

Computed Tomography Assessment of Airways Throughout Bronchial Tree Demonstrates Airway Narrowing in Severe Asthma

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Abbreviations and Acronyms

AUC
area under the receiver operating characteristics curve
CT
computed tomography
FEV₁
forced expiratory volume in 1 second
FVC
forced vital capacity
LA
lumen area
MDCT
multidetector row computed tomography
WA
wall area
WA%
WA expressed as a percentage of total bronchial area (LA + WA)

Rationale and Objectives: To analyze airway dimensions throughout the bronchial tree in severe asthmatic patients using multidetector row computed tomography (MDCT) focusing on airway narrowing.

Materials and Methods: Thirty-two patients with severe asthma underwent automated (BronCare software) analysis of their right lung bronchi, with counts of airways >3 mm long arising from the main bronchi (airway count) and bronchial dimension quantification at segmental and subsegmental levels (lumen area [LA], wall area [WA], and WA%). Focal bronchial stenosis was defined as >50% narrowing of maximal LA on contiguous cross-sectional slices. Severe asthmatics were compared to 13 nonsevere asthmatic patients and nonasthmatic (pooled) subjects (Wilcoxon rank tests, then stepwise logistic regression). Finally, cluster analysis of severe asthmatic patients and stepwise logistic regression identified specific imaging subgroups.

Results: The most significant differences between severe asthmatic patients and the pooled subjects were bronchial stenosis (subsegmental and all bronchi: $P < .002$) and WA% ($P < .0003$). Stepwise logistic regression retained WA% as the only explanatory covariable ($P = .002$). Two identified clusters of severe asthmatic patients differed for parameters characterizing airway narrowing (airway count: $P = .0002$; focal bronchial stenosis: $P = .009$). Airway count was as discriminant as forced expiratory volume in 1 second/forced vital capacity ($P = .01$) to identify patients in each cluster, with both variables being correlated ($r = 0.59$, $P = .005$).

Conclusions: Severe asthma-associated morphologic changes were characterized by focal bronchial stenoses and diffuse airway narrowing; the latter was associated with airflow obstruction. WA%, dependent on airway caliber, is the best parameter to identify severe asthmatic patients from pooled subjects.

Key Words: Asthma; airway remodeling; multidetector computed tomography; imaging; three-dimensional.

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Asthma is a heterogeneous condition, which may be characterized in terms of clinical, functional, and biological phenotypes (1,2). Approximately, 5%–10% of asthmatic patients have severe disease (3), associated with airway inflammation that induces structural changes over time. These changes are known as airway wall remodeling (4) and include subepithelial fibrosis, enlarged mucous glands, smooth muscle hypertrophy and hyperplasia (5,6). Remodeling in severe asthma has functional consequences, with decreased forced expiratory volume in 1 second (FEV₁) (7) and persistently increased bronchial hyper-responsiveness (3). However, whether functional alterations are associated with three-dimensional (3D) in vivo bronchial

geometry modifications due to airway narrowing remains to be demonstrated.

Bronchial remodeling can be assessed quantitatively on bronchial biopsy specimens but histologic examination does not provide information on its variability throughout the bronchial tree (8). Moreover, data on bronchial tree geometry are sparse, mainly based on examination of rubber casts of airways (9). Nowadays, the morphologic consequences of remodeling in severe asthma need to be better understood as it would contribute to choosing the best adapted among new emerging treatments (10).

Computed tomography (CT) represents a valuable, noninvasive method for assessing airways throughout the bronchial tree. Most CT studies have focused on bronchial dimensions of proximal airways and evaluation of airway wall area (WA) in asthma (11). That quantification has also been considered a biomarker of remodeling (12) through WA measurement and calculation of WA as a percentage of total bronchial area [$WA\% = WA/(LA + WA) \times 100$] (11,13–17). However, data on lumen area (LA) changes all along the bronchial tree are lacking. Multidetector row CT (MDCT) and automated software (18) advances make such assessments possible and provide information on remodeling distribution and severity, from the bronchus origin to its distal divisions, and its consequences on the airway lumen caliber (19). Those findings would be relevant to help phenotype the disease and select appropriate treatment, such as, bronchial thermoplasty (20) (aiming to reduce the airway smooth muscle and induce bronchodilatation).

The primary study objective was to analyze bronchial tree morphologic changes, including airway wall thickening and airway narrowing, that can be visualized and measured with 3D/2D multiparametric airway analysis derived from the MDCT acquisitions of severe asthmatic patients. The second goal was to investigate whether airway morphologic parameters could identify specific subgroups of severe asthma patients.

