

DIAGNOSIS

Lung-volume controlled computerised tomography in real-life acute severe asthmaXun Li, MD, MBBS¹, Parm Naidoo, MBBS, FRANZCR², Paul Guy, BSc CRFS¹, Paul Finlay, Dip App Sci CRFS¹, Soo-Wei Foo, MBBS¹, Kais Hamza, PhD³, and Phil Bardin, PhD, FRACP¹¹Department of Respiratory and Sleep Medicine, ²Department of Diagnostic Imaging, and ³School of Mathematical Sciences, Monash University and Hospital, Melbourne, Australia**Abstract**

Objective: It is not known how airway structure is altered during real-life acute asthma exacerbations. The aim of this study was to examine changes in airway structure during acute asthma exacerbations and at convalescence by using lung-volume controlled high resolution computerised tomography (HRCT). **Methods:** Eight subjects with acute asthma exacerbation admitted to hospital were recruited. HRCT was performed within 72 h of admission ($n = 8$) and repeated after 8 weeks of convalescence ($n = 7$). Individual airways were carefully matched on acute and convalescent CT data sets for comparisons of airway parameters. A novel methodology was employed for standardisation of lung volumes to permit valid comparisons of lung imaging. Measurements of bronchial cross sectional airway area (Aa) and bronchial luminal area (Ai) for each matched airway were obtained using a validated program. **Results:** The airway wall thickness was analysed as wall area (WA) calculated as a percentage: $WA\% = WA/Aa \times 100$. Wilcoxon signed-rank testing was used to compare acute and convalescent asthma and Spearman's correlation to examine associations. Airway lumen (Ai) areas were similar in both acute and stable asthma phases ($6.6 \pm 3.1 \text{ mm}^2$ versus $7.2 \pm 3.8 \text{ mm}^2$ $p = 0.8$). However, the airway wall was significantly thickened during acute asthma exacerbations compared to convalescence ($62 \pm 4\%$ versus $55 \pm 7\%$; $p = 0.01$). There was no correlation between airway structure dimensions and lung function measurements. **Conclusions:** This is the first study to demonstrate an increase in airway wall thickness during real-life acute asthma exacerbation. However, narrowing of the airway lumen area was variable and will require larger studies able to detect small differences. These results suggest that airway wall thickening linked to mucosal inflammation is likely to characterise acute asthma *in vivo* but that changes in the airway lumen accompanying bronchoconstriction may be more heterogeneous.

Introduction

Asthma exacerbations occur unpredictably, are an important cause of morbidity and mortality, and contribute significantly to increased healthcare costs. The heterogeneity of stable asthma is highlighted by different phenotypes identified using cluster analysis [1]. Dividing a multidimensional disease complex such as asthma into distinct phenotypes may help prevent exacerbations more effectively as exemplified by the success of eosinophils airway inflammation-directed corticosteroid and anti-interleukin 5 (IL-5) treatment [2–4]. Whether comparable asthma exacerbation phenotypes exist is not known and there is a critical gap in our understanding of how altered airway structure during acute exacerbation is linked to airway obstruction.

Technical advances in medical imaging have provided an opportunity to examine human airways non-invasively and

Keywords

Acute asthma, airway wall thickness, HRCT

History

Received 18 August 2013

Revised 10 October 2013

Accepted 23 October 2013

Published online 17 December 2013

more accurately than ever before. High-resolution computed tomography (HRCT) has emerged as a reliable and accurate tool for non-invasive quantitative assessment of the site, magnitude, and distribution of airway structure changes *in vivo*. A number of investigators have used HRCT to study asthmatic airways and provided information that improves understanding of the role of airway structure in pathophysiology of asthma. However, no study of acute asthma exacerbation has ever been conducted using modern HRCT techniques.

We hypothesised that key airway dimensions as assessed by CT are significantly altered during acute asthma exacerbation. The study compared acute and convalescent asthma in the context of equivalent lung volumes, evaluated variations in airway structure and related these changes back to overall measurements of lung function.

