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Original Article

The effect of omalizumab on ventilation and perfusion in adults with allergic asthma

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Abstract: Omalizumab promotes clinical improvement in patients with allergic asthma, but its effect on pulmonary function is unclear. One possibility is that omalizumab improves asthma symptoms through effects on the regional distributions of ventilation, perfusion, and ventilation/perfusion matching, metrics which can be assessed with Nitrogen-13-saline Position Emission Tomography (PET). Four adults with moderate to severe uncontrolled allergic asthma underwent symptom assessment, spirometry and functional pulmonary imaging with Nitrogen-13-saline PET before and after 4-5 months of treatment with omalizumab. PET imaging was used to determine ventilation/perfusion ratios, the heterogeneity (coefficient of variation, COV) of ventilation and perfusion, and lung regions with ventilation defects. There were no significant changes in spirometry values after omalizumab treatment, but there was a trend towards an improvement in symptom scores. There was little change in the matching of ventilation and perfusion. The COV of perfusion was similar before and after omalizumab treatment. The COV of ventilation was also similar before (0.57 (0.28)) and after (0.66 (0.13)) treatment, and it was similar to previously published values for healthy subjects. There was a non-significant trend towards an increase in the extent of ventilation defects after omalizumab treatment, from 5 (15)% to 12.8 (14.7)%. Treatment of moderate to severe uncontrolled allergic asthma with omalizumab did not result in a significant improvement in ventilation and perfusion metrics assessed with functional PET imaging. The normal COV of ventilation which was unaffected by treatment supports the hypothesis that omalizumab exerts its clinical effect on lung function during allergen exposure rather than in between exacerbations.

Keywords: PET functional imaging, omalizumab, Xolair, asthma, V/Q ratios

Introduction

Asthma is a chronic lung disease characterized by episodic inflammation and bronchoconstriction, affecting approximately 300 million people worldwide [1]. Subjects with allergic asthma often continue to have frequent asthma symptoms and reduced quality of life despite receiving beta-agonists and high doses of inhaled and/or systemic corticosteroids. In those subjects who fail to respond to traditional asthma treatments, the addition of omalizumab (Xolair), a recombinant humanized monoclonal antibody against IgE, to the asthma treatment regimen can be beneficial. Allergic asthma is an inflammatory disease, and IgE is one of its major mediators. Allergens in the airway bind to IgE, which is attached to the surfaces of mast cells and basophils. These cells release numerous inflammatory mediators in response to allergen binding to IgE. This inflammatory response leads to both early and delayed bronchoconstriction, thus increasing airway resistance and decreasing ventilation. A decrease in ventilation can lower local oxygen levels, thus causing hypoxic pulmonary vasoconstriction, which decreases perfusion. By binding to and inhibiting the effects of IgE, omalizumab has the potential to disrupt this inflammatory cascade, thus affecting both ventilation and perfusion. Omalizumab has been shown to reduce the frequency of asthma exacerbations [2-10], emergency room visits [6], and hospital admissions for asthma [5], all while maintaining an excellent safety profile [11]. Furthermore, the addition of omalizumab allows for dose reduc-

tions or the cessation of inhaled corticosteroids [2-5, 8, 9, 12] and reduced rates of rescue beta-agonist use [2, 4, 9, 10, 12]. In a majority of studies, omalizumab improves overall asthma symptoms [2, 4-6, 10, 12] and asthma-related quality of life [6, 12-14].

Despite the overwhelming evidence that omalizumab leads to an improvement in asthma symptoms and quality of life, the ability of omalizumab to improve pulmonary function remains unclear. Several studies demonstrate a significant beneficial effect of omalizumab on measures of lung function such as peak expiratory flow (PEF) [4, 6, 10] or forced expiratory volume in one second (FEV1) [2, 4, 6, 8, 10]. However, other studies have failed to demonstrate the same improvement in spirometric measures [3, 5, 9, 15, 16] or airway hyper-responsiveness to methacholine [15]. Thus, it remains unclear by what physiologic mechanism omalizumab exerts its beneficial effect on the clinical course of asthma.

Our hypothesis was that omalizumab may promote clinical improvement in subjects with allergic asthma through effects on alveolar ventilation ($\dot{V}_A$), perfusion ($\dot{Q}$), and $\dot{V}_A/\dot{Q}$ matching. Lung functional imaging with Nitrogen-13-saline (^{13}NN-saline) Position Emission Tomography (PET) can provide a detailed assessment of these physiologic parameters. In an animal model of bronchoconstriction, PET imaging has been used to examine ventilation, perfusion, ventilation/perfusion matching, and to use this data to accurately predict arterial blood gas results [17]. In human subjects with asthma experiencing bronchoconstriction, PET can identify changes in perfusion and areas of decreased ventilation [18-20]. PET imaging may be able to detect omalizumab's physiologic impact on patients with allergic asthma. Therefore, the aim of this pilot study was to assess the effects of omalizumab treatment on ventilation, perfusion and the matching of ventilation and perfusion in subjects with allergic asthma using ^{13}NN-saline PET imaging.

