

Effect of Reducing Field of View on Multidetector Quantitative Computed Tomography Parameters of Airway Wall Thickness in Asthma

Ajay Sheshadri, MD,* Alfonso Rodriguez, MS,† Ryan Chen, MD,‡ James Kozlowski, MS,* Dana Burgdorf, RN,* Tammy Koch, RN,* Jaime Tarsi, MPH,* Rebecca Schutz, RN,* Brad Wilson, MA,§ Kenneth Schechtman, PhD,§ Joseph K. Leader, PhD,|| Eric A. Hoffman, PhD,¶ Mario Castro, MD, MPH,* Sean B. Fain, PhD,† and David S. Gierada, MD#

Objective: We reduced the computed tomography (CT)-reconstructed field of view (FOV), increasing pixel density across airway structures and reducing partial volume effects, to determine whether this would improve accuracy of airway wall thickness quantification.

Methods: We performed CT imaging on a lung phantom and 29 participants. Images were reconstructed at 30-, 15-, and 10-cm FOV using a medium-smooth kernel. Cross-sectional airway dimensions were compared at each FOV with repeated-measures analysis of variance.

Results: Phantom measurements were more accurate when FOV decreased from 30 to 15 cm ($P < 0.05$). Decreasing FOV further to 10 cm did not significantly improve accuracy. Human airway measurements similarly decreased by decreasing FOV ($P < 0.001$). Percent changes in all measurements when reducing FOV from 30 to 15 cm were less than 3%.

Conclusions: Airway measurements at 30-cm FOV are near the limits of CT resolution using a medium-smooth kernel. Reducing reconstructed FOV would minimally increase sensitivity to detect differences in airway dimensions.

Key Words: quantitative CT imaging, Asthma, airway remodeling, reconstruction field of view

(*J Comput Assist Tomogr* 2015;00: 00–00)

Patients with asthma undergo structural airway changes that include subepithelial fibrosis, smooth muscle hypertrophy, airway wall edema, and blood vessel hyperplasia, collectively referred to as airway remodeling.^{1–4} These changes lead to airway wall thickening, are more pronounced in patients with severe asthma,^{3,5} and are associated with irreversible airflow obstruction.⁶ Measuring airway wall thickness (WT) metrics with computed

tomography (CT) can provide noninvasive indices of airway remodeling that correlate with lung function, asthma severity, and histologic measures of airway remodeling.^{7–9}

Most CT methods used to quantify airway WT and wall area (WA) overestimate these measures and underestimate airway lumen measurements.¹⁰ Although the reasons are multifactorial, this is in part due to the similar scale of CT image pixel dimension and airway WT, which leads to partial volume averaging and can be problematic in measurement of smaller airways.^{10,11} Reducing in-plane voxel size by decreasing the reconstructed field of view (FOV) increases the number of pixels across airway walls and can potentially decrease the small airway measurement error.^{12,13} The aim of our study was to determine whether decreasing CT-reconstruction FOV, thereby decreasing in-plane voxel size, would improve the accuracy of airway WT measurement in both a phantom with artificial airways of known dimensions and in human subjects with asthma and healthy controls.

METHODS

Participants

This study was approved by the Washington University School of Medicine institutional review board. We used CT examinations from 29 nonsmoking participants in the Severe Asthma Research Program (SARP), Asthma and Allergic Disease Cooperative Research Centers study, or the Bronchial Thermoplasty Responder registry (ClinicalTrials.gov No. NCT01185275) at 3 sites: (Washington University in St Louis, MO; Cleveland Clinic in Cleveland, OH; and University of Wisconsin in Madison, WI). We performed spirometry before and after administration of an inhaled bronchodilator according to the American Thoracic Society guidelines.¹⁴ We categorized participants as having severe asthma if they met the criteria defined by the American Thoracic Society workshop on refractory asthma (one major and 2 minor criteria),¹⁵ as nonsevere (mild or moderate) asthma if they met the criteria defined by the National Asthma Education and Prevention Program guidelines,¹⁶ and as normal if they did not meet the previously mentioned criteria for asthma and had a negative methacholine challenge (PC20, or the concentration of inhaled methacholine required to induce a 20% decline in forced expiratory volume in 1 second (FEV₁) of greater than 16 mg/mL).

CT Imaging

Phantom Experiments

We performed CT scans on the COPDGene phantom,¹⁷ which contains polycarbonate tubes of known dimensions embedded in polyurethane foam having attenuation similar to lung tissue, using the same 64-detector row CT systems used for human subject scanning (GE Healthcare CT 750 [Waukesha, WI] and

From the *Division of Pulmonary and Critical Care Medicine, Department of Medicine, Washington University School of Medicine, St Louis, MI; †Department of Medical Physics, University of Wisconsin-Madison, Madison, WI; ‡Department of Surgery, University of Louisville School of Medicine, Louisville, KY; §Division of Biostatistics, Washington University School of Medicine, St Louis, MI; ||Department of Radiology, University of Pittsburgh School of Medicine, Pittsburgh, PA; ¶Department of Radiology, University of Iowa College of Medicine, Iowa City, IA; and #Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MI. Received for publication September 4, 2014; accepted February 3, 2015.

