

## ORIGINAL ARTICLE

# High resolution computed tomographic assessment of airway wall thickness in chronic asthma: reproducibility and relationship with lung function and severity

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**Background:** In some patients chronic asthma results in irreversible airflow obstruction. High resolution computed tomography (HRCT) has been advocated for assessing the structural changes in the asthmatic lung and permits investigation of the relationships between airway wall thickening and clinical parameters in this condition.

**Methods:** High resolution CT scanning was performed in 49 optimally controlled asthmatic patients and measurements of total airway and lumen diameter were made by two independent radiologists using electronic callipers. Wall area as % total airway cross sectional area (WA%) and wall thickness to airway diameter ratio (T/D) were calculated for all airways clearly visualised with a transverse diameter of more than 1.5 mm, with a mean value derived for each patient. Intra- and inter-observer variability was assessed for scope of agreement in a subgroup of patients. Measurements were related to optimum forced expiratory volume in 1 second (FEV<sub>1</sub>), forced mid expiratory flow, carbon monoxide gas transfer, two scores of asthma severity, airway inflammation as assessed with induced sputum, and exhaled nitric oxide.

**Results:** Neither observer produced a statistically significant difference between measurements performed on two occasions but there was a significant difference between observers (limits of agreement –2.6 to 6.8 for WA%,  $p < 0.0001$ ). However, mean WA% measured on two occasions differed by no more than 5.4% (limits of agreement –4.0 to 5.4; mean (SD) 0.7 (2.4)). Statistically significant positive associations were observed between both WA% and T/D ratio and asthma severity ( $r_s = 0.29$  and 0.30, respectively, for ATS score), and an inverse association with gas transfer coefficient was observed ( $r_s = -0.43$  for WA% and  $r_s = -0.41$  for T/D). No association was identified with FEV<sub>1</sub> or airway inflammation.

**Conclusions:** The airway wall is thickened in more severe asthma and is associated with gas transfer coefficient. This thickening does not relate directly to irreversible airflow obstruction as measured with FEV<sub>1</sub>.

Asthma is characterised by reversible airway narrowing but results in irreversible airflow obstruction in a subgroup of individuals.<sup>1</sup> The mechanisms remain unclear but may relate to remodelling in the airway. The subgroup of asthmatic subjects with irreversible airflow obstruction is of importance because they experience considerable morbidity and account for a high percentage of the health costs of asthma.

Airway wall thickening has been noted in post-mortem studies of asthmatic patients<sup>2</sup> and the development of high resolution computed tomography (HRCT) has provided a potential non-invasive technique for its measurement in vivo. Optimising spatial resolution by employing the narrowest feasible collimation beam (usually 1–1.5 mm diameter) and a high spatial frequency reconstruction algorithm ("bone algorithm") has improved resolution such that features of 100–200  $\mu$ m size can be identified, allowing assessment of small airways in the region of 1.5–2 mm diameter.<sup>3</sup> Consequently, HRCT scanning is increasingly being used as a research tool for studying obstructive lung disease.<sup>4–6</sup>

The structural changes in asthma comprise mucoid impaction and atelectasis, air trapping, bronchiectasis, bronchial dilatation, and bronchial wall thickening, although some causes of wall thickening such as airway wall oedema, mucoid impaction, and bronchoconstriction are potentially reversible. Thickened airway walls have been noted in asthmatic subjects

compared with normal controls,<sup>4</sup> with greater thickening in those with more severe asthma.<sup>7</sup>

The relevance of particular abnormalities to the clinical condition needs to be assessed and, in particular, the relationship of airway wall thickening to other clinical parameters of asthma severity and lung function remains unclear. However, the reliability of airway wall measurements needs to be studied. Reproducibility has received some attention in measuring sweet potato cylinders<sup>8</sup> and in cadaveric lungs.<sup>9</sup> The influence of window width and level settings on CT measurements has also been examined in phantoms and cadaveric lungs,<sup>8,9</sup> but few assessments have been made of the reproducibility of these measurements in patients with asthma.

