Hyperpolarized $^3$He magnetic resonance imaging ventilation defects in asthma: relationship to airway mechanics

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Abstract
In patients with asthma, magnetic resonance imaging (MRI) provides direct measurements of regional ventilation heterogeneity, the etiology of which is not well-understood, nor is the relationship of ventilation abnormalities with lung mechanics. In addition, respiratory resistance and reactance are often abnormal in asthmatics and the frequency dependence of respiratory resistance is thought to reflect ventilation heterogeneity. We acquired MRI ventilation defect maps, forced expiratory volume in one-second (FEV1), and airways resistance (Raw) measurements, and used a computational airway model to explore the relationship of ventilation defect percent (VDP) with simulated measurements of respiratory system resistance ($R_{rs}$) and reactance ($X_{rs}$). MRI ventilation defect maps were experimentally acquired in 25 asthmatics before, during, and after methacholine challenge and these were nonrigidly coregistered to the airway tree model. Using the model coregistered to ventilation defect maps, we narrowed proximal (9th) and distal (14th) generation airways that were spatially related to the MRI ventilation defects. The relationships for VDP with Raw measured using plethysmography ($r = 0.79$), and model predictions of $R_{rs>14}$ ($r = 0.91, P < 0.0001$) and $R_{rs>9}$ ($r = 0.88, P < 0.0001$) were significantly stronger ($P = 0.005; P = 0.03$, respectively) than with FEV1 ($r = -0.68, P = 0.0001$). The slopes for the relationship of VDP with simulated lung mechanics measurements were different ($P < 0.0001$); among these, the slope for the VDP-$X_{rs>14}$ relationship was largest, suggesting that VDP was dominated by peripheral airway heterogeneity in these patients. In conclusion, as a first step toward understanding potential links between lung mechanics and ventilation defects, impedance predictions were made using a computational airway tree model with simulated constriction of airways related to ventilation defects measured in mild-moderate asthmatics.
**Introduction**

Pulmonary imaging using inhaled gas magnetic resonance imaging (MRI) has previously revealed spatially and temporally persistent ventilation defects in chronic obstructive pulmonary disease (COPD) and asthma (de Lange et al. 1999, 2007; Altes et al. 2001; Samee et al. 2003; Parraga et al. 2007). While ventilation MRI is typically acquired in breath-hold, ventilation defects may reflect the ventilation heterogeneity previously estimated using multibreath gas washout (Verbanck et al. 2003; Downie et al. 2007) and positron emission tomography (PET) imaging (Venegas and Musch 2005; Venegas et al. 2005) typically measured using tidal breathing techniques. The size and extent of MRI ventilation defects was previously evaluated in relation to the forced expiratory volume in 1 s (FEV$_1$) and showed modest correlations in asthma (de Lange et al. 2006) and COPD (Kirby et al. 2010, 2011). In addition, previous work (Costella et al. 2012) also showed weak-tomore relationships for $^3$He MRI ventilation defect percent (VDP) and FEV$_1$. Recently, we explored the relationship of MRI ventilation defects and abnormally remodeled airways in asthmatics with and without ventilation defects (Svenningsen et al. 2014), and observed that asthmatics with ventilation defects reported significantly greater inflammation, airways resistance, airflow limitation, and hyper-responsiveness than asthmatics without defects. However, there are still many unanswered questions and some controversy about the role that biomechanical lung abnormalities may play in the temporally and spatially persistent ventilation abnormalities that are visibly and quantitatively obvious in asthmatics.

Pulmonary biomechanics can be estimated using the forced oscillation technique (FOT). Previous FOT studies showed that respiratory system resistance ($R_{rs}$) and reactance ($X_{rs}$) were sensitive to heterogeneous airway narrowing (Lutchen and Gillis 1997; Kaczka et al. 1999) and that $X_{rs}$ was particularly sensitive to distal or peripheral airway narrowing (Kaczka et al. 1999). Modeling studies also showed that PET-derived ventilation defects were correlated with respiratory system resistance measured at 0.15 Hz (Tgavalekos et al. 2005, 2007). By simulating bronchoconstriction in an asymmetric branching airway tree model, the relationship of ventilation defects with predictions of $R_{rs}$ and $X_{rs}$ at 6 Hz (Leary et al. 2014) were also shown. In other modeling studies, the distribution of narrowed airways responsible for generating ventilation defects was evaluated as was the relationship of ventilation defects with different frequency-dependent patterns of impedance (Tgavalekos et al. 2005; Campana et al. 2009; Kaczka et al. 2011). The relationship of ventilation defects with respiratory impedance is not well understood; while the frequency dependence of $R_{rs}$ (typically $R_{rs}$ at 5 Hz minus $R_{rs}$ at 20 Hz) and $X_{rs}$ are sensitive to peripheral airway heterogeneity (Lutchen and Gillis 1997; Kaczka et al. 1999), their relative sensitivities, and the physiological relevance of this have not been determined.

