

Lumen area change (Delta Lumen) between inspiratory and expiratory multidetector computed tomography as a measure of severe outcomes in asthmatic patients

Sung Shine Shim, MD,^a Mark L. Schiebler, MD,^b Michael D. Evans, MS,^c Nizar Jarjour, MD,^d Ron L. Sorkness, PhD,^e Loren C. Denlinger, MD, PhD,^d Alfonso Rodriguez, MS,^f Sally Wenzel, MD,^g Eric A. Hoffman, PhD,^h Ching-Long Lin, PhD,^h David S. Gierada, MD,^j Mario Castro, MD,^{i,j} and Sean B. Fain, PhD,^{b,f,k} for the National Heart, Lung, and Blood Institute's Severe Asthma Research Program Seoul, Korea, Madison, Wis, Pittsburgh, Pa, Iowa City, Iowa, and St Louis, Mo

Background: Quantitative computed tomographic (QCT) biomarkers of airway morphology hold potential for understanding and monitoring regional airway remodeling in asthmatic patients.

Objective: We sought to determine whether the change in airway lumen area between total lung capacity (TLC) and functional residual capacity (FRC) lung volumes measured from CT imaging data was correlated with severe outcomes in asthmatic patients.

Methods: We studied 152 asthmatic patients (90 female and 62 male patients) and 33 healthy subjects (12 female and 21 male subjects) using QCT. Postprocessing of airways at generations 1 to 5 (1 = trachea) was performed for wall area percentage, wall thickness percentage (WT%), lumen area at baseline total lung capacity (LA_{TLC}), lumen area at baseline functional residual capacity (LA_{FRC}), and low attenuation area at FRC. A new metric (reflecting remodeling, distal air trapping, or both), Delta Lumen, was determined as follows: Percentage difference in lumen area $(LA_{TLC} - LA_{FRC})/LA_{TLC} \times 100$.

Results: Postprocessing of 4501 airway segments was performed (3681 segments in the 152 patients with asthma and 820 segments in the 33 healthy subjects; range, 17-28 segments per subject). Delta Lumen values were negatively correlated with WT% and low attenuation area ($P < .01$) in asthmatic patients. Delta Lumen values were significantly lower for airway generations 3 to 5 (segmental airways) in subjects undergoing hospitalization because of exacerbation and in patients with refractory asthma requiring treatment with systemic corticosteroids. WT% and low attenuation area were positively and Delta Lumen values were negatively associated with systemic corticosteroid treatment ($P < .05$), suggesting that a reduced Delta Lumen value is a potential outcome biomarker in patients with severe asthma.

Conclusion: Reduced Delta Lumen value in the central airways measured by using QCT is a promising exploratory biomarker of unstable refractory asthma that warrants further study. (J Allergy Clin Immunol 2018;■■■:■■■-■■■.)

Key words: Quantitative computed tomography, asthma, airway remodeling, severe asthma, air trapping

From ^athe Department of Radiology, Mokdong Hospital, Ewha Womans University School of Medicine, Seoul; ^bthe Department of Radiology, ^cthe Department of Biostatistics and Medical Informatics, ^dthe Department of Medicine, ^ethe School of Pharmacy, ^fthe Department of Medical Physics, and ^kthe Department of Biomedical Engineering, University of Wisconsin, Madison; ^gthe Department of Medicine, University of Pittsburgh; ^hthe Departments of Radiology, Biomedical Engineering, Mechanical and Industrial Engineering, and Medicine, University of Iowa; and ⁱthe Department of Medicine and ^jthe Department of Radiology, Washington University, St Louis.

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Corresponding author: Sean B. Fain, PhD, 1111 Highland Ave, Rm 1005, Madison, WI 53705-2275. E-mail: sfain@wisc.edu.
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Quantitative computed tomographic (QCT) imaging is emerging as a useful tool in the study of asthma that can provide structural and functional information not readily available through traditional measures.^{1,2} QCT measures of airway wall remodeling and air trapping correlate well with lung function, asthma severity, and histology.³⁻⁵ Specifically, the airway parameters of wall thickness percentage (WT%), wall area percentage (WA%), and air trapping (ie, percentage of low attenuation area <−850 HU at functional residual capacity [FRC], hereafter low attenuation area at functional residual capacity [air trapping; LAA]) derived from single coached breath-hold QCT of the lungs are increased in asthmatic patients

Abbreviations used

CT:	Multidetector computed tomography
Delta lumen:	Percentage difference in lumen area ($LA_{TLC} - LA_{FRC}$)/ $LA_{TLC} \times 100$
FRC:	Functional residual capacity
LAA:	Low attenuation area at functional residual capacity (air trapping)
LA_{FRC} :	Lumen area at baseline functional residual capacity
LA_{TLC} :	Lumen area at baseline total lung capacity
QCT:	Quantitative computed tomography
SARP:	Severe Asthma Research Program
TLC:	Total lung capacity
WA%:	Wall area percentage
WT%:	Wall thickness percentage

compared with healthy control subjects.^{3,6,7} Additionally, these measures are typically greater in those patients with more severe asthma.^{8,9}

Despite prior QCT imaging studies focusing on airway remodeling caused by increased WT% and WA% in asthmatic patients, there are only a few reports addressing potential mechanical changes in airway lumen area (LA) as a function of lung volume, a measure thought to be related to static airway compliance.¹⁰ Other works define airway LA change with lung volume variously by using terms like collapsibility, distensibility, and elasticity and have shown positive correlation with lung function.¹¹⁻¹⁴ However, there are multiple factors that can contribute to LA change between total lung capacity (TLC) and FRC, including airway remodeling and distal air trapping, serving to reduce the FRC/TLC lung volume ratio. Because of this issue, we chose a descriptive term, Delta Lumen, which was defined as follows:

$$\text{Percentage difference in LA} = (LA_{TLC} - LA_{FRC}) / LA_{TLC} \times 100.$$

Delta Lumen is specifically defined here as “the percentage change in airway LA between FRC and TLC as measured from the midportion of the airway perpendicular to the centerline.” Additionally, prior results were derived from a single cross-section of a specific bronchus.^{12,14} Newer postprocessing algorithms are capable of measuring Delta Lumen values at multiple segments of the tracheobronchial tree from the trachea to the fifth-generation bronchi.