MATERIALS AND METHODS

Patients

The study was approved by the appropriate institutional and ethics committees according to French law. Written informed consent was obtained from each patient. Thirty-two patients with severe asthma, according to the World Health Organization definition (21), were prospectively recruited by a Department of Respiratory Medicine between July 2009 and February 2012. Their clinical and functional data are summarized in Table 1. These patients underwent MDCT scans as part of their standard workup, temporally far (>6 weeks) from any exacerbation or infection. Seven patients with milder asthma, recruited during the same period by the same pulmonologists (blinded, blinded), also underwent MDCT scans according to the same protocol. Six nonasthmatic subjects, who underwent MDCT for atypical thoracic

pain ($n = 4$) or to rule out pulmonary metastasis ($n = 2$) and having no pulmonary abnormality on MDCT, were also included. The latter two groups were pooled to serve as controls.

MDCT Acquisitions

Acquisitions were obtained on a 64-channel MDCT (Light-Speed VCT; GE Medical Systems, Milwaukee, WI), according to a standard acquisition protocol (120 kVp; automated mA exposure with a noise index of 35 and z -axis modulation) and 0.625-mm collimation (0.984 pitch). The dose $\times$ length product was always <250 mGy/cm. No contrast material was used. Overlapping 0.625-mm reconstructions every 0.3 mm were obtained to have near-isotropic images, using a bone kernel. No iterative reconstruction was used. Images were focused on the right lung because of potential cardiac motion artifacts in the left lower lobe lingula which could impair measurement. A 512^2 pixel matrix was used, giving a constant pixel length (0.42–0.5 mm).

Airway Computations

The volumetric, high-resolution CT lung data sets were analyzed with a dedicated workstation using BronCare software (ARTEMIS Department, Telecom SudParis, Evry, France). This software automatically processes MDCT data for 3D airway lumen segmentation (22,23), central-axis computation of the airway tree (skeletonization), and 2D reconstruction of manually selected bronchi in a cross-sectional plane orthogonal to this axis, with automatic computation of LA, WA, and WA% (24). To study bronchial LA geometry, the interval between each reconstructed slice was <1 mm. Finally, to generate the 3D color-coded LA caliber map, corresponding to every point on the lumen surface, the lumen dimension at each point is measured and colored. It reports the radius of the maximal sphere inscribed in the lumen volume and tangent to its surface at this point (25) (Fig 1).

Bronchus Analysis

Two radiologists (both blinded) reviewed 2D reconstructed slices and 3D-lumen caliber images of the bronchi to consensus, in a random order. That analysis described the geometry of the distal airway tree (airway count) and the proximal bronchi (with evaluation of LA, WA, WA%, and detection of bronchial stenoses). First, from the skeletonization of the airway tree, the number of ≤ 3 -mm-long bronchi (to exclude artifacts mainly due to bronchial diverticula) segmented by the software was counted from the main bronchus. The derived parameter (airway count) served as a surrogate of distal airway caliber. The underlying concept is that the segmentation algorithm uses detection of airway candidates, followed by constrained propagation, which retrieves the distal airway segments (23). In the case of airway obstructions

TABLE 1. Comparisons of Clinical and Functional Parameters Between Severe Asthmatic Patients and the Pooled Group

Clinical Parameter	Severe Asthma (n = 32)	Pooled Group (n = 13)		P
		Nonsevere Asthma (n = 7)	Nonasthmatic Subjects (n = 6)	
Age (years)	48.6 (41–58)	42.7 (32–54)		.24
Weight (kg)	76.6 (66.5–87)	46.8 (32–58)	38 (26–52)	.27
		70.7 (64–77)		
		72.5 (57–93)	68.5 (65–77)	
Size (m)	1.67 (1.62–1.71)	1.67 (1.69–1.72)		.3
		1.66 (1.63–1.71)	1.72 (1.68–1.75)	
Sex (female/male)	21/11	8/5		1
Smoker (yes/no)	7/25	5/2	3/3	.6
		2/5	—	
Asthma history*				
Duration (years)	21.9 (9–33.5)	33.8 (18–50)		.08
Atopy (yes/no)	16/15	33.8 (18–50)	—	.2
		6/1	—	
Oral maintenance steroid therapy (yes/no)	10/21	0/7	—	.15
		0/7	—	
PFT*				
FEV ₁ (% predicted)	71.8 (58–86)	80.5 (65–97)		.36
FEV ₁ /FVC (%)	62.2 (50–73)	80.5 (65–97)	—	.1
		71.2 (60–81)	—	
		71.2 (60–81)	—	
Reversibility (yes/no)	10/21	4/3	4/3	.38
			—	

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PFT, pulmonary function tests.

