# Noninvasive Quantification of Airway Inflammation Following Segmental Allergen Challenge with Functional MR Imaging: A Proof of Concept Study

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## Purpose:
To evaluate oxygen-enhanced T1-mapping magnetic resonance (MR) imaging as a noninvasive method for visualization and quantification of regional inflammation after segmental allergen challenge in asthmatic patients compared with control subjects.

## Materials and Methods:
After institutional review board approval, nine asthmatic and four healthy individuals gave written informed consent. MR imaging (1.5 T) was performed by using an inversion-recovery snapshot fast low-angle shot sequence before (0 hours) and 6 hours and 24 hours after segmental allergen challenge by using either normal- or low-dose allergen or saline. The volume of lung tissue with increased relaxation times was determined by using a threshold-based method. As a biomarker for oxygen transfer from the lungs into the blood, the oxygen transfer function (OTF) was calculated. After the third MR imaging examination, eosinophils in bronchoalveolar lavage fluid were counted. Differences between times and segments were analyzed with nonparametric Wilcoxon matched-pairs test and Spearman correlation.

## Results:
In lung segments treated with the standard dose of allergen, the OTF was decreased at 6 hours in asthmatic patients, compared with saline-treated segments ($P = .0078$). In asthmatic patients at 24 hours, the volume over threshold was significantly increased in normal allergen dose–treated segments compared with saline-treated segments ($P = .004$). In corresponding lung segments, the volume over threshold at 24 hours in the asthmatic group showed a positive correlation ($r = 0.65$, $P = .0001$) and the OTF at 6 hours showed an inverse correlation ($r = −0.67$, $P = .0001$) with the percentage of eosinophils in the bronchoalveolar lavage fluid.

## Conclusion:
OTF and volume over threshold are noninvasive MR imaging–derived parameters to visualize and quantify the regional allergic reaction after segmental endobronchial allergen challenge.

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Online supplemental material is available for this article.
Recent advances in the understanding of the pathophysiologic characteristics of asthma gave room for the development of many promising new drugs (1). The testing of new drugs requires highly efficient, as well as safe, techniques to obtain reliable information in a small number of patients.

Allergen challenge in asthmatic patients is an important model for drug testing (2). While inhaled allergen challenge is the reference standard to investigate global changes in lung function, segmental allergen challenge has intensively been used to decipher inflammatory responses after allergen provocation (3–5) but has also been used to study the effectiveness of investigational newer drugs (6).

Following segmental endobronchial challenge with allergen, subsequent bronchoalveolar lavage is performed to identify the number of eosinophils, representing a marker for local inflammation. With this technique, only a small amount of allergen in an anatomically well-defined lung area is needed, reducing the systemic side effects. Overall, this procedure is accepted as a safe and reliable technique (7). However, bronchoscopy with bronchoalveolar lavage can provoke an acute phase response, which occasionally leads to discomfort and local, as well as mild, systemic side effects (8). Therefore, development of newer noninvasive imaging techniques for the evaluation of local inflammatory responses is of great interest.

Functional pulmonary magnetic resonance (MR) imaging has emerged into clinical practice in the past years (9–12). Hyperpolarized helium 3 (3He) MR imaging of the lungs was previously used for the detection of ventilation defects following a methacholine challenge in healthy and asthmatic individuals (13), as well as in ventilation analysis of children with asthma (14). Oxygen-enhanced MR imaging was shown to accurately depict clinical stages of different pulmonary diseases, including chronic obstructive pulmonary disease (15,16). In a group of asthmatic patients, it was shown that regional pulmonary function can be assessed by using oxygen-enhanced MR imaging (17).

As a functional parameter, the oxygen transfer function (OTF) has been introduced. The OTF is an imaging parameter that reflects airflow, oxygen diffusion capacity, and regional blood oxygenation and is therefore expected to change in areas of inflammation (18,19). We hypothesized that the volume of inflamed lung tissue may be detected with T1-mapping MR imaging and that this volume, as well as the OTF, may correspond to the severity of the inflammatory reaction determined by the percentage of eosinophils in the bronchoalveolar lavage fluid.