The purpose of this study was to quantify Delta Lumen measures from the trachea to the fifth generation of the central airways and correlate these measurements with clinical and other QCT-based imaging biomarkers of airway disease in asthmatic patients. We hypothesized that decreased Delta Lumen values at different airway generations would be associated with poorer asthma outcome, especially for patients with severe asthma, in whom there is known to be significant airway remodeling and increased air trapping.⁵

METHODS

Study population

Subjects were enrolled at 7 sites that comprise the Severe Asthma Research Program (SARP) network¹⁵ during SARP I and SARP II between June 2003 and May 2011. Eighty-eight of 123 subjects acquired in SARP I overlap with prior published work.⁴ Another 97 subjects are new and derived from

the SARP II study. Both inspiratory (supine TLC) and expiratory (supine FRC) lung volumes were required for Delta Lumen measurement. This was a HIPAA-compliant and institutional review board–approved prospective study. All subjects signed an informed consent form. One hundred fifty-two asthmatic patients (90 female and 62 male patients) and 33 healthy subjects (12 female and 21 male subjects) were included in the study, and their demographics are summarized in Table 1. Outcome metrics analyzed for comparison with image measures included asthma exacerbations, emergency department visits, intubations, and hospitalizations.

The QCT acquisition methodology is summarized in Table E1 and covered in the Methods section of this article's Online Repository at www.jacionline.org.

Image analysis

All anonymized multidetector computed tomographic (CT) scan data were downloaded to the VIDA software platform (PW version 2.0; VIDA Diagnostics, Coralville, Iowa), where airway LA, WA%, and WT% were measured per airway generation (from trachea = 1, 2 [main bronchi], 3 [lobar], 4 [segmental], and 5 [first subsegmental bronchi]) for each subject by using differences in segmented average outer and inner area and diameter (Fig 1). The airway LA was derived by subtracting the average lumen area at baseline total lung capacity (LA_{TLC}) and lumen area at baseline functional residual capacity (LA_{FRC}) lung volumes to mitigate the effect of local variations. Delta Lumen values were normalized as the percentage of LA_{TLC} determined mathematically $((LA_{TLC} - LA_{FRC}) / LA_{TLC} \times 100)$ for each respective airway segment. Airway segment measures were then grouped by airway generation given the competing needs for sufficient statistical power, normalization of expected anatomic variations in airway size,¹⁶ and desire to capture regional variations in disease. Whole lung air trapping was measured as the percentage low attenuation area of less than -850 HU at the FRC lung volume.

Statistical analysis

SPSS (version 12.0; SPSS, Chicago, Ill), SAS (version 9.4; SAS Institute, Cary, NC), and R (version 3.2.0; Vienna, Austria) software were used for analysis. Airway generations 1 through 5 were represented by up to 1, 2, 3, 9, and 11 measurements, respectively, in each subject. Average CT measures for each generation were calculated by averaging across all available segments in a generation for each subject. Mixed-effect linear models were fit with fixed-effect covariates for clinical characteristics, airway generation, characteristic-by-generation interaction, sex, age, body mass index, and study (SARP I or SARP II) to compare airway measures based on clinical characteristics (asthma severity, emergency department, hospitalization, or systemic corticosteroids) at each airway generation and a random-effect covariate for subjects to account for correlation of multiple measurements in each subject. Results are reported as least-squares means with 95% CIs. Correlations among LAA, WT%, and Delta Lumen values in each airway generation were evaluated by using the Spearman rank test. A *P* value of less than .05 was considered statistically significant.

RESULTS

Analysis of airway trees segmented from CT scans included 4501 total airway segments with a range of 17 to 28 segments represented per subject. The number of segments represented did not differ by asthma severity or between healthy subjects and asthmatic patients.

Delta Lumen, WT%, and LAA values are compared for different asthma severities by airway generation in Fig 2. As reported in prior studies,^{4,5} WT% was found to be increased for the subsegmental airways (20.6% vs 21.8% at generation 5 for nonsevere vs severe asthma, *P* = .004), and LAA was globally increased in patients with severe asthma compared with healthy

TABLE I. Demographics and pulmonary function test results and indices of study subjects

Index	Healthy subjects (n = 33)	Asthmatic patients		
		Nonsevere asthma (n = 63)	Severe asthma (n = 89)	All asthma (n = 152)
Age (y)	31.6 (9.2)	33.3 (11.2)	38.4 (13.2)	36.4 (12.5)
Sex (female/male)	12/21	39/24	51/38	90/62
Smoking history (pack years)	0.27 (0.48)	1.31 (1.48)	1.99 (2.09)	1.73 (1.87)
Asthma duration (y)	—	19.5 (11.4)	23.8 (13.1)	22.1 (12.6)
Body mass index (kg/m ²)	27.4 (8.8)	28.4 (6.9)	30.2 (7.2)	29.4 (7.1)
Baseline FEV ₁ (% predicted)	99.4 (9.2)	86.2 (17.3)	63.1 (22.4)	72.5 (23.1)
Baseline FVC (% predicted)	99.7 (9.7)	97.5 (13.6)	80.3 (18.5)	87.4 (18.7)
Baseline FEV ₁ /FVC ratio (% predicted)	99.6 (6.4)	88.0 (11.8)	74.7 (19.4)	80.2 (17.9)
Postbronchodilator FEV ₁ (% predicted)	—	92.4 (17.8)	70.9 (21.3)	80.1 (22.4)

Data are expressed as means (SDs), where applicable.

FVC, Forced vital capacity.

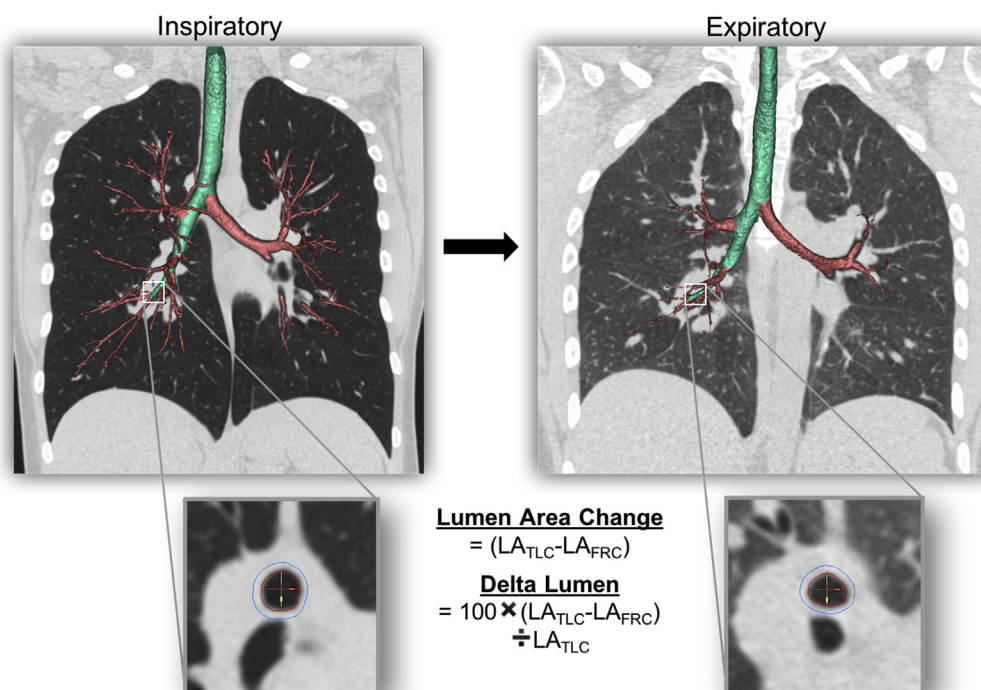


FIG 1. Airway LAs were measured per airway generation for each subject by using differences in the inner area (red lines) averaged over the middle third of each segment at TLC (LA_{TLC}) and FRC (LA_{FRC}) lung volumes by using commercial software (PW version 2.0; VIDA Diagnostics). Delta Lumen values were normalized as a percentage of LA_{TLC} ((LA_{TLC} - LA_{FRC})/LA_{TLC} × 100) for each respective airway segment. Airway segment measures were then grouped by airway generation for analysis.

