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Airway wall thickness of allergic asthma caused by weed pollen or house dust mite assessed by computed tomography

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KEYWORDS

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Summary

Purpose: Little was known about Airway wall thickness of asthma patients with different allergen allergy. So we explored the possible difference of Airway wall thickness of asthma patients mono-sensitized to weed pollen or HDM using high-resolution computed tomography.

Materials and methods: 85 severe asthma patients were divided into weed pollen group and HDM group according to relevant allergen. 20 healthy donors served as controls. Airway wall area, percentage wall area and luminal area at the trunk of the apical bronchus of the right upper lobe were quantified using HRCT and compared. The values of pulmonary function were assessed as well.

Results: There were differences between HDM group and weed pollen group in WA/BSA, WA% and FEF_{25–75%} pred, and no significant difference in FEV₁%pred, FEV₁/FVC and LA/BSA. In weed pollen group, WA/BSA was observed to correlate with the duration of rhinitis, whereas in HDM group, WA/BSA and LA/BSA was observed to correlate with the duration of asthma. In weed pollen group, FEV₁/FVC showed a weak but significant negative correlation with WA%, but in HDM group FEV₁/FVC showed a significant positive correlation with WA% and a statistical negative correlation with LA/BSA. FEV₁/FVC and FEF_{25–75%} pred were higher and WA/BSA and

Abbreviations: HDM, house dust mite; HRCT, high-resolution computed tomography; BSA, body surface area; WA, airway wall area; WA%, percentage wall area; LA, luminal area; FEF_{25–75%}, forced expiratory flow during the middle half of the FVC.

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LA/BSA were lower in healthy control group than asthma group. FEV₁%pred and WA% was no significant difference between asthma patients and healthy subjects.

Conclusion: There are differences between HDM mono-sensitized subjects and weed pollen mono-sensitized subjects, not only in airway wall thickness, but also small airway obstruction.

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Introduction

Asthma is defined a heterogenous disease, usually characterized by chronic airway inflammation and structural changes in the airway [1], the latter is shown airway wall thickening [2], which is referred as remodeling of airway [3]. Airway wall thickening involves epithelial changes, increased smooth muscle mass, increased numbers of activated fibroblasts/myofibroblasts, subepithelial fibrosis, and vascular changes, and is considered the consequence of chronic inflammation and responsible for the pathogenesis and clinical manifestations of asthma [4]. It has been demonstrated that these structural changes which result in persistent airflow limitation, a decrease in lung function and airway hyperresponsiveness can occur not only in the central, but also the peripheral small airways [5]. Some evidences have demonstrated that the degree of airway wall thickening related to the severity of disease, the degree of airflow obstruction, and the duration of asthma or older age [6,7]. Airway remodeling was previously determined by postmortem studies and bronchial biopsy [8,9]. However, these ways were invasive. High-resolution computed tomography is an effective and sensitive noninvasive tool to investigate morphological changes of the lung and bronchi in vivo [10,11], CT-derived indices have been defined and proposed as useful tool for evaluating airway wall thickness [2,12].

Allergic asthma is the most easily recognized asthma phenotype, which often is triggered by one or more common airborne allergens, such as HDM, weed pollen, grass pollen, animal dander and molds. Airway inflammation may be variably associated with changes in different allergens [13]. Some authors concluded that Sensitization to indoor allergens, e.g. HDM, is generally more important than sensitization to outdoor allergens, e.g. weed pollen, for the development of asthma [14]. Patients with weed pollen allergy, whose exposure is only a few months, will need longer time of development of asthma [15]. Some searchers ever thought that pollens had little important contribution to the pathogenesis of asthma, because they thought that pollen grains were too large to penetrate the small airways where asthma occurs [16], and the later studies had proved that winds, wet weather and other disturbances can disperse the pollens to fragments which can penetrate into the lower airways [17]. Sensitization to weed pollen is an independent risk factor for developing asthma [18]. Different from weed pollen, HDM don't need other special environment to trigger asthma attacks. Data coming from histological studies have shown that the two allergens are different but also similar in the pathogenesis of triggering asthma attacks or exacerbations, inflammatory cells and

mediators and clinical features [15,19,20]. To the best of our knowledge, there were few studies which explored the difference in airway wall thickness of allergic asthma with sensitization to different allergens.