Therefore, this study aims to evaluate oxygen-enhanced T1-mapping MR imaging as a noninvasive method for visualization and quantification of the regional inflammation after segmental allergen challenge in asthmatic patients compared with control subjects.

Materials and Methods

Study Population

This prospective study was approved by the institutional ethical review board of Hannover Medical School, Hannover, Germany. Written informed consent was obtained from all volunteers.

Study subjects were recruited from the database of the clinical research site or by advertisement in newspapers. Inclusion criteria for all subjects in this study included the following: age of 18–55 years; nonsmokers with a history of less than one pack-year, having been nonsmokers for at least the past 5 years; and forced expiratory volume in 1 second (FEV1) greater than 80% of predicted. Additional inclusion criteria for asthmatic patients were as follows: a physician diagnosis of mild asthma according to the Global Initiative for Asthma, or GINA, guidelines (20), a positive skin prick test and positive responses to inhaled house dust mite allergen or grass pollen allergen (decrease of FEV1 of greater than 20% following inhalation with either grass mix or house dust mite).

Implication for Patient Care

- Oxygen-enhanced T1-mapping MR imaging is feasible for monitoring segmental inflammation in an experimental setup and should be evaluated for therapy monitoring in patients with asthma.
Additional inclusion criteria for healthy control subjects included the following: healthy status with no clinical evidence of allergic rhinitis, no clinical evidence of any other respiratory disease, and a negative skin prick test at or within 12 months prior to inclusion in this study. Furthermore, control subjects needed to show a negative response to an incremental methacholine challenge (provocative concentration of methacholine needed to produce a 20% decrease in FEV₁ from baseline > 8 mg/mL) and a total serum immunoglobulin E (IgE) level of less than 100 IU/mL (0.24 mg/L).

Upper or lower respiratory disease at the time of the first imaging examination or up to 4 weeks before was regarded as an exclusion criterion. Also, insufficient MR image quality (eg, breathing artifacts, anatomic mismatch of room air and oxygen images more than 7.5 mm) and contraindications for MR imaging (ie, pacemaker) were exclusion criteria.

The study population characteristics are detailed in the Table. No significant difference between the age of male and female participants was found (Mann-Whitney U test, \( P = .91 \)).

### Study Protocol

All subjects underwent three MR imaging examinations. The first MR imaging examination was performed on the day prior to the first time bronchoscopy (0 hours) and segmental allergen challenge were performed. Subsequent MR imaging examinations were performed at 6 and 24 hours after segmental challenge. Bronchoscopy was performed the second time at 24 hours and was completed within 1–2 hours after the final MR imaging examination.

### Bronchoscopy and Segmental Allergen Challenge

Subjects underwent bronchoscopy twice at 24 hours apart. The preparation, conduct, and observation of the bronchoscopy with segmental allergen challenge has been described in detail before (5). At the first time bronchoscopy was performed, all subjects underwent baseline bronchoalveolar lavage in the left lower lobe. In patients with asthma, instillation was performed with the standard dose of allergen, determined as described before (4), in two segments of contralateral lungs (ie, right middle lobe and lingula, respectively) to study individual reproducibility. Allergen 1 and allergen 2 were individually chosen for each patient, following a positive skin prick test. Moreover, instillation was performed in another segment in the right upper lobe with one-tenth of the standard allergen dose (low allergen dose). In addition, instillation was performed in one segment in the middle lobe unaffected by allergen with 10 mL of normal saline to control for specificity of the procedure (Fig 1, A).

In healthy subjects, instillation was performed only three times, and only one instillation with the standard dose of allergen was performed because reproducibility was not a question. In contrast, in one additional segment in the right middle lobe, lavage was performed with 150 mL of saline at the first time bronchoscopy was performed to increase the total number of recovered cells for separate in vitro experimentation.