In a radiological study of airway structural changes, patient groups need to be well characterised with optimal asthma control to exclude the influence of the potentially reversible airway changes. The HRCT techniques employed to study structural changes have differed with some groups only conducting measurements on larger airways<sup>10–12</sup> in which thickening may not be seen, and no attempt has been made to optimise asthma control.<sup>7,10,12</sup> In some studies the images have been analysed with window settings that make visualisation of the airways easier but do not produce anatomically accurate results.<sup>13</sup>

This study has examined a group of individuals with well controlled chronic asthma in whom a variety of airway sizes have been measured at a window level and width that most

accurately reflect the bronchial anatomy.<sup>3, 14</sup> The reproducibility of the measurements and the relationship of various clinical parameters to these measures of airway wall thickening were studied.

## METHODS

Patients were recruited from the respiratory outpatient clinic and from community contacts. All had a diagnosis of asthma, according to the American Thoracic Society criteria,<sup>15</sup> for at least 5 years and had had no acute exacerbation within the preceding month. All were non-smokers or, if ex-smokers, had stopped a minimum of 5 years earlier and had smoked a maximum of 10 pack-years. The study was approved by the West Ethics Committee, West Glasgow Hospitals University NHS trust, and all volunteers gave informed consent.

### Study design

To ensure optimum asthma control and lung function, a 2 week course of oral prednisolone at a dose of 30 mg/day or, where oral steroids were contraindicated in three volunteers because of previous side effects, 2000 µg of fluticasone was administered via a Volumatic spacer each day. At baseline and following steroid administration the patients performed spirometric tests (Vitalograph Ltd, Buckingham, UK) with reversibility to 2.5 mg nebulised salbutamol, exhaled nitric oxide measurement, and induced sputum. The ATS and Aas severity scores<sup>16, 17</sup> were recorded and a patient self-assessment symptom score completed.<sup>18</sup> Following the course of steroids, gas transfer was measured using the single breath technique with carbon monoxide (CO) as trace gas (Sensormedics System 2000 using mass flow sensor), and bronchial hyperresponsiveness to histamine was assessed. Computed tomographic scanning was performed after steroid and β<sub>2</sub> agonist. The best forced expiratory volume in 1 second (FEV<sub>1</sub>) as a percentage of the predicted value for age, sex, and height was taken as that following the steroid course and nebulised bronchodilator.

### Measurements

#### Sputum induction

Sputum induction was performed following assessment of reversibility to salbutamol using hypertonic (3%) saline administered via an ultrasonic nebuliser (Sonix 2000, Medix Ltd, Harlow, Essex, UK) over a period of 20 minutes.<sup>19</sup> The subjects were encouraged to expectorate at any time throughout the procedure and, in addition, inhalation was stopped every 5 minutes to allow expectoration and to allow spirometric tests to be performed. The sample was collected in a sterile container and transferred to the laboratory on ice as soon as possible, and in all cases in less than 2 hours.

All samples were processed without the laboratory staff being aware of the clinical information relating to the individual subject, and the procedure followed was similar to that described by Popov *et al.*<sup>20</sup> Differential cell counts were produced, expressed after exclusion of squamous epithelial cells which are taken to represent salivary contamination.

#### Exhaled nitric oxide

Exhaled nitric oxide measurements were performed using a Logan Research analyser (Logan Research Ltd, Rochester, Kent, UK) which operates on the principle of chemiluminescence. The technique used was that recommended by the European Respiratory Society Task Force.<sup>21</sup>

#### Histamine inhalational challenge

Bronchial hyperresponsiveness to histamine was established using doubling doses of inhaled histamine from 0.0625 to 16 mg/ml.<sup>22</sup>