Materials and methods

Subject characteristics

This study was approved by the Human Research Committee of the Massachusetts General Hospital (Protocol Number: 2007-P-000974). All subjects provided written informed consent. Subjects were recruited through referrals by Partners Healthcare System physicians who planned on starting omalizumab for better symptom control. Subjects were considered eligible if they were over age 18, carried a diagnosis of asthma, met the NIH definition for moderate to severe asthma upon questioning, had a positive skin test or in vitro reactivity to a perennial aero-allergen and had inadequately controlled symptoms with inhaled corticosteroids. The subject's physician must have planned on starting omalizumab for better symptom control but had not yet initiated this therapy before enrollment in this study. The dose of omalizumab prescribed by the physician was determined according to the package insert, based on body weight and total IgE level. Subjects were excluded if they were a member of the study staff, had other lung diseases besides asthma, had heart disease, smoked in the 3 months prior to screening, had a greater than 10 pack-year history of smoking, had been treated for an asthma exacerbation within 1 month of screening, had taken oral steroids in the past year for asthma treatment, were pregnant or breast-feeding, were unresponsive to albuterol (by history), or had been exposed to more than half of the expected radiation dose for the protocol in the past year (3.75 mSv).

Study protocol

All subjects attended the Massachusetts General Hospital for 3 separate visits. The first was a screening visit to confirm study eligibility. The second and third visits included PET imaging sessions before and after 4-5 months of treatment with omalizumab, respectively.

The screening visit included measurements of height, weight, blood pressure, heart rate, and oxygen saturation. In addition, baseline demographic data was obtained, a full medical history was taken, and a complete physical examination was performed.

During the two imaging visits, subjects first had a physical examination, followed by the completion of both the Asthma Control Test questionnaire (ACT) and the standardized Asthma Quality of Life (AQOL) questionnaire. The ACT provides a measure of a patient's asthma control [21]. The AQOL assesses the impact of asthma on a patient's quality of life, in terms of

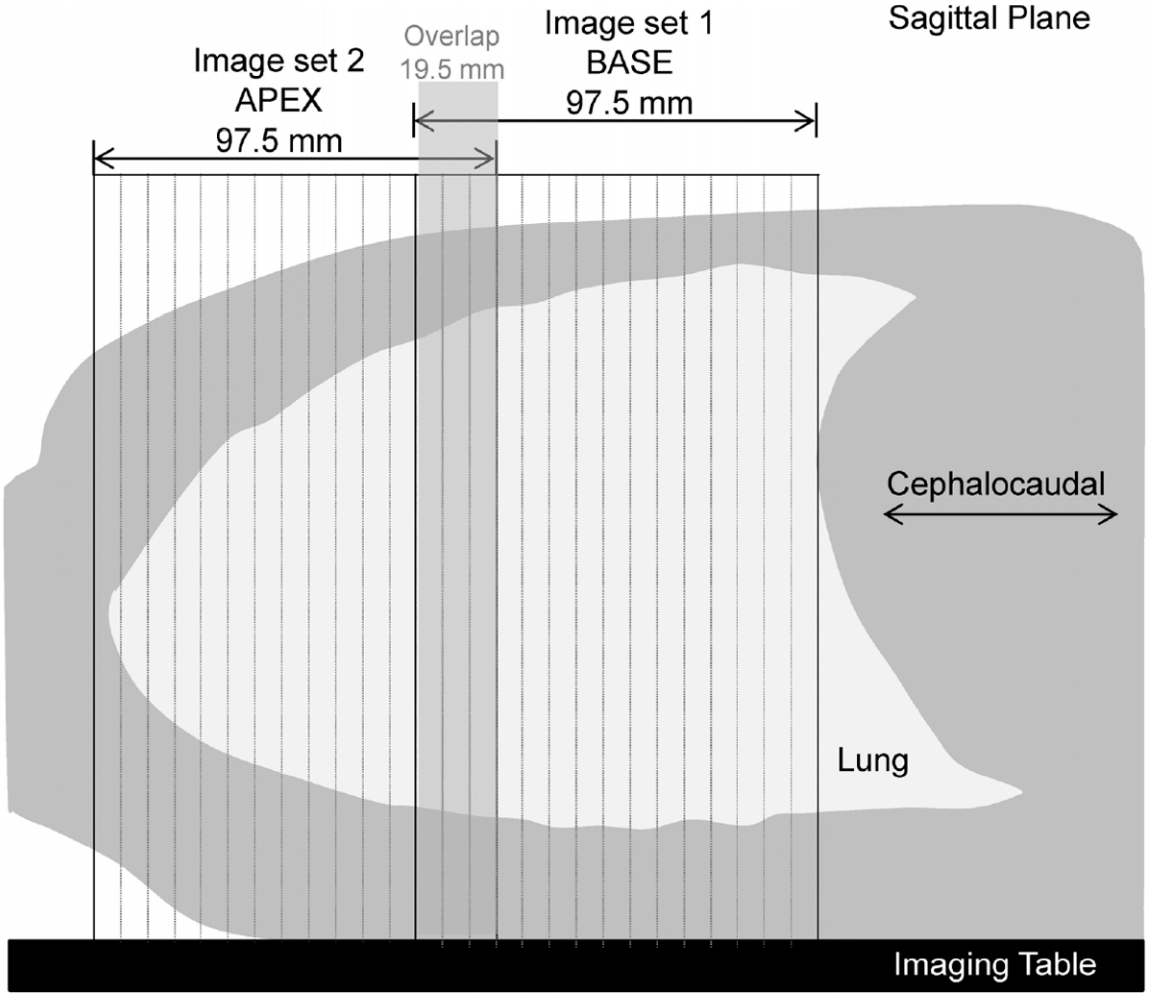

Figure 1. Subject positioning. Diagrammatic representation of subject positioning in the PET scanner for the two series of image acquisitions.

