

CHEST[®]

Official publication of the American College of Chest Physicians



Airway Remodeling Measured by Multidetector CT Is Increased in Severe Asthma and Correlates With Pathology

Ravi S. Aysola, Eric A. Hoffman, David Gierada, Sally Wenzel, Janice Cook-Granroth, Jaime Tarsi, Jie Zheng, Kenneth B. Schechtman, Thiruvamoor P. Ramkumar, Rebecca Cochran, E. Xueping, Chandrika Christie, John Newell, Sean Fain, Talissa A. Altes and Mario Castro

Chest 2008;134;1183-1191; Prepublished online July 18, 2008;
DOI 10.1378/chest.07-2779

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
<http://chestjournal.org/cgi/content/abstract/134/6/1183>

CHEST is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright 2007 by the American College of Chest Physicians, 3300 Dundee Road, Northbrook IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder (<http://www.chestjournal.org/misc/reprints.shtml>). ISSN: 0012-3692.

A M E R I C A N C O L L E G E O F
 C H E S T
P H Y S I C I A N S[®]

Airway Remodeling Measured by Multidetector CT Is Increased in Severe Asthma and Correlates With Pathology*

Ravi S. Aysola, MD; Eric A. Hoffman, PhD; David Gierada, MD; Sally Wenzel, MD, FCCP; Janice Cook-Granroth; Jaime Tarsi, RN, MPH; Jie Zheng; Kenneth B. Schechtman, PhD; Thiruwamoor P. Ramkumar, PhD; Rebecca Cochran; E. Xueping, MD, PhD; Chandrika Christie; John Newell, MD, FCCP; Sean Fain, PhD; Talissa A. Altes, MD; and Mario Castro, MD, MPH, FCCP

Background: To prospectively apply an automated, quantitative three-dimensional approach to imaging and airway analysis to assess airway remodeling in asthma patients.

Methods: Using quantitative software (Pulmonary Workstation, version 0.139; VIDA Diagnostics; Iowa City, IA) that enables quantitative airway segment measurements of low-dose, thin-section (0.625 to 1.25 mm), multidetector-row CT (MDCT) scans, we compared airway wall thickness (WT) and wall area (WA) in 123 subjects participating in a prospective multicenter cohort study, the National Institutes of Health Severe Asthma Research Program (patients with severe asthma, n = 63; patients with mild-to-moderate asthma, n = 35); and healthy subjects, n = 25). A subset of these subjects underwent fiberoptic bronchoscopy and endobronchial biopsies (n = 32). WT and WA measurements were corrected for total airway diameter and area: WT and WA, respectively.

Results: Subjects with severe asthma had a significantly greater WT% than patients with mild-to-moderate asthma and healthy subjects (17.2 ± 1.5 vs 16.5 ± 1.6 [p = 0.014] and 16.3 ± 1.2 [p = 0.031], respectively) and a greater WA percentage (WA%) compared to patients with mild-to-moderate asthma and healthy subjects (56.6 ± 2.9 vs 54.7 ± 3.3 [p = 0.005] and 54.6 ± 2.4 [p = 0.003], respectively). Both WT% and WA% were inversely correlated with baseline FEV₁ percent predicted ($r = -0.39$, p < 0.0001 and $r = -0.40$, p < 0.0001, respectively) and positively correlated with response to a bronchodilator ($r = 0.28$, p = 0.002 and $r = 0.35$, p < 0.0001, respectively). The airway epithelial thickness measure on the biopsy sample correlated with WT% ($r = 0.47$; p = 0.007) and WA% ($r = 0.52$; p = 0.003). In the same individual, there is considerable regional heterogeneity in airway WT.

Conclusion: Patients with severe asthma have thicker airway walls as measured on MDCT scan than do patients with mild asthma or healthy subjects, which correlates with pathologic measures of remodeling and the degree of airflow obstruction. MDCT scanning may be a useful technique for assessing airway remodeling in asthma patients, but overlap among the groups limits the diagnostic value in individual subjects. (CHEST 2008; 134:1183–1191)

Key words: airway remodeling; asthma; chest CT scan

Abbreviations: LA = luminal area; LA% = percent of luminal area; LR = lamina reticularis; MDCT = multidetector-row CT; PC₂₀ = provocative concentration of methacholine causing a 20% fall in FEV₁; RUL = right upper lobe; SARP = Severe Asthma Research Program; TA = total area; WA = wall area; WA% = wall area percent; WT = wall thickness; WT% = wall thickness percent

Studies of the airways of patients who die from asthma demonstrate thickened airway walls due to increases in smooth muscle mass, infiltration with inflammatory cells, deposition of connective tissue,

vascular changes, and mucous gland hyperplasia, a condition that is termed *airway remodeling*.^{1–4} Airway remodeling may be a feature of milder and even asymptomatic asthma.^{5–7} The remodeling of airways

can result in the worsening of airway narrowing, airflow obstruction, and disease progression.^{8,9}

Airway remodeling in asthma patients has been studied *in vivo* by performing endobronchial biopsies, the samples from which can then be evaluated for structural and inflammatory changes.^{10–12} Multi-detector CT (MDCT) scan studies have recently been used to evaluate the extent of airway wall thickening as a noninvasive, highly reproducible method for studying individual airways. Several studies^{7,13–15} using MDCT scanning have demonstrated that the airway walls of asthmatic patients are thicker than those of healthy subjects, and that airway wall thickness (WT) is related to the severity of disease and airflow obstruction. This thickening may be partially reversible with inhaled corticosteroid treatment in steroid-naïve patients and may increase in the absence of inhaled corticosteroid treatment. The airway lumen area of stable patients with asthma is not narrowed compared with that of healthy control subjects and may even be dilated in those with more severe disease.¹⁶ These studies are often limited by the number of airways studied, small subject numbers, or the use of semi-quantitative techniques. Thus, the purpose of our study was to apply an automated airway analysis software comparing airway wall measurements among patients with severe and mild-to-moderate asthma and healthy subjects, and to correlate this with remodeling measurements of biopsy specimens from matched airway segments.