### High resolution computed tomography

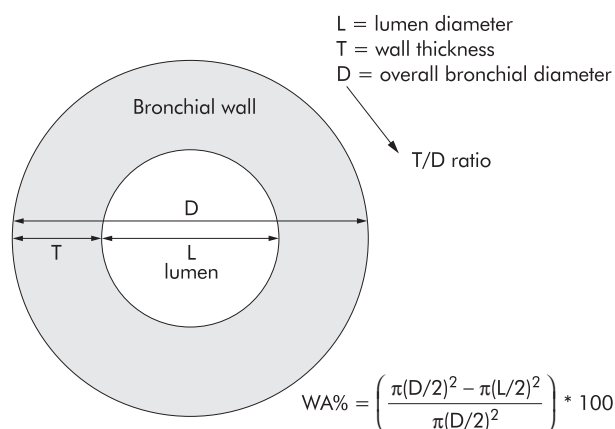
All the CT studies were performed on a Philips Tomoscan AV scanner using a high resolution technique: collimation 1.5 mm, images reconstructed using a high spatial frequency algorithm and a 512 × 512 matrix. The scan time was 1 second, kV 120, mAs 200. The images were analysed on a window width of 1500 Hounsfield Units (HU) and window level of -600 HU. Five sections were obtained from an initial "scanogram": top of the aortic arch, main carina, 1 cm below the main carina, level of the pulmonary veins, and 2 cm above the right hemidiaphragm. Data were collected at full inspiration with additional scans at the five levels on expiration for assessment of air trapping and mosaic perfusion.<sup>23, 24</sup>

The images were viewed on a work station using a magnification of ×5, and measurements of overall (D) and internal (L) diameter of the bronchi were made using electronic callipers, with wall thickness (T) being derived from these measurements ( $T = (D - L)/2$ ). All bronchi of more than 1.5 mm in diameter clearly seen in cross section were measured in each slice of the inspiratory scans. Oblique sections influence wall thickness, and the long to short diameter ratio was used to assess "roundness" with an upper limit of 1.5 being permitted and measurements then being performed across the short diameter.<sup>3</sup>

Measurements were conducted by two experienced thoracic radiologists (MC and MS) working independently. Wall area was calculated as a percentage of total airway cross sectional area (WA%; fig 1), thereby relating wall thickness to bronchial size, and a mean value was calculated for each patient for each observer from all the bronchi measured. Given that two independent observers may identify a different position for the wall edge, we combined the data from the observers to obtain a consensus measurement of wall thickness, taking the mean of the average values obtained for the two observers for each assessment. Wall thickness was expressed as a ratio to the total airway diameter (T/D ratio) and a consensus value for each patient was created in the same way, giving single measures of WA% and of T/D ratio.

For the first 35 scans, measurements of wall thickness were performed on two separate occasions giving a total of four reports for each scan (report 1 and report 2 for both observers X and Y). To assess intra-observer variability we compared the value of WA% and T/D ratio for each patient from report 1 and report 2 for each observer. Inter-observer variability was examined by comparison of the value for report 1 from observer X with the value for report 1 from observer Y. By comparing the consensus report 1 with consensus report 2 we derived an overall assessment of reproducibility.

Each HRCT scan was also assessed for a variety of structural abnormalities that can occur both in the acute setting or represent longstanding change. In each section evidence was



**Figure 1** Measurement of bronchial and lumen diameter with calculation of WA% and T/D ratio.

**Table 1** Characteristics of study subjects

	Mean (SD)	Median (interquartile range)
Age (years)	54.3 (11.7)	
Duration of asthma (years)	30.8 (16.3)	
Dose of inhaled steroid ( $\mu$ g beclomethasone)		1000 (800–2000)
Baseline FEV <sub>1</sub> (% predicted)	60.6 (21.8)	
Best FEV <sub>1</sub> (% predicted)	72.8 (21.7)	
Baseline FEF <sub>25-75</sub> (% predicted)	38.7 (23.2)	
Best FEF <sub>25-75</sub> (% predicted)	50.8 (27.7)	
Kco (% predicted)	101.0 (21.8)	
Log PC <sub>20</sub> to histamine	−0.18 (0.7)	
Post-steroid absolute neutrophil count ( $\times 10^6$ cells/ml sputum plug)		22.9 (12.0–33.6)
Post-steroid percentage neutrophil count		73.0 (48.0–81.0)
Post-steroid absolute macrophage count ( $\times 10^6$ cells/ml sputum plug)		8.0 (6.8–14.0)
Post-steroid percentage macrophage count		25.0 (18.0–52.0)
Post-steroid exhaled nitric oxide (ppb)		6.1 (4.2–9.5)
Wall area as % bronchial cross sectional area (WA%)	75.5 (3.2)	
Wall thickness/bronchial diameter ratio (T/D ratio)	0.26 (0.02)	