After 24 hours, lavage was performed in all segments in which instillation was conducted, and cells were counted and differentiated as described before (5).

### Spirometry

Spirometric measurements were performed according to the American Thoracic Society and European Respiratory Society recommendations immediately after the first MR imaging examination, before the second MR imaging examination, and before the second bronchoscopy. Spirometric measurements were repeated on two of the MR images and during the second bronchoscopy. Spirometry was used to determine a provocative concentration of methacholine needed to produce a 20% decrease in FEV₁ from baseline (PC₂₀). Spirometry was not used to assess the degree of airway nonuniformity within the lungs.
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imaging examination, and at 24 hours after provocation (21).

MR Imaging Sequences and Protocol

For rapid lung T1 mapping, an inversion-recovery snapshot fast low-angle shot sequence at 1.5 T (Avanto; Siemens Healthcare, Erlangen, Germany) with an eight-channel torso phased-array coil was used, which has been described in detail by Jakob et al (22): repetition time msec/echo time msec, 3.0/0.8; flip angle, 8°; inversion times, 32, with a time frame of 200–6400 milliseconds; acquisition matrix, 128 × 64; field of view, 50 × 50 cm; section thickness, 15 mm; gap, 7.5 mm. Three to four coronal sections covering the challenged segments were acquired in a single breath hold each. The subjects were instructed to breathe normally and stop breathing at the end of a normal inspiration (23). T1 maps were obtained while the patient was breathing room air and again while the patient was breathing 100% oxygen administered by using a standard face mask with a reservoir of 2 L (Adult Non Re-Breather Mask; Mallinkrodt Covidien, Mansfield, Mass) (24). Six minutes of wash-in time before image acquisition was allowed. For identification of segmental arteries, coronal images were acquired by using a true fast imaging with steady-state precession sequence: 412/1.16; flip angle, 70°; acquisition matrix, 256 × 256; field of view, 45 × 45 cm; section thickness, 4 mm; gap, 2 mm.

T1 Map Generation and Segmentation

T1 maps were generated as previously described (22,23): Registration of the individual magnitude images obtained at 100% oxygen onto room air images was performed by using a nonrigid registration algorithm (Advanced Normalization Tools; http://stnava.github.io/ANTs/ [25]). Afterward T1 maps were calculated from the magnitude images by using a nonlinear fit (26) within a self-developed Matlab script (MatLab 2012a, MathWorks, Natick, Mass). One radiologist (J.R., with 2 years of experience in thoracic radiology), who was blinded to the bronchoalveolar lavage results, manually segmented both lungs. Segmental arteries were identified on an additionally acquired coronal true fast imaging with steady-state precession sequence, and segmental borders were drawn according to a lung segment model (Lung: Segmental Anatomy; http://svhrad.com/DigLib/Pulmonary/Segmental%20Anatomy/Segmental%20Anatomy.htm). For segmentation and quantification, image processing software (Mevislab Ver. 2.4, 64bit Macintosh version; MeVis Medical Solutions, Bremen, Germany) was used.

Quantification of Segmental Inflammation

For quantification of segmental inflammation, two parameters were evaluated:

1. An automatic threshold–based method (Fig E1 [online]). The threshold value for quantification of the volume of inflamed tissue was defined as 2 standard deviations above the mean T1 value of all sections covering the segments used for this experiment (ie, three to four anterior sections) at baseline (0 hours) at room air. The volume of lung tissue over this threshold was calculated at all three times. At first, this volume was analyzed for all acquired coronal sections. In a second analysis, the volume over threshold was determined for each segment and compared with the corresponding alveolar lavage data.

