Imaging of the distal airways

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Imaging techniques of the lung continue to advance, with improving ability to image the more distal airways. Two imaging techniques are reviewed: computed tomography and magnetic resonance with hyperpolarized helium-3. (J Allergy Clin Immunol 2009;124:S78-83.)

Key words: *Imaging, asthma, distal airways, small airways, computed tomography, high-resolution computed tomography, hyperpolarized magnetic resonance*

Abbreviations used

ADC: Apparent diffusion coefficient
BDP: Beclomethasone dipropionate
CFC: Chlorofluorocarbon
CT: Computed tomography
$FEF_{25\%-75\%}$: Forced expiratory flow from 25% to 75% of forced vital capacity
HFA: Hydrofluoroalkane
HRCT: High-resolution computed tomography
LAC: Lung attenuation curve
MR: Magnetic resonance
QIA: Quantitative image analysis
^{3}He: Helium-3
VDS: Ventilation defects per image slice

COMPUTED TOMOGRAPHIC IMAGING TECHNIQUES FOR THE DISTAL LUNG IN PATIENTS WITH ASTHMA

The underlying rationale for using regional ventilation as a surrogate for small airways disease in asthma is that the small airways are mainly responsible for the distribution of ventilation to the gas-exchanging surface of the distal lung; when the small airways are narrowed by disease, the distribution of ventilation becomes uneven, and air that was inhaled becomes trapped behind prematurely (anatomically or functionally) closed small airways. This might not be reflected by changes in residual volume (measured by means of body plethysmography) because the latter measurement is a global measure of lung volume and is likely to be a less sensitive measure of regional ventilation that can be assessed by using imaging techniques with quantitative image analysis (QIA).[1,2] Although it is also possible to use thoracic high-resolution computed tomography (HRCT) to directly assess changes in conducting airway structure (airway wall thickness and luminal area), with current computed tomographic (CT) technology, such assessment can only reliably be carried out to the level of the subsegmental bronchi (ie, the fifth generation of the tracheobronchial tree), which are proximal to the portion of the respiratory tract that comprises the small airways (seventh or eighth generation and distally). Thus CT imaging currently provides only an indirect assessment of small airways disease.

Advances in CT technology over the last decade have led to the development of multidetector CT scanners that allow shorter scanning times and provide higher spatial and temporal resolution. Therefore whereas older scanners required 32 seconds of scanning time to acquire images throughout the lung with an axial slice thickness of 5 mm, the latest 64-detector scanners can acquire whole-lung data in only 4 seconds with slice thickness down to 0.4 mm. Thus earlier studies were greatly restricted in examination of the airways. More recent studies using 64-detector scanners can acquire whole-lung data that can process image data volumetrically, with anatomic segmentation into the 5 lobes and 18 bronchopulmonary segments. Therefore examining regional changes within all of the anatomically relevant regions of the lung and assessing the regional heterogeneity of small airways involvement between lobes and segments, as well as within these anatomic units, can be performed.

Of importance is the cooperation of the subject for the validity of the information. Imaging is routinely performed under controlled conditions with the patient supine at residual volume or functional residual capacity during a suspended breath hold. Spirometry is used to ensure that the subjects hold their breath at the stipulated volume.

Assessment of regional air trapping was based on analyses of frequency distribution curves of lung attenuation units (so-called lung attenuation curves [LACs]) by using a validated software package developed at the University of California, Los Angeles, and thus not subject to interobserver or intraobserver variation.[1] Shifts in these curves toward lower or higher attenuation (indicating an increase or decrease in regional air trapping, respectively) were also assessed with computer software.[1,2] Studies conducted in healthy volunteers provided normal reproducibility data, indicating that shifts in the LAC of greater than 7% represent an abnormal change.[2]

