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Heather M Young

Fumin Guo

Rachel L Eddy

Geoffrey Maksym

Grace Parraga

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RESEARCH ARTICLE

# Oscillometry and pulmonary MRI measurements of ventilation heterogeneity in obstructive lung disease: relationship to quality of life and disease control

Heather M. Young,<sup>1,2</sup> Fumin Guo,<sup>1,3</sup> Rachel L. Eddy,<sup>1,2</sup> Geoffrey Maksym,<sup>4</sup> and Grace Parraga<sup>1,2,3</sup>

<sup>1</sup>Robarts Research Institute, Western University, London, Ontario, Canada; <sup>2</sup>Department of Medical Biophysics, Western University, London, Ontario, Canada; <sup>3</sup>Graduate Program in Biomedical Engineering, Western University, London, Ontario, Canada; and <sup>4</sup>School of Biomedical Engineering, Dalhousie University, Halifax, Nova Scotia, Canada

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**Young HM, Guo F, Eddy RL, Maksym G, Parraga G.** Oscillometry and pulmonary MRI measurements of ventilation heterogeneity in obstructive lung disease: relationship to quality of life and disease control. *J Appl Physiol* 125: 73–85, 2018. First published March 15, 2018; doi:10.1152/jappphysiol.01031.2017.—Ventilation heterogeneity is a hallmark finding in obstructive lung disease and may be evaluated using a variety of methods, including multiple-breath gas washout and pulmonary imaging. Such methods provide an opportunity to better understand the relationships between structural and functional abnormalities in the lungs, and their relationships with important clinical outcomes. We measured ventilation heterogeneity and respiratory impedance in 100 subjects [50 patients with asthma, 22 ex-smokers, and 28 patients with chronic obstructive pulmonary disease (COPD)] using oscillometry and hyperpolarized <sup>3</sup>He magnetic resonance imaging (MRI) and determined their relationships with quality of life scores and disease control/exacerbations. We also coregistered MRI ventilation maps to a computational airway tree model to generate patient-specific respiratory impedance predictions for comparison with experimental measurements. In COPD and asthma patients, respectively, forced oscillation technique (FOT)-derived peripheral resistance (5–19 Hz) and MRI ventilation defect percentage (VDP) were significantly related to quality of life (FOT: COPD  $\rho = 0.4$ ,  $P = 0.004$ ; asthma  $\rho = -0.3$ ,  $P = 0.04$ ; VDP: COPD  $\rho = 0.6$ ,  $P = 0.003$ ; asthma  $\rho = -0.3$ ,  $P = 0.04$ ). Patients with poorly controlled asthma (Asthmatic Control Questionnaire >2) had significantly increased resistance (5 Hz:  $P = 0.01$ ; 5–19 Hz:  $P = 0.006$ ) and reactance (5 Hz:  $P = 0.03$ ). FOT-derived peripheral resistance (5–19 Hz) was significantly related to VDP in patients with asthma and COPD patients (asthma:  $\rho = 0.5$ ,  $P < 0.001$ ; COPD:  $\rho = 0.5$ ,  $P = 0.01$ ), whereas total respiratory impedance was related to VDP only in patients with asthma (resistance 5 Hz:  $\rho = 0.3$ ,  $P = 0.02$ ; reactance 5 Hz:  $\rho = -0.5$ ,  $P < 0.001$ ). Model-predicted and FOT-measured reactance (5 Hz) were correlated in patients with asthma ( $\rho = 0.5$ ,  $P = 0.001$ ), whereas in COPD patients, model-predicted and FOT-measured resistance (5–19 Hz) were correlated ( $\rho = 0.5$ ,  $P = 0.004$ ). In summary, in patients with asthma and COPD patients, we observed significant, independent relationships for FOT-measured impedance and MRI ventilation heterogeneity measurements with one another and with quality of life scores.

**NEW & NOTEWORTHY** In 100 patients, including patients with asthma and ex-smokers, <sup>3</sup>He MRI ventilation heterogeneity and respiratory system impedance were correlated and both were independently related to quality of life scores and asthma control. These findings demonstrated the critical relationships between respiratory system impedance and ventilation heterogeneity and their role in

determining quality of life and disease control. These observations underscore the dominant role that abnormalities in the lung periphery play in ventilation heterogeneity that results in patients' symptoms.

asthma; COPD; forced oscillation technique; hyperpolarized <sup>3</sup>He MRI; respiratory system impedance

## INTRODUCTION

Ventilation heterogeneity is a hallmark consequence of obstructive lung diseases such as asthma (26, 30, 56, 83) and chronic obstructive pulmonary disease (COPD) (13, 82) and is related to disease symptoms and control (13, 14, 30, 76). Ventilation heterogeneity can be measured using a variety of techniques, including multiple-breath gas washout methods (10, 63, 64) and pulmonary imaging (3, 31, 68, 79, 81). Despite decades of research that focused on the quantification and development of our understanding of causes and clinical implications of ventilation abnormalities, many patients with obstructive lung disease and ventilation heterogeneity still have poor disease control and quality of life (4, 17, 60, 74). This may be due in part to the fact that the complex structural and biomechanical changes underlying ventilation heterogeneity are still not fully understood (2, 23, 66), including those contributed by airway abnormalities such as heterogeneous airway diameter and tone (15, 55).

The forced oscillation technique (FOT), first developed over 50 yr ago (28), noninvasively probes the mechanical properties of the respiratory system (respiratory system impedance) during quiet breathing by applying multifrequency pressure oscillations at the mouth. The measured impedance reflects both resistance and reactance and is acquired at multiple frequencies to ascertain the frequency dependence of resistance, which is believed to be related to changes in the lung periphery (73). This is extremely important, as the mechanical properties of the lung periphery are known to be important determinants of lung function (9). FOT has been used extensively to study patients with COPD (25, 80, 86) and asthma (19, 24, 29, 80, 86), including the measurement of responses to bronchoconstriction in asthma (29) and to bronchodilation (24, 80, 86). Previous studies have shown that both resistance and reactance are sensitive to heterogeneous airway narrowing in asthma (41, 54), but the exact location of this airway narrowing could not be identified. On the other hand, hyperpolarized <sup>3</sup>He MRI ventilation imaging has been used to identify the spatial location of ventilation abnormalities (which may reflect ventilation

Address for reprint requests and other correspondence: G. Parraga, Robarts Research Institute, 1151 Richmond Street N., London, ON, Canada N6A 5B7 (e-mail: gparraga@robarts.ca).

heterogeneity) in patients with asthma (3, 21, 22, 65, 66) and patients with COPD (44, 50, 57, 62). MRI ventilation defects reflect the severity of airflow obstruction (22, 49) and respond to provocation in asthma (20, 65, 79) and treatment (3, 46, 48, 67). In addition, MRI-derived ventilation heterogeneity was recently shown to be independently predictive of asthma control (68) and COPD exacerbations (47) and is related to respiratory resistance and airway hyperresponsiveness in asthma (53).

Computational airway modeling has also been used to study the relationship between airway caliber and ventilation heterogeneity. Using an anatomical computational airway tree model (69), the caliber of the airway lumen can be manipulated to study the effects on respiratory impedance or ventilation distribution. Previous studies suggest that airway narrowing must occur heterogeneously throughout the entire airway tree to replicate experimentally measured impedance in asthma (16, 71, 73). Airway narrowing near ventilation defects alone is not sufficient (71, 73), and neither is narrowing large airways alone (16). Another modeling study showed that ventilation abnormalities were positively correlated with increased resistance (51). Numerous studies have probed structure-function relationships in asthma using biomechanical models informed by  $^3\text{He}$  MRI (16, 52), PET (71, 73), and single photon emission computed tomography (SPECT) (31), and some studies have incorporated measured respiratory impedance in model calculations (16, 71, 72). However, only a single study in a small group of patients with asthma has generated both model predictions of impedance and experimental measurements of impedance in the same patients for direct comparison (31).

There is a clear need for multiscale studies that combine functional lung imaging, computational airway models, and experimental oscillometry measurements to provide a deeper understanding of the relationships between structure and function in obstructive lung disease. Ultimately, this should lead to an understanding of how disease control and quality of life can be improved in patients (8, 11, 42, 75). Therefore, the primary objective of this work was to evaluate the relationships between patient outcomes such as disease control/exacerbations and quality of life and hyperpolarized  $^3\text{He}$  MRI ventilation defects and FOT-measured respiratory impedance. Our secondary objective was to incorporate ventilation MRI data in a computational airway tree model to generate patient-specific predictions of respiratory impedance and to compare these predictions to FOT-measurements to better understand the relationships between ventilation defects and biomechanical changes in the lung periphery.

