

CT Attenuation of the Bronchial Wall in Patients With Asthma: Comparison With Geometric Parameters and Correlation With Function and Histologic Characteristics

Mathieu Lederlin^{1,2,3}
 François Laurent^{1,2,3}
 Yann Portron¹
 Annaïg Ozier^{2,3,4}
 Hubert Cochet^{1,3}
 Patrick Berger^{2,3,4}
 Michel Montaudon^{1,2,3}

Keywords: airway, asthma, attenuation, quantitative CT, remodeling

DOI:10.2214/AJR.11.8396

Received December 16, 2011; accepted after revision May 13, 2012.

¹Unité d'Imagerie Thoracique et Cardiovasculaire, CHU de Bordeaux, Hôpital du Haut-Lévêque, 5 Ave de Magellan, 33604 Pessac, France. Address correspondence to M. Montaudon (michel.montaudon@chu-bordeaux.fr).

²Laboratory of Cellular Respiratory Physiology, Université de Bordeaux, Bordeaux, France.

³Institut National de la Santé et de la Recherche Médicale (INSERM), Bordeaux, France.

⁴Department of Pulmonary Function Tests, CHU de Bordeaux, Pessac, France.

AJR 2012; 199:1226–1233

0361–803X/12/1996–1226

© American Roentgen Ray Society

OBJECTIVE. The purposes of this study were to compare airway wall attenuation in subjects with asthma and subjects without asthma; to correlate this value with pulmonary function test results, standard bronchial CT parameters, and immunohistologic data; and to identify CT parameters that influence obstructive indexes.

SUBJECTS AND METHODS. Bronchial airway wall attenuation was averaged over four bronchi in 27 subjects with asthma and 15 control subjects without asthma. The following five standard bronchial parameters also were assessed: lumen area, wall area, wall thickness, wall-to-lumen area ratio, and wall-to-total area ratio (wall area percentage). These parameters were compared between groups and correlated with functional data. Ability to predict patient group with these parameters was determined by comparison of receiver operating characteristic curves and areas under the curve. The influence of the parameters on obstructive indexes was assessed by multivariate analysis. Correlations between wall attenuation value and histologic data were studied in 11 patients with asthma.

RESULTS. Wall attenuation value was greater in patients with asthma (-322 ± 79 HU) than in control subjects (-463 ± 69 HU). Correlation coefficients of wall attenuation value with functional obstructive parameters were significant and greater than those obtained for any other CT parameter. The area under the curve of wall attenuation value was greater than that of bronchial lumen area and bronchial wall area. In the model of multiple regression that included wall attenuation value and wall-to-total area ratio, wall attenuation value was the only measurement that significantly influenced obstructive indexes ($R^2 = 0.39\text{--}0.43$). Wall attenuation value correlated with mast cell infiltration.

CONCLUSION. Compared with the usual bronchial CT parameters, airway wall attenuation better differentiates patients with asthma from control subjects and better correlates with obstruction.

Airway changes in asthma are considered a continuum from inflammation to remodeling [1] and involve the whole bronchial tree [2]. Inflammatory cells in the bronchial wall, including eosinophils, T lymphocytes, and mast cells, interact with smooth-muscle cells, and the interaction leads to remodeling [3, 4]. The latter is closely related to an irreversible decrease in lung function and includes smooth-muscle hypertrophy and hyperplasia, collagen deposition on the basement membrane, epithelial detachment, goblet cell hyperplasia, and angiogenesis [5]. Noninvasive biomarkers are being evaluated for differentiating subtypes of asthma [6, 7]. Although not useful for assessing and quantifying inflammation and remodeling, in vivo imaging of the

bronchial wall, notably CT, has potential for providing information about bronchial changes.

CT has been found to be a powerful and reliable noninvasive tool for measuring both small and large airways in asthma. Bronchial wall changes assessed with quantitative CT correlate with clinical, functional, and histologic patterns in subjects with asthma [8–13]. Therefore, quantitative CT has potential for phenotyping of patients with asthma and may thus help in adapting therapeutic strategies. However, because of the heterogeneity and complexity of the algorithms needed, such postprocessing programs are not yet used in routine practice [14–16]. Beyond geometric measurements, CT has the unique capability of tissue attenuation measurements. For an object, determinants of attenuation include physical density and size

CT of Asthma

[17, 18], the relative part of the latter increasing as the point spread function of the CT system is approached. Thus, because the thickness of the bronchial wall is close to the spatial resolution of CT devices, measurement of the attenuation of the wall remains challenging. Several authors [19–21] have found the value of bronchial wall attenuation in patients with chronic obstructive pulmonary disease. They found significant differences in wall attenuation values between subjects with chronic obstructive pulmonary disease and healthy subjects and also found significant correlations with obstructive functional indexes. To our knowledge, however, no such study has been performed with subjects with asthma.

Because geometric and histologic airway changes occurring in asthma are likely to influence CT bronchial wall attenuation, we sought to investigate this parameter. Our aims were to compare airway wall attenuation value in patients with asthma with that in healthy subjects; to correlate wall attenuation value with results of pulmonary function tests (PFTs), standard bronchial CT parameters, and immunohistologic data; and to identify CT parameters influencing functional obstructive indexes.

