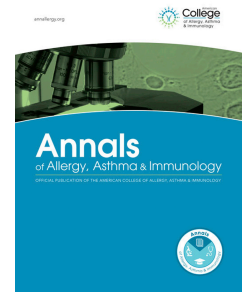


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Small airway dysfunction may be an indicator of early asthma: findings from high-resolution CT

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Title

Small airway dysfunction may be an indicator of early asthma: findings from high-resolution CT

Authors

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There are no conflicts of interest to declare.

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Contribution of each author

Dan Jiang: conception and design of the study, analysis of images, interpretation of the data and preparation of the manuscript

Zhimin Wang: patients and control subjects recruiting

Cong Shen: patients and control subjects recruiting

Chenwang Jin: analysis of the data

Nan Yu: interpretation of the data

Jun Wang: analysis of the data

Nan Yin: preparation of the manuscript

Youmin Guo: conception and design of the study

1 Introduction

2 Asthma is a common chronic respiratory disease that affects approximately 300
3 million individuals worldwide and brings a major health care burden ¹. Chronic
4 airway inflammation and characteristic structural changes, often described as “airway
5 remodeling”, are observed in the airways of patients with asthma. Evidence from
6 surgically resected lung tissue, autopsy lung specimens, and transbronchial biopsies
7 suggests that airway inflammation and structural changes (subepithelial fibrosis,
8 increased airway smooth muscle, increased blood vessels in the walls of the airways,
9 and mucus hypersecretion) occurs in both the central and peripheral airways ²⁻⁹.
10 Further research indicates that pathological abnormalities in the peripheral
11 bronchioles and small airway dysfunction can be detected in patients with asthma
12 regardless of severity and treatment stage ¹⁰⁻¹². Moreover, treatment with small particle
13 inhaled corticosteroids is more effective than with large particle inhaled
14 corticosteroids ¹³⁻¹⁶. Increasing attention is now focused on the role of the small
15 airways in asthma and small airway dysfunction is now considered a distinct clinical
16 phenotype or a sensitive indicator of early disease ¹⁷.
17 Many studies have assessed the structural changes in the large airways of patients
18 with asthma using high-resolution computed tomography (HRCT) and demonstrated
19 that the airway walls of these patients are thicker than those of healthy subjects ¹⁸⁻²³.
20 However, to the best of our knowledge, few studies have explored the structural
21 changes in the large airways of patients with impaired small airway function, i.e., the
22 small airway asthma phenotype. In this study, airway dimension indices, such as

luminal area(LA), wall area (WA), and wall area percentage (WA%), were measured from the 2nd to 6th generation and compared between patients with small airway asthma and the healthy controls to investigate whether there are structural changes in the large airways in patients with small airway asthma.

Methods

Participants

All the patients enrolled in the study were recruited from the asthma outpatient department at our hospital between October 2016 and November 2017. The following inclusion criteria were applied: (1) asthma diagnosed by a respiratory physician based on the history of characteristic symptom patterns and evidence of variable airflow limitation; (2) age ≥ 18 years; (3) lifetime nonsmoking status; (4) no other respiratory disease (according to medical history and examinations); and (5) Forced expiratory volume in the first second (FEV_1)% predicted $\geq 80\%$, forced expiratory flow over the middle half of the forced vital capacity (FEF_{25-75})% predicted $< 60\%$, resistance at 5 Hz (R_5) $> 150\%$, and a difference between resistance at 5 Hz and 20 Hz ($R_5 - R_{20}$) $> 0.10 \text{ Kpa/L} \cdot \text{s}$.

The severity of asthma was assessed according to the GINA (Global Initiative for Asthma) guidelines based on the level of treatment required to control symptoms and exacerbations²⁴.

The healthy controls were lifetime nonsmokers who were free from respiratory symptoms and respiratory diseases. All the controls were recruited from the health examination center at our hospital. The study was approved by our institutional ethics

committee and written informed consent was obtained from all study participants.

Pulmonary function tests

The pulmonary function tests were performed by an experienced technician in a blinded manner using the Jaeger Master-Screen System (Vyair Medical, Höchberg, Germany). All study participants underwent standard spirometric measurements of lung function. The following indices were recorded: including FEV₁% (percent predicted), forced vital capacity(FVC), and FEF₂₅₋₇₅% (percent predicted). The resistance of the respiratory system was measured using impulse oscillometry (IOS, Jaeger MasterScreen, Erich Jaeger GmbH & Co. KG, Würzburg, Germany) according to standard recommendations²⁵. The R5 and R5-R20 were recorded.