We hypothesize that quantitative measurements derived from FOT and MRI, reflecting respiratory impedance and peripheral heterogeneity, are predictive of disease control/exacerbations and quality of life in ex-smokers, COPD patients, and patients with asthma. This would support the understanding that heterogeneity, especially in the lung periphery, is a determinant of reduced lung function.

## METHODS

**Study design.** All participants provided written informed consent to study protocols (NCT# NCT02351141, NCT02263794, NCT02279329) approved by the local research ethics board. Participants between ages 18 to 70 yr with a current diagnosis of asthma and patients between ages 50 to 90 yr with a history of smoking were

recruited from a tertiary care center and evaluated using spirometry, plethysmography, FOT, and pulmonary MRI in a single visit. Ex-smokers with COPD were identified using the Global initiative for chronic Obstructive Lung Disease (GOLD) criteria (84). Disease control was evaluated in patients with asthma using the Asthma Control Questionnaire [ACQ (40) with permission], and ex-smokers' exacerbation events requiring hospitalization were used as a surrogate measure of disease control. The number of exacerbations requiring hospitalization was determined using patient hospital records during the 2.5-yr period following the visit to the research center. Patient quality of life was evaluated using the Asthma Quality of Life Questionnaire [AQLQ (39) with permission] for asthma and the St. George's Respiratory Questionnaire [SGRQ (38) with permission] for ex-smokers. For participants with asthma, all imaging and pulmonary function tests were acquired at baseline and within 1.5 h after administration of four 100- $\mu\text{g}$  doses of Novo-Salbutamol HFA (Teva Novopharm, Toronto, ON, Canada) using a metered dose inhaler with an AeroChamber Plus spacer (Trudell Medical International, London, ON, Canada). In this work, baseline measurements were investigated. For ex-smokers, all data were acquired within 1.5 h after administration of four 100- $\mu\text{g}$  doses of salbutamol as described for patients with asthma. Spirometry and body plethysmography were performed according to the American Thoracic Society guidelines (58) using a whole-body system (MedGraphics Corporation, Saint Paul, MN). FOT measurements were acquired at multiple frequencies from 5 to 37 Hz using the TremoFlo C-100 Airwave Oscillometry System (Thorasy, Montreal, QC, Canada). For this study, only measurements at 5 and 19 Hz were included, as they have been previously identified to reflect impedance throughout the respiratory system and changes in the lung periphery.

**Image acquisition and analysis.** MRI was performed on a whole-body 3T system (MR750 Discovery, GEHC, Milwaukee, WI) with broadband imaging capability.  $^3\text{He}$  MRI was acquired using a single-channel, rigid elliptical transmit/receive chest coil (RAPID Biomedical GmbH, Wuerzburg, Germany). The  $^3\text{He}$  gas was polarized to 30%–40% polarization using a spin-exchange optical polarizer (Polarean Inc., Durham, NC). Subjects were positioned supine in the scanner with their arms raised above their head and inhaled a 1-liter gas mixture of  $^3\text{He}/\text{N}_2$  (25%  $^3\text{He}$  by volume) from functional residual capacity. Image acquisition was performed under breath-hold conditions (62). The hyperpolarized  $^3\text{He}$  magnetic resonance (MR) images were analyzed using custom software as previously described (34). Briefly, a single user (H.M.Y.) placed seeds on the  $^1\text{H}$  and  $^3\text{He}$  MR images to label the lung and the surrounding tissue, and image segmentation was completed using a convex optimization technique.  $^3\text{He}$  ventilation defects were identified using a k-means clustering approach (45), and ventilation defect percentage (VDP) was calculated as the total ventilation defect volume normalized to the thoracic cavity volume. The ventilation cluster map for each subject was then nonrigidly registered to the computational airway tree as previously described (52).

**Computational modeling.** We adapted a three-dimensional (3-D) airway tree consisting of 64,895 airways (M. Tawhai, University of Auckland) to generate a computational airway tree model. A full description of the model was previously provided (69). To summarize, the airway tree was derived from a thoracic X-ray computed tomography image including up to the eighth-generation airways and the remaining generations were constructed using a volume filling algorithm that preserved the anatomical branching geometry (69).

Airways located within two voxels (6.25 mm) of an MRI ventilation defect or distal to a ventilation defect were labeled as related to the defect. These airways were identified using custom software designed in MATLAB and narrowed to 10% of their initial diameter, effectively increasing their resistance by a factor of  $10^4$  according to Poiseuille's law (52). Airways larger than the 14th generation in the airway tree were excluded to ensure that we evaluated only small airways  $<2$  mm in diameter. We evaluated the impact of small airway

constriction, which has been shown to play a critical role in increased airway impedance and ventilation defects (16). Figure 1 shows a schematic outlining MR image processing steps and the integration of MRI data into the computational model to generate patient-specific predictions. Airway impedance predictions were generated as previously described from these individually modified airway trees (12, 52). First, the airway lengths and diameters were reduced to 80% of their original total lung capacity volume. The flow in the nonterminal airways was described using Womersley flow (43) using the following equation:

$$Z_a(f) = \frac{i2f\rho_{\text{air}}l_a}{r_a^2} \left[ 1 - \frac{2J_1(\alpha_a\sqrt{-i})}{\alpha_a\sqrt{-i}J_0(\alpha_a\sqrt{-i})} \right]^{-1} \quad (1)$$

where  $i$  is the unit imaginary number,  $f$  is the oscillation frequency in Hz,  $\rho_{\text{air}}$  is the density of air ( $1.16 \text{ kg/m}^3$ ),  $l_a$  is the length and  $r_a$  is the radius of the airway,  $J_0$  and  $J_1$  are the complex Bessel functions of order 0 and 1, respectively, and  $\alpha_a$  is the Womersley number for the airway given by

$$\alpha_a = r_a \sqrt{\frac{2\pi\rho_{\text{air}}f}{\mu_{\text{air}}}} \quad (2)$$

where  $\mu_{\text{air}}$  is the dynamic viscosity of humid air at  $37^\circ\text{C}$  ( $1.85 \times 10^{-5} \text{ Pa}\cdot\text{s}$ ).

To model the compliance of the lung parenchyma, each terminal airway was modeled as an alveolar compartment with a known elastance. Then, the impedance of a terminal airway is given by

$$Z_t = Z_a - i\frac{Et}{\omega} \quad (3)$$

where  $E$  is the elastance of the terminal airway unit, set to  $53 \text{ cmH}_2\text{O/l}$  as was done previously (52). The resistance of the upper airways and the chest wall were each assigned a value of  $0.5 \text{ cmH}_2\text{O}\cdot\text{s/l}$  (6, 7, 59), and the elastance of the chest wall was assigned a value of  $10.6 \text{ cmH}_2\text{O/l}$  (5). Finally, the effects of upper airway shunt were included using previously published values (18). These values were added to the lung resistance and reactance to calculate the final values for respiratory system resistance and reactance.

**Statistics.** The Shapiro-Wilk test was used to test data normality, and nonparametric tests were used when the data were not normally distributed. Independent sample  $t$ -tests and Mann-Whitney  $U$ -tests were used to evaluate differences between patients with asthma and COPD patients. Levene's test for equality of variances was used to test if the variance in the data was equal between two groups, and when the variance was not equal, Welch's correction was applied to two-tailed independent sample  $t$ -tests. The Holm-Bonferroni correction was used to adjust for multiple comparisons. Univariate relationships were evaluated using Spearman correlations ( $\rho$ ) because the data were not normally distributed. Significant relationships identified using Spearman correlations were evaluated using linear regression. Results were considered statistically significant when the probability of making a Type I error was less than 5% ( $P < 0.05$ ). All statistical tests were performed using SPSS 24.0 (IBM).