MATERIALS AND METHODS

Study Design

As part of the Severe Asthma Research Program (SARP) at the National Institutes of Health, a prospective cohort of subjects,

*From the Division of Pulmonary and Critical Care Medicine (Drs. Aysola, Ramkumar, Xueping, and Castro, Ms. Tarsi, Ms. Cochran, and Ms. Christie), the Department of Radiology (Dr. Gierada), and the Division of Biostatistics (Ms. Zheng and Dr. Schechtman), Washington University School of Medicine, St. Louis, MO; the Department of Radiology (Dr. Hoffman and Ms. Cook-Granroth), Carver College of Medicine, University of Iowa, Iowa City, IA; the University of Pittsburgh Medical Center (Dr. Wenzel), Pittsburgh, PA; National Jewish Medical and Research Center (Dr. Newell), Denver, CO; the University of Wisconsin (Dr. Fain), Madison, WI; and Children's Hospital of Philadelphia (Dr. Altes), Philadelphia, PA.

This research was supported by National Institutes of Health grants HL69149, HL64368, HL69349, HL69170, HL-69155, HL69174, HL69130, HL69167, HL69116, and HL69174–05. Manuscript received December 2, 2007; revision accepted June 5, 2008.

Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml).

Correspondence to: Mario Castro, MD, MPH, FCCP, Washington University School of Medicine, Campus Box 8052, 660 South Euclid Ave, St. Louis, MO 63110-1093; e-mail: castrm@wustl.edu

DOI: 10.1378/chest.07-2779

following informed consent, underwent detailed testing and MDCT scanning using a standardized protocol that was developed by the SARP.¹⁷ MDCT scan data were analyzed and compared in a total of 123 subjects, as follows: patients with severe asthma, $n = 63$; patients with mild-to-moderate asthma, $n = 35$; healthy subjects, $n = 25$. In a subset of patients who underwent airway biopsies ($n = 32$), we correlated segmental airway WT and wall area (WA) from MDCT scans with measures of airway remodeling from biopsy specimens, including epithelial and lamina reticularis (LR) thickness, from the corresponding segment. All subjects at the Washington University SARP site were given the option of participating in the airway biopsy substudy. The study was approved by Institutional Review Board at each site and monitored by an independent Data and Safety Monitoring Board.

Human Subjects

The inclusion criteria by group were as follows: for healthy subjects: 18 to 60 years of age; in good overall health; no smoking within past 5 years; < 5 pack-years of smoking; and a provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀) of > 16 mg/mL; for patients with mild-to-moderate asthma¹⁸: 18 to 60 years of age; physician diagnosis of asthma; receiving asthma therapy for > 12 months; daytime asthma symptoms more than two times per week but less than continual and/or nocturnal asthma symptoms more than two times per month but less than nightly; no smoking within the past 5 years and < 5 pack-years of smoking; no concurrent lung disease; and PC₂₀ of ≤ 8 mg/mL or $\geq 15\%$ improvement in FEV₁ postbronchodilator therapy; for patients with severe asthma: 18 to 60 years of age; subjects with one or both of two major criteria and two of the minor criteria (American Thoracic Society workshop¹⁹). The major criteria include (in order to achieve control to a level of mild-to-moderate persistent asthma), the following: (1) continuous or nearly continuous treatment with (*ie*, $\geq 50\%$ of the previous year) oral corticosteroids; or (2) treatment with high-dose inhaled corticosteroids (beclomethasone [$> 1,260$ $\mu\text{g}/\text{d}$]; budesonide [$> 1,200$ $\mu\text{g}/\text{d}$]; flunisolide [$> 2,000$ $\mu\text{g}/\text{d}$]; fluticasone [> 880 $\mu\text{g}/\text{d}$]; or triamcinolone [$> 2,000$ $\mu\text{g}/\text{d}$]). The minor criteria include the following: (1) daily treatment with a long-term controller medication in addition to inhaled corticosteroids (*eg*, long-acting β -agonist, theophylline, or leukotriene antagonist); (2) asthma symptoms requiring short-acting β -agonist use on a daily or nearly daily basis; (3) persistent airflow obstruction (FEV₁, $< 80\%$ predicted and diurnal peak flow variability $> 20\%$); (4) one or more urgent care visits for asthma per year; (5) three or more oral corticosteroid "bursts" per year; (6) prompt deterioration with $\leq 25\%$ reduction in the dosage of oral or inhaled corticosteroids; and (7) a near-fatal asthma event in the past. In these subjects with severe asthma, conditions other than asthma were excluded, exacerbating factors were treated, and the subject did not have a history of poor adherence to treatment.

CT Scan Technique

All subjects underwent an MDCT scan of the chest with 16 or 64 detector rows (Light Speed Ultra 16; GE Healthcare; Milwaukee, WI; or Volume Zoom, Sensation 16 or 64; Siemens; Forchheim, Germany) after maximal bronchodilation with albuterol (540 to 720 μg) to minimize the effect of acute bronchoconstriction on airway dimensions. Subjects were administered increasing doses of albuterol until the FEV₁ percent predicted difference was $\leq 5\%$ or a maximal dose of albuterol (8 puffs or 720 μg) was reached. Suspended full inspiratory measurements were obtained at the following settings: for the GE scanner: pitch, 1.675 to 1.75 (mm table increment per rotation/detector

collimation × number of detectors); rotation time, 0.6 s; 120 kV; reconstructed slice thickness, 0.625 to 1.25 mm; and medium smooth “standard” reconstruction algorithm; for the Siemens scanner: pitch, 1.5; rotation time, 0.5 s; 120 kV; reconstructed slice thickness, 1 mm; medium smooth reconstruction algorithm; and effective, mAs 30 to 57. To obtain isotropic voxels, the slice reconstruction interval was set to equal the in-plane spatial resolution (field of view measured in millimeters per 512 pixels).