To better understand the relationship of respiratory system mechanics and MRI ventilation defects, we coregistered MRI ventilation maps with a computational multi-branch airway tree and simulated respiratory measurements after closing airways close to ventilation abnormalities. We explored the relationship of ventilation defects with $R_{rs}$ and the frequency dependence of $R_{rs}$ and $X_{rs}$ as well as experimentally measured FEV$_1$ and airways resistance (Raw). We hypothesized that lung impedance predictions could be simulated using a model that incorporated ventilation defects measured in asthma patients to help better understand these relationships.

**Methods**

**Study design and subjects**

We adapted a three-dimensional airway tree consisting of 64,895 airways (M. Tawhai, U. Auckland), with 32,447 terminal airways (dimension distributions shown in Table 1), to generate an airway tree computational model. A full description of the model was previously provided (Tawhai et al. 2004); briefly, the airway tree was derived from a volume rendered lung X-ray computed tomography (CT) acquired in a patient including the eighth-generation airways with the remaining generations constructed using a volume filling algorithm (Tawhai et al. 2009).

As previously described (Costella et al. 2012), participants between 18 and 60 years of age with diagnosis of asthma and FEV$_1 \geq$60%, provided written informed consent to a protocol approved by a local research ethics board. During a single two-hour visit, MRI and spirometry were performed at baseline, post-methacholine (at the provocative concentration resulting in a 20% decrease in FEV$_1$ (PC$_{20}$) or the final dose) and 25 min after administration of 200 mg salbutamol through a pressurized metered dose inhaler (pMDI) and Aero Chamber Plus valve holding chamber (Trudell Medical International, London, Canada). Spirometry was performed using an ndd EasyOne spirometer (ndd Medizintechnik AG, Zurich, Switzerland). Plethysmography was performed 10 min prior to methacholine challenge using a MedGraphics Elite Series unit (MedGraphics, St. Paul, MN). Methacholine challenge was performed in the seated position according to ATS guidelines (Crapo et al. 2000) using an AeroEclipse II Breath Actuated Nebulizer (Trudell Medical International) until PC$_{20}$ was achieved or a maximum dose of 16.0 mg/mL was administered.
Image acquisition

Anatomical proton (1H) and hyperpolarized 3He MR images were acquired using a 3 Tesla Discovery MR750 system (General Electric Health Care; Milwaukee, WI), as previously described. Subjects (Parraga et al. 2007) were instructed to inhale a fixed 1 L gas mixture (N2 for 1H MRI and a3He/N2 for 3He MRI) from functional residual capacity (FRC), and coronal images were acquired under breath-hold conditions. It is important to note that as previously described, (Costella et al. 2012) the same volume of inhaled gas was used, regardless of FRC or TLC (Table 2). While the signal-to-noise ratio (SNR) was preserved (because we were not in the SNR-limited range), the lung volume relative to TLC for image acquisition was slightly different for each patient. Scans at all time points were performed in the supine position and completed within five minutes of patient positioning in the scanner. Conventional 1H MRI was performed before 3He MRI using the whole-body radiofrequency coil and a fast gradient-recalled echo method (total data acquisition time = 12 sec; TR/TE/flip-angle = 4.3 msec/1.0 msec/30°; FOV=40 × 40 cm; matrix=128 × 80 (zero-padded to 128 × 128); partial echo percent = 62.5%; BW = 62.50 kHz; one excitation; 14 sections; section thickness, 15 mm; zero gap), as previously described.(Parraga et al. 2007) Hyperpolarized 3He MRI was enabled using a rigid linear bird-cage transmit/receive chest coil (RAPID Biomedical GmbH, Wuerzburg, Germany) and 3He gas was polarized to 30–40% using a commercial spin-exchange polarizer system (Polarean Inc, Durham, NC). 3He coronal static ventilation images were acquired using a fast gradient-recalled echo method with partial echo (total data acquisition time = 10 sec; TR/TE/flip-angle = 3.8 msec/1.0 msec/7°; FOV = 40 × 40 cm; matrix = 128 × 80 (zero-padded to 128 × 128); partial echo percent = 62.5%; BW = 62.50 kHz; one excitation; 14 sections; section thickness, 15 mm; zero gap), as previously described.(Parraga et al. 2007).