HRCT scan

HRCT scan was performed within 1 day of the pulmonary function tests. Volumetric whole-lung scans were performed using a multi-detector CT scanner (GE Light Speed VCT, General Electric, Milwaukee, WI, USA) with the following parameters: collimation, 64 × 0.625mm; 120 kVp; 160 mAs; rotation time, 0.6s; pitch, 0.984. All study participants were scanned in the supine position at full-inspiration (inspiratory breath hold was rehearsed prior to the CT scan) and with the arms held over the head. The images were reconstructed using a high-spatial frequency algorithm with a slice thickness of 1.25 mm and an interval of 1.25 mm. A three-dimensional bronchial skeleton was automatically reconstructed using the volumetric data. The apicoposterior segmental bronchus in the left upper lobe (LB1+2) and the posterior basal segmental bronchus in the left lower lobe (LB10) were selected and

automatically converted to curved multiplanar reconstruction images. These bronchi were selected because they are relatively perpendicular to the HRCT images and less affected by cardiac motion artifacts. The 2nd to 6th generation airways of each bronchus were identified and analyzed. The LA, WA, and WA% values of each generation were calculated automatically. The WA and WA% were derived from the total area (TA) and LA as follows: $WA = TA - LA$, $WA\% = WA / TA \times 100\%$. The processes of bronchus selection, identification and calculation were inspected carefully using the longitudinal and short-axis images simultaneously by one author (DJ) who was blinded to the participants' information.

Statistical analysis

The normally distributed data were analyzed parametrically and expressed as the mean and standard deviation. Age and body mass index (BMI) were compared between the patients with small airway asthma and the healthy controls using unpaired *t*-tests or chi-squared tests. The LA, WA, and WA% were compared between the two study groups using analysis of variance. A *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 17.0 software (IBM Corp., Armonk, NY, USA).

Results

9 patients with small airway asthma and 20 healthy controls were included in the study. The characteristics of the study participants are shown in Table 1. In 9 patients 5 were classified as mild (medication: as-needed short-acting β_2 -agonist (SABA) or Budesonide 200 mcg bid plus as-needed SABA), the other 4 were classified as

moderate (medication: budesonide 160 mcg /formoterol 4.5 mcg 1~2 press bid) according to the GINA guidelines. There was no significant difference in age, sex, BMI, FEV₁, FVC, or FEV₁/FVC between the patients with small airway asthma and the healthy controls.

The 2nd to 6th generation of LB1+2 and LB10 were identified in 7 and 9 patients with small airway asthma, and in 20 and 19 healthy controls, respectively,. The only significant difference found between the patients with small airway asthma and the healthy controls was in the WA% of the 6th generation (LB1+2, $P = 0.040$; LB10, $P = 0.033$). The WA% of the 6th generation in the patients with small airway asthma was higher than that in the healthy controls. Table 2 shows the LA, WA, and WA% values from the 2nd to 6th generation of LB1+2 and LB10.

Discussion

In this study, we compared the airway dimension indices of LB1+2 and LB10 from the 2nd (lobar) generation to the 6th generation between patients with small airway asthma and healthy controls using HRCT. We found a significant structural difference in the 6th generation airway between the patients and controls, even though these patients had preserved FEV₁. Previous studies that measured large airway dimension indices using HRCT found that airway wall thickening occurred from the 3rd to 6th generation airways in patients with asthma and was related to air-flow obstruction^{18, 19, 21, 22, 26}, furthermore, airway remodeling in asthma has been reported to be more prominent in the distal airways²⁷. Therefore, we speculated that the structural changes in the large airways in patients with small airway asthma might be an early stage of

the disease.

The only significant difference found between the patients with small airway asthma and the healthy controls was in the WA% of the 6th generation bronchus. The larger WA% was a common consequence of the smaller LA and the larger WA and should be considered as an integrated indicator of airway structural changes in both the airway wall and lumen rather than simply as the result of airway wall thickening.

In this study, as the patients have a relative normal FEV₁% predicted, FEF₂₅₋₇₅% predicted <60% was regarded as airflow limitation, and average daily diurnal PEF variability >10% was regarded as excessive variability in lung function. We used FEV₁≥80%, FEF₂₅₋₇₅<60%, R₅>150%, and R₅-R₂₀>0.10kPa/L.s as the diagnostic criteria for small airway asthma as recommended¹⁷. So far there is still no universally accepted method or algorithm for detection of abnormalities in the small airway, therefore various functional techniques and inflammatory markers have been used as surrogates. FEF₂₅₋₇₅ is the most commonly used marker of small airway function, however it is a volume-dependent measurement with uncertain reproducibility and reliability^{28, 29}. Therefore, we used IOS in addition to an abnormal FEF₂₅₋₇₅ to confirm the diagnosis of small airway dysfunction. IOS is an effort-independent test that is performed during normal quiet tidal breathing and requires minimal patient cooperation²⁵. R₅ represents the resistance of the large and small airways, whereas R₂₀ only represents the resistance in the larger airways, hence, R₅-R₂₀ is the resistance in the peripheral small airways.