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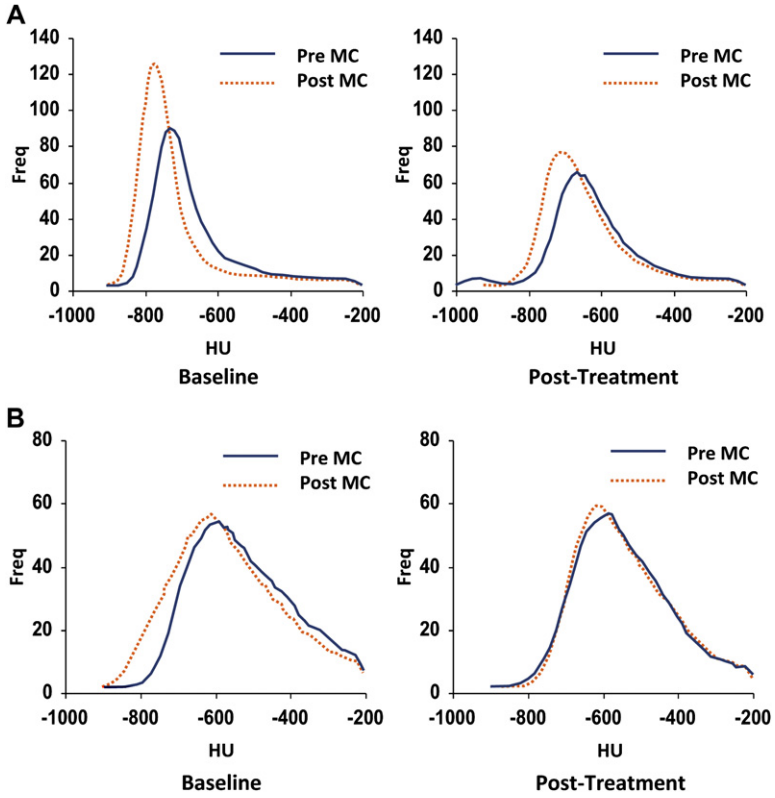

FIG 1. LACs from individual subjects using matched right upper lobe images before and after methacholine challenge at baseline and after treatment with BDP-CFC **(A)** and BDP-HFA **(B)**. The small-particle inhaled steroid (HFA-BDP) blocks the increase in air trapping after methacholine. The study was performed at residual volume. *Freq*, Frequency; *HU*, Hounsfield units (more negative number represents more air trapping); *MC*, methacholine.

STUDIES DOCUMENTING THE UTILITY OF HRCT IMAGING

Beclomethasone-hydrofluoroalkane versus beclomethasone-chlorofluorocarbon

An early interventional study tested the hypothesis that treatment for 1 month with an extrafine steroid aerosol (beclomethasone dipropionate [BDP]–hydrofluoroalkane [HFA]) in 31 steroid-naive asthmatic subjects would have a greater effect in reducing regional air trapping than the same microgram dose of the same molecule delivered from a conventional suspension steroid aerosol (BDP–chlorofluorocarbon [CFC]) with a randomized, double-blind parallel-group design.[3] The results indicated a significant shift in the LAC in the direction of greater attenuation (less regional air trapping) in the BDP-HFA–treated subjects but no shift in either direction in the BDP-CFC–treated subjects, the difference in the mean shifts in the 2 groups being statistically significant ($P < .05$). Moreover, although both groups of subjects showed similar shifts in the direction of lower attenuation (more air trapping) with methacholine at baseline, this methacholine-induced shift increased in the CFC-treated group (a representative example is shown in Fig 1, *A*) but diminished substantially in the HFA-treated group (a representative example is shown in Fig 1, *B*), with the difference between the 2 groups being statistically significant ($P < .04$). The latter findings suggest that regional hyperresponsiveness of smaller airways is reduced by the extrafine steroid aerosol but not by the larger-particle suspension steroid aerosol, implying that the former but not the latter penetrated the distal lung to an extent that suppressed inflammation (and thus hyperresponsiveness) in the small airways.