subjects (9.0% vs 4.2%, $P = .004$) but not compared with patients with nonsevere asthma (9.0% vs 6.3%, $P = .09$). Note that WA% showed nearly identical trends to WT%. Absolute measures of WT% and WA% are summarized in Table E2 in this article's Online Repository at www.jacionline.org. The Delta Lumen value also increased with airway generation in the asthma compared with healthy groups at generations 3 and 4 ($P < .05$), whereas Delta Lumen values trended higher in both patients with severe and those with nonsevere asthma compared with the healthy group (22.6% with severe and 23.3% with nonsevere asthma vs 16.2% healthy subjects at generation 4, respectively; $P < .09$). It should be noted that absolute measures of LA at TLC and FRC (see Table E3 in this article's Online Repository at

www.jacionline.org) were smaller in the asthma versus healthy groups, especially at FRC, but their change on lung inflation was overall greater for both Delta Lumen values and the absolute difference in airway LA (ie, LA_{TLC} - LA_{FRC}) by airway generation (see Figs E1 and E2 in this article's Online Repository at www.jacionline.org).

Delta Lumen values differed markedly for subpopulations of asthmatic patients. Values were typically smaller in asthmatic patients with severe outcomes of asthma exacerbation requiring hospitalization within 12 months of imaging (Fig 3) and those with refractory asthma requiring systemic corticosteroid therapy (Fig 4). These subpopulations with more severe outcomes are summarized in Table II. Subjects undergoing exacerbations

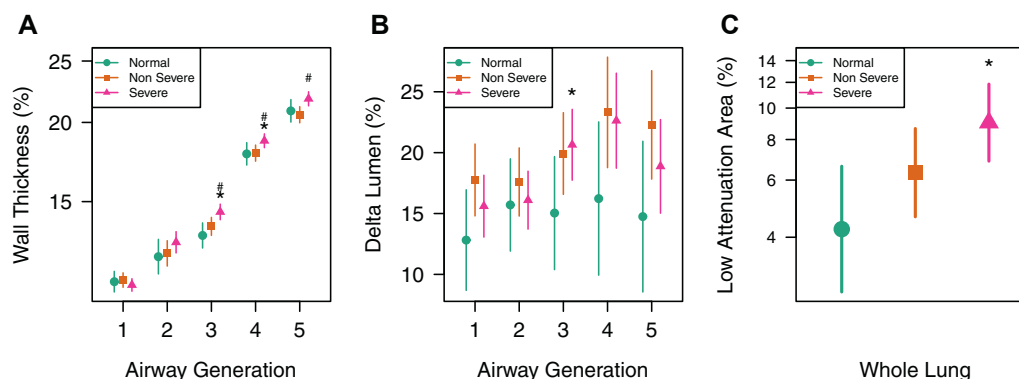


FIG 2. Asthma severity groups and CT biomarkers. *Significance for severe asthma versus healthy groups and #significance for severe versus nonsevere asthma groups at a P value of less than .05. **A**, Mean and 95% CI for wall thickness as a percentage of airway diameter measured at inspiratory lung volume (WT%) is greater in the severe asthma group versus other groups for generations 3 and 4; generations 3 and 4 mark the transition to subsegmental airways. **B**, Mean change and 95% CI for airway LA between expiratory and inspiratory lung volumes as a percentage (Delta Lumen) is significantly greater in the asthma versus healthy groups for generations 3 and 4, which are predominantly lobar and segmental airways, respectively. **C**, Mean and 95% CI for percentage of the lung with LAA of less than -850 HU for expiratory lung volume is significantly greater in the severe asthma versus healthy group.

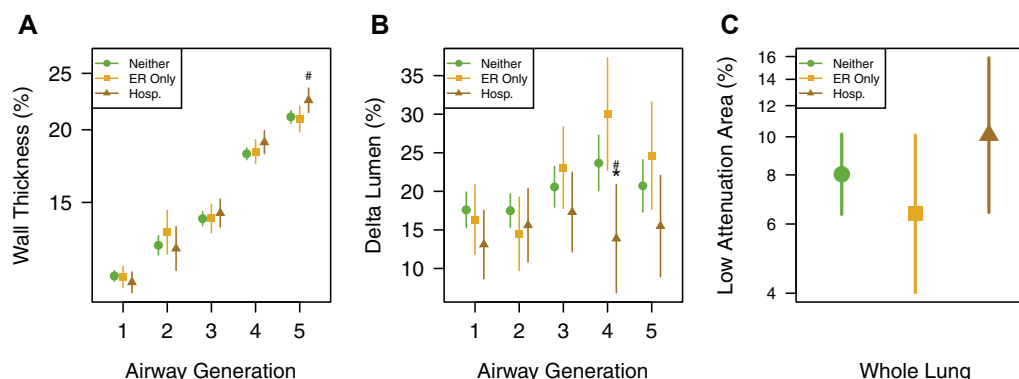


FIG 3. Outcomes of severe exacerbations in terms of emergency department visits (*ER Only*) and those leading to hospitalizations (*Hosp.*) or neither in the last 12 months compared with CT biomarkers. *Significance for hospitalizations versus neither and #significance for hospitalizations versus emergency department visits at a P value of less than .05. **A**, Means and 95% CIs for WT% is greater for hospitalization at generations 5 (subsegmental airways) compared with those leading to ED visits only and subjects reporting neither outcome. **B**, Means and 95% CIs for Delta Lumen values are significantly reduced in exacerbations, leading to hospitalization at generation 4, compared with both emergency department visits and subjects reporting neither outcome. **C**, Means and 95% CIs for LAA in percentage of expiratory lung volume do not differ for these outcomes.

leading to hospitalization were associated with decreased Delta Lumen values for the segmental airways (ie, generation 4; 14% hospitalization vs 30% emergency department visit without hospitalization, $P < .0001$) in conjunction with increased WT% in the subsegmental airways (ie, generation; $P = .03$) and trended toward decreased Delta Lumen values in the subsegmental airways ($P = .08$) with no significant differences in LAA ($P = .16$). Subjects undergoing systemic corticosteroid treatment showed a more pronounced association with decreased Delta Lumen values at multiple airway generations that had the largest difference at subsegmental generation 5 (12.6% vs 23.2%, $P < .0001$) and included significantly increased WT% ($P = .005$) also at generation 5 and increased whole lung LAA ($P = .008$) compared with nonsystemic corticosteroids, implying segmental and subsegmental airway remodeling and overall increased air trapping. Importantly, a higher exposure to systemic

corticosteroids (Systemic corticosteroid dose $\times$ Number of months taken) was found to be associated with reduced Delta Lumen values at generation 5 (see Table E4 in this article's Online Repository at www.jacionline.org), further supporting the association of reduced Delta Lumen values with less well-controlled asthma.