FEV<sub>1</sub>=forced expiratory volume in 1 second; FEF<sub>25-75</sub>=mid forced expiratory flow; Kco=carbon monoxide transfer coefficient. Data are listed as mean (SD) for normally distributed variables and as median (interquartile range) for non-parametric variables. The airway cell counts and exhaled nitric oxide measurement are the values at optimum asthma control following the steroid trial.

sought for airspace opacity, mucoid impaction, atelectasis, vascular distortion, hyperlucent areas, bullae, bronchiectasis, mosaic perfusion, and air trapping. From the data acquired the presence or absence of these features was documented for five areas: right upper, middle and lower lobes, and left upper and lower lobes. Dividing patients on the basis of optimum FEV<sub>1</sub> following the steroid trial and bronchodilator treatment, the relative frequency of these features was reviewed and reported as a percentage of the total number of areas assessed.

### Statistical analysis

Statistical analyses were performed using SAS for Windows Version 6.12. The data were summarised using the mean and standard deviation for continuous approximately normal data, proportions for categorical data, and the median and interquartile range in all other cases. Analyses of reproducibility were graphically assessed using the methods of Bland and Altman<sup>25</sup> and formal analyses were carried out using the paired *t* test. Correlations between factors were assessed using the Spearman rank correlation coefficient ( $r_s$ ) to account for any deviations from normality.

## RESULTS

### Subjects

Forty nine patients (27 male) completed the study, with three having a trial of high dose inhaled steroids rather than oral prednisolone. Descriptive data are listed in table 1; the mean (SD) age was 54.3 (11.7) years, duration of asthma 30.8 (16.3) years, and median dose of inhaled steroid was equivalent to 1000  $\mu$ g beclomethasone. Seven patients were ex-smokers

with a mean of 3.3 pack-years who had stopped smoking for a mean of 27.4 years. The baseline mean (SD) FEV<sub>1</sub> was 60.6 (21.8)% predicted and the best FEV<sub>1</sub> following the trial of steroid and bronchodilator was 72.8 (21.7)% predicted. The two radiologists performed measurements of a total of 797 bronchi with a mean (SD) diameter of 4.7 (1.5) mm (range 2.2–10.7 mm). Reproducibility was assessed in the first 35 patients.

### HRCT wall area reproducibility

The observers each measured a mean (SD) of 8.0 (3.0) bronchi in each scan on each occasion. The mean (SD) diameter of the bronchi measured was 4.8 (1.5) mm (range 2.3–9.6 mm).

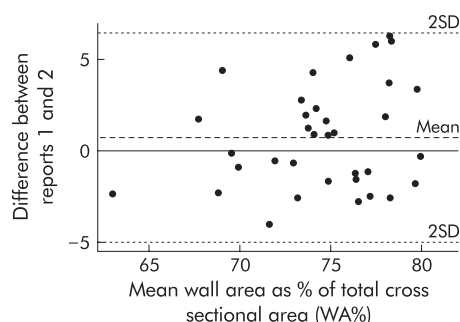
Two average measurements of wall thickness/area (T/D ratio and WA%) were produced for each patient for each observer (reports 1 and 2 for observers X and Y). Comparison of the two reports for each observer for intra-observer variability revealed scatter of values but no statistically significant difference in either WA% or T/D ratio (table 2, Bland-Altman plots in figs 2 and 3). To determine inter-observer variability the first reports (report 1) from each observer were compared and a statistically significant difference was seen between the two observers for both WA% and T/D ratio ( $p < 0.0001$ ; fig 4).

A consensus value for both WA% and T/D ratio was created by taking the average of the values from both observers to create consensus reports 1 and 2. These two reports were then compared both in terms of WA% and T/D ratio and no statistically significant difference was seen between them (fig 5). The maximum (SD) difference between the two reports was 5.4 (2.4) for WA% and 0.028 (0.012) for T/D ratio.