Methods**Patients**

Eight consecutive subjects with an acute asthma exacerbation who attended to the Emergency Department of Monash

Correspondence: Dr Xun Li, Department of Respiratory and Sleep Medicine, Monash University and Medical Centre, 246 Clayton Rd, Clayton 3168, Melbourne, Australia. Tel: +61 3 95942281. Fax: +61 3 95946415. E-mail: xun.li@southernhealth.org.au

Medical Centre, Melbourne, were recruited. One subject was lost to follow-up. Patients were diagnosed with asthma according to American Thoracic Society criteria [5]. All patients were non-smokers or ex-smokers who had smoked less than 5 packs-years. Six patients had received inhaled glucocorticosteroid (ICS) therapy for >10 years prior to study. One patient used only salbutamol as required. All patients gave written, informed consent. The study protocol was approved by the Human Research Ethics Committee of Monash Health, Melbourne.

HRCT and standardisation of lung volumes

HRCT chest was performed within 72 h of attendance at the emergency department and repeated during the convalescent phase. Patients had to be able to stay in a recumbent position for 10 min and HRCT was done at least 2 h after use of beta-agonists to reduce the impact of medication on airway measurements. The method for HRCT chest as described by King et al. [6] entailed obtaining a 20 mm axial length of lung caudal to the carina during a single breath-hold; this yielded 20 contiguous images of 1 mm thickness.

The established relationship between airway calibre and lung volume [7–9] required equalisation of lung volumes during acute and convalescent asthma since RV is expected to occupy a greater proportion of the vital capacity (VC) during acute asthma due to increased gas trapping (Figure 1). Lung function tests including lung volume study were performed on the same day as HRCT. Each subject had spirometry test and

lung volumes assessed in the seated position using a whole body constant-volume plethysmograph (Master-Lab, E. Jaeger GmbH). VC, expiratory reserve volume (ERV), thoracic gas volume (TGV), total lung capacity (TLC) and residual volume (RV) were measured. Prior to HRCT, lung volumes were re-measured with a portable spirometer (Sensormedics V_{max}) to validate plethysmographic measures in the seated and supine positions. Since we were unable to measure static lung volumes in the supine position (during HRCT), RV was assumed to vary within individuals in the seated and supine position by the same volume in acute and convalescent asthma.

HRCT in acute asthma: to measure the absolute lung volume at which HRCT images were taken the patient breathed in to TLC and exhaled to 50% (or 75%) of the supine VC (VC50 and VC75) when the mouthpiece was occluded using the balloon circuit of the Vmax system and Sensormedics proprietary “gated spirometry” software (SensorMedics Corporation, Yorba Linda, CA). HRCT volume was calculated as: $HRCTvol = (0.5 \times VC) + RV_{acute}$, where $RV = TGV - ERV$. Mouth pressure was monitored throughout to prevent Valsalva or Mueller manoeuvres which could distort the chest and airways. HRCT were performed at both VC75 and VC50 (Figure 1).

HRCT in convalescence: to match the absolute lung volume of the acute exacerbation HRCT, dynamic volumes were reassessed in the manner previously described and the volume expired from TLC calculated to have the same absolute volume in the chest when the convalescent HRCT was done (Figure 1).