Reprints: David S. Gierada, MD, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Washington University School of Medicine, Campus Box 8131, 510 S. Kingshighway Blvd, St Louis, MI 63110 (e-mail: gieradad@wustl.edu).

Accepted for Presentation at the American Thoracic Society International Meeting, 2014.

Funding: Supported by the National Institutes of Health (NIH) (Grant Nos. U10HL109257-01, U19 A1070489-08, T32HL007317-34, UL1TR000448).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jcat.org).

The authors declare no conflict of interest.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Siemens Sensation64 [Erlangen, Germany]). Computed tomographic acquisition parameters included 120 kVp, 90 effective mAs, acquisition FOV of 500 mm, and a pitch of 0.984 (GE) or 1.0 (Siemens). Images were reconstructed using a 512×512 matrix at 30-, 15-, and 10-cm FOVs to achieve in-plane voxel dimensions of 0.59, 0.29, and 0.20 mm, respectively (Fig. 1). Other reconstruction parameters included a medium-smooth reconstruction algorithm (GE “Standard” and Siemens “B35f”) and contiguous 0.625 mm (GE) or 0.6 mm (Siemens) thick sections. Medium-smooth reconstruction algorithms were chosen as they are used in other studies of airway disease including SARP, COPDGene, and Subpopulations and Intermediate Outcome Measures in COPD.

Human Subjects

Human subjects received a chest CT scan at full inspiration after maximal bronchodilation with albuterol (540–720 μ g). Computed tomographic acquisition parameters included 120 kVp, 75 to 195 effective mAs, and pitch of 0.65 to 1. Images were reconstructed at a 30-cm FOV that included both sides of the lungs, and then at both a 15- and 10-cm FOV for the right and left sides of the lung separately. Reconstruction thickness, interval, and kernel were identical to the phantom scans.

Measurement of Airway Wall Parameters

All human and phantom airway measurements were performed on a personal computer workstation using Airway Inspector

v2.8 (Surgical Planning Laboratory at Brigham and Women's Hospital, Boston, MA), an image analysis program that performs automated measurements of specific airways after manually depositing the cursor in the airway lumen. We performed all human and phantom airway measurements using phase-congruency (PC) edge detection.¹⁸ In addition, we measured all phantom airways using the full-width half-maximum (FWHM) method to estimate the relative effects of FOV on airway measurements of the 2 different algorithms.¹⁹ In the phantom, we measured 3 artificial airways of differing size and WT oriented perpendicular to the scan plane on 20 adjacent images at the same slice positions for each FOV, and reported the mean for each airway metric at each FOV. Actual phantom airway dimensions are listed in Table 1.

In CT images for human subjects, we measured segmental and smaller airways along the following paths: right upper lobe, apical segment; right lower lobe, posterior basilar segment; left upper lobe, apicoposterior segment; and left lower lobe, posterior basilar segment. We chose these paths because of their relatively perpendicular orientation relative to the transverse plane. We measured airways in cross section on transverse CT images, obtaining a single measurement approximately halfway between each pair of contiguous branch points beyond the lobar bronchi. We selected all airways for measurement at a 30-cm FOV and then performed measurements at the identical slice positions for the 15- and 10-cm FOV. Thus, we ensured that the image thickness and position of each measured airway cross section were identical at each FOV and that only the FOV varied. We excluded airways