MDCT Scan Airway Evaluation Software

MDCT scans were analyzed using automated, quantitative software that was designed to reliably label and segment the first five to six airway generations, and to allow the accurate measurement of airway wall and lumen diameters obtained perpendicular to the long axis of each airway (Pulmonary Workstation, version 0.139; VIDA Diagnostics; Iowa City, IA).^{20–23} Previous studies^{24,25} have validated the lung and airway segmentation methods when compared to manual measurements. Airway measurements for each segment were made at each centerline voxel and were averaged over the middle third of the segment. The specific MDCT scan measurements used included airway WT, percentage of WT (WT%), WA, percentage of WA (WA%), luminal area (LA) and percentage of LA (LA%). The calculations are as follows: WT = average outer diameter – average inner diameter; WT% = (WT/average outer diameter) × 100; WA = total area (TA) – LA; WA% = (WA/TA) × 100; and LA% = (LA/TA) × 100 (Fig 1).

In the primary analysis, we averaged third-generation airway wall measurements for all automatically segmented and labeled airways in each subject. An average of 18 third-generation airways per subject were measured (9 for each lung). In the secondary analysis of subjects who underwent biopsies, we obtained cross-sectional CT scan measurements of each biopsied airway in a plane perpendicular to the airway long-axis at a distance 30% of the segment length distal to the origin of the airway segment. Two independent readers trained in the use of the Pulmonary Workstation were blinded to the subject status or the results of the biopsy measurements. Interrater reliability on a random sample of 50 subjects between these two readers was excellent (intraclass correlation, 0.98).

Pulmonary Function Tests

Spirometry, methacholine bronchoprovocation tests, and plethysmographic lung volume measurements were performed within 1 to 2 days of the MDCT scan among the SARP sites in accordance with standardized American Thoracic Society criteria.^{26,27} Subjects were asked to abstain from the use of long-acting β_2 agonists for 12 h and from the use of short-acting β_2 agonists for 4 h prior to assessment. Spirometry was performed before and after therapy with a short-acting β_2 -agonist (4 puffs or 360 μ g of albuterol) was delivered by metered-dose inhaler and spacer.

Endobronchial Biopsies

A subset of 32 subjects (15 subjects with severe asthma; 9 subjects with mild-to-moderate asthma; and 8 healthy subjects) underwent bronchoscopy, and 12 to 16 endobronchial biopsy specimens were obtained from the third-generation segmental carinas of the upper lobes. Three readers independently measured the areas of the epithelium and LR of at least three biopsy specimens with intact airway epithelium using software for morphometric analysis (ImageJ software; <http://rsbweb.nih.gov/ij/>). The areas of the epithelium and LR were normalized for the length of the basement membrane, yielding an epithelial and LR ratio.²⁸ The average of these measurements made in triplicate was then used for subsequent analysis.

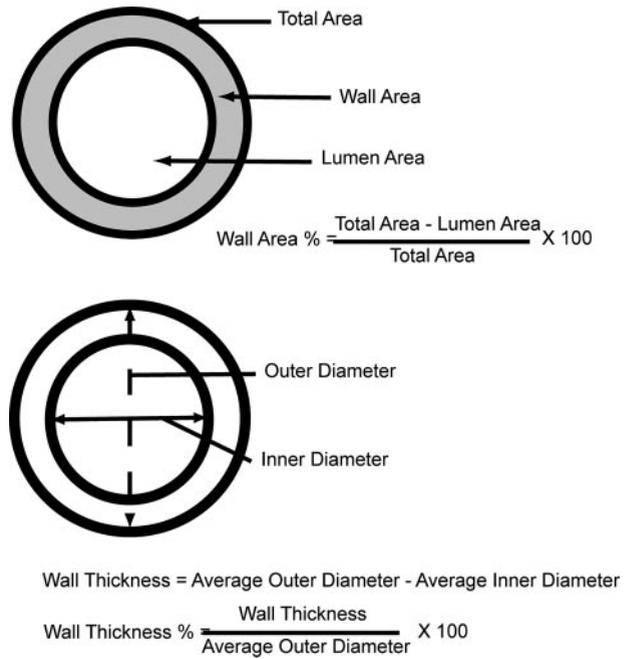


FIGURE 1. Airway measurements by MDCT scanning. Multiple airway measurements can be performed (using the Pulmonary Workstation program; VIDA Diagnostics). Depicted are the two primary measurements used in the current study. WT is measured over the middle one third of each segment at each centerline voxel. This value is averaged, resulting in a single WT value for each segment. The average outer diameter for the segment is calculated in a similar fashion. The WT% for each segment is calculated by dividing the WT by the average outer diameter. TA and LA are similarly calculated at each centerline voxel and averaged over the middle one third of the segment. WA was calculated by subtracting the LA from the TA. WA% was calculated by dividing the WA by the TA.

Statistical Analysis

All data were analyzed using analysis of variance and χ^2 tests to compare continuous and categorical variables across groups (SAS, version 9; SAS Institute; Cary, NC). Stepwise multiple linear regression identified variables that had independent significant associations with outcome measures that included FEV₁ percent predicted, WA%, and WT%. Variables were retained in these models if they had a significant ($p < 0.05$) or borderline significant ($p < 0.1$) association with the outcome measure.

