Thin-Section CT Evidence of Bronchial Thickening in Children with Stable Asthma:

Bronchoconstriction or Airway Remodeling?[1]

Loren Ketai, MD, Cecelia Coutsias, MD, Susan Williamson, MD, Vageli Coutsias, PhD

Rationale and Objectives. The authors performed this study to determine if bronchial wall thickening is present in children with moderate to severe asthma during periods free from clinical bronchoconstriction.

Materials and Methods. The authors obtained low (radiation) dose thin-section computed tomographic (CT) scans in each of 18 control subjects and 21 children with moderately severe but stable asthma. Spirometry was performed on all subjects at the time of CT scanning. Bronchial wall thickness and bronchial wall area were measured, and the percentage wall area (bronchial wall area divided by bronchial cross-sectional area) was calculated. The authors performed best-fit regression analysis of wall thickness and percentage wall area versus bronchial diameter and qualitative analysis of images for bronchial wall thickening.

Results. In asthmatic patients, the mean percentage of the predicted forced expiratory volume in 1 second was 0.88 ± 0.09. The best fit regression line that demonstrated the relationship between wall thickness and bronchial diameter for patients with asthma differed significantly from that for control subjects ($P < .005$). The regression line that demonstrated the relationship between the percentage wall area and bronchial diameter for patients with asthma differed from that of the control subjects when bronchial wall thickness measurements were used to calculate the percentage wall area ($P < .05$). Results of qualitative analysis also showed significantly more bronchial wall thickening in asthmatic patients than in control subjects ($P < .001$).

Conclusion. Bronchial wall thickening detected at thin-section CT in children with moderately severe asthma cannot be attributed solely to bronchoconstriction and may represent airway inflammation or remodeling.

Key Words. Asthma; bronchi, abnormalities; computed tomography (CT), thin-section.

Asthma is a disease state of airway hyperresponsiveness usually related to chronic airway inflammation (1). Unfortunately, the activity of the underlying airway inflammation has proved difficult to measure directly, particularly in children. Pulmonary function tests are at best an indirect measure of inflammation and are made inaccurate by the variability of bronchoconstriction over time. Bronchoalveolar lavage with fiberoptic bronchoscopy can be performed in adults but is problematic in children, and tissue biopsy can rarely be performed in clinical practice. Because of these limitations, there is no well established method for assessing the activity of inflammation in children's lungs as a means to guide treatment of asthma with anti-inflammatory agents.

Thin-section computed tomography (CT) performed in adult asthmatic patients has shown a variety of permanent architectural abnormalities in the lung, including bronchiectasis and emphysema. Reversible abnormalities at thin-

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[1] From the Department of Radiology, University of New Mexico Health Science Center, 915 Camino de Salud, Albuquerque, NM 87131 (L.K., S.W.); the Department of Radiology, Johns Hopkins School of Medicine, Baltimore, Md (C.C.); and the Department of Mathematics, University of New Mexico, Albuquerque (V.C.). Received October 25, 2000; revision requested November 7; revision received and accepted November 13. Supported by a pilot program grant from the American Lung Association Asthma Funded Research Center at the University of New Mexico. **Address correspondence to** L.K.

section CT include bronchial wall thickening, focal low attenuation secondary to air trapping, ground-glass opacities, and centrilobular nodules and branching structures (presumably) due to bronchiolar inflammation (2–4). Of these thin-section CT findings, the presence or absence of bronchial wall thickening may be the most useful. The results of previously performed radiographic and anatomic studies (5,6) have suggested that bronchial wall thickening is a more constant finding in patients with severe or uncontrolled asthma. Furthermore, data from a preliminary thin-section CT study (7) show that bronchial wall thickening in adult asthmatic patients may be reversible with use of systemic corticosteroids.