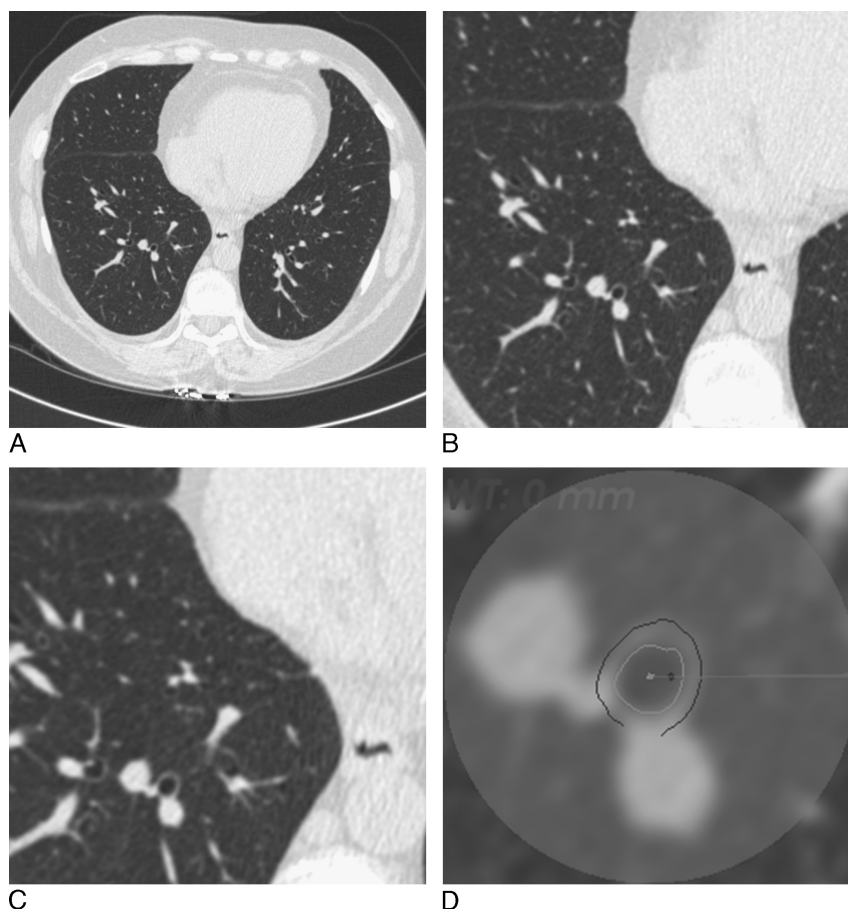


FIGURE 1. A representative airway (RB10) from the CT scan of a human subject at 30-cm (A), 15-cm (B), and 10-cm (C) FOV. D, A representative airway measurement using Airway Inspector.

TABLE 1. True Phantom Airway Dimensions

	Airway 1	Airway 2	Airway 3
ID, mm	3	6	6
WT, mm	0.6	0.9	1.5
WA, mm ²	6.786	19.509	35.342
WA%*	48.98	40.83	55.56

*WA% is dimensionless and calculated as follows: WA/total area $\times$ 100.

from the analysis if the ratio of long to short axis of an ellipse contour fitting the lumen was greater than 2 or if the airway was not measurable on all 3 FOVs.

Cross-sectional airway metrics included internal perimeter (Pi), mean WT, mean WA, WA percent (WA%) ($100 \times \text{WA}/\text{total area}$), and airway inner diameter (ID). We defined Pi10 as the square root of the WA of a hypothetical airway with Pi of 10 mm and determined this metric by calculating a regression line for the relationship between the square root of WA and the Pi from all airway measurements in each subject FOV.²⁰ We defined large airways as those with an ID greater than or equal to 3 mm and small airways as those with an ID less than 3 mm when measured at a 30-cm FOV. Two readers performed airway measurements on a separate portion of the reconstructed human scans, while a single reader performed phantom airway measurements. Both readers analyzed an overlapping sample of 10 randomly chosen human CT scans at 15-cm FOV, and Pi10 values were compared to assess interobserver agreement.

Statistical Methods

We analyzed all data using SAS software version 9.3 (SAS Institute, Cary, NC). We assessed interobserver agreement with intraclass correlation of Pi10 measurements. We compared clinical features among asthma severity groups with a 1-way analysis of variance (ANOVA) for continuous measures and Fisher exact test for categorical measures. Comparisons among FOV for CT airway

metrics (WT, WA, WA%, Pi10) were performed using a mixed-model repeated-measures ANOVA. Analyses of the phantom data were performed using repeated-measures ANOVA. We performed all pairwise comparisons using Tukey correction for post hoc comparisons. Percent differences between measurements at 30- and 15-cm FOV were calculated by subtracting the 15-cm FOV measurement from the 30-cm FOV measurement, dividing the result by the 30-cm FOV measurement, and multiplying by 100. The percent differences between measurements at 30 and 15 cm were compared using the Wilcoxon signed rank test. Percent differences between mean PC and mean FWHM measurements were calculated by subtracting the mean PC measurement from the mean FWHM measurement, dividing the result by the mean PC measurement and multiplying by 100. We measured the association between CT airway metrics and lung function using the Pearson correlation coefficient.

RESULTS

Phantom Airway Measurements

With the PC algorithm, ID increased minimally in magnitude to become more accurate with only the largest airway as FOV decreased from 30 to 15 cm ($P < 0.0001$; Table 2). Airway thickness and area measurements (WT, WA, WA%) decreased in magnitude in all artificial airways as FOV decreased from 30 to 15 cm ($P < 0.05$), with the exception of WT in airway 3, which was increasingly underestimated with the PC algorithm as FOV decreased. Decreasing FOV from 15 to 10 cm did not significantly change measurements of ID or airway thickness/area measurements. Differences in airway thickness/area measurements by FOV were greatest in airways 1 and 2. Airway 1 measurements were 0.7% to 2.0% smaller, and airway 2 measurements were 1.1% to 2.1% smaller at a 15-cm FOV compared with a 30-cm FOV, depending on the parameter, whereas airway 3 measurements were 0.6% to 0.7% smaller at 15-cm FOV compared with 30-cm FOV. Wall area percent measurements had the least variability as

