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Longitudinal changes in airway remodeling and air trapping in severe asthma

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Abstract

Rationale and Objectives—Previous cross-sectional studies have demonstrated that airway wall thickness and air trapping are greater in subjects with severe asthma than in those with mild-to-moderate asthma. However, a better understanding of how airway remodeling and lung density change over time is needed. This study aims to evaluate predictors of airway wall remodeling and change in lung function and lung density over time in severe asthma.

Materials and Methods—Phenotypic characterization and quantitative multidetector computed tomography (MDCT) of the chest was performed at baseline and ~2.6 years later in 38 participants with asthma (severe n=24, mild-moderate n=14) and 9 normal controls from the Severe Asthma Research Program.

Results—Subjects with severe asthma had a significant decline in post-bronchodilator FEV1% predicted over time ($p = <0.001$). Airway wall thickness measured by MDCT was increased at

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multiple airway generations in severe asthma compared to mild-to-moderate asthma (wall area percent (WA%): $p < 0.05$) and normals ($p < 0.05$) at baseline and year 2. Over time, there was an increase in WA% and wall thickness (WT%) in all subjects ($p = 0.030$ and 0.009 respectively) with no change in emphysema-like lung or air trapping. Baseline pre-bronchodilator FEV1% inversely correlated with WA% and WT% (both $p = < 0.05$). In a multivariable regression model, baseline WA%, race and healthcare utilization were predictors of subsequent airway remodeling.

Conclusions—Severe asthma subjects have a greater decline in lung function over time than normal subjects or those with mild-to-moderate asthma. MDCT provides a noninvasive measure of airway wall thickness that may predict subsequent airway remodeling.

Keywords

Severe asthma; computed tomography; airway remodeling

Introduction

Over 25 million people in the United State are afflicted with asthma.¹ The increased rate of decline in forced expiratory volume in 1 second (FEV₁) in subjects with asthma compared to normal subjects has been reported to be 5-25 ml/year.²⁻⁴ The majority of the longitudinal studies to date have focused primarily on decline in lung function in asthma and response to treatment.^{5,6} When compared to controls, airway walls are thicker in older but not younger subjects with fatal asthma, suggesting that airway remodeling is a progressive process over time.⁷ Airway remodeling defined by histologic airway wall thickening has been associated with airway hyperreactivity⁸ and airflow obstruction.⁹

In cross-sectional studies, increased airway wall area (WA) and thickness (WT) measured by computed tomography (CT) correlate with asthma severity and negatively correlate with FEV₁.^{10,11} Airway WA measured by CT also correlates with histologic airway wall thickening on endobronchial airway biopsies.^{10,12} Studies focusing on the progression of the airway remodeling in asthma radiographically and pathologically over time have been limited.

Identifying predictors of airway remodeling early in the course of asthma will allow stratification and treatment of subjects based on the likelihood of each individual patient progressing in severity. In this study, our aim was to examine a subgroup of the National Institutes of Health Severe Asthma Research Program (SARP) cohort longitudinally over a greater than 2 year period to look for predictors of airway remodeling as demonstrated by WT on quantitative multidetector row CT (MDCT). We also assessed the relationships between airway remodeling and lung hyperinflation and air trapping as determined by CT lung density.

Materials and Methods

47 subjects from the SARP cohort were followed longitudinally with MDCT imaging at full inspiration post-maximal bronchodilation at least one year apart at two sites (St. Louis MO, Madison WI) after Institutional Review Board approval (ID#201206102). Informed consent

was obtained in writing after the nature of the procedure had been fully explained. All subjects underwent detailed characterization at baseline and at follow-up as previously described.¹³ Pulmonary function testing before and after bronchodilator and methacholine bronchoprovocation was performed according to American Thoracic Society guidelines.¹⁴ Additional detail is available in the online supplement.

All subjects had baseline volumetric MDCT chest with 16 or 64 row scanners (Light Speed 16, Light Speed Pro 16, Light Speed VCT; GE Healthcare, Milwaukee, WI; or Sensation 16, Volume Zoom; Siemens, Forchheim, Germany). Images were acquired after bronchodilation with albuterol (540-720 mcg). The MDCT scan was repeated on average 2.6 years later (Year 2 CT).

