conventional proton images of the lungs were obtained using the body coil or a four-element body phased array coil (Siemens Medical Systems, Iselin, New York). A FLASH sequence was used with typical parameters: repetition time = 15 msec, echo time=6 msec, flip angle = 30°, field of view = 50 cm, slice thickness = 1 cm, and matrix 128 × 256. These images were obtained to ensure that there were no sources of susceptibility arti-

facts that could create the appearance of ventilation defects on the helium images.

Image Evaluation

A consensus panel of two radiologists, who were blinded to all information about the subjects and were not present during image acquisition, evaluated the ^{3}He lung images. The technical adequacy of each study was evaluated on the four-point scale: excellent, good, fair, and poor. Excellent studies had good distribution of gas and adequate signal-to-noise ratio throughout the lungs. Good studies were of diagnostic quality throughout the lungs, but had decreased signal in the apices or bases. Fair studies had signal drop-out in the apices or bases, and were inadequate for diagnosis in these regions. Poor studies were inadequate for diagnosis over a large portion of the lungs. The presence and severity of artifacts were also noted. Ventilation defects were defined as regions of the lung that would normally be ventilated, but in which helium was likely absent. Volume averaging with adjacent ventilated lung could cause the signal in small ventilation defects to be reduced but not absent. Thus, a complete absence of signal was not required in small ventilation defects. The presence or absence of defects and the number, size, and location of defects were noted. The location of ventilation defects was classified as either posterior or non-posterior. Posterior defects were confined to the most posterior three slices of the study. Posterior defects were, by definition, in the most dependent portions of the lung, since all subjects were imaged supine. A ventilation pattern with patchy regions of higher and lower signal intensity was called an inhomogeneous ventilation pattern. At the time of imaging, the proton images were evaluated for the presence of potential sources of artifact on the helium images.

RESULTS

All 20 subjects cooperated with the required breath hold and tolerated the MR scanning procedure well. The blood oxygen saturation dropped by 10% or less in all of the subjects during the breath hold and the 30 minutes following imaging. None of the asthmatic subjects reported a subjective worsening of their symptoms following helium inhalation.

The pre-imaging spirometry for the asthmatic subjects is shown in Table 1. The values are given in terms of the percent of the predicted volume for age, sex, and height matched subjects. Values between 80% and 120% are considered normal. The spirometry values were within the normal range for most of the subjects, as shown in Table 1. Subject 2, who had unusually large FVC and FEV_1, was an extremely well controlled asthmatic and an accomplished athlete. Subjects 4 and 5 had low FEV_{25-75} but otherwise normal spirometry. At the time of imaging, asthmatic subjects 1 and 3 had mildly abnormal spirometry and were mildly symptomatic, with a subjective feeling of chest tightness but no wheezing. None of the other asthmatic subjects were symptomatic at the time of imaging.

Table 1
Spirometry Data for the 10 Asthmatic Subjects Obtained Immediately Prior to Imaging

Subject	FVC (%pred)	FEV1 (%pred)	%FEV1	FEV25-75 (%pred)
1	75	78	89	72
2	141	126	76	87
3	89	62	58	25
4	109	91	70	59
5	119	108	78	77
6	115	108	81	91
7	123	113	92	86
8	93	93	86	82
9	125	117	81	96
10	81	73	77	50

FVC is forced vital capacity, FEV_1 is the forced expiratory volume in the first 1 s, $\%FEV_1$ is the ratio of FEV_1 and FVC, and FEV_{25-75} is the mean forced expiatory flow during the middle of FVC.

Image Evaluation

The consensus panel rated 12 of the 32 studies excellent, 13 good, 5 fair, and 2 poor. Thus 25 (78%) of the 32 studies were adequate for diagnosis in all regions. Both the Helmholtz and the wrap helium coils had physical dimensions which were not adequate to reliably provide full coverage of the lungs, which resulted in signal loss at the apices or bases in 18 (56%) of 32 studies. Signal loss was particularly noticeable in tall subjects. The two poor studies were likely due to insufficient inhaled hyperpolarized ^{3}He either, secondary to technical difficulties with the gas polarizer or with dispensing the gas. Fortunately the two poor studies occurred in imaging sessions in which the second study was adequate for diagnosis. The five fair studies had significant signal loss in the apices and/or bases due to a combination of the inadequate coverage of the coil and a generally low signal-to-noise ratio from a lower-than-average amount of inhaled hyperpolarized ^{3}He. Cardiac motion, respiratory motion, and other artifacts were uncommon, occurring in only 2 (7%) of 30 studies. No sources of potential magnetic susceptibility artifact were identified on the proton images.