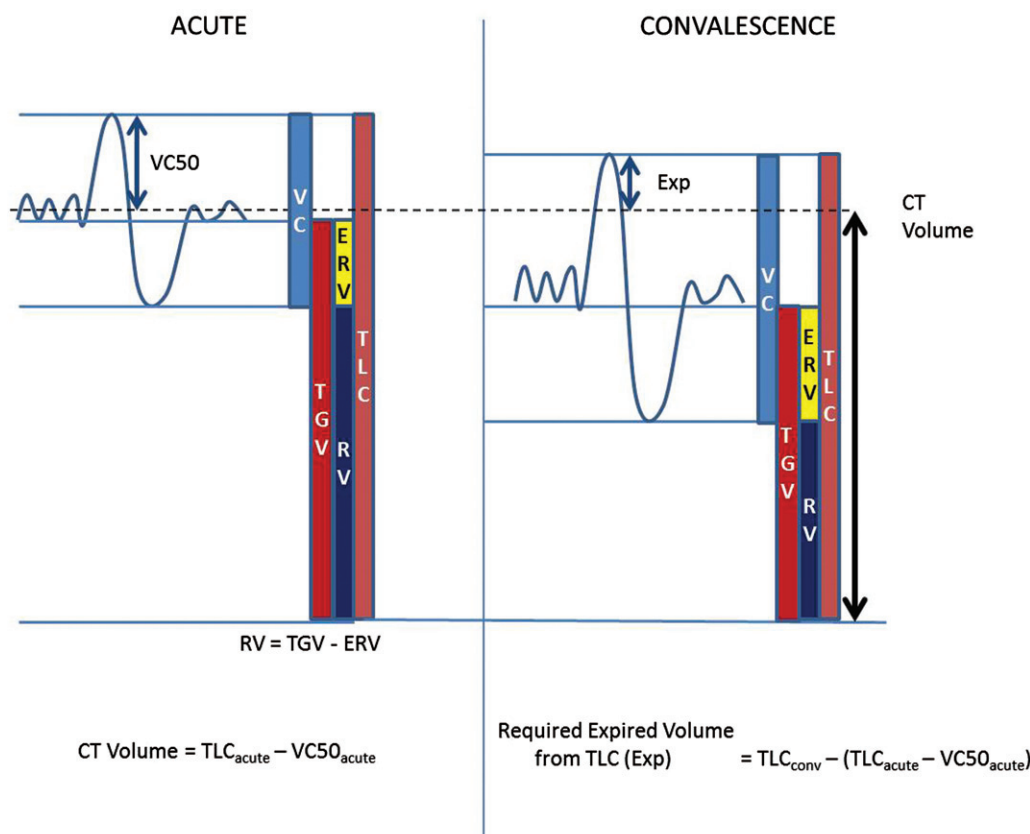


Figure 1. Diagram showing how equal lung volumes during acute and convalescent asthma were achieved at the time of HRCT. Acute phase volume was set at a percentage of VC (e.g. 50% for VC50). Expiration from TLC during convalescent phase image was determined to match volume in the chest during the acute phase image.

Image analysis

Airways were selected for direct comparison between acute and convalescent studies for each of the VC75 and VC50 data sets. For any individual airway to be eligible for measurement and thus comparison, it had to be visualized as a complete ring on a single image “slice”; either circular or elliptical. Further, a sectioned airway was only deemed eligible for inclusion and measurement if it could be unequivocally matched with the same bronchus on both acute and convalescent data sets. This was achieved using the intrinsic morphology of the particular airway and adjacent non-bronchial anatomical landmarks (vessels, fissures, septae; Figure 2).

Measurement of the bronchial diameter (outer wall to outer wall), cross sectional airway area (Aa) and bronchial luminal area (Ai) for each matched sectioned airway were obtained using a validated automated program [10]. The airway wall area (WA) was calculated as $Aa - Ai$. The airway wall thickness is presented as wall area percentage ($WA\% = WA / Aa \times 100$).

Statistical analysis

All data are presented as mean $\pm$ SD. Wilcoxon signed-rank testing (a non-parametric alternative to the paired *t*-test) was used to compare airway dimensions obtained by HRCT and to compare clinical indices of lung function between acute and convalescent asthma. The relationships between airway

dimensions measured on HRCT and overall lung function were evaluated using Spearman’s correlation. Heterogeneity of airway calibre was assessed as SD of mean lumen area grouped by their convalescent external diameter. Matched measurements of lumen area in every airway were used to compare whether airway narrowing/dilatation had occurred at these times. We then evaluated whether the extent of heterogeneity was greater during acute or convalescent asthma using analysis of variance. Statistical significance was accepted if $p < 0.05$.

Results

Demographic characteristics and clinical indices of subjects are presented in Table 1. Mean age of study subjects was 28 years (range 19–38 years). Duration of asthma symptoms was 2–30 years. All except one subject were treated with ICS for >10 years at doses $\geq 500 \mu\text{g}$ beclomethasone equivalent daily prior to ED presentation. Three subjects had long acting beta agonists (LABA) added as combined therapy. All patients were treated in hospital with oral glucocorticosteroids and 4–6 h beta-agonists by nebulizer as per standard of care. One patient was treated with intravenous antibiotics for possible RUL pneumonia. No patients needed ICU admission and one patient required brief non-invasive ventilation.