TABLE 2. Phantom Airway Measurements with PC at Different FOVs

Airway	Airway Metric	FOV			ANOVA*	P		
		30 cm	15 cm	10 cm		10 cm vs. 30 cm†	15 cm vs. 30 cm†	10 cm vs. 15 cm†
1‡	ID, mm	2.232 $\pm$ 0.043	2.246 $\pm$ 0.039	2.255 $\pm$ 0.037	0.0908	N/A	N/A	N/A
	WT, mm	1.195 $\pm$ 0.014	1.174 $\pm$ 0.015	1.174 $\pm$ 0.014	<0.0001	<0.0001	<0.0001	0.7277
	WA, mm ²	12.860 $\pm$ 0.123	12.609 $\pm$ 0.139	12.604 $\pm$ 0.124	<0.0001	<0.0001	<0.0001	0.9812
	WA%§	76.608 $\pm$ 0.701	76.078 $\pm$ 0.701	75.936 $\pm$ 0.659	0.0014	0.0018	0.0146	0.6411
2	ID, mm	5.730 $\pm$ 0.024	5.732 $\pm$ 0.013	5.732 $\pm$ 0.013	0.8505	N/A	N/A	N/A
	WT, mm	1.138 $\pm$ 0.004	1.117 $\pm$ 0.005	1.116 $\pm$ 0.005	<0.0001	<0.0001	<0.0001	0.7790
	WA, mm ²	24.535 $\pm$ 0.119	24.022 $\pm$ 0.110	24.003 $\pm$ 0.110	<0.0001	<0.0001	<0.0001	0.7630
	WA%§	48.758 $\pm$ 0.185	48.217 $\pm$ 0.169	48.199 $\pm$ 0.155	<0.0001	<0.0001	<0.0001	0.8861
3	ID, mm	6.140 $\pm$ 0.021	6.162 $\pm$ 0.013	6.162 $\pm$ 0.013	<0.0001	<0.0001	<0.0001	0.9991
	WT, mm	1.296 $\pm$ 0.009	1.287 $\pm$ 0.007	1.286 $\pm$ 0.007	<0.0001	<0.0001	<0.0001	0.8977
	WA, mm ²	30.227 $\pm$ 0.261	30.105 $\pm$ 0.214	30.080 $\pm$ 0.203	0.0029	0.0045	0.0141	0.9042
	WA%§	50.554 $\pm$ 0.209	50.242 $\pm$ 0.143	50.223 $\pm$ 0.155	<0.0001	<0.0001	<0.0001	0.9200

*Overall test of differences among FOV levels from repeated-measures ANOVA.

†Tukey-adjusted pairwise comparison.

‡Airway 1 includes measurements from only 18 images due to errors in obtaining PC measurements on 2 noncontiguous images.

§WA% is dimensionless and calculated as follows: WA/total area $\times$ 100.

N/A, not applicable.

FOV decreased from 30 to 15 cm (airway 1, 0.7%; airway 2, 1.1%; airway 3, 0.6%).

The same patterns in artificial airway measurements were found using the FWHM method for edge detection, except that ID increased in magnitude and became more accurate for all 3 airways as FOV decreased from 30 to 15 cm, and WT was overestimated but decreased in magnitude and became more accurate as FOV decreased for airway 3 as well as the other airways ($P < 0.01$; Supplemental Table 1, <http://links.lww.com/RCT/A36>). In all 3 airways and at all 3 FOVs, PC measurements showed a larger ID and smaller thickness/area metrics compared with the equivalent FWHM measurement ($P < 0.0001$). Differences in ID measurements between the PC and FWHM edge detection methods were greater in airway 1 (12.1%–13.2%, depending on FOV) than in airways 2 and 3 (6.3%–8.6%). Differences in thickness/area metrics between PC and FWHM were greatest with the largest airway and decreased with airway size (airway 3, 25.1%–40.5%; airway 2, 20.9%–31.6%; airway 1, 11.0%–30.6%, depending on FOV and metric; Supplemental Table 2, <http://links.lww.com/RCT/A36>).

Comparisons of measurements obtained with the Siemens and GE scanners revealed differences in the thickness-related measures and ID for the smallest airway, phantom airway 1, of around 12%. In the larger airways, these measures differed by only approximately 2% on average. Differences by FOV for the GE scanner showed the same patterns as with the Siemens scanner.

Human Airway Measurements

The cohort consisted of 13 healthy participants, 7 participants with nonsevere asthma, and 9 participants with severe asthma.

The groups differed in age, race, and FEV₁ (Table 3). Intraclass correlation between the 2 readers was 0.87 for Pi10 measurements in the random sample of 10 cases measured by both readers at 15-cm FOV. A total of 942 airways were measureable at all 3 FOVs, ranging from 15 to 63 per participant (median, 31; interquartile range, 26.5–34.75).

Airway thickness/area measurements became smaller and ID increased in magnitude as the FOV was decreased from 30 to 15 cm (Table 4). Repeated-measures ANOVA showed that all CT measurements differed significantly among all FOVs ($P < 0.0001$). Pairwise comparisons for ID showed statistically significant but very small differences between 30- and 15-cm FOV (2.2% larger at 15 cm, $P < 0.001$) but not between 15 and 10 cm (0.3%, $P = 0.22$). Pairwise comparisons for thickness/area measurements also showed statistically significant but very small differences between 30 and 15-cm FOV (1.1%–2.0% smaller at 15 cm, $P < 0.0001$). Differences between 15 and 10-cm FOV were statistically significant but were up to more than 10 times smaller (0.3%–0.7% smaller at 10 cm, $P < 0.05$).

