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Uncontrolled asthma phenotypes defined from parameters using quantitative CT analysis

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Abstract

Objective Asthma is a heterogeneous disease with diverse clinical phenotypes that have been identified via cluster analyses. However, the classification of phenotypes based on quantitative CT (qCT) is poorly understood. The study was conducted to investigate CT determination of uncontrolled asthma phenotypes.

Methods Sixty-five patients with uncontrolled asthma (37 with severe asthma, 28 with non-severe asthma) underwent detailed clinical, laboratory, and pulmonary function tests, as well as qCT analysis. Twenty-five healthy subjects were also included in this study and underwent clinical physical examinations, pulmonary function tests, and low-dose CT scans.

Results The mean lumen area/body surface area ratio was smaller in patients with severe uncontrolled asthma compared with that in healthy subjects (9.84 mm^2 [SD, 2.57 mm^2], 11.96 mm^2 [SD, 3.09 mm^2]; $p = 0.026$). However, the percentage of mean wall area (WA) was greater (64.39% [SD, 2.55%], 62.09% [SD, 3.81%], $p = 0.011$). Air trapping (measured based on mean lung density and VI_{-856} [%] on expiratory scan) was greater in patients with severe uncontrolled asthma than in those with non-severe uncontrolled asthma and was higher in all patients with uncontrolled asthma than that in healthy subjects (all $p < 0.001$). Three CT-determined uncontrolled asthma phenotypes were identified. Cluster 1 had mild air trapping with or without proximal airway remodeling. Cluster 2 had moderate air trapping with or without proximal airway remodeling. Cluster 3 had severe air trapping with proximal airway remodeling.

Conclusions There was obvious air trapping and proximal airway remodeling in patients with severe uncontrolled asthma. The three CT-determined uncontrolled asthma phenotypes might reflect underlying mechanisms of disease in patient stratification and in the different stages of disease development.

Key Points

- *Obvious air trapping and proximal airway remodeling were present in patients with severe uncontrolled asthma.*
- *CT air trapping indices showed a good correlation with disease duration, total IgE, atopy, and OCS and ICS doses, and were even more strongly correlated with clinical lung function.*
- *Three CT-determined uncontrolled asthma phenotypes were identified, which might reflect underlying mechanisms of disease in patient stratification and in the different stages of disease development.*

Keywords Asthma · Airway remodeling · Tomography, X-ray computed · Phenotype

Xiaoxian Zhang and Tingting Xia contributed equally to this work.

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Abbreviations

BSA	Body surface area
LA	Lumen area
LB10	The posterior basal segmental bronchus of the left lower lobe
LV	Lung volume
MLD	Mean lung density
MLD E/I	Mean lung density expiratory/inspiratory ratio
Pi10WA	Wall area of a hypothetical airway with an internal perimeter of 10 mm
qCT	Quantitative computer tomography
RB1	The apical segmental bronchus of the right upper lobe

RB10	The posterior basal segmental bronchus of the right lower lobe
T	Thickness of airway wall
TA	Total area
VI	Voxel index
VI_{-856} E-I (%)	Voxel index change of percent voxels less than − 856 HU on paired inspiratory and expiratory CT scans
VI_{-856} (%)	Percent voxels less than − 856 HU
$VI_{-856/-950}$ E-I (%)	Voxel index change of percent voxels between − 950 and – 856 HU on paired inspiratory and expiratory CT scans
VI_{-950} (%)	Percent voxels less than – 950 HU
WA	Wall area
WA%	Wall area percentage

Introduction

Asthma is a worldwide problem, and uncontrolled asthma in particular has far-reaching socioeconomic repercussions. This is due not only to the burden of health care costs but also to loss of productivity in the workplace and, especially for younger/working class people, disruption to the family. Asthma is burdensome to patients (symptoms either during the day or at night can interfere with physical activity) and is a risk factor for future exacerbations, which are sometimes fatal. The long-term goals of asthma management are to achieve good symptom control and to minimize future risk of exacerbations, fixed-airflow limitations, and treatment side effects.

Asthma is a chronic inflammatory disease of the airway that is characterized by airway inflammation, airway hyper-responsiveness, and reversible airflow limitation. Chronic inflammation in asthma can lead to changes in airway structure. Airway remodeling, which includes narrowing of the airways and bronchial wall thickening, is a consequence of chronic injury, and repair and may be reversible or irreversible [1–4]. These changes affect all parts of the tracheobronchial tree but are initially located in the small airway and progress to the large airway [1, 4–6]. Distal small airways (less than 2 mm in diameter) become narrow or obstructed during expiration, leaving redundant air in the lungs, which is known as air trapping [7, 8].

Asthma can be divided into different phenotypes according to heterogeneity. Phenotypes are outward physical manifestations of interactions between gene types and environmental factors. They can be identified by such factors as airway inflammation, age of onset, inducing factors, clinical symptoms, disease severity, and response to treatment. Statistical methods, such as factor and cluster analyses, have been used to assess asthma heterogeneity and to identify different clinical phenotypes [9–11]. With recent advances in imaging technology, qCT analysis can be used to provide detailed information about airway changes in a non-invasive manner [12–19]. Not only can the location of air trapping be observed, but also the changes in airway structure can be intuitively assessed. The aim of the present research was to investigate CT-derived uncontrolled asthma phenotypes that reflect the stratification of proximal airway remodeling and air trapping. This may provide critical information about the underlying mechanisms of the disease and may lead to individualized therapies for asthma patients.

Materials and methods

Subjects

A total of 65 patients with uncontrolled asthma (37 severe and 28 non-severe), 42 females and 23 males, average age 47.6 ± 11.7 years, were enrolled in the study at the First Affiliated Hospital of Guangzhou Medical University from March 2014 to May 2017. Inclusion criteria: (1) Subjects were 18 to 65 years old. (2) Asthma in all subjects had been diagnosed and level of asthma control was characterized according to the criteria recommended by GINA revised 2012 [20]. (3) Patients with asthma could be classified as severe and non-severe.