Control subjects generally had uniform distribution of the gas throughout the lungs (Fig. 1). Small posterior (dependent) ventilation defects were common, occurring in 3 of 10 normal subjects and 6 of 10 asthmatics. The other 7 normal subjects had no ventilation defects. Non-posterior ventilation defects were seen only in the asthmatic subjects. These defects were pleural-based, frequently wedge-shaped, and varied in size from tiny to segmental. Seven of the 10 asthmatic subjects had at least one non-posterior ventilation defect as compared to none of 10 normal subjects ($P < 0.01$). All six of the asthmatics with posterior ventilation defects also had non-posterior defects. Subject 2, the well-controlled asthmatic with better-than-normal spirometry, had a single non-posterior ventilation defect in the right upper lobe, shown in Fig. 2.

The two asthmatic subjects (1 and 3) who were mildly symptomatic at the time of imaging had larger and more numerous defects than the asymptomatic asthmatics. Subject 1, a mildly symptomatic asthmatic, had multiple pleural-based ventilation defects throughout her

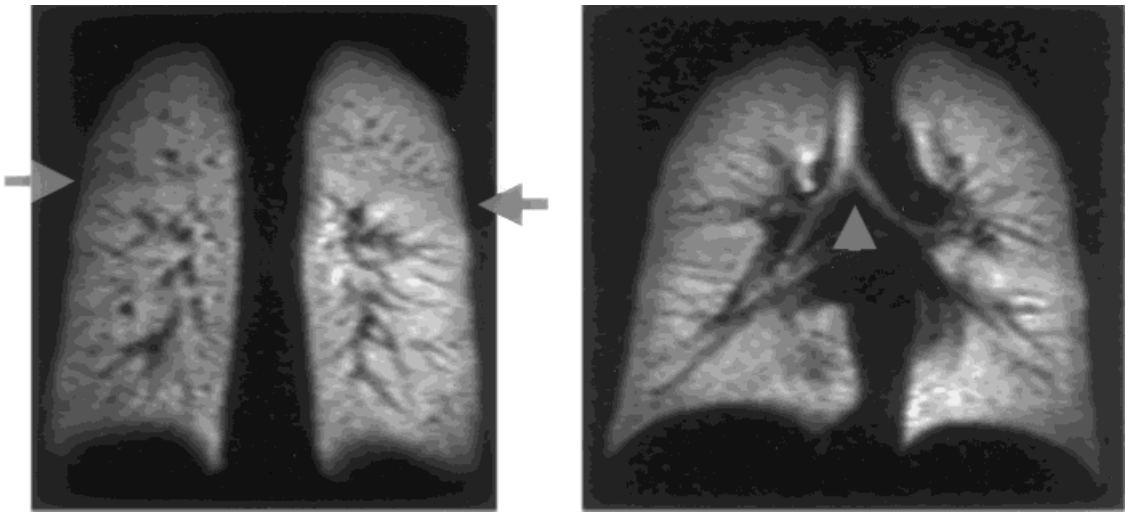

Figure 1. Coronal H^{3}He MR images of a normal subject demonstrating homogeneous gas distribution throughout the lungs and no discrete ventilation defects. There is good delineation of the fissures (long arrows) and the proximal tracheobronchial tree (arrowhead). The pulmonary vasculature creates tapered and linear signal voids within the lungs.

lungs (Fig. 3A). Subject 1 was imaged a second time 3 weeks following the initial session, when the subject was again mildly symptomatic with abnormal spirometry (FVC = 74%, FEV_1 = 80%, FEV1 = 108%, FEV_{25-75} = 85%). Again there were multiple ventilation defects, but in different locations (Fig. 3B). This subject was imaged again approximately thirty minutes later, but in the interval an inhaled bronchodilator (albuterol, 2 puffs) was administered. The multiple ventilation defects completely resolved (Fig. 3C), and spirometry following imaging was normal.