Subjects and Methods

Study Population

The design of the study was prospective and approved by our institutional review board. All participants gave written informed consent. Twenty-seven patients with asthma (mean age, 51.96 ± 14.9 [SD] years) as defined by the American Thoracic Society [22] and 15 nonsmoker control subjects (mean age, 53.47 ± 14.63 years) were included through the clinical investigation center of our university hospital. Exclusion criteria were the presence of other pulmonary disease and occupational dust exposure, the occurrence of any acute thoracic event within 6 weeks of the examinations, the presence of extensive bronchial calcifications on CT images, and a history of medication with warfarin [23]. For control subjects, additional exclusion criteria were abnormal CT or PFT results. Control subjects were referred for exclusion of parenchymal blebs before scuba diving ($n = 7$), whole-body CT screening before colorectal neoplasia surgery ($n = 6$), and a single episode of hemoptysis ($n = 2$). None of the patients with neoplasia had abnormal lung CT findings at 1-year follow-up evaluation. Neither of the patients with hemoptysis had abnormal fiberoptic endoscopic or clinical follow-up findings.

Exploration Protocol

Explorations were performed within 48 hours under stable conditions without modification of anti-asthma treatment.

Pulmonary Function Test Technique

PFTs were performed with body plethysmography (BodyBox 5500, Medisoft) according to the American Thoracic Society–European Respiratory Society guidelines [24, 25]. The functional parameters assessed for each subject were forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), forced expiratory flow between 25% and 75% of FVC ($FEF_{25-75\%}$), total lung capacity, and residual volume.

CT Protocol

All CT scans were obtained with a 16-MDCT system (Somatom Sensation 16, Siemens Healthcare). The device was calibrated on air daily, and quality control was performed monthly. Data were obtained at suspended full inspiration after patients were trained in the preparation room. Acquisitions were performed with no contrast injection and with the following parameters: 100- to 120-kV tube voltage, 50- to 60-mAs tube current, and 0.75-mm collimation. Images were reconstructed with a smooth standard algorithm (B30f), 1-mm-thick sections, 1-mm interval, 280- to 380-mm² FOV, and 512×512 matrix. Images were transferred to a workstation after the name of the patient and the date of examination were deleted. Images were displayed with parenchymal window width and level (width, 1500 HU; level –450 HU) for further analysis [9].

Image Analysis Software

Images were analyzed in random presentation with Myrian software (Intrasense) by a single observer with 5 years of experience in chest CT. The apical bronchus (B1) of the upper lobes and the posterobasal bronchus (B10) of the lower lobes were identified. The slice where each bronchus had minimal contact with the adjacent vessel was selected for measurements. The observer, who was blinded to clinical and PFT data, manually selected all pixels in the bronchial wall then all pixels in the bronchial lumen to measure the mean wall attenuation value, wall area, and lumen area. The following geometric indexes were also computed [26, 27]: wall area percentage, calculated as $[WA / (WA + LA)]$, where WA is wall area and LA is lumen area; WA / LA ; and wall thickness, calculated as $[(WA + LA) / \pi]^{1/2} - (LA / \pi)^{1/2}$. All values were averaged over the four bronchi studied. The SD of air attenuation was also averaged over eight regions of interest (one at each angle of the volume dataset). Reconstructed pixel size was recorded for each patient.

Histologic Analysis

Bronchoscopy with systematic biopsy of the middle lobe bronchus spur was performed on patients with refractory asthma ($n = 11$) as usually performed at our institution. Specimens were embedded in

TABLE 1: Anthropometric, Pulmonary Function Test, and CT Results

Characteristic	Control Subjects	Subjects With Asthma	<i>p</i>
Age (y)	53.5 ± 14.6	52.0 ± 14.9	0.75
Sex ratio (M/F)	10/5	10/17	0.07 ^a
Weight (kg)	77.9 ± 15.1	77.5 ± 16.1	0.95
Height (cm)	168.8 ± 8.5	165.7 ± 10.3	0.33
Total lung capacity (%)	96.8 ± 14.6	97.5 ± 14.9	0.89
Residual volume (%)	81.7 ± 10.8	112.6 ± 34.4	$< 0.01^b$
Forced expiratory volume in 1 second (FEV_1) (%)	109.8 ± 13.8	75.2 ± 24.3	< 0.001
Forced vital capacity (FVC) (%)	105.9 ± 15.7	87.5 ± 23.3	< 0.01
FEV_1/FVC	83.6 ± 9.8	72.0 ± 13.4	0.01^b
Forced expiratory flow between 25% and 75% of FVC (%)	98.1 ± 20.0	51.8 ± 27.7	< 0.001
Air SD (HU)	14.3 ± 2.7	14.3 ± 3.4	0.94
Pixel size (mm)	0.71 ± 0.04	0.67 ± 0.06	0.04^b
Wall attenuation value (HU)	-463 ± 69	-322 ± 79	< 0.001
Lumen area (mm ²)	18.2 ± 3.8	14.1 ± 4.5	< 0.01
Wall area (mm ²)	28.4 ± 5.0	27.1 ± 4.6	0.42
Wall thickness (mm)	1.44 ± 0.13	1.51 ± 0.15	0.13
Ratio of wall area to lumen area	1.63 ± 0.20	2.16 ± 0.60	$< 0.001^b$
Wall area percentage (ratio of wall area to total area)	0.61 ± 0.02	0.67 ± 0.05	< 0.001

Note—Comparisons between groups were made with unpaired Student *t* test except as noted.

^aComparison performed with chi-square test.