Exclusion criteria: (1) Exacerbation of asthma within 8 weeks preceding the study. (2) Other chronic diseases, such as rheumatoid arthritis, ankylosing spondylitis, and/or diabetes. (3) Other chronic respiratory diseases, such as chronic obstructive pulmonary disease, bronchiectasis, interstitial lung disease, and/or tuberculosis. (4) A smoking history of > 10 packs per year. (5) Women who were pregnant or lactating. All of the subjects underwent detailed clinical characterization, pulmonary function tests, and chest CT scans. Twenty-five healthy subjects (12 males, 13 females; mean age, 40.4 ± 12.3 years) seen in the outpatient department of our hospital between March 2014 and May 2017 and identified by clinical histories, physical examinations, and normal pulmonary function tests were recruited at the same time as the subjects with asthma formed the control group. None of the volunteers smoked. Volunteers with pulmonary disease as observed by CT were excluded. The Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University approved the study. All of the participants received information regarding radiation exposure and all gave written informed consent in advance of their participation in the study.

CT scanning equipment and parameters

A 16-detector row Toshiba Aquilion CT scanner was used to image all subjects. The scanner was calibrated each day before scanning. The scanning parameters were tube voltage 120 kV,

tube current 30 mAs, helical pitch 0.938, and rotation time 0.5 s. Images were reconstructed with a slice thickness of 1.0 mm and a slice interval of 0.8 mm using a low-spatial-frequency algorithm (Fc01) through 512 × 512. All of the subjects were briefly trained to take a deep breath, hold it, and exhale deeply. All were determined able to perform the above satisfactorily before they were included in the experiments. Two scans were obtained at full inspiration (near total lung capacity) and at the deep end of expiration (near residual volume) for each subject.

QCT analysis

Fully automated software, VIDA Workstation, software version 1.2 (VIDA Diagnostics), was used for quantitative airway and pulmonary function analysis [2, 21–23]. The lumen perimeter (Pi) was recorded for the airways of interest. Pi10 was defined as the hypothetical airway with an internal perimeter of 10 mm [21, 24, 25]; thus, the Pi10WA was the wall area of the hypothetical airway with an internal perimeter of 10 mm. The mean dimensions of the three segmental bronchi (RB1, RB10, and LB10) were calculated for analysis.

Quantification of CT pulmonary function was performed using whole-lung densitometry during inspiratory and expiratory CT scans. CT air trapping in asthmatic patients was graded based on expiratoryVI_{-856} (%) values: (1) none or mild, lower than the upper limit of the 99.5% confidence interval (CI) of healthy control subjects; lower than 13.4%; (2) severe, greater than the lower limit of the 99.5% CI of severe asthmatic patients, greater than 34.4%; and (3) moderate, between 13.4 and 34.4%.

A concrete analysis process of proximal airway and CT pulmonary function is given in detail in Appendix.

Pulmonary function tests are described in detail in Appendix.

Statistical analysis

Parametric data are expressed as mean ± standard error of the mean (SEM) and non-parametric data are described as median (interquartile range [IQR]). The Levene method was used to test for multiple-sample homogeneity of variance. Log-transformation or sqrt-transformation was used to reduce skewness of the data. Multiple groups were compared using one-way analysis of variance (ANOVA) with a Bonferroni correction (parametric data) and a Kruskal–Wallis test with a Dunn intergroup comparison (non-parametric data). An independent-sample *t* test was used for comparisons between two groups. The χ^2 and Fisher exact tests were used to compare ratios. Principal component analysis was performed to extract factors that best described the underlying relationship among the qCT variables and cluster analysis was used to determine cluster membership of all asthmatic patients. SPSS software version 22.0 (IBM) and Prism version 6.01 (GraphPad) were used for statistical analyses. $p < 0.05$ was considered significant.

The principal component and cluster analyses are described in detail in Appendix.

Results

Characteristics of participants

Baseline demographics of participants are shown in Table 1. Patients with severe asthma had a longer disease duration, more serious obstructive ventilation dysfunction, greater air trapping, and greater airway resistance, and required higher doses of ICS compared with patients with non-severe asthma.

Proximal airway remodeling

The mean dimensions of three (RB1, RB10, and LB10) segments of the bronchus on inspiratory CT scan are presented in Table 2. The mean LA/BSA ratio was smaller and the mean WA% was greater in patients with severe asthma compared with that in healthy control subjects (9.84 mm^2 [SD, 2.57 mm^2], 11.96 mm^2 [SD, 3.09 mm^2], mean LA/BSA, $p = 0.026$; and 64.39% [SD, 2.55%], 62.09% [SD, 3.81%], mean WA%, $p = 0.011$) (Figs. 1 and 2). There was no significant difference in other airway parameters among the three groups (all $p > 0.05$).

CT pulmonary densitometry

Densitometric parameters, assessed by qCT are shown in Table 3. Expiratory lung volume was smaller in healthy control subjects compared with that in patients with severe asthma and non-severe asthma (1.9 L [SD, 0.5 L], 2.7 L [SD, 0.8 L], 2.4 L [SD, 0.5 L], $p < 0.001$). MLD, $VI_{-856/-950}$ (%), and VI_{-856} (%) were higher in patients with severe asthma than in those with non-severe asthma (− 756.2 HU [SD, 48.5 HU], − 716.1 HU [SD, 44.3 HU], MLD, $p = 0.021$; 20.2% [IQR, 23.6%], 11.0% [IQR, 14.0%], $VI_{-856/-950}$ [%], $p = 0.039$; and 22.1% [IQR, 26.4%], 11.2% [IQR, 12.2%], VI_{-856} [%], $p = 0.015$), and were higher in all asthmatic patients than those in healthy subjects (all $p < 0.05$). Other air trapping indexes, MLD E/I, $VI_{-856/-950}$ E-I (%), and VI_{-856} E-I (%), were significantly greater in patients with severe asthma compared with those in healthy control subjects ($p = 0.011$, $p < 0.001$, and $p = 0.003$, respectively).

Relationships between structure and function, CT air trapping and clinical lung function in uncontrolled asthma, and low-dose CT radiation are described in detail in Appendix.