An inhomogeneous ventilation pattern was seen in 3 of the 10 normal subjects and 5 of the 10 asthmatics (P = 0.65). Two of the 3 normal subjects with posterior defects had an inhomogeneous ventilation pattern compared with only 1 of the 7 normal subjects with no defects. Four of the 7 asthmatics with either type of ventilation defect had inhomogeneous ventilation compared with 1 of the 3 without ventilation defects.

Of the 10 subjects (6 asthmatics and 4 normal subjects) who were imaged twice in a single session, there was concordance between the two runs as to the presence, location, and size of ventilation defects, with the exception of asthmatic subject 5. In this case, the two runs were disparate in quality, with one rated as excellent and the other fair. More defects were seen in the higher-quality images, and the difference in image quality may have contributed to the discordant reading.

DISCUSSION

To our knowledge, this study is the first systematic evaluation of hyperpolarized gas MR lung imaging in asthmatics. We found that ventilation defects were common in asthmatics, with 7 of 10 of the asthmatic subjects having ventilation defects distributed throughout the lungs. Moreover, these defects were larger and more numerous in the two subjects who had abnormal spirometry and who were mildly symptomatic at the time of imaging. Thus, these preliminary results suggest that the ventilation defects seen with ^{3}He hyperpolarized gas imaging may correlate with asthma activity. None of the normal subjects had similar defects, although 3 of 10 subjects had small ventilation defects in the most-dependent portions of the lung. Others have noted similar defects in normal and abnormal subjects (11). Although the cause of these defects is uncertain, they are thought to represent changes of hypoaeration from lying in a supine position with the coil inhibiting adequate ventilation. It is not uncommon to see dependent atelectasis on chest CT even in normal subjects. The posterior defects were larger and more numerous in the asthmatics, perhaps indicating increased susceptibility to dependent atelectasis.

It is established that poorly controlled asthma can lead to airway remodeling and progressive loss of lung function (16). Early diagnosis and adequate treatment of this disease is therefore imperative (17). Our preliminary results indicate that hyperpolarized gas lung im-

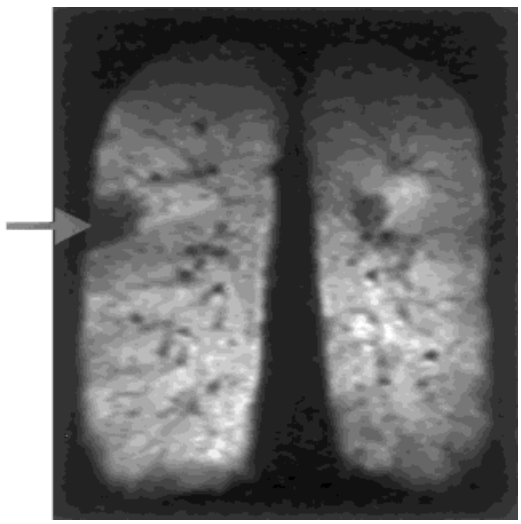

Figure 2. Coronal H^{3}He image of a well controlled, asymptomatic asthmatic with a single lateral, wedge-shaped, pleural-based ventilation defect (arrow). Loss of signal is seen in the apices secondary to the limited range of the helium coil.

