Using magnetic resonance imaging to quantify the inflammatory response following allergen challenge in allergic rhinitis

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Abbreviations
ARDX, Acoustic rhinometry distance of minimal cross sectional area; ARMXCA, Acoustic rhinometry of nasal volume and minimum cross sectional area; ARV, Acoustic rhinometry volume; ARX, Acoustic rhinometry cross sectional area; METASV, Average airspace sectional area; MIXA, Minimum cross sectional area; MRI, Magnetic resonance imaging; NCV, Nasal cavity volume; nNO, Nasal nitric oxide; NSSC, Nasal symptom score for congestion; NTIV, Nasal tissue volume; PD, Proton density; PNIF, Peak nasal inspiratory flow; PNIFMAX, Maximum peak nasal inspiratory flow; TASSV, Total airspace volume; TMSA, Total mucosal surface area; TNCV, Total nasal cavity volume; TNCVm, Normalized TNCV; TNSS, Total nasal symptom score; TNTV, Total nasal tissue volume; T2, Transverse relaxation time; VAS, Visual analog scale; VASCR, Visual analog scale score

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Abstract
Current rhinometric and flow assessments measure nasal patency and are often poorly correlated with rhinitis symptoms. To evaluate magnetic resonance imaging (MRI) as a new method to measure inflammatory changes in nasal and sinus mucosa following nasal allergen challenge. A pilot study (n = 6) determined the optimal technical settings for MRI to measure inflammatory change which were then adopted for the main study. This study was a single blind, placebo-controlled, three-way crossover trial in 14 subjects with seasonal allergic rhinitis. Effects of cetirizine, cetirizine and pseudoephedrine (Cet+PE), or placebo on total nasal symptom scores (TNSS), peak nasal inspiratory flow (PNIF), nasal nitric oxide (nNO), acoustic rhinometry, and MRI end points following nasal intranasal allergen challenge were measured. There were significant changes in all parameters after allergen challenge (P < 0.01), except for nNO. MRI end points were less variable and more consistent than PNIF and acoustic rhinometry in detecting changes after allergen challenge. Total nasal airspace volume was the most sensitive and reproducible MRI measurement, with a mean reduction from 5.37 cm³ (95% CI 7.35, 3.38; P < 0.001), which was maximal 60 min after allergen challenge. A change of one in TNSS corresponded to a change in MRI volume of 0.57 cm³.

There was an improvement in all parameters (except nNO) in subjects taking Cet+PE compared with placebo, however this did not achieve significance probably because of the small study size (overall analysis P > 0.07; comparison of active versus placebo P > 0.09). MRI provides novel insights into the anatomical inflammatory changes post allergen challenge and provides a new method for assessment of nasal patency and objective measurement of inflammatory responses.

Introduction
Nasal provocation has been used to investigate the pathophysiology of allergic and non-allergic rhinitis, and is thought to have potential value for the evaluation of mechanisms of inflammation in both upper and lower airways, because of the similarity of the inflammatory responses to allergen challenge [1]. Traditionally, the evaluation of therapies for allergic rhinitis have used symptom-based scores (total nasal symptom score; TNSS) or visual analog scale (VAS) methods, despite the subjective
nature and high variability of these tests [2–5]. There is a
need for more objective and reproducible biomarkers
of allergic inflammation which are non-invasive to
facilitate the clinical assessment of novel anti-
inflammatory drugs.

H1-receptor antagonists (anti-histamines) are widely
prescribed for the treatment of allergic rhinitis but
have limited clinical efficacy. Anti-histamines may relieve
symptoms of itch, sneeze, and discharge but are less effective
treatments for nasal blockage. Nasal blockage may result
from oedema and vascular congestion. Therefore, the
combination of the antihistamine cetirizine (Cet) [6] and
a decongestant, such as pseudoephedrine (PE), has a logical
rationale [7, 8]. We compared the effect of single doses of Cet
(10 mg) alone or Cet (10 mg) and PE (120 mg) in
combination versus placebo to evaluate MRI end points
against symptom scores (TNSS, VAS, and nasal symptom
score for congestion NSSC), measurements of nasal
patency [4, 9], acoustic rhinometry, peak nasal inspiratory
flow (PNIF), acoustic rhinometry of nasal volume and
minimum cross sectional area (ARMXCA) and nasal nitric
oxide (nNO) [10–12]. The study was conducted in two parts,
with an initial pilot phase to determine the relevant MRI
parameters and a second study as a single-blind three-way
cross over study.

