Rapid publication

Imaging the lungs in asthmatic patients by using hyperpolarized helium-3 magnetic resonance: Assessment of response to methacholine and exercise challenge

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Background: Imaging of gas distribution in the lungs of patients with asthma has been restricted because of the lack of a suitable gaseous contrast agent. Hyperpolarized helium-3 (HHe3) provides a new technique for magnetic resonance imaging of lung diseases.
Objective: We sought to investigate the use of HHe3 gas to image the lungs of patients with moderate or severe asthma and to assess changes in gas distribution after methacholine and exercise challenge.
Methods: Magnetic resonance imaging was performed in asthmatic patients immediately after inhalation of HHe3 gas. In addition, images were obtained before and after methacholine challenge and a standard exercise test.
Results: Areas of the lung with no signal or sharply reduced HHe3 signal (ventilation defects) are common in patients with asthma, and the number of defects was inversely related to the percent predicted FEV_1 ($r = 0.71$, $P < .002$). After methacholine challenge (n = 3), the number of defects increased. Similarly, imaging of the lungs after exercise (n = 6) showed increased ventilation defects in parallel with decreases in FEV_1. The increase in defects after challenge in these 9 asthmatic patients was significant both for the number ($P < .02$) and extent ($P < .02$) of the defects. The variability and speed of changes in ventilation and the complete lack of signal in many areas is in keeping with a model in which the defects result from airway closure.
Conclusion: HHe3 magnetic resonance provides a new technique for imaging the distribution of inhaled air in the lungs. The technique is suitable for following responses to treatment of asthma and changes after methacholine or exercise challenge. (J Allergy Clin Immunol 2003;111:1205-11.)

Key words: *Asthma, helium, magnetic resonance imaging, imaging, ventilation, lungs*

The introduction of a stepwise approach has helped to categorize asthma and guide therapy.[1] However, patient symptoms and spirometry are the only guides used during routine office visits, and there has been little improvement in techniques to visualize regional lung impairment. Computed tomography (CT) or high-resolution CT has been used with different breathing maneuvers to confirm the presence of air trapping.[2,3] Nuclear medicine scans have been used to image regional ventilation and perfusion mismatch, but spatial resolution is limited, and the technique is not helpful in asthma evaluation. With the introduction of new gaseous magnetic resonance imaging (MRI) contrast agents, such as xenon-129 and helium-3, MR techniques have been developed that provide new means of visualizing lung ventilation without ionizing radiation exposure.[4-6] In human subjects hyperpolarized helium-3 (HHe3) has been used to visualize ventilation patterns in the lungs of healthy patients, as well as in the lungs of patients with chronic lung diseases.[7] We have also reported that patients with mild asthma have visible defects in ventilation.[8] Helium-3 is an isotope of helium that has 2 protons and 1 neutron, whereas the more abundant isotope helium-4 has 2 protons and 2 neutrons. An odd number of nucleons allows helium-3 to be polarized outside of the MR scanner, such that a large proportion of the atomic nuclei are aligned with their nuclear spins in the same direction. This alignment of nuclear spin produces a large MR signal but does not alter the chemical properties of the gas.[4,9]

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Supported in part by Siemens Medical Solutions; Amersham Health; the Commonwealth Technology Research Fund; National Institutes of Health grants AI20565, PO1-NIEHS/NIAID-50989, R-44-HL59022, and R01HL66479; and the Society of Pediatric Radiology.
Received for publication November 21, 2002; revised March 3, 2003; accepted for publication March 21, 2003.