four domains: activity limitations, symptoms, emotional function, and exposure to environmental stimuli [22]. The subjects then underwent spirometry. Following spirometry, the subjects had an intravenous catheter placed, impedance plethysmography bands were positioned on the subjects' thorax, and serum pregnancy tests were performed on female subjects of childbearing age. Following instrumentation, subjects were positioned supine in the PET scanner and functional lung imaging was performed (details below). Lung volume was monitored continuously by impedance plethysmography (SomnoStar PT, SensorMedics Corp., Yorba Linda, CA, USA) with the signal continuously displayed to the subject via video goggles (Argo Cinema Goggles, Welton Electronics Inc., Hong Kong).

The patients began treatment with omalizumab after the first imaging session and thereafter received a subcutaneous injection every 2 weeks. On the follow-up imaging day, after 4-5 months of treatment with omalizumab, the physical examination, questionnaires, spirometry, and PET imaging sequence were repeated in a similar manner to the first session. At this second session, the subject was positioned in the PET scanner so that the imaging field approximated the portion of lung that was imaged on the first session. At the final imaging visit, both the subjects and their treating physicians also completed the Global Evaluation of Treatment Effectiveness (GETE) questionnaire, which is a measure of the overall effectiveness of the study treatment on asthma control [23].

PET imaging protocol

A PET scanner (PC-4096 Scanditronix AB, Uppsala, Sweden) with a 97.5 mm long axial

Table 1. Baseline characteristics

	Subject A	Subject B	Subject C	Subject D
Age, years	48	45	51	31
Gender	Female	Male	Female	Male
Ethnicity	Non-Hispanic	Non-Hispanic	Hispanic	Non-Hispanic
Race	White	White	Multiple	Black; NA*
BMI, kg/m^2	32.6	35.6	35.8	37.2
Blood IgE level, IU/ml	346	154	154	1420
Omalizumab dose, mg	300	375	375	375

*Native American. BMI denotes body mass index.

field of view and two-dimensional acquisition of 15 transverse slices of 6.5 mm thickness was used to perform the lung functional imaging. In order to image the majority of the lung within the axial limits, two sets of images (with each set including transmission and emission scans) were obtained at each imaging visit. In the first image set the subject was positioned so that the diaphragm dome was adjacent to the most caudal slice of the field of view (BASE image set). In the second image set, the subject was moved cranially 78 mm with respect to the field of view, allowing for an overlap of 19.5 mm in the imaged portion of the lung (APEX image set, **Figure 1**). Transmission scans, of 10 minutes duration, were obtained using a rotating pin source of ^{68}Ge/^{68}Ga and used to correct the emission scans for attenuation caused by body tissues. For the subsequent emission scan, the subject was instructed to take two deep breaths. During the exhalation phase of the second breath, the subject was instructed to breath-hold at the subject's mean lung volume (average lung volume determined during tidal breathing prior to the deep breaths). At the onset of the 20-30 second breath-hold, the emission image acquisition was commenced and the subject received a bolus injection of ^{13}NN in saline solution (25 ml injected intravenously at 5 ml/s) [24]. Following the breath-hold, the subject resumed normal tidal breathing for the remaining duration of the image. As previously described [17, 24], the emission scans obtained included 28 frames (8 x 2.5 seconds, 16 x 5 seconds, and 4 x 30 seconds) and were used to measure regional specific ventilation ($s\dot{V}$) and $\dot{Q}$, accounting for intravoxel ventilation-perfusion heterogeneity using two-compartment analysis [17]. PET images were reconstructed using conventional convolution back-projection with a voxel size of 4 x 4 x 6.5 mm.

Image analysis

For each image set, the transmission and emission scans were analyzed as outlined below in order to obtain metrics of ventilation, perfusion, and $\dot{V}_A/\dot{Q}$. Specifically, the BASE and APEX image sets were treated separately for steps 1-3 and then combined to establish the 'whole lung' results. All image analysis was completed using MATLAB (Mathworks, Natick, MA, USA).

Step 1: Determination of the lung fields. The transmission scan was processed to derive an image of fractional gas content (F_{gas}) [18], from which the lung fields (masks) were defined by thresholding the F_{gas} image to include only those voxels with an $F_{gas} > 0.5$. Lastly, the lung fields were manually refined to exclude the extra-pulmonary airways and large pulmonary vessels.

Step 2: Emission image analysis. Emission images were filtered in 3D using a moving average filter with edge effect correction to yield a resolution of 13 mm (effective imaging resolution of 13 x 13 x 13 mm). The overlapping slices between the APEX and BASE images were excluded and then each emission image was normalized by the injected activity, to allow for appropriate merging of the parameters derived from the APEX and BASE images.