The possible clinical significance of these findings is suggested by the observation that shortness of breath (assessed by daily diary with a Likert scale) improved significantly more in the BDP-HFA group than in the BDP-CFC group. Moreover, the same subjects showed no changes in the dimensions of larger airways assessed at functional residual capacity in response to either formulation of BDP, suggesting that changes in larger airways were not responsible for the reduction in lung attenuation or improvement in symptoms in the BDP-HFA group.

Cat room antigen challenge

Approximately 25% of Fel d 1 antigen shed by cats is in the submicronic size range and therefore is capable of reaching the small airways and inducing an inflammatory response in this region of the lung. We therefore examined whether naturalistic exposure to cat allergen in a 50-m^3 room that contained 2 neutered cats could induce late allergic responses in the small airways detectable by means of HRCT with QIA techniques.

Ten subjects with cat-induced asthma were examined both physiologically and with HRCT before and 6 and 22 hours after a cat room challenge.[4] Although there was no significant decrease in FEV_1 at 6 or 22 hours, HRCT with QIA revealed increased

regional air trapping at both 6 and 22 hours after challenge; a representative example is shown in Fig 2, *A*. Forced expiratory flow at 25% to 75% of forced vital capacity ($FEF_{25\%-75\%}$) did decrease significantly at 6 hours but not at 22 hours, and closing volume, but not plethysmographically determined residual volume, increased significantly at both times periods after challenge. Interestingly, although the PC_{20} measured by using FEV_1 did not change from baseline after 22 hours, the change in CT attenuation in a selected region of the lung increased in response to methacholine at 22 hours after challenge occurred, indicating an increase in regional hyperresponsiveness (an example is shown in Fig 2, *B*).

These findings indicate that a real-world exposure to cat allergen can cause narrowing of the small airways evident at 6 hours (late asthmatic reaction) that persists for as long as 22 hours and is associated with regional hyperresponsiveness detectable by means of HRCT 22 hours after challenge that is not detectable spirometrically. Moreover, changes in 2 of the sensitive physiologic measures (closing volume and $FEF_{25\%-75\%}$) paralleled the HRCT findings at 1 or both time points, supporting the validity of the latter findings. It is noteworthy, however, that subjects had no symptoms of asthma 22 hours after the cat room challenge despite the significant HRCT changes. Although the clinical significance of these findings is therefore uncertain, it is possible that these changes represent clinically and physiologically silent distal lung inflammation that could serve as a substratum on top of which clinically significant asthma events could be superimposed.

Thus QIA of HRCT scans is a sensitive and noninvasive method of assessing involvement of the small airways in asthmatic patients and is capable of detecting narrowing of the distal airways (regional air trapping) and increased responsiveness of these airways to methacholine (regional increases in air trapping after methacholine) in response to various interventions when changes in traditional physiologic test results are largely undetectable. At present, QIA of HRCT remains a research tool, the clinical utility of which remains to be determined. Limitations of this technique include radiation exposure, particularly with repeated imaging, and expense.