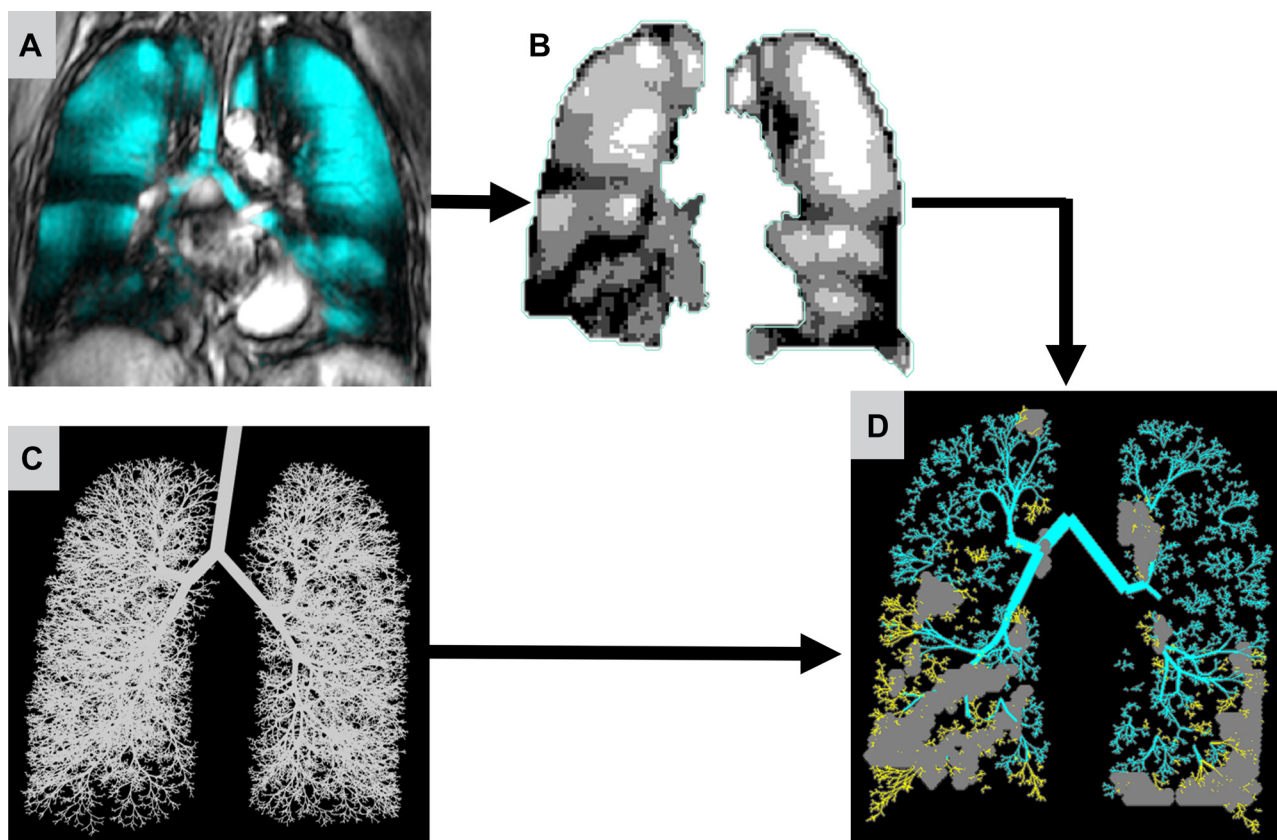


Fig. 1. Pipeline for coregistration of MRI ventilation defects with computational airway tree model. *A*: hyperpolarized  $^3\text{He}$  MRI shown in cyan coregistered with anatomical  $^1\text{H}$  MRI in greyscale. *B*: thoracic cavity, including the lungs, was automatically segmented using a manually seeded algorithm and ventilation defects identified, shown in black. *C*: an asymmetric branching computational airway tree model used to calculate respiratory system impedance. *D*: ventilation defect map was coregistered to the airway tree model. Small airways that were within or distal to a ventilation defect were identified and narrowed to 10% of their original diameter. Ventilation defects are in grey and the airways related to defects are in yellow.

## RESULTS

**Participant demographics.** As shown in Table 1, 100 participants were evaluated, including 50 subjects with asthma (17 mild-moderate and 33 severe) and 50 ex-smokers. Within the ex-smoker group, 28 subjects had COPD [12 mild (GOLD I), 11 moderate (GOLD II), and 5 severe (GOLD III)]. The ex-smokers were significantly older than the subjects with asthma ( $P < 0.001$ ). Forced expiratory volume in 1 s ( $FEV_1$ ) was significantly higher in the ex-smokers as compared with the subjects with asthma ( $P < 0.001$ ) and the subjects with COPD ( $P < 0.001$ ), and plethysmography-measured airways resistance was significantly greater in the asthma group as compared with the COPD group ( $P < 0.001$ ) and the ex-smokers ( $P < 0.001$ ). As shown in Fig. 2, subjects with COPD had significantly greater VDP than ex-smokers ( $P < 0.001$ ) and subjects with asthma ( $P < 0.001$ ), but there was not a significant difference in VDP between subjects with asthma and ex-smokers ( $P = 0.4$ ). FOT-measured reactance (5 Hz) was significantly more negative in patients with asthma as compared with COPD subjects ( $P = 0.04$ ) and ex-smokers ( $P = 0.02$ ). FOT-measured resistance at 5 Hz and 5–19 Hz, related to the obstruction of all airways and in the lung periphery respectively, was significantly greater in patients with asthma as compared with COPD (resistance 5 Hz:  $P < 0.001$ ; resistance 5–19 Hz:  $P < 0.001$ ) and ex-smokers (resistance 5 Hz:  $P < 0.001$ ; resistance 5–19 Hz:  $P < 0.001$ ). There was no significant difference in FOT-measured resistance (5 Hz:  $P = 1.0$ ; 5–19 Hz:  $P = 0.8$ ) or reactance ( $P = 1.0$ ) between ex-smokers and COPD patients.

**Pulmonary function test, forced oscillation technique, and  $^3He$  MRI VDP relationships.** In the asthma and COPD patient groups, VDP was significantly related to measures of airway obstruction from the pulmonary function tests. In subjects with asthma, VDP was significantly related to  $FEV_1$  ( $\rho = -0.7$ ,  $P < 0.001$ ), forced vital capacity (FVC) ( $\rho = -0.4$ ,  $P = 0.003$ ), and  $FEV_1/FVC$  ( $\rho = -0.7$ ,  $P < 0.001$ ). In the patients with COPD, VDP was also significantly related to  $FEV_1$  ( $\rho = -0.5$ ,  $P = 0.004$ ) and  $FEV_1/FVC$  ( $\rho = -0.6$ ,  $P = 0.002$ ), and the relationship between VDP and FVC was borderline significant ( $\rho = -0.4$ ,  $P = 0.051$ ). In the non-COPD ex-smoker group, VDP was not significantly related to  $FEV_1$  ( $\rho = 0.2$ ,  $P = 0.5$ ), FVC ( $\rho = 0.2$ ,  $P = 0.5$ ), or  $FEV_1/FVC$  ( $\rho = -0.1$ ,  $P = 0.7$ ).

Plethysmography-measured airways resistance and FOT-measured respiratory system resistance have previously been studied together and shown to have a moderately strong correlation (36). We repeated this analysis in our patients and found moderately strong correlations between plethysmography-measured airways resistance and FOT resistance at 5 Hz, as expected (asthma:  $\rho = 0.7$ ,  $P < 0.001$ ; ex-smokers:  $\rho = 0.7$ ,  $P < 0.001$ ; COPD:  $\rho = 0.6$ ,  $P = 0.001$ ).

As shown in Fig. 3, MRI VDP was moderately but significantly correlated with FOT-measured respiratory system resistance (5 Hz:  $\rho = 0.3$ ,  $P = 0.02$ ) and reactance (5 Hz:  $\rho = -0.5$ ,  $P < 0.001$ ) in subjects with asthma, whereas these measurements were not correlated in COPD patients (resistance 5 Hz:  $\rho = -0.04$ ,  $P = 0.8$ ; reactance 5 Hz:  $\rho = -0.2$ ,  $P = 0.4$ ) or ex-smokers (resistance 5 Hz:  $\rho = -0.3$ ,  $P = 0.2$ ; reactance 5 Hz:  $\rho = 0.3$ ,  $P = 0.2$ ). In both subjects with asthma ( $\rho = 0.5$ ,  $P < 0.001$ ) and patients with COPD ( $\rho = 0.5$ ,  $P = 0.01$ ), resistance reflecting peripheral abnormalities (5–19 Hz) was significantly correlated with VDP, but these measurements were not correlated in ex-smokers ( $\rho = -0.2$ ,  $P = 0.4$ ).