Methods

Subjects

Asymptomatic subjects with a diagnosis of seasonal allergic
rhinitis and a previous positive skin prick test for Timothy
grass pollen at or within the 12 months preceding the
screening visit were selected. Six subjects were recruited to
part 1 of the study. Fourteen subjects were randomized in
part 2, this included the six subjects from part 1. All
subjects were included in the analysis, the average age
of subjects was 31 years with a male to female ratio of
12:2. Full details of the subject characteristics at baseline
can be found in the supplemental data online (Table SI).
This prospective study was approved by the East London
and the City Research Ethics Committee (07/Q0603/3)
and written informed consent was obtained from all
subjects.

Pilot study to optimize MRI parameters

A pilot study (data not shown) determined the technical
parameters for MRI imaging and the optimal times to
perform MRI scans post allergen challenge. Two MRI
scans were performed after the allergen challenge: an
early scan after 15–30 min and a second scan at 45–60 min.
The MRI data were reviewed by a radiologist and
MRI parameters were defined for all subsequent scans
in the main study (see Results). The optimal time to
perform the MRI scan was found to be at 60 min post-
challenge when there were maximal inflammatory changes.
However, at this time point the TNSS response was
submaximal at 80% of the peak response which occurred at
the earlier 15 min time point as we have previously
described [13].

Controlled trial of rhinitis therapies

The study design is shown in Figure 1. This was a
randomized, single-blind, placebo-controlled, double-dum-
my, three period, crossover single oral dose study in patients
with allergic rhinitis. Subjects were assessed at baseline with
MRI scan, symptom scores, plus measurements of nasal
patency. The same order of investigations were repeated at
the different time points throughout the study. Subjects were
then dosed according to the randomization code. Subjects
were blindfolded before each dose administration. Active
treatments and double dummy placebo were administered
with 50 mL water and tablets swallowed under direct
observation by the study nurse. The study medications
were as follows: CONTACT 120 mg (pseudoephedrine
hydrochloride). Zirtek 10 mg (cetirizine hydrochloride).
There were matching placebo tablets for both Zirtek, and
CONTACT 120.

The MRI scan and all measurements were repeated 60 min
after drug administration and immediately before the
allergen challenge procedure. Nasal allergen challenge was
then performed (see below). The final MRI scan was
repeated at 60 min post-allergen challenge and all other
measurements repeated. Each treatment period was separat-
ed by a wash-out period of at least 7 days. This time period
allowed the nasal mucosal process to return to a non-
symptomatic baseline.

Nasal allergen challenge

Nasal allergen challenge was performed as previously
described [1, 13] with Timothy grass pollen (Alk-Abello,
Denmark). Application of the allergen to the nasal mucosa was undertaken using a nasal pump spray (Dolphin nasal applicator, Valois [14–16]. A total dose of 1 μg was given as 100 μL to each nostril (500 BU/mL to each nostril).

**Acoustic rhinometry and PNIF**

Rhinometry was performed at screening pre-challenge pre-dose, and 60 min after challenge. Rhinometry assessments were made of nasal volume and minimum cross sectional area (ARMXCA) using an A1 acoustic rhinometer (GM Instruments, Kilwinning, UK). With a nosepiece inserted, subjects were asked to breathe in and hold their breath. The measurement was repeated three times. PNIF and maximum PNIF (PNIFMAX) were measured with a Portable Nasal Inspiratory Flow Meter (Clement Clark, Harlow, UK), with full exhalation beforehand. The PNIF was a short, sharp inspiratory action of approximately one second duration within an anesthetic mask tightly applied to the face. The measurement was repeated three times and the highest result recorded.

**nNO**

nNO was measured using the NIOX analyser (Aerocrine, Stockholm, Sweden) with sample time of 40 s, with tidal breathing for approximately 5 s. The subject inhaled to total lung capacity over 2–3 s with the mouth open, then closed the mouth and held the breath as long as possible. Sample flow did not fall more than 1.5 mL/s below its normal value (around 5 mL/s). The procedure was repeated to obtain three readings within 10% of each other.