RESULTS

Demographics

The characteristics of the subjects in our study (Table 1) demonstrated that those with severe persistent asthma, on average, were older, reported more frequent symptoms of allergies, and had elevated levels of IgE, increased airway hyperresponsiveness, and decreased baseline FEV₁ percent predicted compared to patients with mild-to-moderate asthma and healthy subjects. Subjects in the biopsy subset were representative of the overall cohort (Table 1) with the

Table 1—Group Characteristics*

Characteristics	Healthy Subjects (n = 25)	Patients With Mild-to-Moderate Asthma(n = 35)	Patients With Severe Asthma(n = 63)	p Value†
Age,‡ yr	30.2 (8)	34.4 (10.6)	37.8 (13.3)	0.023
Female sex§	16 (64)	21 (60)	37 (59)	0.9
Age at diagnosis of asthma,‡ yr		13.6 (13.8)	13.4 (14.9)	0.9
Duration of asthma,† yr		20.8 (13.2)	24.4 (13.2)	0.2
Baseline FEV ₁				< 0.001
L	3.64	2.82	1.98	
% predicted	101	81	61	
FEV ₁ PC ₂₀ ,‡ mg/mL		1.66 (1.67)	1.20 (1.80)	0.051
Atopic, %	33.3	100	100	< 0.001
IgE,‡ IU	97 (174)	226 (291)	456 (697)	< 0.001
Medication use, %				
Any β-agonist		88.2	98.3	< 0.001
Long-acting β-agonist		41.2	91.7	< 0.001
Inhaled corticosteroid		52.9	98.3	< 0.001
Oral corticosteroid		2.9	60	< 0.001
ED or hospital visits in the past 12 mo, %		19.2	42.9	< 0.001
Hospitalizations in past 12 mo, %		0	25.9	0.002
History of intubation, %		0	20.3	0.001

*ED = emergency department.

†Comparing groups by χ^2 or analysis of variance after IgE was log transformed. Nonparametric Wilcoxon test was used for PC₂₀ comparison.

‡Values are given as mean (SD).

§Values are given as No. (%).

||Percentage of subjects with one or more positive allergy skin test results.

exception that patients with mild-to-moderate asthma had an earlier onset of asthma (11.6 vs 13 years, respectively; $p = 0.01$) and a greater number of emergency department visits within the last 12 months (50% vs 5.6%, respectively; $p = 0.02$).

MDCT Scan Airway WT/WA/LA

There was no significant difference in average WT among the groups. To account for differences in airway size, we calculated the WT% (Fig 1) for the labeled airways in each subject. Patients with severe asthma had significantly greater WT% than those with mild-to-moderate asthma and healthy subjects (Fig 2, Table 2). There was no significant difference in WT% between patients with mild-to-moderate asthma and healthy subjects. The increase in WT% inversely correlated with baseline FEV₁ percent predicted ($r = -0.39$; $p < 0.0001$), and positively correlated with the change in FEV₁ percent predicted post-bronchodilator therapy ($r = 0.28$; $p = 0.002$). This finding was primarily due to the relationship between WT% and FEV₁ percent predicted ($r = -0.47$; $p = 0.0003$) in patients with severe asthma. There was no significant relationship between WT% and FEV₁ percent predicted in patients with mild-to-moderate asthma and healthy subjects. There was no significant correlation between WT% and FEV₁ PC₂₀.

There was no statistically significant difference in WA among the groups. The analysis of WA% showed

that patients with severe asthma had greater WA% compared to patients with mild-to-moderate asthma and healthy subjects. There was no significant difference in WA% between patients with mild-to-moderate asthma and healthy subjects (Fig 2, Table 2). WA% was inversely correlated with baseline FEV₁ percent predicted ($r = -0.4$; $p < 0.0001$), and positively correlated with change in FEV₁ percent predicted post-bronchodilator therapy ($r = 0.35$; $p < 0.0001$). The correlation between WA% and baseline FEV₁ percent predicted was due to the relationship in patients with severe asthma ($r = -0.49$; $p = 0.0001$). There was a significant inverse correlation between WA% with FEV₁ PC₂₀ (all asthmatic subjects: $r = -0.29$; $p = 0.02$; patients with severe asthma: $r = -0.48$; $p = 0.01$).

LA was not significantly different among the groups. Patients with severe asthma had a smaller LA% compared to those with mild-to-moderate asthma and healthy subjects. There was no significant difference in LA% between patients with mild-to-moderate asthma and healthy subjects (difference was not significant).

Segmental MDCT Scan Comparisons

Individual airways segments were compared among the three groups in regard to WT% and WA%. WT% in a few airways and WA% in most airways were significantly greater in patients with severe asthma compared to those with mild-to-moderate asthma and healthy subjects (Table 3). Because segmental WT

