8-6-2019

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R.L.E. supported by a Natural Science and Engineering Research Council (NSERC) of Canada Doctoral award. S.S. supported by a Canadian Institutes of Health Research (CIHR) Banting postdoctoral fellowship. G.P. supported by NSERC, CIHR, and holds a Tier 1 Canada Research Chair.

Conflicts of interest are listed at the end of this article.

See also the editorial by Stojanovska in this issue.

Radiology 2019; 293:212–220 • https://doi.org/10.1148/radiol.2019190420 • Content codes: CH MR

Background: Longitudinal progression to irreversible airflow limitation occurs in approximately 10% of patients with asthma, but it is difficult to identify patients who are at risk for this transition.

Purpose: To investigate 6-year longitudinal changes in hyperpolarized helium 3 (^{3}He) MRI ventilation defects in study participants with mild-to-moderate asthma and identify predictors of longitudinal changes in postbronchodilator forced expiratory volume in 1 second (FEV_1) reversibility

Materials and Methods: Spirometry and hyperpolarized ^{3}He MRI were evaluated in participants with mild-to-moderate asthma in two prospectively planned visits approximately 6 years apart. Participants underwent methacholine challenge at baseline (January 2010 to April 2011) and pre- and postbronchodilator evaluations at follow-up (November 2016 to June 2017). FEV_1 and MRI ventilation defects, quantified as ventilation defect volume (VDV), were compared between visits by using paired *t* tests. Participants were dichotomized by postbronchodilator change in FEV_1 at follow-up, and differences between reversible and not-reversible groups were determined by using unpaired *t* tests. Multivariable models were generated to explain postbronchodilator FEV_1 reversibility at follow-up.

Results: Eleven participants with asthma (mean age, 42 years ± 9 [standard deviation]; seven men) were evaluated at baseline and after mean 78 months ± 7. Medications, exacerbations, FEV_1 (76% predicted vs 76% predicted; $P = .91$), and VDV (240 mL vs 250 mL; $P = .92$) were not different between visits. In eight of 11 participants (73%), MRI ventilation defects at baseline were at the same location in the lung at follow-up MRI. In the remaining three participants (27%), MRI ventilation defects worsened at the same lung locations as depicted at baseline methacholine-induced ventilation. At follow-up, postbronchodilator FEV_1 was not reversible in six of 11 participants; the concentration of methacholine to decrease FEV_1 by 20% (PC_{20}) was greater in FEV_1-irreversible participants at follow-up ($P = .01$). In a multivariable model, baseline MRI VDV helped to predict postbronchodilator reversibility at follow-up ($R^2 = 0.80$; $P < .01$), but PC_{20}, age, and FEV_1 did not ($R^2 = 0.63$; $P = .15$).

Conclusion: MRI-derived, spatially persistent ventilation defects predict postbronchodilator reversibility 78 months ± 7 later for participants with mild-to-moderate asthma in whom there were no changes in lung function, medication, or exacerbations.

Online supplemental material is available for this article.

In patients who have asthma, chronic airways disease typically results in variable airflow obstruction that may be partially or completely reversed by using bronchodilators (1). Many people with asthma maintain stable lung function and bronchodilator reversibility over time, whereas a subset of patients may experience accelerated lung function decline and eventually lose postbronchodilator reversibility (2–4). Recent epidemiologic studies showed that in up to 10% of people with asthma, airways disease may lead to chronic, persistent airflow obstruction and chronic obstructive pulmonary disease (5,6), but the mechanisms underlying these changes are not fully understood.

Airway remodeling caused by chronic inflammation has been suggested to mediate changes that result in airflow obstruction that is not bronchodilator reversible (7). Asthma involves both the small and large airways and it is difficult to measure small airway dysfunction by using spirometry measurements of the forced expiratory volume in 1 second (FEV_1) because it is insensitive to peripheral airway changes.

The morphologic structure of remodeled and inflamed airways can be directly measured by using thoracic radiographic CT (8–10), and airway function may also be viewed by using expiratory CT lucency of gas trapping (11,12) or parametric response mapping (13,14). Parametric response map gas trapping was shown (14) to be increased in participants with severe asthma compared with participants with nonsevere asthma and control participants. Inhaled hyperpolarized gas MRI directly probes ventilation as a consequence of both central and peripheral airway function and has revealed the presence of nonrandom ventilation defects (15) that are the functional consequences of

Abbreviations

FEV_1 = forced expiratory volume in 1 second, PC_{20} = concentration of methacholine causing a 20% decrease in FEV_1, VDV = ventilation defect volume

Summary

In study participants with mild-to-moderate asthma, MRI ventilation defect volume predicted reversibility of postbronchodilator forced expiratory volume in 1 second 6 years later.

Key Results

- Helium 3 (^{3}He) MRI ventilation defects at year 1 predicted bronchodilator reversibility 6 years later (R^2 = 0.80; $P < .01$).
- In eight of 11 study participants, MRI ventilation defects remained in the same location at the 6-year follow-up MRI.
- In three of 11 participants, MRI ventilation defects showed clinically significant worsening at the 6-year follow-up MRI in the same lung regions that had worsened in response to methacholine at year 1.

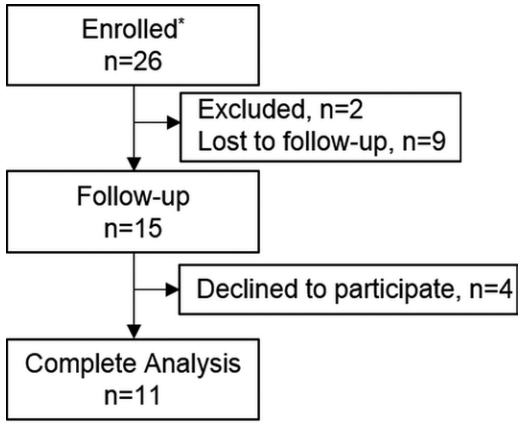

Figure 1: Study flowchart of patient inclusion and exclusion. Two participants were excluded because they did not have current asthma. * Enrolled per Svenningsen et al (17).

airway remodeling, inflammation, and/or intraluminal plugging (16–18). In patients with asthma, MRI ventilation defects are spatially related to abnormally remodeled airways (16,17), positively correlated with disease severity (19), and improved in response to bronchodilators (15,20). The size and spatial locations of MRI ventilation abnormalities persist over time (21,22) and are related to asthma exacerbations (23), asthma control, and quality of life (24).