Image analysis

3He MRI semiautomated segmentation was performed using an algorithm implemented in MATLAB (The Math-
works Inc., Natick, MA), as previously described (Kirby et al. 2012). Briefly, and as shown in Figure 1, 3He MRI static ventilation images were segmented using a K-means approach that classified voxel intensity values into five clusters ranging from signal void (cluster 1, C1 or ventilation defect volume [VDV]) and hypointense (or partial volume) to hyperintense signal (C5). The delineation of the ventilation defect boundaries was performed using a seeded region-growing algorithm that segmented the 1H MRI thoracic cavity, as previously described (Kirby et al. 2012). This approach was previously validated using ventilation images in patients with asthma, cystic fibrosis, and COPD, and was based on a previous definition of ventilation defect volume as cluster 1 based on an expert visual interpretation of a series of images. Based on this previous information and numerous previous studies (Costella et al. 2012; Kirby et al. 2012; Svenningsen et al. 2014; Pike et al. 2015), we used this definition in this study.

### Coregistration of MRI ventilation maps to airway tree

We used rigid and nonrigid registration algorithms in MATLAB to coregister the MRI ventilation cluster map with the airway tree model. Briefly, the lung model was first resampled anterior-to-posterior into the same number of 15 mm slices as the coronal MRI datasets. A transformation matrix was generated so that each of the MRI coronal slices was rigidly coregistered to the mesh in the x, y, and z direction. Next, eight to 10 fiducial landmarks were manually located along the outer lung boundaries for each slice and using these fiducials, individual slices were rigidly coregistered to the mesh. This was performed for all datasets. It is also important to note that the rather coarse spatial resolution of the MR coronal slices was 3.13 mm x 3.13 mm x 15 mm, and this places a conservative limit on registration accuracy. We note that we have routinely coregistered CT airway trees from individual patients to the MRI functional datasets in this manner (Pike et al. 2015) with fiducial localization error of 3–6 mm in the x and y plane and Dice similarity coefficients similar to what was achieved here (mean DSC = 83 ± 3%). In Figure 2, we show the coregistration

#### Table 2. Baseline demographic characteristics and pulmonary function measurements.

| Parameter (±SD) | Asthmatics (n = 25) |
|----------------|---------------------|
| Age years      | 35 (11)             |
| BMI kg/m²      | 26 (5)              |
| FEV₁%pred      | 84 (15)             |
| FVC %pred      | 93 (11)             |
| FEV₁/FVC %     | 74 (11)             |
| IC %pred       | 111 (15)            |
| FRC %pred      | 92 (15)             |
| RV %pred       | 113 (25)            |
| TLC %pred      | 101 (9)             |
| Raw %pred      | 126 (69)*           |
| Gaw %pred      | 63 (38)*            |
| PC₂₀ mg/mL     | 6 (23)              |

SD, Standard Deviation; BMI, Body Mass Index; FEV₁, Forced Expiratory Volume in 1s; %pred, Percent Predicted; FVC, Forced Vital Capacity; IC, Inspiratory Capacity; FRC, Functional Residual Capacity; RV, Residual Volume; TLC, Total Lung Capacity; Raw, Airways Resistance; Gaw, Airway Conductance; PC₂₀, provocative concentration of methacholine sufficient to induce a 20% decrease in FEV. *n = 24.

Figure 1. Pipeline for segmentation of 3He MRI ventilation defects. Raw image data from 3He MRI and conventional proton MRI are coregistered and a k-means cluster algorithm was used to segment ventilation defects (shown as Cluster 1).
results for three slices for each of the two subjects. The DSC ranged from 86 to 75% for Subject 1 and 91–82% for Subject 2, and this provides good evidence of coregistration accuracy. Figure 2 also shows the spatial relationship of 14th generation airways that were narrowed proximal to ventilation defects in these subjects.