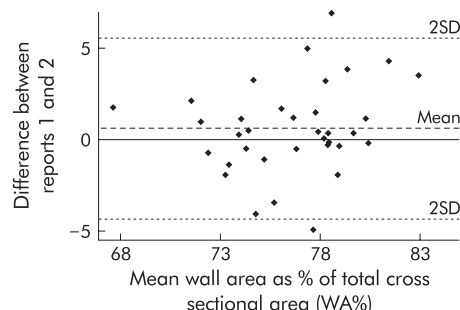
**Table 2** Assessment of agreement

	Mean difference (report 2 – report 1)	SD of difference	Limits of agreement	p value
Wall area (WA%)				
Observer X, intra-observer agreement	0.7	2.9	−5.0 to 6.5	0.14
Observer Y, intra-observer agreement	0.6	2.5	−4.4 to 5.6	0.14
Inter-observer agreement	2.1	2.3	−2.6 to 6.8	<0.0001
Agreement in consensus views for reports 1 and 2	0.7	2.4	−4.0 to 5.4	0.10
T/D ratio				
Observer X, intra-observer agreement	0.004	0.014	−0.025 to 0.033	0.11
Observer Y, intra-observer agreement	0.003	0.013	−0.024 to 0.030	0.18
Inter-observer agreement	0.011	0.012	−0.013 to 0.034	<0.0001
Agreement in consensus views for reports 1 and 2	0.004	0.012	−0.021 to 0.028	0.10

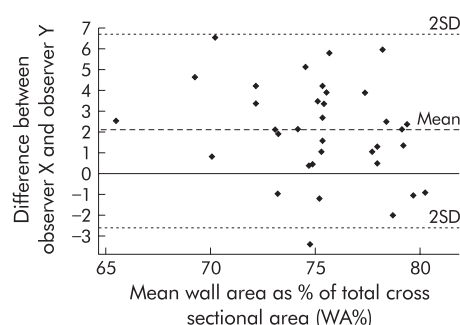
WA%=wall area as % total airway cross sectional area; T/D=wall thickness to airway diameter ratio.



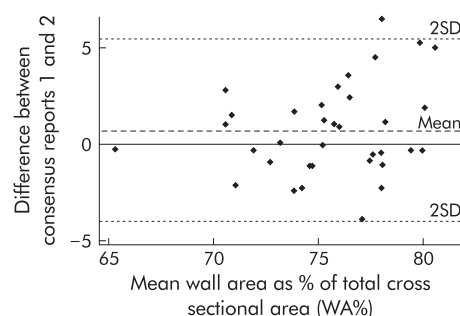
**Figure 2** Bland-Altman plot of intra-observer variability for WA% for observer X.



**Figure 3** Bland-Altman plot of intra-observer variability for WA% for observer Y.



**Figure 4** Bland-Altman plot of inter-observer variability for WA%.



**Figure 5** Bland-Altman plot of intra-observer variability for consensus reports of WA%.

### Descriptive CT assessment

The presence of various structural features increased with increasing airflow obstruction (table 3). Only five of 13 scans (38.5%) were normal in the group with an  $FEV_1$  of  $<60\%$  predicted compared with 14 of 21 scans (66.7%) in those with an  $FEV_1$  of  $\geq 80\%$  predicted. In terms of lung areas assessed, 52% were normal in the former group and 82% in the latter group.

### Associations

The associations between WA%, T/D ratio, and various clinical parameters are shown in table 4. There were statistically significant positive associations between wall thickening (expressed as both WA% and T/D ratio) and the ATS and Aas severity score (WA%:  $p=0.044$  and  $p=0.023$ ; T/D ratio:  $p=0.035$  and  $p=0.019$ , respectively). Negative associations were observed between wall thickening and carbon monoxide gas transfer coefficient ( $K_{CO}$ ) following the steroid trial and bronchodilator treatment (fig 6). No statistically significant associations were identified between wall area/thickness (WA% and T/D) and airway cell counts or exhaled nitric oxide either at baseline or following the steroid trial.

A trend to a negative association was observed between wall thickness and  $FEV_{25-75}\%$  predicted following the steroid trial and bronchodilator but this did not quite reach statistical significance. No association was identified between  $FEV_1$  and wall thickness.

### DISCUSSION

We have shown that, although differences occur when repeating measurements of airway wall thickness on HRCT images, there was no systematic bias between each of the two reports produced by the two experienced radiologists. A statistically significant difference was noted between the results for each observer, suggesting that each selects a slightly different position for the wall edge. However, when an average measurement was taken for the two observers, there was no statistically significant difference between two consensus reports. The greatest difference between reports for WA% was 5.4% and this value must be considered if assessing potential longitudinal changes in airway wall thickness as determined by HRCT scanning.