Interestingly, Delta Lumen values correlate only weakly with whole lung-spirometric measures of airflow obstruction (see Table E5 in this article's Online Repository at www.jacionline.org). Delta Lumen values are moderately and inversely correlated with WT% for the segmental and subsegmental airways, most prominently in patients with severe asthma ($r = -0.224$ to -0.349 , $P < .05$; Table III). Delta Lumen values are also moderately and inversely correlated with LAA in both patients with nonsevere and those with severe asthma, most prominently for the trachea through lobar airway segments ($r = -0.246$ to

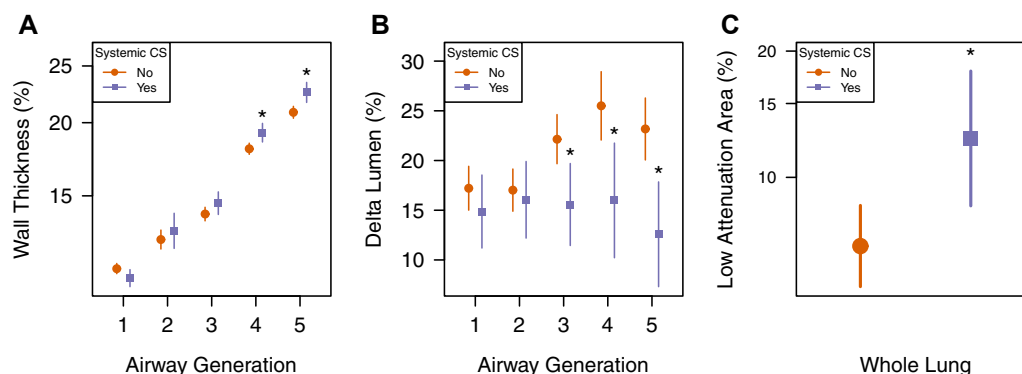


FIG 4. Patients with refractory asthma, as indicated by systemic corticosteroid (CS) treatment, compared with subjects receiving other nonsystemic therapies are starkly different for all CT biomarkers. *Significance at a P value of less than .05. **A**, Means and 95% CIs show significantly greater WT% for systemic corticosteroid treatment at generations 4 and 5 (ie, subsegmental airways). **B**, Means and 95% CIs for Delta Lumen values are reduced in subjects treated with systemic corticosteroids at generations 3 to 5. **C**, Means and 95% CIs for LAA in percentage of expiratory lung volume is greater in subjects treated with systemic corticosteroids.

TABLE II. Fractions of severe versus nonsevere asthma groups that fall into different treatment category outcomes that were compared with CT biomarkers

Outcome	Nonsevere asthma	Severe asthma
Neither	90% (56/62)	52% (45/87)
ED only	10% (6/62)	22% (19/87)
Hospitalization	0% (0/62)	26% (23/87)
Systemic corticosteroids	0% (0/63)	45% (40/89)

Emergency department visits (ED), hospitalizations, and subjects undergoing neither in the previous 12 months add to 100%. Systemic corticosteroid treatment is a distinct group exclusive to patients with severe asthma compared with subjects receiving other nonsystemic therapies, as defined in our study cohort.

–0.630, $P < .05$; Table IV). Sputum WBC measurements were available in 87 of 185 total subjects in our study. We found no correlations between Delta Lumen values and sputum inflammatory markers in our study population (see Table E6 in this article's Online Repository at www.jacionline.org).

DISCUSSION

In this work we explored a potential new QCT biomarker based on the percentage change in each generation's airway LA derived from their respective change in measurements between inspiratory and expiratory lung volumes (Delta Lumen). Automated postprocessing of CT scans enabled bronchial lumen extraction up to fifth-generation bronchi.¹⁷ Similar to wall thickness measures, Delta Lumen values were found to vary with bronchial generation. Reduced subsegmental (bronchial) Delta Lumen values were found to be significantly associated with asthma exacerbations, leading to hospitalization and asthma that was refractory to treatment. These subpopulations were exclusively patients with severe asthma, representing 26% and 45% of our total severe asthma study population, respectively (Table II). The decrease in Delta Lumen values found in subpopulations with severe outcomes generally coincided with other CT biomarkers of airway remodeling (eg, WT% and LAA). We also found that Delta Lumen values correlated negatively with QCT biomarkers of remodeling (ie, WA% and WT%) and obstructive physiology (LAA). The main value of

the current work is as a feasibility study to guide future prospective studies to further establish Delta Lumen value as a reliable biomarker of severe outcomes in asthmatic patients. Airway LA offers potential advantages as a biomarker because it can be measured more accurately and precisely than wall thickness or wall area because of the current spatial resolution limitations of CT imaging.¹⁸

Taken together, the increase in wall thickness and air trapping and decrease in Delta Lumen values are highly suggestive of airway remodeling associated with severe clinical outcomes. The reduced Delta Lumen values in a subset of patients with severe refractory asthma can result from increased wall thickening in concert with regional air trapping, measures that are all detectable on QCT. The coincidence of all 3 markers might provide a functional measure of more persistent airway remodeling versus purely airway inflammation. Measuring Delta Lumen values in more persistent versus reversible airway segments might be useful for predicting which subjects are at risk for severe exacerbations, enabling follow-up with more intensive or alternative therapy approaches for individual patients. Observations of WT%, Delta Lumen values, and LAA could eventually guide future treatment by targeting airway fibrosis to improve outcomes in patients with severe asthma.¹⁹ Improving outcomes in asthmatic patients through the use of personalized clinical and imaging biomarkers that are shown to cluster with phenotype severity has been one of the primary goals of the SARP project.¹⁵

Delta Lumen is distinguished from other QCT biomarkers by its potential relationship to the biomechanical properties of the central airways from the bronchial to the subsegmental generations. Delta Lumen in the current work is a composite of airway segment lengthening, remodeling, and coupling to the lung parenchyma. Structural remodeling leading to compliance changes in the asthma group can encompass both features of airways stiffening and abnormal segment lengthening and smooth muscle changes leading to regional heterogeneity in muscle tone despite bronchodilation.^{20–24} We suspect that Delta Lumen values are probably most sensitive to subepithelial fibrosis, a well-known cause of increased airway stiffness, as opposed to other sources of remodeling, such as smooth muscle hyperplasia, because an