Correlations between postbronchodilator FEV₁% and WA% at the 3 FOVs were strong (30 cm: $r = -0.678$; 95% confidence interval [CI], -0.837 to -0.415 ; 15 cm: $r = -0.710$; 95% CI, -0.854 to -0.465 ; 10 cm: $r = -0.715$; 95% CI, -0.857 to -0.473) but were not statistically different at different FOVs ($P > 0.05$).

Effect of Airway Size

Airway thickness/area metrics were significantly different among the FOVs for both large airways (≥ 3 mm ID) and small airways (< 3 mm ID), with the exception of WA% in large

TABLE 3. Baseline Demographics

Variable	Normal (n = 13)	Nonsevere Asthma (n = 7)	Severe Asthma (n = 9)	All Groups (n = 29)	P*
Age at Enrollment, y	24.9 ± 6.8	30.4 ± 14.8	45.9 ± 7.6	32.7 ± 13.0	<0.001†
BMI, kg/m ²	26.4 ± 6.0	27.0 ± 5.0	31.3 ± 5.8	28.0 ± 5.9	0.14
Duration of Asthma, y	N/A	18.2 ± 14.2	22.1 ± 15.6	20.4 ± 15.2	0.63
Race					
White, % (n)	46.2 (6)	100.0 (7)	77.8 (7)	69.0 (20)	0.13
Black, % (n)	38.5 (5)	0	22.2 (2)	24.1 (7)	
Other, % (n)	15.4 (2)	0	0	6.9 (2)	
Sex					
Male, % (n)	61.5 (8)	71.4 (5)	66.7 (6)	65.5 (19)	1.00
Female, % (n)	38.5 (5)	28.6 (2)	33.3 (3)	34.5 (10)	
FEV ₁ , L (% predicted)					
Pre-BD	3.97 ± 0.66 (102.6 ± 9.4)	4.17 ± 1.04 (99.9 ± 12.3)	2.20 ± 0.57 (64.5 ± 17.1)	3.47 ± 1.13 (90.1 ± 21.4)	<0.001‡ (<0.001§)
Post-BD	4.15 ± 0.71 (106.5 ± 9.9)	4.57 ± 1.06 (109.3 ± 11.0)	2.43 ± 0.63 (71.2 ± 18.0)	3.71 ± 1.17 (96.2 ± 21.3)	<0.001¶ (<0.001)

*Comparison among all groups using ANOVA for continuous measures or Fisher exact test for categorical measures.

†Uncorrected pairwise comparisons: nonsevere vs. normal, $P = 0.22$; severe vs. normal, $P \leq 0.0001$; nonsevere vs. severe, $P = 0.003$.

‡Pairwise comparison using Tukey correction: nonsevere vs. normal, $P = 0.84$; severe vs. normal, $P \leq 0.0001$; nonsevere vs. severe, $P < 0.001$.

§Pairwise comparison using Tukey correction: nonsevere vs. normal, $P = 0.89$; severe vs. normal, $P \leq 0.0001$; nonsevere vs. severe, $P < 0.001$.

¶Pairwise comparison using Tukey correction: nonsevere vs. normal, $P = 0.49$; severe vs. normal, $P \leq 0.0001$; nonsevere vs. severe, $P < 0.001$.

||Pairwise comparison using Tukey correction: nonsevere vs. normal, $P = 0.89$; severe vs. normal, $P \leq 0.0001$; nonsevere vs. severe, $P < 0.001$.

N/A, not applicable.

TABLE 4. Human CT Airway Measurements at Different FOVs

Airway Metric	FOV			P			
	30 cm	15 cm	10 cm	ANOVA*	10 cm vs. 30 cm†	15 cm vs. 30 cm†	10 cm vs. 15 cm†
WT, mm	1.319 ± 0.132	1.293 ± 0.142	1.285 ± 0.143	<0.0001	<0.0001	<0.0001	0.01
WA, mm ²	18.587 ± 4.154	18.375 ± 4.246	18.249 ± 4.249	<0.0001	<0.0001	0.0001	0.03
WA%‡	72.679 ± 3.624	71.799 ± 3.647	71.584 ± 3.663	<0.0001	<0.0001	<0.0001	0.04
Pi10, mm	4.368 ± 0.271	4.310 ± 0.290	4.292 ± 0.290	<0.0001	<0.0001	<0.0001	0.03
ID, mm	2.891 ± 0.500	2.956 ± 0.493	2.966 ± 0.495	<0.0001	<0.0001	<0.0001	0.22

*Overall test of 10-cm FOV vs. 15-cm FOV vs. 30-cm FOV.

†Pairwise comparison using Tukey correction.

‡WA% is dimensionless and calculated as follows: WA/total area × 100.

airways (Table 5; $P < 0.001$ -0.003). There was no significant difference between ID measurements at 30- and 15-cm FOV when examining only large or only small airways. In pairwise comparisons between 30- and 15-cm FOV, differences were significant ($P < 0.05$) for all thickness/area metrics for both small and large airways, other than WA% for large airways. There were no significant differences between measurements at 15- and 10-cm FOV when examining large and small airways separately. The magnitudes of the differences between 30- and 15-cm FOV were very small in both large and small airways. Percent change in WA% when reducing FOV from 30 to 15 cm was greater in small airways compared with large airways, in which there was minimal change (small: 1.05%, large: -0.003%; $P = 0.001$). This pattern was seen for WT as well but did not meet statistical significance (small: 2.61%, large: 1.97%; $P = 0.06$). There was no significant difference in percent changes in WA or Pi10 between large and small airways when reducing FOV to 15 cm ($P > 0.05$).