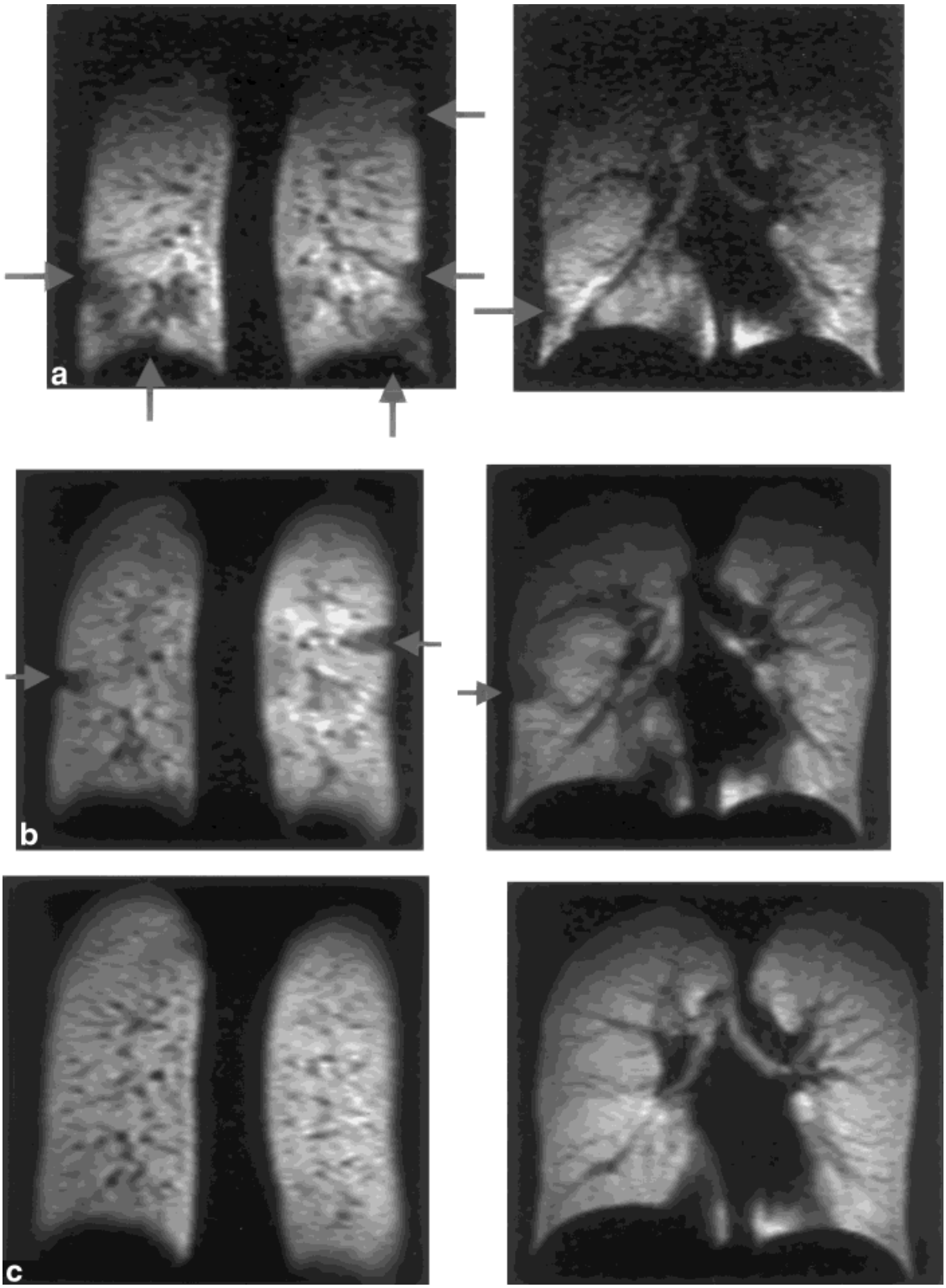

Figure 3. Mildly symptomatic asthmatic. **a:** Mildly symptomatic asthmatic. Multiple ventilation defects (arrows) are present throughout the lungs. The signal is poor in the apices due to the inadequate coverage of the wrap coil. **b:** Images of the same individual, obtained three weeks later and at the same anatomic levels as in Figure 3a, show that the multiple ventilation defects (arrows) are in different locations. **c:** Images at the same levels, obtained 30 minutes after Figure 3b, show that the ventilation defects resolved completely following the use of an inhaled bronchodilator.

aging may be more sensitive to disease activity than clinical assessment, subjective symptoms, or spirometry, since ventilation defects were seen in well-controlled, asymptomatic asthmatics with normal spirometry. It is known that asymptomatic asthmatics with normal spirometry can have evidence of airway inflammation on bronchoscopy (1). Thus, hyperpolarized ^{3}He imaging may provide a non-invasive method of visual-

izing airway closure that is the result of subclinical airway inflammation. By using hyperpolarized ^{3}He imaging to guide therapy, it may be possible to better treat what has previously been subclinical asthma. Whether this will improve long term outcome remains to be determined.