TABLE III. Correlation of airway Delta Lumen area with WT% by airway generation in healthy subjects and asthmatic patients

Airway generation	Healthy subjects (n = 33)		Patients with nonse- vere asthma (n = 63)		Patients with severe asthma (n = 89)		Total asthmatic patients (n = 152)	
	r_s	P value	r_s	P value	r_s	P value	r_s	P value
1	0.03	.87	−0.18	.15	−0.07	.51	−0.11	.19
2	−0.20	.27	−0.21	.10	−0.22*	.04	−0.24*	<.01
3	−0.07	.70	−0.03	.83	−0.03	.81	−0.00	.99
4	−0.19	.28	0.14	.29	−0.22*	.04	−0.05	.56
5	−0.31	.08	−0.07	.56	−0.51*	<.01	−0.35*	<.01

*Spearman correlation: $P < .05$.**TABLE IV.** Correlation of airway Delta Lumen area with LAA by airway generation in healthy subjects and asthmatic patients

Airway generation	Healthy subjects (n = 33)		Patients with nonsevere asthma (n = 63)		Patients with severe asthma (n = 89)		Total asthma (n = 152)	
	r_s	P value	r_s	P value	r_s	P value	r_s	P value
1	−0.13	.48	−0.63*	<.01	−0.34*	<.01	−0.45*	<.01
2	−0.22	.23	−0.37*	<.01	−0.32*	<.01	−0.34*	<.01
3	−0.26	.16	−0.44*	<.01	−0.25*	.02	−0.30*	<.01
4	−0.04	.84	−0.16	.20	−0.23*	.04	−0.20*	.01
5	−0.05	.78	−0.22	.08	−0.24*	.02	−0.25*	<.01

*Spearman correlation: $P < .05$.

inhaled bronchodilator was given before CT scanning. Regional bronchial inflammation and changes in airway parenchymal coupling in the presence of air trapping likely also play a role in our Delta Lumen measures, arguing for evaluation by individual segments rather than by generation in future studies. Moreover, the order of lung inflation volumes acquired by using CT scanning and the presence of smooth muscle tone are potential confounders because of the known hysteresis²⁵ of lung inflation and dependence of airway compliance on smooth muscle tone in asthmatic patients.²⁶ However, we believe these sources of variation are relatively well controlled for in this study given that all asthmatic patients were scanned after bronchodilation and with TLC lung volume, followed by FRC lung volume. These results suggest that discrete changes in airway lumen after bronchoconstriction or bronchodilation, even for just 2 lung volumes, might add additional information related to the biomechanical and functional changes indicative of severe outcomes in asthmatic patients because of increased airway stiffness related to either remodeling^{27,28} or volume changes secondary to air trapping.²⁹

Airway remodeling encompassing increased airway smooth muscle, subepithelial fibrosis, submucosal gland hyperplasia, increased airway vascularization, and inflammation make up the phenomenon of airway wall thickening on QCT and is considered a marker of severe asthma.³⁰ However, among these, subepithelial fibrosis has been observed in patients with moderate-to-severe asthma while being absent in patients with mild persistent asthma and healthy control subjects.²² The results of our study in patients with severe asthma requiring systemic corticosteroids for asthma control support the hypothesis that the remodeling process thickens the airways in patients with severe refractory asthma, possibly making them stiffer and less compliant and leading to persistent airflow obstruction during expiration.^{23–25} Our results also confirm that WA% and WT% are positively associated with disease severity and negatively to lung function. Brackel et al³¹ have also shown that asthmatic airways might be less collapsible or distensible and concluded that airway remodeling can result in stiffer dynamic elastic properties of the central airway walls in

asthmatic patients. Subsequently, the use of WA% and WT% for airway assessment in asthmatic patients has been extensively investigated by others.^{6,11,32,33} A number of studies have shown that the degree of airway thickening was related to the duration, severity of disease, and level of airflow limitation.^{3,4,34,35}

LAA, a measure of air trapping, and Delta Lumen values were negatively correlated to each other in our study. A similar relationship was also observed by Yamashiro et al¹⁴ for the trachea in which they found that the expiration/inspiration ratio of tracheal volume showed negative correlations with FEV₁/forced vital capacity and residual volume/TLC. They hypothesized that greater changes in tracheal LA are associated with less severe airflow limitation and lower amounts of air trapping. Because overall LA is smaller in asthmatic patients (see Table E3), these results might be explained by the higher closing volume for end-expiratory scans in patients with more severe asthma.³⁶ A prior study that divided asthmatic patients by LAA of greater versus less than a median threshold found associations between higher LAA and severe outcomes, including intubation history and hospitalization.⁵ In our study associations of Delta Lumen values and LAA were analyzed by using mixed-effect linear models. Delta Lumen values were negatively associated with asthma exacerbations, leading to hospitalizations and use of systemic corticosteroids, whereas LAA was positively associated only with steroid use.

Proposed mechanism of dynamic airway response in asthmatic patients

With respect to asthma overall, our data show a qualitative increase in Delta Lumen values for segmental and subsegmental bronchi compared with healthy subjects, which is difficult to explain. One possibility is that normalization based on the LA_{TLC} value is artificially amplifying the percentage change in Delta Lumen value because the LA_{TLC} is smaller overall in asthmatic patients. From Table E3, asthmatic patients have lower LA_{FRC} values for segments 3 to 5 compared with healthy subjects but not lower LA_{TLC} values, especially for patients with nonsevere asthma. Moreover, for the absolute difference measured between

LA_{TLC} and LA_{FRC} (in square millimeters) at different airway generations, the qualitative and quantitative relationships for asthma subgroups and outcomes are still observed without normalization (see Fig E1). One interpretation is that the central airways in asthmatic patients are more compliant overall than healthy airways after bronchodilation, with a subpopulation of patients with severe asthma demonstrating relative stiffening that is associated with severe outcomes. For example, reduced Delta Lumen area is associated with increased wall thickness (Table IV), despite the regional heterogeneity introduced by averaging across segments within an airway generation. However, multiple factors can influence Delta Lumen values, including air trapping, which has been demonstrated to be increased in patients with severe asthma.⁵ The complexity introduced by regional air trapping and impracticality of measuring transbronchial pressure in conjunction with QCT in the clinical setting complicates the mechanistic interpretation of the Delta Lumen measure. The sample size for healthy subjects ($n = 33$) is substantially smaller and predominantly male compared with that in the asthma subgroups in our study and therefore might not represent the full range of variability in the general healthy population. Future work developing this exploratory biomarker will necessarily depend on creation of a model that includes more normative data and accounts for disease heterogeneity by using statistical modeling that considers individual airway segments rather than grouping by generation.