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0091-6749/2003 $30.00 + 0
doi:10.1067/mai.2003.1544

Abbreviations used
CT: Computed tomography
HHe3: Hyperpolarized helium-3
MR: Magnetic resonance
MRI: Magnetic resonance imaging

Conventional MRI relies on hydrogen atoms found in water or organic molecules as a source of its signal. Because the concentration of hydrogen is very low in the lung relative to solid tissues, such as the brain or muscles, the lung produces a weak signal and typically appears dark on conventional MRI. The large signal produced by HHe3 provides enough signal to image the airspaces of the lung, despite the low physical density of the gas. Because of the low solubility of helium in water or lipids, HHe3 fills the lung and is not absorbed into the tissue or blood, producing an image of ventilated air spaces. The purpose of the present study was to examine asthmatic patients with varying degrees of airway obstruction and also to image the lungs after challenge with methacholine or exercise.

METHODS

Subjects

Subjects 18 to 40 years of age were recruited through the Asthma and Allergic Diseases Center at the University of Virginia and through local advertisement. The use of HHe3 in human subjects was performed under a Food and Drug Administration–approved physician's Investigational New Drug application (no. 57,866). All studies were performed under a protocol approved by the institutional review board. In total, 39 subjects, 19 asthmatic patients (age, 20-40 years; mean age, 27 years) and 20 healthy subjects (age, 22-35 years; mean age, 27 years), underwent baseline spirometry and HHe3 MRI. Exclusion criteria included a history of smoking, a recent respiratory illness, other underlying lung disease, and MR incompatibility (prostheses, metal in the orbit, claustrophobia, or pregnancy). The presence of asthma was either physician diagnosed or there was a self-reported history of wheezing, nocturnal cough, or wheezing with exposure to environmental triggers or exercise. The healthy control subjects did not have a history of asthma, wheezing, or atopic diseases. After obtaining a history, physical examination, blood chemistry measurement, spirometry, electrocardiography, and chest radiography were performed as required by the Investigational New Drug protocol. In addition, spirometry from full inspiration was performed immediately before (ie, within 15 minutes) the subject was placed in the MR scanner. A baseline MRI with HHe3 was performed to assess the appearance of each subject's lung ventilation. Ten asthmatic patients and 2 healthy subjects with ventilation defects were treated with 2 inhalations of albuterol administered through a metered-dose inhaler and reimaged.

Hyperpolarized helium-3

Images were obtained by means of methods previously described.[6,8] Briefly, gas polarization was achieved with collisional spin exchange between HHe3 and optically pumped rubidium vapor by using a prototypic system (Amersham Health, Durham, NC). Because the efficiency of polarization varies, to achieve consistent imaging, the HHe3 was diluted with nitrogen (approximately 300 mL of HHe3 to 700 mL of nitrogen). The MR scanner was a commercially available broadband 1.5 T whole-body imager (Magnetom Vision; Siemens Medical Solutions, Iselin, NJ) modified to the HHe3 frequency. A wrap-around helium-3 chest radiofrequency coil (IGC Medical Advances, Milwaukee, Wis) was used for data acquisition and was placed around the subject's thorax. A 3-lead electrocardiogram and oxygen saturation levels were continuously monitored while subjects underwent HHe3 imaging. Once the subject was placed supine in the scanner, HHe3 was dispensed at room temperature and atmospheric pressure into a plastic bag with a short tube and valve. The subject was asked to maximally inhale approximately 1 L of HHe3/N_2, which was usually accomplished in less than 5 seconds. Imaging commenced immediately after inhalation, with the patient performing a single breath hold for 10 to 13 seconds. MRI used a fast low-angle shot pulse sequence with typical parameters: repetition time/echo time, 9/3.7 ms; flip angle, 10° to 15°; matrix, 100×256; field of view, 38×50 cm; and section thickness, 10 mm. For imaging asthmatic patients with varying degrees of severity and in performing the methacholine challenge studies, we obtained 10 to 15 coronal images in 1-cm sections to cover the lungs during a single breath hold. For exercise challenge studies, we obtained the images in axial (transverse) orientation because improvements of the pulse sequence technique allowed the acquisition of a greater number (20-25) of 1-cm-thick images during a single breath hold.