**Relationships with disease control and quality of life scores.** All participants with asthma were stratified using the ACQ (well controlled =  $ACQ \leq 2$ , poorly controlled =  $ACQ > 2$ ) as previously described (68). Ex-smokers (including subjects with and without COPD) were classified based on the presence of an exacerbation requiring hospitalization within 2.5 yr, such that patients who had been hospitalized at least once because of COPD or pneumonia (and would clinically be considered exacerbators) were classified as poorly controlled. Nine out of fifty ex-smokers experienced exacerbations, including seven patients with COPD and two subjects from the non-COPD group. As shown in Fig. 4,  $FEV_1$  was significantly lower in patients with poorly controlled asthma ( $P = 0.04$ ) but not ex-smokers with exacerbations ( $P = 0.08$ ). Plethysmography-measured airways resistance was significantly greater in patients with poorly controlled asthma ( $P = 0.03$ ) and ex-smokers with exacerbations ( $P = 0.04$ ), whereas VDP was significantly greater in patients with poorly controlled asthma ( $P = 0.03$ ) but not in ex-smokers with exacerbations ( $P = 0.1$ ). In subjects with poorly controlled asthma, FOT-measured respiratory system reactance (5 Hz:  $P = 0.03$ ), resistance of all airways (5 Hz:  $P = 0.01$ ), and the resistance-reflecting peripheral airways (5–19 Hz:  $P = 0.006$ ) were significantly different

Table 1. Subject demographics

	All (n = 100)	Asthma (n = 50)	COPD (n = 28)	Ex-Smokers (n = 22)	Asthma-COPD (P)	Asthma-Ex-Smokers (P)	COPD-Ex-smokers (P)
Male, n	54	21	19	14			
Age, yr	61 ± 16	49 ± 12	75 ± 8	70 ± 10	>0.001	<0.001	0.2
BMI, kg/m <sup>2</sup>	28 ± 4	28 ± 4	26 ± 4	30 ± 4	0.5	0.03	0.003
Height, cm	168 ± 8	168 ± 8	170 ± 8	168 ± 8	1.0	1.0	1.0
$FEV_1$ , % <sub>pred</sub>	78 ± 26	70 ± 23	74 ± 25	102 ± 20	1.0	<0.001	<0.001
FVC, % <sub>pred</sub>	89 ± 20	83 ± 20	94 ± 19	95 ± 20	0.06	0.1	1.0
$FEV_1/FVC$ , %	65 ± 15	64 ± 15	56 ± 10	80 ± 15	0.02	<0.001	<0.001
TLC, % <sub>pred</sub>	102 ± 15	103 ± 15	107 ± 16	95 ± 13	0.8	0.1	0.02
RV/TLC, %	43 ± 9	41 ± 9	47 ± 9	40 ± 8	0.04	1.0	0.04
DLCO, % <sub>pred</sub>			60 ± 21	83 ± 15			<0.001
$R_{aw}$ , % <sub>pred</sub>	127 ± 80	171 ± 83	95 ± 43	65 ± 25	<0.001	<0.001	0.6

Values are means ± SD; n = no. of subjects. Significance of difference between groups determined with a one-way ANOVA with Bonferroni post hoc test. %<sub>pred</sub>, percentage of predicted value; BMI, body mass index; COPD, chronic obstructive pulmonary disorder; DLCO, diffusing capacity of the lung for carbon monoxide;  $FEV_1$ , forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume;  $R_{aw}$ , airways resistance.

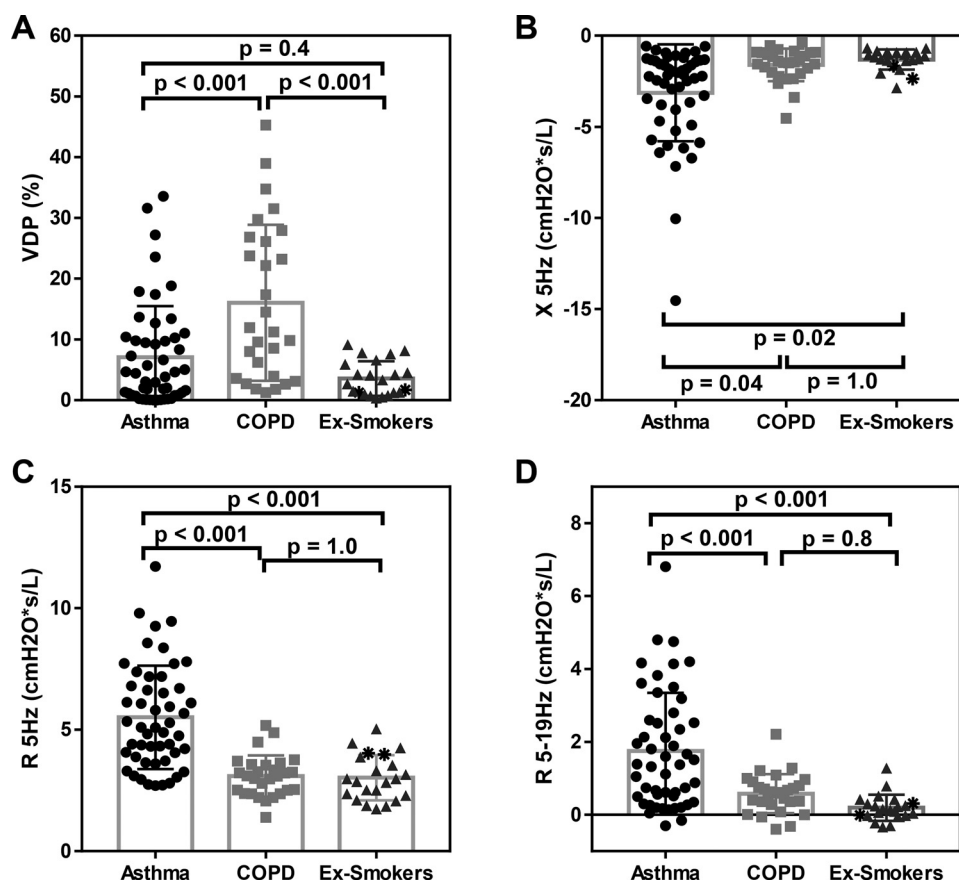


Fig. 2. VDP and FOT-measured resistance and reactance in asthmatic, COPD, and ex-smoker subgroups. **A:** VDP for asthma ( $n = 50$ ) and COPD ( $n = 28$ ,  $P < 0.001$ ), and COPD and ex-smoker subgroups ( $n = 22$ ,  $P < 0.001$ ) were significantly different, but VDP was not different between asthmatic and ex-smoker groups ( $P = 0.4$ ). **B:** FOT-measured reactance at 5 Hz was significantly greater in the asthmatic as compared with the COPD subgroup ( $P = 0.04$ ) and the ex-smoker group ( $P = 0.02$ ). Respiratory system reactance was not different between COPD and ex-smoker subgroups ( $P = 1.0$ ). **C:** FOT-measured resistance at 5 Hz was significantly greater in the asthmatic as compared with the COPD ( $P < 0.001$ ) and ex-smoker ( $P < 0.001$ ) subgroups, but it was not different between COPD and ex-smoker subgroups ( $P = 1.0$ ). **D:** FOT-measured resistance at 5–19 Hz was significantly greater in the asthmatic as compared with the COPD ( $P < 0.001$ ) and ex-smoker ( $P < 0.001$ ) subgroups but was not different between COPD and ex-smokers ( $P = 0.8$ ). The two non-COPD ex-smokers who experienced exacerbations are indicated by asterisk symbol (\*). ES4:  $FEV_1 = 102\%_{pred}$ ,  $FVC = 97\%_{pred}$ ,  $FEV_1/FVC = 80\%$ , resistance at 5 Hz =  $4.0 \text{ cmH}_2\text{O}\cdot\text{s/l}$ , reactance at 5 Hz =  $-1.7 \text{ cmH}_2\text{O}\cdot\text{s/l}$ , resistance at 5–19 Hz =  $0.0 \text{ cmH}_2\text{O}\cdot\text{s/l}$ , VDP = 2%. ES14:  $FEV_1 = 81\%_{pred}$ ,  $FVC = 70\%_{pred}$ ,  $FEV_1/FVC = 88\%$ , resistance at 5 Hz =  $4.0 \text{ cmH}_2\text{O}\cdot\text{s/l}$ , reactance at 5 Hz =  $-2.4 \text{ cmH}_2\text{O}\cdot\text{s/l}$ , resistance at 5–19 Hz =  $0.3 \text{ cmH}_2\text{O}\cdot\text{s/l}$ , VDP = 1%. %<sub>pred</sub>, percentage of predicted value; COPD, chronic obstructive pulmonary disease; ES, ex-smoker;  $FEV_1$ , forced expiratory volume in 1 s; FOT, force oscillation technique; FVC, forced vital capacity; VDP, ventilation defect percentage.

than in patients with well-controlled asthma. None of the FOT measures of airway impedance (reactance 5 Hz:  $P = 0.2$ ; resistance 5 Hz:  $P = 0.6$ ; resistance 5–19 Hz:  $P = 0.3$ ) were significantly different in ex-smokers with exacerbations.