**Impedance Predictions**

Airways within ventilation defects (>10 voxels in the x or y direction (or 3 cm)) were narrowed to 10% of initial diameter as this effectively increased resistance by a factor of 10⁴ according to Poiseuille’s law and avoided diameters of zero in the simulations (Tgavalekos et al. 2005). We occluded airways located within ventilation defects and within two voxels of their boundary at two different airway generations (9th or 14th generations) as shown in Figure 2 for two representative subjects, with airways proximal to ventilation defects shown in yellow and the ventilation abnormalities shown in gray. The rationale for choosing both 9th and 14th generation airways was based on previous work (Tgavalekos et al. 2005) that endeavored to explore simulations stemming from the medium and small airways. It is important to note that for trained image observers, it is quite straightforward to identify the specific airways leading to ventilation defects including the relatively large continuous spatial clusters >10 voxels we evaluated here. It is also worth pointing out that many ventilation defects were segmental and subsegmental defects as shown in Figures 2 and 3, and in these cases, the airway ventilation defect spatial concordance is also anatomically obvious.

Lung model impedance predictions were generated as previously described (Bhatawadekar et al. 2015) where the initial lung volume was reduced from TLC to FRC by reducing the airway diameters and lengths to 80%, achieving a volume ratio of 0.5. Flow was described by Womersley (Kaczka et al. 2007) where the complex impedance of each nonterminal airway branch was calculated as

\[
Z_a(f) = \frac{j2f \rho_{air} l_a}{r_a^2} \left[1 - \frac{2J_1(x_a \sqrt{-j})}{x_a \sqrt{-j} J_0(x_a \sqrt{-j})}\right]^{-1}
\]

where \(r_a\) is the radius and \(l_a\) is the length of the airway, \(f\) is the oscillation frequency in Hz, \(\rho_{air}\) is the density of air (1.16 kg/m³), \(J_0\) and \(J_1\) are the complex Bessel functions of order 0 and 1, respectively, \(j\), the unit imaginary num-

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**Figure 2.** Coregistration of MRI and airway mesh model for three center slices in two representative asthmatics. For Subject 1 and 2, left panels show center, and 2 slices anterior (A) and posterior (P) to center coronal slice MRI; middle panels show corresponding model-to-MRI lung cavity coregistration; right panels show coregistration of model-to-ventilation defects coregistration with 14th generation airways proximal to ventilation defects closed in yellow. Slice-specific Dice similarity coefficients (DSC) reflect registration accuracy for each of the three slices coregistered to the airway model for each of Subject 1 and 2.
Figure 3. MRI and model-to-MRI coregistration for three asthmatics showing colocalization of airway tree and ventilation defects post-methacholine. Center coronal slice MRI ventilation in blue coregistered to anatomical MRI in gray scale at baseline, post-methacholine and post-salbutamol. For each subject, the corresponding post-methacholine mesh models with closure of airways from 9th (Row 3 across) or 14th generation (Row 4 across) are shown. For the mesh model, gray reflects an MRI ventilation defect, yellow segments are specific to mesh model airways located within a ventilation defect and cyan segments airways were mesh model airways that did NOT lead to ventilation defects. White circles show differences reflected by closure of either the 9th (row 3) or 14th (row 4) generation airways in the model. Subject 3: 36-year-old female; baseline/post-methacholine/post-salbutamol FEV₁ = 66/45/71% pred, VDP = 9/50/10%, R<sub>r>9</sub> = 2.97/4.64/3.12 cmH₂O.s.L⁻¹, R<sub>r>9</sub> = 2.71/3.54/2.78 cmH₂O.s.L⁻¹. Subject 4: 42 year-old male; baseline/post-methacholine/post-salbutamol FEV₁ = 72/50/77% pred, VDP = 8/25/9%, R<sub>r>9</sub> = 2.71/4.08/3.04 cmH₂O.s.L⁻¹, R<sub>r>14</sub> = 2.67/3.21/2.76 cmH₂O.s.L⁻¹. Subject 5: 46-year-old male; baseline/post-methacholine/post-salbutamol FEV₁ = 72/50/77% pred, VDP = 8/25/9%, R<sub>r>9</sub> = 2.71/4.08/3.04 cmH₂O.s.L⁻¹, R<sub>r>14</sub> = 2.67/3.21/2.76 cmH₂O.s.L⁻¹.
ber, and \( x_a \) is the Womersley number of the airway branch given by

\[
x_a = \frac{2\pi\rho_{\text{air}} f}{\mu_{\text{air}}}
\]

where \( \rho_{\text{air}} \) is the dynamic viscosity of humid air at 37°C (1.85 \times 10^{-5} \text{ Pa.s}). Lung compliance was distributed evenly at terminal airways as each served as an alveolar compartment accounting for parenchymal stretch, surface tension, and gas compression (Tgavalekos et al. 2003). We recognize that this approach neglects the contributions of airway wall compliance and gas compression within airways, but this effect is much smaller than the effect of the alveolar compartment (Mead 1979; Leary et al. 2014). The impedance of each terminal airway was defined as