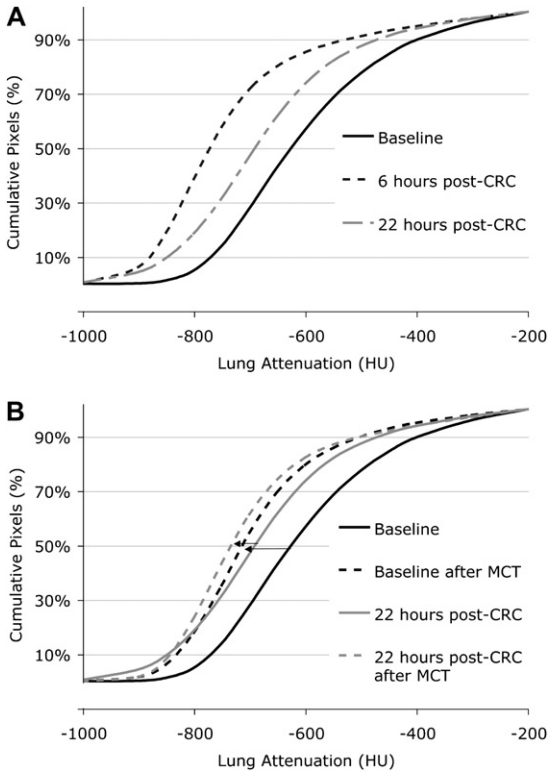

FIG 2. **A**, LACs before (baseline, *solid black line*) and 6 *(dashed black line)* and 22 *(dot-dashed grey line)* hours after cat room challenge. At 6 hours and to a lesser degree at 22 hours, there is an increase in air trapping. A left shift in the LAC indicates more air trapping. **B**, LACs before *(solid lines)* and after *(dashed lines)* methacholine before (baseline, *black lines*) and 22 hrs after *(gray lines)* cat room challenge. Methacholine causes an increase in air trapping (left shift in lung attenuation). However, 22 hours after cat room challenge, methacholine produces a further increase in air trapping. *CRC*, Cat room challenge; *HU*, Hounsfield units; *MCT*, methacholine challenge test.

HYPERPOLARIZED HELIUM-3 MAGNETIC RESONANCE IMAGING OF THE DISTAL LUNG

Magnetic resonance (MR) imaging with inhaled hyperpolarized helium-3 (^{3}He) gas is an investigational technique with which high-resolution images of the lung airspaces can be acquired.[5,6] Before imaging, the ^{3}He gas needs to be hyperpolarized in a special device (polarizer), and it typically takes several hours to produce liter quantities of the gas. When ^{3}He gas is inhaled and imaging is performed, the gas polarization quickly decreases (loses signal) by the radiofrequency pulses of the MR scanner, and as a result, the number of images that can be obtained from 1 inhalation of gas is limited. This is in contrast to conventional hydrogen-based MR imaging, a technique with which unlimited numbers of images can be acquired, because the strong magnetic field of the MR scanner causes the polarization of the nuclei to quickly recover after each pulse. However, conventional hydrogen-based MR imaging is poorly suited for airway imaging because the concentration of conventional hydrogen-based nuclei (ie, water) in air is low.

When the ^{3}He gas is inhaled, the gas distributes evenly in the healthy lung, and the airspaces are shown as homogeneous bright (white) structures.[7-9] When there is airflow obstruction, such as from airway closure, as seen in patients with asthma, the airspaces distal to the obstruction do not fill and are shown as black because of the lack of signal (Fig 3).[10] These foci of decreased or absent signal are also referred to as ventilation defects, and quantification of the defects provides a measure of the regional airflow. Because airflow obstruction forms the mainstay of the disease, ventilation defects are commonly found in patients with asthma, and we demonstrated in a recent study involving 58 asthmatic subjects with differing severity and 18 age-matched healthy subjects that the number and size of the defects correlate with clinical measures of disease severity and with spirometric results (Figs 4 and 5).[10] It was also shown that the mean number of ventilation defects per image slice (VDS) for the asthmatic subjects with moderate and severe persistent disease[11] was significantly greater than that for those with mild intermittent and mild persistent disease (1.37 ± 0.24 vs 0.53 ± 0.12, $P < .001$). Another interesting finding was that there were more asthmatic subjects with abnormal VDS than with abnormal FEV_1, forced vital capacity, FEV_1/forced vital capacity ratio, or peak expiratory flow. The number of asthmatic subjects with abnormal VDS and abnormal $FEF_{25\%-75\%}$ values was about the same. This could imply that VDS most closely correlates with $FEF_{25\%-75\%}$. It has