In patients with asthma, as shown in Fig. 5, the AQLQ score was weakly correlated only with FOT-measured peripheral resistance (5–19 Hz:  $\rho = -0.3$ ,  $P = 0.04$ ) and VDP ( $\rho = -0.3$ ,  $P = 0.04$ ), and not with any other measurement acquired. It should be noted that when evaluating quality of life using the AQLQ, a higher score indicates a better patient-perceived quality of life, but when using the SGRQ, a higher score indicates worse patient-perceived quality of life. Quality of life in patients with COPD measured using the SGRQ score was significantly correlated with  $FEV_1$  ( $\rho = -0.5$ ,  $P = 0.006$ ), plethysmography-measured airways resistance ( $\rho = 0.4$ ,  $P = 0.03$ ), FOT-measured resistance of the lung periphery, (5–19 Hz:  $\rho = 0.4$ ,  $P = 0.04$ ), and VDP ( $\rho = 0.6$ ,  $P = 0.003$ ). SGRQ scores were not significantly related to FOT-measured resistance (5 Hz:  $\rho = 0.1$ ,  $P = 0.5$ ) or reactance (5 Hz:  $\rho = -0.2$ ,

$P = 0.3$ ). In the non-COPD ex-smoker group, SGRQ scores were only significantly related to plethysmography-measured airways resistance ( $\rho = 0.5$ ,  $P = 0.01$ ).

**Experimental and model impedance measurements.** As shown in Fig. 6, FOT-measured resistance of all airways (5 Hz<sub>meas</sub>) was not significantly related to model-predicted resistance (5 Hz<sub>pred</sub>) in subjects with asthma ( $\rho = 0.2$ ,  $P = 0.2$ ) or in ex-smokers ( $\rho = -0.3$ ,  $P = 0.2$ ) and COPD patients ( $\rho = 0.001$ ,  $P = 1.0$ ). However, FOT-measured respiratory system reactance (5 Hz<sub>meas</sub>) was significantly related to model-predicted reactance (5 Hz<sub>pred</sub>) in subjects with asthma (slope =  $1.4 \pm 0.6$ ,  $\rho = 0.5$ ,  $P = 0.001$ ) but not in COPD patients ( $\rho = 0.2$ ,  $P = 0.4$ ) or ex-smokers ( $\rho = -0.3$ ,  $P = 0.2$ ). In contrast, FOT-measured peripheral resistance (5–19 Hz<sub>meas</sub>) was significantly correlated with model-predictions (5–19 Hz<sub>pred</sub>) in COPD patients (slope =  $2.6 \pm 0.7$ ,  $\rho = 0.5$ ,  $P = 0.004$ ) but not in ex-smokers ( $\rho = -0.1$ ,  $P = 0.6$ ) or subjects with asthma ( $\rho = 0.2$ ,  $P = 0.1$ ).

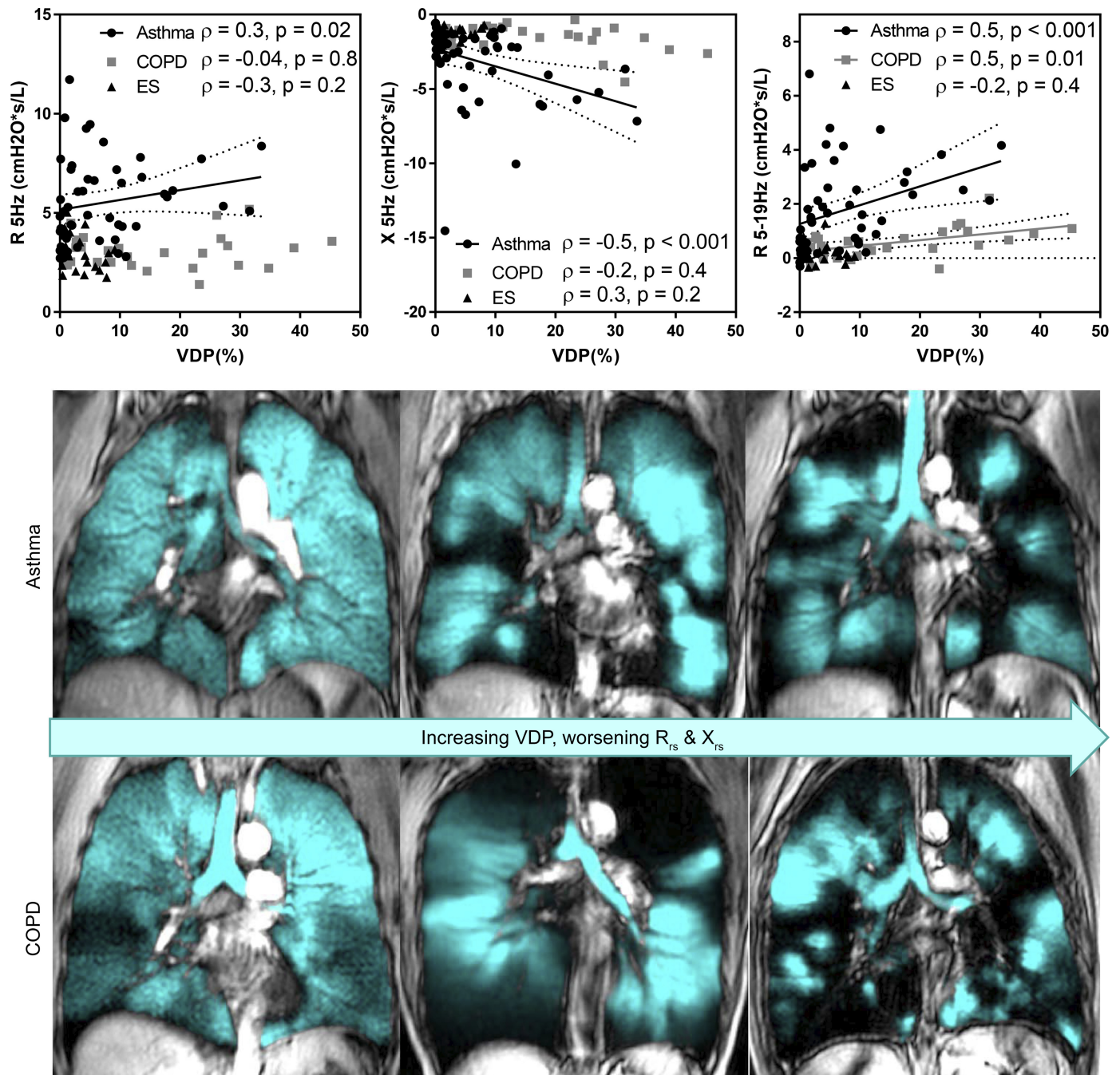


Fig. 3. Relationships for VDP and FOT measurements. *Top*: FOT-measured resistance at 5 Hz was weakly but significantly correlated with VDP in subjects with asthma ( $n = 50$ ; slope =  $0.05 \pm 0.03$ ,  $\rho = 0.3$ ,  $P = 0.02$ ) but not in COPD patients ( $n = 28$ ;  $\rho = -0.04$ ,  $P = 0.8$ ) or ex-smokers ( $n = 22$ ;  $\rho = -0.3$ ,  $P = 0.2$ ). FOT-measured reactance at 5 Hz was significantly correlated with VDP in patients with asthma (slope =  $-0.12 \pm 0.04$ ,  $\rho = -0.5$ ,  $P < 0.001$ ) but not in COPD patients ( $\rho = -0.2$ ,  $P = 0.4$ ) or ex-smokers ( $\rho = 0.3$ ,  $P = 0.2$ ). FOT-measured resistance at 5–19 Hz was significantly correlated with VDP in both patients with asthma (slope =  $0.07 \pm 0.02$ ,  $\rho = 0.5$ ,  $P < 0.001$ ) and COPD patients (slope =  $0.02 \pm 0.007$ ,  $\rho = 0.5$ ,  $P = 0.01$ ) but not in ex-smokers ( $\rho = -0.2$ ,  $P = 0.4$ ). *Middle*: three representative subjects with asthma with worsening VDP and FOT-measured impedance from left to right. *Bottom*: three representative COPD subjects with worsening VDP and FOT-measured impedance from left to right. COPD, chronic obstructive pulmonary disease; FOT, force oscillation technique; VDP, ventilation defect percentage.