**Symptoms**

Patient assessment of nasal patency was performed using VAS 0–100 mm. and TNSS completed by the subject. TNSS were recorded before and at frequent intervals after nasal allergen challenge. Nasal congestion, rhinorrhoea, sneezing, and nasal itch were scored from 0 to 3 (0 no, 1 mild, 2 moderate, 3 severe symptoms). The scores were then added up to give a final TNSS out of a maximum of 12.

**MRI measurements**

MRI measurements were made using a Siemens 1.5T MRI scanner (Siemens Heathcare, Erlangen, Germany) with an average scan time for each subject approximately 15 min. Settings were 4–5 min for proton density (PD) and transverse relaxation time (T2) coronal views (4–5 min) with 40 slices, the dimensions were field of view (the size of the two dimensional spatial encoding area of the image; 160 × 143 mm²), matrix (384 × 205) and voxel size (0.7 × 0.4 × 0.3 mm³); time to equal (PD weighting = 43 ms; T2 weighting = 128 ms); time to repeat (6120 ms). Cross-sectional airspace area (and thus also airspace volume) of the nasal passages was measured. Within subject, the cross-sectional airspace area is directly proportional to the airspace volume per slice.

The primary endpoint was average airspace sectional area (METASV). Secondary MRI endpoints were: volume of fluid identified adjacent to the airspace; total mucosal surface area (TMSA); total nasal cavity volume (TNCV; a single value which could be applied to all time points per patient—either the single value derived following image registration, or the average of the values used for each time point per patient visit) and nasal tissue volume (NTV) derived from the nasal cavity volume less airspace and fluid volumes (the resulting volume included cartilage, bone, enclosed airspace and other factors and was only indicative of the tissue volume).

All MRI endpoints were considered in two ways: regularly defined intervals along the nasal passage, to allow standardized subject profiles to be plotted, and totals or averages along the entire length of the nasal passage to provide a simple subject-level summary at each time point (additionally, the smallest cross-sectional airspace area in any slice along the nasal passage and the location of this slice was determined). The maximum number of slices per subject was 21 so location specific MRI measurements were derived over 20 slices. MRI assessments of congestion included: total airspace volume (TASV), METASV, minimum cross-sectional area (MIXA), TNCV, and TMSA.

**Statistics**

This exploratory study was not formally powered, but was based on feasibility and exploratory statistics were used. Subjects were randomized with RANDALL. All statistical analyses were performed using SAS® on a windows or UNIX platform. Most displays were generated in the harmonization of Analysis and Reporting Program environment which uses SAS version 8.2 on a UNIX platform. Trellis plots were generated using S-Plus version 7.0. Average air space sectional area was analyzed by mixed effect model, looking at change from baseline at pre- and post-challenge. The model used fitted terms for baseline value, period, treatment, time and treatment–time interaction. The average baseline TNCV was explored as a covariate. The UNR correlation structure between time points was used. Subject was fitted as random variable. Point estimates and 95% confidence intervals were constructed using the appropriate variance term for the estimating the change from baseline at pre- and post-challenge and the difference between pre- and post-challenge for each treatment. The Kenward Roger correction...
was employed. Estimates of both within- and between-subject variability were calculated for future studies, with 95% confidence intervals based on Satterthwaite’s approximation. Similar models were used to analyse MIXA, TASV, and TMSA as well as normalized airspace volume (TNCV/m). Similar models, but without adjusting for TNCV at baseline, were used to analyse total NTV (TNTV) and normalized nasal tissue. Acoustic rhinometry endpoints: nasal volume and MIXA, VAS, and PNIF changes from baseline were also analysed in a similar way to MRI endpoint without the adjustment for TNCV.