Step 3: Analysis of ventilation and perfusion. For each emission image, specific ventilation and perfusion were determined using previously described models [17, 25]. Specifically, the ventilation of each voxel was modeled by either a single compartment (mono-exponential decay), a two compartment (bi-exponential decay), a partial intra-regional air trapping or a complete air trapping model. The Akaike information criterion was used to identify the most suitable model [26].

Step 4: APEX and BASE image fusion. Voxel-by-voxel specific ventilation and perfusion determined for the APEX and BASE images were fused to allow final calculation of $\dot{V}_A/\dot{Q}$ ratios and associated metrics from the entire portion

Table 2. Spirometry and questionnaire results

	Baseline	Post-Omalizumab Treatment	*P* Value*
Spirometry, upright			
FEV_1, % predicted	59.05 (27.53)	71 (26.9)	NS
FVC, % predicted	75.75 (30.13)	82.1 (14.45)	NS
FEV_1/FVC	0.77 (0.32)	0.78 (0.14)	NS
Spirometry, supine^			
FEV_1, % predicted	52.9 (22.3)	69.8 (15.85)	NS
FVC, % predicted	63.2 (15.55)	83.3 (13.8)	NS
FEV_1/FVC	0.81 (0.17)	0.74 (0.05)	NS
ACT Score†	9.5 (5.5)	14.5 (4.75)	< 0.05
AQOL Score°			
Total	13.15 (2.48)	18.85 (5.31)	NS
Activity Limitations	3.86 (0.91)	4.55 (1.41)	NS
Symptoms	3.21 (1.56)	4.8 (1.25)	NS
Emotional Function	3.2 (1.3)	4.6 (1.15)	NS
Exposure to Stimuli	2.88 (1.31)	4.13 (1.31)	NS
GETE Score§			
Patient	-	2 (0)	-
Doctor	-	2.5 (1)	-

Data are expressed as median (inter-quartile range). NS denotes not significant, FEV1 denotes forced expiratory volume in one second, FVC denotes forced vital capacity. *P values were calculated with the Wilcoxon signed-rank test. ^One of the subjects did not complete spirometry in the supine position, so the data shown are for the remaining three subjects. †Scores on the Asthma Control Test (ACT) range from 5-25, with higher scores indicating better asthma control. °Each domain on the Asthma Quality of Life (AQOL) questionnaire is scored from 1-7, with higher scores indicating better quality of life. §The Global Evaluation of Treatment Effectiveness (GETE) questionnaire asks the physician (MD) or patient "What is the physician (patient)'s overall impression of the study medication and its effects on the typical symptoms of allergic asthma during this study?" The MD and the patient can each provide a score of 1-5, with lower scores indicating better control. 1 indicates excellent (complete) control, 2 is good (marked improvement), 3 is moderate (limited improvement), 4 is poor (no change), and 5 is worsening of asthma. Predicted spirometric values were calculated using data from Hankinson et al. [29].

of imaged lung. Specifically, $\dot{V}_A$ was calculated by multiplying $s\dot{V}$ by voxel gas volume.

Step 5: Assessment of ventilation, perfusion and $\dot{V}_A/\dot{Q}$ matching. Using voxel-by-voxel $s\dot{V}$ and $\dot{Q}$ within the fused images we determined the mean $s\dot{V}$, the heterogeneity in $s\dot{V}$ (coefficient of variation), and the heterogeneity in $\dot{Q}$ (coefficient of variation). To quantify the $\dot{V}_A/\dot{Q}$ distribution, we determined the mean and standard deviation of the $\dot{V}_A$ weighted $\log_{10}$ ($\dot{V}_A/\dot{Q}$) and the $\dot{Q}$ weighted $\log_{10}$ ($\dot{V}_A/\dot{Q}$) [17].

Step 6: Ventilation defects. We determined the ventilation defect (Vdef) portion of the lung, as described by Harris et al [18]. Briefly, an 'end washout' image was generated from both the APEX and BASE emission images by taking the average activity of the final two image frames. The portion of the lung defined as a Vdef was determined from this image by selecting the set of voxels with activity within 80% of the highest tracer concentration within the end-washout image and then refining it to only include regions that were greater than twice the voxel size. The 80% threshold value was a compromise between obtaining a region large enough to reduce the effect of noise and small enough to include only areas of significant tracer retention.

Data analysis

Given the small sample size in this pilot study, the effect of omalizumab on lung function (ventilation, heterogeneity of ventilation and perfusion, distribution of ventilation and perfusion, and size of ventilation defects), spirometry, and scores on the ACT and AQOL questionnaires was assessed using the Wilcoxon signed-rank test. Data are expressed as median (inter-quartile range) unless otherwise stated. Significance was accepted as a two-sided $p < 0.05$. Statistical analysis was performed using STATISTICA (StatSoft, Inc., Tulsa, OK, USA). No interim analyses were performed.

Results

Study population

From April 2008 to November 2010, five subjects were recruited for participation in the study. One subject did not complete the study, and the baseline characteristics for the remaining four subjects are included in **Table 1**. The median (inter-quartile range) number of days between the initial and follow-up imaging sessions was 127 (18.5).