Methacholine protocol

Three asthmatic patients and one healthy subject were enrolled in the methacholine challenge protocol. Before imaging, subjects underwent methacholine challenge according to the 1999 American Thoracic Society guidelines.[9] Methacholine, prepared by the hospital pharmacist, was administered by using the 5-breath dosimeter method (Koko DigiDoser; PDS Instrumentation, Louisville, Colo) with methacholine concentrations of 0.025, 0.25, 2.5, 10, and 25 mg/mL. The concentration that decreased FEV_1 by 20% (PC_{20Meth}) was noted. After challenge, the subjects received albuterol by means of a nebulizer to restore lung function. The methacholine imaging study was performed within a week after the standard challenge test. The PC_{20Meth} was administered by using dry compressed air and the 2-minute tidal breathing method because of the compatibility of the apparatus with the MR scanner. Spirometry was performed, and each individual underwent HHe3 MRI within 5 minutes of methacholine inhalation.

Exercise challenge

Six patients with a history of wheezing with exercise and one healthy subject were enrolled in the exercise challenge protocol. Subjects were instructed to not use bronchodilators 8 hours before the study. None of the patients were taking long-acting β_2-agonists. Exercise challenge, per the 1999 American Thoracic Society protocol,[9] lasted 6 to 8 minutes on a treadmill, with 4 to 6 minutes at 80% to 90% of the subjects' target heart rate (220 beats/min minus age in years). The test was discontinued if they had any significant respiratory or cardiac distress. A nose clip was applied, and the subject's heart rate and oxygen saturation were continuously monitored with a pulse oximeter (N-395; Nellcor Puritan Bennett Inc, Pleasanton, Calif) during the challenge. Exercise was performed in a room with ambient temperature ranging from 70°F to 75°F and 65% to 70% relative humidity. Spirometry was measured at baseline and 1, 3, 5, and 7 minutes after cessation of exercise. HHe3 MRI was performed within 20 minutes of cessation of exercise. Those with significant respiratory symptoms had their symptoms reversed with nebulizer albuterol.

Evaluation of images

To our knowledge, there does not exist a validated or even widely accepted scoring system for evaluating HHe3 MR images. A variety of scoring methods have been used for scoring images