Although epidemiologic studies (5,6,25) suggest that asthma progression to chronic obstructive pulmonary disease may be relatively common, it is difficult to identify patients who are at risk. Because hyperpolarized helium 3 (^{3}He) and xenon 129 (^{129}Xe) MRI are sensitive tools to help simultaneously measure both small and large airway function, we hypothesized that MRI ventilation abnormalities would be predictive of future FEV_1 bronchodilator reversibility and, at the same time, ventilation defects would remain spatially persistent during follow-up. Accordingly, the purpose of this study was to investigate 6-year longitudinal changes in hyperpolarized ^{3}He MRI ventilation defects in study participants with mild-to-moderate asthma and identify predictors of longitudinal changes in postbronchodilator FEV_1 reversibility.

Materials and Methods

Study Participants and Design

Between January 2010 and April 2011, we consecutively recruited study participants from a tertiary care pulmonary clinic who had mild-to-moderate asthma (ie, prescribed medium-high dose inhaled corticosteroid or long-acting β agonist or less treatment for asthma controller medication) according to the Global Initiative for Asthma treatment step criteria (1), and were aged 18–70 years with less than 1 pack-year smoking history. Participants provided written informed consent to an ethics-board-approved, Health Insurance Portability and Accountability Act–compliant, registered (*ClinicalTrials.gov*: NCT02351141) protocol for baseline and 6-year follow-up visits (November 2016–June 2017). Exclusion criteria included the following: FEV_1 greater than 80% predicted and concentration of methacholine required to decrease FEV_1 by 20% from baseline (PC_{20}) greater than 8 mg/mL, claustrophobia, inability to undergo spirometry, body mass index greater than 40 kg/m^2, and contraindications to MRI (ie, metal, electronic, or magnetic implants). Baseline measurements were previously reported (17) and focused on the cross-sectional analyses; in our study, we reported the longitudinal follow-up measurements after 6 years and compared them with baseline measurements. Data generated during our study are available from the corresponding author.

Spirometry, plethysmography, CT, and MRI were performed at both study visits. At baseline, participants underwent a methacholine challenge, with MRI and spirometry performed before methacholine, after methacholine, and after bronchodilator recovery, and plethysmography and CT before methacholine. At follow-up, participants underwent all tests before and after bronchodilator only (no methacholine challenge at follow-up), with CT performed after bronchodilator. We used electronic health records and participant self-reports to measure exacerbations and changes in medication during the study visit interval (26).

Pulmonary Function Tests and Methacholine Challenge

Spirometry was performed according to American Thoracic Society guidelines (27) by using a spirometer (ndd EasyOne; ndd Medizintechnik AG, Zurich, Switzerland). Plethysmography was performed by using a plethysmograph (MedGraphics Elite Series; MedGraphics Diagnostics, St Paul, Minn) to measure lung volumes and airways resistance. Methacholine challenge was performed according to American Thoracic Society guidelines (28) with the 2-minute tidal breathing method up to and including PC_{20} by using a breath-actuated nebulizer (AeroEclipse II; Trudell Medical International, London, Ontario, Canada). Bronchodilation was achieved after four separate doses of 100 μg of novo-salbutamol hydrofluoroalkane (Teva Novopharm, Toronto, Ontario, Canada) through a pressurized metered-dose inhaler by using a spacer (AeroChamber Plus; Trudell Medical International). Bronchodilator reversibil-

Table 1: Participant and MRI Measurements at Baseline and Follow-up

Parameter	Baseline				Follow-up				*P* Value, Baseline vs Follow-up
	All Participants (*n* = 11)	Stable VDV (*n* = 8)	Worse VDV (*n* = 3)	*P* Value	All Participants (*n* = 11)	Stable VDV (*n* = 8)	Worse VDV (*n* = 3)	*P* Value	
Age (y)	42 ± 9	42 ± 10	43 ± 6	.92	49 ± 9	49 ± 10	49 ± 7	>.99	...
No. of women	4	2	2	...	4	2	2	...	...
BMI (kg/m^2)	27 ± 4	26 ± 4	29 ± 2	.33	28 ± 4	27 ± 5	29 ± 2	.48	.03
FVC*	87 ± 13	88 ± 13	85 ± 14	.78	85 ± 14	87 ± 15	79 ± 5	.39	.47
FEV_1 (L)	2.80 ± 0.86	2.89 ± 1.00	2.56 ± 0.37	.60	2.65 ± 0.85	2.76 ± 0.92	2.35 ± 0.69	.51	.19
FEV_1*	76 ± 12	76 ± 14	75 ± 7	.94	76 ± 12	78 ± 12	72 ± 11	.53	.91
FEV_1/FVC (%)	70 ± 7	69 ± 7	72 ± 6	.52	73 ± 8	72 ± 7	74 ± 11	.69	.13
RV*	126 ± 20	127 ± 14	124 ± 26	.85	136 ± 26	136 ± 18	135 ± 48	.96	.02
TLC*	103 ± 9	104 ± 7	101 ± 13	.55	104 ± 11	105 ± 9	102 ± 15	.71	.56
RV/TLC*	123 ± 18	123 ± 16	122 ± 24	.98	129 ± 17	129 ± 15	128 ± 27	.96	.08
R_{aw}*	172 ± 68	177 ± 70	160 ± 75	.75	178 ± 44	159 ± 35	230 ± 6	.01	.77
VDV (mL)	240 ± 180	290 ± 180	120 ± 130	.19	250 ± 210	180 ± 110	440 ± 330	.06	.92
VDP (%)	5 ± 3	5 ± 3	3 ± 2	.27	5 ± 4	3 ± 2	8 ± 6	.31	.99
ICS dose (μg/day)†	400 (0–1600)	400 (0–800)	600 (400–1600)	.19	400 (0–1600)	400 (0–800)	800 (0–1600)	.50	.32
OCS dose (mg/day)	0	0	0	...	0	0	0	...	...