Mean predicted FEV₁ during acute asthma was 62% (range 31–89%) and increased to 92% (range 80–132%) during convalescence. Similarly, FVC was reduced during acute

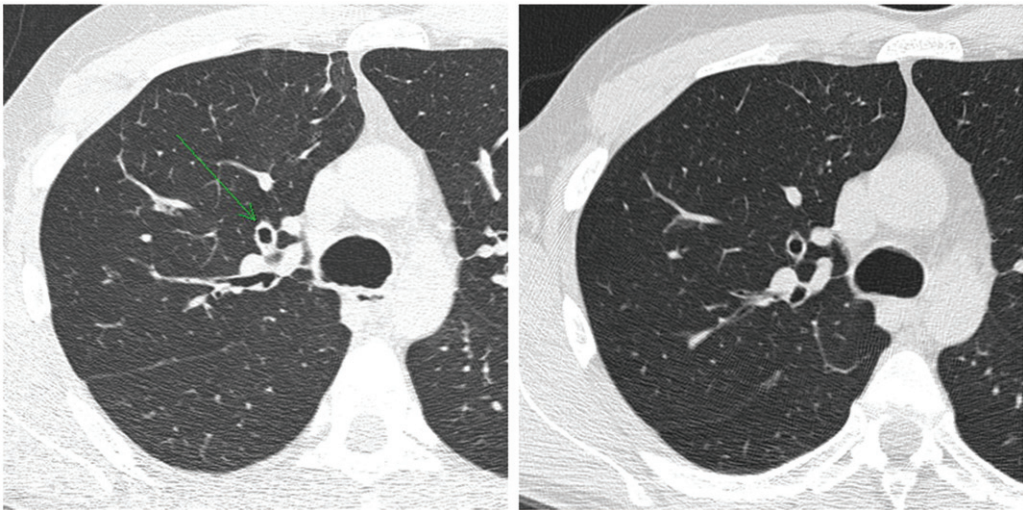


Figure 2. Axial HRCT images showing matching of airways during acute asthma (left panel) and at convalescence (right panel). Note that almost perfect matching had to be achieved for images to be ‘eligible’ for analyses.

Table 1. Demographic characteristics of seven asthmatic patients studied during acute asthma and at convalescence.

Patient	Age	Gender	BMI (kg/m ²)	Treatment (before asthma exacerbation)	Duration of asthma (years)	FEV ₁ (% predicted at convalescence)
1	24	F	21	FP/S 500/50 mcg bid*	20	80
2	32	F	27	Budesonide 200 mcg bid	13	90
3	35	M	24	FP/S 500/50 mcg bd	30	86
4	20	F	21	FP/S 500/50 mcg bid	19	88
5	19	M	22	FP 500 mcg bid	13	80
6	38	M	25	Salbutamol prn	2	123
7	32	M	23	FP 500 mcg bid	3	100

*FP/S, fluticasone propionate/salmeterol.

Table 2. Measurements of lung function during acute asthma and at convalescence.

Patient	A-FEV ₁ (%)	C-FEV ₁ (%)	A-FVC (%)	C-FVC (%)	A-TLC (%)	C-TLC (%)	A-RV (%)	C-RV (%)	A-RV/TLC	C-RV/TLC
1	66	80	84	102	108	112	149	140	40	36
2	74	90	96	101	100	96	99	88	31	29
3	49	86	77	100	108	102	182	128	46	34
4	80	88	108	118	110	114	111	113	28	27
5	46	80	68	100	99	92	191	111	45	28
6	89	123	105	123	130	97	162	73	38	23
7	31	100	66	110	108	114	211	115	55	29
Mean	62	92*	86	108*	109	104	158	110*	40	29*
SD	21	15	17	9	10	9	41	23	9	4

A, Acute asthma; C, Convalescent asthma; RV, residual volume; TLC, total lung capacity.

* $p < 0.05$ compared to acute asthma.

asthma and improved significantly during convalescence (Table 2). Interestingly, TLC was not significantly different comparing acute and convalescence asthma but RV/TLC was significantly increased during acute asthma (acute asthma $40 \pm 9\%$ versus $29 \pm 4\%$; $p = 0.05$). As expected, these findings indicated the presence of significant air trapping associated with airway obstruction during acute asthma.