Data are expressed as means (upper to lower quartile).

*Patients with and without severe asthma were compared.

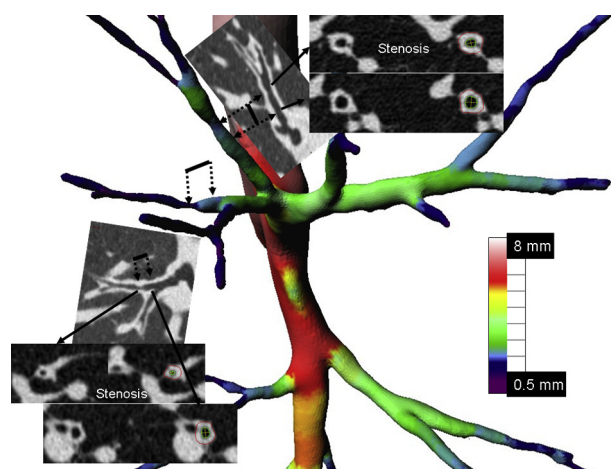


Figure 1. Lateral view of the bronchi in the right upper lobe showing a 3D color-coded lumen image of a distal stenosis at segmental level (B1) of the apical bronchus and a long stenosis at subsegmental level (B3) on the posterior bronchus. Corresponding orthogonal reconstructions and segmented images of lumen area (LA) and wall area (WA) at the levels of the stenoses, and maximum LA of each bronchus are shown. Coronal oblique reconstruction in the plane of the selected bronchi was added. Color scale corresponds to the radius of the maximal sphere inscribed in the lumen volume and tangent to its surface at every point on the lumen surface. (Color version of figure is available online.)

or narrowing $<2 \text{ mm}^2$ (considering our image acquisition settings), the distal propagation stops because of opacities in the lumen or a partial volume effect. Thus, the resulting 3D airway segmentation is a reflection of the airways visible on the CT scan, and the airway count indicates the number of distal segments reached, which is correlated with the distal caliber. Hence, the airway count can be considered a biomarker for an entire cohort, when the same CT acquisition settings and the same (default) software parameters are applied, which is the case for this study.

Then, the segmental and subsegmental bronchi included in the right upper lobe (B1, B2, and B3), and the anterior, lateral, and posterior segments of the right lower lobe (B8, B9, B10) were selected by the radiologists for evaluation. Airway caliber analysis along the bronchial tree allowed detection of focal stenoses, defined as $>50\%$ LA decrease compared to the maximum LA, calculated along the selected bronchus. The location of any focal bronchial stenoses was characterized as proximal (just beyond the bronchus origin), distal (giving the bronchus a conical shape), or extended (when involving more than half of the bronchus length). This analysis was based on axial transverse images and 3D lumen caliber. Vascular compression was also considered for short asymmetrical stenoses of the 3D lumen caliber with vessel imprint confirmed

TABLE 2. Comparisons of MDCT Parameters Between Patients with Severe Asthma and Pooled Subjects