MDCT scans were quantitatively analyzed for airway wall thickness and lung density using Pulmonary Workstation 2 (VIDA Diagnostics, Iowa City, IA).¹⁵⁻¹⁷ Previous studies have validated the lung and airway segmentation methods compared to manual methods.^{18,19} Airway wall measurements for each segment were made perpendicular to the centerline path at the centerline voxel and averaged over the middle third of the segment between branch points. Specific measurements included: airway wall area (WA) and percent (WA%), airway wall thickness (WT) and percent (WT%) and lumen area (LA). Whole lung density measurements were performed using Pulmonary Workstation 2. Emphysema-like lung was defined as the percent of lung with density of <-950 HU at total lung capacity (TLC). Air trapping was defined as percent of lung with density of <-850 HU at functional residual capacity (FRC).

Results were analyzed using SASv.9.3. All results are presented as mean $\pm$ standard deviation in untransformed units or percents. Comparisons across time were made using repeated-measures, mixed-model analysis of variance (ANOVA) with pairwise comparisons performed. Prediction models for year 2 outcomes were performed using multivariable regression. A p-value of less than 0.05 was considered statistical significant.

Results

Participant characteristics

47 subjects from the SARP cohort underwent volumetric MDCT at full inspiration and expiration post-maximal bronchodilation and again 2.6 $\pm$ 1.1 years later (range 1.2-5.5 years). The cohort included 9 normal subjects, 14 mild-to-moderate asthma subjects, and 24 severe asthma subjects. Subjects with asthma had greater atopy than normal individuals and those with severe asthma had greater healthcare utilization than those with mild-to-moderate asthma (Table 1). At baseline, pre-bronchodilator lung function was significantly different amongst the groups (Table 2).

Change in lung function over time

In the severe asthma group, there was a significant absolute decline in post-bronchodilator FEV₁% predicted (-9.4%, 95% CI -13.2%, -5.5%, p<0.001) and FEV₁/forced vital capacity (FVC) ratio (-4.1%, 95% CI -6.0, -2.0, p=0.001) (Table 2). There was no significant change in lung function in the normal or the mild-to-moderate asthma subjects.

More subjects with severe asthma had an absolute decline in FEV₁% predicted 5% (n = 13/24, 54%) than those with mild-to-moderate asthma (n = 3/14, 21%) (p=0.04) (Figure 1). There was no significant change in methacholine PC₂₀ over time (p=NS).

Change in airway wall thickness by quantitative MDCT chest over time

In all subgroups, there was a significant increase in WA% from baseline and Year 2 at generation 3 (0.008, 95% CI 0.001,0.016, p=0.03). This finding was not significant within any subgroup. Changes in WA% over time by subgroups are shown in Table 3. WA% by MDCT was significantly increased in severe asthma compared to normal and mild-to-moderate asthma groups for generations 3 and 5 at baseline (Figure 2A) (all p<0.05). WA% was significantly increased in severe asthma compared to normal and mild-to-moderate asthma groups for generation 3 at Year 2 (Figure 2B) (all p<0.01). There was no significant difference in WA% between mild-to-moderate asthma and normal subjects at any measured generation at baseline or Year 2.

When evaluating all subgroups, there was a significant increase in WT% between baseline and Year 2 at generations 3 (0.019, 95% CI 0.005,0.033, p < 0.01), generation 5 (0.022, 95% CI 0.003,0.042, p = 0.03), and generation 6 (0.034, 95% CI 0.003,0.064, p=0.03). This finding was not significantly different for any one subgroup. WT% was significantly increased in the severe asthma compared to normal subgroup for generation 3 at baseline (p=0.02) though this relationship was not present at Year 2 (Figure 3A and B). There was no significant difference between severe and mild-to-moderate asthma or mild-to-moderate asthma and normal subgroups for any generation at baseline or Year 2 (Figure 3A and B). WA% and WT% are listed by time point and generation for all subgroups in Table 3.

Relationship between lung function and airway remodeling measured by MDCT

Pre-bronchodilator FEV₁% predicted at baseline negatively correlated with WA% at baseline in generations 3-5 (R = -0.39 to -0.61, p<0.05) (Table E1). Post-bronchodilator FEV₁% predicted at baseline negatively correlated with WA% at baseline in generation 4 (R = -0.40, p=0.006). Pre-bronchodilator FEV₁% predicted at Year 2 negatively correlated with WA% at Year 2 in generation 3 (R = -0.33, p=0.02) and generation 4 (R = -0.47, p<0.001) (Table E2). Post-bronchodilator FEV₁% predicted at Year 2 negatively correlated with WA% at Year 2 in generation 4 (R = -0.40, p<0.01).