This bronchial wall thickening has been attributed to airway inflammation or airway remodeling (8,9). Airway remodeling refers to structural changes in the airway wall such as the hyperplasia or hypertrophy of smooth muscle and the proliferation of mucous glands (8,9). Prior work in humans has shown there to be little change in airway wall area with acute bronchoconstriction from methacholine or subsequent bronchodilatation with inhaled albuterol (10). Bronchoconstriction, however, could cause apparent bronchial wall thickening by decreasing the diameter of the bronchus, thereby increasing the wall thickness relative to bronchial size.

To separate the component of apparent bronchial wall thickening caused by bronchoconstriction from that caused by true airway inflammation or remodeling, it is necessary to measure airways in patients without acute bronchospasm. We hypothesized that bronchial wall thickening would be present in children with moderately severe asthma despite the absence of substantial bronchospasm as measured by means of airflow obstruction. We sought to detect the presence of bronchial wall thickening in these children with stable asthma both qualitatively and quantitatively.

MATERIALS AND METHODS

Subjects

Subject participation was approved by the Human Research Review Committee at the University of New Mexico Health Science Center, Albuquerque. Informed consent was obtained from the parents of all asthmatic patients and control subjects. We enrolled 20 patients from the general pediatric and pediatric pulmonary clinics at the University of New Mexico Health Science Center. We identified patients between the ages of 7 and 18 years with moderate ($n = 14$) to severe ($n = 6$) chronic asthma, as defined with a scoring system used by Chetta et al (9) to correlate with airway remodeling in adults. The scoring system is based on bronchodilator use, symptom frequency, and variability in peak flow rates recorded during a period of several weeks (Fig 1). With this scoring system, patients with moderate to severe asthma may have normal spirometric findings at any given point in time. Patients with clinical evidence of a respiratory tract infection or history of systemic corticosteroid therapy within 4 weeks were excluded.

Frequency of Symptoms
0 = none
1 = symptoms occur less than once a week
2 = symptoms occur more than once a week but not daily
3 = symptoms occur daily without nocturnal asthma
4 = asthma wakes patient up at night

Frequency of Bronchodilator Use
0 = none
1 = less than once a week
2 = more than daily
3 = one to four times a day
4 = more than four times a day

Peak Flow Variability
0 = <6%
1 = 6%–10%
2 = 10%–15%
3 = 15%–25%
4 = >25%

Figure 1. Clinical criteria for the entry of asthmatic children into the study. Points were given according to the frequency of symptoms, the frequency of bronchodilator use, and the peak expiratory flow rate variability ([highest flow − lowest flow]/highest flow × 100). A severity score of 0–5 indicated mild disease; a score of 6–8, mild disease; and a score of 9–12, severe disease. Patients were enrolled in the study if they had a score of 6 or greater.

Nineteen age-matched control subjects were also recruited. No subject had a history of chronic pulmonary disease or evidence of acute respiratory infection within the 4 weeks prior to the study. One subject had a history of early childhood asthma but had been asymptomatic for several years. Because screening spirometry performed at CT showed evidence of air flow obstruction and a marked bronchodilator response, the patient was moved from the control to the asthmatic group before the CT evaluation. In their final configuration, there were nine girls and nine boys in the control group and 12 girls and nine boys in

the asthmatic group. The control subjects ranged in age from 7 to 16 years (mean ± standard deviation, 10.7 years ± 2.9), and the patients ranged in age from 7 to 17 years (mean ± standard deviation, 11.2 years ± 2.9).

CT Scanning

CT scanning was performed with a PQ 2000 CT scanner (Picker, Cleveland Heights, Ohio). Imaging was performed with 130 kVp and approximately 40 mAs. Low (radiation) dose scanning was performed to limit radiation exposure and has been shown to image the lung parenchyma adequately (11,12). Scans were obtained with a 20–25-cm field of view. Five 1.5-mm-thick sections were obtained with a high-spatial-frequency reconstruction algorithm at intervals of 10–20 cm, depending on the subject's size. To reduce radiation dose, a topogram was not obtained. The effective dose for all subjects was 0.06–0.09 mSv or less. The initial scan was obtained at the angle of Louis to approximate the level of the main carina. On the basis of the initial CT scan, the locations of additional sections were chosen such that the completed study included three sections below the main carina, one section at or near the main carina, and one section above the main carina. All scans were obtained at maximal inspiration.