^bComparison performed with Wilcoxon signed rank test.

paraffin and processed by a single blinded pathologist [3]. Remodeling and inflammation components were quantified for each patient. The remodeling components corresponded to the smooth-muscle area, epithelial area, and subepithelial area normalized to the whole area of the corresponding biopsy and expressed as percentages of the whole area. The inflammation components corresponded to mast cells, T lymphocytes, monocytes-macrophages, neutrophils, and eosinophils. Inflammatory cell counts were assessed by immunohistochemical analysis of 9 of 11 specimens (there was insufficient material in two specimens from patients with asthma to perform immunohistochemical analysis). Specimens were incubated with the following primary monoclonal mouse antibodies: antihuman tryptase (AA1, Dako), antihuman *c-kit* R (Dako), antihuman CD3 (Dako), antihuman CD68 (Dako), antihuman neutrophil elastase (NE, Dako), and antihuman activated eosinophil cationic protein (EG2, Pharmacia Diagnostics) to assess the number of nondegranulated mast cells, total mast

cells, T lymphocytes, monocytes-macrophages, neutrophils, and eosinophils. The number of positive cells per square millimeter was automatically assessed with Quancoul software (Quant' image) at a magnification of $\times 200$, giving the total population of each subset of cells in the bronchial wall [28].

Statistical Analysis

A priori estimation of the sample size necessary to detect a difference in wall attenuation value between subjects with asthma and control subjects with 5% error probability and 95% power was performed with the G*Power program [29]. Given the bronchial wall attenuation values obtained in eight healthy subjects and eight subjects with asthma who were not included in the analysis, G*Power yielded a 1.73 effect size and required a minimal total sample size of 20 subjects (10 subjects per group).

Subject characteristics and PFT and CT results were compared by unpaired Student *t* test or the

Wilcoxon signed rank test according to data distribution that was assessed with the D'Agostino skewness, kurtosis, and omnibus tests. Receiver operating characteristic curves were used to analyze the sensitivity-to-specificity relation for CT parameters. Areas under the curve (AUCs) were compared by use of *Z* statistics. Pearson correlation coefficients were determined between wall attenuation value, standard bronchial parameters, and PFT results. Stepwise forward multiple regressions were performed to determine the CT parameter that best influenced FEV₁ and FEV_{25-75%}. Among the standard bronchial parameters, we chose the one that best correlated with the dependent variable to limit multicollinearity. Spearman correlation coefficients were calculated between wall attenuation value and histologic results. Analyses were performed with NCSS software (NCSS 2001, NCSS Statistical Software). Values of $p < 0.05$ were considered significant. Data are shown as mean $\pm$ SD unless otherwise stated.

Results

Subject Characteristics and Pulmonary Function Test and CT Results

Subject characteristics and PFT and CT results in each group are shown in Table 1. Wall attenuation value was greater in subjects with asthma (-322 ± 79 HU) than in control subjects (-463 ± 69 HU) (Figs. 1 and 2). All standard CT parameters except wall area and wall thickness made it possible to differentiate subjects with asthma from control subjects. Tube voltage and air SD (i.e., image noise) did not differ between groups.

Diagnostic Performance of CT Parameters

The receiver operating characteristic curves of wall attenuation value, wall area percentage, ratio of wall area to lumen area, and lumen area for the diagnosis of asthma are shown in Figure 3. The AUCs for each CT parameter are shown in Table 2. The AUC was significantly greater than 0.5 for each parameter except wall area and wall thickness. The utility of wall attenuation value for predicting whether a subject had asthma was significantly greater than that of lumen area, wall area, and wall thickness ($p < 0.01$).