The main limitation of our study was its small sample size of 9 patients. Persistent

small airway dysfunction was detected in at least 60% of patients with asthma receiving British Thoracic Society treatment steps 2 to 4¹². However no more than 10% of our patients with asthma met the criteria for small airway asthma, i.e., small airway dysfunction with preserved FEV₁. Therefore, there is a need for multicenter prospective studies with large sample size to confirm our findings. We are continuing to monitor the patients in our present study to obtain more information on the natural history of airways involvement in patients with small airway asthma.

In summary, our findings indicate that airway structural changes occur in the large airways of patients with small airway asthma, which may be an indicator of early asthma.

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Table 1 Characteristics of subjects.

	Asthma (N=9)	Control (N=20)	P value
Age (years)	35.22 (9.04)	38.25 (6.64)	0.361*
Sex (Male/Female)	3/6	11/9	0.348 [†]
BMI (kg/m ²)	23.02 (2.31)	24.59 (2.81)	0.650*
Disease severity (Mi/Mo)	5/4		
FEV ₁ (% predicted)	91.22 (6.14)	103.15(4.79)	0.372*
FVC	94.67(6.82)	102.15(5.08)	0.161*
FEV ₁ /FVC (%)	82.79(4.33)	84.60(4.59)	0.448*
FEF ₂₅₋₇₅ % (% predicted)	29.89 (12.43)	90.35(4.65)	0.008*
R5 (% predicted)	203.47 (38.20)		
R5-R20 (Kpa/L·s)	0.32 (0.12)		

Abbreviations: N, number; BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; Mi, mild; Mo, moderate; Se, severe.

* unpaired *t*-test

[†] χ^2 -test

Table 2 Comparison of LA, WA and WA% of LB1+2 and LB10

		N	G2	G3	G4	G5	G6
LB1+2							
LA (mm ²)	Asthma	7	47.83 (3.35)	24.72 (3.42)	12.43 (1.08)	6.07 (0.58)	4.64 (0.55)
	Control	20	48.42 (5.67)	25.35 (2.03)	13.69 (1.83)	7.19 (0.98)	3.79 (0.32)
	P value*		0.929	0.876	0.558	0.335	0.192

WA (mm ²)	Asthma	7	27.32 (2.43)	20.20 (1.94)	16.12 (1.51)	13.52 (1.12)	13.16 (1.11)
	Control	20	26.73 (1.44)	19.44 (1.15)	15.07 (0.89)	12.28 (0.66)	10.96 (0.65)
	<i>P</i> value*		0.836	0.739	0.554	0.351	0.099
WA%	Asthma	7	0.37 (0.01)	0.48 (0.01)	0.64 (0.03)	0.73 (0.02)	0.81 (0.03)
	Control	20	0.35 (0.02)	0.46 (0.02)	0.61 (0.02)	0.70 (0.01)	0.73 (0.02)
	<i>P</i> value*		0.464	0.395	0.326	0.248	0.040
LB10							
LA (mm ²)	Asthma	9	43.70 (5.56)	24.69 (2.99)	14.23 (2.17)	7.78 (1.25)	5.16 (0.51)
	Control	19	44.08 (3.83)	26.81 (2.06)	16.52 (1.49)	9.65 (0.86)	6.51 (0.74)
	<i>P</i> value*		0.955	0.565	0.393	0.227	0.141
WA (mm ²)	Asthma	9	25.79 (1.58)	19.53 (1.19)	15.39 (0.79)	13.12 (0.64)	11.38 (0.77)
	Control	19	25.26 (2.30)	18.77 (1.73)	14.56 (1.15)	12.37 (0.93)	10.32 (0.53)
	<i>P</i> value*		0.851	0.720	0.554	0.513	0.267
WA%	Asthma	9	0.39 (0.02)	0.47 (0.02)	0.57 (0.03)	0.65 (0.02)	0.71 (0.01)
	Control	19	0.37 (0.01)	0.45 (0.01)	0.53 (0.02)	0.61 (0.02)	0.65 (0.02)
	<i>P</i> value*		0.482	0.313	0.273	0.150	0.033

Abbreviations: G2 (3-6), the 2nd (3rd-6th) generation airway; LA, luminal area; N, number;

WA, wall area; WA%, wall area percent

* multivariate ANOVA