2. The functional parameter OTF (18). The OTF was calculated on a voxel-by-voxel basis by using coregistered T1 maps acquired at room air and at 100% oxygen, as shown in the following equation:

\[
\text{OTF} = \frac{1}{\frac{T1_{100\%O_2}}{C_{100\%O_2}} - \frac{T1_{21\%O_2}}{C_{21\%O_2}}},
\]

where \(T1_{100\%O_2}\) is the T1 value breathing 100% \(O_2\) and \(T1_{21\%O_2}\) is the T1 value acquired breathing room air (21% \(O_2\)) and \(C\) is the concentration of \(O_2\) (18). The volume over threshold on the 6-hour image was defined as the maximum affected lung area per treated segment. To compare these voxels on

Figure 1: T1 maps covering the challenged lung segments (S). A, Segmental model of the challenged lung segments. B, MR T1 maps acquired with the patient breathing room air in one asthmatic patient at all three times. Representative regions of interest (○) show T1 times over time. ms = Milliseconds.
all three MR images, the volume was copied to the 0-hour, as well as the 24-hour, image and manually adjusted to fit the same area. No additional registration has been used between the different MR images. In segments with no volume over threshold, corresponding areas were segmented manually on the 6-hour image and applied to the 0- and 24-hour images.

The first analysis with respect to time kinetics was made by using the standard-dose–allergen segments in the healthy volunteers and the asthmatic patients. The second analysis compared saline, low-dose, and standard-dose segments within the asthmatic patient group. Furthermore, the OTF was compared with the bronchoalveolar lavage fluid data, again on a per-segment basis in the asthmatic patients.

**Statistical Analysis**

Using the D’Agostino-Pearson omnibus normality test, some of the observed values were found not to follow a Gaussian distribution. Therefore, and because of the relatively low numbers of participants within the groups, non-parametric statistical analysis was chosen for the whole experiment.

A P value less than .05 was considered to indicate a significant difference. To account for multiple comparisons, Bonferroni correction was used, and corrected P values are given where applicable. For comparison between different times, as well as between different lung segments within the groups, the Wilcoxon matched-pairs signed-rank test was used. For comparison of the absolute T1 values under room air between asthmatic patients and the control group, the Mann-Whitney test for rank comparison was used.

For correlation between the percentage of eosinophilic cells in the bronchoalveolar lavage fluid with the volume over threshold, as well as the OTF, nonparametric Spearman correlation was used. Results are given as median and 25% and 75% quartiles. For statistical analysis and illustrations, software (Prism 6.0c; GraphPad Software, La Jolla, Calif) was used.

**Results**

**Study Group**

All participants except one completed the full study protocol without side effects. This subject was excluded from the study because of an accident outside the testing facility, which was not related to the study. Two subjects were excluded because of inadequate MR image quality: In one patient, the T1 maps acquired with the subject breathing oxygen did not colocalize to the room-air images, and in the other patient, it was not possible to calculate T1 maps because of severe breathing artifacts.

**Lavage Fluid**

The percentage of eosinophils of total cells in the bronchoalveolar lavage fluid was significantly higher in the allergen-treated segments compared with the saline-treated segment (Fig 2, A).

For the control group, in all segments, less than 2% eosinophilic cells and no significant differences between the segments were detectable.

The absolute number of cells per milliliter of lavage fluid was not significantly different after Bonferroni correction (level of significance, P = .0125) between saline- and allergen-challenged segments in the control group (P > .5 for each comparison). For the asthmatic patients, the absolute number of eosinophils in the normal-dose segments increased significantly (allergen 1, P = .0078; allergen 2, P = .0039) but not in the low-dose segment (P = .16), both compared with saline-treated segments.

**Spirometry**

The FEV₁ in percentage of the predicted value decreased significantly (Bonferroni-corrected P value, P < .025) after 4 hours (median, 83.8% [25th and 75th quartiles, 77.2% and 93.5%]; P = .012), as well as after 25 hours (median, 83.8% [25th and 75th quartiles, 78.7% and 98.5%]; P = .0039) compared with baseline (median, 93.4% [25th and 75th quartiles, 99.1% and 113.0%]) in the asthmatic patient group. In the control group, there was no significant difference between values at 4 hours and baseline (P = .25), as well as between values at 25 hours and baseline (P = .125).