So the aim of this study was to compare the airway dimensions quantified using HRCT, and the pulmonary function between asthma patients with HDM allergy or weed pollen allergy, evaluating whether there were differences in airway remodeling depending on the sensitization to different relevant allergens.

Materials and methods

Patients

All patients, came from eastern china, aged 18–55 years, had previously received medication and were being followed at our outpatient clinic. Patients were eligible in the spring of 2014 if they met the following criteria: (1) clinical diagnosis of severe asthma according to the level of treatment required to control symptoms and exacerbations defined by the updated GINA guidelines [1], (2) Urban residents, and lifetime Nonsmokers, (3) who only accepted a treatment with Salmeterol/Fluticasone propionate (50/250 µg twice daily) and had maintained control for at least 6 months when they were recruited, the rhinitis was equally well controlled with Fluticasone Propionate Nasal Spray at the same time (4) positive immediate responses on skin prick test only to HDM or only to weed pollens (such as artemisia pollen, Humulus scandens pollen and so on) , and the allergic sensitization had the relevance with clinical presentation and prior history. Patients were excluded if they merged with Chronic obstructive pulmonary disease (COPD), pulmonary interstitial diseases, bronchiectasis, bronchial lung cancer and other lung diseases. Patients who had received prior immunotherapy were also excluded.

The healthy control subjects coming from our hospital staff were lifetime nonsmokers and had no respiratory symptoms and no history of asthma or other respiratory diseases, and had negative immediate responses on skin prick test to all allergens tested in the study.

Ethical permission to conduct the study was granted by local ethics committees. All subjects had signed informed consent before enrollment.

Skin prick tests

Skin prick tests were performed on both forearms with 26 common aeroallergens: Dermatophagoides pteronyssinus, Dermatophagoides farinae, grass, birch, mugwort, cat, dog,

Alternaria tenuis, and *Cladosporiumherbarum* (Allergopharma) and so on. Negative (saline) and positive (e.g. 9% histamine hydrochloride solution) controls were performed. The positive control should show a Wheal diameter ≥ 3 mm. Wheal diameter ≥ 3 mm was considered as a positive result of the test [21].

High-resolution computed tomography scanning

Because its geometry nearly perpendicular to the axial plane and it is easily identified on CT scans, the bronchial wall thickness at the trunk of the apical bronchus of the right upper lobe was quantified by a helical CT scanner (Brilliance CT 64 slice, Philips, Germany). The first step, all subjects were scanned at full inspiration using conventional 5-mm thick contiguous scanning, in order to screening of chest abnormalities, i.e. pulmonary interstitial diseases, bronchiectasis, bronchial lung cancer, Emphysema, pulmonary bullae and other lung diseases. And the second, The HRCT images of the subjects without chest abnormalities were remodeled by Lung Enhanced software using 1-mm thick. The HRCT images were photographed with a window setting appropriate for evaluating airway walls. And the longest diameter exceeded the shortest diameter by a factor of ≥ 1.5 were discharged. In order to avoid intra- and interobserver variability and parallax errors, the images were analyzed in random order by 2 radiologists after the name of the patients were deleted and the measurements were averaged. The two parameters were measured with electrical calipers: the airway intraluminal area (LA) and the total bronchial area (WT). Then the airway wall area (WA) = WT - LA, $WA\% = (WA/WT) \times 100\%$. To reduce interindividual variability, WA, WT and LA were normalized on body surface area (BSA) [22].

Pulmonary function

Pulmonary Function tests were performed by an experienced technician in a blinded manner using the Master-Screen System (JAEGER Co, Hoechberg, Germany). All subjects underwent standard spirometric measures of lung function. The following indices of airflow obstruction were documented, including FEV₁% (percentage of predicted), FEV₁/FVC, and FEF_{25–75%} pred.

Statistical analysis

Reproducibility of airway dimensions was carried out using MedCalc statistical software (version 11.4.2.0; MedCalc, Mariakerke, Belgium). Other statistical analysis were performed with the statistical SPSS 17.0 software (SPSS, Chicago, IL, USA). Data were expressed as means $\pm$ standard deviation (SD). Comparison between two groups was performed using unpaired *t* tests or χ^2 -test. Comparisons between groups were done with analysis of variance (ANOVA). For analysis of correlations, Pearson's correlation coefficient was calculated for data with a normal distribution, and Spearman's rank correlation test was used otherwise. Statistical tests were 2-tailed, a *p* value of less than 0.05 was considered to indicate statistical significance.