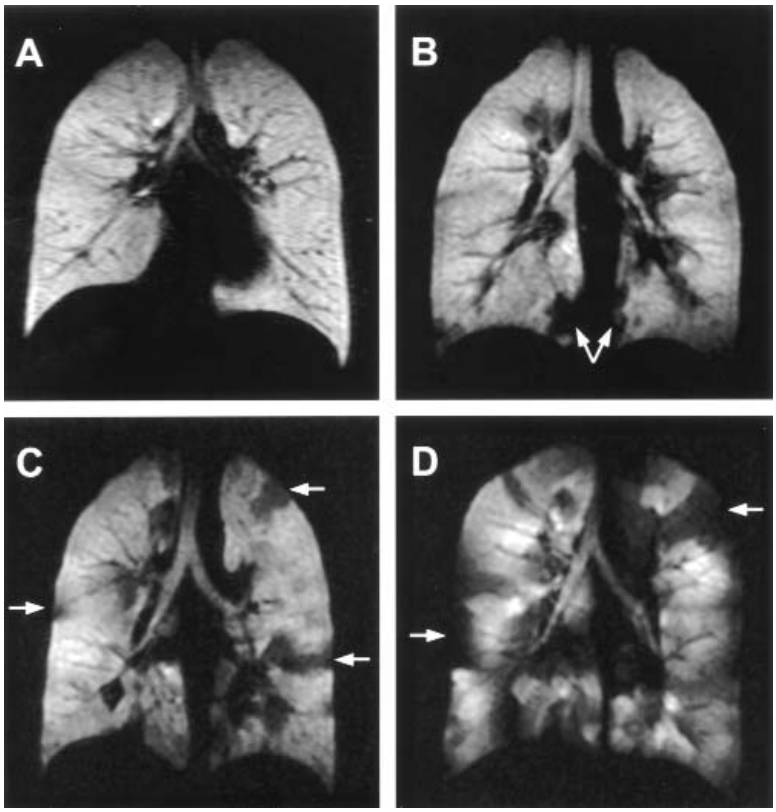

FIG 1. Coronal MR images obtained immediately after inhalation of HHe3 gas in a healthy normal volunteer **(A)** and in patients with mild (FEV_1 of 132% of predicted value; **B**), moderate (FEV_1 of 83% of predicted value; **C**), and severe (FEV_1 of 34% of predicted value; **D**) asthma. The distribution of the gas is homogenous in the normal volunteer, and ventilation defects are seen with increasing numbers in the asthmatic patients with increasing severity (*arrows* pointing at several defects).

of chronic lung disease. Most have been based on either counting the number of ventilation defects or estimating the percentage of the lung that is ventilated. Scoring systems on the basis of a simple count of the number of defects might have underestimated the extent of disease because large and small defects are scored similarly. Scoring systems on the basis of the percentage of ventilated lung might be insensitive in patients with mild disease because a few small defects represent a very small fraction of the total lung volume. We used 2 scoring systems, one on the basis of each method. For the first scoring system, 2 reviewers (SS, TA) counted by consensus the number of ventilation defects present on each imaging slice from a patient. The number of defects in each slice was summed over all of the images in that study to yield the defect score. Defects that appeared on multiple slices were counted on each slice in which they appeared. Thus large defects that appeared on more than one slice were given more weight than small defects that appeared on only one slice but not in proportion to the defect volume. For the second scoring system, 2 readers (JMC, EEdL) independently estimated the percentage of the lung volume that was ventilated on each imaging slice from a patient. The percentage of ventilated lung was averaged over all of the images in a study to yield the percentage of ventilated lung for each subject. The scores from the 2 reviewers were averaged.

RESULTS

Imaging the lungs of patients with mild, moderate, and severe obstruction

We have previously reported the presence of ventilation defects in the HHe3 images of patients with asthma. Imaging patients with more severe disease, we found a more consistent presence of defects and more extensive defects (Fig 1). In the series of baseline scans on 19 asthmatic patients, with FEV_1 values ranging from 36% to 130% of predicted value, the number of ventilation defects was inversely correlated with FEV_1 percent predicted ($r = 0.68$, $P < .01$). For the total scans (n = 38), this correlation was highly significant ($r = 0.71$, $P < .002$). In general, the lesions became both more extensive and more numerous with increasing severity of disease. However, the current data are not sufficient to make a simple statement about the relationship between ventilation defects and severity of disease.