MDCT Parameter	Severe Asthma (<i>n</i> = 32)	Pooled Group (<i>n</i> = 13)		<i>P</i>
		Nonsevere Asthma (<i>n</i> = 7)	Nonasthmatic Subjects (<i>n</i> = 6)	
Airway count, <i>n</i>	99 (62–118)	153 (100–196) 137.1 (86–193)	181.2 (140–222)	.01
Stenosis, <i>n</i>				
Subsegmental bronchi	3.1 (1–5)	0.9 (0–1) 1.4 (0–3)	0.3 (0–1)	.002
Segmental bronchi	0.8 (0–1)	0.1 (0–0) 0.3 (0–1)	0 (0–0)	.6
All bronchi	3.9 (2–6)	1 (0–2) 1.7 (0–3)	0.3 (0–1)	.002
LA (mm ²)				
Subsegmental bronchi	7.7 (4.8–9.1)	10.8 (8.3–11.1) 10.3 (9–11.1)	11.2 (8.1–14.9)	.01
Segmental bronchi	14.4 (10.4–19.1)	18.9 (15.1–22.2) 18.7 (15.3–22.9)	19.1 (14.6–22.4)	.02
All bronchi	9.8 (6.8–11.7)	13.3 (10.5–14.7) 13 (12.2–14.7)	13.6 (10.4–17.2)	.01
WA (mm ²)				
Subsegmental bronchi	14.7 (12.8–16.8)	13 (11.6–13.7) 12.9 (12.5–13.7)	13.1 (11.1–15.4)	.049
Segmental bronchi	25 (21.3–27.9)	21.7 (19–24) 22.2 (19–24)	21.1 (14.8–24.1)	.6
All bronchi	17.6 (15.3–19.6)	15.5 (10.5–14.7) 15.6 (14.9–16.1)	15.4 (13.4–18.5)	.04
WA%				
Subsegmental bronchi	68.2 (61.8–74.2)	56.5 (52.3–59.8) 57 (51.9–61.4)	56 (52.3–59.2)	.0004
Segmental bronchi	65.4 (59.3–70.5)	54.7 (49.5–59) 55.5 (48.8–60)	53.7 (49.3–57.3)	.0008
All bronchi	67.4 (61.4–73)	56 (52.6–59.6) 56.5 (50.9–60.7)	55.4 (52.6–59.6)	.0003

LA, lumen area; WA, wall area; WA%, WA expressed as a percentage of total bronchial areas (LA + WA).
Data are expressed as means (upper to lower quartile).

on axial transverse images. For every selected bronchus, LA, WA, and WA% were calculated for every slice but, for the statistical analysis, we retained only the measurement of a single slice near the midpoint.

Statistical Analysis

LA, WA, and WA% were averaged so that only one value was considered for statistical analysis of each patient's segmental, subsegmental, or all bronchi. To determine which MDCT parameter best identified patients with severe asthma, severe asthmatic patients and the pooled subjects were compared using two-sample Wilcoxon rank tests. Then, stepwise logistic regression and receiver operating characteristics curve analyses were performed to identify the most discriminating covariables (among clinical, functional, and MDCT parameters listed in Tables 1 and 2) and their best-performing thresholds. Covariables entered into the stepwise regression model (26) were those achieving $P < .1$ in the univariate analysis. The final

model contained covariables significant ($P < .05$) in the Wald test. Next, bronchial stenoses were subjected to descriptive analysis. Finally, to determine whether MDCT can identify specific severe asthma subgroups, cluster analysis was performed (27). It was based on a hierarchical classification of the patients obtained using the Ward distance. Then, logistic regression analysis was conducted to identify which clinical, functional, and MDCT-derived parameters best characterized each cluster. Correlations between discriminating variables were calculated using the Spearman correlation test. SAS version 9 statistical package was used for all computations.

RESULTS

Identification of Severe Asthmatic patients

Patients' clinical and functional parameters are presented in Table 1. Regarding MDCT parameters, the two study groups differed significantly for airway dimensions (Table 2). Severe

TABLE 3. Stenoses of the Segmental and Subsegmental Bronchi Included in the Right Upper Lobe (B1, B2, and B3) and Anterior, Lateral, and Posterior Segments of the Right Lower Lobe (B8, B9, and B10) (40).

Bronchus	Segmental Level			Subsegmental Level		
	Severe Asthma (n = 32)	Nonsevere Asthma (n = 7)	Nonasthmatic Subjects (n = 6)	Severe Asthma (n = 32)	Nonsevere Asthma (n = 7)	Nonasthmatic Subjects (n = 6)
B1	5	1		a: 4; b: 7	a: 1; b: 2	
B2	2	1		a: 10; b: 4	a: 2	
B3	5			a: 7; b: 10	a: 1; b: 1	
B8	3			a: 8; b: 6		
B9	9	1		a: 7; b: 6	a: 1	a: 1
B10	3			a: 11, b, c: 3; b: 8, c: 8	b: 1	a: 1
Total	27	3	0	99	9	2

TABLE 4. Comparisons of Clinical and Functional Parameters of the Two Severe Asthma Patient Clusters