Table 1 Clinical characteristics of patients with uncontrolled asthma and healthy subjects

	Patients with severe asthma	Patients with non-severe asthma	Healthy control subjects	*p* value
Subjects	37	28	25	
Age (years)	48.4 ± 11.8	46.5 ± 11.8	40.4 ± 12.3	0.09
Gender (male %)	29.7	75.0	48.0	0.28
BMI (kg/m^2)	23.4 ± 3.1	23.0 ± 3.1	23.6 ± 3.7	0.80
BSA (m^2)	1.6 ± 0.2	1.6 ± 0.1	1.7 ± 0.2	0.32
Smoking (%)	5.4	7.1	0	0.56
Disease duration (years)	10.0 (15.0)*	3.5 (7.0)*	–	0.001
Atopy (%)	71.4	91.7	–	0.14
Bronchodilator response (%)	17.4 ± 9.7	21.2 ± 17.0	–	0.52
Pre-bronchodilator FEV1 (% predicted)	55.6 ± 18.1*#	69.8 ± 11.3*¥	104.3 ± 10.9#¥	
Pre-bronchodilator FEV1/FVC (%)	53.5 ± 14.3*#	59.8 ± 6.8*¥	86.8 ± 4.6#¥	
Post-bronchodilator FEV1 (% predicted)	66.2 ± 19.2*	81.2 ± 9.3*	–	0.004
Post-bronchodilator FEV1/FVC (%)	61.5 ± 16.9	68.4 ± 5.6	–	0.08
FVC (% predicted)	88.3 ± 15.2#	94.8 ± 11.1	104.3 ± 10.9#	< 0.001
PEF (% predicted)	58.4 ± 21.7*#	76.5 ± 19.2*¥	110.8 ± 16.1#¥	< 0.001
MMEF (% predicted)	22.3 ± 17.9*#	46.4 ± 25.1*¥	97.4 ± 18.0#¥	< 0.001
MEF_{50}% (% predicted)	24.7 ± 20.2*#	50.2 ± 24.9*¥	107.3 ± 23.1#¥	< 0.001
MEF_{25}% (% predicted)	21.9 ± 17.7*#	41.1 ± 24.1*¥	92.9 ± 24.0#¥	< 0.001
RV/TLC (%)	47.8 ± 9.4*	39.0 ± 10.7*	–	0.012
Z_5 (% predicted)	1.8 (1.2)*	1.3 (0.7)*	–	0.019
R_5 (% predicted)	1.6 (1.1)*	1.3 (0.7)*	–	0.024
R_{20} (% predicted)	1.5 (0.4)	1.3 (0.6)	–	0.08
R_5-R_{20}	0.5 (0.2)*	0.3 (0.2)*	–	0.001
X_5 (% predicted)	2.6 (4.2)	0.6 (9.0)	–	0.13
D_{LCO}/VA (% predicted)	95.1 ± 25.4	97.8 ± 14.8	–	0.74
Blood EOS (×10^9/l)	0.3 (0.4)	0.3 (0.3)	–	0.74
FeNO (ppb)	33.5 (40)	32.0 (69)	–	0.72
Total IgE (KU/ml)	302.0 (530.6)	257.7(230.5)	–	0.37
Sputum EOS (%)	26.5 (62.8)	28.5 (62.3)	–	0.75
Sputum Neu (%)	23.5 (73.0)	33.0 (38.3)	–	0.60
ICS dose, BDP (μg/day)	800 (1100.0)*	400 (0.0)*	–	0.001
LABA (%)	95	97	–	0.84
OCS (%)	60	0	–	–
OCS dose, prednisone (mg/day)	10 (20.0)	0	–	–
Leukotriene receptor antagonist (%)	53	68	–	0.69
Theophylline (%)	21	6	–	0.99

BMI body mass index, *BSA* body surface area, *EOS* eosinophilic granulocyte, *Neu* neutrophil granulocyte, *FeNO* fraction of nitric oxide in exhaled breath, *ICS* inhaled corticosteroid, *BDP* beclomethasone dipropionate, *LABA* long-acting β2-agonist

*$p < 0.05$, patients with severe asthma versus patients with non-severe asthma; #$p < 0.05$, patients with severe asthma versus healthy control subjects; and ¥$p < 0.05$, patients with non-severe asthma versus healthy control subjects

CT-determined uncontrolled asthma phenotypes

Eleven characteristic qCT parameters were screened from airway remodeling and lung densitometric indices (see Appendix for details). These parameters were performed by principal component analysis, and three common factors were extracted. These factors were used in cluster analysis and three clusters were identified. QCT parameters and clinical characteristics of the three asthma phenotypes are shown in Tables 4 and 5.

All three of the asthma clusters demonstrated air trapping, the degrees of which were significantly different. According

Table 2 Quantitative airway CT parameters of the segmental bronchus averaged by RB1, RB10, and LB10 in patients with uncontrolled asthma and healthy subjects

	Patients with severe asthma	Patients with non-severe asthma	Healthy control subjects	*p* value
Subjects	37	28	20	
Inspiratory				
Mean LA/BSA (mm^2/m^2)	9.8 ± 2.6#	10.5 ± 2.8	12.0 ± 3.1#	0.026
Mean T/BSA (mm/m^2)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.79
Mean WA/BSA (mm^2/m^2)	17.5 ± 3.4	18.4 ± 3.8	19.6 ± 3.3	0.10
Mean TA/BSA (mm^2/m^2)	27.3 ± 5.9	29.0 ± 6.5	31.6 ± 6.2	0.05
Mean WA%	64.4 ± 2.6#	64.1 ± 2.1	62.1 ± 3.8#	0.011
Mean Pi10WA (mm^2)	18.2 ± 2.8	17.7 ± 2.8	16.9 ± 2.1	0.24

#$p < 0.05$, patients with severe asthma versus healthy control subjects

to the graded air trapping index of expiratory VI_{-856} (%), cluster 1 was none or mild (9.2% [9.4%]), cluster 2 was moderate (25.6% [19.8%]), and cluster 3 was severe (42.9% [17.3%]). Asthmatic patients in cluster 3, in addition to severe air trapping, had a greater mean WA% and mean Pi10WA than patients in clusters 1 and 2 (cluster 1: mean WA% = 64.3% [2.1%] and mean Pi10WA = 16.4 mm^2 [1.2 mm^2]; cluster 2: mean WA% = 62.3% [1.2%] and mean Pi10WA = 16.6 mm^2 [3.2 mm^2]; cluster 3: mean WA% = 65.2% [2.6%] and mean Pi10WA = 18.6 mm^2 [3.2 mm^2]) (Fig. 3).