Spirometry was performed immediately before CT and immediately after CT and the administration of inhaled albuterol, a bronchodilator.

Quantitative Interpretation of CT Scans

Images were reconstructed with a thin-section technique and saved to magnetic tape. The images were later reviewed and the airways measured with a Voxel Q workstation (Picker). Measurements were performed on images magnified with a zoom factor of three at standardized window and level values of 1,500 and −450 HU, respectively. We identified all airways segmental or smaller with 360° of contiguous bronchial wall. Bronchi with very high degrees of obliquity (including all airways seen only on the longitudinal section) were therefore excluded. The following measurements were obtained for each bronchus: the bronchial wall thickness at the narrowest point in the bronchial wall circumference, the smallest and largest outer bronchial diameter, the area of the outer circumference of the bronchus, and the area of the bronchial lumen. Bronchial wall thickness measurements were made with electronic calipers. Areas were measured with the semiautomated edge-detection option of the workstation, which was supplemented with a manual technique for cases in which the automatic method failed. All measurements were made six times, and the mean values were recorded.

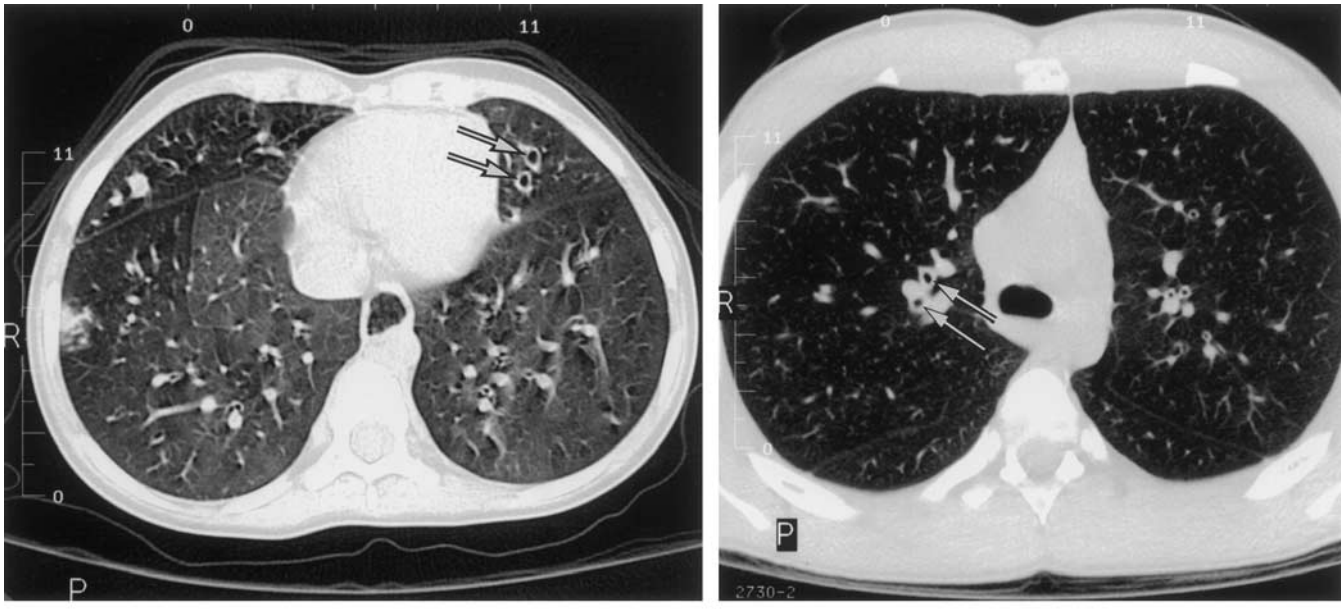
Wall area was calculated in two manners. First, wall area was calculated from linear measurements by using the method described by Awadh et al (5). We assumed that true airway wall thickness (WT) is constant in a cross-sectional plane and, by using the outer diameter (OD) of each airway, calculated the inner diameter (ID) as follows: ID = OD − 2WT. Luminal area (A_{lumen}) and total airway cross-sectional area (A_{total}) were calculated from the inner diameter and outer diameter, respectively, by using the general equation: area = $\pi(D/2)^2$, where D is the ID for A_{lumen} and D is the OD for A_{total}. Wall area was calculated with the following formula: $A_{total} - A_{lumen}$. Wall area was also calculated by subtracting the area of the outer bronchial circumference from the area of the bronchial lumen. The percentage wall area was calculated as the wall area divided by the area of the outer bronchial circumference. Obliquity was calculated by dividing the largest outer diameter by the smallest outer diameter. Airways with an obliquity of greater than 1.5 were excluded from the analysis of percentage wall area derived from area measurements owing to potential inaccuracies in measurement caused by volume averaging of the oblique sections.