## DISCUSSION

In ex-smokers and patients with asthma,  $^3\text{He}$  MRI ventilation heterogeneity and oscillometry measurements were evaluated as was their relationship with one another, with quality of life scores and with disease control/exacerbations. We also generated respiratory impedance predictions using an airway

tree model that was modified based on patient-specific MRI ventilation maps and evaluated model-based and experimental impedance measurements. We made a number of important observations, including the following: 1) in subjects with asthma, MRI VDP was related to FOT-measured reactance at 5 Hz, resistance at 5 Hz, and resistance at 5–19 Hz, but in

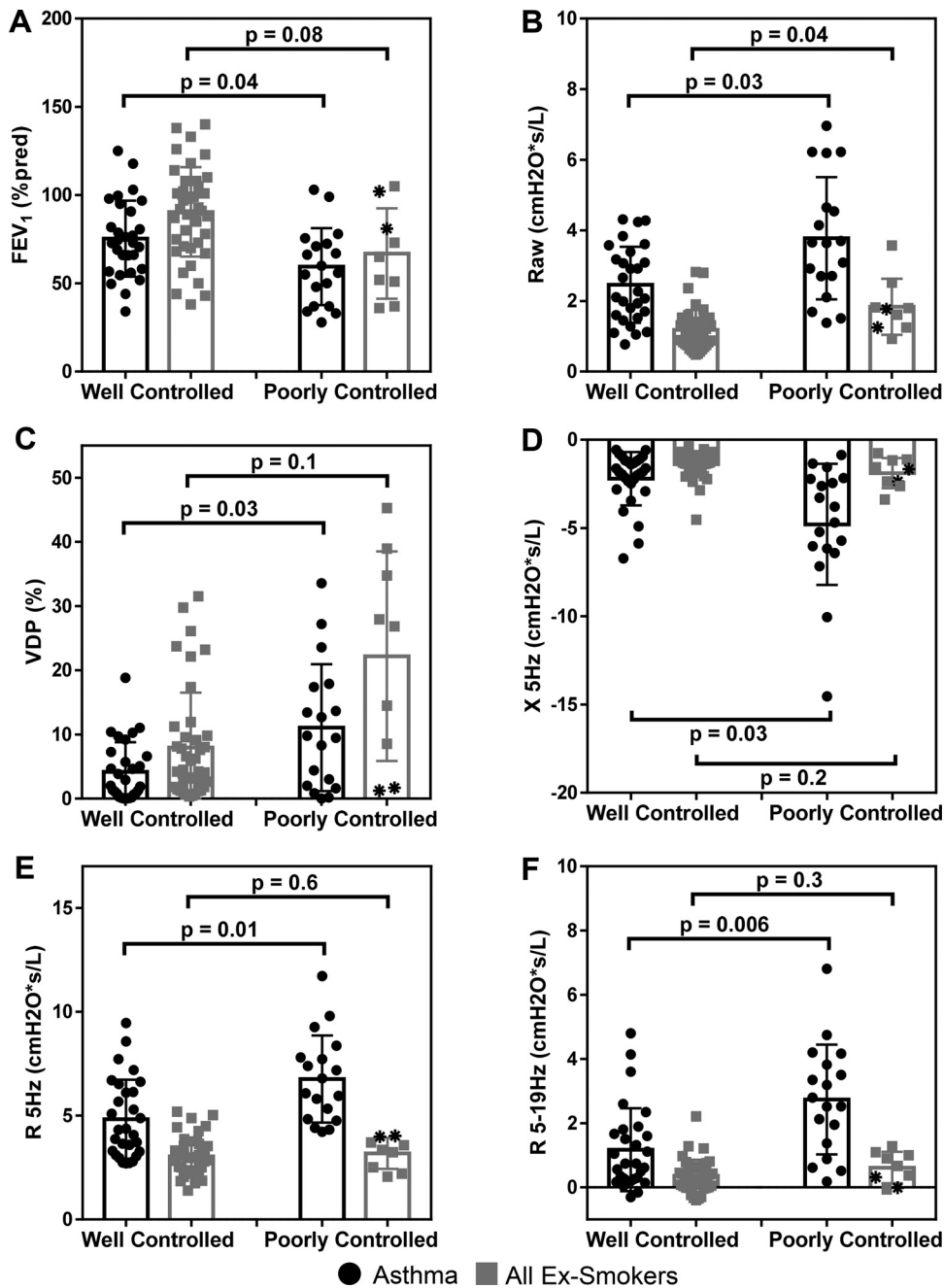


Fig. 4. Differences in FEV<sub>1</sub>, VDP, and FOT impedance stratified by disease control. Subjects were stratified based on disease control using the Asthma Control Questionnaire (ACQ) for patients with asthma (*n* = 50) or the presence of at least a single exacerbation requiring hospitalization in ex-smokers [including those with and without COPD (*n* = 50)]. *A*: FEV<sub>1</sub> was significantly different in patients with asthma with poor control (*P* = 0.04) but not in ex-smokers with exacerbations (*P* = 0.08). *B*: plethysmography-measured airways resistance was significantly decreased in patients with poorly controlled asthma (*P* = 0.03) and COPD exacerbators (*P* = 0.04). *C*: VDP was significantly increased in patients with poorly controlled asthma (*P* = 0.03) but not in ex-smokers experiencing an exacerbation (*P* = 0.1). *D*: FOT-measured reactance at 5 Hz was significantly different in patients with poorly controlled asthma (*P* = 0.03) but not in ex-smokers experiencing an exacerbation (*P* = 0.2). *E*: FOT-measured resistance at 5 Hz was significantly increased in patients with poorly controlled asthma (*P* = 0.01) but not in COPD exacerbators (*P* = 0.6). *F*: FOT-measured resistance at 5–19 Hz was significantly different in patients with poorly controlled asthma (*P* = 0.006) but not in patients with COPD exacerbations (*P* = 0.3). The two non-COPD ex-smokers who experienced exacerbations are indicated by asterisk (\*). COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 s; FOT, force oscillation technique; FVC, forced vital capacity; VDP, ventilation defect percentage.

COPD patients, only VDP and resistance at 5–19 Hz were related, and in ex-smokers, MRI VDP was not related to FOT-measured impedance; 2) VDP and FOT-measured reactance and resistance were independently correlated with AQLQ (in patients with asthma) and SGRQ (in COPD patients) but were not correlated with SGRQ in ex-smokers without COPD; 3) FOT-measured impedance and MRI VDP were independently related to disease control in patients with asthma but not in ex-smokers or COPD patients; and finally 4) in patients with asthma, measured and predicted respiratory impedance (5 Hz) were significantly correlated, whereas in patients with COPD, only measured and predicted resistance reflecting the lung periphery (5–19 Hz) were related.

First, we observed that FOT-measured resistance and reactance were correlated with MRI VDP, providing direct evidence that the biomechanical properties of the respiratory system are related to ventilation heterogeneity as defined by VDP in both patients with asthma and COPD patients. In particular, in subjects with asthma, resistance at 5 Hz, reactance at 5 Hz, and resistance at 5–19 Hz were weakly to moderately related to VDP, but in COPD, only resistance at 5–19 Hz was moderately related. This suggests that there may be differences in the etiology of ventilation defects in patients with asthma and patients with COPD, and that in the COPD patients studied here, VDP was dominated by resistance reflecting the lung periphery. In subjects with asthma, the rela-