Note.—Unless otherwise indicated, data are mean ± standard deviation. Mean follow-up was 78 months ± 7 (median, 79 months; range, 68–87 months) from baseline. BMI = body mass index, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, ICS = inhaled corticosteroid, OCS = oral corticosteroid, R_{aw} = airways resistance, RV = residual volume, TLC = total lung capacity, VDP = ventilation defect percent, VDV = ventilation defect volume.

* Data are percent predicted.

† Data are median shown as budesonide equivalent; data in parentheses are range. Ten participants were prescribed inhaled corticosteroid with long-acting β agonist.

ity of FEV_1 was defined as a postbronchodilator increase of 200 mL and 12% (29); participants were dichotomized as reversible or not reversible FEV_1 at follow-up. The minimal clinically important difference for FEV_1 was used to determine changes in FEV_1 between visits as previously described (29,30). Participants withheld asthma medications according to American Thoracic Society guidelines (28) before both visits as follows: short-acting β agonists were withheld for 8 hours, long-acting β agonists were withheld for 48 hours, and long-acting muscarinic agents were withheld for 24 hours.

MRI Parameters and Analysis

We performed anatomic proton (hydrogen 1 [^{1}H]) and ^{3}He static ventilation MRI at the coronal plane within 5 minutes by using a whole-body 3.0-T imager (Discovery MR750; GE Healthcare, Milwaukee, Wis) with broadband capability as previously described (31). Participants were instructed to inhale a gas mixture from a 1.0-L bag (Tedlar; Jensen Inert Products, Coral Springs, Fla) from functional residual capacity, and 15 coronal sections were acquired in 8–15 seconds at breath-hold. We performed ^{1}H MRI before hyperpolarized ^{3}He during 1.0-L breath-hold of high purity, medical-grade nitrogen (N_2; Spectra Gases, Alpha, NJ) by using the whole-body radiofrequency coil and a fast-spoiled gradient-recalled echo sequence (partial echo acquisition; total acquisition time, 8 seconds; repetition time msec/echo time msec, 4.7/1.2; flip angle, 30°; field of view, 40 × 40 cm^2; bandwidth, 24.4 kHz; 128 × 80 matrix, zero padded to 128 × 128; partial echo percentage, 62.5%; 15–17 sections; section thickness, 15 mm; no gap). ^{3}He gas was polarized to 30%–40% by using a commercial turn-key polarizer (HeliSpin; Polarean, Durham, NC). We performed ^{3}He static ventilation MRI during 1.0-L breath-hold of hyperpolarized ^{3}He diluted to 25% by volume with N_2 by using a single-channel rigid elliptical transmit-receive chest coil (Rapid Biomedical, Wuerzburg, Germany) and a two-dimensional multisection fast-gradient-recalled echo sequence (partial echo acquisition; total acquisition time, 11 seconds; 3.8/1.0; flip angle, 7°; field of view, 40 × 40 cm^2; bandwidth, 48.8 kHz; 128 × 80 matrix, zero padded to 128 × 128; partial echo percentage, 62.5%; 15–17 sections; section thickness, 15 mm; no gap).

Quantitative MRI analysis was performed by a single observer (R.L.E., with 4 years of experience) who was blinded to baseline and follow-up visits by using in-house segmentation software (smallest detectable difference [32] and minimal clinically important difference [33]) in Matlab R2016a (Mathworks, Natick, Mass) as previously described (32). Static ventilation images were segmented by using three-dimensional k-means clustering that classified voxel intensities into five clusters ranging from signal void or ventilation defects (cluster 1) to hyperintense signal (cluster 5; all ventilated volume clusters 2–5). Ventilation abnormalities were quantified as the ventilation defect volume (VDV) and as the ventilation defect percent (VDV normalized to the MRI-measured volume of the thoracic cavity). Repeatability of MRI VDV and ventilation defect percent in this study