**T1 Relaxation Changes in Lung Tissue**

Before treatment, the median T1 value of the total lung at room air was 1181 milliseconds (25th and 75th quartiles, 1141 and 1207 milliseconds) in allergic asthmatic patients, which was significantly lower (Mann-Whitney test, P = .004) compared with the T1 value for healthy control subjects (median, 1314 milliseconds [25th and 75th quartiles, 1201 and 1404 milliseconds]). The heterogeneity of T1 values, measured by the coefficient of variation, was not significantly different between asthmatic patients (median, 0.061 [25th and 75th quartiles, 0.038 and 0.075]) and healthy control subjects (median, 0.062 [25th and 75th quartiles, 0.023 and 0.075]) (Mann-Whitney test, P = .61).

In asthmatic patients, the total volume of lung tissue over threshold on all acquired sections showed a significant increase for both the 6-hour (P = .0039; Bonferroni-corrected P value, P < .025), as well as the 24-hour (P = .0078) images, compared with saline-treated segments (Fig 3, A). In the healthy volunteers, there was no significant difference in the volume over threshold for both the 6-hour image (P = .125), as well as the 24-hour image (P = .875), compared with saline-treated segments (Fig 3, B). In a segmental analysis, there was a significantly increased volume over threshold at 24 hours in the asthmatic patient group, with higher volumes in the allergen-treated segments for both allergens used (Fig 2, B). A positive correlation between the percentage of eosinophils and the volume over threshold at 24 hours (P = .05, r = 0.0001) was observed in the asthmatic patient group, including all treated segments (Fig 4, A). There was no correlation between the volume over threshold and the total number of cells in the lavage fluid.

**Oxygen Transfer Function**

The OTF in the segments treated with the standard dose of allergen differed in the asthmatic patient group over time:
Figure 2

![Graph A](image1)

**A** Eosinophils

<table>
<thead>
<tr>
<th></th>
<th>Eosinophils ( % of total cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>0</td>
</tr>
<tr>
<td>1/10 allergen</td>
<td>1.75</td>
</tr>
<tr>
<td>Allergen 1</td>
<td>11.3</td>
</tr>
<tr>
<td>Allergen 2</td>
<td>31.1</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Saline</th>
<th>1/10 allergen</th>
<th>Allergen 1</th>
<th>Allergen 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>0.0</td>
<td>1.75</td>
<td>11.3</td>
<td>31.1</td>
</tr>
<tr>
<td>Median</td>
<td>0.250</td>
<td>5.50</td>
<td>30.8</td>
<td>51.3</td>
</tr>
<tr>
<td>75%</td>
<td>1.25</td>
<td>27.6</td>
<td>56.0</td>
<td>66.0</td>
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</table>

**B** Volume over threshold (24h)

<table>
<thead>
<tr>
<th></th>
<th>Volume [ml]</th>
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</thead>
<tbody>
<tr>
<td>Saline</td>
<td>1.85</td>
</tr>
<tr>
<td>1/10 allergen</td>
<td>3.26</td>
</tr>
<tr>
<td>Allergen 1</td>
<td>17.7</td>
</tr>
<tr>
<td>Allergen 2</td>
<td>9.87</td>
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</table>