Subjects in cluster 1 were younger than those in clusters 2 and 3 ($p = 0.041$ and $p = 0.033$, respectively), while the

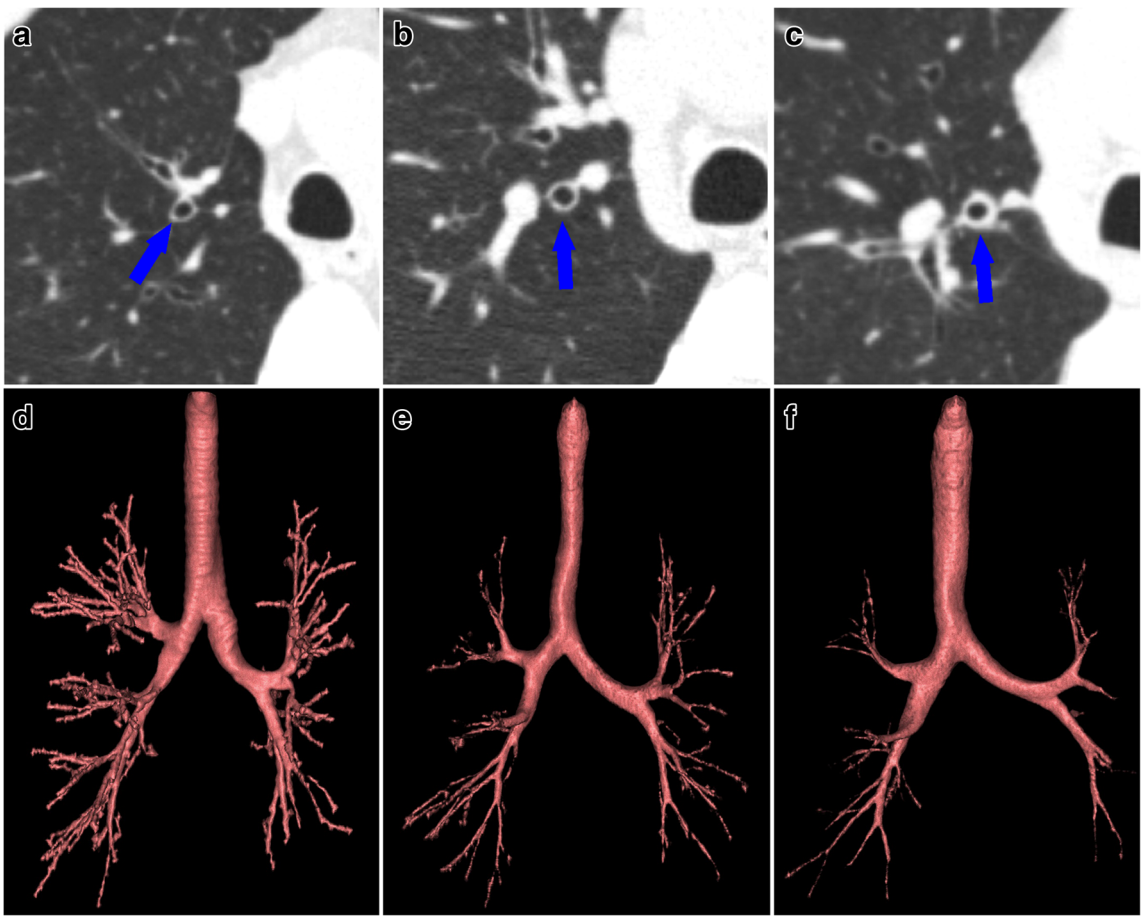

Fig. 1 Inspiratory CT scan. (**a**, **b**, and **c**) The third segmented bronchus at the midpoint of horizontal axis images of RB1 (blue arrow). (**d**, **e**, and **f**) Image reconstruction of tracheobronchial tree by using VIDA Workstation, version 1.2 software. **a**, **d** Healthy control subject. **b**, **e** Patients with non-severe uncontrolled asthma. **c**, **f** Patients with severe uncontrolled asthma

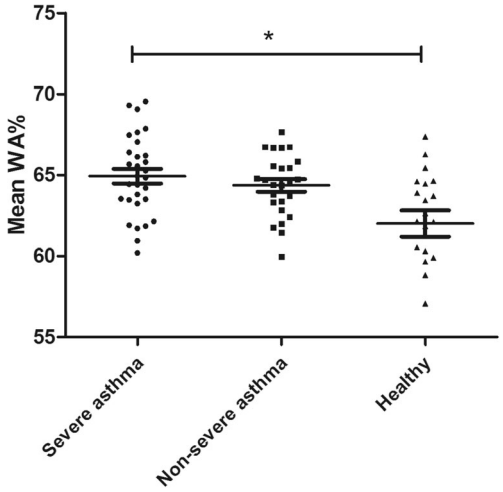

Fig. 2 Mean WA% of the third segmented bronchus on an inspiratory CT scan in patients with uncontrolled asthma and healthy subjects (*$p < 0.05$, ANOVA)

percentage of subjects with atopy was significantly higher. In cluster 3, the proportion of patients with severe asthma was greater than in that cluster 1 and cluster 2, and also the ICS dose and OCS dose were higher. Post-bronchodilator FEV1 (% predicted) was significantly higher in cluster 1 subjects compared with those in other clusters. Pre-bronchodilator FEV1 (% predicted), post- and pre-bronchodilator FEV1/FVC ratio values, ventilation function (percent predicted values of PEF), and small airway ventilation indexes (percent predicted values of MMEF, $MEF_{50\%}$ and $MEF_{25\%}$) were greater in cluster 1 compared with those in cluster 3 (all $p < 0.05$). RV/TLC% values were lower in cluster 1 compared with those in clusters 2 and 3 ($p = 0.009$ and $p = 0.002$, respectively). For X_5 (% predicted) values in the impulse oscillometry (IOS) test, cluster 1 was significantly lower than that in cluster 3 ($p = 0.012$).

Discussion

Results of this study demonstrated obvious proximal airway remodeling in patients with severe uncontrolled asthma. Air trapping was present in all of the uncontrolled asthmatic patients, but was more obvious in those with severe asthma than in those with non-severe asthma. Three different CT-determined phenotypes were identified in patients with uncontrolled asthma, based on air trapping and proximal airway remodeling indexes by cluster analysis, which clearly demonstrated asthma heterogeneity.