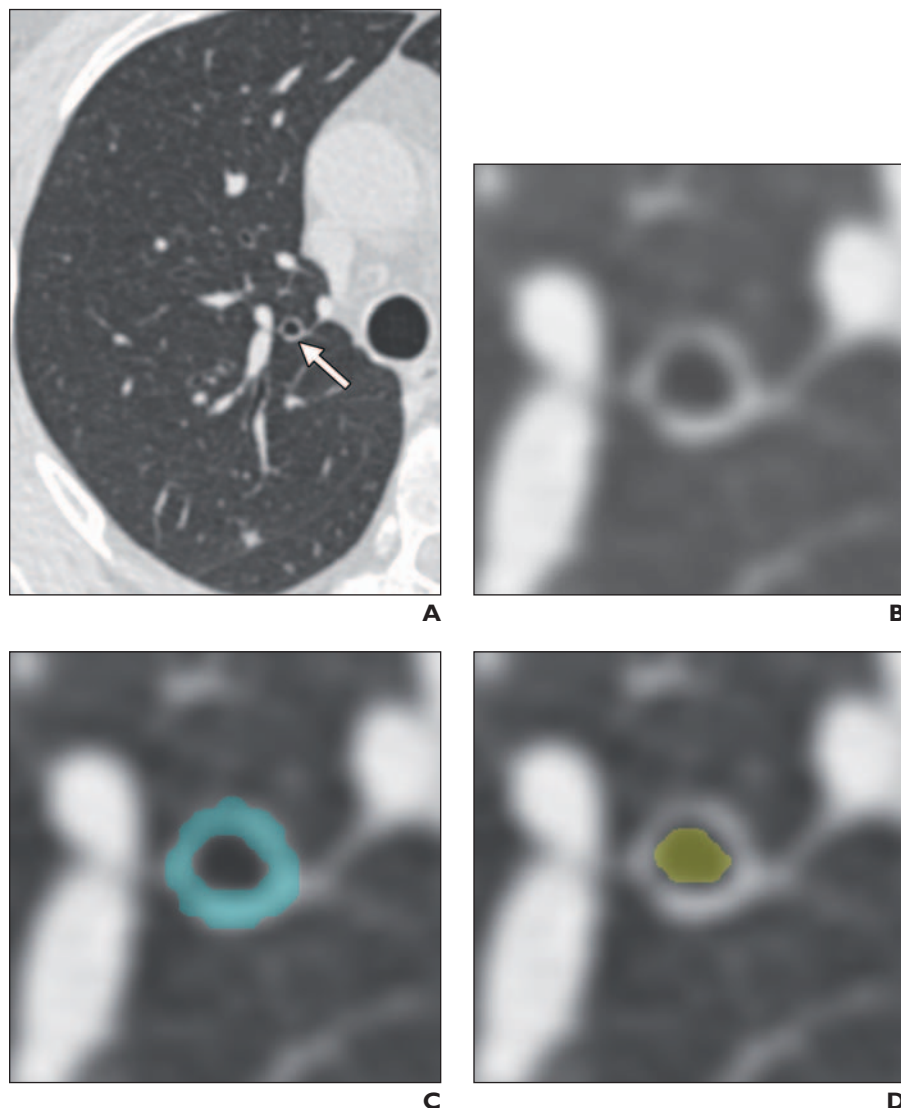
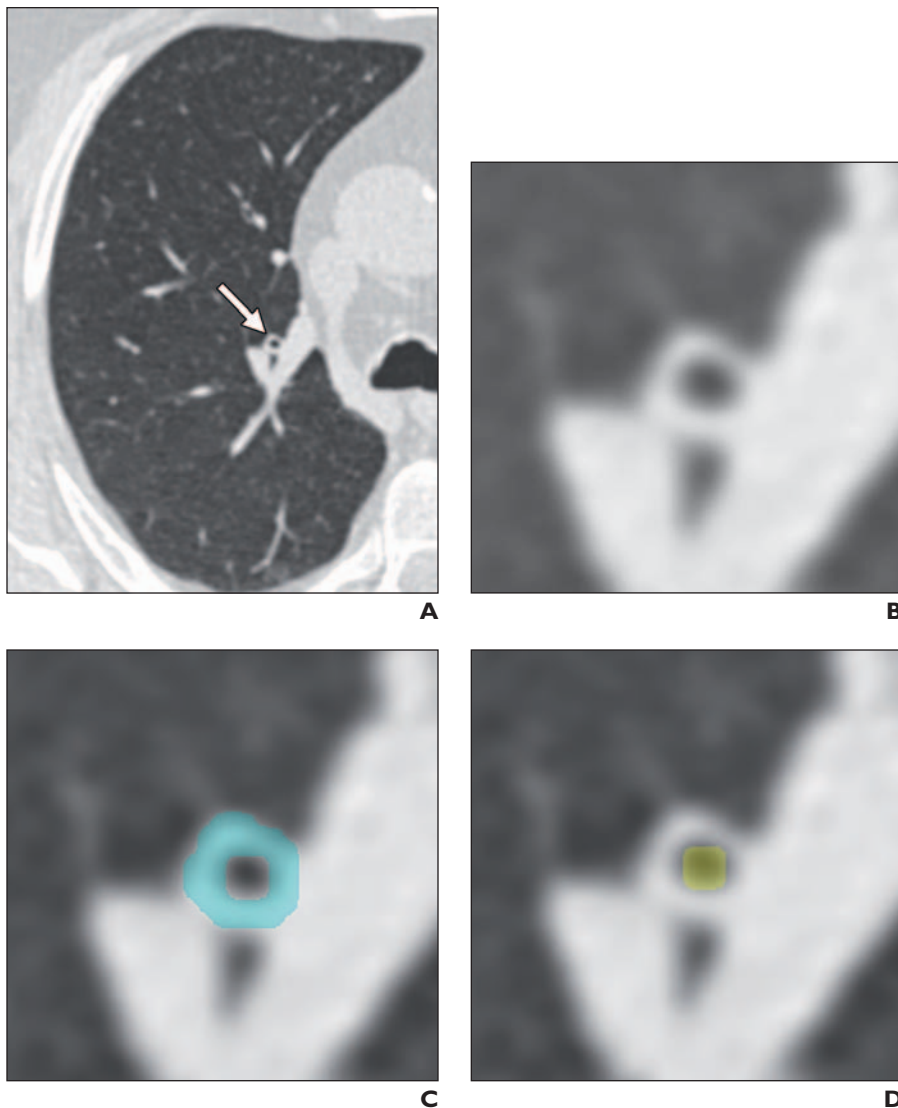


Fig. 1—50-year-old healthy man. Representative thin-section CT images. **A**, Original image shows right B1 bronchus (arrow). **B–D**, Subsequent images show magnification of bronchus of interest (**B**) and delineation of bronchial wall (blue, **C**) and bronchial lumen (yellow, **D**). Wall attenuation value is -491 HU.

Fig. 2—57-year-old man with asthma. Representative thin-section CT images.

A, Original image shows right B1 bronchus (arrow). **B–D**, Subsequent images show magnification of bronchus of interest (**B**) and delineation of bronchial wall (blue, **C**) and bronchial lumen (yellow, **D**). Wall attenuation value is -250 HU.



Correlations Between Pulmonary Function Test Results and CT Parameters

Significant correlations were found between CT parameters and PFT results (Table 3 and Fig. 4). Wall attenuation value best correlated with FEV_1 and $FEF_{25-75\%}$. Pearson correlation coefficients of wall attenuation value and each PFT parameter were always greater than those obtained for any standard bronchial parameter. Wall attenuation value significantly correlated with all standard bronchial parameters except wall thickness (Table 3). Conversely, no correlation was found between wall attenuation value and total lung capacity, residual volume, image noise, or pixel size.