Pre-bronchodilator FEV₁% predicted at baseline negatively correlated with WT% at baseline in generation 3 (R = -0.46, p=0.001) and generation 4 (R = -0.50, p<0.001) (Table E1). Post-bronchodilator FEV₁% predicted at baseline negatively correlated with WT% at baseline in generation 3 (R = -0.32, p=0.03) and 4 (R = -0.50, p<0.001). Prebronchodilator FEV₁% predicted at Year 2 did not correlate with Year 2 WT% in any generation (Table E2). Post-bronchodilator FEV₁% predicted at Year 2 negatively correlated with WT% at Year 2 in generation 6 (R = -0.34, p=0.03).

Predictors of changes in airway remodeling as measured by MDCT

Baseline measures that were predictive of WA% at follow-up in *all subgroups* include: MDCT WA% (at all generations, p<0.0001-0.01, R = 0.42 to 0.68), asthma severity (for

generations 3 and 4, $p=0.001-0.03$, $R = 0.32$ to 0.45), race (for generations 3, 4 and 6, $p=0.01-0.03$, $R = 0.32$ to 0.36), and body mass index (BMI) (for generation 3, $p=0.005$, $R = 0.43$). Multivariable regression analysis showed WA% at baseline was predictive of WA% at Year 2 (for generations 3-6, $p=0.02-0.0001$). Black race was also predictive of WA% at Year 2, but only for generation 6 ($p=0.01$).

Baseline measures that were predictive of WA% at follow-up in *subgroups with asthma* include: MDCT WA% (for generations 3-6, $p=0.009-0.0001$, $R = 0.47$ to 0.70), asthma severity (mild-to-moderate versus severe asthma, for generations 3 and 4, $p=0.04-0.003$, $R = 0.33$ to 0.46), BMI (for generation 3, $p=0.04$ and $R = 0.33$), and healthcare utilization (for generations 3-4, $p=0.001-0.0003$, $R = 0.51$ to 0.55). Multivariable regression analysis showed WA% at baseline was predictive of WA% at Year 2 (at generations 3-6, $p=0.02-0.0001$). Health care utilization was predictive (for generations 3 and 4, $p=0.02-0.03$). No other demographic variables in those subjects with asthma were predictive of WA% at Year 2.

Change in lung density by quantitative MDCT chest over time

Emphysema-like lung (% of lung <-950 HU at TLC) was analyzed for differences between subgroups at both time points and between baseline and Year 2 for all subjects and within severity group. There were no other significant differences between emphysema-like lung at baseline and Year 2 and over time in all subjects and within subgroups (Table E3). There was a significant higher degree of emphysema-like lung in severe asthma subjects compared to normal ($p=0.04$, adjusted for TLC (cm^3)) and in severe asthma subjects compared to mild-to-moderate asthma ($p=0.03$, adjusted for TLC (cm^3)) at baseline.

Air trapping (% of lung <-850 HU at FRC) was analyzed for differences between subgroups at both time points and between baseline and Year 2 for all subjects and within severity groups (Table E3). There was a statistically significant difference in air trapping at Year 2 between normal and severe asthma subjects ($p = 0.03$, adjusted for FRC (cm^3)). No other values were significantly different at either time point or over time.

Discussion

Subjects with severe asthma have evidence of airway wall thickening detectable by multiple modalities. Qualitative analysis of high resolution CT (HRCT) scans in severe asthma subjects reveals abnormalities in 80% of subjects.²⁰ Airway wall thickness measured by quantitative MDCT, represented by WA% and WT%, is increased in subjects with severe asthma compared to mild-to-moderate asthma and control subjects and correlates both with degree of airflow obstruction and pathologic measures of remodeling.²¹ Subjects with severe asthma have repeatedly been shown to have airway wall thickening pathologically, including increased epithelial and lamina reticularis thickness and smooth muscle.^{10,22-25} In a cluster analysis of asthma subjects, increased WA% in RB1 was associated with increased sputum neutrophilia.²⁶ In a Turkish population, subjects with asthma underwent HRCT of the chest at baseline and 6 years later and were shown to have no resolution in qualitative abnormal findings of remodeling on HRCT, including bronchial wall thickening,

bronchiectasis, and mucous plugging.²⁷ Our study reaffirms that airway wall thickness in severe asthma progresses over time using robust quantitative measures of wall thickness.