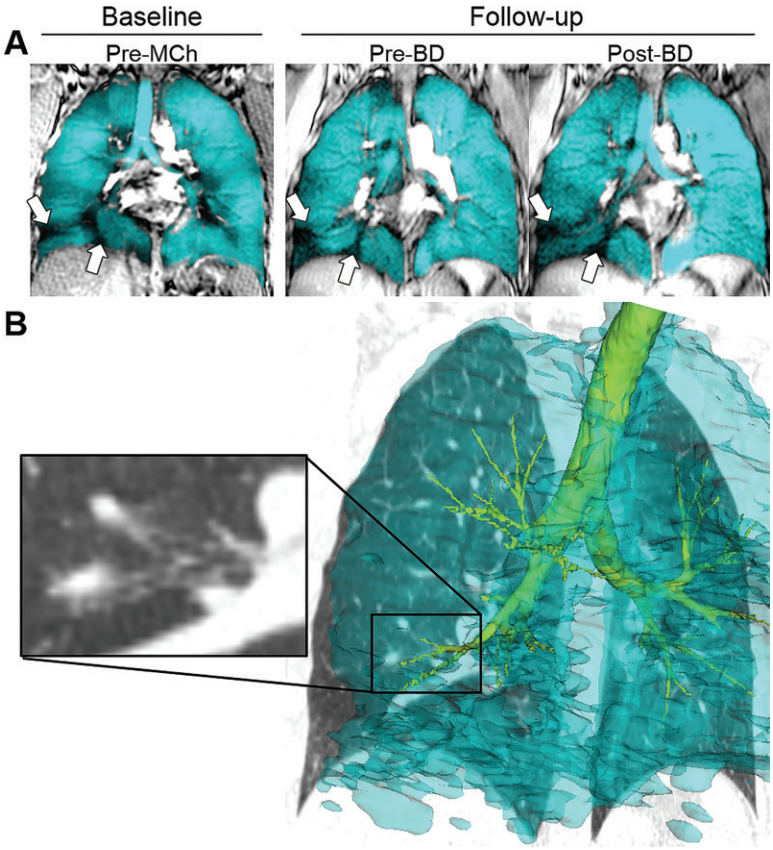

Figure 2: Images show helium 3 (^{3}He) MRI ventilation in a 28-year-old man (participant S03) with mild-to-moderate asthma and stable ventilation between baseline and follow-up. *A*, Center coronal section ^{3}He ventilation MRI (cyan, administered as an inhaled contrast agent) coregistered to anatomic hydrogen 1 (^{1}H) MRI (gray scale) for baseline premethacholine challenge (pre-MCh) and follow-up before and after bronchodilator (pre-BD and post-BD, respectively). Persistent defects between visits are shown (arrows). *B*, Follow-up three-dimensional ^{3}He MRI shows ventilation coregistered to CT with three-dimensional airway tree at oblique angle. Inset (coronal view) shows RB8 bronchus subsegmental bifurcation. Inferior daughter branch leading to persistent defect between baseline and follow-up appears narrowed compared with superior daughter branch. Participant S03 was a man with mild-to-moderate asthma (baseline and follow-up, respectively: age, 28 years and 35 years; forced expiratory volume in 1 second, 3.97 L and 4.19 L; ventilation defect volume, 340 mL and 260 mL).

was evaluated by a single observer (R.L.E., blinded for segmentation) in five randomly selected participants. Blinded participant selection and randomization between repeated segmentation rounds was provided by an additional observer who did not participate in the data analysis. Quantitative, clinically relevant MRI changes were evaluated by using the following equation: $\Delta VDV > |110|$ mL, which is the published minimal clinically important difference for VDV (33), where ΔVDV is change in VDV. The spatial locations of ventilation defects were visually and qualitatively compared between visits (R.L.E.).

CT Parameters and Analysis

Thoracic CT was performed within 10 minutes of MRI by using a 64-section system (LightSpeed VCT; GE Healthcare) at breath-hold after inhalation of 1.0 L of N_2 from functional residual capacity to volume match to MRI. Participants were transported from MRI to CT by wheelchair to avoid exercise-induced changes. At baseline, CT was performed at a 4–10 cm axial region of interest with visually obvious ventilation defects as previously described (17) to reduce radiation dose. At follow-up, a full CT image of the thorax was acquired by using a low-dose protocol as previously described (34).

Thoracic CT images were analyzed by using a commercial workstation (Pulmonary Workstation 2.0; Vida Diagnostics, Coralville, Iowa) to segment and measure the three-dimensional airway tree. The measurements between visits were compared within the region of the partial CT image acquired at baseline.

Statistical Analysis

Data were tested for normality by using Shapiro-Wilk tests with commercially available software (SPSS Statistics 25.0; IBM, Armonk, NJ). When data were not normally distributed, they were log transformed. Measurements for each visit were compared by using paired *t* tests, and bronchodilator-reversible and bronchodilator-not-reversible subgroup measurements were compared by using unpaired *t* tests (SPSS; IBM). MRI VDV and ventilation defect percent repeatability were determined by using the coefficient of variation and two-way mixed effects intraclass correlation coefficient (SPSS; IBM). Univariable relationships were evaluated by using Pearson correlation coefficients (*r*) in commercially available software (GraphPad Prism 7.00; GraphPad Software, La Jolla, Calif) for follow-up postbronchodilator change in FEV_1 with baseline measurements related to the methacholine challenge. These included FEV_1 and VDV before methacholine with differences between challenge states (ie, postmethacholine challenge − premethacholine challenge) and PC_{20}. On the basis of univariable relationships, multivariable models were generated (SPSS; IBM) by using the enter approach to determine the largest influence for predicting FEV_1 bronchodilator reversibility (postbronchodilator change in FEV_1 in milliliters) at follow-up for the following two models: *(a)* baseline variables that had significant univariable relationships with postbronchodilator change in FEV_1 follow-up; and *(b)* age, FEV_1, and PC_{20} at baseline, which have been shown (2,4,35) to predict future bronchodilator reversibility, along with baseline VDV. The regression coefficients for the variables in the multivariable models were expressed as standardized β. Results were considered statistically significant when the probability of making a type I error was less than 5% ($P < .05$).

Results

Study Participants

The study flowchart is provided in Figure 1; 26 participants were enrolled (17) but two participants (8%) did not have asthma and were excluded. Of 24 participants who com-

pleted the baseline visit, nine participants (35%) were lost to follow-up because they moved farther than 500 km away or could not be contacted, and four participants (15%) declined the follow-up visit. In total, 11 participants (seven men and four women) with mild-to-moderate asthma (Global Initiative for Asthma treatment steps 1–4 [1]) were evaluated twice within mean 78 months ± 7 (standard deviation; median, 79 months; range, 68–87 months). Mean participant age was 42 years ± 9 at baseline (men, 41 years ± 10; women, 44 years ± 6; P = .63) and 49 years ± 9 at follow-up (men, 48 years ± 10; women, 51 years ± 7; P = .62). Table E1 (online) shows the baseline measurements for participants who completed longitudinal follow-up (11 participants; 42%) and those who were lost to follow-up (15 participants; 58%). Participants who completed longitudinal follow-up compared with those who did not complete longitudinal follow-up were older (mean age, 42 years ± 9 vs 28 years ± 9, respectively; $P < .01$) with worse lung function overall (all $P < .05$ except forced vital capacity and total lung capacity) and ventilation defect percent (5% ± 4 vs 2% ± 1, respectively; $P < .01$).