\[
Z_t = Z_a - \frac{j \omega E_t}{\sigma}
\]

where \( E_t \) is the elastance of the terminal airway unit. The model lung impedance (\( Z_{L,\text{mod}} \)) was evaluated from series and parallel summations of all airway impedances assuming a lumped element approach, and separated into resistance (\( R_{L,\text{mod}} \)) and reactance (\( X_{L,\text{mod}} \)), and evaluated from 0.2 to 32 Hz.

Upper airway resistance (\( R_{\text{central}} \)) and chest wall resistance (\( R_{cw} \)) were assigned values of 0.5 cmH2O·s·L⁻¹ each (Nagels et al. 1980; Barnas et al. 1987, 1989) and these were added to \( R_{L,\text{mod}} \) to obtain the model respiratory system resistance \( R_{rs} \). Due to the high-frequency dependence of \( X_{rs} \) we also computed elastance which is largely frequency independent in healthy lung. Chest wall elastance (\( E_{cw} = 10.6 \text{ cmH}_2\text{O·s·L}^{-1} \)) (Barnas et al. 1985) was summed with lung elastance (\( E_{rs,\text{mod}} \)) to obtain the respiratory system elastance (\( E_{rs} \)), where \( E_{rs} = 2\pi f X_{rs}(f) \). We computed \( E_{rs} \) for low frequencies only where \( X_{rs} \) was dominated by elastic mechanics. The frequency dependence of \( R_{rs} \) was evaluated over two ranges: 1) the low-frequency range of 0.2–5 Hz (\( R_{rs,0.2–5} \)) which is normally not accessible by common forced oscillation methods (but where the frequency dependence of \( R_{rs} \) is more easily observed), and, 2) the oscillometry frequency range of 5–20 Hz (\( R_{rs,5–20} \)). Finally, the effects of upper airway shunt (\( Z_{\text{raw}} \)) were implemented using previously published \( Z_{\text{raw}} \) values (Cauberghs and Van de Woestijne 1983) and extrapolated values of shunt resistance and reactance at 0.2 Hz as previously described (Bhatawadekar et al. 2015).

### Statistical analysis

Data were tested for normality using the Shapiro–Wilk normality test and nonparametric tests were performed when data were not normal. Univariate relationships were evaluated using linear regressions (\( r^2 \)), Pearson correlations (\( r \)), and Spearman correlations (\( \rho \)) when the data were not normal generated using GraphPad Prism version 4.00 (GraphPad Software, Inc., San Diego, CA). The Fisher z transformation was used to determine significant differences between \( r \) values. Significant differences in the VDP-impedance relationship slopes were determined using analysis of covariance (ANCOVA). Holm–Bonferroni corrections were used for multiple comparisons. All results were considered statistically significant when the probability of making a Type 1 error was less than 5% (\( P < 0.05 \)).

### Results

#### Subjects

Table 2 provides subject demographic and pulmonary function measurements for 25 mild-moderate participants with asthma (mean age 35 ± 11 years), moderately abnormal FEV1/FVC and airways resistance (\( \text{Raw} = 126 \pm 69\%_{\text{pred}} \)). Figure 3 shows ventilation images (pre and post-methacholine and post-salbutamol) and model-to-MRI coregistration results (post-methacholine) for three asthmatics. For all three subjects, methacholine induced a larger size and greater number of ventilation defects that partially resolved post-salbutamol. The coregistered model-to-MRI results show the spatial localization of the 14th or 9th generation airways closed within ventilation defects and used to generate the simulated impedance measurements.

#### Model and experimental measurements

In Figure 4, the frequency-dependent \( R_{rs} \) and \( X_{rs} \) predictions at baseline, post-methacholine, and post-salbutamol are provided. Table 3 shows measurements acquired and model predictions related to these three conditions. FEV1, VDP, and model predictions of \( R_{rs} \) and \( X_{rs} \) at 5 Hz were significantly different post-methacholine and post-salbutamol. Underscoring these significant differences, in Table 4, the fractional changes (baseline – post-methacholine and post-salbutamol – post-salbutamol) are shown for \( R_{rs,>14} \) at different frequencies and frequency bands.