Clinical Parameter	Severe Asthma Patients (n = 32)		P
	Cluster 1 (n = 13)	Cluster 2 (n = 19)	
Age (years)	48.6 (41–58)		
	45.2 (32–56)	50.9 (45–60)	.26
Weight (kg)	76.6 (66.5–87)		
	73.5 (63–82)	78.8 (70–87)	.18
Size (m)	1.67 (1.62–1.71)		
	1.69 (1.64–1.70)	1.66 (1.61–1.72)	.34
Sex (female/male)		21/11	
	8/5	13/6	.7
Smoker (yes/no)		7/25	
	3/10	4/15	1
Asthma history			
Duration (years)	21.9 (9–33.5)		
	17.8 (7–33)	24.8 (13–36)	.13
Atopy (yes/no)		16/15	
	7/6	9/9	1
Oral maintenance steroid therapy (yes/no)		10/21	
	3/10	7/11	.45
PFT			
FEV ₁ (% predicted)	71.8 (58–86)		
	88 (80–93)	60.1 (52–72)	.0002
FEV ₁ /FVC (%)	62.2 (50–73)		
	74.5 (72–80)	53.4 (47–60)	.0002
Reversibility (yes/no)		10/21	
	4/9	6/12	1

PFT, pulmonary function tests; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

Data are expressed as means (upper to lower quartile).

asthmatics had significantly fewer software-segmented bronchi (airway count; 99 vs. 151; $P = .01$), reflecting a probable lumen caliber decrease in their distal airways, and significantly more focal bronchial stenoses (Table 3) per patient than the pooled subjects (3.9 [2–6] vs. 1 [0–2], $P = .002$ for all bronchi). The latter difference was still significant when only subsegmental bronchi were considered ($P = .002$). Focal stenoses of segmental and subsegmental bronchi in severe asthmatics totaled 27 and 99, respectively, classified as 50 distal, 40 extended, 32 proximal, and 4 vascular compressions. Severe asthmatic patients' segmental and subsegmental

bronchi LA were significantly smaller than those of pooled subjects ($P = .01$ for all bronchi).

Among airway morphologic parameters, WA% differed significantly between severe asthmatics and pooled subjects. Their respective mean WA% values for all bronchi per patient were 67.4 (upper–lower quartile, 61.4–73) versus 56 (upper–lower quartile, 52.6–59.6; $P = .0003$). The difference remained significant when only segmental or subsegmental bronchi were analyzed ($P = .0008$ and .0004, respectively). WA comparisons between severe asthmatic patients and the pooled subjects for all bronchi ($P = .04$) and subsegmental

bronchi ($P = .049$) also differed significantly. However, the difference was no longer significant when only segmental bronchi were considered.

WA% was the only significant covariable remaining in the final logistic regression model to identify severe asthmatic patients ($P = .002$; odds ratio [95% confidence interval], 1.29 [1.09–1.52]; logistic regression C-index, 0.88). The optimal WA% cutoff value to differentiate severe asthmatic patients from pooled subjects was 62% (75% sensitivity, 92% specificity, 91% positive predictive value, and 79% negative predictive value).

Cluster Analysis of Severe Asthmatic Patients

Cluster analysis of severe asthmatic patients identified two clusters that differed according to pulmonary function tests ($P = .0002$ for FEV_1 and FEV_1/FVC ; Table 4) and MDCT parameters describing airway narrowing ($P = .0002$ for airway count and $P = .009$ for number of focal bronchial stenoses; Table 5). Two equivalent univariate logistic regression models based on airway count or FEV_1/FVC ($P = .01$; odds ratio [95% confidence interval], 0.89 [0.81–0.97]) identified patients belonging to each cluster (Fig 2). The plot of the FEV_1/FVC ratio, the clinical parameter whose 70% threshold routinely defines airflow obstruction (28), versus airway count (Fig 3) shows that the two variables were correlated ($r = 0.59$, $P = .005$), so that most patients with low airway counts (cluster 2) had $FEV_1/FVC < 70\%$.

DISCUSSION

Our results showed that airway morphologic changes observed in severe asthmatic patients were characterized by lumen narrowing, wall thickening, and focal bronchial stenoses. Two clusters identified for our severe asthmatic patients differed according to parameters characterizing airway narrowing ($P = .0002$ for airway count, $P = .009$ for bronchial stenosis). Airway count was as discriminant as FEV_1/FVC ($P = .01$) to identify patients belonging to each cluster, with the two variables being correlated ($r = 0.59$, $P = .005$). Regarding airway wall thickening, we observed that WA%, which depends on airway caliber, was the best parameter to identify patients with severe asthma from nonsevere asthmatic and nonasthmatic subjects ($P = .002$).