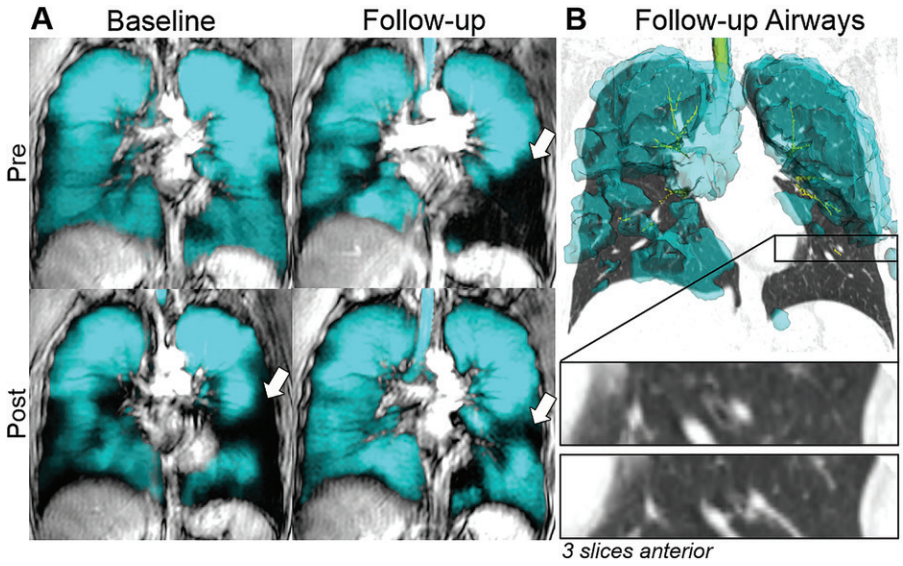

Figure 3: Images show helium 3 (^{3}He) MRI ventilation in a 36-year-old woman (participant S01) with mild-to-moderate asthma and worse ventilation at 6-year follow-up. *A*, Center coronal section ^{3}He ventilation MRI (cyan, administered as an inhaled contrast agent) coregistered anatomic hydrogen 1 MRI (gray scale) for baseline premethacholine challenge (pre) and after methacholine challenge (post), and follow-up before (pre) and after (post) bronchodilator. Worsened defects were shown between visits (arrows). *B*, Follow-up three-dimensional ^{3}He MRI shows ventilation coregistered to CT with three-dimensional airway tree at oblique angle. Inset on top (coronal view) shows LB8 bronchus leading to worsened follow-up defect. Lumen appears clear and open but is abruptly truncated within three sections anteriorly (inset on bottom). Participant S01 was a woman with mild-to-moderate asthma (baseline and follow-up, respectively: age, 36 and 41 years; forced expiratory volume in 1 second, 2.28 L and 1.71 L; ventilation defect volume, 270 mL and 780 mL).

Table 1 provides demographic, pulmonary function test, and MRI measurements. A participant listing is provided in Table E2 (online) and a detailed list of asthma medications is provided in Table E3 (online). Between the baseline and follow-up visits, mean body mass index (27 kg/m^2 ± 4 vs 28 kg/m^2 ± 4, respectively; P = .03) and mean residual volume (126% predicted ± 20 vs 136% predicted ± 26, respectively; P = .02) were different; all other measurements were not different ($P > .05$). All participants were never-smokers (0 pack-years) and none reported an asthma exacerbation between study visits. All participants except one (participant S06) were prescribed inhaled corticosteroids and/or inhaled corticosteroid with long-acting β agonist at baseline. During the interval between visits, nine participants (82%) remained on the same type and dose of medication whereas a single participant (participant S03) changed the type of inhaled corticosteroid and long-acting β agonist controller while administered the same daily inhaled corticosteroid dose. Against medical advice, a single participant (participant S11) refused to self-administer prescribed asthma medications during the interval between the baseline and follow-up visits.

^{3}He MRI Ventilation at Baseline and Follow-Up

MRI measurements were highly repeatable with coefficient of variation of 5% (95% confidence interval: 3%, 7%) and intraclass correlation coefficient of 1.00 (95% confidence interval: 0.98, 1.00) for both VDV and ventilation defect percent. For eight study participants (of 11 participants; 73%), MRI ventilation defects remained in the same location at the 6-year follow-up MRI and were similar in size (change in VDV between visits, <110 mL). Figure 2 shows ^{3}He MRI ventilation at baseline and follow-up and airway corresponding to a persistent defect for a representative participant with stable VDV (participant S03). A subsegmental bifurcation in the RB8 bronchus showed narrowing in the inferior daughter branch compared with the superior daughter branch. For the remaining three participants (of 11; 27%), follow-up prebronchodilator ventilation defects were visually and quantitatively larger than baseline defects (change in VDV between visits, >110 mL) and were in the same lung regions as baseline postmethacholine ventilation defects. Figure 3 shows ^{3}He MRI ventilation and airway corresponding to worsened follow-up defect for a representative participant with worse VDV at follow-up (participant S01). The LB8 bronchus leading to the worsened follow-up defect was abruptly truncated.

Table 2 shows CT airway measurements including airway wall area percent, lumen area, wall thickness, and number of mucus plugs at baseline and follow-up, and total airway count at follow-up. For all participants at baseline versus follow-up, mean wall area percent (70% ± 2 vs 69% ± 1, respectively; P = .14) and wall thickness (28.3 mm ± 2.1 vs 27.8 mm ± 3.3, respectively; P = .66) were not different, whereas mean lumen

Table 2: CT Measurements

	Baseline (n = 11)				Follow-up (n = 11)				
Participant	WA (%)	LA (mm^2)	WT (mm)	Mucus	WA%	LA (mm^2)	WT (mm)	Mucus	TAC
Stable VDV at follow-up (n = 8)									
S02	69	6.7	28.3	0	69	8.8	24.5	0/0	170
S03	72	4.8	28.5	0	70	5.9	27.2	0/0	130
S04	72	3.5	25.7	0	69	6.0	25.3	0/0	166
S06	72	5.7	28.7	0	67	7.8	23.6	0/0	145
S07	72	4.9	27.0	0	69	7.1	27.3	0/0	180
S08	69	3.0	24.5	0	69	4.5	25.3	0/0	202
S09	74	4.3	31.6	0	71	6.5	29.3	0/0	165
S10	69	6.7	28.3	0	68	7.8	29.7	0/0	141
Mean	71 ± 2	5.0 ± 1.4	27.8 ± 2.1	…	69 ± 1	6.8 ± 1.4	26.5 ± 2.2	…	162 ± 23
Worse VDV at follow-up (n = 3)									
S01	70	3.4	27.6	0	72	4.5	26.3	1/3	114
S05	66	3.8	29.3	0	71	5.7	31.5	0/0	224
S11	69	6.8	28.6	0	67	8.2	31.1	0/0	196
Mean	68 ± 2	4.7 ± 1.9	28.5 ± 0.9	…	70 ± 3	6.1 ± 1.9	29.7 ± 2.9	…	178 ± 57
Group differences (n = 11)									
P value	.12	.87	.72	…	.66	.30	.59	…	.51
Mean	70 ± 2	5.4 ± 1.9	28.3 ± 2.1	…	69 ± 1	6.9 ± 1.6	27.8 ± 3.3	…	167 ± 33
Difference from baseline (P value)					.14	<.001	.66	…	…