Limitations

Several design limitations of the current study are acknowledged. First, the sample size for bronchi at each generation was not equivalent in this analysis across subjects. This was due to smaller and more distal airway pruning at the fifth generation for FRC “expiratory” CT lung volumes simply because of inadequate spatial resolution (ie, small airway and lumen size), mucous plugging, and/or cardiac motion. However, it should be noted that the number of airway segments represented did not differ across groups or by asthma severity.

Second, other CT parameters in this study, such as WA% and WT%, showed relatively lower SDs than Delta Lumen measures, even at the fifth airway generation. Grouping airway segments by airway generation likely contributed to this variability, and future studies could seek to analyze by airway segment rather than grouping by generation.

Third, an unknown fraction of the variability in airway measures is almost certainly due to the multicenter design of SARP, which necessitated breath-hold coaching by the local research coordinator without spirometric control because of the situation in which most sites performed the studies on clinical scanners but not research scanners with more time flexibility. Additionally, the sites used different CT scanner platforms, and there was evolution in CT scanner architecture and software over the time interval in which CT scans were included.

Finally, the inflammatory state was not controlled specifically, although a major criterion for severe asthma was based on corticosteroid dose necessary to control symptoms.¹⁵ No withdrawal or dose tapering of steroid use was required before imaging. From a conceptual perspective, there will clearly be an effect of inflammation on multiple factors affecting airway mechanics. We hypothesize that Delta Lumen values could

complement WT% as a means to monitor response to interventions to control inflammation, as well as subepithelial fibrosis. Recent advances in CT detector technology and image reconstruction^{18,37,38} have made low-dose lung imaging feasible, thus supporting safer acquisition of multiple CT lung volumes before and after intervention. From a translational perspective, distinguishing likely fibrosis from inflammation by means of imaging before and after treatment would potentially be valuable for monitoring individual patient response.

Despite the limitations of the present work, the evidence presented supports Delta Lumen values as a promising exploratory biomarker that might capture mechanical changes caused by airway remodeling and parenchymal coupling in severe outcomes of asthma. Further study will use Delta Lumen values to complement wall thickness and air trapping measures in longitudinal studies of severe asthma, especially to test the hypothesis that airway remodeling in severe asthma subpopulations can be used as a prospective marker for likelihood of severe exacerbations and other adverse outcomes.

Conclusion

We studied the change in airway LA from TLC to FRC (Delta Lumen) by using airway generation on QCT as an exploratory biomarker of severe outcomes in asthmatic patients. We showed that Delta Lumen values have morphologic correlates to wall thickness measures that are known to reflect airway remodeling on CT and was significantly decreased in asthmatic subpopulations that reflect severe clinical outcomes. Future work will further study Delta Lumen values and other QCT biomarkers longitudinally as prospective biomarkers for predicting severe asthma exacerbations and for monitoring response to therapy.

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Key messages

- Airway remodeling is a known feature of severe asthma, as is increased air trapping. In this work a new QCT biomarker is developed that measures the percentage change in airway LA of the central airways between 2 lung volumes (Delta Lumen) as a biomarker associated with severe asthma and reflective of both airway remodeling and air trapping.
- The Delta Lumen value at the level of the segmental airways is associated with clinical outcomes of severe asthma, including exacerbations leading to hospitalization and systemic corticosteroid therapy, as an indicator of severe disease that has not been controlled by inhaled corticosteroids.
- Delta Lumen value on QCT is an accessible and measurable feature of the central airways in asthmatic patients with potential for identifying patients with less stable asthma.

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METHODS

QCT imaging

The specific acquisition and reconstruction parameters used for QCT data are shown in [Table E1](#). All subjects underwent a CT scan of the chest with 16 or 64 detector rows (Light Speed Ultra 16 or VCT [GE Healthcare, Milwaukee, Wis] or Sensation 16 or 64 [Siemens, Forchheim, Germany]) after maximal bronchodilation with albuterol (540–720 μ g) to minimize the effect of acute bronchoconstriction on airway dimensions. Subjects were administered increasing doses of albuterol until the FEV₁ percent predicted difference was 5% or less between consecutive doses or a maximal dose of albuterol (8 puffs or 720 μ g) was reached. For this work, breath-held full inspiratory (TLC) followed by end-tidal breathing (FRC) CT scans were performed in sequential order. Scout scans were performed before each high-resolution CT. Breath-hold coaching was performed independently for

each lung volume after a deep inhalation respiratory maneuver to conform to TLC and FRC lung volumes on the expiratory limb. CT acquisition and reconstruction parameters were as follows. Values for GE scanners were as follows: pitch, 0.984 to 1.675 (millimeter table increment per rotation/detector collimation $\times$ number of detectors); rotation time, 0.5 seconds; 120 kV; and reconstructed slice thickness, 0.5 to 0.625 mm; we used a medium smooth standard or detail equivalent reconstruction algorithm. Values for the Siemens scanners were as follows: pitch, 1.0 to 1.5; rotation time, 0.5 seconds; 120 kV; reconstructed slice thickness, 0.5 to 1 mm; medium smooth reconstruction algorithm (B30 or B35); and effective milliampere-seconds (mAs) from 25 to 180 depending on subject size. The slice reconstruction interval was set to equal the in-plane spatial resolution to obtain isotropic voxels (field of view was measured in millimeters per 512 pixels). Total effective dose (both TLC and FRC scans) ranged from 3 to 4 mSv depending on subject size.

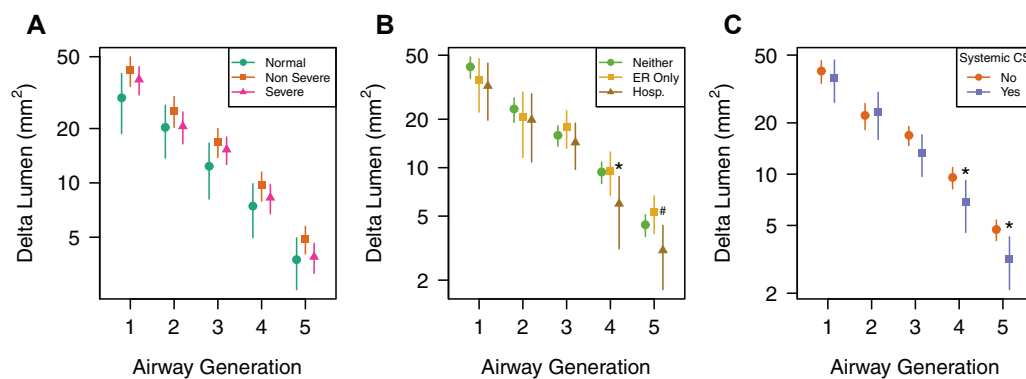


FIG E1. Asthma severity groups and absolute LA change (unnormalized to LA_{TLC}). *Significance for severe asthma versus healthy groups and #significance for severe versus nonsevere asthma groups at a *P* value of less than .05. **A**, Mean and 95% CI for absolute LA change in asthma severity groups. **B**, Mean change and 95% CI for absolute LA change in asthma according to exacerbation outcome. **C**, Mean and 95% CI for absolute LA change in asthma for systemic corticosteroid (CS) therapy.