Spirometry and questionnaires

There were no significant differences between FEV1, FVC or the FEV1/FVC ratio measured at baseline and post-omalizumab treatment,

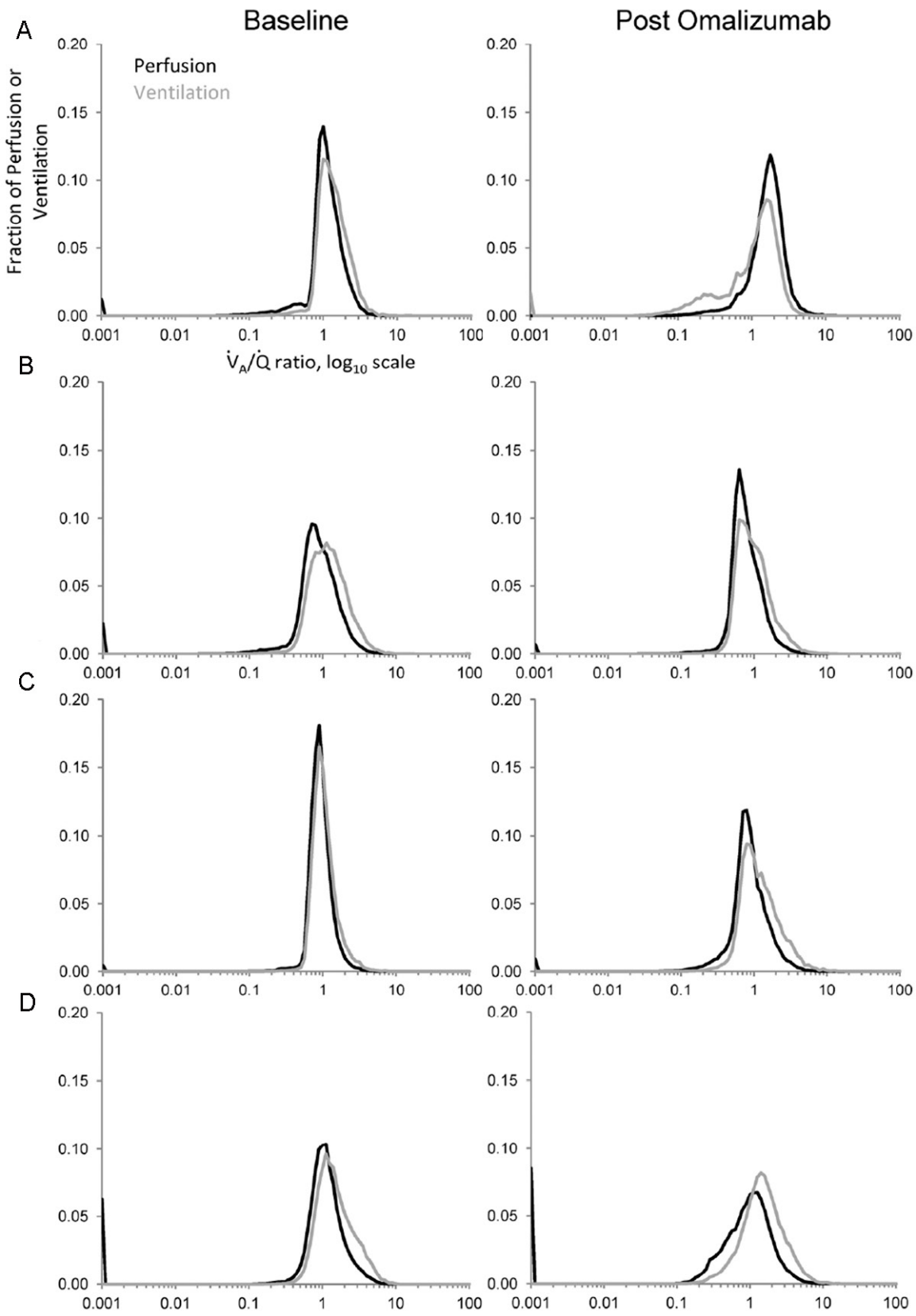

Figure 2. Distribution of ventilation and perfusion. Fraction of specific ventilation ($s\dot{V}$) or perfusion ($\dot{Q}$) within the lung, plotted against the $\dot{V}_A/\dot{Q}$ ratio, for subjects A-D. 1 on the x-axis (which uses a log scale) represents a $\dot{V}_A/\dot{Q}$ ratio of 1 and is considered ideal gas exchange.

Table 3. PET ventilation and perfusion data

	Baseline	Post-Omalizumab Treatment	*P* Value*
$s\dot{V}$^	0.05 (0.022)	0.054 (0.026)	NS
Coefficient of variation of $s\dot{V}$†	0.57 (0.283)	0.655 (0.134)	NS
Coefficient of variation of $\dot{Q}$°	0.45 (0.177)	0.513 (0.091)	NS
Mean of $\dot{V}_A$ weighted $\log_{10}(\dot{V}_A/\dot{Q})$§	0.104 (0.078)	0.121 (0.119)	NS
SD of $\dot{V}_A$ weighted $\log_{10}(\dot{V}_A/\dot{Q})$	0.302 (0.083)	0.391 (0.082)	NS
Mean of $\dot{Q}$ weighted $\log_{10}(\dot{V}_A/\dot{Q})$#	0.003 (0.08)	-0.042 (0.055)	< 0.05
SD of $\dot{Q}$ weighted $\log_{10}(\dot{V}_A/\dot{Q})$	0.213 (0.049)	0.28 (0.095)	NS
Percentage of Vdefs	5 (15)	12.8 (14.7)	NS