Note.—Mean data are ± standard deviation. Measurements are matched for segments within partial CT images acquired at baseline, except mucus plugging at follow-up shown as matched partial CT/whole thoracic CT. Mucus indicates mucus plugging. LA = lumen area, TAC = total airway count, VDV = ventilation defect volume, WA = wall area, WT = wall thickness.

area was greater at follow-up (baseline vs follow-up, 5.4 mm^2 ± 1.9 vs 6.9 mm^2 ± 1.6, respectively; $P < .001$). Airway measurements were not different between subgroups ($P > .05$). One participant (participant S01) had three subsegmental mucus plugs at follow-up in the LB4, RB2, and RB10 bronchi, which did not correspond to ventilation defects.

FEV_1 and Ventilation Defects Postbronchodilator Reversibility Measurements

Table 3 shows FEV_1 and MRI ventilation defects postbronchodilator reversibility measurements for each participant by groups with stable and worse VDV at follow-up. At follow-up, six participants were not FEV_1 bronchodilator reversible and eight participants had marginal MRI ventilation defect (change in VDV was greater than −110 mL) bronchodilator reversibility. We compared measurements between FEV_1 reversible and not reversible participant groups and, as shown in Figure 4, PC_{20} was greater (ie, more normal) in participants who were not reversible (Fig 4, *A*; $P = .01$), whereas the ratio of residual volume to total lung capacity was greater in participants who were bronchodilator reversible (Fig 4, *B*; $P < .001$). All other measurements were not different between reversible and not reversible participant groups (Table E4 [online]; $P > .05$). We also plotted baseline measurements against postbronchodilator change in FEV_1 at follow-up, and the univariable relationships are shown in Figure 4, *C*, *D*. PC_{20} ($r = -0.61$; $P = .049$) and premethacholine challenge VDV ($r = 0.67$; $P = .02$) at baseline were related to postbronchodilator change in FEV_1. All other measurements were not correlated with postbronchodilator change in FEV_1 (Table E5 [online]; $P > .05$).

Multivariable Analysis

We generated multivariable models to explore potential predictors of postbronchodilator FEV_1 reversibility at follow-up (Table 4). Baseline premethacholine challenge VDV (standardized β = 0.89; $P = .01$) and premethacholine challenge–to–postbronchodilator change in VDV (standardized β = 0.58; $P = .03$) predicted postbronchodilator change in FEV_1 (model 1: $R^2 = 0.80$; $P = .01$). A second model including FEV_1, age, and PC_{20} did not predict postbronchodilator change in FEV_1 (model 2: $R^2 = 0.63$; $P = .15$).

Discussion

Recent epidemiologic studies (5,6,25) showed that in up to 10% of people with asthma, airways disease may lead to chronic, persistent airflow obstruction and chronic obstructive pulmonary disease but the underlying mechanisms of these changes are not fully understood. In our study, we investigated 6-year longitudinal changes in hyperpolarized helium 3 (^{3}He) MRI ventilation defects in individuals with mild-to-moderate asthma and sought to identify predictors of longitudinal changes in postbronchodilator forced expiratory volume in 1 second (FEV_1) reversibility. We showed that MRI ventilation helps to predict long-term postbronchodilator FEV_1 reversibility in mild-to-moderate asthma. We observed the following: *(a)* negligible postbronchodilator

Table 3: Changes in Forced Expiratory Volume in 1 second and Ventilation Defects

Participant	Baseline PostBD − PreMCh Challenge		Baseline PostBD − PostMCh Challenge		Follow-up PostBD − PreBD Challenge	
	Change in FEV_1 (mL)	Change in VD (mL)	Change in FEV_1 (mL)	Change in VD (mL)	Change in FEV_1 (mL)	Change in VD (mL)
Stable VDV at follow-up (n = 8)						
S02	−520 (−15)	−190 (−3)	+780 (+35)	−420 (−7)	+680 (+24)	−200 (−4)
S03	+380 (+10)	−120 (−2)	+1360 (+45)	−1710 (−25)	+220 (+5)*	−90 (−2)*
S04	+30 (+2)	−10 (0)	+360 (+37)	−80 (−2)	+220 (+15)	−20 (0)*
S06	+70 (+3)	+10 (0)	+810 (+43)	−1150 (−19)	+150 (+5)*	−10 (0)*
S07	−90 (−2)	−210 (−4)	+1080 (+53)	−870 (−11)	+950 (+37)	−250 (−2)
S08	+470 (+26)	−30 (−1)	+1010 (+81)	−230 (−4)	+260 (+14)	−10 (0)*
S09	−350 (−9)	−70 (−2)	+650 (+21)	−340 (−5)	+400 (+11)*	−50 (−2)*
S10	−30 (−1)	+10 (0)	+580 (+29)	−630 (−9)	+60 (+2)*	+20 (0)*
Mean	−10 ± 330 (+2 ± 12)	−80 ± 120 (−1 ± 3)	+830 ± 310 (+43 ± 18)	−680 ± 480 (−10 ± 7)	+370 ± 300 (+14 ± 11)	−80 ± 100 (−1 ± 2)
Worse VDV at follow-up (n = 3)						
S01	−110 (−5)	+190 (+5)	+800 (+58)	−1040 (−19)	+1030 (+60)	−580 (−11)
S05	+200 (+7)	−60 (0)	+600 (+23)	−430 (−6)	+160 (+5)*	−100 (−1)*
S11	−140 (−6)	+40 (+1)	+740 (+48)	−340 (−7)	+110 (+5)*	−40 (−1)*
Mean	−20 ± 190 (−1 ± 7)	+60 ± 130 (+2 ± 3)	+710 ± 100 (+42 ± 18)	−600 ± 380 (−10 ± 7)	+430 ± 520 (+23 ± 32)	−240 ± 300 (−4 ± 6)
All participants (n = 11)						
Mean	−10 ± 270 (+1 ± 10)	−30 ± 100 (0 ± 2)	+760 ± 270 (+40 ± 18)	−570 ± 500 (−9 ± 8)	+300 ± 370 (+14 ± 18)	−100 ± 160 (−2 ± 3)