James and Wenzel (29) previously detailed airway narrowing in asthmatic patients as being marked by airway wall thickening, with or without smooth muscle shortening around the airway and/or airway wall collapse. However, the lumen diameter decrease remains controversial on MDCT studies. Indeed, Gupta et al. (30), but not others (13,15), found smaller MDCT-measured bronchus LA. Herein, analysis of 3D bronchial geometry changes demonstrated the decreased airway lumen caliber in severe asthma and showed that airway narrowing could include focal bronchial stenoses and diffuse airway lumen narrowing. Our results do not enable us to

TABLE 5. Comparisons of MDCT Parameter Differences Between the Two Clusters of Severe Asthma Patients

Parameter	Severe Asthma Patients ($n = 32$)		<i>P</i>
	Cluster 1 ($n = 13$)	Cluster 2 ($n = 19$)	
Airway count, <i>n</i>	99 (62–118)		
	135.3 (111–158)	74.2 (57–91)	.0002
Stenosis, <i>n</i>			
Subsegmental	3.1 (1–5)		
bronchi	1.9 (1–2)	3.9 (2–5)	.02
Segmental	0.8 (0–1)		
bronchi	0.3 (0–1)	1.2 (0–2)	.09
All bronchi	3.9 (2–6)		
	2.2 (1–2)	5.1 (3–6)	.009
LA (mm ²)			
Subsegmental	7.7 (4.8–9.1)		
bronchi	9.2 (7.3–10.4)	6.7 (4.3–8.5)	.02
Segmental	14.4 (10.4–19.1)		
bronchi	16.3 (13–19.6)	13.1 (9.4–15.7)	.06
All bronchi	9.8 (6.8–11.7)		
	11.3 (10.1–12.9)	8.8 (6.2–10.8)	.03
WA (mm ²)			
Subsegmental	14.7 (12.8–16.8)		
bronchi	15.1 (12.8–16.6)	14.6 (12.9–16.9)	.96
Segmental	25 (21.3–27.9)		
bronchi	25.1 (21.4–25.5)	25.1 (21.2–28.3)	.6
All bronchi	17.6 (15.3–19.6)		
	17.6 (10.1–12.9)	17.6 (15.6–20.8)	.6
WA%			
Subsegmental	68.2 (61.8–74.2)		
bronchi	64 (57.7–70)	71.2 (65.8–77.6)	.03
Segmental	65.4 (59.3–70.5)		
bronchi	61.2 (56.5–65.3)	68.2 (62.6–75.4)	.04
All bronchi	67.4 (61.4–73)		
	63.3 (57.4–68.4)	70.3 (66.2–76.9)	.04

LA, lumen area; WA, wall area; WA%, WA expressed as a percentage of total bronchial areas (LA + WA).

Data are expressed as means (upper to lower quartile).

definitively conclude that bronchial architectural changes result from either remodeling or passive increased basal tone or both, but they suggest that focal stenoses, extended stenoses, and lower airway counts are different facets of those processes.

In our study, focal bronchial lumen stenoses concerned all bronchi, every lobe, and bronchial orientation and predominated at the subsegmental level. They could be classified as distal, proximal, or extended. Because bronchus diameter tends to decrease in size from the hilum to the periphery, it is difficult to conclude whether distal bronchial stenoses are abnormal or not. Indeed, a few years ago, Matsuoka et al. (31) demonstrated that LA decreased on asymptomatic subjects' contiguous 2-mm CT sections extending from the origin of the right posterior basal segmental bronchi to the posterior subsegmental bronchi for the majority of bronchi, and this diminution could sometimes exceed 50%.