Data are expressed as median (inter-quartile range). NS denotes not significant, SD denotes standard deviation, Vdefs denotes ventilation defects. *P values were calculated with the Wilcoxon signed-rank test. ^Determined by plotting the tracer activity over time during washout breathing. †A lower number represents less heterogeneity of ventilation within the lung and is generally considered more desirable. °A lower number represents less heterogeneity of perfusion within the lung and is generally considered more desirable. There is no measure for overall perfusion (as there is for specific ventilation) because the study design did not include a real-time measure of cardiac output. §Represents where the mean ventilation is located on the x-axis of the $\dot{V}_A/\dot{Q}$ plots in Figure 2. A lower (or more negative number) means that more ventilation is going to areas with a lower $\dot{V}_A/\dot{Q}$ ratio and that less ventilation is going to areas with a higher $\dot{V}_A/\dot{Q}$ ratio. #Represents where the mean perfusion is located on the x-axis of the $\dot{V}_A/\dot{Q}$ plots in Figure 2. A lower (or more negative number) means that more perfusion is going to areas with a lower $\dot{V}_A/\dot{Q}$ ratio and that less perfusion is going to areas with a higher $\dot{V}_A/\dot{Q}$ ratio. Note, all of the median values on this table are normalized and are relative rather than absolute, and thus there are no units of measurement.

either in the upright or supine position (**Table 2**). There was a significant improvement in scores on the ACT questionnaire after omalizumab treatment, suggesting improved asthma control. There were non-significant increases in the total AQOL score and on each of its four domains (activity limitations, symptoms, emotional function, and exposure to environmental stimuli), indicating a trend towards improved quality of life. Furthermore, both the physician and patient GETE scores suggested good-to-moderate effects of omalizumab on the patients' symptoms of asthma.

Ventilation and perfusion

All subjects at baseline had PET-based $\dot{V}_A/\dot{Q}$ distributions for $\dot{V}_A$ and $\dot{Q}$ that were uni-modal and narrow (**Figure 2**). No significant differences were found in the widths of the $\dot{V}_A/\dot{Q}$ distributions for $\dot{V}_A$ and $\dot{Q}$ following omalizumab treatment.

The median $s\dot{V}$ of the lungs was unchanged following omalizumab treatment (**Table 3**). There was no significant change in the heterogeneity of ventilation (0.57 (0.28) to 0.66 (0.13)) or perfusion (0.45 (0.18) to 0.51 (0.09)). There was a statistically significant decrease in the mean $\dot{Q}$ weighted $\log_{10}(\dot{V}_A/\dot{Q})$, but there was no significant change in the $\dot{V}_A$ weighted $\log_{10}(\dot{V}_A/\dot{Q})$. At baseline, 5 (15)% of the imaged lung contained ventilation defects. Following treatment with omalizumab the percentage of Vdefs increased to 12.8 (14.7)%, although this increase was not significant.

Representative $s\dot{V}$ and $\dot{Q}$ images for matched lung slices at baseline and following omalizumab treatment for each subject are included in **Figure 3**. Representative Vdef images of the lungs at baseline and following omalizumab treatment in one subject are included in **Figure 4**.

Discussion

Our study is the first to utilize PET functional imaging to assess whether omalizumab leads to improvements in ventilation and perfusion in subjects with allergic asthma. In the four studied subjects, omalizumab therapy did not significantly improve the heterogeneity of ventilation or perfusion, nor did it improve the matching of ventilation and perfusion or the extent of ventilation defects. Therefore, it remains unclear which physiologic parameters are improved by omalizumab and are responsible for the reported improvement in symptoms in the literature.

There are several possible explanations for the lack of a demonstrable positive effect of omali-