There are various potential sources of error in the measurement of wall thickness on HRCT images. Airway secretions and bronchospasm may result in an overestimate of airway wall thickness, and some changes are potentially reversible.<sup>26</sup> It is therefore essential that asthma is optimally controlled before HRCT assessment and all our patients were examined following a steroid trial, with the post-steroid, post-bronchodilator  $FEV_1$  being taken as a surrogate marker for irreversible airflow obstruction. The patients were well characterised, included a broad spectrum of lung function, and any with a significant smoking history were excluded to avoid confusion from smoking related lung disease. The HRCT scans were performed and displayed in accordance with the recommended technical considerations. We measured bronchi throughout the lung, taking a mean value for each individual, given that structural changes are not homogeneous. The resulting measurements of wall thickness are comparable to those reported from a previous study where similar techniques were used.<sup>7</sup>

Varying the window settings can skew the image appearance and give a sharp wall definition. While potentially improving measurement reproducibility,<sup>27</sup> the images are less physiological, with varying effects on lumen diameter depending upon the window level.<sup>8</sup> The error produced by "incorrect" window settings is constant in absolute terms and hence a smaller percentage as airway size or wall thickness increases.<sup>13</sup> Window width may be more important than window level when measuring wall thickness *in situ*,<sup>9</sup> and in most human studies the window level has been set at between  $-450$  and  $-700$  HU with a window width of  $1350$ – $1600$  HU.<sup>3, 14</sup>

A further issue involves orientation of the bronchi on the CT slices, with oblique sections influencing wall thickness. The long to short diameter ratio of the airway lumen has been used to assess airway "roundness" with an upper limit of 1.5 for this ratio commonly being used,<sup>3</sup> although this assumes that the lumen of the airway is always round and even a ratio of 1.5



**Table 3** Descriptive assessment of CT scans for various structural changes (values recorded as percentage of total number of areas assessed for each group)

FEV <sub>1</sub> (% predicted)	No of patients	No of areas assessed	Normal areas	Hyperlucent areas	Vascular distortion	Bullae	Mosaic perfusion	Air trapping	Bronchiectasis	Mucoid impaction	Atelectasis	Airspace opacity
≥80%	21	105	82	0	0	0	7.6	0	4.8	0	0	0
60–79%	15	75	84	0	0	0	6.7	0	1.3	0	0	1.3
<60%	13	65	52	16.9	24.6	12.3	13.8	7.7	24.6	0	7.7	4.6

**Table 4** Correlation of WA% and T/D ratio with lung function, asthma severity and duration, patient age, and airway inflammation

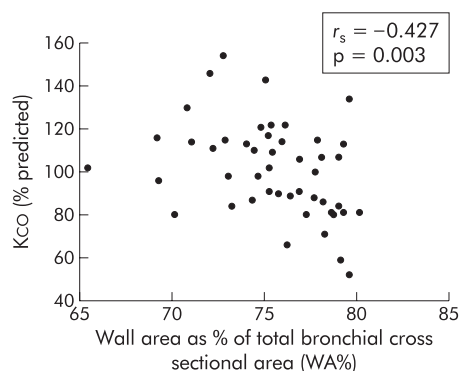
	WA%	T/D ratio
Baseline FEV <sub>1</sub> (% predicted)	−0.174 (0.23)	−0.196 (0.18)
Best FEV <sub>1</sub> (% predicted)	−0.108 (0.46)	−0.119 (0.42)
Baseline FEF <sub>25–75</sub> (% predicted)	−0.252 (0.08)	−0.266 (0.07)
Best FEF <sub>25–75</sub> (% predicted)	−0.237 (0.10)	−0.246 (0.09)
Kco (% predicted)	−0.427 (0.003)	−0.414 (0.003)
Duration of asthma	0.141 (0.33)	0.151 (0.30)
Patient age at entry to trial	0.136 (0.35)	0.149 (0.31)
Log PC <sub>20</sub> to histamine	−0.171 (0.24)	0.179 (0.22)
ATS severity score	0.290 (0.044)	0.302 (0.035)
Aas severity score	0.325 (0.023)	0.334 (0.019)
Post-steroid absolute neutrophil count	−0.090 (0.62)	−0.047 (0.79)
Post-steroid percentage neutrophil count	−0.169 (0.35)	−0.130 (0.47)
Post-steroid absolute macrophage count	0.057 (0.75)	0.035 (0.85)
Post-steroid percentage macrophage count	0.110 (0.54)	0.074 (0.68)
Post-steroid exhaled nitric oxide	−0.153 (0.38)	−0.154 (0.38)