Note.—FEV_1 data in parentheses are percent change and VD data in parentheses are change in ventilation defect percent; mean data are ± standard deviation. Change in FEV_1 shown as absolute difference in milliliters and as a percent of baseline. Change in VD shown as absolute VDV difference in milliliters and as absolute ventilation defect percent difference. BD = bronchodilator, FEV_1 = forced expiratory volume in 1 second, MCh = methacholine challenge, VD = ventilation defect, VDV = VD volume.

* Not reversible FEV_1 (n = 6) and VDV (n = 8).

reversibility in six of 11 participants at follow-up, *(b)* MRI ventilation defects at baseline predicted follow-up postbronchodilator reversibility (R^2 = 0.80; P = .01), *(c)* MRI ventilation defects persisted in the same spatial locations 6.5 years later, and *(d)* ventilation defects worsened in three of 11 participants in the same lung regions that previously worsened during methacholine challenge 6.5 years before.

MRI ventilation defects persisted in the same spatial locations at follow-up. For three participants (participants S01, S05, and S11), ventilation defects also worsened in the same spatial regions that worsened during a methacholine challenge approximately 6.5 years before. Previous studies evaluated MRI ventilation defects for up to approximately 1.5 years (21,22) and revealed spatially persistent defects (21), suggesting that fixed asthma airway abnormalities are spatially heterogeneous. We also evaluated CT airway measurements to investigate the underlying pathophysiologic structures of persistent and worsening ventilation defects, which showed interindividual differences and mucus plugs in a single participant who worsened. However, there was no spatial relationship between ventilation worsening and mucus plugs in this participant with mild-to-moderate asthma.

The prevalence of negligible bronchodilator reversibility in our participant cohort (six of 11; 55%) was higher than previously reported in epidemiologic studies (5,6). In all but one of these participants, there were no changes in medication (except for participant S11 who refused prescribed inhaled corticosteroid and long-acting β agonist) or exacerbations. Moreover, at follow-up, two participants in this subgroup (participants S06 and S10) met the criteria for fixed airflow obstruction consistent with chronic obstructive pulmonary disease (36) and two others (participants S05 and S11) had worse VDV at follow-up. Airway remodeling caused by chronic inflammation has been suggested to mediate changes that result in airflow obstruction not reversed by bronchodilators (7) and patients with asthma who do not undergo regular treatment may progress to irreversible obstruction (4). We did not test for airway inflammation and therefore it is possible that inadequately controlled inflammation was responsible for the lack of reversibility consistent with our finding at CT of mucus plugs in one participant.

For two participants (participants S04 and S08) there was poorly reversible postbronchodilator VDV alongside physiologically relevant FEV_1 reversibility, and in participant S11, who stopped all asthma medications, there was neither FEV_1 nor

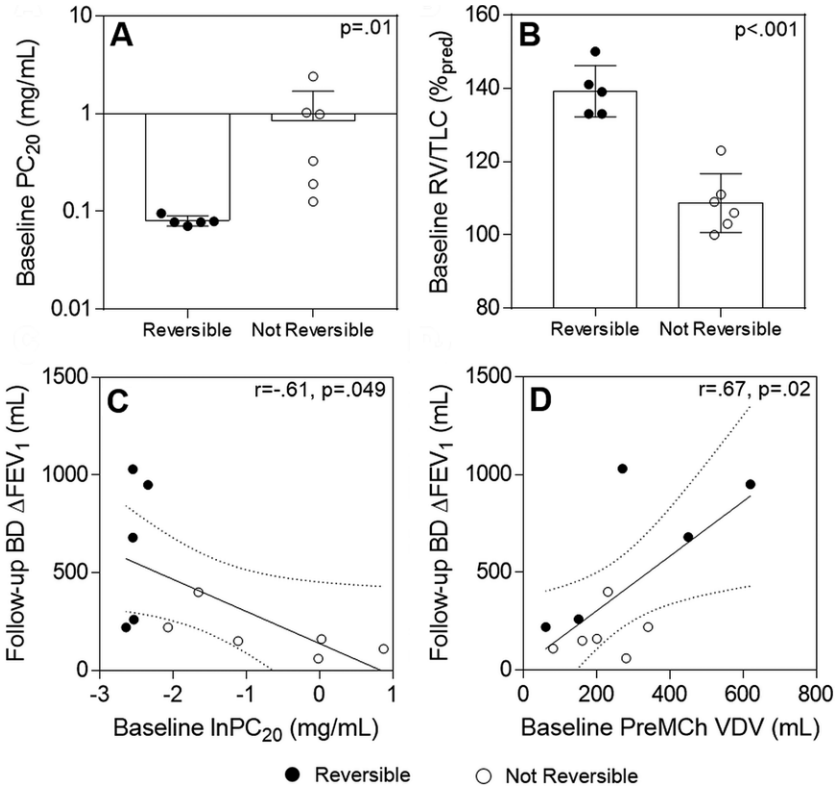

Figure 4: Graphs show group differences and univariable relationships for postbronchodilator (BD) forced expiratory volume in 1 second (FEV_1) reversibility. *A*, Baseline concentration of methacholine required to decrease FEV_1 by 20% (PC_{20}; log scale) was lower (ie, worse) in FEV_1-reversible participants ($P = .01$) and, *B*, baseline residual volume (RV)–to–total lung capacity (TLC) ratio (RV/TLC) was greater in reversible participants ($P < .001$). *C*, Natural logarithm of PC20 (lnPC20; $r = -0.61$; $P = .049$) and, *D*, premethacholine challenge (preMCh) VDV ($r = 0.67$; $P = .02$) were related to BD change in FEV_1 (ΔFEV_1) at follow-up.