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Saline</th>
<th>1/10 allergen</th>
<th>Allergen 1</th>
<th>Allergen 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>5.92</td>
<td>5.24</td>
<td>30.4</td>
<td>29.4</td>
</tr>
<tr>
<td>Median</td>
<td>12.4</td>
<td>27.3</td>
<td>61.8</td>
<td>43.8</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>OTF [10^-4 s^-1 x %0.2%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>9.09</td>
</tr>
<tr>
<td>1/10 allergen</td>
<td>5.17</td>
</tr>
<tr>
<td>Allergen 1</td>
<td>2.65</td>
</tr>
<tr>
<td>Allergen 2</td>
<td>3.54</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Saline</th>
<th>1/10 allergen</th>
<th>Allergen 1</th>
<th>Allergen 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>12.7</td>
<td>6.61</td>
<td>4.99</td>
<td>5.04</td>
</tr>
<tr>
<td>Median</td>
<td>14.9</td>
<td>13.2</td>
<td>6.21</td>
<td>7.81</td>
</tr>
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</table>

There was a significant (P = .0007; Bonferroni-corrected P value, P < .025) decrease at 6 hours and normalization to baseline values at 24 hours (P = .229, compared with saline) (Fig 3, C). In the standard-dose–allergen treated segments of the healthy control subjects, the OTF remained unchanged (Fig 3, D). For low-dose treated segments (P = .19), there was no significant difference in both groups. In the asthmatic patient group at 6 hours, the OTF differed between the segments and was significantly reduced in the standard-dose–allergen treated segments compared with the saline-treated segments (allergen 1, P = .0078; allergen 2, P = .0117; Bonferroni-corrected P value, P < .0125) (Fig 2, C). The low-dose–treated segments showed a trend toward decreased OTF values, but they were not significantly different (P = .027) compared with the saline-treated segments after Bonferroni correction.

In the asthmatic patient group, an inverse correlation between the percentage of eosinophils and the OTF at 6 hours (r = −0.67, P = .0001) was observed, including all treated segments (Fig 4, B). There was no correlation between the OTF and the total number of cells in the lavage fluid.

**Discussion**

This study shows two new MR imaging-derived parameters—volume over threshold (24 hours after challenge) and OTF (6 hours after challenge)—that correlate with the percentage of eosinophils in the bronchoalveolar lavage, an established marker of pulmonary inflammation in asthma patients.

The T1 relaxation times found for healthy control subjects before endobronchial allergen challenge are in the same range as previously published (27). The T1 values in the asthmatic patient group were significantly lower, which may reflect the pathophysiological changes of the lung parenchyma in asthma, including basal membrane thickening, vascular remodeling, airway smooth muscle hypertrophy, as well as hyperinflation (28). Interestingly, the heterogeneity of the lung tissue T1 was not significantly different between the control group and the asthmatic patients, which may indicate that changes of absolute T1 in the...
asthmatic patients without current exacerbation are diffuse throughout the lung parenchyma.

Though not significant, the T1 values at 6 hours showed a notable trend toward increased T1 values in the challenged segments for healthy individuals and a significant increase for asthmatic patients, which may in part be caused by an unspesific response to bronchoscopy. Also, the amount of instilled saline (10 mL), which may be incompletely cleared, may have led to elevated T1 times in both groups 6 hours after challenge.

The allergic reaction in asthmatic patients leads to an acute inflammation, predominantly an eosinophilic response (type I allergic reaction) (29). This leads to airway constriction and hypoventilation in the distal airways and may account for the reduced OTF seen at 6 hours in the asthmatic patient group, which was not observed in the control subject group. The decreased OTF at 6 hours also corresponds to the mild decrease of the FEV1 percentage predicted values at 4 hours, which was observed only for the asthmatic volunteers. Therefore, the OTF might reflect the regional change in lung function at the side of the inflammation.

The long-term reaction leads to prolonged inflammation with edema formation (30). A previous study of an asthma model in mice showed that 24 hours after sensitization a signal intensity increase on gradient-echo MR images was predominantly caused by edema formation (31). Furthermore, it was shown that, in myocardial edema, increased T1 values can be detected (32). This may explain the elevated T1 values in the allergen-treated segments of the asthmatic patients at 24 hours, which were at baseline levels in the control subject group at this time. Mainly edema due to regional inflammation may account for this difference. In addition, consolidation of lung tissue following infiltration with inflammatory cells such as eosinophils or T cells may also add to the change in T1 relaxation time.