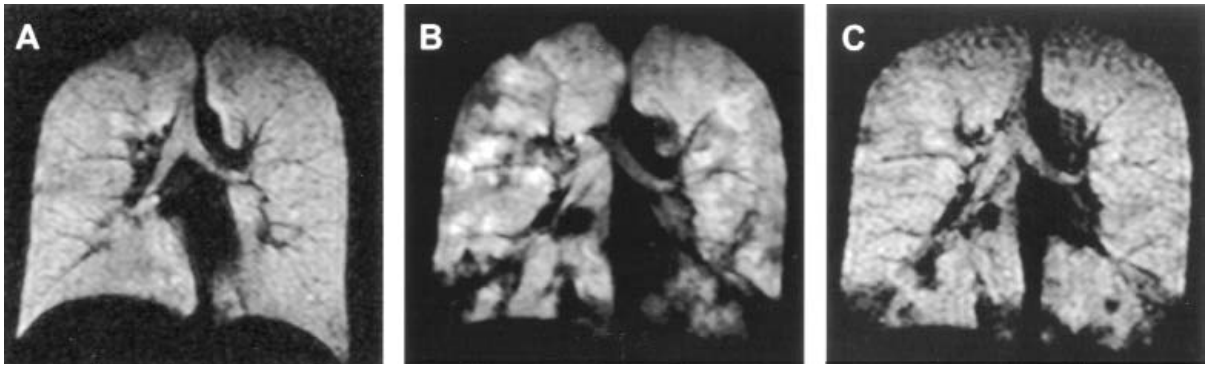

FIG 2. Methacholine challenge. **A,** Baseline coronal HHe3 MR image of the lungs in a patient with mild asthma (FEV_1 of 118% of predicted value) shows relative homogenous distribution of the gas in the lungs. **B,** Image obtained after methacholine challenge testing (FEV_1 of 73% of predicted value) demonstrates a large number of ventilation defects. **C,** Image obtained after inhalation of albuterol shows improvement of the ventilation defects.

TABLE I. Methacholine challenge

Subject no.	Age (y)	Sex	Predicted FEV_1	FEV_1	% Predicted	Postmethacholine % predicted FEV_1	Δ FEV_1	Postalbuterol % predicted FEV_1	No. of ventilation defects*		Nonventilated (%)†	
									Before	After	Before	After
168	25	F	3.35‡	3.96	118	73	–38%	136	25	154	5	40
178	21	M	4.05‡	5.34	132	118	–11%	140	8	39	2	5
215	23	M	3.62§	3.43	95	48	–50%	83	31	148	8	60
Control subject												
210	26	F	3.11§	3.45	111	100	–11%	102	2	2	<1	<1

*Score obtained by counting the number of defects.
†Blind evaluation by 2 radiologists of the percentage of lungs ventilated.
‡Adult predicted normal values from Knudson.[83]
§Adult predicted normal values from Morris.[71]

Methacholine challenge

At baseline, the 3 individuals studied had ventilation defects, and the individual with the lowest FEV_1 value had the greatest number of ventilation defects. The PC_{20} dose for each of the asthmatic patients was 2.5 mg/mL. Even though the control subject did not respond to the highest dose, she was given the 10 mg/mL dose (Table I). Changes in ventilation after methacholine in one asthmatic subject is shown in Fig 2. In all 3 cases there were numerous new defects with a range of sizes after the administration of methacholine. There were also areas of increased signal intensity that were not present in the baseline MRI. There was a definite inhomogeneity (patchy) in certain ventilated areas compared with areas that appeared ventilated or unventilated. The control subject did not have any ventilation defects with the administration of methacholine. The images obtained after albuterol administration demonstrated an improvement in ventilation defects but not complete reversal.

Exercise challenge

Four of the 6 subjects with a history of exercise-induced bronchospasm had obvious ventilation defects at baseline despite normal spirometric results (Table II). In some cases initial ventilation defects improved after exercise, whereas new defects appeared. Two subjects had major changes in their ventilation patterns with the development of large defects (one subject is shown in Fig 3). Surprisingly, they believed that the exercise challenge in the laboratory was not as strenuous as their normal exercise routines. There was a marked inhomogeneous pattern in some of the images, again with a patchy appearance. Currently, it is unclear what this represents. The oxygen saturation of the subjects did not decrease to less than 90% while exercising. We were unable to perform postalbuterol imaging because of the limitation in the supply of HHe3 gas. The control subject did not have any ventilation defects. Taking the challenge studies together, there was a significant increase in the number of defects ($P < .02$, t test) and a decrease in the percentage of lung ventilated ($P = .02$, Fig 4).