#### Relationships for experimental measurements and model predictions

Table 5 shows correlation coefficients for FEV1, Raw%, and model-derived \( R_{rs} \) and \( X_{rs} \) at 5 Hz with VDP. There were moderate correlations for VDP with FEV1% and Raw% and significantly stronger correlations with \( R_{rs} \) and \( X_{rs} \). Some of these relationships are also shown in Figure 3 and
4. Figure 5 shows the relationship of Raw% measured before methacholine provocation with model predictions of Rrs when airways were closed from the 9th (r = 0.71, P < 0.0001) and 14th generation (r = 0.71, P = 0.0003).

As shown in Figure 6, Rrs was increased and Xrs at 5 Hz was diminished in relation to increasing (or worse) VDP. Figure 6A and B show impedance predictions at 5 Hz and the strong correlations between Rrs and VDP for 9th gener-

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**Table 3.** Baseline, post-methacholine and post-salbutamol FEV1, VDP and model predictions.

| Parameter (±SD) | Baseline (n = 25) | Post-methacholine (n = 25) | Post-Salbutamol (n = 25) | P-value* |
|-----------------|-------------------|-----------------------------|--------------------------|----------|
| Experimental    |                   |                             |                          |          |
| FEV1%pred       | 84 (15)           | 64 (15)                     | 87 (15)                  | <0.0001  |
| VDP %           | 4 (4)             | 11 (10)                     | 4 (2)                    | 0.0002   |
| Model           |                   |                             |                          |          |
| Rrs>9 cmH2O.s.L⁻¹ | 1.99 (0.26)       | 2.33 (0.67)                 | 1.92 (0.11)              | 0.003    |
| Rrs>14 cmH2O.s.L⁻¹ | 1.85 (0.09)       | 2.00 (0.24)                 | 1.84 (0.06)              | 0.002    |
| Xrs>9 cmH2O.s.L⁻¹ | −1.16 (0.34)      | −1.54 (0.73)                | −1.07 (0.18)             | 0.0008   |
| Xrs>14 cmH2O.s.L⁻¹ | −0.95 (0.13)      | −1.14 (0.27)                | −0.92 (0.09)             | <0.0001  |

SD, Standard Deviation; FEV1, Forced Expiratory Volume in 1s; %pred, Percent Predicted; VDP, Ventilation Defect Percent; Rrs, lung resistance; Rrs>9, model prediction of Rrs when airways were closed distal to the 9th generation; Rrs>14, model prediction of Rrs when airways were closed distal to the 14th generation; Xrs, lung reactance; Xrs>9, model prediction of Xrs when airways were closed distal to the 9th generation; Xrs>14, model prediction of Xrs when airways were closed distal to the 14th generation.

*Repeated measures analysis of variance.
Table 4. Fractional changes in VDP, FEV1, and model predictions post-methacholine (relative to baseline) and post-salbutamol (relative to post-methacholine).

| Parameter (±SD) | Post- methacholine/Baseline (n = 25) | Post-Salbutamol/Post-methacholine (n = 25) |
|----------------|--------------------------------------|-------------------------------------------|
| FEV1%pred      | 0.76 (0.07)                          | 1.37 (0.17)                               |
| VDP (%)        | 2.96 (1.50)                          | 0.38 (0.20)                               |
| Rrs10.2        | 1.31 (0.19)                          | 0.77 (0.26)                               |
| Rrs15.20       | 1.25 (0.16)                          | 0.07 (0.23)                               |
| Xrs10.2        | 1.56 (0.22)                          | 0.45 (0.34)                               |
| Xrs15.20       | 1.14 (0.08)                          | 0.86 (0.11)                               |
| Xrs20          | 1.26 (0.10)                          | 0.78 (0.16)                               |
| Xs<20          | 0.99 (0.01)                          | 1.02 (0.01)                               |

SD, Standard Deviation; FEV1, Forced Expiratory Volume in 1s; %pred, Percent Predicted; VDP, Ventilation Defect Percent; Rrs, lung resistance; Rrs10.2, model prediction of Rrs measured at 0.2 Hz; Rrs15.20, model prediction of Rrs measured at 5 Hz; Xrs15.20, model prediction of Xrs measured at 5 Hz; Xs<20, model prediction of Xs measured at 20 Hz.