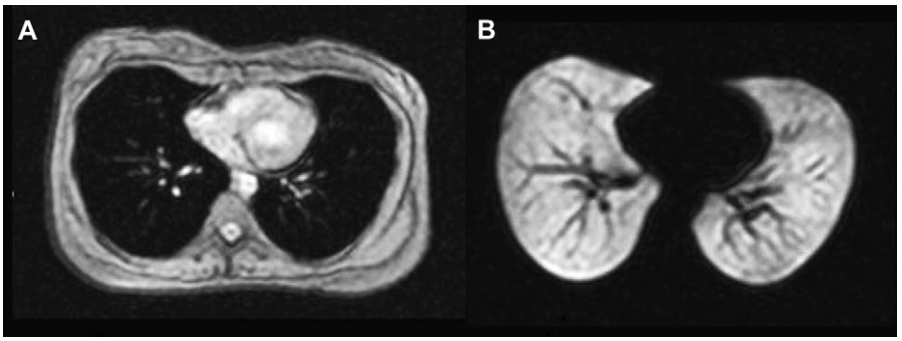

FIG 3. Healthy subject. **A**, Conventional axial hydrogen-based MR image of the chest showing the soft tissues of the chest. The airspaces of the lung are dark because of the low water content. **B**, A corresponding ^{3}He MR image obtained immediately after inhalation of the hyperpolarized ^{3}He gas shows a homogeneous bright appearance of the gas-filled airspaces. The dark linear structures within the lungs represent the pulmonary vessels. Reprinted with permission from de Lange et al.[10]

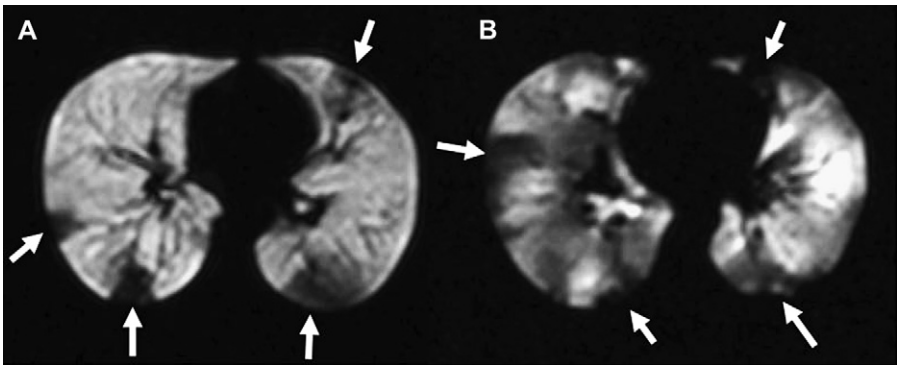

FIG 4. Axial ^{3}He MR ventilation images of moderate **(A)** and severe **(B)** persistent asthma. There are few defects in Fig 4, *A*, whereas there are many in Fig 4, *B* (several defects are indicated with *arrows*). The defects in Fig 4, *B*, are mostly pleural based, suggesting subsegmental narrowing or complete obstruction of the small airways. In Fig 4, *B*, the defects also involve the central portions of the lung, indicating that the proximal airways are also involved. Reprinted with permission from de Lange et al.[10]

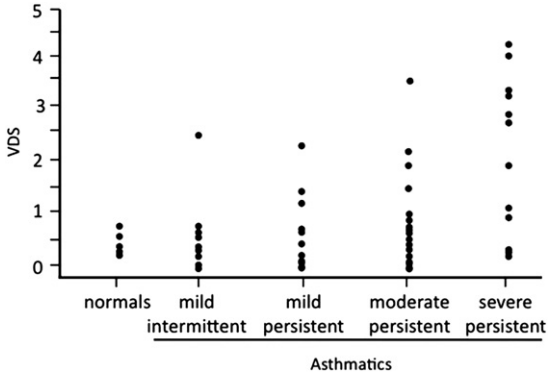

FIG 5. Scatterplot showing distribution of mean VDS for each subject by disease severity. Within asthma subgroups, there is a positive correlation between mean VDS and asthma severity ($r = 0.39$, $P = .003$), with the number of ventilation defects becoming greater with increasing disease severity. Reprinted with permission from de Lange et al.[10]

been suggested that $FEF_{25\%-75\%}$ is sensitive to narrowing of the small airways, and thus the abnormal VDS might be related to changes involving those airways.[12,13] However, other studies have had difficulty identifying objective changes in the small airways,[14,15] and therefore it remains uncertain which airways are involved when abnormalities in VDS are found in patients with asthma.