DISCUSSION

The diagnosis and management of asthma is largely dependent on measurements of expiratory airflow.[10,11] Transient decreases in peak expiratory flow or FEV_1 are

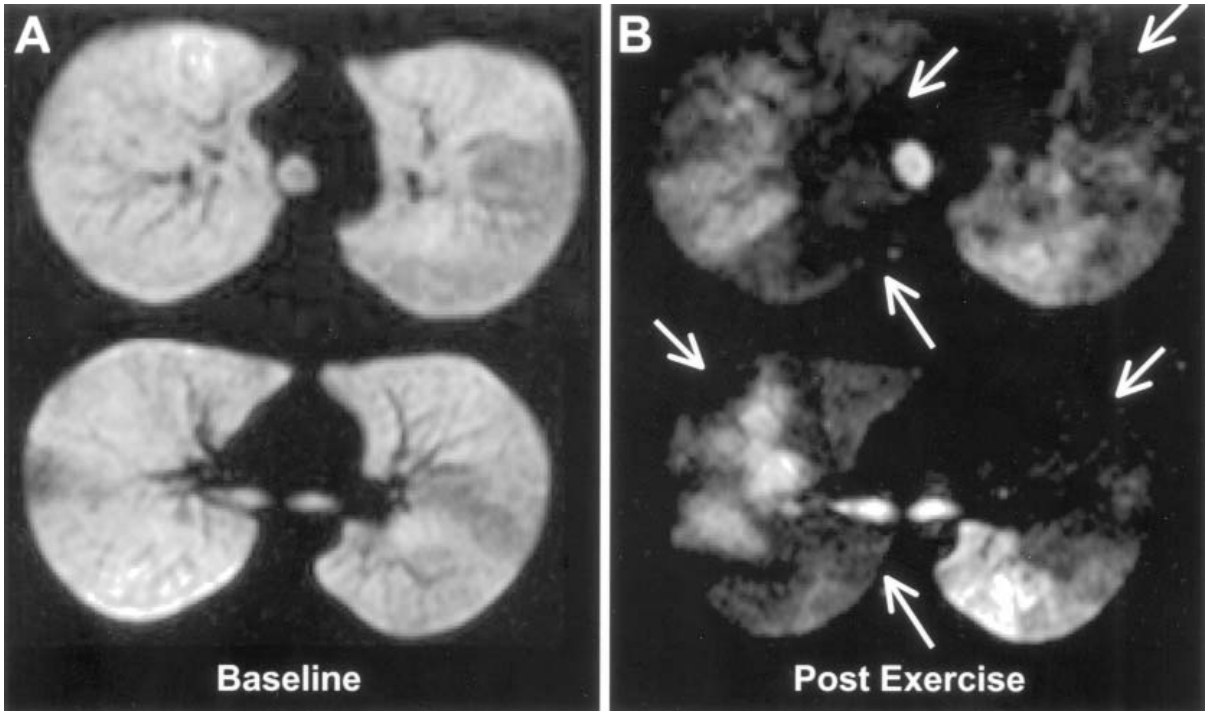

FIG 3. A, Axial HHe3 MR image of patient with mild asthma at baseline (FEV_1 of 103% of predicted value) shows mildly heterogeneous distribution of the gas in the lungs. **B,** After exercise (FEV_1 of 39% of predicted value), very extensive ventilation defects have developed. Two levels of the lung are shown for subject 395.

TABLE II. Exercise challenge

Subject no.	Sex	Age (y)	Predicted FEV_1*	Before exercise		After exercise		No. of ventilation defects		% Non-ventilated	
				FEV_1	% Predicted	% Nadir	% Predicted	Before	After	Before	After
357	F	33	2.70	2.68	99	2.37 (3 min)	71	6	12	2	4
358	F	20	3.36	3.61	107	2.70 (5 min)	80	22	31	3	5
381	F	28	3.04	3.03	100	2.64 (4 min)	87	21	29	4	6
383	F	26	3.33	4.17	125	4.08 (5 min)	122	16	54	5	10
391	F	24	3.29	3.45	105	3.21 (3 min)	98	7	22	1	5
395	F	22	2.99	3.08	103	1.16 (3 min)	39	14	113	4	50
Control subject											
382	F	24	2.87	3.34	116	3.18 (5 min)	111	9	8	1	1