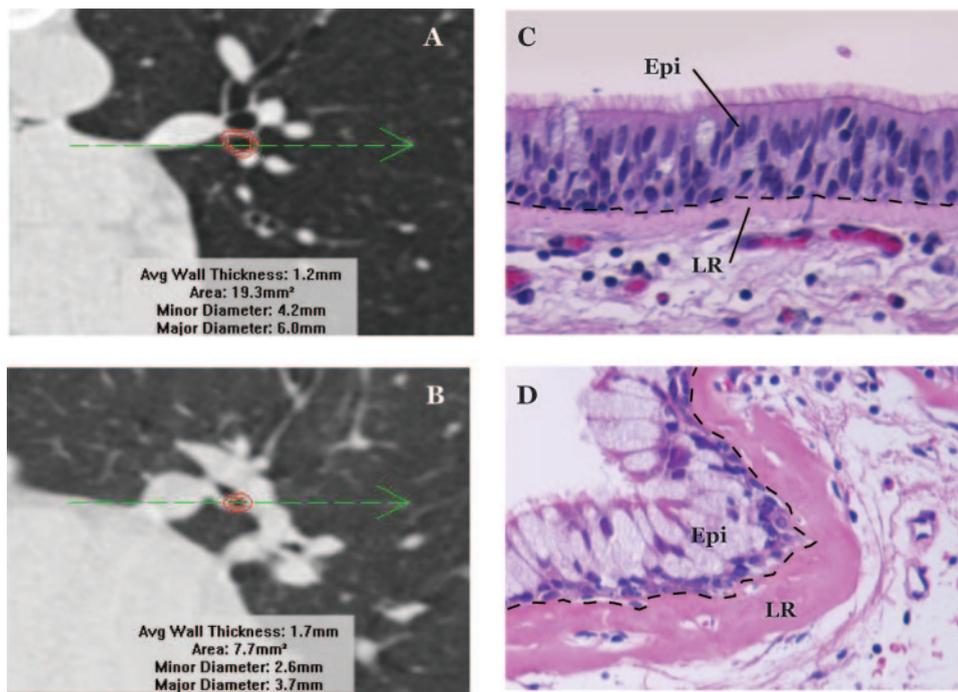


FIGURE 2. MDCT scan images and bronchial biopsy specimens from healthy subjects and patients with severe asthma. Representative images from matching MDCT scan analyses and hematoxylin-eosin-stained sections from an endobronchial biopsy specimen from a healthy control subject (*top left, A*, and *top right, C*) and a patient with severe asthma (*bottom left, B*, and *bottom right, D*) are demonstrated. The MDCT scan analysis was performed using the Pulmonary Workstation software (VIDA Diagnostics), and a screen capture of the cross-sectional MDCT scan image is demonstrated. The hematoxylin-eosin-stained sections were obtained from endobronchial biopsy specimens that were processed as described in the “Materials and Methods” section. The epithelial layer (Epi), LR, and the basement membrane (dashed line) are indicated.

measurements are not independent of each other, we calculated a slope of airway WT% and WA% from the apex to the base of the lung in each individual subject.²¹ The slopes for WT% and WA% were not significantly different among the groups.

The range (*ie*, the minimum to maximum measurement) in airway thickness across segments per subject for WT% was 9.7 to 29.9 for healthy subjects,

9.7 to 29.6 for patients with mild-to-moderate asthma, and 9.8 to 30.1 for patients with severe asthma; for WA%, the range was 38.6 to 65.5 for healthy subjects, 38.9 to 64.7 for patients with mild-to-moderate asthma, and 39.0 to 67.3 for patients with severe asthma. The variability of WA% across segments was significantly different among groups, with the patients with severe asthma ($28.3 \pm$

Table 2—MDCT Scan Airway Measurements by Group*

MDCT Scan Measurement	Healthy Subjects (n = 25)	Patients With Mild-to-Moderate Asthma (n = 35)	Patients With Severe Asthma (n = 63)	p Value†	
				Healthy Subjects vs Patients With Severe Asthma	Patients With Moderate-to-Severe Asthma vs Patients With Severe Asthma
WT, mm	1.59 (0.13)	1.66 (0.14)	1.66 (0.2)	NS	NS
WT%, mm	16.3 (1.2)	16.5 (1.6)	17.2 (1.5)	0.031	0.014
WA, mm ²	41.2 (5.5)	44.1 (6.4)	42.2 (7.4)	NS	NS
WA%	54.6 (2.4)	54.7 (3.3)	56.6 (2.9)	0.003	0.005
LA, mm	42.5 (7)	45.9 (9.3)	42 (9.1)	NS	NS
LA%, mm	45.4 (2.4)	45.3 (3.3)	43.4 (2.9)	0.005	0.003
TA, mm ²	83.7 (12.2)	90 (15)	84.1 (16.1)	NS	NS

*Values are given as the mean (SD), unless otherwise indicated. NS = not significant.

†Comparisons were made by *t* test.

Table 3—MDCT Scan Airway Wall Measurements Among Individual Airway Segments With Respect to Anatomic Location*

Bronchial Segment	WT%				WA%					
	Healthy Subjects (n = 25)	Patients With Mild-to-Moderate Asthma (n = 35)	Patients With Severe Asthma (n = 63)	p Value†		Healthy Subjects (n = 25)	Patients With Mild-to-Moderate Asthma (n = 35)	Patients With Severe Asthma (n = 63)	p Value†	
				S vs M	S vs N				S vs M	S vs N
L1	20.6 (3.5)	21 (4.5)	21.7 (4.6)			63.2 (3.9)	62.7 (4.1)	63.7 (3.0)		
L2	21 (5.6)	23.3 (6.4)	20.8 (5.3)			63.8 (5.8)	60.2 (5.3)	62.2 (3.7)		
L3	18.9 (7.9)	17.3 (3.6)	18.7 (4.2)			57.1 (4.5)	58 (5.2)	60.3 (4.5)	0.029	0.008
L4	18.6 (5.9)	22 (5.6)	20.2 (5.3)			58.9 (4.5)	58.6 (4.7)	61.1 (4.1)	0.030	0.073
L5	19.7 (4.1)	21.5 (7.8)	20.1 (4.5)			58.8 (4.4)	60.8 (3.9)	60.9 (4.3)		
L6	17.2 (4.6)	17.2 (4.5)	18.3 (4.6)			57.4 (4.7)	57.6 (5.5)	60.1 (5.3)	0.027	0.031
L8	17.9 (4.3)	17.8 (5.8)	19.5 (6.2)			57.2 (3.9)	57.9 (4.8)	61.3 (4.5)	0.001	< 0.001
L9	17 (3.1)	19 (5.4)	18.8 (5.0)			58.2 (3.7)	59.4 (4.6)	60.2 (4.7)		
L10	17.2 (3.9)	17 (4.7)	18.8 (4.1)			57.9 (4.3)	57.4 (4.7)	60.2 (4.4)	0.006	0.041
R1	17.4 (3.4)	17.4 (3.9)	19.4 (4.0)	0.020	0.032	59 (5.3)	60 (5.5)	62.6 (4.5)	0.015	0.003
R2	18.9 (4.5)	18.8 (4.5)	19.1 (4.2)			59 (3.9)	58.3 (4.3)	60.3 (3.7)	0.027	0.076
R3	18.4 (5.3)	17.6 (3.6)	17.8 (3.4)			58.4 (3.3)	58 (5.3)	60.1 (4.5)		
R4	20 (5.1)	18.5 (4.7)	21.1 (5.5)			60 (2.5)	59 (5.3)	61.4 (4.4)	0.013	0.229
R5	19.5 (4.1)	20.2 (4.3)	21.2 (4.8)			58.7 (3.0)	60.1 (4.6)	62.4 (4.0)	0.014	0.001
R6	18.3 (3.7)	19.4 (5.2)	19.4 (5.8)			58.6 (3.7)	58.3 (4.7)	58.9 (5.3)		
R7	20 (4.7)	19.6 (4.0)	21.2 (5.7)			61 (4.6)	61.3 (4.0)	64.3 (4.6)	0.002	0.003
R8	19.5 (5.8)	20 (5.4)	20.1 (5.2)			60 (3.9)	59.4 (5.0)	61.2 (4.8)		
R9	17.6 (2.7)	18.8 (4.4)	20.1 (3.6)	0.153	0.009	59.1 (4.1)	58.6 (4.2)	61.7 (3.8)	0.001	0.011
R10	18.5 (3.4)	19 (5.2)	18.8 (4.3)			59.1 (3.5)	58.7 (5.0)	60.7 (4.8)		
Slope‡	0.02 (0.49)	0.22 (0.44)	0.08 (0.37)			0.05 (0.46)	0.09 (0.44)	-0.004 (0.38)		