FEV<sub>1</sub>=forced expiratory volume in 1 second; FEF<sub>25–75</sub>=mid forced expiratory flow; Kco=carbon monoxide transfer coefficient; WA%=wall area as % total airway cross sectional area; T/D=wall thickness to airway diameter ratio. Values are given as Spearman correlation coefficient with p values in parentheses.

could permit a significant deviation from perpendicular to the scanning plane. While a potential problem, this is not easily addressed.

The issue of human error has been addressed with computerised techniques, although initial studies did not assess reproducibility<sup>28</sup> or involved suboptimal scanning techniques.<sup>29</sup> Computerised methods hold promise for the future and a recent study extended such analysis through the development of an algorithm to measure airway wall and lumen area directly.<sup>30</sup> The technique also permitted assessment of the angle of orientation of the airway, and comparison was made with manual measurements. However, the study used phantoms and excised pig lung and remains to be validated in human studies.

Although reproducibility has been assessed in phantom and cadaveric studies, it is essential to extend the work to humans.

**Figure 6** Plot of bronchial wall area, expressed as a percentage of overall bronchial cross sectional area, and carbon monoxide transfer coefficient as percentage of predicted value.

One recently published study has done so,<sup>12</sup> but the technique includes potentially confounding factors. Some patients were scanned at first presentation with uncontrolled asthma and measurements were performed on only a single large bronchus which, while potentially improving reproducibility, is not applicable to a process which is unlikely to be homogeneous throughout the airways. Furthermore, helically acquired scans were used with consequent loss of spatial resolution, further distorting the true wall thickness.

In this study we have also examined the association of various clinical parameters in chronic asthma with HRCT determined airway wall thickness in a group of individuals with optimally controlled disease. Structural changes are more prevalent in those with greater airflow obstruction, and a relationship was identified between asthma severity (as determined by the ATS and Aas severity scores) and airway wall thickness. Two additional important observations are also apparent from the results: no association was seen between wall thickness and FEV<sub>1</sub>, and a statistically significant inverse association was identified with gas transfer coefficient.

The association between asthma severity and wall thickness has previously been suggested,<sup>7</sup> with increased bronchial wall thickening observed in patients with severe asthma as defined by the Aas severity score,<sup>17</sup> although the assessment was subjective with no attempt to measure either wall area or thickness.<sup>26</sup> However, FEV<sub>1</sub> in chronic asthma does not appear to reflect bronchial wall thickness as assessed by HRCT scanning. The wall thickening seen radiologically encompasses smooth muscle hyperplasia/hypertrophy, subepithelial fibrosis, and extracellular matrix and structural changes in one of these may be more influential. The subsequent effects on airway mechanics remain unclear, although thickening of the subepithelial layer decreases the airway luminal area and exacerbates the effect of airway smooth muscle shortening.<sup>31–32</sup> The trend towards the association seen in this

study with FEF<sub>25-75</sub> suggests that small airway function may be influenced more by bronchial wall thickening than is FEV<sub>1</sub>.

A previous study of airway wall thickening also found no association with lung function but, in addition, no relationship was found with other clinical features.<sup>11</sup> The HRCT protocol differed, using a window width of 1000 HU and performing measurements manually on images magnified via an overhead projector, potentially influencing resolution. The asthmatic group included a substantial number with an unspecified smoking history and, as with other studies, no attempt was made to optimise asthma control before scanning.