The ventilation defects can be remarkably persistent over time. Investigation recently showed that patients who were imaged twice within 42 to 82 minutes had 75% of their defects remaining in the same location and that most (71%) of these defects did not change in size.[16] When patients were imaged at longer (1-476 days) intervals, there was relatively little change in the total number of defects for each asthmatic subject, although the number of defects that remained in the same location decreased over time. However, a considerable number of defects remaining in the same location did not change size, with 67% of these still unchanged in size after 31 days (median interval), 43% after 41 days, and 38% after 85 days (Fig 6).[16] Thus in certain regions of the lungs, the airways appeared to remain persistently narrowed with time. This trend was regardless of disease severity or whether the patients used asthma medications.

It has also been shown that ventilation defects increase in number and extent when bronchoconstrictor (methacholine) is administered, as can be expected from the increase in airflow obstruction caused by the medication. This can also be demonstrated with exercise in patients who are sensitive to this.[17]

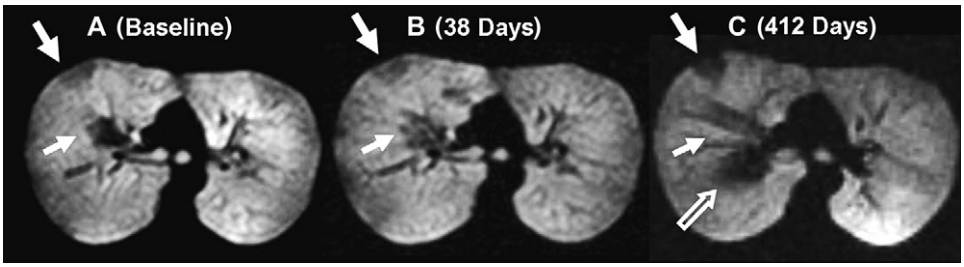

FIG 6. Long-term assessment of ventilation defects. **A**, Large *(large arrow)* and small *(small arrow)* defects are shown at baseline. **B**, The defects are unchanged in location and size *(arrow)* 38 days later. **C**, The large defect is also unchanged at 412 days *(large arrow)*. The small defect *(small arrow)* has slightly decreased in size, and a new central defect *(open arrow)* has developed. Reprinted with permission from de Lange et al.[16]