Qualitative Interpretation of CT Scans

All thin-section CT scans were reviewed by S.W. and L.K., who were blinded as to the patient's name and the presence or absence of asthma. Before interpreting the scans, both readers reviewed thin-section CT scans of children with cystic fibrosis (Fig 2). From these studies, images were chosen to serve as standards for bronchial wall thickening. These images were chosen to represent a threshold level for bronchial wall thickening. The study patients' thin-section CT scans were then reviewed, and each hemithorax was given a score of 0 or 1 for the presence of bronchial wall thickening. Scoring was done by consensus. The scores for each hemithorax were then summed, such that a maximal score would be 10.

Statistical Analysis

Measurements of wall thickness and percentage wall area in asthmatic and nonasthmatic subjects were plotted against outer airway diameter. Because the percentage wall area decreases as the bronchial diameter increases, we chose not to compare asthmatic patients to control subjects with use of analysis of variance, as was per-



a. b.

Figure 2. **(a)** Thin-section CT scan obtained in a child with cystic fibrosis. Two bronchiectatic bronchi are seen in the lingula (arrows). These bronchi were identified as having mildly thickened walls. This CT scan was used as one of the imaging standards. **(b)** Thin-section CT scan obtained in a child with asthma. Two right upper lobe bronchi (arrows) are seen with approximately the same outer bronchial diameter as those seen in **a**. After comparison with the standard, these bronchi were classified as having thickened walls.

formed in other studies (10,13). In analysis of variance, the differences between the percentage wall area and wall thickness in asthmatic patients and control subjects might be masked owing to the variation within these groups caused by differences in airway size. This would be particularly important in our study, where only a limited number of airways could be measured. With use of a program written by an author (V.C.) with MATLAB software (Mathworks, Natick, Mass), least squares fit analysis was performed by using linear and quadratic regression for all four data sets, and residual analysis was performed. The curves with the best fit for asthmatic and control subjects were then compared by using the F statistic with an appropriate *df* (14).

Qualitative scores for bronchial wall thickening were compared by using SPSS software (SPSS, Chicago, Ill) to perform a Mann-Whitney *U* analysis.

RESULTS

Despite our attempt to examine asthmatic patients during clinical stability, the results of the pulmonary function tests in control subjects differed from those in asthmatic patients. The observed percentage of the predicted forced expiratory volume in 1 second (FEV_1) in asthmatic patients was slightly lower, but significantly different, than that in control subjects (0.88 ± 0.09 vs 0.94 ± 0.06, $P < .05$). Six of the asthmatic subjects demonstrated a statistically significant response to the bronchodilator, which was defined by an improvement in the FEV_1 of greater than 12% or an improvement in the FEV_1/forced vital capacity of greater than 17%. The only control subject to demonstrate a statistically significant response to the bronchodilator was moved to the asthmatic group for analysis.