A recently published study has also assessed various clinical indices in relation to airway wall thickening observed by CT scanning.<sup>12</sup> While various correlations were noted between wall area and lung function, the study results are potentially compromised because some patients were scanned at first presentation with uncontrolled asthma when the wall area observed is likely to include airway oedema which is potentially reversible with optimum treatment. Furthermore, measurements were performed on only a single bronchus to assess a process which is unlikely to be homogeneous throughout the airways, and were made on helically acquired scans with consequent loss of spatial resolution, further distorting the true wall thickness. Our own results suggesting a trend for an association with FEF<sub>25-75</sub> indicate that small airway dimensions are of importance and should be included in such measurements.

Niimi and colleagues assessed wall area in absolute terms and also in relation to bronchial size (WA%) and body surface area.<sup>12</sup> Absolute wall area is affected by bronchial size and, while body surface area is a surrogate for changes in bronchial dimensions, it may avoid the potential influence of bronchiectasis or bronchoconstriction. The latter is not an issue if scans are performed after steroid and bronchodilator administration, but the effect of the former may be more difficult to assess. Our own technique uses a mean of many measurements and should reduce this influence.

Airway inflammation is central to the pathophysiology of asthma and it is suggested that uncontrolled inflammation may result in airway remodelling.<sup>33</sup> Increased levels of neutrophils have been identified in biopsy samples,<sup>34</sup> lavage fluid,<sup>35</sup> and induced sputum<sup>36</sup> from severe asthmatics. In this study, however, and consistent with the lack of association with FEV<sub>1</sub>, we have observed no association between airway inflammatory cells in induced sputum and the airway wall thickening observed on HRCT scans.

An explanation for the association between bronchial wall thickening and gas transfer coefficient is not immediately obvious, but further raises the issue of air trapping and "emphysema" in asthma. Low attenuation areas have been seen on CT images in asthma and could be a consequence of regional reduction of pulmonary blood flow,<sup>37</sup> gas trapping, emphysema, or a combination of these. HRCT is certainly sensitive to the changes of emphysema but, although similar changes have been identified, it remains unknown whether they represent emphysema with alveolar wall destruction or non-destructive hyperinflation, and the specificity of the technique for asthmatics is unclear. Estimates of the prevalence of emphysema in asthmatic subjects using CT/HRCT scanning therefore range from 0% to 80%.<sup>4 6 26 38</sup> "Terminal air space enlargement" may result from fibrotic changes and airway remodelling and further work is required to define the pathology being identified by HRCT scanning in non-smoking asthmatics.

Most CT studies are performed with full inspiration, but expiratory scans are more effective for identifying air trapping<sup>23 24</sup> which can result either from fixed processes that occlude or narrow the airways or from a reactive process that increases resistance (such as asthma). During exhalation the lung normally increases in CT attenuation as the amount of air

in the volume of the lung being scanned is reduced. With air trapping the involved lung parenchyma remains more lucent than the surrounding lung.<sup>39</sup> Clearly, if the process is diffuse rather than local, the differential in attenuation will not exist and hence diffuse air trapping can be difficult to identify. In our study we identified no emphysema and air trapping was observed in just one individual, with mosaic perfusion in a further four suggesting air trapping. The association of bronchial wall thickness with gas transfer may be a consequence of air trapping not visible on HRCT scans secondary to narrowing of the smaller airways as demonstrated by the trend with FEF<sub>25-75</sub>.

We have radiologically assessed bronchial wall thickening in patients with chronic asthma and examined the relationships with various clinical parameters. We have addressed the various potential confounding factors, optimising disease control in a group of well characterised asthmatic subjects and using accepted parameters for HRCT scanning together with a collimation of 1.5 mm to limit volume effects. A small difference occurred when measurements were repeated, being at most 5.4% of the total bronchial cross sectional area. This must be borne in mind if the technique is used for the assessment of longitudinal changes in bronchial wall thickness, either for examining progression of airway remodelling or the influence of intervention. We found a trend towards an association with FEF<sub>25-75</sub> but not with FEV<sub>1</sub>. Although remodelling influences the dimensions of the small airways, the irreversible airflow obstruction of chronic asthma relates perhaps to one element of the process or its effects on airway function.

While this technique may prove useful in the research setting, especially in longitudinal studies of remodelling and the effect of treatment, it is likely to be too time consuming for a clinical role. The association with gas transfer coefficient therefore requires further examination as this offers a potential marker of bronchial wall thickening without recourse to HRCT scanning with its associated radiation exposure and labour intensive measurements.

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