Numbers of matched airways (i.e. during acute and convalescent asthma) for each subject that were suitable for analysis by HRCT were 11 ± 8 (range 5–27). The size of the airway external diameter (i.e. mean of all the different airways measured averaged together) was 4.2 ± 1.0 mm (range 3.5–5.9 mm) in acute asthma and 4.0 ± 0.7 mm (3.2–5.3 mm) in the convalescent phase ($p = \text{NS}$). The mean airway lumen size was similar during acute asthma compared with convalescent asthma ($p = 0.8$; Figure 3). However, the airway wall was thickened during acute asthma compared with convalescent asthma ($62 \pm 7\%$ versus $55 \pm 4\%$ $p = 0.01$; Figure 4). Results of airway dimensions on HRCT at VC50 were similar (data not shown).

There was no significant correlation between airway dimensions and measurements of lung function during both acute and convalescent asthma. Similarly, the difference in airway dimensions between acute and convalescent asthma did not correlated with changes in lung function measurements. Specifically, there were no correlations between changes in RV and airway wall thickness ($r = 0.5$; $p = 0.12$, data not shown). Limited analyses of the extent of heterogeneity were conducted to compare its prevalence in acute and convalescent asthma. No differences were detected (data not shown).

Discussion

This novel study demonstrated that there is significant bronchial wall thickening during real-life acute asthma exacerbations. In contrast (and surprisingly) the bronchial lumen size was not reduced at the same anatomical locations although pulmonary function measurements clearly identified overall airway obstruction. The findings suggest uncoupling of the link between a thickened airway wall (due to amplified airway inflammation and oedema) and corresponding reductions in airway calibre caused by bronchial obstruction and hence imply that for a given airway, the wall was thickened but the lumen did not narrow significantly.

A number of investigators have compared airway dimensions in normal and asthmatic subjects by using HRCT.

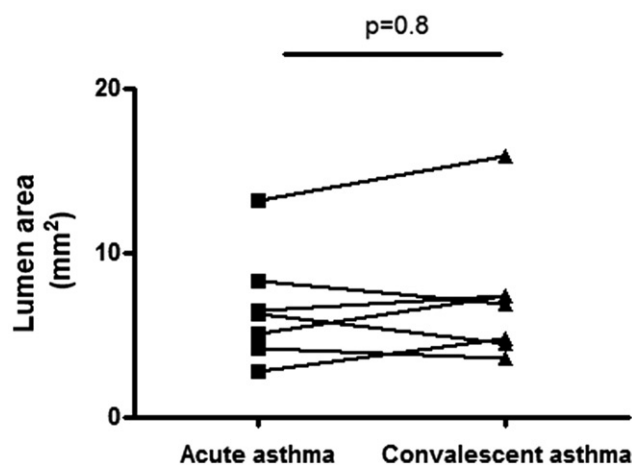


Figure 3. Measurements of airway lumen size are depicted during acute asthma exacerbation and following convalescence. There were no significant differences noted ($p = 0.8$).

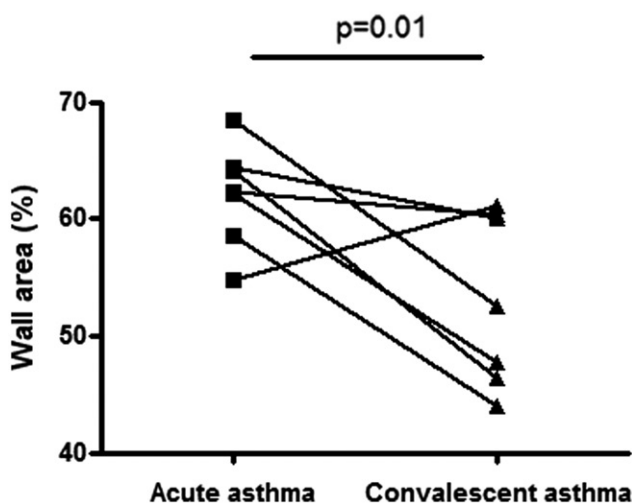


Figure 4. Measurements of bronchial wall thickness are depicted in seven patients during acute asthma and at convalescence. The airway wall was significantly thickened during an asthma exacerbation compared to stable disease ($p = 0.01$).