Thin-section CT scans depicted 162 airways well enough to allow measurement of the percentage wall area and wall thickness. Quadratic equations provided the best fit in relating wall thickness and percentage wall area to bronchial diameter. The regression line relating wall thickness to outer bronchial diameter in asthmatic patients was significantly different from the line generated for nonasthmatic subjects ($P < .005$) and showed asthmatic airways with an outer diameter of 6–10 mm to have a greater wall thickness than similar-sized airways in healthy subjects (Fig 3a). When asthmatic patients with a bronchodilator response were excluded, the difference between the curves remained statistically significant (Fig 3b).

When the percentage wall area derived from linear measurements was plotted against the outer diameter, the

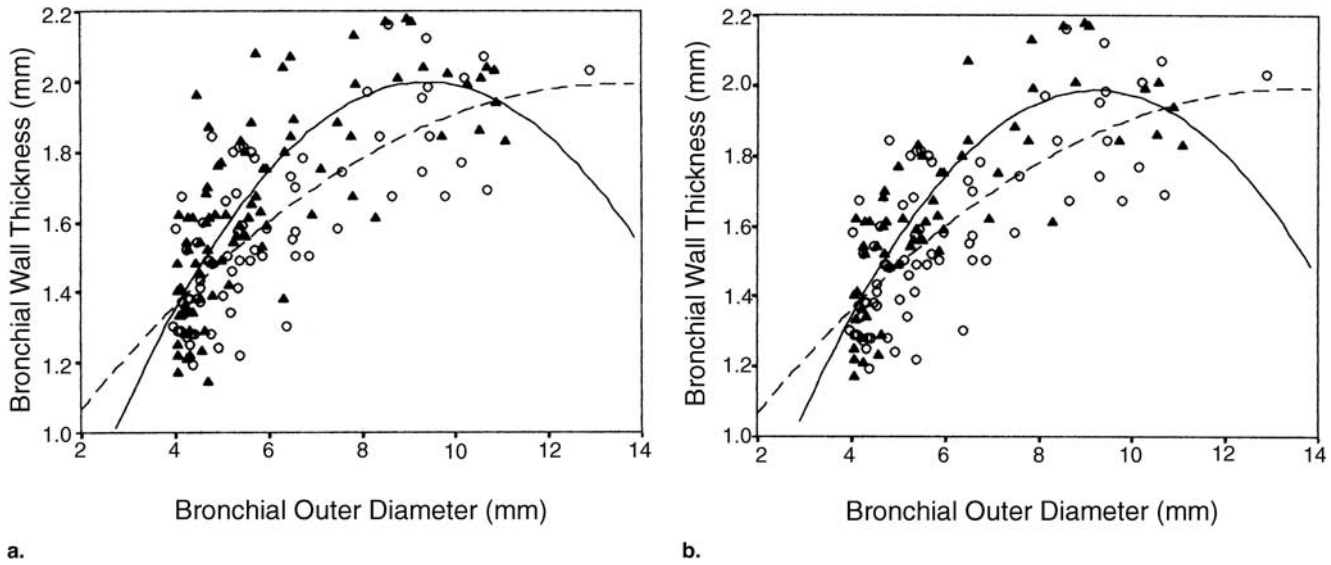


Figure 3. **(a)** Graph of bronchial wall thickness versus bronchial outer diameter for all asthmatic patients (▲, solid line) and control subjects (○, dashed line). The curve representing asthmatic patients was significantly different from that of control subjects ($P < .005$). The greatest increase in wall thickness in asthmatic patients appeared to occur in bronchi with diameters of 5–10 mm. **(b)** Graph of bronchial wall thickness versus bronchial outer diameter for asthmatic patients who did not have a positive response to a bronchodilator (▲, solid line) and control subjects (○, dashed line). The quadratic equation describing the asthmatic patients changed minimally.