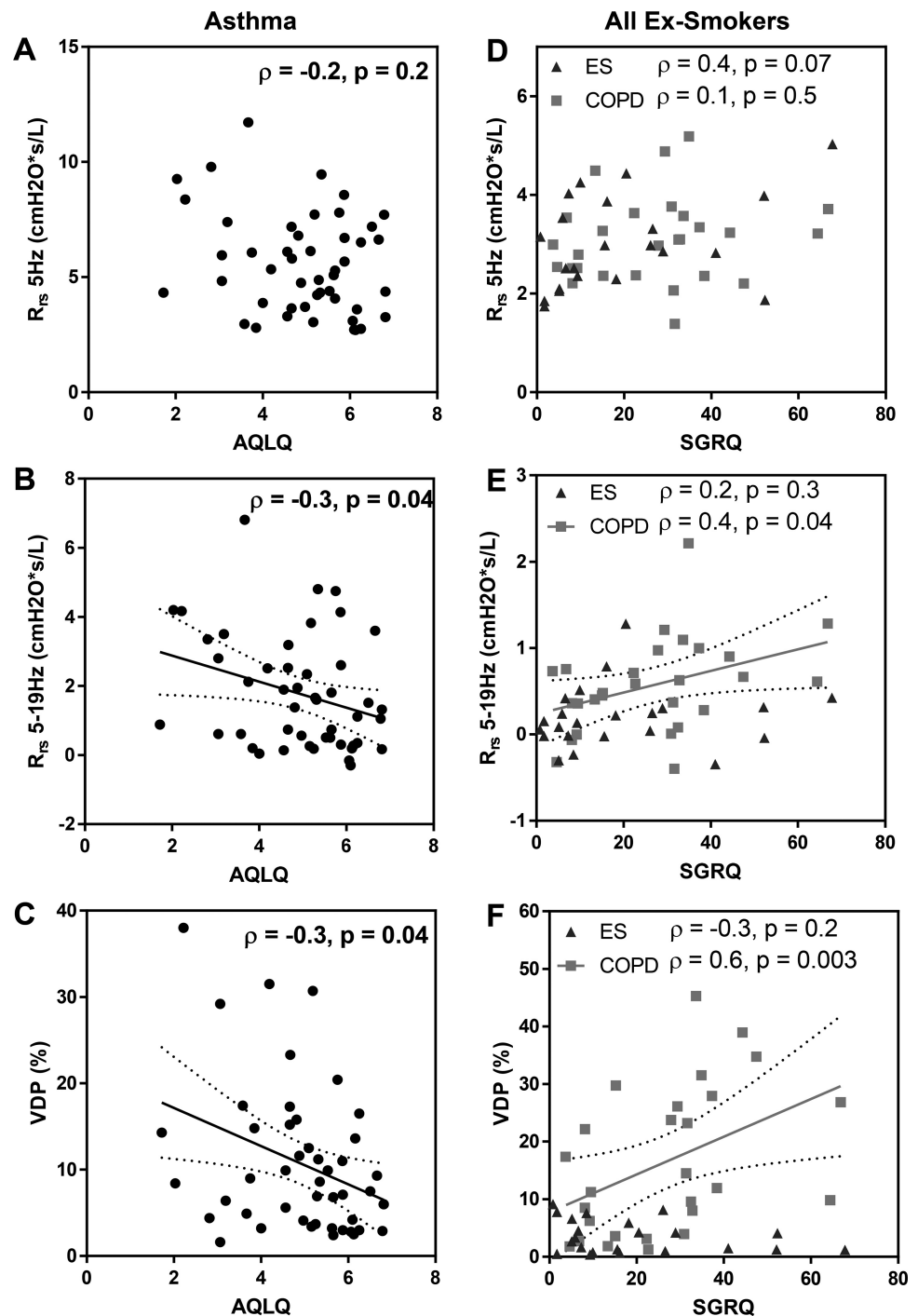


Fig. 5. Relationships between FOT-measured resistance and MRI VDP with quality of life. Quality of life was measured using the Asthma Quality of Life Questionnaire (AQLQ) in patients with asthma ( $n = 50$ ) and the St. George's Respiratory Questionnaire (SGRQ) in ex-smokers ( $n = 22$ ) and COPD patients ( $n = 28$ ). In patients with asthma, AQLQ relationships with FOT-measured resistance at 5 Hz ( $\rho = -0.2, P = 0.2$ ) (A), FOT-measured resistance at 5–19 Hz (slope =  $-0.4 \pm 0.2, \rho = -0.3, P = 0.04$ ) (B), and MRI-measured VDP (slope =  $-2.2 \pm 0.9, \rho = -0.3, P = 0.04$ ) (C). In COPD patients and ex-smokers, SGRQ relationships with FOT-measured resistance at 5 Hz (COPD:  $\rho = 0.1, P = 0.5$ ; ES:  $\rho = 0.4, P = 0.07$ ) (D), FOT-measured resistance at 5–19 Hz (COPD: slope =  $0.01 \pm 0.006, \rho = 0.4, P = 0.04$ ; ES:  $\rho = 0.2, P = 0.3$ ) (E), and MRI-measured VDP (COPD: slope =  $0.3 \pm 0.1, \rho = 0.6, P = 0.003$ ; ES:  $\rho = -0.3, P = 0.2$ ) (F). COPD, chronic obstructive pulmonary disease; ES, ex-smoker; FOT, force oscillation technique; VDP, ventilation defect percentage.

tionships between respiratory system resistance and reactance with VDP are not strong and there is a great deal of variability in the relationships, especially at low VDP. Certainly, these correlations were quite weak, and to some extent, a small group of patients (subjects with asthma with elevated VDP and respiratory impedance) helped to drive these associations. This also highlights the fact that only some of the ventilation abnormalities caused by increased resistance are captured by VDP. Future work with higher spatial resolution images will include an investigation of higher order MRI ventilation heterogeneity biomarkers (like texture features) to determine if

these higher order features explain some of this variance. On the other hand, oscillometry did not fully explain ventilation defects observed in MRI, although elevated resistance and ventilation defects are both known to be mechanistically due to airway narrowing in asthma. Finally, the fact that elevated Resistance [ $R$  (5-19Hz)] and VDP may contribute to reduced quality of life in patients with asthma and COPD patients is important, but it is also clear that there are additional factors involved that were not accounted for here.

In patients with asthma, there was some contribution to total resistance and reactance, as well as resistance reflecting the

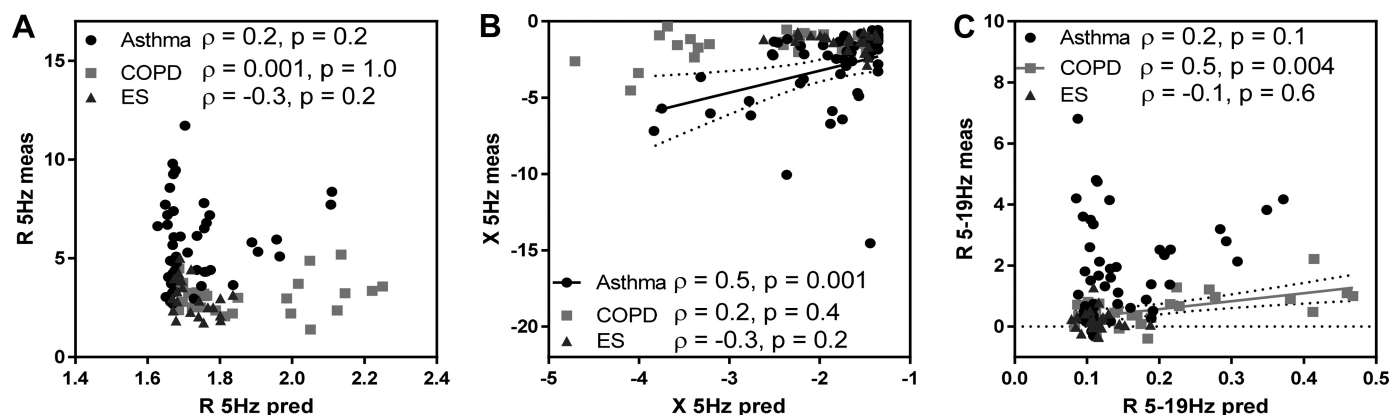


Fig. 6. Relationships for model-predicted and FOT-measured respiratory system impedance. A: FOT-measured resistance at 5 Hz<sub>meas</sub> was not significantly related to model-predicted resistance at 5 Hz<sub>pred</sub> in patients with asthma ( $n = 50, \rho = 0.2, P = 0.2$ ), COPD patients ( $n = 28, \rho = 0.001, P = 1.0$ ), or ex-smokers ( $n = 22, \rho = -0.3, P = 0.2$ ). B: FOT-measured reactance at 5 Hz<sub>meas</sub> was significantly related to model-predicted reactance at 5 Hz<sub>pred</sub> in patients with asthma (slope =  $1.4 \pm 0.6, \rho = 0.5, P = 0.001$ ) but not in COPD patients ( $\rho = 0.2, P = 0.4$ ) or ex-smokers ( $\rho = -0.3, P = 0.2$ ). C: FOT-measured resistance at 5–19 Hz<sub>meas</sub> was significantly correlated with model-predicted resistance at 5–19 Hz<sub>pred</sub> in COPD (slope =  $2.6 \pm 0.7, \rho = 0.5, P = 0.004$ ) but not in patients with asthma ( $\rho = 0.2, P = 0.1$ ) or ex-smokers ( $\rho = -0.1, P = 0.6$ ). COPD, chronic obstructive pulmonary disease; FOT, force oscillation technique; VDP, ventilation defect percentage.

lung periphery, supporting the idea that asthma involves all airways. In addition, it is clear from the plots shown in Fig. 3 that for some patients with asthma, respiratory impedance is severely elevated while VDP remains low, weakening the relationship between impedance and VDP. This suggests that there is a mechanism causing elevated respiratory impedance that is not reflected in VDP. Future investigations may reveal the mechanism behind this phenomenon and how this may be captured using hyperpolarized noble gas MRI. Interestingly, non-COPD ex-smokers had similar small airway resistance to the subjects with COPD but had significantly lower VDP. This suggests that similar biomechanical changes are present in the lung periphery in ex-smokers, but they are not severe enough to cause ventilation defects. These findings certainly support the ongoing conversation about the important role of small airways disease in COPD patients (37) and provide new impetus for the development of small airways treatments of COPD. Previously described computational modeling (16) and ventilation heterogeneity studies (27, 53) have focused on asthma, but to our knowledge, our observations in COPD patients are novel. A recent SPECT study (31) evaluated the impact of bronchoconstriction in patients with asthma and suggested that respiratory impedance may be too complex to be directly evaluated using ventilation imaging. However, here we showed that MRI ventilation abnormalities may be explained in part by oscillometry measurements, and surprisingly, MRI ventilation abnormalities measured during a static breath-hold are significantly related to impedance measurements made during tidal breathing.