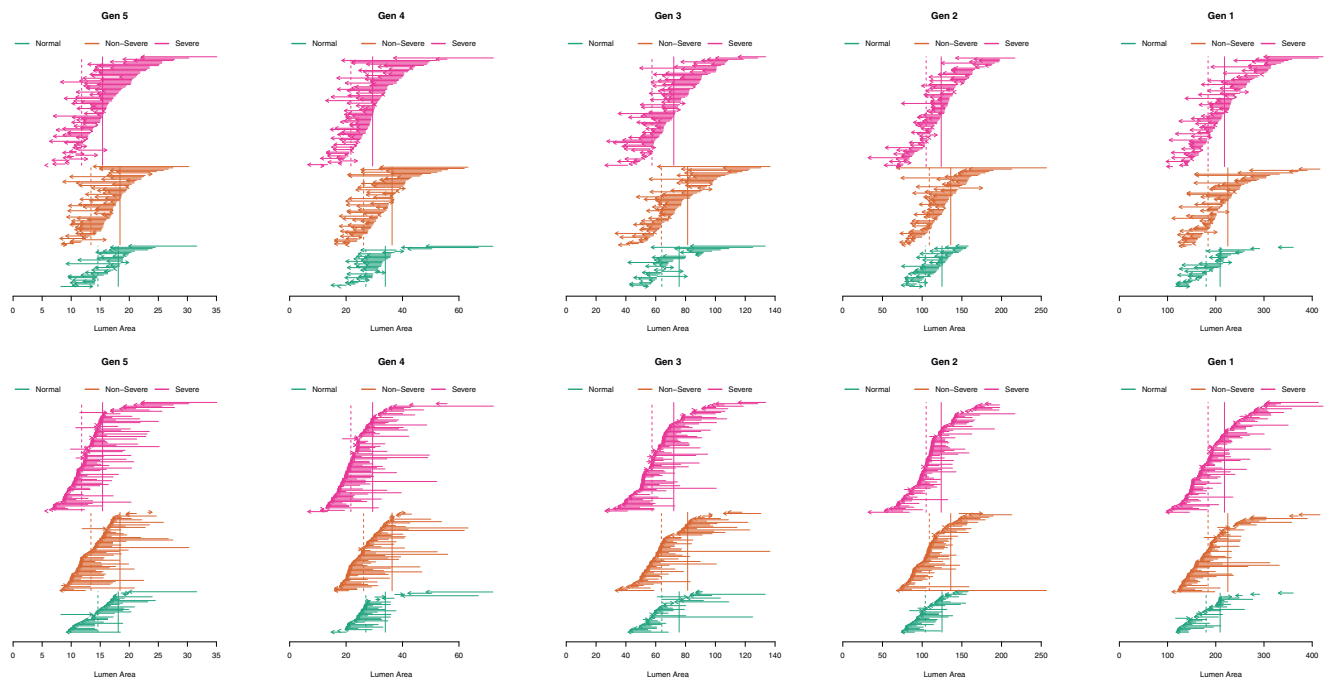


FIG E2. Graphs capture the pattern of absolute change in Delta Lumen value for each group of airway generations on the horizontal axis by connecting the LA_{TLC} to the LA_{FRC} for each subject and sorted vertically from smallest to largest LA_{TLC} (*top row*) and LA_{FRC} (*bottom row*) within each of the severity groups (color coded). *Vertical lines* indicate mean values for LA_{TLC} (*solid line*) and LA_{FRC} (*dotted line*).

TABLE E1. CT acquisition parameters

CT parameter	16 Detector	64 Detector
Collimation	16 × 0.75-1.25 mm	64 × 0.6-0.625 mm
Rotation time (sec)	0.5	0.5
Pitch	1.675	0.984-1.0
Effective milliamperere-seconds	25-33	100-180
Peak kilovoltage (kVp)	120	120
Matrix	512 × 512	512 × 512
Acquired slice thickness (mm)	1-1.25	0.626-0.75
Interval (mm)	0.5-1.0	0.5-0.625
Reconstruction Algorithm	B30, standard or detail	B35, standard or detail

TABLE E2. Wall thickness measures in healthy subjects and asthmatic patients and patients with nonsevere and severe asthma by airway generation

	WA%					WT%				
Airway generation (no.)	1 (183)	2 (183)	3 (183)	4 (184)	5 (183)	1 (183)	2 (183)	3 (183)	4 (184)	5 (183)
Healthy subjects	40.3 (39.3-41.4)	43.1 (42.3-43.8)	46.5 (45.5-47.4)	54.8 (53.5-56.0)	59.0 (57.9-60.2)	11.2 (10.8-11.6)	12.3 (11.5-13.1)	13.3 (12.7-13.9)	17.8 (17.1-18.6)	20.9 (20.0-21.7)
Patients with nonsevere asthma	40.7 (40.0-41.4)	42.7 (42.2-43.3)	46.4 (45.7-47.1)	56.4 (55.5-57.3)	61.5 (60.6-62.4)	11.3 (11.0-11.6)	12.4 (11.9-13.0)	13.7 (13.3-14.2)	17.9 (17.4-18.4)	20.6 (20.0-21.2)
Patients with severe asthma	40.4 (39.8-41.1)	43.2 (42.7-43.7)	47.9 (47.3-48.5)	58.5 (57.6-59.3)	63.7 (63.0-64.5)	11.1 (10.8-11.3)	12.9 (12.4-13.4)	14.4 (14.0-14.9)	18.7 (18.2-19.2)	21.8 (21.2-22.4)
<i>P</i> value										
Healthy subjects vs patients with nonsevere asthma	.59	.51	.87	.04*	.0007*	.80	.76	.24	.92	.58
Healthy subjects vs patients with severe asthma	.89	.76	.01*	<.0001*	<.0001*	.59	.16	.002*	.05*	.07
Patients with nonsevere vs severe asthma	.59	.22	.001*	.001*	.0002*	.31	.19	.02*	.02*	.004*

Data are summarized as means (95% CIs), where applicable.