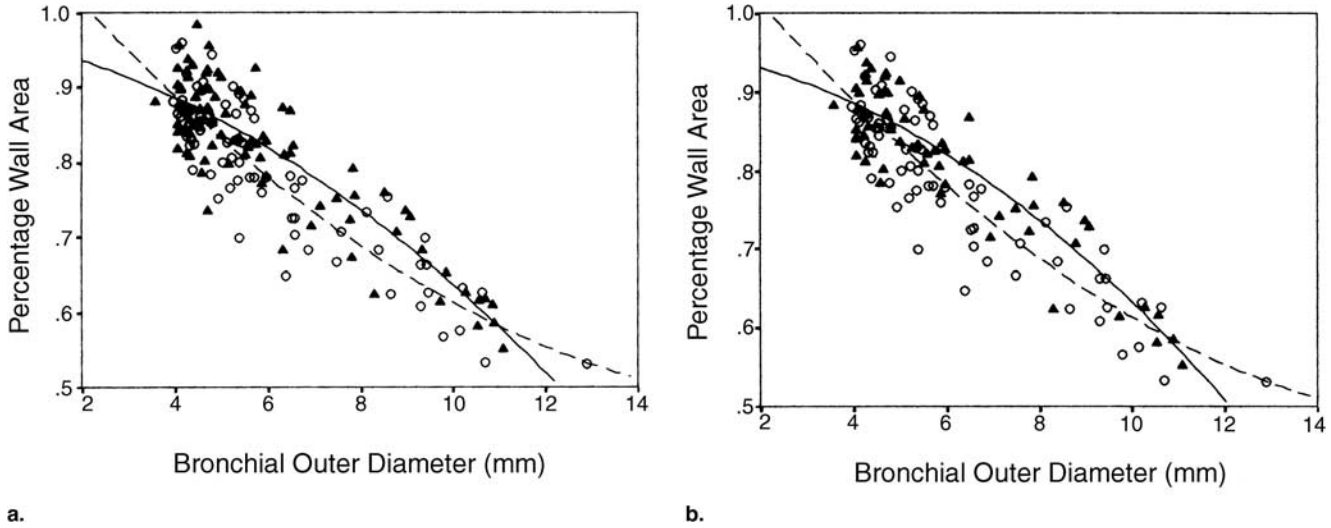


Figure 4. **(a)** Graph of percentage wall area as determined with linear measures versus outer bronchial diameter in asthmatic patients (▲, solid line) and control subjects (○, dashed line). The regression line representing asthmatic patients was significantly different from that of control subjects ($P < .05$). **(b)** Graph of percentage wall area as determined with linear measures versus outer bronchial diameter for patients who did not have a positive response to a bronchodilator trial (▲, solid line) and control subjects (○, dashed line). The quadratic equation describing the asthmatic patients changed minimally.

airways of the asthmatic patients were again significantly different from those of the control subjects ($P < .05$) (Fig 4). Calculation of the percentage wall area from area measurements was performed in 122 bronchi with an obliquity of 1.5 or less. When the percentage wall area derived from area measurements was plotted against outer diameter, the configuration of the curves was similar to that derived from linear measurements; however, the curves for asthmatic patients did not differ significantly from control subjects ($P > .1$) (Fig 5).

Qualitative scoring of thin-section CT scans showed asthmatic subjects to be significantly more likely than control subjects to have bronchial wall thickening ($P < .001$) (Fig 6). Fourteen of the 21 asthmatic patients