Beigelman-Aubry et al. [11] demonstrated a lower baseline lumen area in asthmatics compared with controls pre-bronchodilator, but the difference was abolished after salbutamol. Conversely, Niimi et al. [12] found no decrease in lumen area in the right apical upper lobe bronchus in asthmatics, irrespective of disease severity, compared with a

healthy group. However, airway wall thickness was increased in asthmatic subjects. Most human studies using HRCT [13–15] found that airway wall thickness is increased in asthmatic subjects, even when asthma is mild. The degree of wall thickening appeared to be related to the duration and severity of asthma and to the level of airway obstruction. However, to date, there have been no reports of studies in patients at the time of asthma exacerbations and it is not known how airway dimensions are temporally altered (or not) in that context. Post-mortem studies have demonstrated a significant increase in airway wall thickness throughout the bronchial tree in fatal asthma compared to non-fatal asthma controls [16]. Awadh et al. [17] compared airway wall thickness in patients with stable asthma and a history of near-fatal asthma versus healthy controls using HRCT and found there was a significant increase in bronchial wall thickness. A recent study [18] compared HRCT findings between Near-Fatal asthma (NFA) and Non-Fatal asthma and found that there was a significant increase in small airway abnormalities measured by prominence of centrilobular structure in NFA group while airway wall thickness was the same between two groups. Five of 16 of NFA and 7 out of 24 non-fatal asthma patients underwent follow-up HRCT more than 6 months later. The wall thickness was significantly decreased in both groups. However, these studies were cross-sectional rather than longitudinal and did not evaluate “real-life” patients during an asthma exacerbation itself. Our study is therefore the first to examine this aspect demonstrating an additional increase in airway wall thickness during acute asthma. The absence of corresponding reductions in airway calibre caused by bronchial obstruction supports other studies showing heterogeneous airway narrowing during overall airway obstruction [6] or conceivably thickening confined to the outer region of the airway wall only. Overall, the bulk of evidence suggests that not all airways are narrowed during acute asthma and a better understanding of the dynamics of this process is essential to improve future treatments.

Studies in acute asthma are difficult. One factor of particular relevance in the current studies is the influence of lung volume on bronchial calibre [7–9]. This is particularly important when comparing stable and acute asthma since hyperinflation may be present when HRCT is done during acute obstructive episodes confounding measurements of calibre. For example, a recent study has demonstrated that bronchial lumen size increased significantly during inspiration compared to expiration in stable asthma [7]. Furthermore, there is evidence of a reduction in airway distensibility in asthma [8] that is not related to lung elastic recoil [19]. These studies indicate that maintaining comparable lung volumes when HRCT is done in acute and convalescent asthma is a vital technical aspect in this setting. We avoided this key confounder by equalising lung volumes when HRCT was performed and this methodology and the procedure should be used in future imaging studies of acute severe asthma.

This was a pilot study with significant constraints imposed by investigation of patients who were acutely unwell; it therefore has important limitations. Only seven patients had both acute and convalescent studies and larger studies are needed using this approach employing modern imaging

modalities with reliable methods to equalise lung volumes. Greater patient numbers will also exclude a type-2 statistical error if there are only very small differences in the size of the airway lumen. We chose to evaluate the lower lung zones only because this region has more airways running in an axial direction and to restrict radiation exposure, consequently information about changes in other parts of the lung was not obtained. Matching the airways between acute and convalescent asthma used visual matching of airways and this method may not have taken into account subtle differences in angle of the HRCT beam [20,21]. However, previous studies have demonstrated that this method has acceptable reproducibility [6,10] and it, in this study, did not preclude detection of differences in airway wall thickness. Newer techniques using HRCT will make it possible to estimate airway dimensions along the longitudinal axis from reconstructed, three-dimensional images minimize errors due to oblique orientation [21]. Finally, we did not find any correlation between lung function measurements and HRCT in contrast to recent studies by Xie et al. [22] and Lee et al. [23]. However, the studies were dissimilar since they examined patients with COPD. In summary, the present study has demonstrated for the first time that airway wall thickness is significantly amplified during acute asthma exacerbation. This abnormality was not characteristically accompanied by corresponding reductions in airway calibre at the same anatomical location. The findings suggest that generalised airway wall thickening is likely to characterise acute asthma but that smooth muscle-associated narrowing of the airway lumen may be heterogeneous.

Declaration of interest

The authors have no any financial, consulting, and personal relationships with other people or organizations that could influence (bias) the current work. They have not received any scientific writing assistance and grant support for the current study.