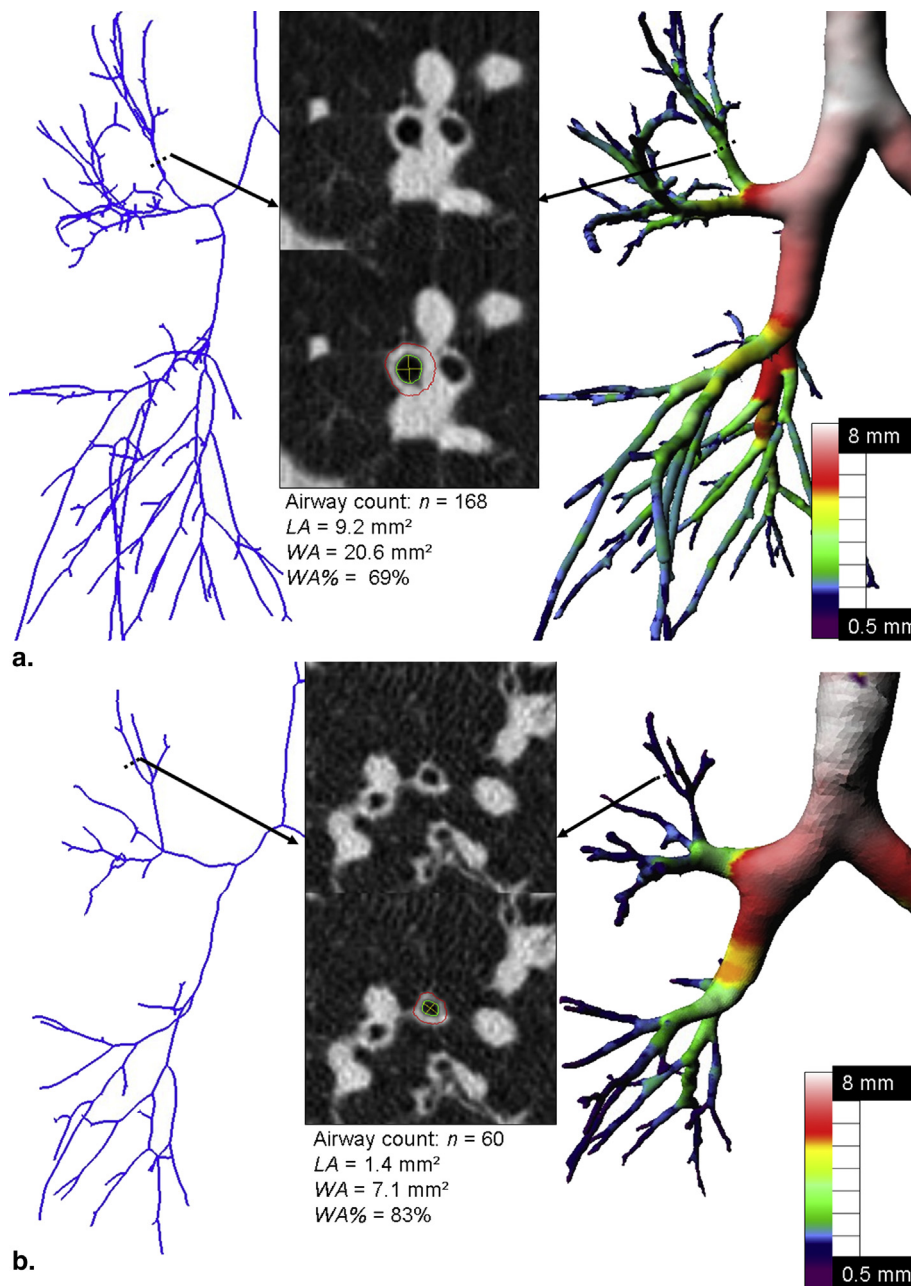


Figure 2. Anterior view of the central-axis reconstruction (left) and 3D color-coded lumen image (right) with corresponding orthogonal reconstruction and segmented images of lumen area (LA) and wall area (WA) at a sub-segmental level in two patients with severe asthma (one from each cluster). The cluster 1 patient (a) had 168 segmented bronchi, whereas the cluster 2 patient (b) had only 60 segmented bronchi (airway count) arising from the main bronchus, giving a dead-tree appearance of the airway tree. Color scale corresponds to the radius of the maximal sphere inscribed in the lumen volume and tangent to its surface at every point on the lumen surface. (Color version of figure is available online.)

Conversely, we think that proximal bronchial stenoses may be a consequence of remodeling because the bronchi tend to change their shape, becoming more oval at their origin. Indirect evidence suggested that focal bronchial stenoses occur in asthma. Aysola et al. (13) used helium-3 magnetic resonance imaging to study ventilation defects and found they could exceed 3 cm in 25% of severely asthmatic patients and usually had a triangular shape (32). Ventilation defects tended to remain constant over time in the majority of patients (33). Both the size of the defects and their fixity over time suggest bronchial remodeling with stenosis and/or occlusion. Notably, de Backer et al. (34) also observed heterogeneous

ventilation distributions for six patients with mild asthma on single-photon emission CT images with inhaled aerosols and computed fluid dynamics simulations using MDCT airway imaging. They reported the formation of local tracer hot spots in proximal airways.