Results

Pharmacodynamic marker results

Allergen challenge produced a significant change across all measurements (Fig. 2 and Table 1). The individual data for TNSS pre- and post-allergen challenge for the different treatment periods are shown in Figure 3. The mean change and changes from baseline for TNSS was Δ6.55 (95%CI 4.16, 8.94; \( P < 0.001 \)), PNIF was Δ−28.77 (95%CI −46.58, −10.96; \( P < 0.002 \)), and VAS was Δ26.67 (95%CI 12.20, −41.14; \( P < 0.001 \)). For the MRI measurements, the change from

![Figure 2](image)

_Figure 2._ Panels for measurements pre-dose and post-nasal allergen challenge for the different treatment groups. (A) Nitric oxide (NO), (B) total nasal symptom score (TNSS), (C) peak nasal inspiratory flow (PNIF), (D) nasal volume, (E) total airspace volume (TASV), (F) normalized TASV, (G) normalized total nasal tissue volume (TNTV). Data are mean ± SD.
Table 1. Changes induced by allergen challenge in the presence of treatment can be detected by most endpoints (LS means (95%CI) of treatment estimate of change from pre-challenge).

| Treatment  | Estimate | Lower  | Upper  | P       |
|------------|----------|--------|--------|---------|
| NSSC       |          |        |        |         |
| Placebo    | 1.41     | 0.64   | 2.18   | 0.001   |
| Cet        | 1.72     | 0.96   | 2.48   | 0.001   |
| Cet + PE   | 1.31     | 0.53   | 2.08   | 0.002   |
| PNIF       |          |        |        |         |
| Placebo    | 33.48    | 55.43  | 11.54  | 0.004   |
| Cet        | 36.29    | 59.14  | 13.45  | 0.003   |
| Cet + PE   | 13.31    | 35.27  | 8.65   | 0.227   |
| TASN       |          |        |        |         |
| Placebo    | 4.77     | 5.80   | 3.38   | 0.001   |
| Cet        | 3.29     | 6.32   | 2.27   | 0.001   |
| Cet + PE   | 2.28     | 4.23   | 0.32   | 0.024   |
| VAS        |          |        |        |         |
| Placebo    | 5.47     | 4.38   | 6.32   | 0.001   |
| Cet        | 6.83     | 7.92   | 5.76   | 0.001   |
| Cet + PE   | 7.01     | 8.01   | 6.01   | 0.001   |
| TNSS       |          |        |        |         |
| Placebo    | 27.08    | 13.64  | 40.52  | 0.001   |
| Cet        | 20.17    | 6.73   | 33.61  | 0.004   |
| Cet + PE   | 26.76    | 12.79  | 40.72  | 0.001   |

Cet, cetirizine; PE, pseudoephedrine; NSSC, nasal symptom score for congestion; PNIF, peak nasal inspiratory flow; TASN, total airspace volume; TNSS, total nasal symptom score; VAS, visual analog score.

baseline values were; TASN Δ−5.37 (95%CI −7.35, −3.38; P < 0.001); NTV Δ5.47 (95%CI 3.25, 7.70; P < 0.001); TNSS Δ−37.74 (95%CI −61.40, −14.08; P < 0.003). TMSA also was also reduced by allergen, mean difference Δ−37.74 (95%CI −61.40, −14.08; P < 0.03).

The variability in the intra-subject response and the different methodologies employed were NSSC 1.08 (95%CI 0.85, 1.53); PNIF 38.32 (95%CI 29.68, 54.11); TASN 2.98 (95%CI 2.30, 4.21); TNSS 3.63 (95%CI 2.82, 5.09); VAS 22.07 (95%CI 16.98, 31.53). The lowest intra-subject variability was seen with MRI measurement of TASN. The MRI profile with slice is shown in Figure 4 and typical MRI images pre- and post-allergen challenge shown in Figure 5. The changes in volume in a typical subject are clearly seen and a unilateral predominance in some subjects (Fig. 5B).

There is some indication of correlation between the MRI and acoustic rhinometry volume (ARV), and some degree of negative correlation between MRI and VAS score. A change of one in the TNSS score on average corresponded with MRI volume of −0.57 cm³, with a range of −0.78 to −0.37. The correlation data can be viewed in the supplemental data online (Figures S1 and S2).

There was a trend towards difference between treatment and placebo although this did not achieve significance because of small numbers (Fig. 2; P = 0.32); across allergen challenge the differences between time-points were highly significant (P < 0.001). There was no evidence of an interaction between time and treatment (P > 0.1).

Overall across all treatments (Fig. 2 and Table 2) the airspace sectional area tended to decrease after challenge. The drop was less pronounced for the combination treatment Cet plus PE, although not significantly different from placebo. Similar results were obtained when analysing airspace volume. The graphical analysis shows the trend for a treatment separation that did not reach statistical significance but illustrates the lower variability with MRI than with other methods (Table 2).