DISCUSSION

We found that reducing in-plane voxel size through the use of a reduced FOV yielded statistically smaller and more accurate measures of airway wall dimensions in phantom artificial airways. We also observed these same patterns with reduced FOV in human

subjects. Measurements of ID did not reliably improve with a reduced FOV in the phantom but were more accurate over the larger range of airway sizes occurring in human subjects. These gains in accuracy are small in magnitude, which limits the clinical significance of a reduced reconstruction FOV.

Previous studies of phantom airways have used other reconstruction algorithms and found different degrees of improvement in airway wall measurement accuracy. Algorithms with a higher frequency modulation transfer function (sharper kernels) have the potential to provide greater spatial resolution, but they also produce an increase in image noise which can affect segmentation performance.²¹ Indeed, Takahashi et al²² found a decrease in measurement error of 17% when FOV was reduced from 30 to 15 cm with the “bone” reconstruction algorithm in a phantom airway with WT of 1 mm, which was substantially greater than what we observed. Similarly, Oguma et al²³ found reductions in measurement error of 5% to 10% with a lung reconstruction algorithm or equivalent, depending on the specific scanner used. Both of these reconstruction algorithms are “sharper” than the reconstruction kernels used in our study, which were chosen because they are the same or similar to those used in ongoing multicenter SARP, COPDGene, and Subpopulations and Intermediate Outcome Measures in COPD studies. In addition, the more pronounced difference between the 2 scanners used in our study in measures of

TABLE 5. Airway Measurements by FOV and Airway Size

Airway Metric	Airway Size	Mean Value ± SD			P			
		30-cm FOV	15-cm FOV	10-cm FOV	ANOVA*	10 cm vs. 30 cm†	15 cm vs. 30 cm†	10 cm vs. 15 cm†
WT, mm	Large	1.425 ± 0.161	1.398 ± 0.176	1.396 ± 0.186	<0.0001	<0.0001	<0.0001	0.8930
	Small	1.260 ± 0.113	1.229 ± 0.125	1.219 ± 0.125	<0.0001	<0.0001	<0.0001	0.0374
WA, mm ²	Large	25.873 ± 4.497	25.139 ± 4.724	25.150 ± 5.007	0.0001	0.0007	0.0006	0.9978
	Small	14.181 ± 2.510	13.815 ± 2.590	13.600 ± 2.644	<0.0001	<0.0001	0.0024	0.1042
WA%‡	Large	64.047 ± 3.611	64.043 ± 3.648	63.888 ± 3.826	0.5392	N/A	N/A	N/A
	Small	77.708 ± 2.014	76.891 ± 2.119	76.800 ± 2.134	<0.0001	<0.0001	<0.0001	0.8175
Pi10, mm	Large	4.399 ± 0.333	4.348 ± 0.355	4.328 ± 0.387	0.0026	0.0023	0.0382	0.5658
	Small	4.538 ± 0.281	4.449 ± 0.312	4.437 ± 0.309	<0.0001	<0.0001	<0.0001	0.7864
ID, mm	Large	4.115 ± 0.363	4.125 ± 0.328	4.128 ± 0.357	0.8115	N/A	N/A	N/A
	Small	2.151 ± 0.224	2.162 ± 0.196	2.167 ± 0.210	0.5768	N/A	N/A	N/A

*Overall test of 10-cm FOV vs. 15-cm FOV vs. 30-cm FOV at specified airway size (large or small).

†Pairwise comparison using Tukey correction at specified airway size (large or small).

‡WA% is dimensionless and calculated as follows: WA/total area × 100.

N/A indicates not applicable.

the smallest phantom airway most likely reflects the slightly greater “sharpness” of the GE Standard compared with the Siemens B35f kernel, increasing the resolvability of smaller structures, as the Siemens B43f kernel may be a closer correlate of GE Standard kernel measurements.²⁴

To our knowledge, no studies have explored the effect of reduced FOV on airway wall measurements in humans. The exact airway wall dimensions in a living human subject are unknown. However, with the exception of WT in the largest phantom airway, we found that the changes in wall and luminal measures observed in healthy and asthma participants were similar in direction and magnitude to those found in the phantom. Therefore, it is likely that in humans, measurements obtained at a smaller FOV and in-plane voxel size provide a real though only marginally more accurate assessment of airway dimensions. This suggests that with a medium-smooth reconstruction kernel on current CT systems, the measurement accuracy of a standard FOV that fully encompasses both sides of the lungs is nearly optimized for segmental and subsegmental bronchi.