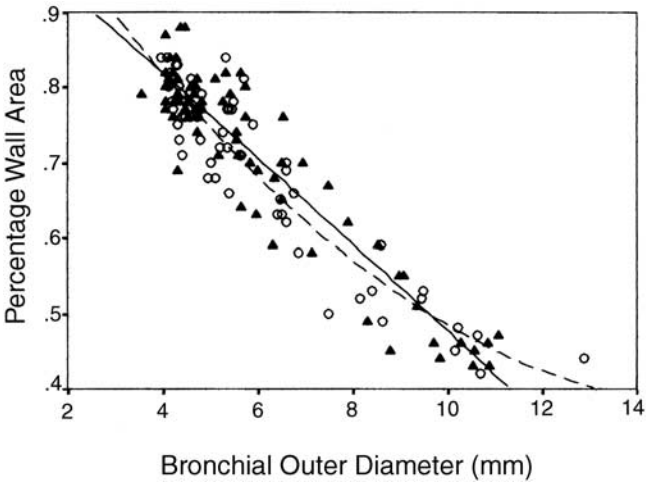


Figure 5. **(a)** Graph shows percentage wall area as determined with measured area versus bronchial diameter for all asthmatic patients (▲, solid line) and control subjects (○, dashed line). Although the shape of the regression lines are similar to those in Figure 4, the difference between the lines for the asthmatic patients and control subjects was not statistically significant ($P > .1$).

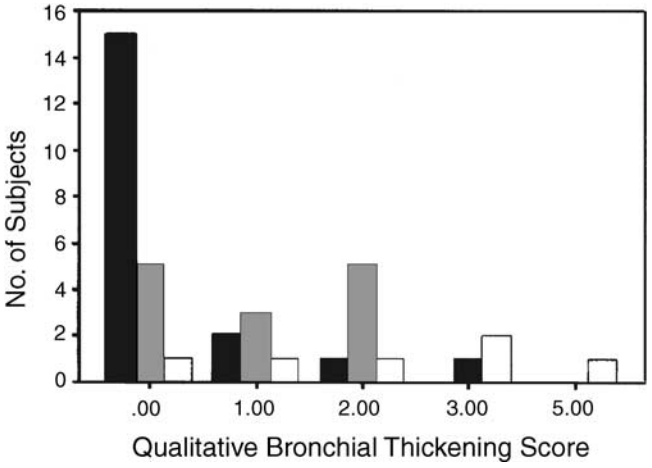


Figure 6. Graph shows the qualitative bronchial wall thickening scores for control subjects (black bars), asthmatic patients who did not respond to a bronchodilator (gray bars), and asthmatic patients who did respond to a bronchodilator (white bars). Taken as a whole, asthmatic patients had significantly higher scores than control subjects ($P < .001$). When data from asthmatic patients who responded to the bronchodilator were removed, the difference persisted ($P < .005$).

showed evidence of bronchial wall thickening at thin-section CT. Bronchial wall thickening was found in only three of the 18 control subjects. When asthmatic patients with a bronchodilator response were excluded, the qualitative CT scores in asthmatic patients still differed significantly from that in control subjects ($P < .005$). The CT scores of asthmatic patients who responded to a bronchodilator did not differ significantly from those of patients who did not respond ($P > .1$).

DISCUSSION

Previous studies with both qualitative and quantitative measures of bronchial morphology have shown evidence of bronchial wall thickening in asthmatic patients (2–6,15). Because of the possible effect of bronchoconstriction on airway wall thickness, it is often uncertain whether the increased wall area detected at thin-section CT actually represents airway inflammation and/or remodeling (increased basement membrane thickness, increased smooth muscle and mucous glands, etc). Although bronchoconstriction alone does not increase bronchial wall area, it does decrease bronchial diameter. If wall area is held constant while bronchial diameter decreases, both bronchial wall thickness and percentage wall area will increase. Therefore, the bronchial wall may appear thickened solely because the airway is narrowed (16).