Factors Influencing Obstructive Indexes

All of the significant variables in Table 3 were entered into stepwise multiple regression analyses to determine the strength of each individual CT parameter for predicting FEV_1 and $FEF_{25-75\%}$. Regarding FEV_1 , the best model associated wall attenuation value and wall area percentage and explained 47.8% ($R^2 = 0.48$) of the variation in this measurement. However, wall attenuation value was the only CT parameter significantly influencing FEV_1 ($R^2 = 0.43$; $t = 12.7$; $p < 0.01$). Regarding $FEF_{25-75\%}$, the best model associated wall attenuation value and wall area percentage and explained 44.8% ($R^2 = 0.45$) of the variation in this measurement. However, wall attenuation value was the only CT parameter significantly influencing $FEF_{25-75\%}$ ($R^2 = 0.39$; $t = 10.7$; $p < 0.01$).

Correlations Between Wall Attenuation Value and Both Remodeling and Inflammation Components

Correlations between wall attenuation value and histologic data are shown in Table 4. The correlation with remodeling patterns did not reach significance. With respect to inflammatory cells, wall attenuation value correlated only with the count of nondegranulated mast cells in the bronchial wall ($r = 0.87$; $p < 0.01$).

Discussion

This study showed that bronchial wall attenuation can be used to differentiate subjects with asthma from control subjects and that this

Fig. 3—Receiver operating characteristic curves for wall attenuation value (black solid line), wall area percentage (dotted line), wall area to lumen area (dashed line), and of lumen area (gray solid line) in prediction of patient group.

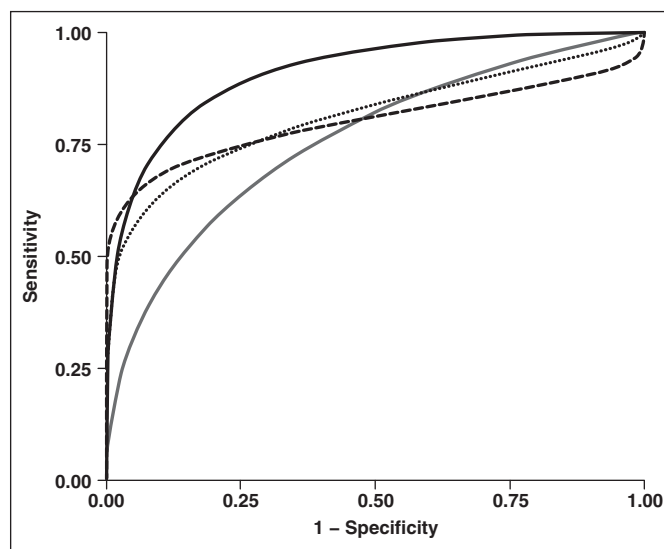


TABLE 2: Diagnostic Value of CT Results

Characteristic	Result
Sensitivity/specificity	
Wall attenuation value (HU)	0.83/0.84 (–396) ^a
Lumen area (mm ²)	0.64/0.74 (15.8)
Wall area (mm ²)	0.58/0.53 (28)
Wall thickness (mm)	0.74/0.44 (1.42)
Ratio of wall area to lumen area	0.79/0.60 (1.68)
Wall area percentage	0.81/0.60 (0.62)
FEV ₁ (%)	0.86/0.72 (101.8)
Area under the curve	
Wall attenuation value (HU)	0.91 (0.78–0.97) ^{b,c}
Lumen area (mm ²)	0.76 (0.57–0.87) ^c
Wall area (mm ²)	0.57 (0.37–0.73)
Wall thickness (mm)	0.64 (0.44–0.78)
Ratio of wall area to lumen area	0.80 (0.64–0.89) ^c
Wall area percentage	0.81 (0.65–0.90) ^c
FEV ₁ (%)	0.89 (0.75–0.96) ^c
<i>z</i>	
Wall attenuation value vs lumen area	2.45 (0.01) ^d
Wall attenuation value vs wall area	3.81 (<0.01)
Wall attenuation value vs wall thickness	2.37 (0.02)
Wall attenuation value vs ratio of wall area to lumen area	1.63 (0.10)
Wall attenuation value vs wall area percentage	1.48 (0.14)
Wall attenuation value vs FEV ₁	0.42 (0.67)

Note—FEV₁ = forced expiratory volume in 1 second. Wall area percentage is ratio of wall area to total area.

^aValues in parentheses are cutoff.

^bValues in parentheses are 95% CI.

^c*p* > 0.5.

^dValues in parentheses are *p*.

value correlates with obstructive indexes and, in a subset of our population, with some immunohistologic parameters. Wall attenuation value was significantly greater in subjects with asthma than in control subjects, a result that has not been reported to date, to our knowledge. Lumen area, wall area percentage, and ratio of wall area to lumen area also made it possible to differentiate subjects with asthma from control subjects, as previously reported [9–11, 13]. The AUC obtained for wall attenuation value was significantly greater than the AUCs for lumen area, wall area, and wall thickness and tended to be greater than those of wall area percentage and ratio of wall area to lumen area.