*Adult predicted normal values from Knudson.[83]

normally interpreted as diffuse narrowing of the bronchi. Indeed, the presence of wheezing or expiratory rales clearly indicates that some tubes are narrowed sufficiently to cause turbulent airflow. On the other hand, it has been clear for many years that some bronchi must close, giving rise to air trapping and decreases in forced vital capacity.[12-14] The physiologic studies cannot define either the distribution of changes in ventilation or the size of the bronchi that close.[15] The techniques used to visualize bronchi and lung parenchyma have included traditional bronchograms, chest radiographs, and fine-section CT scans. For imaging of the lung ventilation, scintigraphy has been used with inhalation of radioactive gases, such as technetium 99m–labeled aerosols, xenon133, xenon-127, or krypton-81.[15] A limitation of these techniques is that images are produced with relatively limited spatial and temporal resolution.

A major advantage of HHe3 is that it is an inert gas with no anesthetic activity or radioactivity. The disadvantages are technical difficulties producing and transporting the gas and the need for the subject to be in the MRI scanner. In addition, there are possible problems with the supply of helium-3, which is a nonradioactive byproduct of radioactivity research in the United States and Russia. The problems producing the polarized gas are rapidly being solved. Because the helium-3 is polar-

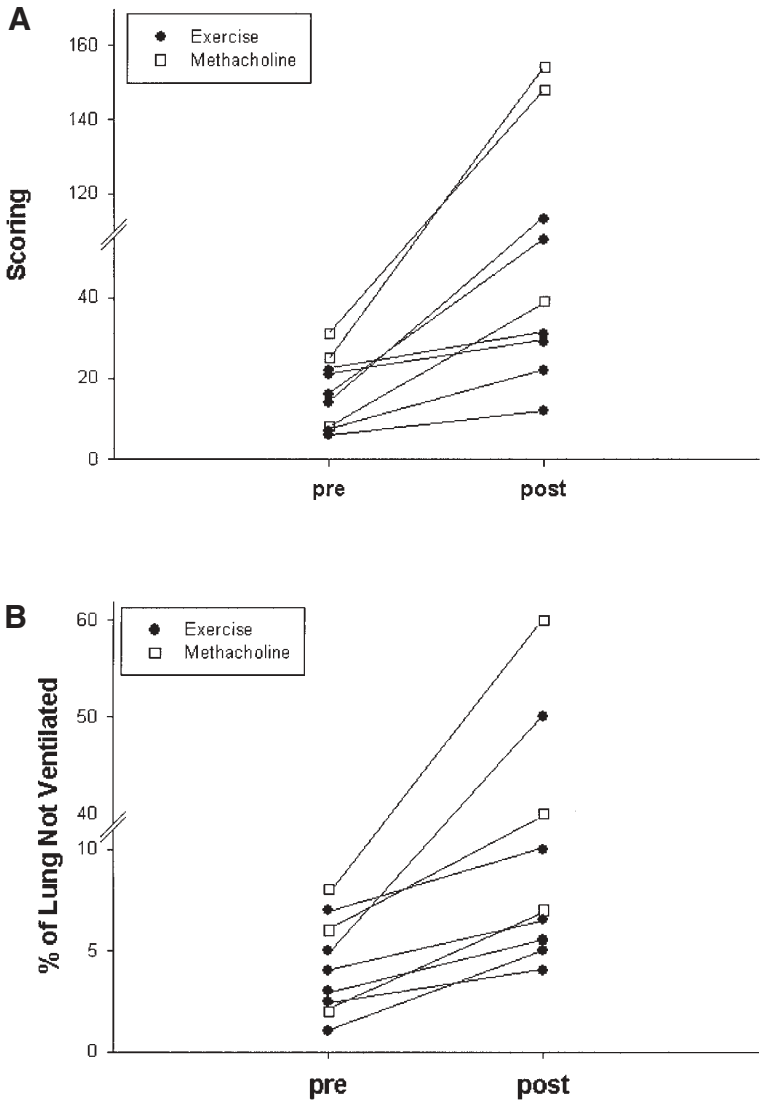

FIG 4. Scoring of defects carried out by counting defects **(A)** or by means of blind assessment of the percentage of lungs ventilated **(B)**. Values before and after ventilation for exercise and methacholine challenge showed significant change ($P < .02$) by each assessment.