In patients with uncontrolled asthma, proximal airway remodeling was characterized by luminal narrowing and increased WA%, which is consistent with that of previous studies [4, 26, 27]. However, there was no significant difference in mean WA/BSA. This indicates that the increase in WA% was mainly driven by the reduction in lumen area, suggesting that airway remodeling in asthma is a complex change in geometry rather than a simple increase in the wall area of the bronchial tube. Air trapping is a reflection of small airway obstruction on HRCT scan [28–32]. Expiratory VI_{-856} (%) was significantly greater in uncontrolled asthmatic patients compared with that in healthy subjects, as well as in subjects with severe asthma compared to those with non-severe asthma. These results are in keeping with observations by other authors [33–35]. Other air trapping indexes (MLD E/I, $VI_{-856/-950}$ E-I [%], and VI_{-856} E-I [%]) were only significantly greater in asthmatic patients compared with those in healthy subjects. These results suggest that expiratory VI_{-856} (%) could be a sensitive index for estimating air trapping. On the other hand, the higher level of air trapping seen in severe asthma compared to that in non-severe asthma could indicate that the small airway remodeling in severe asthma is more obvious, which is consistent with the results of proximal airway

Table 3 Quantitative CT-assessed lung function analysis in patients with uncontrolled asthma and healthy subjects

	Patients with severe asthma	Patients with non-severe asthma	Healthy control subjects	*p* value
Subjects	37	28	20	
Expiratory				
LV (l)	2.7 ± 0.8#	2.4 ± 0.5¥	1.9 ± 0.5#¥	< 0.001
MLD (HU)	− (756.2 ± 48.5)*#	− (716.1 ± 44.3)*¥	− (663.6 ± 42.8)#¥	< 0.001
$VI_{-856/-950}$ (%)	20.2 (23.6)*#	11.0 (14.0)*¥	1.5(6.2)#¥	< 0.001
Air trapping indexes				
Expiratory VI_{-856} (%)	22.1(26.4)*#	11.2(12.2)*¥	2.3(6.3)#¥	< 0.001
MLD E/I	0.9 ± 0.1#	0.8 ± 0.2	0.8 ± 0.1#	0.011
$VI_{-856/-950}$ E-I (%)	− 42.5 (30.3)#	− 54.3 (29.1)	− 65.3 (16.5)#	< 0.001
VI_{-856} E-I (%)	− 50.7 (27.4)#	− 58.0 (31.4)	− 68.8(18.6)#	0.003

HU Hounsfield unit

*$p < 0.05$, patients with severe asthma versus patients with non-severe asthma; #$p < 0.05$, patients with severe asthma versus healthy control subjects; and ¥$p < 0.05$, patients with non-severe asthma versus healthy control subjects

Table 4 Quantitative airway CT parameters and CT-assessed lung function indexes in three uncontrolled-asthma phenotypes and healthy control group

	Cluster 1: mild air trapping	Cluster 2: moderate air trapping	Cluster 3: severe air trapping with bronchial wall thickening	*p* value
Subjects	43	7	15	
Proximal airway dimensions (inspiratory)				
Mean LA/BSA (mm^2/m^2)	10.2 ± 2.7	10.5 ± 3.0	9.8 ± 2.6	0.83
Mean T/BSA (mm/m^2)	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	0.22
Mean WA/BSA (mm^2/m^2)	17.9 ± 3.7	17.2 ± 3.6	18.0 ± 3.4	0.86
Mean TA/BSA (mm^2/m^2)	28.2 ± 6.4	27.7 ± 6.5	27.8 ± 5.8	0.97
Mean WA%	64.3 ± 2.1	62.3 ± 1.2¥	65.2 ± 2.6¥	0.024
Mean Pi10WA (mm^2)	16.4 ± 1.8#	16.6 ± 3.2	18.6 ± 3.2#	0.014
Air trapping indexes				
expiratory MLD	− (714.9 ± 36.7)*#	− (754.3 ± 26.4)*¥	− (797.8 ± 40.6)#¥	< 0.001
expiratoryVI_{-856} (%)	9.2(9.4)*#	25.6(19.8)*¥	42.9(17.3)#¥	< 0.001
MLD E/I	0.84 ± 0.95*#	0.93 ± 0.04*	0.91 ± 0.03#	< 0.001
$VI_{-856/-950}$ E-I (%)	− 54.9(17.4)*#	− 15.9(14.7)*	− 27.6(20.3)#	< 0.001
VI_{-856} E-I (%)	− 59.6(16.4)*#	− 23.8(13.7)*	− 33.3(14.8)#	< 0.001

*$p < 0.05$, cluster 1 versus cluster 2; #$p < 0.05$, cluster 1 versus cluster 3; ¥$p < 0.05$, cluster 2 group versus cluster 3

remodeling in this study. In the current study, CT air trapping indices showed good correlation with disease duration, total IgE, and atopy, as well as OCS and ICS doses. In addition, CT air trapping indices were much more strongly correlated with lung function, especially RV/TLC (%) which represents air trapping indices of clinical lung function.

Three different CT-determined phenotypes were identified in this study. Cluster 1 demonstrated none or mild air trapping with or without proximal airway remodeling. Cluster 2 was characterized by moderate air trapping with or without proximal airway remodeling. Cluster 3 was characterized by severe air trapping with proximal airway remodeling. Air trapping reflects changes in small airways [36–38]. Therefore, it is reasonable to speculate that (1) the presence of air trapping in the three clusters indicated that there was small airway remodeling and obstruction in three phenotypes, and (2) the airway remodeling of the tracheobronchial trees in clusters 1 to 3 was progressive and reflected the heterogeneity of airway remodeling in three phenotypes. So, when cluster 3 demonstrated severe air trapping, the airway remodeling had developed to proximal airway. Therefore, the CT-derived phenotypes in this study represented different aspects of asthma based on airway structural changes and may imply a progressive disease captured at different stages of airway remodeling. Moreover, lack of proximal airway remodeling in clusters 1 and 2 implied that both phenotypes represented asthmatic patients with non-severe disease. There was proximal airway remodeling in cluster 3, suggesting that this phenotype represents severe disease in asthmatic patients. Similarly, at the beginning of this study, there were no significant differences in airway dimensions between patients with non-severe asthma and healthy subjects. These findings were similar to those of other studies [23, 39]. Therefore, it could be speculated that the three different phenotypes in this study represented different stages of asthma.