The greater improvements in accuracy of airway measurements found by previous phantom studies that used sharper image reconstruction kernels suggests that sharper kernels may be needed to fully obtain the benefits to spatial resolution of a reduced FOV in human airways. This may be important in small airways, where partial volume effects are greatest^{10,13} and which are relevant to airflow obstruction in chronic obstructive pulmonary disease²⁵ and to the pathogenesis of asthma.²⁶ We found that WA% was essentially the same in large airways but decreased in magnitude in small airways when reducing FOV from 30 to 15 cm, suggesting that small airways may benefit more from the small improvement in accuracy when reducing FOV. The lack of further accuracy improvement at a 10-cm FOV compared with a 15-cm FOV suggests that a 15-cm FOV is approaching the limits of CT resolution with medium-smooth image reconstruction, although further improvements may occur at 10 cm with sharp image reconstruction (Rodriguez et al,²⁷ presented at the 2012 Radiological Society of North America Scientific Assembly and Annual Meeting).

Our results also likely depend in part on the image analysis algorithms used. Similar to previous findings from Estepar et al,²⁸ we found that PC is preferable to FWHM as an edge detection algorithm for smaller airways due to superior accuracy and fewer errors in segmentation of human airways, particularly when a blood vessel abuts a portion of the airway wall. Moreover, FWHM is overly sensitive to the maximum attenuation of the wall, which becomes ambiguous for smaller airways.¹⁰ Achenbach et al¹³ found that decreasing voxel size by increasing matrix size from 512² to 1024² reduced error in tube thickness measurements using the FWHM method, but did not affect error when using a more accurate integral-based method. Similarly, Saba et al¹² showed that a 15-cm FOV produced more accurate measurements than either 25- or 35-cm FOV in phantom measurements of tube radius using both the FWHM method and a custom model-based method, with greater error reductions with the custom method. The previously noted results of Takahashi et al²² were obtained using a watershed segmentation algorithm. Dedicated matching of reconstruction kernel and image analysis algorithm may be needed to achieve optimal results.

There was no significant improvement in correlation between WA% and lung function as FOV was reduced in our study. Because this correlation seemed to trend higher with progressive decrease in FOV, statistical power to detect a difference may have been limited by the sample size, but based on our data, any such effect is likely to be small. However, although the minimal improvement in the airway measurement accuracy with reduced FOV is of

doubtful clinical significance, it may be meaningful in studies with repeated measures of airway remodeling. Haldar et al²⁹ found that WA/body surface area decreased by only 1.1 mm²/m² after administration of mepolizumab in severe refractory asthma. We showed that reducing CT-reconstruction FOV from 30 to 15 cm decreased measurement of raw WA by 0.22 mm², an improvement in accuracy that could have important implications for studies using changes in within-participant CT airway metrics as clinical end points.

Although reducing FOV improved accuracy in general for large phantom airways, we found that WT was underestimated by PC in the largest phantom airway, and reducing FOV minimally increased this underestimation. The measurements obtained with the PC method are partly a function of the “resolution” setting within the Airway Inspector program, which was held constant for all artificial airways. Increasing the resolution settings produced increased WT measurements for all artificial airways (data not shown) and may be more appropriate for airways similar in size to the largest phantom airway. There were very few human airways of the same caliber as the largest phantom airway, suggesting that this phenomenon did not have a great impact on our human airway data. However, the ideal methodology for measurement of larger airways with PC needs further investigation.

There are a few limitations with our study. Restriction of image analysis to the transverse plane limited the improvement in partial volume effects which might have been afforded by decreasing the in plane voxel size when airways were not exactly perpendicular to the reconstructed plane. Although we did not evaluate the effect of scanner type on human airway measurements, our phantom data suggest that consistency of scanner type and kernel is important for making reliable comparisons. However, this does not impact the human airway data in our study due to the paired nature of the comparisons on multiple FOV reconstructions within each acquisition. Finally, the study results depend, in part, on the inherent resolution of the specific scanners used and could be different with other scanner models. As scanner resolution improves, it is expected that a reduced FOV will further aid in the extraction of more accurate measures of airway measurements, especially in more peripheral airway segments. In addition, we expect that greater improvement can be realized with current scanners by use of higher-resolution reconstruction kernels. Larger matrix sizes implemented in certain CT scanners also effectively decrease voxel size and theoretically offer the same benefits as reducing FOV.

In conclusion, we demonstrate that in both a phantom model and human subjects, the reduction of voxel size through a reduction of FOV to 15 cm improves accuracy of the measurement of CT measures of airway WT. However, the observed differences were very small using current CT scanner technology with kernels typical of current clinical trial protocols. Studies of CT airway remodeling in obstructive lung disease, particularly those with comparative or longitudinal outcomes, should consider whether the small expected gain in accuracy afforded by reducing FOV with medium-smooth kernels is of potential benefit. Future studies are necessary to evaluate the role of sharper reconstruction kernels in maximizing the accuracy gained when CT-reconstruction FOV is reduced.

ACKNOWLEDGMENTS

The authors thank Dr Raúl San José Estépar (Brigham and Women's Hospital, Harvard Medical School, Department of Radiology, Boston, MA) and Dr Barbara Lutey (Washington University School of Medicine, St Louis, MO) for their invaluable assistance with Airway Inspector.