Table 4: Multivariable Model to Predict Bronchodilator Reversibility

Parameter	Unstandardized *B* Value	Standardized β Value	*P* Value
Model 1			
Baseline PreMCh VDV	1.86* ± 0.47	0.89*	.01
Baseline PostBD − PreMCh Change in VDV	1.80* ± 0.67	0.58*	.03
PC_{20} (mL^2/mg)†	−0.11 ± 0.05	−0.41	.05
Model 2			
Baseline PreMCh VDV	1.15* ± 0.67	0.55*	.14
Baseline PreMCh FEV_1	−0.01* ± 0.01	−0.14*	.72
Age (mL/y)	−0.01 ± 0.02	−0.26	.54
PC_{20} (mL^2/mg)†	−0.08 ± 0.10	−0.29	.48

Note.—Model 1 is FEV_1 reversibility at follow-up ($n = 11$; $R^2 = 0.80$; $P < .01$); model 2 is FEV_1 reversibility at follow-up ($n = 11$; $R^2 = 0.63$; $P = .15$). *B* values are ± standard error. BD = bronchodilator, FEV_1 = forced expiratory volume in one second, MCh = methacholine challenge, PC_{20} = concentration of methacholine causing 20% decrease in FEV_1, VDV = ventilation defect volume.

* Unitless because independent and dependent variables have the same units.

† Log-transformed PC_{20}. For all models, the predicted dependent variable was BD change in FEV_1 in milliliters at follow-up ($FEV_{1postBD} - FEV_{1preBD}$, where postBD indicates after BD and preBD indicates before BD). Percent predicted was used for preMCh FEV_1 to account for age, sex, height, and race/ethnicity differences, and absolute differences in milliliters were used for change in FEV_1.

VDV postbronchodilator reversibility and ventilation defects worsened at follow-up. These findings are consistent with unresolved small airway abnormalities or mucus plugs (37) leading to persistent ventilation defects that are not reversed by using salbutamol, which mainly has receptors in the central airways. This could be consistent with airway inflammation (18) and suggests that irreversible FEV_1 and worsening ventilation defects may result from inadequate treatment and/or poor adherence to prescribed asthma medication.

MRI VDV at baseline predicted bronchodilator reversibility at follow-up whereas age, PC_{20}, and FEV_1 did not predict bronchodilator reversibility. Although baseline VDV had the greatest relative influence, the difference between ventilation defects before administration of methacholine and postchallenge recovery (postBD − PreMCh = change in VDV, where postBD indicates after bronchodilator and preMCh indicates before methacholine challenge) also significantly contributed. Abnormal FEV_1 and reduced postbronchodilator FEV_1 reversibility were previously shown to predict postbronchodilator FEV_1 reversibility (4). Diminished (4) and augmented (2,35) airway hyperresponsiveness were also shown to predict FEV_1 decline and irreversible airflow obstruction in people with asthma. Severe airway hyperresponsiveness was previously suggested (4) to have a protective effect on the airways by preventing airway narrowing, thereby preserving bronchodilator reversibility. Whereas postbronchodilator FEV_1 changes after administration of methacholine have been evaluated before (38), to our knowledge, this is the first exploration of the potential longitudinal consequence of ventilation defects induced by using methacholine. It is counterintuitive that diminished ventilation at baseline predicted postbronchodilator reversibility 6 years later. MRI ventilation defects can be caused by large and small airway smooth muscle abnormalities, inflammation, and/or intraluminal mucus plugging (17,18,36); that baseline ventilation defects and the postbronchodilator change in ventilation defects after a methacholine challenge predict future FEV_1 reversibility suggests that it is airway smooth muscle abnormalities and not inflammation or mucus plugging that drive MRI-based predictions of future postbronchodilator reversibility. However, the near complete lack of mucus plugs in the

participants studied here means we cannot test the role of mucus in our longitudinal findings. Nevertheless, these results highlight the utility and sensitivity of MRI ventilation measurements for hypothesis-driven, mechanistic studies, especially when combined with pulmonary function tests and thoracic CT. It is important to point out that MRI and CT are complementary. In other words, MRI in combination with CT provides a way to discern the airway structural and luminal determinants of ventilation abnormalities in asthma.

We acknowledge the small sample size as a limitation, and the fact that this study was limited to two time points, both of which limited the generalizability of the multivariable models. Baseline and follow-up MRI evaluations were also different, but this allowed us to explore different relationships between airway hyperresponsiveness, ventilation defects, and bronchodilator reversibility. Finally, we recognize that, compared with ^{3}He MRI, ^{129}Xe MRI offers a less costly and highly sensitive alternative to measure small airway function (20), and by using ^{129}Xe MRI, we would expect similar if not more sensitive detection of ventilation defects.

In study participants with mild-to-moderate asthma, MRI ventilation defect volume predicted reversibility of postbronchodilator forced expiratory volume in 1 second 6 years later, suggesting that pulmonary functional MRI may help to identify patients at risk for the transition from asthma to fixed airflow obstruction and chronic obstructive pulmonary disease.

Author contributions: Guarantor of integrity of entire study, G.P.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, R.L.E., G.P.; clinical studies, R.L.E., S.S., D.G.M., G.P.; experimental studies, R.L.E., G.P.; statistical analysis, R.L.E.; and manuscript editing, all authors.

Disclosures of Conflicts of Interest: **R.L.E.** disclosed no relevant relationships. **S.S.** Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: disclosed money paid to author for lectures including service on speakers bureaus from AstraZeneca. Other relationships: disclosed no relevant relationships. **C.L.** disclosed no relevant relationships. **D.G.M.** disclosed no relevant relationships. **G.P.** disclosed no relevant relationships.

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