The current study reaffirms that airway WT as measured by quantitative MDCT is greater in subjects with severe asthma than milder disease and that these relationships are maintained over time. In addition, we found that airway wall thickness increased at multiple airway generations over time in all subjects, though we did not observe more pronounced airway remodeling in the severe asthma cohort. Although our sample size limits subgroup analysis, this raises the possibility that the airway wall becomes thickened over time in both normal subjects and asthma subjects. It will be interesting to see if the rate of thickening increases over time in subjects with severe asthma compared to milder asthma. Additionally, asthma severity was associated with greater decline in lung function supporting the concept that there is a specific endotype of progressive airway remodeling.²⁸

In all subjects, baseline WA%, asthma severity, race, and BMI was predictive of airway remodeling over time. In those subjects with asthma these factors plus healthcare utilization was predictive of airway remodeling over time. Multivariate analysis found that only baseline WA% was predictive of subsequent remodeling in all airways analyzed but in some generations race and healthcare utilization were significant. Healthcare utilization may be a surrogate marker of the effect of recurrent exacerbations on airway remodeling. Similarly, acute exacerbations of chronic obstructive pulmonary disease are associated with progression of emphysema on MDCT.²⁹ These results suggest that multiple factors contribute to airway remodeling and further prospective studies are needed to confirm these results.

Analysis of lung density revealed correlations between WT% and lung density at both time points with a trend towards baseline WT% predicting subsequent air trapping. Previously we have demonstrated that air trapping in subjects with asthma is associated with asthma severity and likelihood of severe exacerbations.³⁰ These findings support further investigations into the relationship between airway wall remodeling and air trapping at a segmental level. Specific regions of air trapping may be associated with proximal airway wall thickening. Assessment of resolution of air trapping over time may warrant further investigation as a marker of therapeutic effectiveness, particularly in severe asthma.

There are several limitations to our study. Our sample size is small, which explains some of the variations in measures for more distal generations of the airway tree. The repeatability and reliability of quantitative MDCT airway measurements is not well described. Preliminary data from 31 subjects in SARP who underwent MDCT of the chest 5 days apart revealed excellent reliability for WA% and WT%, though variability increased in the distal generations.³¹ Increased radiation exposure with repeated MDCT makes frequent assessment impractical, though with low radiation dose protocols, adequate shielding, and appropriate scanning protocols the risk of radiation exposure can be minimized.²⁸ The amount of time between evaluations was an average of 2.6 years but varied in each subject. The small magnitude of change in MDCT airway wall thickness over time is likely due to relatively short follow-up. Further longitudinal follow-up of patients with severe asthma with these metrics will provide invaluable data concerning the progression of remodeling of

the airways and the relationships between airway remodeling and decline in lung function and healthcare utilization.

Clinically, subjects with asthma are managed based upon subjective measures such as symptoms, use of rescue medications, frequency of exacerbations, and objective measures such as lung function. Currently, we cannot predict which subjects with asthma will worsen in severity or experience a decline in lung function. Quantitative MDCT provides an objective measure of airway remodeling which may guide medical management of asthma. In addition, current trials of asthma therapy which target airway remodeling are limited to sequential random airway biopsies. With the current advances of quantitative MDCT and demonstration of disease progression by CT in subjects with asthma, it is time for CT airway thickness to be tested as a disease marker in clinical trials of biologics and devices which may have an impact on airway remodeling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
CI	confidence interval
CT	computed tomography
FEV₁	forced expiratory volume in one second
FEV₁/FVC	forced expiratory volume in one second/forced vital capacity
FVC	forced vital capacity
FRC	functional residual capacity
HRCT	high resolution computed tomography
HU	Hounsfield unit
MDCT	multidetector-row computed tomography
PC₂₀	provocative concentration of methacholine required to decrease FEV ₁ by 20%
SARP	Severe Asthma Research Program
TLC	total lung capacity
WA%	wall area percent
WT%	wall thickness percent

Figure 1.
Change in FEV₁% predicted post-bronchodilation by asthma severity between baseline and Year 2. *p = < 0.05 Severe asthma versus mild-to-moderate asthma

Figure 2.