VAS, TNSS, and PNIF

There was no evidence of treatment difference or treatment time interaction (all P > 0.5) and, overall across all treatments, the VAS increased after challenge (P < 0.001; Fig. 2). The increase was less pronounced for the combination treatment Cet plus PE, although not significantly different from placebo. The TNSS results were similar to those of VAS (Fig. 2). PNIF showed a trend to fall after allergen challenge and across all treatment groups (Fig. 2).

Acoustic rhinometry

There was no evidence of difference between treatments or an interaction between time and treatment (P> 0.1; Table 2). There was evidence of difference between time points (P< 0.001; Fig. 2 and Table 1). The trend was similar to the one observed when analysing the MRI METASV.

nNO

There were no significant changes in nNO across the allergen challenge procedure (Fig. 2). On placebo pre-dose values...
were 1304 ± 762 ppb; post-dose 1699 ± 485; post-challenge 1509 ± 522; Cet treated group pre-dose value was 1587 ± 565; post-dose 1609 ± 500; 1599 ± 523 post-challenge. In the combination group, the values were pre-dose 1574 ± 589; post-dose 1904 ± 500; post-challenge 1570 ± 430. The data showed no significant change (Fig. 2) following allergen challenge.

Safety

There were no serious adverse events reported. The MRI scans and procedure was well tolerated. Adverse events were mostly related to the allergen challenge and were mild in nature and self-limiting.

Discussion

This is the first study in man to evaluate nasal allergen responses using MRI imaging before and after nasal allergen challenge. Animal studies have reported the effect of nasal challenge in response to histamine and methacholine on MRI images using gadolinium enhancement to localize edema formation [17–21]. Clinically, MRI has mainly been used for the evaluation of the para-nasal sinuses and may replace CT for the evaluation of pathological mucosal abnormalities [22, 23]. A recent report describes the use of MRI to evaluate the inflammation produced by segmental bronchial allergen challenge [24].

Nasal allergen challenge produced a highly significant change in all the measured variables including all MRI endpoints. The timing and magnitude of the changes seen after allergen challenge seen in this study for symptom-based scores and measurements of nasal patency were similar to that reported in a recent review, which included a dose-response analysis to nasal administration of nasal allergen [1]. Therefore, the findings in our study that MRI endpoints, particularly TASV, were more sensitive and less variable than the conventional measurements of symptom scores and nasal patency would suggest that MRI may prove a useful and objective method for assessment of the inflammatory response post-allergen challenge. A negative change is indicative of smaller free nasal airspace. A drop in airspace volume was expected after allergen challenge. A smaller negative change from baseline would represent a lower reaction from the nasal tissues to the allergen challenge and that would then be reflected in wider free nasal airspace.

The clearest separation of the different treatments was seen in the MRI measures of the volume of the respiratory space and the soft tissue, normalized total nasal tissue volume (TNTV; Fig. 2). An advantage of MRI is the ability to measure mucosal inflammatory changes and edema as well as volume changes directly.

In some instances, the changes in volume were localized to one side, as shown in Figure 5B. This is consistent with an asymmetry of nasal volume changes post-allergen challenge, (with greater changes on the non-patent side) which was related to the endogenous nasal cycling rhythm [25]. Measures of cross-sectional area have been compared between MRI and acoustic rhinometry [26], although the extent of the correlation has been reported to depend on the state of congestion which limits its value in challenge.

Figure 4. Box plot of MRI versus standardized slice number with total airspace volume (TASV) mm for placebo group (10 yellow, blue 60, and red 120 min relative to dosing with allergen). Bars represent median, upper and lower quartiles, whiskers represent 5–95% percentiles. Outliers are represented as symbols o and x.
The lack of correlation between the different variables illustrates the difficulty in utilization of symptom-based scores to assess the effects of nasal challenge \[3, 4, 28\] and it should be pointed out that one method for assessment is not adequate for allergic rhinitis assessment and that multiple methods should be used. There was a weak correlation between the MRI and ARV, and a weak negative correlation between MRI and VAS (supplemental data). A lack of correlation with symptom VAS score and cross-sectional area measurements by acoustic rhinometry was also seen in a histamine challenge \[29\]. No difference was seen in nNO data. The baseline values are in the range reported by Kharitonov \[30\] and somewhat higher than the values in normal controls reported in other studies \[31\]. However, the effects of nasal allergen challenge are varied with decreases in nNO reported \[30\], or no change \[32\], probably dependent on the degree of sinus obstruction.