Increased basal tone could be the predominant mechanism in the formation of extended stenoses. In our opinion, it also could explain the lower airway counts in severe asthmatic patients, which seem to correspond to a more diffuse process involving the airways. On central-axis reconstructions of airways (skeletonization), airway narrowing tended to give a characteristic dead-tree appearance (Fig 2b), with decreased

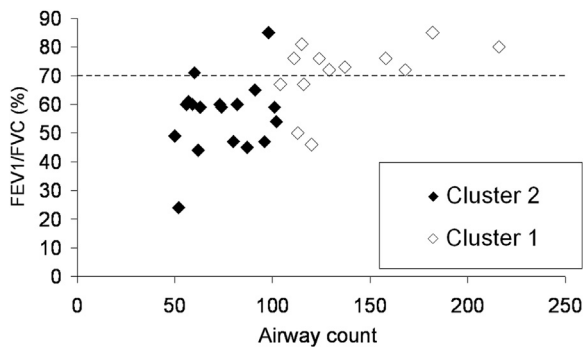


Figure 3. Plotting forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ratios versus airway counts of severe asthmatic patients revealed that most patients with lower airway counts (cluster 2) had obstructed airflow, as routinely assessed clinically (FEV₁/FVC <70).

complexity of airway branching. Such observations were reported by others (9,19) after measurement of the fractal dimension of the airway tree. Indeed, in severe asthmatic patients, a fractal dimension decrease was observed based on airways casts, which was attributed to bronchial tree trimming because of bronchoconstriction and mucous plugs on computer simulation (9) and confirmed more recently on MDCT images of the segmented airways of severe asthmatic patients (19).

As previously reported (13,15,16), we also observed that WA% was increased for severe asthmatic patients and enabled their differentiation from pooled subjects (with an optimal WA% threshold of 62). Even though WA% remains the cornerstone of quantitative asthma measurements, there are several concerns about its measurement. First, the fact that WA% is usually measured at the midpart of the bronchus should be considered a sampling limitation (8) because structural modifications could predominate at any bronchus level (and, notably, bronchial stenoses could be observed at bronchial bifurcations or more distally) and be heterogeneous along the airway tree (Fig 1) (9,35–37). Second, Brightling et al. recently shed light on WA% dependency on bronchus lumen mechanics (17); it was a critical finding because LA may change under treatment (38). The dependency of airway-wall thickening on airway caliber could also explain why WA%, and not WA, provided significant results for all our cases. Thus, better assessment of asthma-induced architectural remodeling, including LA measurement and detection of bronchial stenoses, should contribute to better understanding of morphologic airway changes and, ultimately, help personalize therapies, especially those targeting airway smooth muscle (particularly bronchial thermoplasty).

Our study has several limitations. First, we had a limited number of clinical variables and patients (which led to pooling nonsevere asthmatic and nonasthmatic subjects for the first part of the statistical analysis). Therefore, MDCT parameters in the statistical analyses might have been accorded too much weight. Second, the roles of proximal and distal bronchi

in airflow obstruction need to be clarified. We concede that expiratory acquisitions would have enabled evaluation of distal airways, but our study was designed to describe proximal airways. Similarly, computed fluid dynamics analysis would have enabled us to define the role of each component. Third, some thresholds were fixed arbitrarily. To define focal bronchial narrowing, the limit was set at 50% of the maximal area, by analogy to the vascular definition of stenosis, but the consequence on airflow remains unknown. For airway counts, limiting to 99 the number of segmented airways to define a cluster was set arbitrarily and corresponded to the mean value for severe asthmatic patients. Using the airway count as a surrogate measurement of airway caliber is another limitation as it depends on the accuracy of software registration of distal airway walls and lumens. If other software were to be used, different results would be obtained, thereby limiting the use of airway count as a biomarker. Finally, concerning the methods used in our study, images obtained from 3D color coding of lumen diameter were intended only to illustrate the technique and were not investigated further. In our opinion, that technique improves the visualization of stenoses and would enhance detection of abnormalities by nonspecialist observers.

In conclusion, severe asthma can be characterized by parameters describing airway narrowing. Some of these parameters (airway count) were correlated to airflow obstruction and enable classification of patients in different clusters according to airway narrowing severity and airflow limitation. Even though the original approach used herein could help phenotype severe asthmatic patients (1), we think that the hypothesis that severe asthmatic patients with bronchial stenosis are good candidates for new treatments (39), including thermoplasty, remains to be demonstrated. Future studies will require histologic correlation studies and follow-up CT examinations before definitive conclusions can be drawn.

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