The etiology of the ventilation defects remains uncertain. The ventilation defects were stable over 30–60 minutes, but the defects were mobile over three weeks in the single subject imaged a second time. In this subject, the ventilation defects completely and rapidly reversed following inhaled bronchodilator therapy. Since asthma is characterized by mucus hypersecretion, airway hyperreactivity, and airway edema, it seems likely that the etiology of the ventilation defects is small airway obstruction from some combination of these factors. The rapid reversal following bronchodilator inhalation is likely due to dilation of the small airways which allows helium to pass through previously-constricted airways or alongside mucus plugs.

An inhomogeneous ventilation pattern was slightly more frequent in the asthmatic subjects as compared with the normal subjects, and was more frequent in subjects with ventilation defects. Others have seen an inhomogeneous ventilation pattern in normal and diseased states, and have postulated that it may be secondary to an inadequate volume of inhaled gas (11,13). We do not believe this was the predominant factor in our study, as inhomogeneous ventilation was not more common in the poor studies, and all subjects received approximately the same total volume of gas. An inhomogeneous ventilation pattern in asthmatics may reflect altered flow dynamics which could be indicative of small airway constriction or mucus plugging that has not progressed to complete obstruction. Dynamic imaging of lung ventilation using hyperpolarized gas is under development (18) and has the potential to demonstrate disturbances of flow from airway narrowing. This may be more sensitive for disease activity in asthmatics than the breath- hold images obtained in this study.

Hyperpolarized gas MR lung imaging is a relatively new technology, with the first human lung images obtained in September, 1995 (9,10). Since then, several groups have evaluated hyperpolarized gas lung imaging in normal subjects and in a variety of disease states (11–14). Ventilation defects have been seen in subjects with emphysema, bronchogenic carcinoma, cystic fibrosis, and bronchiectasis. The only prior report of an asthmatic imaged with hyperpolarized gas was a single subject who had small, mobile ventilation defects (13). This subject had a history of asthma but was asymptomatic at the time of imaging. The results of our study confirm and extend that initial observation. All of the previously reported series have been small, varying from 4 to 18 subjects, and most have included healthy volunteers and subjects with a variety of lung diseases. Thus, this study is one of the largest reported series, and it is the first to systematically evaluate the potential utility of this technology in the evaluation of a particular lung disease.

The primary limitations of this study are that the number of subjects imaged was small and that serial imaging was not performed on all of the asthmatics. Serial imaging could provide a better understanding of the ventilation defects' fluctuations with time. The response to inhaled bronchodilator treatment needs to be verified in a larger number of subjects. Some asthmatics may be less responsive to bronchodilator therapy, and there may be factors that contribute to resistance to therapy which are not now understood, but which could be elucidated with MR lung imaging.

Hyperpolarized ^{3}He MR lung imaging appears to depict the regional ventilation abnormalities that were known to occur in asthma but were previously difficult to quantify. Furthermore, since there is no ionizing radiation and the gas rapidly depolarizes, the examination can be repeated multiple times in a single subject and can be performed before and after an intervention. This may allow improved understanding of the basic pathophysiology of asthma and the response to treatment. Clinically, there may be a role for hyperpolarized ^{3}He MR lung imaging in the diagnosis of asthma, particularly to discriminate between patients with asthma and those with diseases that can mimic asthma, such as vocal cord syndrome. Hyperpolarized ^{3}He MR lung imaging may also prove useful in the severe asthmatic to optimize treatment by evaluating the individual's response to the various asthma medications. In addition, there may be a role for hyperpolarized ^{3}He MR in the evaluation of the efficacy of new asthma treatments. Thus, hyperpolarized gas lung imaging has the potential to increase our understanding of the pathophysiology of asthma, and possibly even to improve clinical management.

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