Table 5. Relationships for FEV1, Raw, and model-derived measurements at 5 Hz with Raw and VDP.

|                      | Raw %pred (n = 24) | VDP %pred (n = 75) |
|----------------------|--------------------|--------------------|
| FEV1%pred            | −0.74 (<0.0001)    | −0.68 (<0.0001)    |
| Raw %pred            | −                   | 0.79 (<0.0001)*    |
| Rrs<9                | 0.71 (<0.0001)     | 0.88 (<0.0001)     |
| Rrs14                | 0.71 (<0.0001)     | 0.91 (<0.0001)     |
| Xrs<9                | −                   | −0.88 (<0.0001)    |
| Xs<20                | −                   | −0.94 (<0.0001)    |

Raw, Airway Resistance; VDP, Ventilation Defect Percent; FEV1, Forced Expiratory Volume in 1s; %pred, Percent Predicted; Rrs, lung resistance; Rrs<9, model prediction of Rrs when airways were closed distal to the 9th generation; Rrs14, model prediction of Rrs when airways were closed distal to the 14th generation; Xrs, lung reactance; Xs<20, model prediction of Xs when airways were closed distal to the 9th generation; Xs14, model prediction of Xs when airways were closed distal to the 14th generation; r = Pearson r correlation coefficient.

Discussion

We used ventilation defect maps acquired in asthmatics to constrain airway closure in a computational airway tree model and simulated measurements of airways resistance to investigate the influence of airway narrowing related to ventilation defects with predictions of lung biomechanical measurements and observed: (1) MRI ventilation measurements in 25 asthmatics acquired before, during, and after methacholine challenge could be used to close specific airways and drive simulations of lung biomechanical behavior, (2) model predictions showed greater mean Rrs and lower Xs when specific airways were narrowed based on their proximity to MRI ventilation defects measured post-methacholine, and (3) when ventilation defects were
used to regionally constrain airway closure, the relationship between model predictions of $X_{rs}$ and VDP was greater when more distal airways (14th vs. the 9th generation) were perturbed.

In asthma patients, ventilation defects increase in number and size during methacholine challenge and respiratory system resistance also increases (Tgavalekos et al. 2007). In a previous study, the relationship between PET-
derived ventilation defects and lung impedance was dependent on distal airway closure (Tgavalekos et al. 2005). Similar to this previous work, our model was constrained to physiologically relevant ventilation defects observed in a relatively wide variety of mild-to-moderate asthmatics. While it was not surprising that impedance increased with experimentally derived VDP, we were surprised that in asthma patients, this relationship was linear and statistically greater at the lower frequencies (in the range typically used by oscillometry). We also observed that when ventilation defects are used to regionally constrain airway closure, the relationship between model predictions of $X_{rs}$ and VDP was greater when more distal airways (14th vs. 9th generation) were perturbed. While the physiological meaning of these findings is yet to be determined, as first demonstrated by Otis (Otis et al. 1956) using a single bifurcating airway, resistance and reactance are interdependent. In a homogeneous bifurcat-

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**Figure 7.** VDP correlations with experimentally measured Raw%pred at baseline, FEV1%pred and model predictions for $R_{rs}$ and $X_{rs}$ over a range of test frequencies.

**Figure 8.** The sensitivity of measurements predicted by the lung model at various frequencies as indicated by the legend. The sensitivity to changes in VDP are indicated by increased slope (slopes for each frequency provided in Table 6). Measurements at lower frequencies showed greater dependence to VDP (i.e., $X_{rs}$ and $E_{rs}$ measured at 0.2 Hz reflected the greatest sensitivity to changes in VDP).

**Table 6.** Relationships for model predictions with VDP.

| Model prediction | Slope  |
|------------------|--------|
| $R_{rs,0.2}$     | 0.223  |
| $R_{rs,5}$       | 0.024  |
| $R_{rs,20}$      | 0.009  |
| $R_{rs,0.2-5}$   | 0.199  |
| $R_{rs,5-20}$    | 0.015  |
| $X_{rs,0.2}$     | -1.356 |
| $X_{rs,5}$       | -0.046 |
| $X_{rs,20}$      | -0.005 |
| $E_{rs,0.2}$     | 1.703  |
| $E_{rs,5}$       | 1.435  |
ing airway tree, $X_{rs}$ yields information related to the combined effect of the elastic and inertive properties of the lung where elastic effects dominate at low frequencies. In obstructive lung diseases like asthma, low-frequency $X_{rs}$, and thus $E_{rs}$, can be strongly influenced by small airway narrowing, even, as our model suggested, when there are no changes in intrinsic tissue stiffness. This may reflect derecruitment of parenchyma whereby airway narrowing prevents distal oscillatory flow to the parenchyma diminishing lung elastance indicated by the more negative $X_{rs}$. Although we observed the $X_{rs5}$–VDP relationship was stronger in the distal airs, it is difficult to be certain about the physical meaning of this finding. It is important to note that we did not observe different $R_{rs5}$–VDP correlations for the distal versus proximal airs. Taken together, however, these data suggest that $R_{rs5}$ may be less sensitive than $X_{rs5}$ and $E_{rs}$ to conditions whereby the small airs are narrowed sufficiently to prevent oscillatory flow. Notably, previous work in pigs showed that $R_{rs}$ was sensitive to airway narrowing and $X_{rs}$ was more sensitive to ventilation defects (Dellaca et al. 2009).