**P* < .05 between groups.

TABLE E3. Airway Delta Lumen percentage and absolute LA in square millimeters at TLC and FRC lung volumes in the healthy and asthmatic groups by airway generation

	Delta Lumen					LA _{TLC}					LA _{FRC}				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Airway generation															
Healthy subjects	12.8 (8.7-16.9)	15.7 (11.9-19.5)	15.0 (10.4-19.7)	16.2 (9.9-22.5)	14.7 (8.6-20.9)	209 (194-225)	124 (115-134)	75.7 (70.0-81.9)	33.9 (30.9-37.2)	18.1 (16.5-19.9)	180 (167-194)	104 (95.3-113)	64.1 (58.9-69.8)	27.0 (24.5-29.8)	14.6 (13.3-15.9)
Patients with nonsevere asthma	17.8 (14.8-20.7)	17.6 (14.8-20.4)	19.9 (16.6-23.3)	23.3 (18.8-27.8)	22.3 (17.8-26.7)	225 (213-237)	136 (129-144)	81.4 (76.8-86.1)	36.3 (33.9-38.9)	18.4 (17.2-19.6)	184 (174-194)	109 (103-117)	63.8 (60.0-67.8)	26.2 (24.4-28.2)	13.4 (12.6-14.3)
Patients with severe asthma	15.6 (13.1-18.1)	16.1 (13.7-18.5)	20.6 (17.7-23.6)	22.6 (18.7-26.5)	18.9 (15.0-22.7)	218 (208-228)	124 (118-130)	72.1 (68.6-75.8)	29.4 (27.7-31.2)	15.4 (14.5-16.3)	184 (176-193)	105 (99.5-111)	57.5 (54.5-60.6)	21.7 (20.4-23.1)	11.8 (11.1-12.4)
<i>P</i> value															
Healthy subjects vs patients with nonsevere asthma	.05	.42	.09	.07	.05	.12	.04*	.14	.24	.82	.62	.33	.92	.63	.13
Healthy subjects vs patients with severe asthma	.25	.86	.04*	.09	.26	.34	.98	.29	.01*	.003*	.62	.83	.03*	.0002*	<.0001*
Patients with nonsevere asthma vs severe asthma	.27	.42	.75	.82	.25	.39	.008*	.002*	<.0001*	.0001*	.98	.32	.01*	<.0001*	.002*

Data are summarized as means (95% CIs), where applicable.

**P* < .05 between groups.

TABLE E4. Comparison of mean Delta Lumen values by airway generation stratified by systemic corticosteroid exposure (dose × number of months taken)

CS exposure: dose × frequency	No.	Gen	Mean	95% CI		P value		
				Lower	Upper	No vs low	No vs high	Low vs high
No systemic CS	143	1	17.4	15.2	19.6	.36	.04	.34
Low: 5-120	17	1	14.6	9.1	20.2			
High: 140-960	15	1	10.8	5.0	16.5			
No systemic CS	143	2	17.2	15.1	19.3	.41	.66	.81
Low: 5-120	17	2	14.7	9.1	20.3			
High: 140-960	15	2	15.8	9.5	22.0			
No systemic CS	143	3	22.3	19.9	24.8	.17	.003	.19
Low: 5-120	17	3	17.6	11.3	23.9			
High: 140-960	15	3	11.6	5.1	18.1			
No systemic CS	144	4	25.7	22.4	28.9	.65	.004	.06
Low: 5-120	17	4	23.6	15.2	32.1			
High: 140-960	15	4	11.8	2.8	20.7			
No systemic CS	144	5	23.3	20.2	26.5	.22	1E-04	.04
Low: 5-120	16	5	17.8	9.5	26.1			
High: 140-960	15	5	5.4	−3.0	13.8			

Low and high exposure categories are split at the median.
CS, Corticosteroid.

TABLE E5. Association of airway Delta Lumen values with pulmonary function tests by airway generation

	Generation 1 (n = 183)		Generation 2 (n = 183)		Generation 3 (n = 183)		Generation 4 (n = 184)		Generation 5 (n = 183)	
	<i>r_s</i>	<i>P</i> value	<i>r_s</i>	<i>P</i> value	<i>r_s</i>	<i>P</i> value	<i>r_s</i>	<i>P</i> value	<i>r_s</i>	<i>P</i> value
Baseline FEV ₁ (% predicted)	0.084	.303	0.264 [†]	.001	0.132	.106	0.100	.221	0.190*	.020
Baseline FVC (% predicted)	−0.059	.478	0.149	.072	0.034	.678	0.037	.657	0.067	.421
Baseline FEV ₁ /FVC (% predicted)	0.273 [†]	.001	0.243*	.003	0.201*	.014	0.132	.106	0.174*	.033
Post-FEV ₁ (% predicted)	0.019	.820	0.173*	.039	0.031	.713	0.012	.888	0.119	.157
FVC (% predicted−MAX)	−0.129	.115	0.092	.266	−0.021	.801	0.052	.531	−0.017	.834
FEV ₁ /FVC (MAX)	0.252 [†]	.002	0.220 [†]	.008	0.159	.056	0.164*	.047	0.198*	.017
FEV ₁ (MAX reversibility)	−0.14	.06	−0.17*	.02	−0.05	.47	−0.09	.25	−0.06	.43

FEV₁/FVC (MAX), FEV₁/forced vital capacity maximum bronchodilation; FVC (% predicted−MAX), forced vital capacity maximum bronchodilation percent predicted.

**P* < .05.

[†]*P* < .01.

TABLE E6. Spearman rank correlation of CT airway measures, Delta Lumen values, and WT% with sputum inflammatory cells

		Generation 1		Generation 2		Generation 3		Generation 4		Generation 5	
		<i>r_s</i>	<i>P</i> value	<i>r_s</i>	<i>P</i> value	<i>r_s</i>	<i>P</i> value	<i>r_s</i>	<i>P</i> value	<i>r_s</i>	<i>P</i> value
Delta Lumen (%)	MAC (%)	−0.04	.72	0.11	.30	−0.29	.01	−0.07	.53	−0.04	.75
Delta Lumen (%)	MAC (no.)	−0.02	.85	−0.02	.88	−0.30	.01	−0.02	.87	−0.04	.73
Delta Lumen (%)	PMN (%)	0.03	.76	−0.04	.68	0.28	.01	0.05	.63	0.01	.93
Delta Lumen (%)	PMN (no.)	0.04	.76	−0.03	.80	0.14	.21	0.06	.60	0.05	.64
Delta Lumen (%)	EOS (%)	0.00	.99	−0.09	.40	0.03	.75	0.05	.66	−0.09	.40
Delta Lumen (%)	EOS (no.)	0.04	.71	−0.08	.47	0.01	.92	0.07	.51	−0.06	.59
WT%	MAC (%)	0.18	.11	0.12	.28	−0.11	.32	−0.12	.26	−0.17	.11
WT%	MAC (no.)	0.16	.14	0.25	.02	−0.02	.88	0.00	.98	−0.02	.88
WT%	PMN (%)	−0.15	.17	−0.23	.03	0.18	.09	0.09	.39	0.19	.07
WT%	PMN (no.)	0.00	1.00	0.01	.94	0.08	.49	0.09	.41	0.07	.52
WT%	EOS (%)	−0.05	.66	0.05	.64	−0.04	.73	0.12	.28	0.11	.29
WT%	EOS (no.)	−0.03	.78	0.05	.69	−0.05	.68	0.06	.59	0.09	.42

EOS, Eosinophils; *MAC*, macrophages in sputum; *PMN*, polymorphonuclear leukocytes or total granulocytes.