References

1. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218–224.
2. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973–984.
3. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, Wardlaw AJ, Pavord ID. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715–1721.
4. Jayaram L, Pizzichini MM, Cook RJ, Boulet LP, Lemièrre C, Pizzichini E, Cartier A, et al. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. *Eur Respir J* 2006;27:483–494.
5. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary diseases (COPD) and asthma. *Am Rev Respir Dis* 1987;136:225–244.
6. King GG, Carroll JD, Muller NL, Whittall KP, Gao M, Nakano Y, Paré PD. Heterogeneity of narrowing in normal and asthmatic airways measured by HRCT. *Eur Respir J* 2004;24:211–218.
7. Chae EJ, Kim TB, Cho YS, Park CS, Seo JB, Kim N, Moon HB. Airway measurement for airway remodelling defined by post-bronchodilator EFV1/FVC in asthma: investigation using inspiration-expiration computed tomography. *Allergy Asthma Immunol Res* 2011;3:111–117.

8. Wilson JW, Li X, Pain MC. The lack of distensibility of asthmatic airways. *Am Rev Respir Dis* 1993;148:806–809.
9. Brown RH, Scichilone N, Mudge B, Diemer FB, Permutt S, Togias A. High-resolution computed tomographic evaluation of airway distensibility and the effects of lung inflation on airway calibre in healthy subjects and individuals with asthma. *Am J Respir Crit Care Med* 2001;163:994–1001.
10. King GG, Müller NL, Whittall KP, Xiang Q-S, Paré PD. An analysis algorithm for measuring airway lumen and wall areas from high-resolution computed tomographic data. *Am J Respir Crit Care Med* 2000;161:574–580.
11. Beigeman-Aubry C, Capderou A, Grenier PA, Straus C, Becquemin MH, Similowski T, Zelter M. Mild intermittent asthma: CT assessment of bronchial cross-sectional area and lung attenuation at controlled lung volume. *Radiology* 2002;223:181–187.
12. Niimi A, Matsumoto H, Amitani R, Nakano Y, Mishima M, Minakuchi M, Nishimura K, 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.
13. Little SA, Sproule MW, Cowan MD, Macleod KJ, Robertson M, Love JG, Chalmers GW, 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.
14. Ketai L, Coutias C, Williamson S, Coutias V. Thin-section CT evidence of bronchial thickening in children with stable asthma: bronchoconstriction or airway remodeling? *Acad Radiol* 2001;8: 257–264.
15. Kasahara K, Shiba K, Ozawa T, Okuda K, Adachi M. Correlation between the bronchial subepithelial layer and whole airway wall thickness in patients with asthma. *Thorax* 2002;57:242–246.
16. Corroll N, Elliot J, Morton A, James A. The structure of large and small airways in nonfatal and fatal asthma. *Am Rev Respir Dis* 1993;147:405–410.
17. Awadh N, Muller NL, Park CS, Abboud RT, Fitzgerald JM. Airway wall thickness in patients with near fatal asthma with or without fixed airflow obstruction. *Thorax* 1998;53:248–253.
18. Lee YM, Park JS, Hwang JH, Park SW, Uh ST, Kim YH, Park CS. High-resolution CT findings in patients with near-fatal asthma: comparison of patients with mild-to-severe asthma and normal control subjects and changes in airway abnormalities following steroid treatment. *Chest* 2004;126: 1840–1848.
19. Brown NJ, Salome CM, Berend N, Thorpe CW, King GG. Airway distensibility in adults with asthma and healthy adults, measured by forced oscillation technique. *Am J Respir Crit Care Med* 2007;176: 129–137.
20. De Jong PA, Muller NL, Pare PD, Coxson HO. Computed tomographic imaging of the airways: relationship to structure and function. *Eur Respir J* 2005;26:140–152.
21. Walker C, Gupta S, Hartley R, Brightling CE. Computed tomography scans in severe asthma: utility and clinical implications. *Curr Opin Pul Med* 2012;18:42–47.
22. Xie XQ, De Jong PA, Oudkerk M, Wang Y, Ten Hacken NHT, Miao J, Zhang GX, et al. Morphological measurements in computed tomography correlated with airflow obstruction in chronic obstructive pulmonary disease: systematic review and meta-analysis. *Eur Radiol* 2012;22:2085–2093.
23. Lee JS, Huh JW, Chae EJ, et al. Response patterns to bronchodilator and quantitative computed tomography in chronic obstructive pulmonary disease. *Clin Physiol Funct Imaging* 2012; 32:12–18.