WA% versus airway generation at Baseline (A) and Year 2 (B). WA% was significantly greater at baseline in generations 3 and 5 in severe asthma versus normal patients and severe asthma versus mild-to-moderate asthma at baseline and at Year 2 in generation 3.

Additionally, WA% increased between baseline and Year 2 at generation 3 across all groups. * $p < 0.05$ severe asthma versus mild-to-moderate asthma and severe asthma versus normal; † $p < 0.05$ WA% in all subjects baseline versus Year 2

Figure 3.

WT% versus generation at baseline (A) and Year 2 (B). WT% was significantly greater at baseline in severe asthma compared to normal patients at baseline. Additionally, WT% increased between baseline and Year 2 at generation 3, 4, and 6 across all groups. * $p < 0.05$ severe asthma versus normal; † $p < 0.05$ WT% in all subjects baseline versus Year 2

Table 1

Baseline Demographics

Variable	Normal (n = 9)	Mild-Moderate Asthma (n = 14)	Severe Asthma (n = 24)	p value (all severity groups) [#]	p value (mild-to-moderate vs severe) [#]
Age at DOE (years)	35.2 ± 9.5	36.5 ± 10.0	36.2 ± 16.3	0.990	0.950
Female, % (n)	66.7 (6)	64.3 (9)	66.7 (16)	0.988	1.000
Race, % (n)	African-American	11.1 (1)	58.3 (14)		
	Caucasian	88.9 (8)	25.0 (6)	0.018	0.190
	Other races	0.00 (0)	16.7 (4)		
BMI (kg/m ²)	30.8 ± 11.0	29.1 ± 5.1	32.3 ± 7.9	0.321	0.120
Age onset (year)	N/A	12.5 ± 13.2	14.8 ± 15.0	0.542	0.540
Duration of asthma (years)	N/A	24.0 ± 13.5	21.4 ± 12.2	0.628	0.630
IgE (IU/ml)	129 ± 167	209 ± 144	777 ± 896*	0.004	0.020
EOS%	2.44 ± 1.51	3.84 ± 3.24	4.04 ± 3.50	0.519	0.700
Atopy, % (n)	62.5 (5)	100.0 (13)	100.0 (17)	0.024	1.000
Ever visited ED, % (n)	N/A	78.6 (11)	95.8 (23)	N/A	0.130
ED during last year, % (n)	N/A	14.3 (2)	50.0 (12)	N/A	0.040
Ever hospitalized, % (n)	N/A	42.9 (6)	87.5 (21)	N/A	0.008
Hospitalized during last year, % (n)	N/A	0.00 (0)	29.2 (7)	N/A	0.033
Ever ICU, % (n)	N/A	7.14 (1)	62.5 (15)	N/A	0.002
ICU during last year, % (n)	N/A	0.00 (0)	12.5	N/A	0.280
Medical therapy					
ICS only % (n) †	0	7 (1)	21 (5)	N/A	0.64
ICS/LABA % (n)	0	57 (8)	88 (21)	N/A	0.099
OCS % (n)	0	0 (0)	63 (15)	N/A	<0.001
LTRA % (n)	0	21	58 (14)	N/A	0.08
Omalizumab % (n)	0	0 (0)	25 (6)	N/A	0.07

DOE = date of entry, BMI = body mass index (kg/m²), N/A = not applicable, ED = emergency department, EOS% = percentage of peripheral blood eosinophils, ICU = admitted to the intensive care unit, IgE = immunoglobulin E, atopy = positive allergy skin test (see Methods), ICS = inhaled corticosteroids, LABA = long-acting beta agonist, OCS = oral corticosteroid, LTRA = leukotriene receptor antagonist

* 2 Severe subjects with history of anti-IgE therapy did not have IgE levels drawn.

Kruskal-Wallis p-value for continuous variables, Fisher's exact p-value for categorical variables.