Second, we observed that FOT-measured peripheral lung resistance and VDP were weakly but significantly related to quality of life scores in patients with asthma and COPD, but not in ex-smokers. This is important because for FEV<sub>1</sub>, which is the most commonly used measurement of obstructive lung disease, relationships with important outcomes like quality of life are generally weak to insignificant (1, 70, 85). As patient-centered care becomes a priority in clinical settings, patient quality of life is becoming an extremely important clinical outcome. Therefore, for research purposes and for treatment

decisions, identifying meaningful relationships between physiological measurements and these outcomes is increasingly important. There is now strong motivation to develop and identify quantitative tools that are related to outcomes such as quality of life so that they may be predicted in individual patients. With this in mind, the primary objective of our study was to evaluate the relationships between ventilation MRI and FOT with patient quality of life and disease control/exacerbations. Although the metrics we studied do not fully explain the variation in quality of life outcomes, the relationships shown here suggest that FOT and MRI do provide clinically useful measurements for this purpose in patients with asthma and COPD patients.

Perhaps more importantly for clinical decision makers, we observed that plethysmography-measured airways resistance was significantly worse in subjects with asthma, ex-smokers, and COPD patients with poorly controlled disease, whereas FOT-measured resistance and reactance as well as VDP were all significantly worse in patients with poorly controlled asthma. Although we did not observe significant relationships in COPD patients or ex-smokers, this result may stem from the small number of exacerbations in these patients, which was used as a surrogate end point for disease control. It is understood that plethysmography-measured airways resistance and FOT respiratory system resistance are significantly correlated, although these correlations are not always strong (36). A power analysis assuming unequal sample size using hospitalizations as a conservative measure of disease control revealed that 104 ex-smokers (including COPD patients) would be required for resistance at 5–19 Hz as a predictor of hospitalizations, whereas only 40 patients would be needed for airways resistance. Larger studies to investigate the power of both FOT and MRI to predict and prevent COPD hospitalization will be important because COPD exacerbations constitute a large health utilization burden in Canada (33, 78) and around the world (32, 61).

Finally, we generated impedance predictions using an airway tree model adapted using ventilation MRI measurements. It is important to note here that we did not include all possible

mechanisms that lead to increased ventilation heterogeneity or pulmonary impedance in these calculations. Rather, our goal was to investigate the role that peripheral airway narrowing may play in ventilation defects observed in obstructive lung disease, independent of other factors such as heterogeneous increased elastance in emphysema. This was done to test our hypothesis that heterogeneous peripheral airway narrowing plays an important role in ventilation heterogeneity, and subsequently in patient quality of life. We were not surprised to find that the experimental and model-predicted values of resistance at 5 Hz were not significantly correlated, because it is likely that some airway narrowing may not directly lead to ventilation defects in patients. We also observed that FOT-measured and model-predicted reactances were significantly related in subjects with asthma, which was in agreement with previous findings (12, 54, 77). Finally, the measured and predicted resistance reflecting the lung periphery (5–19 Hz) was significantly correlated in COPD patients, but not subjects with asthma, which is consistent with our understanding that small airways disease plays a dominant role in COPD (37), whereas in asthma, both large and small airways are involved (35).

It is important to note that although there were moderately strong correlations between the measured and predicted impedance values, the predicted values were significantly smaller (based on the slopes of the linear regression). This was expected because previous work (12) showed that up to 75% of the small airways need to be constricted to achieve model and experimental measurement agreement. Impedance predictions were systematically underestimated (12) when only airways within a defect were considered, supporting previous demonstrations (71) that showed constriction of airways beyond those proximal to ventilation defects is required to simulate impedance measurements in patients with asthma.

We acknowledge and recognize a number of study limitations, including the fact that we considered ventilation defects only and not regions of decreased or partial ventilation. Based on previous modeling studies (71) and MRI evidence of patchy ventilation sometimes observed in subjects with asthma and ex-smokers, it would be relevant to consider hyperintense ventilation regions as well as hypointense regions that are not captured by VDP. We note as well that the airway tree (69) used in the modeling studies was not patient-specific, nor were the impedance values of the upper airway and chest wall. However, we expect these factors to contribute much less to respiratory impedance than the changes occurring within the lung itself in obstructive lung disease. An additional limitation to this work is the fact that only airway caliber was modified in our modeling calculations, not elastance. In both asthma and COPD patients, a uniform elastance was assumed for all terminal airways, which is not always true in COPD. This simple model was used to highlight the impact of small airway abnormalities. Despite these limitations, which likely contributed to the substantial variability observed in the relationships, we observed some significant correlations between measured and model-predicted impedance reflecting the lung periphery in this simplified model. This suggests that our model identifies a significant driving factor in the relationship between ventilation heterogeneity and respiratory impedance, which is important for further model development. Future work will include the addition of variable elastic or viscoelastic parameters

to simulate changes to parenchymal tissue and an investigation of how the size and spatial distribution of defects are related to changes in respiratory impedance. We are now refining the image registration and airway tree so that we can study this in more detail with data acquired with higher spatial resolution in 3-D. For example, we are developing image-processing tools to answer the questions related to central versus peripheral defects and their relationship with resistance. We also think that these approaches may help explain constriction or obstruction proximal to a defect after a methacholine challenge and after treatment with a bronchodilator. All of these analyses are ongoing with new  $^{129}\text{Xe}$  MRI data sets that are now being acquired in 3-D with improved isotropic spatial resolution.

Another limitation of this work is the use of hospitalizations as a surrogate measure of disease control in ex-smokers. Although hospitalizations have the highest impact on patients and the health care system (78), only 9 of 50 ex-smokers studied here experienced an exacerbation, which certainly diminished statistical power; larger studies will be needed to explore these relationships. An additional limitation of this work is the relatively mild disease severity of the COPD population. Although our patient population did include severe COPD subjects, most subjects had mild to moderate disease, and none had very severe (GOLD IV) disease. Further studies including more subjects with severe disease may be required to verify the applicability of our findings to severe disease. The FOT-derived results were certainly limited by our use of raw values, which were not corrected for age or anthropomorphic factors. This means that the respiratory impedance differences observed may be due, in part, to differences in age and body mass index, and this is a limitation of our approach. Although we showed that patient height was not different between groups, patient size should be considered when evaluating FOT values. Finally, although we observed significant relationships between FOT measurements of resistance and reactance with MRI VDP and patient quality of life, these relationships were of moderate to weak strength, which means other factors, not determined here, play a role.

In conclusion, we made oscillometry and MRI measurements in ex-smokers and patients with asthma and directly compared these measurements with disease control/exacerbations and patient quality of life scores. We observed significant relationships for FOT-measured impedance and VDP with quality of life, providing evidence that airway resistance and reactance are reflective of MRI ventilation defects, and importantly, they are both related to patient quality of life. We also used MRI ventilation defects to generate patient-specific computational airway model predictions of respiratory system impedance and, for the first time, compared these predictions with experimental measurements. Taken together, these results provide strong motivation for multiscale studies that explore how small airways disease and ventilation abnormalities may explain and help improve disease control and quality of life in patients.

#### DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

#### AUTHOR CONTRIBUTIONS

G.P. conceived and designed research; H.M.Y. and R.L.E. performed experiments; H.M.Y. and F.G. analyzed data; H.M.Y., F.G., R.L.E., G.M., and

G.P. interpreted results of experiments; H.M.Y. prepared figures; H.M.Y. drafted manuscript; H.M.Y., R.L.E., G.M., and G.P. edited and revised manuscript; H.M.Y., R.L.E., and G.P. approved final version of manuscript.

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