CT measurements used for assessing the bronchial wall, that is, geometric and densitometric parameters, are more or less impaired by partial volume effects, a consequence of the point spread function of CT devices, which leads to poor spatial resolution compared with bronchial wall thickness [16]. Because partial volume effects with air have been associated with overestimation of wall area [30], they are likely to decrease the actual attenuation value of the bronchial wall, yielding negative values, a result also found by others [19–21]. However, owing to its arithmetic concept, wall attenuation value may be less dependent on spatial resolution than standard geometric parameters are. Attenuation measurement is based on a mean, whereas area measurement is based on summing numeric values. Therefore, the influence of wrong values due to partial volume

TABLE 3: Correlations Between CT Data, Lung Function, and Anthropometric Parameters

Characteristic	Wall Attenuation Value (HU)	Lumen Area (mm ²)	Wall Area (mm ²)	Wall Thickness (mm)	Ratio of Wall Area to Lumen Area	Wall Area Percentage
Age (y)	0.19 (0.22)	0.01 (0.96)	0.03 (0.86)	0.05 (0.77)	0.10 (0.53)	0.06 (0.69)
Weight (kg)	0.04 (0.80)	–0.11 (0.47)	–0.14 (0.39)	–0.09 (0.58)	0.10 (0.52)	0.06 (0.72)
Height (cm)	–0.23 (0.15)	0.21 (0.17)	0.15 (0.36)	0.00 (1.00)	–0.13 (0.43)	–0.17 (0.29)
Total lung capacity (%)	–0.24 (0.12)	0.24 (0.12)	–0.03 (0.84)	–0.22 (0.16)	–0.24 (0.12)	–0.31 (0.05)
Residual volume (%)	0.24 (0.12)	–0.12 (0.46)	–0.09 (0.57)	0.02 (0.88)	0.13 (0.40)	0.14 (0.36)
FEV ₁ (%)	–0.65 (<0.001)	0.53 (<0.001)	0.20 (0.21)	–0.21 (0.19)	–0.50 (<0.001)	–0.56 (<0.001)
FVC (%)	–0.52 (<0.001)	0.37 (0.02)	0.05 (0.76)	–0.27 (0.08)	–0.44 (<0.01)	–0.49 (<0.01)
FEV ₁ /FVC	–0.48 (<0.01)	0.39 (0.01)	0.23 (0.14)	–0.05 (0.78)	–0.33 (0.04)	–0.35 (0.03)
FEF _{25–75%} (%)	–0.63 (<0.001)	0.54 (<0.001)	0.22 (0.16)	–0.19 (0.23)	–0.49 (<0.001)	–0.54 (<0.001)
Air SD (HU)	0.02 (0.89)	–0.14 (0.39)	–0.19 (0.24)	–0.12 (0.04)	0.13 (0.41)	0.07 (0.67)
Pixel size (mm)	–0.22 (0.16)	0.20 (0.21)	0.33 (0.03)	0.26 (0.09)	–0.02 (0.90)	–0.05 (0.75)
Wall attenuation value (HU)		–0.66 (<0.001)	–0.43 (<0.01)	0.03 (0.84)	0.54 (<0.001)	0.56 (<0.001)

Note—Data are Pearson coefficients of correlation with *p* in parentheses (*n* = 42). FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, FEF_{25–75%} = forced expiratory flow between 25% and 75% of FVC. Wall area percentage is ratio of wall area to total area.

CT of Asthma

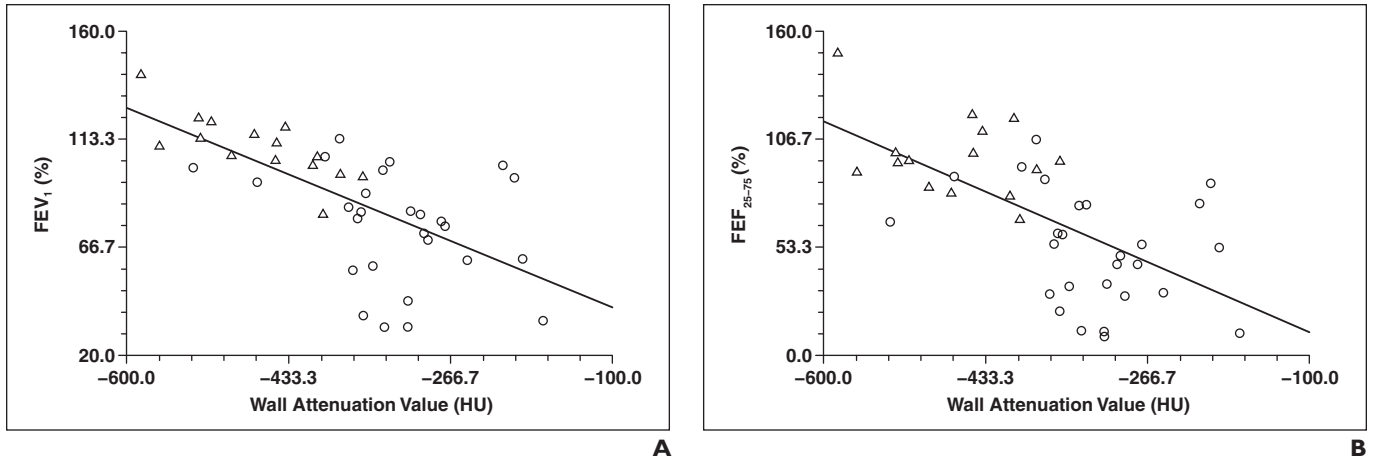


Fig. 4—Correlation results. Triangles indicate control subjects; circles, subjects with asthma; solid line, regression line.

A, Graph shows correlation between bronchial wall attenuation value and forced expiratory volume in 1 second (FEV_1).

B, Graph shows correlation between bronchial wall attenuation value and forced expiratory flow between 25% and 75% of forced vital capacity ($FEF_{25-75\%}$).

effects could be less detrimental to wall attenuation value than to wall area measurements. This hypothesis is corroborated by the significant correlation between wall area and pixel size, whereas the latter did not correlate with wall attenuation value in the range of pixel sizes used in our study.