Results

Reproducibility

Fig. 1 displays a scatter diagram of the differences plotted against the averages of the two measurements of LA or WT of the two observers. For each plot, the mean difference did not apparently deviate from zero, and the limits of agreement were small. Interobserver reproducibility of WT and LA measurement was good.

Subject characteristics

85 patients (49 with HDM allergy and 36 with weed pollen allergy) and 20 healthy subjects completed the full protocol. The characteristics of the subjects are shown in Table 1. There were no significant differences between the groups in mean age and sex. More patients with weed pollen allergy had merged of rhinitis compared with patients with HDM allergy, and the difference was statistically significant.

Comparison of weed pollen group vs. HDM group and healthy control group vs. asthma group

Table 2 shows the parameters of HRCT analysis and Lung function, and the Comparison of weed pollen group vs. house dust mite group. The Comparison of healthy control

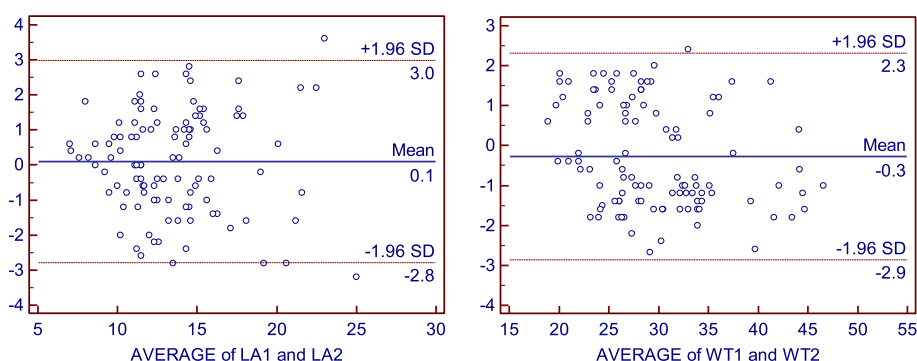


Figure 1 Interobserver error for the measurement of wall area (LA) and (WT). The average of and difference between two measurements are plotted. The dotted and dashed lines represent the mean and the mean $\pm$ 2 SD of the difference, respectively.

Table 1 Baseline characteristics of subjects included in this study.

	Health control (n = 20)	House dust mites (n = 49)	Weed pollen (n = 36)	p value
Mean age (years)	35.3 ± 9.3	33.9 ± 10.1	35.0 ± 9.8	0.192 ^{b,d}
Female (n (%))	12(60%)	30(61.2%)	21(58.3%)	0.965 ^{c,d}
Duration of asthma (years)	—	6.1 ± 6.7	5.9 ± 4.8	0.896 ^{a,e}
Rhinitis (n (%))	—	38(77.6%)	36(100%)	0.007 ^{c,e}
Duration of Rhinitis (years)	—	6.8 ± 6.9	8.7 ± 4.7	0.154 ^{a,e}

^a unpaired *t*-test.^b ANOVA.^c χ^2 -test.^d Comparison of the three groups.^e Comparison of HDM group vs. Weed pollen group.

group and asthma group, which was the combination of weed pollen group and HDM group, are presented in Table 3.

Lung function

There was a significantly different value between HDM group and weed pollen group in FEF_{25–75%} pred. However, there was no significant difference in FEV₁%pred, FEV₁/FVC. The value of FEV₁/FVC and FEF_{25–75%} pred were higher in healthy control group than asthma group. There was no significant difference in FEV₁ between asthma patients and healthy subjects. We also respectively compared the healthy control group with the weed pollen group and HDM group. When comparing healthy control group with the weed pollen group, there was significant difference in FEV₁, but not in FEF_{25–75%} pred.

Airway wall thickness

There was significantly difference between HDM group and weed pollen group in WA/BSA, WA%, especially WA/BSA of HDM group was remarkably higher than weed pollen group ($p < 0.01$), which reflecting the airway remodeling. There

Table 2 Comparison of weed pollen group vs. HDM group.