ized outside the MR scanner, a large static magnetic field is not required for MRI. Thus it would be possible to use a small, relatively inexpensive scanner for imaging hyperpolarized gas. In turn, this could be modified for use in an emergency room setting.

When the HHe3 gas is inhaled and MR pulse sequences are applied, the gas filling the airspaces of the lung appear bright on the images. When an area of the lung is not filled with the gas, this area appears as a black defect on the images. Therefore in these studies the complete lack of signal suggests that the lesions seen represent airway closure of segmental or subsegmental bronchi. Lesions of this kind in chronic obstructive pulmonary disease might well be due to air trapping in dilated bronchi or alveoli. However, in patients with moderate or mild asthma, airway closure is a more likely explanation for the defects. We have documented many different sizes of defects both spontaneously in patients with moderate persistent or severe asthma and also during episodes of decreased airflow after challenge. From preliminary data, the spontaneously occurring defects appear to be stable over hours but highly variable over days. By using 2 puffs of albuterol, both spontaneous and induced defects have been observed to reverse; however, this treatment typically produces only partial reversal of both FEV_1 and ventilation defects. Our data are sufficient to establish that there is a correlation between changes in ventilation defects and changes in FEV_1. However, it is not possible to estimate what proportion of changes in FEV_1 can be attributed to the visible defects. We are currently developing 3-dimensional imaging that will allow more accurate measurement of defects. Part of the problem with scoring defects is that there are

mild changes in the texture and density of the signal from areas of the lung without defects.[6-8]

If there are medium-size bronchi that close, this is clearly relevant to the question of mechanisms of obstruction. Dilatation of bronchial blood vessels, edema formation, and increased secretions might all be relevant and can occur rapidly. However, the speed of major changes after challenge suggests that a neurologic mechanism could also be involved. It is tempting to speculate that the spontaneously occurring and migrating defects seen in patients with moderate asthma reflect activity of the nonadrenergic noncholinergic system.[16] However, because all of the patients studied here were allergic, the process is almost certainly occurring on the background of inflamed airways. It is interesting to consider the relevance of closure to the other techniques of studying changes in the airways. We predict that the closed airways would not contribute to bronchoalveolar lavage fluid,[17] exhaled nitric oxide,[18] or exhaled condensate.[19]

We were surprised and indeed concerned by the extent of changes after methacholine or exercise challenge in some of the patients. It is clear that we had assumed that most of the responses to exercise represented diffuse narrowing of the bronchi. The evidence shown here suggests that a large part of the change might be due to closure or near closure of segments of the lungs.[14] This would of course explain the well-recognized discrepancy between audible wheezing and the severity of obstruction. The documented changes in subject 395 might provide insight into the ways in which very severe episodes can develop after exercise. Strikingly, the same subject is fit and can climb 1000 meters vertical in 2½ hours with suitable premedication and warm-up.

In conclusion, imaging of the lungs with HHe3 provides a completely new approach to following changes in the distribution of gases in the lungs. The images are striking and might provide insight into the ways in which obstruction develops. Indeed, these studies support the proposal of several groups that transient closure of the bronchi is a major part of the obstruction in moderate asthma, both spontaneously and after challenge.[12,14] The technique has the major advantage that because it requires no radiation, it can be used repeatedly. With current developments in the speed of imaging, it could become the technique of choice for evaluating ventilation in the acute setting. In addition, sequential imaging of the lungs provides a new approach to evaluating treatment.

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