† Defined as either ICS use as sole controller medication or ICS use in addition to ICS/LABA

Table 2

Baseline and Year 2 Lung Function

	Time-point	Pre-or Post-BD	Normal (n=9)	Mild-Moderate Asthma (n=14)	Severe Asthma (n=24)	p value (all groups) [#]	p value (mild-to- moderate vs severe) [#]	p value comparing baseline to Yr 2 (all groups) [#]	p value comparing baseline to Yr 2 (severe asthma only) [#]
FEV ₁ % predicted	Baseline	Pre-	96.2 ± 6.7	83.1 ± 12.3	76.1 ± 19.7	<0.01	0.24	-	-
		Post-	100.0 ± 6.6	91.9 ± 11.5	91.2 ± 16.7	0.26	0.89	-	-
	Year 2	Pre-	93.3 ± 5.6	80.2 ± 12.9	69.0 ± 23.0	<0.01	0.11	0.14	0.14
		Post-	97.8 ± 6.6	90.0 ± 14.6	81.9 ± 21.2 [†]	0.06	0.21	<0.01	<0.01
% Change in FEV ₁ after BD	Baseline		4.0 ± 2.2	11.0 ± 6.9	24.9 ± 32.6	0.02	0.11	-	-
			4.72 ± 3.1	12.6 ± 8.8	23.5 ± 24.0	0.046	0.12	0.91	0.94
	Year 2	Pre-	0.83 ± 0.09	0.74 ± 0.09	0.69 ± 0.11	<0.01	0.20	-	-
		Post-	0.84 ± 0.07	0.78 ± 0.09	0.75 ± 0.11	0.048	0.28	-	-
FEV ₁ /FVC	Baseline	Pre-	0.81 ± 0.06	0.71 ± 0.07	0.65 ± 0.11	<0.01	0.10	0.06	0.06
		Post-	0.85 ± 0.05	0.77 ± 0.09	0.71 ± 0.10 [†]	<0.01	0.046	0.09	0.02
	Year 2		>16.0	1.66 ± 1.94	0.87 ± 1.17	N/A	0.21	-	-
			-	1.04 ± 1.47	1.96 ± 3.47	N/A	0.69	-	0.69
PC ₂₀ [*] (mg/dl)	Baseline (n=27)								
	Year 2 (n=13)								

FEV₁: forced expiratory volume in 1 second, BD: bronchodilation (maximum bronchodilation after 540-720 µg albuterol), FVC: forced vital capacity, PC₂₀: provocative concentration of methacholine required to decrease FEV₁ by 20%, N/A = not applicable

* Subjects with FEV₁ % < 70% or acute asthma exacerbation within 10 days did not have methacholine bronchoprovocation performed.

[†] Severe asthma subjects had significant decline between Baseline and Year 2 (p < 0.01)

[#] Analysis of variance p-value

Table 3
Change in MDCT Airway Remodeling Over Time

		Baseline				Year 2			
Generation [†]		Normal Control	Mild-Moderate Asthma	Severe Asthma	All Groups	Normal Control	Mild-Moderate Asthma	Severe Asthma	All Groups
3	WA % *	0.598±0.009	0.609±0.026	0.630±0.031	0.618±0.029	0.610±0.025	0.612±0.028	0.640±0.026	0.626±0.030
	WT% *	0.302±0.017	0.322±0.048	0.347±0.050	0.331±0.048	0.339±0.049	0.331±0.062	0.360±0.047	0.347±0.053
4	WA %	0.649±0.022	0.658±0.032	0.668±0.033	0.662±0.031	0.653±0.025	0.653±0.026	0.670±0.023	0.662±0.025
	WT%	0.406±0.042	0.420±0.058	0.445±0.081	0.430±0.070	0.446±0.082	0.434±0.082	0.463±0.069	0.451±0.075
5	WA %	0.675±0.024	0.672±0.031	0.694±0.020	0.684±0.026	0.681±0.021	0.682±0.019	0.693±0.018	0.687±0.019
	WT%	0.488±0.045	0.507±0.112	0.538±0.067	0.520±0.079	0.524±0.057	0.527±0.084	0.532±0.061	0.529±0.065
6	WA %	0.683±0.023	0.682±0.025	0.690±0.033	0.686±0.029	0.681±0.025	0.691±0.022	0.697±0.029	0.693±0.027
	WT%	0.560±0.050	0.505±0.074	0.544±0.071	0.539±0.069	0.550±0.070	0.575±0.068	0.585±0.073	0.576±0.071

* Multidetector CT chest (MDCT) WA% and WT% are dimensionless units calculated as follows:

$$WA\% \text{ calculated by } WA/\text{total area (TA)} \times 100$$

$$WT\% \text{ calculated by } WT/\text{average outer diameter} \times 100$$

[†] Generation refers to airway generation where generation 3 is the first segmental bronchus