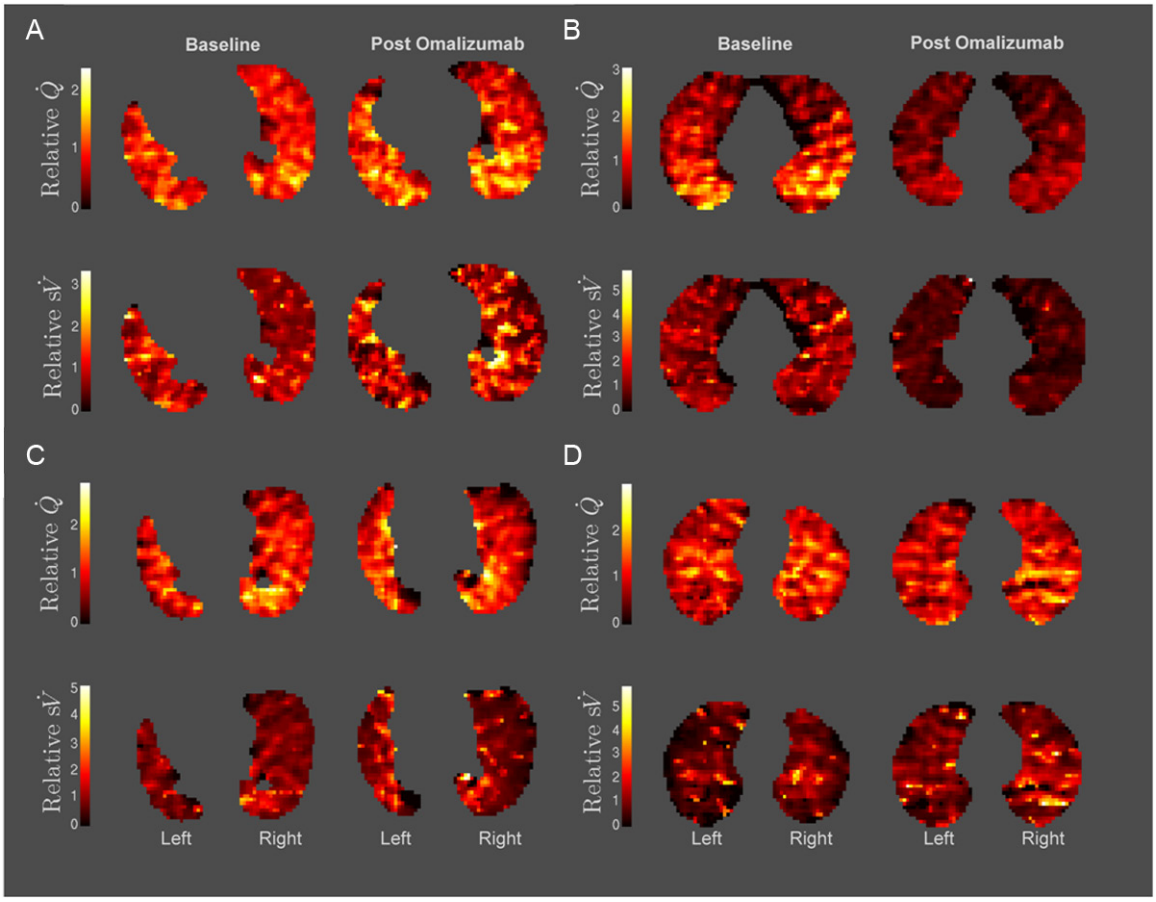

Figure 3. Perfusion and ventilation before and after omalizumab treatment. These example transaxial lung slices demonstrate perfusion and specific ventilation and were taken from the same anatomical position in each subject (A-D). Areas with more yellow color represent areas with more perfusion (or specific ventilation).

zumab on ventilation and perfusion metrics assessed using PET functional imaging. First, omalizumab may not affect the baseline distribution of ventilation and perfusion in a patient prior to allergen exposure, but instead act by reducing the changes in ventilation and perfusion that occur in response to allergen exposure. This assertion is supported by the low COV $s\dot{V}$ at baseline (0.57 (0.28)), which is nearly identical to previously published values for healthy volunteers [27]. Such a low heterogeneity in ventilation would mean that there is unlikely to be significant improvement in lung function from omalizumab treatment in the absence of allergen exposure. Specifically, by binding to IgE, omalizumab likely reduces both the early-phase and late-phase allergic inflammatory response in patients with asthma, which may thus serve to prevent or lessen symptoms following allergen exposure [15]. Therefore, it is possible that had we compared the effect of allergen exposure on ventilation and perfusion pre and post omalizumab treatment, we may have identified an effect of omalizumab on the response to allergen exposure. Second, although there was a trend towards improvement in clinical measures of asthma control and quality of life after omalizumab treatment as measured by our questionnaires, the lack of improvement in spirometry suggests that these particular subjects may not have experienced a strong physiologic benefit from omalizumab. This could explain the lack of improvement in their PET-measured ventilation and perfusion parameters. In the future, specifically examining subjects with both spirometric and clinical improvements following omalizumab treatment may help to reveal more notable changes on PET imaging.

There was a statistically significant decrease in the mean $\dot{Q}$ weighted $\log_{10}$ ($\dot{V}_A/\dot{Q}$), suggesting that omalizumab treatment leads to more perfusion going to areas of the lung with a lower