Through the analysis of the three phenotypes' clinical features and laboratory test results, we found that clusters 2 and 3 demonstrated poorer lung function compared with cluster 1. This indicates that airflow limitations in clusters 2 and 3 were more severe than that in cluster 1.The RV/TLC% values in clusters 2 and 3 were significantly higher than those in cluster 1, suggesting that the gas residue in cluster 1 was the lowest, which is in accordance with air trapping results obtained via qCT in the three phenotypes. Likewise, the elastic resistance of the peripheral airways (X_5 [%predicted]) was significantly lower in cluster 1 than that in cluster 3. All of the above indicate that the airway obstruction in cluster 3 was more pronounced than in the other 2 clusters and that lung function was worse, which is supported by air trapping and airway remodeling results of the three phenotypes in this study.

In addition, the mean age of subjects in cluster 1 was lower than that in the other 2 clusters, while the proportion of atopy was the highest in cluster 1 subjects. This suggests that patients with allergic asthma were younger than patients with non-allergic asthma. Cluster 3 had the highest proportion of subjects with severe asthma and severe air trapping. This is yet more evidence that air trapping is more obvious in cases of severe asthma, which is consistent with the qCT results of pulmonary densitometry in this study. In addition, inhaled corticosteroid doses and oral-corticosteroid doses were higher in cluster 3 than those in clusters 1 and 2, most likely due to the higher proportion of those with severe asthma in this

Table 5 Clinical characteristics of three uncontrolled-asthma phenotypes

	Cluster 1: mild air trapping	Cluster 2: moderate air trapping	Cluster 3: severe air trapping with bronchial wall thickening	*p* value
Subjects	43	7	15	
Age (years)	44.4 ± 12.3*#	53.6 ± 6.0*	53.9 ± 8.2#	0.016
Gender (male %)	39.5	14.3	33.3	0.53
BMI (kg/m^2)	23.4 ± 3.4	23.2 ± 2.3	22.8 ± 2.5	0.84
BSA (m^2)	1.6 ± 0.2	1.6 ± 0.1	1.6 ± 0.2	0.29
Patient with severe asthma (%)	44.2	57.1	93.3	0.005
Disease duration (years)	5 (10)	10 (16)	10 (15)	0.13
Smoking history < 10 packs per year (%)	7.0	0.0	6.7	0.99
Atopy	81.6	42.9	40.0	0.004
Bronchodilator response (%)	18.3 ± 15.7	16.6 ± 9.9	24.1 ± 15.9	0.55
Pre-bronchodilator FEV1 (% predicted)	69.5 ± 13.2#	49.5 ± 22.3	44.8 ± 11.2#	< 0.001
Pre-bronchodilator FEV1/FVC (%)	61.5 ± 9.2#	55.5 ± 16.1	44.4 ± 11.2#	< 0.001
Post-bronchodilator FEV1 (% predicted)	81.0 ± 11.8*#	57.7 ± 25.3*	55.1 ± 13.2#	< 0.001
Post-bronchodilator FEV1/FVC (%)	72.0 ± 9.7#	60.8 ± 20.1	48.9 ± 9.5#	< 0.001
FVC (% predicted)	94.5 ± 12.4*	71.6 ± 20.1*	87.1 ± 13.9	0.019
PEF (% predicted)	75.3 ± 18.2#	48.1 ± 24.1	46.6 ± 16.4#	< 0.001
MMEF (% predicted)	37.3 ± 22.6#	28.2 ± 21.1	13.2 ± 6.2#	0.001
$MEF_{50\%}$ (% predicted)	40.8 ± 23.3#	31.0 ± 23.0	14.8 ± 7.5#	0.001
$MEF_{25\%}$ (% predicted)	33.9 ± 21.8#	28.5 ± 20.4	12.8 ± 5.6#	0.005
RV/TLC (%)	39.0 ± 8.7*#	54.1 ± 10.5*	51.2 ± 8.0#	< 0.001
Z_5 (% predicted)	1.5 ± 0.7	1.2 ± 0.4	1.9 ± 0.7	0.15
R_5 (% predicted)	1.45 ± 0.6	1.2 ± 0.4	1.9 ± 0.7	0.08
R_{20} (% predicted)	1.4 ± 0.3	1.0 ± 0.2	1.5 ± 0.4	0.05
R_5-R_{20}	0.4 ± 0.1	0.4 ± 0.1	0.6 ± 0.2	0.05
X_5 (% predicted)	0.6(9.4)#	2.7(3.8)	4.3(8.9)#	0.008
D_{LCO}/VA (% predicted)	101.7 ± 14.0	92.7 ± 6.9	87.0 ± 33.5	0.27
Blood EOS (×10^9/l)	0.3(0.6)	0.4(0.5)	0.5(0.6)	0.22
FeNO (ppb)	55.0(61.8)	70.0(169.5)	43.0(68.0)	0.41
Total IgE (KU/ml)	180.5(333.5)	114.8(134.2)	210.7(249.6)	0.23
Sputum EOS (%)	17.8(56.5)	33.8(66.4)	41.0(74.3)	0.25
Sputum Neu (%)	35.3(42.8)	14.5(69.6)	43.0(70.3)	0.47
ICS dose, BDP (μg/day)	400(400)	400(1200)	1000 (1600)	0.011
LABA (%)	94.9	100	100	0.99
OCS (%)	25.6	33.3	60.0	0.065
OCS dose, prednisone (mg/day)	0(3)	0 (4)	15 (20)	0.021
Leukotriene receptor antagonist (%)	53.8	71.4	66.7	0.586
Theophylline (%)	7.7	14.3	26.7	0.17

OCS, oral corticosteroid

*$p < 0.05$, cluster 1 versus cluster 2; #$p < 0.05$, cluster 1 versus cluster 3

cluster. Therefore, the CT-derived phenotypes we describe here represented distinct asthma endotypes [11] with discrete pathogenic pathways and indicated that a progressive disease captured at different stages of airway remodeling was certain and reliable.