*Values are given as the mean (SD), unless otherwise indicated. Only third-generation airways were included; there is no L7 segment. S = patients with severe asthma; M = patients with moderate-to-severe asthma; N = healthy subjects.

†The between-group comparisons were conducted by analysis of variance. The p values for patients with severe persistent asthma vs those with mild-to-moderate persistent asthma and healthy subjects were presented when the p value of the overall F test was < 0.05.

‡For the slope analysis, we calculated a slope of airway WT% and WA% from the measurement of the apex to the base of the lung in each individual subject (B1 to B10), numbered in descending order from apex to base.

3.4) having more variability than those with mild-to-moderate asthma (25.8 ± 3.4) or healthy subjects (26.9 ± 4.0 ; $p = 0.0035$); but, this was not the case for WT% ($p = 0.92$). The WT% and WA% ranges in an individual's segmental airways are highly variable and are dependent on the underlying disease status. However, if one focuses on the right upper lobe (RUL) apical segment (previously used in other studies^{5,15}), there was a statistically significant correlation between the RUL apical segment WA% ($r = 0.75$; $p < 0.0001$) and the WT% ($r = 0.52$; $p < 0.0001$) with all other segments (up to 19).

Multivariate Analysis of WA/WT

The variables that distinguished patients with severe asthma from those with mild-to-moderate asthma and healthy subjects included the following: age; baseline FEV₁ percent predicted and FVC percent predicted; log IgE; and change in FEV₁ post-bronchodilator therapy. We also found that WT% and WA% were significantly greater in patients with severe asthma compared to patients with

mild-to-moderate asthma and healthy subjects. Stepwise multiple regression models used FEV₁ percent predicted, WA%, and WT% as dependent variables. The only significant independent predictors of FEV₁ percent predicted were WT% ($p = 0.0004$) and group ($p < 0.0001$; $R^2 = 0.48$). When WT% was the dependent variable in the stepwise regression, the significant independent correlates were FEV₁ percent predicted ($p < 0.0001$) and history of intubation ($p = 0.04$; $R^2 = 0.415$). The only significant independent correlate of WA% was FEV₁ percent predicted ($p < 0.0001$; $R^2 = 0.331$).

Correlation Between MDCT Scan Airway Indexes and Remodeling

The epithelial thickness ratio was positively correlated with both WT% and WA% ($r = 0.47$, $p = 0.007$; and $r = 0.52$, $p = 0.003$, respectively) [Fig 3]. The relationship between LR thickness ratio and WT% and WA% demonstrated a similar trend ($r = 0.33$, $p = 0.07$; and $r = 0.33$, $p = 0.06$, respectively). The sum of epithelial and LR ratios was also

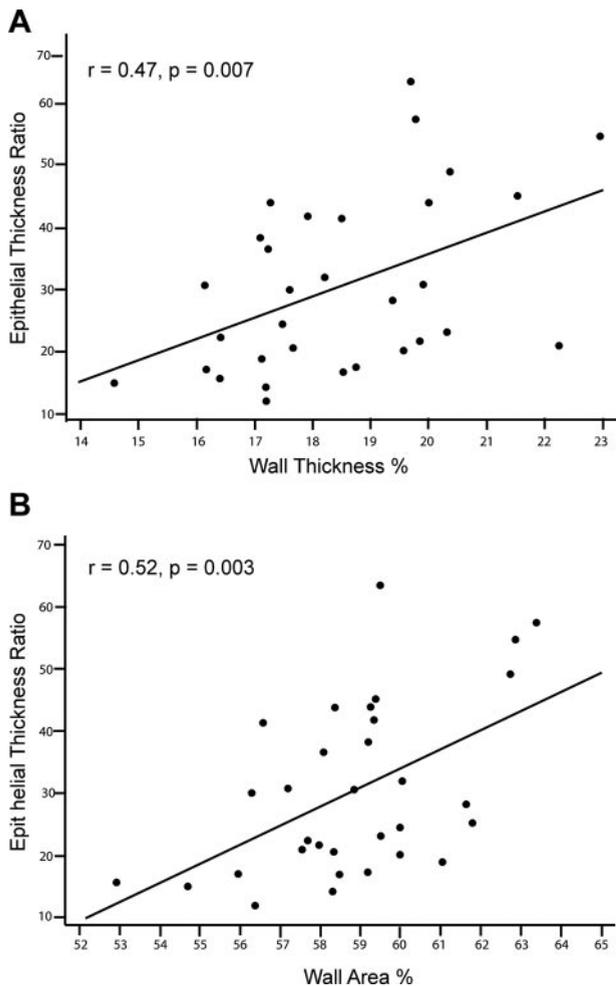


FIGURE 3. MDCT scan WT% and WA% are correlated with airway remodeling. In a subset of patients ($n = 32$), endobronchial biopsies were performed. Epithelial thickness was measured in micrometers and was normalized for the length of the basement membrane, resulting in an epithelial ratio. These morphometric measurements were then correlated with the radiographic indexes WT% and WA%. *Top, A:* WT% is correlated with epithelial thickness ($r = 0.47$; $p = 0.007$). *Bottom, B:* WA% is correlated with epithelial thickness ($r = 0.52$; $p = 0.003$).

positively correlated with WT% and WA% ($r = 0.46$, $p = 0.008$; and $r = 0.49$, $p = 0.004$, respectively).