We did find differences in the appearance of airways in asthmatic patients when compared with those in healthy subjects. Qualitative evaluation of the CT scans showed a greater prevalence of bronchial wall thickening in asthmatic patients compared with control subjects. Quantitative analysis of the bronchial wall thickness showed asthmatic patients to have thicker bronchial walls than control subjects relative to bronchial size. The percentage wall area relative to bronchial size was greater in asthmatic patients than in control subjects but reached statistical significance only when calculated from linear measurements. Measurements of both airway thickness and percentage wall area showed the differences between asthmatic patients and control subjects to occur in bronchi with an outer diameter of 4–10 mm. The lack of apparent wall thickening in airways greater than 10 mm in diameter may be real, as suggested by results of a previous study that failed to show wall thickening in the bronchus intermedius of asthmatic patients (17). The failure to find differences between asthmatic patients and control subjects in airways with an outer diameter of less than 4 mm (lumen less than 2 mm) more likely reflects the lower limits of our image resolution.

These findings raise two important points. First, qualitative scoring may be useful for detecting morphologic changes in the airway. This has been shown in previous studies of asthmatic adults (5,18). Qualitative differences in our study were more striking than the quantitative difference between the two groups. In part, this may reflect the ability to analyze airways with high degrees of obliq-

uity to the axial plane. These airways might be useful for qualitative scoring but would be excluded from quantitative analysis. This might be particularly important in studies such as ours, where only a limited amount of lung tissue is imaged, and, therefore, a limited number of airways are sampled.

Second, we believe the data suggest that at least some of the apparent bronchial wall thickening seen in the asthmatic children is due to airway remodeling. As mentioned earlier, to detect airway remodeling it is first important to exclude the possibility that airway wall thickening is due to bronchospasm. Results of thin-section CT studies of asthmatic adults have suggested an increased relative frequency of small airways (13). If bronchial wall area is held constant, such a widespread decrease in bronchial size caused by bronchospasm will increase bronchial wall thickness and percentage wall area.

In our study, results of pulmonary function tests showed evidence of only mild air flow obstruction within the asthmatic patients overall. A subset of asthmatic patients had evidence of active bronchospasm as detected with a bronchodilator response. The exclusion of these subjects from analysis did not diminish the differences between asthmatic and control subjects with respect to airway thickness and percentage wall area plotted against bronchial diameter. This suggests that bronchospasm did not play a substantial role in the morphologic changes seen in asthmatic children.

Our study was affected by difficulty in accurately measuring bronchial wall area. Although the curves generated by calculating wall area from linear measurements and those generated by using direct measurements of bronchial wall area show trends in the same direction, their configurations differ. Recent work in monitoring lung nodule growth would suggest that the calculations made from direct wall area measurements would be preferable (19). This work has shown that area measurements of lung nodules are more accurate than simple linear measurement of lung nodule diameter. Similarly, direct measurement of wall area would be expected to be a more sensitive method for detecting bronchial wall thickening. Investigators who have used this measurement successfully, however, have used special techniques such as score-guided erosion to determine the wall area (20). In contrast, the methods used for edge detection on proprietary workstations may vary, and it can be difficult to obtain specific information regarding the measurement algorithm from the manufacturer. With these proprietary methods, the inner margin of the bronchial wall is readily defined. The detection of the outer border, however, may be problematic owing to adjacent soft-tissue structures such as pulmonary arteries.

In contrast to wall area, bronchial wall thickness is easy to measure with proprietary software, with reproducible results. By performing the measurement on the narrowest portion of the contiguous bronchial wall, we selected a segment of bronchial wall perpendicular to the imaging plane. This eliminated the potential errors produced by airway obliquity and allowed us to include more airways in our data set when measuring bronchial wall thickness than when measuring the percentage wall area. This is particularly important when studying children, in whom the number of CT sections must be limited despite the use of a low (radiation) dose technique.

In summary, children with moderate to severe, stable asthma do have evidence of bronchial wall thickening. The observation that this bronchial wall thickening appears to be independent of a physiologic bronchodilator response suggests that these changes are due to airway inflammation or remodeling rather than bronchoconstriction. Direct measurement of wall area is likely to be the most accurate method for assessing morphologic changes in bronchi. Area measurements, however, are limited by the need for specialized software and by airway obliquity. When a limited number of airways are assessed with thin-section CT, regression analysis of linear wall measurements may be a useful adjunct.

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