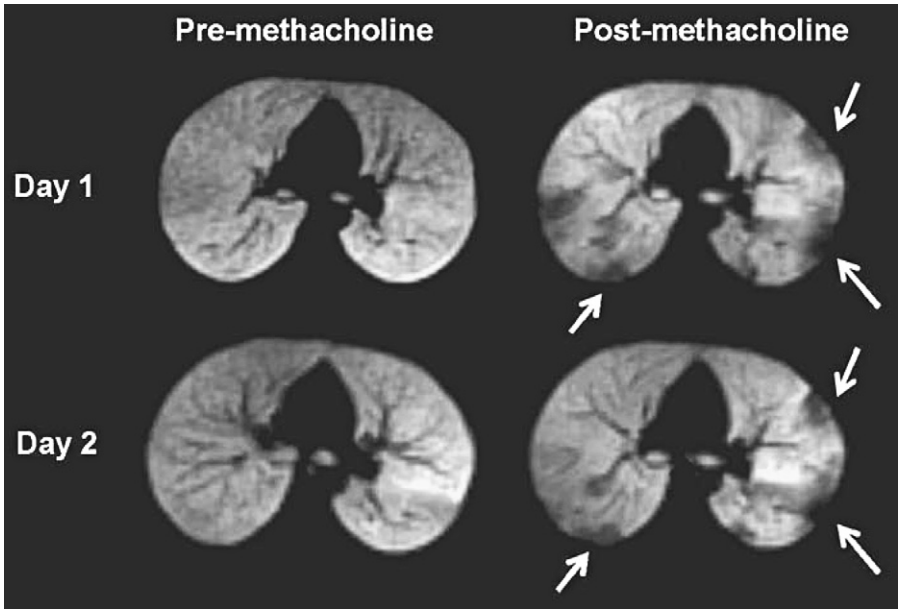

FIG 7. Premethacholine *(left)* and postmethacholine *(right)* images from day 1 are shown at the *top*, and those from day 2 (97 days later) are shown at the *bottom*. All images are from the same subject and at the same anatomic level. At baseline, there are no ventilation defects at this slice position on both days. After methacholine, multiple defects *(arrows)* have developed, with many of these in the same location on both days (several indicated with *arrows*). Reprinted with permission from de Lange et al.[18]

However, when methacholine is administered repeatedly (ie, the same dose on 2 different days), there appears to be a marked tendency for certain airways to respond to the same degree with each challenge.[18] More specifically, we found that 69% of the ventilation defects that appeared at the first challenge also occurred at the second challenge, and of those, 43% had the same size (Fig 7). These findings seem to suggest that certain airways are more sensitive to methacholine than others and that some are not sensitive at all. We have also shown that when a β-agonist is administered, the defects decrease in number and FEV_1 increases, as would be expected from the improvement of airflow caused by the bronchodilator.[19] When the effects of the medication wear off, the airways close down again, and the defects recur.[20] In a few patients one can see an increase in defects after a bronchodilator is administered, suggesting paradoxic bronchoconstriction.[21,22]

By using ^{3}He MR, one can also obtain spatial information about the lung microstructure by measuring the diffusivity of the gas in the lung (ie, the degree to which ^{3}He atoms move within the airspaces). Studies have demonstrated that the ^{3}He diffusivity is increased in patients whose airspaces are known to be enlarged, such as those with chronic obstructive pulmonary disease.[23] It has also been found in an animal study that the increase in the apparent diffusion coefficient (ADC) of ^{3}He correlates directly with the size of the alveolar space.[24] Initial investigations with this technique have shown variable results in patients with asthma.[25] However, using a more sensitive method for measuring ^{3}He diffusivity in 14 patients with severe, difficult-to-treat asthma, we found a slight but significant increase in ADC compared with that seen in healthy subjects, although the values were substantially lower than those seen in patients with chronic obstructive pulmonary disease.[26] Another interesting finding was that the ADC values remained increased when patients were treated with oral steroids, whereas there was improvement of the regional airflow, as evidenced by a decrease in the number of ventilation defects.[27] In

many of these patients, no abnormalities were shown with CT. Therefore the cause of the ADC increase in the patients with severe asthma is uncertain but might reflect permanent alterations of the airway structure or tissue remodeling.

In summary, with hyperpolarized ^{3}He MR imaging, the changes of airflow in the distal airways can be assessed in great detail and are depicted as ventilation defects. These defects can be markedly persistent in some areas of the lung, suggesting a relative regional distribution of the disease. A focal distribution of disease is also suggested from the relative persistent regional response that can occur after repeat methacholine challenge. Although medications such as short-acting bronchodilators and oral steroids lead to improvement of the regional airflow, as evidenced by the decrease in the number and size of the ventilation defects, persistent alterations in ^{3}He diffusivity can be demonstrated in the lungs of subjects with severe asthma, possibly reflecting permanent structural changes of the airways or tissue remodeling. Hyperpolarized ^{3}He MR imaging might become an important tool for assessing the distal airways in patients with asthma.

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