REFERENCES

- James AL, Pare PD, Hogg JC. The mechanics of airway narrowing in asthma. *Am Rev Respir Dis*. 1989;139:242–246.
- Hoshino M, Nakamura Y, Sim JJ. Expression of growth factors and remodelling of the airway wall in bronchial asthma. *Thorax*. 1998;53:21–27.
- James AL, Elliot JG, Jones RL, et al. Airway smooth muscle hypertrophy and hyperplasia in asthma. *Am J Respir Crit Care Med*. 2012;185:1058–1064.
- Hirota N, Martin JG. Mechanisms of airway remodeling. *Chest*. 2013;144:1026–1032.
- Cohen L, E X, Tarsi J, Ramkumar T, et al. Epithelial cell proliferation contributes to airway remodeling in severe asthma. *Am J Respir Crit Care Med*. 2007;176:138–145.
- Benayoun L, Druilhe A, Dombret MC, et al. Airway structural alterations selectively associated with severe asthma. *Am J Respir Crit Care Med*. 2003;167:1360–1368.
- Niimi A, Matsumoto H, Amitani R, et al. Airway wall thickness in asthma assessed by computed tomography. Relation to clinical indices. *Am J Respir Crit Care Med*. 2000;162:1518–1523.
- Kasahara K, Shiba K, Ozawa T, et al. Correlation between the bronchial subepithelial layer and whole airway wall thickness in patients with asthma. *Thorax*. 2002;57:242–246.
- Aysola RS, Hoffman EA, Gierada D, et al. Airway remodeling measured by multidetector CT is increased in severe asthma and correlates with pathology. *Chest*. 2008;134:1183–1191.
- Reinhardt JM, D'Souza ND, Hoffman EA. Accurate measurement of intrathoracic airways. *IEEE Trans Med Imaging*. 1997;16:820–827.
- Lutey BA, Conradi SH, Atkinson JJ, et al. Accurate measurement of small airways on low-dose thoracic CT scans in smokers. *Chest*. 2013;143:1321–1329.
- Saba OI, Hoffman EA, Reinhardt JM. Maximizing quantitative accuracy of lung airway lumen and wall measures obtained from x-ray CT imaging. *J Appl Physiol*. 2003;95:1063–1075.
- Achenbach T, Weinheimer O, Dueber C, et al. Influence of pixel size on quantification of airway wall thickness in computed tomography. *Journal of computer assisted tomography*. 2009;33:725–730.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:319–338.
- American Thoracic Society. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. *Am J Respir Crit Care Med*. 2000;162:2341–2351.
- Kelly HW. Rationale for the major changes in the pharmacotherapy section of the National Asthma Education and Prevention Program guidelines. *J Allergy Clin Immunol*. 2007;120:989–994 quiz 995–986.
- Sieren JP, Newell JD, Judy PF, et al. Reference standard and statistical model for intersite and temporal comparisons of CT attenuation in a multicenter quantitative lung study. *Med Phys*. 2012;39:5757–5767.
- Estepar RSJ, Washko GG, Silverman EK, et al. Airway Inspector: an open source application for lung morphometry. In: *First International Workshop on Pulmonary Image Processing*. New York, NY; Lulu.com, 2008: 293–302.
- Amirav I, Kramer SS, Grunstein MM, et al. Assessment of methacholine-induced airway constriction by ultrafast high-resolution computed tomography. *J Appl Physiol*. 1993;75:2239–2250.
- Nakano Y, Wong JC, de Jong PA, et al. The prediction of small airway dimensions using computed tomography. *Am J Respir Crit Care Med*. 2005;171:142–146.
- Li B, Avinash GB, Hsieh J. Resolution and noise trade-off analysis for volumetric CT. *Med Phys*. 2007;34:3732–3738.
- Takahashi M, Okada H, Oguni N, et al. How accurate is CT morphometry of airway? Phantom and clinical validation study. *Eur J Radiol*. 2011;80:e524–e530.
- Oguma T, Hirai T, Niimi A, et al. Limitations of airway dimension measurement on images obtained using multi-detector row computed tomography. *PLoS One*. 2013;8:e76381.
- Solomon JB, Christianson O, Samei E. Quantitative comparison of noise texture across CT scanners from different manufacturers. *Med Phys*. 2012;39:6048–6055.
- McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med*. 2011;365:1567–1575.
- van den Berge M, ten Hacken NH, Cohen J, et al. Small airway disease in asthma and COPD: clinical implications. *Chest*. 2011;139:412–423.
- Rodriguez A, Fain S, Ranallo F, et al. Comparisons of lung CT airway measurement accuracy for filtered back projection and iterative reconstructions at low X-ray dose. Radiological Society of North America 2012 Scientific Assembly and Annual Meeting, November 25 – November 30, 2012 ,Chicago IL. Available at: <http://archive.rsna.org/2012/12034515.html>. Accessed April 16, 2015.
- Estepar RSJ, Washko GG, Silverman EK, et al. Accurate airway wall estimation using phase congruency. In: *Ninth International Conference on Medical Image Computing and Computer-Assisted Intervention*. Denmark: Springer-Verlag; 2006: 125–134.
- Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med*. 2009;360:973–984.