The lack of a clear difference between drug treatments and placebo may have been due to the single dose administration of active drugs and restricted time-point analysis. The study was not powered to show statistically significant differences between drug treatments and placebo. There was a clear trend that suggested a positive treatment effect after combination therapy (Cet + PE); the data showed a reduction in symptom scores, improvement in nasal patency, and MRI end points (Fig. 2), although statistical significance was not achieved perhaps because of the small numbers involved \((n = 14)\). These changes may result from the effect of PE in reducing vascular congestion and edema. Other studies have also demonstrated that the combination of anti-histamines with vasoconstrictor agents increases efficacy in the treatment of allergic rhinitis \[7, 12\].

By contrast, a single dose of Cet failed to abrogate the effects of allergen challenge and post-allergen measurements were no different from placebo. A similar lack of effect of Cet on nasal patency as recorded by acoustic rhinometry (MIXA) has also been reported \[29\]. Antihistamines have minimal effects on nasal congestion, which remains one of the less well-treated symptoms of allergic rhinitis. After single dosing with anti-histamines, effects are typically seen on cutaneous topical challenge wheal and flare responses up to 24 h after a single dose \[33\]. More often effects of anti-histamines have been examined after chronic dosing. The

Table 2. Effect of allergen challenge on MRI endpoints. LS means (95% CI) of treatment comparison for change from pre-challenge.

| Treatment | Ref | Test-ref | Lower | Upper | \(P\) |
|-----------|-----|----------|-------|-------|-----|
| NSSC      |     |          |       |       |     |
| Cet       | Cet | PE       | 0.41  | −0.46 | 1.27| 0.34|
| Cet + PE  | Placebo | PE | 0.31  | −0.56 | 1.17| 0.47|
| Placebo   | Placebo | PE | −0.10 | −1.00 | 0.79| 0.82|
| PNIF      |     |          |       |       |     |
| Cet       | Cet | PE       | −2.29 | −53.80| 7.84| 0.14|
| Cet + PE  | Placebo | PE | −2.81 | −33.50| 27.88| 0.85|
| Placebo   | Placebo | PE | 20.17 | −9.98 | 50.33| 0.18|
| TASV      |     |          |       |       |     |
| Cet       | Cet | PE       | −2.02 | −4.43 | 0.39| 0.10|
| Cet + PE  | Placebo | PE | −0.53 | −2.99 | 1.92| 0.66|
| Placebo   | Placebo | PE | 1.49  | −0.92 | 3.90| 0.21|

Cet, cetirizine; PE, pseudoephedrine; NSSC, nasal symptom score for congestion; PNIF, peak nasal inspiratory flow; TASV, total airspace volume; TNSS, total nasal symptom score; VAS, visual analog score.

Figure 5. (A) MRI at baseline and at 60 min following challenge; subject 1 shows decreased airspace in both nostrils, the changes are representative for all but one of the subjects where the baseline scan showed movement artifact; (B) MRI at baseline and at 60 min following challenge; subject 2 shows unilateral changes with decreased airspace in right nostril, increased airspace in left nostril.
effect of anti-histamines is greatest on the itching and sneezing symptoms scores [28], typically measured at steady state. However, in a study comparing skin and nasal responses of five anti-histamines, inhibitory effects were seen after single dosing [11]. Additionally, single dose studies with anti-histamines using the Vienna Chamber [34] showed significant reductions in symptoms score of approximately 30% within 1 h post-dosing, but with much larger sample sizes (n = 65). Evidence of synergy of the effects has been previously reported for the combination of PE and Cet in chronic dosing studies [7, 8]. Differences between single dose and multiple dose effects are also seen in other studies with theophylline [35] and with corticosteroids, where acute and chronic effects seen with inhaled corticosteroids differ when administered immediately before challenge corticosteroids have a small effect on early phase symptoms and inhibit predominantly the late phase TH2 mediated responses (IL-4, -5, -13) [15, 16]. In contrast, multiple dosing with corticosteroids inhibits symptoms in the early phase (approximately 30% [15, 36] and attenuates predominantly the late phase production of TH2 cytokines in response to allergen challenge [15, 36]. Changes in the airway calibre measured with acoustic rhinometry with corticosteroids, showed a trend but did not reach statistical significance again in contrast to effects of inhaled corticosteroid on symptom scores [37]. The variability of rhinometric measurements varies from 10% to 30% and is beset by intrinsic problems of the non-linear relationship between flow and volume [4]. Additionally, expressing the rhinometric measurements as a minimal cross sectional area to depict resistance is complicated by non-uniform flow and change between laminar and turbulent flow [9, 38].