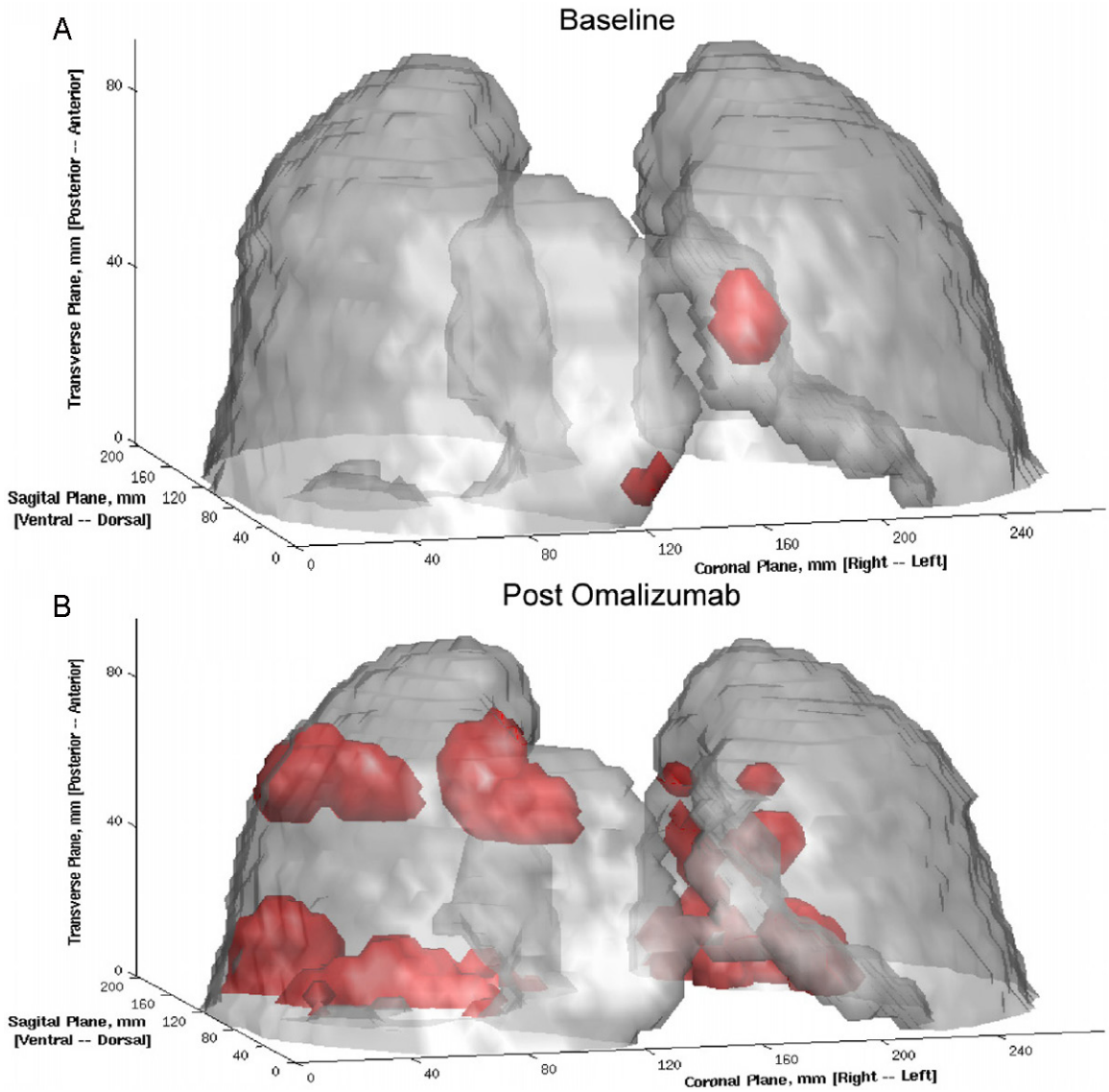

Figure 4. Ventilation defects. These three-dimensional images of the lungs at the end of ventilation were taken in subject B before and after therapy with omalizumab. Red areas represent ventilation defects, where the tracer was not successfully removed from the alveoli through ventilation.

$\dot{V}_A/\dot{Q}$ ratio. However, we think this most likely represents a chance finding. We tested multiple physiologic variables on a small population of subjects, increasing the odds of observing a statistically significant result on one of the variables. However, none of the other examined ventilation or perfusion metrics showed a significant change after omalizumab treatment, and furthermore we cannot conceive of a physiologic mechanism for this isolated result.

Despite the inability of the current study to demonstrate a prominent impact of omalizumab on ventilation and perfusion, the metrics obtained from PET imaging indicated a trend towards an increased percentage of ventilation defects. Although omalizumab's complete biologic mechanism of action in patients with allergic asthma remains uncertain, it is still difficult to reconcile how omalizumab could improve symptoms while worsening physiologic parameters such as the extent of ventilation defects. It is more plausible that omalizumab improves some aspect of pulmonary physiology (perhaps only after allergen exposure), but it may take a larger sample size or a different measuring tool to demonstrate this effect.

A strength of the study is that the treatment period (> 4 months) was more than sufficient to

demonstrate an omalizumab response in those subjects who would be responders [28]. The primary limitation of this pilot study is the small sample size, which makes it more difficult to attain statistical significance in any of the study outcomes, especially if the effect size is small or if only a fraction of patients may respond to treatment. However, image-derived parameters are in most cases based on large numbers of data points, which reduces the error of measurement in these parameters. Thus, if the response of subjects to an intervention is consistent then small sample sizes may be sufficient to demonstrate the effect of an intervention. The absence of a control group also makes it difficult to determine which changes (or lack thereof) were due to omalizumab and which were due to other factors, such as intra-subject variability in $\dot{V}_A/\dot{Q}$.

In conclusion, ^{13}NN-saline PET imaging of a small cohort of omalizumab-treated patients with allergic asthma was unable to demonstrate an effect on the size of ventilation defects, $\dot{V}_A/\dot{Q}$ matching, heterogeneity of ventilation, or heterogeneity of perfusion. Given the low pre-treatment ventilation heterogeneity in these subjects, these data are consistent with the hypothesis that omalizumab may dampen the allergic response when patients are exposed to allergen rather than improving baseline lung function. It is possible that future studies examining the effects of omalizumab on allergen challenged subjects might elucidate the physiologic mechanism for the improvement in patient-reported symptoms, exacerbations and hospitalizations. Until then, the physiologic basis for the improvement in asthma symptoms and quality of life following treatment with omalizumab remains uncertain.

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Disclosure of conflict of interest

None.

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