DISCUSSION

Airway remodeling describes structural changes that in the asthmatic airway collectively result in thickening of the airway wall.^{2,3,8,9} CT imaging of the airways is being developed as a technique to study airway remodeling *in vivo*. Multiple studies^{5–8,13–15} have documented increased airway WT in asthma using CT. Most of these studies^{5,13–15} employed manual tracing methods, using either manual or digital measurement of airway dimensions. These

previous studies using manual tracing methods have demonstrated significant differences in comparing asthma patients to healthy subjects, though these differences may be related to selection bias. Kasahara et al¹³ found that the radiographic measurements of WT and WA were increased in asthma patients, correlated with LR, and inversely related to FEV₁. A pediatric study²⁹ found similar, although less robust, results. To improve objectivity, reproducibility, and efficiency, automated airway segmentation and analysis methods have been implemented.³⁰ However, automated assessments previously have been restricted to those airways that are nearly round in transaxial images, so that the long axis is roughly perpendicular to the scan plane. Consequently, quantitative measurements were obtained only on (nearly) round airways in a limited number of slices, which may lead to potential selection bias as our data demonstrate significant regional heterogeneity in segmental airway remodeling. The automated technique we used eliminated selection bias by segmenting, labeling, and measuring all of the proximal airways, and allowing comparison of those airways that may have been excluded using previous methods.

In this study, we used an automated, quantitative software program to analyze and measure the differences in airway WT between patients with severe asthma and those with milder disease. We found that when using MDCT scan indexes of airway WT that account for TA, specifically WT% and WA%, patients with severe asthma have on average slightly more thickened airway walls compared to those with mild-to-moderate asthma and healthy subjects. Interestingly, there was no significant difference when comparing airway WT% or WA% in patients with mild-to-moderate asthma with those in healthy subjects. Previous studies^{13,30} normalized airway measurements to the total airway diameter/area or body surface area. Our data demonstrate that there is substantial variability in the measurement of airway diameter and lumen between airways in the same subject and between subjects, and that this must be taken into consideration when averaging data. Our measurements were normalized for segmental total thickness or TA, which accounts for the interairway variability.

Furthermore, we found that the MDCT scan indexes WT% and WA% correlated with physiologic measures of airflow obstruction across subjects. Similarly, Kasahara et al¹³ also found that WT, WA, and LR were all inversely correlated with post-bronchodilator therapy FEV₁. Increased segmental airway thickness may correlate with more distal, small airway narrowing.³¹ Gono et al⁵ compared expiratory and inspiratory lung density measurements to assess airtrapping as a measure of small airways disease. Asthmatics

with irreversible airflow obstruction had significantly higher expiratory/inspiratory ratios than asthma patients whose expiratory flows normalized after bronchodilation. Hasegawa et al,³² in a study using three-dimensional measurements of airway dimensions in COPD patients, focused their analysis on two bronchi (the RUL and right lower lobe) and found statistically significant correlations among LA, WA%, and FEV₁ percent predicted. They also found³² a stronger correlation when distal smaller airways (up to sixth generation) were analyzed. These findings suggest that airway remodeling in more proximal airways reflects similar changes occurring in more distal airways, resulting in measurable airflow limitation and airtrapping.

A current limitation of MDCT scan measures of airway thickness is the inability to be more specific about which component of the airway has truly changed. In our study, we are unable to discern whether the MDCT scan findings of increased WT% and WA% in patients with severe asthma truly reflect increases in epithelial and LR changes or some other feature of airway remodeling such as increased smooth muscle mass.^{1,3} This particular aspect of airway remodeling has not been well characterized due to the limited sample of smooth muscle available with an endobronchial approach. Future longitudinal studies are needed to evaluate temporal changes in airway WT within individual patients and to evaluate the effects of different treatments.

There are limitations to our ability to measure airway remodeling and accurately obtain airway biopsy specimens from the same segment measured by MDCT scan. The biopsy sites were obtained from the upper lobes only; therefore, we are not able to generalize our remodeling measures to other lung segments. Accurate histologic measurement of the epithelial and LR layers requires that the biopsy specimens have an intact epithelium²⁸; therefore, not all biopsy specimens were included in our analysis.

The natural history of airway remodeling in asthma patients, its rate of progression, and its response to treatment are questions that remain unanswered. Noninvasive measures of airway remodeling using MDCT scanning would allow us to longitudinally monitor the effects of various stimuli and treatments on remodeling. Eventually, this technique may help to identify individuals with asthma in whom severe disease is likely to develop and who may benefit from early targeted, aggressive therapy.