Wall attenuation value correlated with functional obstructive indexes better than standard bronchial parameters did. Such correlations have previously been reported in chronic obstructive pulmonary disease [19–21] and in a microscopic CT study on asthmatic mice [31]. In our multiple regression analyses, both FEV_1 and $FEF_{25-75\%}$ were influenced by wall attenuation value with no significant influence of standard bronchial parameters. This predominant influence of wall attenuation value was also found in patients with chronic obstructive pulmonary disease [19].

Considering correlations between wall attenuation value and other CT parameters, as expected, we found significant relations, mainly with wall area percentage, the most widely used index. Conversely, wall attenuation value did not correlate with wall thickness and correlated only poorly with wall area, a result that might be associated with the absence of significant difference in wall thickness and wall area between subjects with asthma and control subjects. Both wall area and wall thickness are nonnormalized measurements that are hence subject to interairway variability, that is, variability between airways in the same patient and variability between patients. As a consequence, wall area and wall thickness usually have less consistent results than normalized parameters such as wall area percentage [11, 13]. In this

TABLE 4: Correlations Between Wall Attenuation Value and Immunohistologic Results Among Patients With Asthma

Result	Correlation with Wall Attenuation Value
Remodeling components ($n = 11$)	
Epithelial layer percentage	−0.04 (0.92)
Subepithelial layer percentage	−0.49 (0.12)
Smooth-muscle layer percentage	0.47 (0.14)
Ratio between smooth muscle layer and subepithelial layer	0.55 (0.08)
Inflammation components ($n = 9$)	
Neutrophil cells	0.25 (0.52)
Nondegranulated mast cells	0.87 (< 0.01)
Degranulated and nondegranulated mast cells	0.5 (0.17)
T lymphocytes	0.05 (0.90)
Eosinophils	0.54 (0.27)
Monocytes-macrophages	0.25 (0.52)

Note—Data are Spearman correlation coefficients with p in parentheses. Remodeling parameters are epithelial, subepithelial, and smooth-muscle layer areas expressed as percentages of the total bronchial wall area and ratio of smooth-muscle layer to subepithelial layer. Inflammation parameters correspond to cell count in the bronchial wall expressed as number of cells per square millimeter.

study, wall thickness had a tendency toward a difference between the groups. We assume that this difference was not significant because of the rather small number of subjects designed for discerning differences in wall attenuation value. As a nonnormalized parameter, lumen area is also subject to interairway variability. Some authors [11] have reported no significant difference in lumen area between subjects with asthma and control subjects, whereas others [13] have found significant narrowing of the bronchial lumen in subjects with asthma compared with control subjects.

In light of our results, wall attenuation value may be a less straightforward but more robust

method than geometry for measuring airway thickening in asthma. What remains to be determined is whether wall attenuation value is only a surrogate of wall thickness or is related to histologic components of the bronchial wall and thereby possibly can become a biomarker. In a subset of our sample, significant correlations were found between wall attenuation value and immunohistologic data. The ratio of smooth muscle to subepithelial layer area is considered a marker of remodeling [32] and had nearly significant correlation with wall attenuation value ($r = 0.55$; $p = 0.08$). Because this marker of remodeling was found to correlate with wall attenuation value in a

mouse model of asthma [31], we believe that it was not statistically significant owing to the small number of histologic samples. Interestingly, the only cellular population correlating with wall attenuation value is mast cells, especially in the smooth-muscle layer. Mast cells have been found to be a key cell in the chronic inflammatory process leading to bronchial smooth-muscle remodeling [3, 33, 34]. These findings suggest that wall attenuation value may be more dependent on remodeling than on inflammation, a result that needs to be confirmed.

The main limitation of our study was the insufficient number of histologic samples, which prevented their inclusion in a stepwise multiple regression analysis. Assessing both immunohistologic and CT data in a large population would help to clarify the main determinants of wall attenuation value. Particularly, such an analysis would make it possible to assess whether wall attenuation value could be a direct or an indirect marker of remodeling. The second main limitation of our study, also reported by others [11], was the practical impossibility of obtaining histologic biopsy specimens from the studied bronchi. Performing endobronchial biopsy perpendicularly to the main axis of a bronchus is particularly challenging, so most operators perform biopsies of bronchial spurs. Because our measurements were made on a circular bronchial section, we were not able to match CT measurements with the site of the biopsy. Finally, delineation of the bronchial wall was performed manually, which is more subjective than semiautomatic methods based on edge detection [35]. However, the manual method has previously shown good intraobserver and interobserver reproducibility for assessment of wall attenuation value [19].

Conclusion

This study showed that wall attenuation value is greater in subjects with asthma than in control subjects and has better correlations with functional data than standard geometric parameters do. Among all CT parameters, wall attenuation value is the main indicator of functional obstructive indexes. Further studies are required to investigate whether wall attenuation value can be used as a noninvasive surrogate of wall thickness or as a marker of histologic changes in asthma.