This is the first reported study of the use of MRI where this technique has been used to quantify the inflammatory changes following nasal allergen challenge. MRI endpoints have been compared directly with conventional assessments, such as symptom scores and measurements of nasal patency, although subjective measures might be variable, they are a good indication to how the participant perceives their allergic rhinitis symptoms, and currently the FDA recognizes TNSS as the only parameter in evaluating new medications, while still considering others. The major MRI limitations remain cost, imaging time, and the potential for claustrophobia. MRI procedures were well tolerated in this small study despite the need to keep perfectly still following allergen challenge, and the acquisition times prevent multiple frequent measurements. MRI provides an objective method for the assessment of the response to nasal challenge, which merits further study in studies with chronic dosing and novel agents. MRI provides novel insights into the anatomical changes in response to allergen and provides a new method for the assessment of nasal patency, vascular congestion, and inflammation.

Conflict of Interest

BRL has received research funding from AstraZeneca, Chiesi, Daiichi-Sankyo, DSP-Sumitomo, GlaxoSmithKline, Pfizer. GS has received research grants from GlaxoSmithKline, ALK, honoraria for articles, consulting, lectures/chairing and/or advisory boards from AstraZeneca, Britannia Pharmaceuticals, Capnia, Church & Dwight, Circassia, GlaxoSmithKline, Groupo Uriach, Meda, Merck, MSD, Ono Pharmaceuticals, Oxford Therapeutics, Sanofi-Aventis, Shionogi, UCB and travel funding from Bayer, GlaxoSmithKline. CRJ has no declared competing interests. PJB has served on Scientific Advisory Boards of AstraZeneca, Boehringer-Ingelheim, Chiesi, Daiichi-Sankyo, GlaxoSmithKline, Novartis, Nycomed, Pfizer, Teva and UCB and has received research funding from Aquinox Pharmaceuticals, AstraZeneca, Boehringer-Ingelheim, Chiesi, Daiichi-Sankyo, GlaxoSmithKline, Novartis, Nycomed, Pfizer and Prosonix. He is also a cofounder of RespiVert (now part of Johnson & Johnson), which has discovered novel inhaled anti-inflammatory treatments for asthma and COPD.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher’s web-site.

Figure S1. Correlation data from MRI for total airspace volume (TASV) versus total nasal symptom score (TNSS). The changes between pre-challenge and post-challenge are plotted. Parameter estimates; 95% confidence limits; slope $-0.57$ ($-0.78, -0.37$).

Figure S2. Trellis plot of MRI derived measurement versus acoustic rhinometry data, all time points all data. The average airspace volume is directly proportional to the total airspace volume. The black box outlines the MRI analyses; total airspace volume (TASV), average airspace sectional area (METASV), minimum cross-sectional area (MIXA), total mucosal surface area (TMSA) and total nasal cavity volume (TNCV). Data for the visual analog scale score (VASCR), acoustic rhinometry distance of minimal cross-sectional area (ARDX), acoustic rhinometry volume (ARV), acoustic rhinometry cross-sectional area (ARX), Maximum peak nasal inspiratory flow (PNIFMAX). There are indications of correlation between the MRI assessments and more conventional endpoints and suggestions of greater correlations between VASCR and ARV (cells with red box outline). Symbols: ‡ placebo, o cetirizine, Δ cetirizine + pseudoephedrine; red 60 min post-challenge, green post-dose, blue pre-challenge.

Table S1. Demographic characteristics of seasonal rhinitis subjects studied. Data are mean ± SD.