OTF was introduced as a marker for the local capacity of oxygen delivery to the blood. Physiologically, it is influenced by perfusion, ventilation, and the diffusion capacity (18). Therefore, the decreased OTF at 6 hours in the allergic asthmatic patient group may reflect local hypoventilation due to bronchoconstriction and decreased gas exchange at the basal membrane level due to the inflammatory response, which is present only in the hypersensitive bronchial system of atopic patients (33). In addition, the OTF correlates negatively with the eosinophilic response measured at the 24-hour time. Therefore, the OTF may enable distinction between allergic patients and healthy control patients at the 6-hour time, while volume over threshold depicted the allergic response best at 24 hours after provocation.

The volume over threshold at 24 hours correlated positively only with the percentage of eosinophils, not with the total number of cells in the lavage fluid. In a study by Blé et al (31) using an asthma mouse model and a gradient-echo MR imaging sequence, a correlation of the increased signal volume with both the total number of cells, as well as the eosinophil count, was reported. However, especially for the assessment of immunologic reactions, it is of great
importance to evaluate possible drug targets in humans because of complex immunologic reaction differences in animal models (34). Although the observed regional T1 changes reflect nonspecific edema and infiltrate and not directly the number of eosinophils within a challenged segment, in this controlled study setting, the volume over threshold at 24 hours was specific for the delayed phase response after regional allergen challenge in asthmatic patients.

Compared with previously published data using positron emission tomography for the detection of eosinophilic inflammation in human subjects (35), oxygen-enhanced MR imaging uses no ionizing radiation and can be easily performed with standard clinical MR imaging systems.

This newer technique, monitoring the local pulmonary inflammation, may also be transferred to other pulmonary diseases, which show regional inflammatory affection of the lung tissue. Application of this technique might include the quantification of neutrophilic events in cystic fibrosis, pneumonia, or bronchiectasis. Predominantly, this technique may enable longitudinal monitoring of patients and the effectiveness of treatment. Further studies are needed to evaluate this role of T1 mapping in pulmonary disease.

A limitation of the presented technique is given by the low resolution of MR images, leading to difficulties in segmentation of lung segments. However, with the presented technique based on higher-spatial-resolution images for vessel detection, sufficient accuracy should be reached. In previous work, it has been shown that T1 time determination for the lungs is reproducible using this technique (23). Furthermore, statistical power is limited, because of the relatively small number of patients, and studies with more patients are needed to underline the presented findings.

In conclusion, the data of the present study show that MR imaging–derived OTF (6 hours after provocation) and volume over threshold (24 hours after provocation) can aid clinicians to monitor noninvasively local allergen response in the lung tissue of volunteers with asthma following segmental allergen challenge. These MR imaging parameters correlate with established markers of inflammation. Therefore these MR imaging–based noninvasive measurements may add value in the characterization and quantification of the inflammatory response in future drug trials and may reduce the number of bronchoscopic examinations needed.

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Disclosures of Conflicts of Interest: J.R. disclosed no relevant relationships. M.G. disclosed no relevant relationships. C.W. disclosed no relevant relationships. C.F. disclosed no relevant relationships. P.J. disclosed no relevant relationships. F.S. disclosed no relevant relationships. J.V. disclosed no relevant relationships. E.W. Financial activities related to the present article: received a grant from BMBF, German Centre for Lung Research (DZL). Financial activities not related to the present article: received grants from Promedicus Ltd; DFG, Rebirth Cluster of Excellence; and Siemens Healthcare. Other relationships: none to disclose. J.M.H. Financial activities related to the present article: received grant DFG SFB878/88 from Deutsche Forschungsgemeinschaft and Disease Area COPD grant from Deutsches Zentrum für Lungenforschung. Financial activities not related to the present article: none to disclose. Other relationships: none to disclose. J.V. disclosed no relevant relationships.

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