References

1. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma: from bronchoconstriction

- to airways inflammation and remodeling. *Am J Respir Crit Care Med* 2000; 161:1720–1745
2. Haley KJ, Sunday ME, Wiggs BR, et al. Inflammatory cell distribution within and along asthmatic airways. *Am J Respir Crit Care Med* 1998; 158:565–572
3. Begueret H, Berger P, Vernejoux JM, Dubuisson L, Marthan R, Tunon-de-Lara JM. Inflammation of bronchial smooth muscle in allergic asthma. *Thorax* 2007; 62:8–15
4. Berger P, Girodet PO, Begueret H, et al. Tryptase-stimulated human airway smooth muscle cells induce cytokine synthesis and mast cell chemotaxis. *FASEB J* 2003; 17:2139–2141
5. Jeffery PK. Remodeling in asthma and chronic obstructive lung disease. *Am J Respir Crit Care Med* 2001; 164:S28–S38
6. Calvo FQ, Fillet M, de Seny D, et al. Biomarker discovery in asthma-related inflammation and remodeling. *Proteomics* 2009; 9:2163–2170
7. Kaminska M, Foley S, Maghni K, et al. Airway remodeling in subjects with severe asthma with or without chronic persistent airflow obstruction. *J Allergy Clin Immunol* 2009; 124:45–51; e1–e4
8. 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
9. 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
10. Okazawa M, Muller N, McNamara AE, Child S, Verburgt L, Pare PD. Human airway narrowing measured using high resolution computed tomography. *Am J Respir Crit Care Med* 1996; 154:1557–1562
11. 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
12. 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
13. Montaudon M, Lederlin M, Reich S, et al. Bronchial measurements in patients with asthma: comparison of quantitative thin-section CT findings with those in healthy subjects and correlation with pathologic findings. *Radiology* 2009; 253:844–853
14. Brillet PY, Fetita CI, Capderou A, et al. Variability of bronchial measurements obtained by sequential CT using two computer-based methods. *Eur Radiol* 2009; 19:1139–1147
15. Matsuo S, Kurihara Y, Nakajima Y, Niimi H, Ashida H, Kaneoya K. Serial change in airway lumen and wall thickness at thin-section CT in asymptomatic subjects. *Radiology* 2005; 234:595–603
16. Sung A, Naidich D, Belinskaya I, Raoof S. The role of chest radiography and computed tomography in the diagnosis and management of asthma. *Curr Opin Pulm Med* 2007; 13:31–36
17. Phelps ME, Gado MH, Hoffman EJ. Correlation of effective atomic number and electron density with attenuation coefficients measured with polychromatic x rays. *Radiology* 1975; 117:585–588
18. Tsai CM, Cho ZH. Physics of contrast mechanism and averaging effect of linear attenuation coefficients in a computerized transverse axial tomography (CTAT) transmission scanner. *Phys Med Biol* 1976; 21:544–559
19. Lederlin M, Laurent F, Dromer C, Cochet H, Berger P, Montaudon M. Mean bronchial wall attenuation value in chronic obstructive pulmonary disease: comparison with standard bronchial parameters and correlation with function. *AJR* 2012; 198:800–808
20. Washko GR, Dransfield MT, Estepar RS, et al. Airway wall attenuation: a biomarker of airway disease in subjects with COPD. *J Appl Physiol* 2009; 107:185–191
21. Yamashiro T, Matsuo S, Estepar RS, et al. Quantitative assessment of bronchial wall attenuation with thin-section CT: an indicator of airflow limitation in chronic obstructive pulmonary disease. *AJR* 2010; 195:363–369
22. Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing, 1999. *Am J Respir Crit Care Med* 2000; 161:309–329
23. Moncada RM, Venta LA, Venta ER, Fareed J, Walenga JM, Messmore HL. Tracheal and bronchial cartilaginous rings: warfarin sodium-induced calcification. *Radiology* 1992; 184:437–439
24. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005; 26:319–338
25. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; 26:511–522
26. Montaudon M, Berger P, Lederlin M, Marthan R, Tunon de Lara JM, Laurent F. Bronchial morphometry in smokers: comparison with healthy subjects by using 3D CT. *Eur Radiol* 2009; 19:1328–1334
27. Montaudon M, Desbarats P, Berger P, de Dietrich G, Marthan R, Laurent F. Assessment of bronchial wall thickness and lumen diameter in human adults using multi-detector computed tomography: comparison with theoretical models. *J Anat* 2007; 211:579–588
28. Berger P, Lavalée J, Rouiller R, Laurent F, Marthan R, Tunon de Lara JM. Assessment of bronchial inflammation using an automated cell recog-

CT of Asthma

- dition system based on colour analysis. *Eur Respir J* 1999; 14:1394–1402
29. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods* 2009; 41:1149–1160
 30. Reinhardt JM, D'Souza ND, Hoffman EA. Accurate measurement of intrathoracic airways. *IEEE Trans Med Imaging* 1997; 16:820–827
 31. Lederlin M, Ozier A, Montaudon M, et al. Airway remodeling in a mouse asthma model assessed by in-vivo respiratory-gated micro-computed tomography. *Eur Radiol* 2010; 20:128–137
 32. Woodruff PG, Dolganov GM, Ferrando RE, et al. Hyperplasia of smooth muscle in mild to moderate asthma without changes in cell size or gene expression. *Am J Respir Crit Care Med* 2004; 169:1001–1006
 33. Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID. Mast-cell infiltration of airway smooth muscle in asthma. *N Engl J Med* 2002; 346:1699–1705
 34. Girodet PO, Ozier A, Trian T, et al. Mast cell adhesion to bronchial smooth muscle in asthma specifically depends on CD51 and CD44 variant 6. *Allergy* 2010; 65:1004–1012
 35. Amirav I, Kramer SS, Grunstein MM, Hoffman EA. Assessment of methacholine-induced airway constriction by ultrafast high-resolution computed tomography. *J Appl Physiol* 1993; 75:2239–2250

FOR YOUR INFORMATION

Mark your calendar for the following ARRS annual meetings:
 April 14–19, 2013—Marriott Wardman Park, Washington, DC
 May 4–9, 2014—Manchester Grand Hyatt San Diego, San Diego, CA
 April 19–24, 2015—Toronto Convention Centre, Toronto, ON, Canada