REFERENCES

- 1 Carroll N, Elliot J, Morton A, et al. The structure of large and small airways in nonfatal and fatal asthma. *Am Rev Respir Dis* 1993; 147:405–410

- 2 James A, Paré P, Hogg J. The mechanics of airway narrowing in asthma. *Am Rev Respir Dis* 1989; 139:242–246
- 3 Kay AB. Pathology of mild, severe, and fatal asthma. *Am J Respir Crit Care Med* 1996; 154:S66–S69
- 4 Kuwano K, Bosken C, Paré P, et al. Small airways dimensions in asthma and in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1993; 148:1220–1225
- 5 Gono H, Fujimoto K, Kawakami S, et al. Evaluation of airway wall thickness and air trapping by HRCT in asymptomatic asthma. *Eur Respir J* 2003; 22:965–971
- 6 Ketai L, Coutsias C, Williamson S, et al. Thin-section CT evidence of bronchial thickening in children with stable asthma: bronchoconstriction or airway remodeling? *Acad Radiol* 2001; 8:257–264
- 7 Awadh N, Muller NL, Park CS, et al. Airway wall thickness in patients with near fatal asthma and control groups: assessment with high resolution computed tomographic scanning. *Thorax* 1998; 53:248–253
- 8 Benayoun L, Druilhe A, Dombret M, et al. Airway structural alterations selectively associated with severe asthma. *Am J Respir Crit Care Med* 2003; 167:1360–1368
- 9 Homer RJ, Elias JA. Consequences of long-term inflammation: airway remodeling. *Clin Chest Med* 2000; 21:331–343, ix
- 10 Adelroth E. How to measure airway inflammation: bronchoalveolar lavage and airway biopsies. *Can Respir J* 1998; 5(suppl):18A–21A
- 11 Bousquet J. The use of biopsy to study airway inflammation. *Respir Med* 2000; 94(suppl):S1–S2
- 12 Chetta A, Foresi A, Del Donno M, et al. Airways remodeling is a distinctive feature of asthma and is related to severity of disease. *Chest* 1997; 111:852–857
- 13 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
- 14 Little SA, Sproule MW, Cowan MD, et al. High resolution computed tomographic assessment of airway wall thickness in chronic asthma: reproducibility and relationship with lung function and severity. *Thorax* 2002; 57:247–253
- 15 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
- 16 Niimi A, Matsumoto H, Takemura M, et al. Clinical assessment of airway remodeling in asthma: utility of computed tomography. *Clin Rev Allergy Immunol* 2004; 27:45–58
- 17 Moore W, Bleecker E, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol* 2007; 119:405–413
- 18 National Asthma Education and Prevention Program. Expert panel report 2: guidelines for the diagnosis and management of asthma. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute, 1997
- 19 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
- 20 Palagyi K, Tschirren J, Sonka M. Quantitative analysis of intrathoracic airway trees: methods and validation. *Inf Process Med Imaging* 2003; 18:222–233
- 21 Tschirren J, Hoffman EA, McLennan G, et al. Intrathoracic airway trees: segmentation and airway morphology analysis from low-dose CT scans. *IEEE Trans Med Imaging* 2005; 24:1529–1539
- 22 Tschirren J, Hoffman EA, McLennan G, et al. Segmentation and quantitative analysis of intrathoracic airway trees from computed tomography images. *Proc Am Thorac Soc* 2005; 2:484–487, 503–504

- 23 Tschirren J, McLennan G, Palagyi K, et al. Matching and anatomical labeling of human airway tree. *IEEE Trans Med Imaging* 2005; 24:1540–1547
- 24 Hu S, Hoffman E, Reinhardt J. Automatic lung segmentation for accurate quantitation of volumetric x-ray CT images. *IEEE Trans Med Imaging* 2001; 20:490–498
- 25 Reinhardt J, Raab S, D'Souza N, et al. Intrathoracic airway measurement: *ex-vivo* validation. In: Hoffman EA, ed. *Medical imaging 1997: physiology and function from multidimensional images*. Bellingham, WA: SPIE, 1997
- 26 Miller M, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005; 26:319–338
- 27 Wanger J, Clausen J, Coates A, et al. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; 26:511–522
- 28 Cohen L, E X, Horiuchi T, et al. Epithelial cell proliferation contributes to airway remodeling in severe asthma. *Am J Respir Crit Care Med* 2007; 176:138–145
- 29 de Blic J, Tillie-Leblond I, Emond S, et al. High-resolution computed tomography scan and airway remodeling in children with severe asthma. *J Allergy Clin Immunol* 2005; 116:750–754
- 30 Matsumoto H, Niimi A, Takemura M, et al. Relationship of airway wall thickening to an imbalance between matrix metalloproteinase-9 and its inhibitor in asthma. *Thorax* 2005; 60:277–281
- 31 Nakano Y, Muller NL, King GG, et al. Quantitative assessment of airway remodeling using high-resolution CT. *Chest* 2002; 122(suppl):271S–275S
- 32 Hasegawa M, Nasuhara Y, Onodera Y, et al. Airflow limitation and airway dimensions in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173:1309–1315

Airway Remodeling Measured by Multidetector CT Is Increased in Severe Asthma and Correlates With Pathology

Ravi S. Aysola, Eric A. Hoffman, David Gierada, Sally Wenzel, Janice Cook-Granroth, Jaime Tarsi, Jie Zheng, Kenneth B. Schechtman, Thiruvamoor P. Ramkumar, Rebecca Cochran, E. Xueping, Chandrika Christie, John Newell, Sean Fain, Talissa A. Altes and Mario Castro
Chest 2008;134;1183-1191; Prepublished online July 18, 2008;
DOI 10.1378/chest.07-2779

This information is current as of December 5, 2008

Updated Information & Services	Updated information and services, including high-resolution figures, can be found at: http://chestjournal.org/cgi/content/full/134/6/1183
References	This article cites 30 articles, 15 of which you can access for free at: http://chestjournal.org/cgi/content/full/134/6/1183#BIBL
Open Access	Freely available online through CHEST open access option
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://chestjournal.org/misc/reprints.shtml
Reprints	Information about ordering reprints can be found online: http://chestjournal.org/misc/reprints.shtml
Email alerting service	Receive free email alerts when new articles cite this article sign up in the box at the top right corner of the online article.
Images in PowerPoint format	Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online article figure for directions.

A M E R I C A N C O L L E G E O F
 C H E S T
P H Y S I C I A N S[®]