Gupta et al [21] reported three different CT-determined asthma phenotypes in 2014. Cluster 1 was severe air trapping, bronchial wall thickening, and bronchial lumen dilatation; cluster 2 was moderate air trapping; and cluster 3 was severe air trapping and bronchial lumen narrowing. These clusters differed from the ones found in the current study. The possible reasons are as follows: First, all of the asthma patients in this study had uncontrolled asthma. Second, in Gupta's study, all of the subjects were scanned within 30 min of inhalation of 2.5 mg

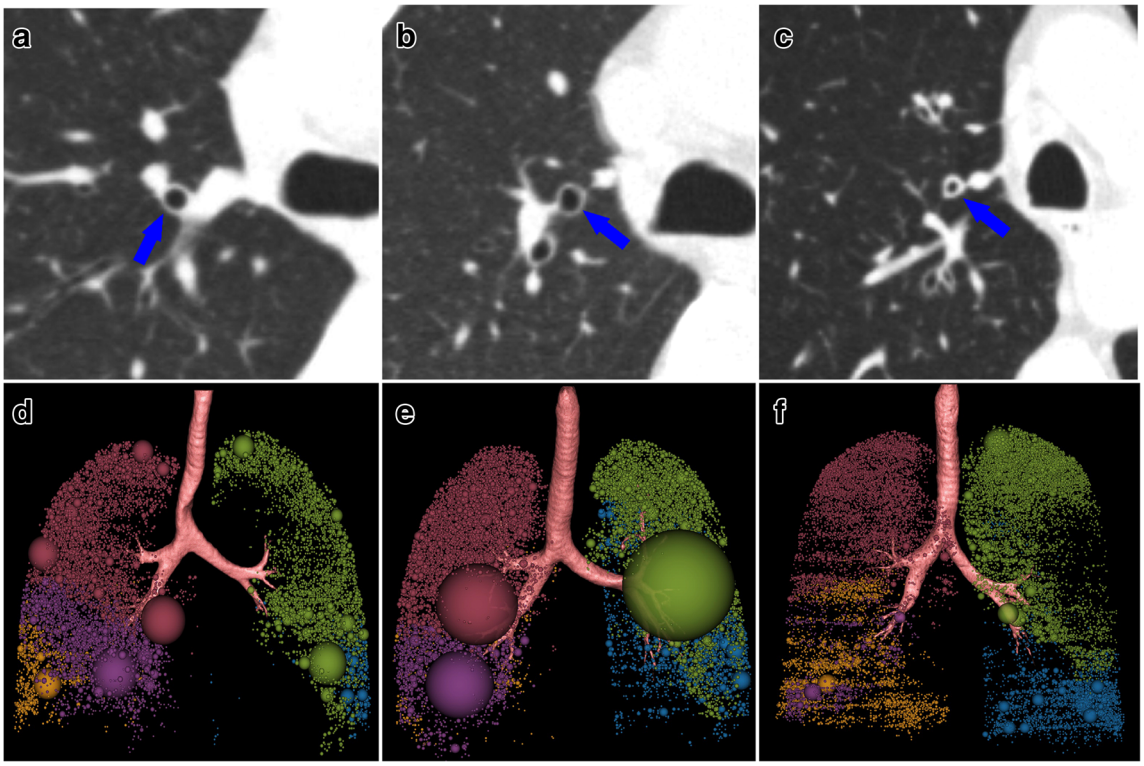

Fig. 3 RB1 CT cross section (below with blue arrow) of uncontrolled asthmatic patients from cluster 1 (**a**), cluster 2 (**b**), and cluster 3 (**c**) are shown. Air trapping in uncontrolled asthma phenotypes. Respective low attenuation of expiratory VI_{-856} (%) of three clusters is shown in **d**–**f**, which were used to assess the size and distribution of air trapping areas

of nebulized salbutamol, while subjects in this study were scanned without salbutamol inhalation. Third, all of the expiratory scans were acquired at the end of normal expiration (near functional residual capacity) in Gupta's study, while expiratory phase images were acquired at the end of deep expiration (near residual volume) in our study. This is because the correlation analysis between the residual pulmonary function index and the qCT air trapping index showed a strong positive correlation between the RV/TLC ratio and expiratory VI_{-856} (%) values, suggesting that scanning at the end of deep expiration is a good reflection of air trapping. This is consistent with results of previous studies [23, 26]. Fourth, the cluster results in the Gupta study were based on qCT analysis of the RB1 segment only. The current study analyzed the average values of three segments of RB1, RB10, and LB10. Fifth, the parameters involved in factor and cluster analysis were different in the two articles, resulting in different representations of the clustering phenotypes.

There are some potential limitations to this study. First, the inspiratory and expiratory CT scans obtained were not spirometrically gated. However, it has been shown that the repeatability of quantitative CT tests is high and not likely to improve with spirometric gating [40, 41]. Second, the number of subjects in cluster 2 was small; studies with larger data sets including a sufficient number of subjects are needed. Third, this study lacked pathological evidence for airway remodeling, and the underlying mechanisms in the development of such different phenotypes remain unclear and warrant further study.

In summary, the CT-derived phenotypes found in our research represent a breakthrough in studying the heterogeneity of uncontrolled asthma. Our findings not only suggest that different asthma phenotypes have different pathogenic pathways, but also indicate that asthma is a progressive disease that can be captured at different stages of airway remodeling. Improved phenotyping may allow for more targeted interventions. In addition, qCT is an effective and non-invasive method that can provide image-based phenotypes for investigating prospective trials of novel therapies.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Yubao Guan.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- case-control study
- performed at one institution