The finding that $X_{rs5}$ and $E_{rs}$ predictions were related to VDP warrants further investigation and experimental confirmation in asthmatics. However, at 0.2 Hz, where the slope for the relationship between $X_{rs}$ and VDP was the greatest, experimental confirmation will be challenging. Low-frequency respiratory impedance can be determined using the optimal ventilation waveforms, but this approach is not amenable to clinical use. At the more common FOT frequencies, such as 5 Hz, model predictions of $X_{rs}$ (and therefore $E_{rs}$) were more sensitive to VDP than the frequency dependence of $R_{rs}$ from 5 to 20 Hz. This sensitivity may arise from the peripheral airway narrowing which leads to alveolar derecruitment. However, the greater sensitivity of $X_{rs}$ at 5 Hz compared to $R_{rs}$ may be explained because resistance measurements at 5 Hz and 20 Hz include a large contribution from mainly unobstructed central airs. Low-frequency $X_{rs}$ and $E_{rs}$ are dominated by the compliant parenchyma, with smaller contributions from the chest wall. This is in contrast to the small contribution of the peripheral airway relative to the upper and central airs to $R_{rs}$, which may explain why airway narrowing in the periphery had a greater effect on $X_{rs}$ than $R_{rs}$.

Our study was limited and in that, we did not experimentally acquire oscillometry measurements; therefore, it is difficult to be certain about the physiological meaning of the relationships observed here between ventilation defects and respiratory resistance/reactance. Given the temporal nature of asthma provocation, it will be very difficult logistically to acquire these data experimentally within a methacholine challenge. Nonetheless, this modeling study cannot be considered definitive, but a hypothesis-generating exploration of how an airway tree model can be used and constrained to help better understand resistance and reactance in asthmatics. Our model was limited and in that, we did not account for small degrees of constriction or dilatation in the airs throughout the remaining lung volume – namely, the ventilated regions or central airs. This is important because lung regions outside of ventilation defects may be partially inflated or hyperinflated and this would alter $R_{rs}$. We recognize that in asthmatics, ventilation defects are unlikely due to airway closure at specific generations. A possible future improvement in the model can be undertaken whereby more complex airway lumen sizing techniques at different generations can be used to scale airway diameter. It is also important to emphasize that we did not test how different spatial distributions of ventilation defects or patterns of bronchoconstriction influenced lung impedance. Therefore, we cannot comment on the sensitivity or specificity of impedance predictions to the spatial pattern of ventilation defects. However, despite normal variation in defect size and distribution among the subjects, we observed that experimentally measured $Raw$ and predicted $R_{rs}$ and $X_{rs}$ at 5 Hz were strongly correlated with VDP. Also, we did not include upper airway narrowing in these simulations, but this could certainly lead to greater $R_{rs}$ variability, relative to $X_{rs}$.

Ventilation heterogeneity is a hallmark finding in both asthma and COPD, but the biomechanical mechanisms responsible for ventilation defects in COPD and asthma may differ. In asthma patients, ventilation defects may be due to increased muscle activation acting on a normal parenchymal tethering load and/or mucous plugging (Downie et al. 2007). In COPD, there is the potential for diminished elastic recoil and thickened airway walls (Hogg et al. 2004). Indeed, in severe COPD, ventilation defects are regionally related to both emphysematous bulae and airway abnormalities (Kirby et al. 2014). In summary, we used an airway tree model to generate simulations of $R_{rs}$ and $X_{rs}$ based on ventilation defects in 25 asthmatics. Model predictions of low-frequency $X_{rs}$ and $E_{rs}$ provide a way to explain airway behavior that may result in ventilation defects in asthmatics.

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**Conflict of Interest**

The authors declare they have no conflicts of interest to declare.
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