References

1. Grenier PA, Beigelman-Aubry C, Fétita C, Prêteux F, Brauner MW, Lenoir S (2002) New frontiers in CT imaging of airway disease. Eur Radiol 12:1022–1044
2. Hartley RA, Barker BL, Newby C et al (2016) Relationship between lung function and quantitative computed tomographic parameters of airway remodeling, air trapping, and emphysema in patients with asthma and chronic obstructive pulmonary disease: a single-center study. J Allergy Clin Immumol 137:1413–1422
3. Shimizu K, Hasegawa M, Makita H, Nasuhara Y, Konno S, Nishimura M (2011) Comparison of airway remodeling assessed by computed tomography in asthma and COPD. Respir Med 105: 1275–1283
4. Montaudon M, Lederlin M, Reich S et al (2009) Bronchial measurements in patients with asthma: comparison of quantitative thin-section CT findings with those in healthy subjects and correlation with pathologic findings. Radiology 253:844–853
5. Niimi A, Matsumoto H, Takemura M, Ueda T, Chin K, Mishima M (2003) Relationship of airway wall thickness to airway sensitivity and airway reactivity in asthma. Am J Respir Crit Care Med 168: 983–988
6. Matsumoto H, Niimi A, Takemura M et al (2005) Relationship of airway wall thickening to an imbalance between matrix metalloproteinase-9 and its inhibitor in asthma. Thorax 60:277–281
7. Jain N, Covar RA, Gleason MC, Newell JD Jr, Gelfand EW, Spahn JD (2005) Quantitative computed tomography detects peripheral airway disease in asthmatic children. Pediatr Pulmonol 40(3):211–218
8. Busacker A, Newell JD Jr, Keefe T et al (2009) A multivariate analysis of risk factors for the air-trapping asthmatic phenotype as measured by quantitative CT analysis. Chest 135:48–56
9. Green RH, Brightling CE, Bradding P (2007) The reclassification of asthma based on subphenotypes. Curr Opin Allergy Clin Immunol 7:43–50
10. Haldar P, Pavord ID, Shaw DE et al (2008) Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 178:218–224
11. Anderson GP (2008) Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. Lancet 372:1107–1119
12. Nakano Y, Muro S, Sakai H et al (2000) Computed tomographic measurements of airway dimensions and emphysema in smokers correlation with lung function. Am J Respir Crit Care Med 162: 1102–1108
13. Berger P, Perot V, Desbarats P, Tunon-de-Lara JM, Marthan R, Laurent F (2005) Airway wall thickness in cigarette smokers: quantitative thin-section CT assessment. Radiology 235:1055–1064
14. Aziz ZA, Wells AU, Desai SR et al (2005) Functional impairment in emphysema: contribution of airway abnormalities and distribution of parenchymal disease. AJR Am J Roentgenol 185:1509–1515
15. Hasegawa M, Nasuhara Y, Onodera Y et al (2006) Airflow limitation and airway dimensions in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 173:1309–1315
16. Coxson HO, Quiney B, Sin DD et al (2008) Airway wall thickness assessed using computed tomography and optical coherence tomography. Am J Respir Crit Care Med 177:1201–1206
17. Hasegawa M, Makita H, Nasuhara Y et al (2009) Relationship between improved airflow limitation and changes in airway calibre induced by inhaled anticholinergic agents in COPD. Thorax 64: 332–338
18. Inui N, Matsushima S, Kato S et al (2015) Effects of indacaterol versus tiotropium on respiratory mechanics assessed by the forced oscillation technique in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 10:1139–1146
19. Yasui H, Inui N, Furuhashi K et al (2013) Multidetector-row computed tomography assessment of adding budesonide/formoterol to tiotropium in patients with chronic obstructive pulmonary disease. Pulm Pharmacol Ther 26:336–341
20. GINA_Global stategy for asthma management and prevention. 2012. Available at: http://www.ginasthma.org/ . Accessed 28 June 2013
21. Gupta S, Hartley R, Khan UT et al (2014) Quantitative computed tomography-derived clusters: redefining airway remodeling in asthmatic patients. J Allergy Clin Immunol 133:729–738
22. Van Tho N, Wada H, Ogawa E, Nakano Y (2012) Recent findings in chronic obstructive pulmonary disease by using quantitative computed tomography. Respir Investig 50:78–87
23. Aysola RS, Hoffman EA, Gierada D et al (2008) Airway remodeling measured by multidetector CT is increased in severe asthma and correlates with pathology. Chest 134:1183–1191
24. Kaminska M, Foley S, Maghni K et al (2009) Airway remodeling in subjects with severe asthma with or without chronic persistent airflow obstruction. J Allergy Clin Immunol 124:45–51
25. Nakano Y, Wong JC, de Jong PA et al (2005) The prediction of small airway dimensions using computed tomography. Am J Respir Crit Care Med 171:142–146.11
26. Gono H, Fujimoto K, Kawakami S, Kubo K (2003) Evaluation of airway wall thickness and air trapping by HRCT in asymptomatic asthma. Eur Respir J 22:965–971
27. Gupta S, Siddiqui S, Haldar P et al (2010) Quantitative analysis of high-resolution computed tomography scans in severe asthma subphenotypes. Thorax 65:775–781
28. Park SW, Park JS, Jeong SH et al (2012) Air trapping is a major determinant of persistent airway obstruction in asthmatics. Respir Med 106:786–793
29. Ito R, Yokoyama A, Hamada H, Yasuhara Y, Kohno N, Higaki J (2006) Effect of inhalated bronchodilators on air trapping in patients with stable asthma. J Asthma 43:125–129
30. Tunon-de-Lara JM, Laurent F, Giraud V et al (2007) Air trapping in mild and moderate asthma: effect of inhaled corticosteroids. J Allergy Clin Immumol 119:583–590
31. Mikos M, Grzanka P, Sladek K et al (2009) High-resolution computed tomography evaluation of peripheral airways in asthma patients: comparison of focal and diffuse air trapping. Respiration 77: 381–388
32. Nakano Y, Van Tho N, Yamada H, Osawa M, Nagao T (2009) Radiological approach to asthma and COPD—the role of computed tomography. Allergol Int 58:323–331
33. Bumbacea D, Campbell D, Nguyen L et al (2004) Parameters associated with persistent airflow obstruction in chronic severe asthma. Eur Respir J 24:122–128
34. Mitsunobu F, Mifune T, Ashida K et al (2001) Low-attenuation areas of the lungs on high-resolution computed tomography in asthma. J Asthma 38:413–422

35. Mitsunobu F, Ashida K, Hosaki Y et al (2003) Complexity of terminal airspace geometry assessed by computed tomography in asthma. Am J Respir Crit Care Med 167:411–417
36. Vikgren J, Bake B, Ekberg-Jansson A, Larsson S, Tylén U (2003) Value of air-trapping in detection of small airways disease in smokers. Acta Radiol 44:517–524
37. Sung A, Naidich D, Belinskaya I, Raoof S (2007) The role of chest radiography and computed tomography in the diagnosis and management of asthma. Curr Opin Pulm Med 13:31–36
38. Ueda T, Niimi A, Matsumoto H et al (2006) Role of small airways in asthma: investigation using high-resolution computed tomography. J Allergy Clin Immunol 118:1019–1025
39. Okazawa M, Muller N, McNamara AE, Child S, Verburgt L, Pare PD (1996) Human airway narrowing measured using high resolution computed tomography. Am J Respir Crit Care Med 154:1557–1562
40. de Jong PA, Müller NL, Paré PD, Coxson HO (2005) Computed tomographic imaging of the airways: relationship to structure and function. Eur Respir J 26:140–152
41. Gierada DS, Yusen RD, Pilgram TK et al (2001) Repeatability of quantitative CT indexes of emphysema in patients evaluated for lung volume reduction surgery. Radiology 220:448–454