Variables	House dust mites (n = 49)	Weed pollen (n = 36)	p value ^a
WA/BSA mm ² /m ²	17.7 ± 2.7	15.4 ± 3.2	0.001
LA/BSA mm ² /m ²	14.3 ± 3.6	13.4 ± 3.7	0.306
WA(%)	55.6 ± 4.1	53.7 ± 4.2	0.048
FEV ₁ %pred	94.6 ± 12.5	93.5 ± 8.6	0.635
FEV ₁ /FVC	81.8 ± 7.7	83.4 ± 7.2	0.331
FEF _{25–75%} pred	85.4 ± 24.7	96.4 ± 9.3	0.006

BSA = body surface area; FEF_{25–75%} = forced expiratory flow during the middle half of the FVC; WA = wall area; LA = luminal area; WA% = WA/WT × 100%.

^a unpaired *t*-test.**Table 3** Comparison of health control group vs. asthma group.^b

Variables	Health control (n = 20)	Asthma (n = 85)	p value ^a
WA/BSA mm ² /m ²	13.4 ± 2.2	16.7 ± 3.0	0.000
LA/BSA mm ² /m ²	11.8 ± 2.1	13.9 ± 3.7	0.001
WA(%)	52.8 ± 5.4	54.8 ± 4.2	0.076
FEV ₁ %pred	98.9 ± 9.3	94.1 ± 10.9	0.078
FEV ₁ /FVC	87.0 ± 4.1	82.5 ± 7.5	0.001
FEF _{25–75%} pred	99.7 ± 13.7	90.0 ± 20.4	0.047

^a unpaired *t*-test.^b asthma group: the combination of weed pollen group and HDM group.

was no significant difference in LA/BSA. The indices WA/BSA and LA/BSA were lower in healthy control group than asthma group. There was no significant difference in WA% between asthma patients and healthy subjects. WA% in HDM group was higher than that in healthy control group.

Correlation between airway wall thickness and clinical indices in asthma patients

We also investigated the correlation between airway wall thickness, clinical indices and Lung function (Table 4). The age of subjects in the weed pollen group and the health control group showed significantly correlation with the value of WA/BSA. In the weed pollen group, the value of WA/BSA was observed to correlate with the duration of rhinitis ($p < 0.05$), and not correlate with the duration of asthma ($p = 0.056$), whereas in the HDM group, the value of WA/BSA and LA/BSA was observed to correlate with the duration of asthma, but not correlate with the duration of rhinitis. In the weed pollen group, FEV₁/FVC showed a weak but significant negative correlation with WA%, but in the HDM group, FEV₁/FVC showed a significant positive correlation with WA%, and a statistical negative correlation with LA/BSA ($p < 0.05$). We also found that in the weed pollen group, the duration of rhinitis showed significantly correlation with FEV₁/FVC and FEF_{25–75%} pred (respectively $r = -0.477$, $p < 0.05$; $r = -0.378$, $p < 0.05$) (data not shown in table).

When the 85 asthmatic subjects were analyzed together (Table 5), the age of subjects showed significantly negative correlation with the value of WA/BSA. The value of WA/BSA and LA/BSA was observed to correlate with the duration of asthma, but not correlate with the duration of rhinitis. In addition, WA/BSA negatively correlated with FEV₁/FVC and FEF_{25–75%}. There was no correlation found for WA% with the clinical indices.

Discussion

Our findings indicate that airway wall thickness and degree of small airway obstruction of severe asymptomatic asthma patients are different due to mono-sensitized to different allergens. It is well known that HDM and weed pollen are the more frequent aeroallergens, and they separately

Table 4 Correlation coefficients between airway wall thickness and clinical indices in weed pollen group and HDM group.

	Weed pollen			HDM		
	WA/BSA (mm ² /m ²)	LA/BSA (mm ² /m ²)	WA(%) (%)	WA/BSA (mm ² /m ²)	LA/BSA (mm ² /m ²)	WA(%) (%)
Age (years) ^a	0.448 [*]	0.26	0.138	0.114	0.178	-0.155
Duration of asthma (years)	0.322	0.206	-0.052	0.537 [*]	0.373 [*]	-0.18
Duration of rhinitis (years)	0.351 [*]	0.214	0.025	0.233	0.065	0.042
FEV ₁ %pred ^a	-0.313	-0.176	-0.119	-0.146	-0.106	0.026
FEV ₁ /FVC ^a	-0.322	-0.019	-0.335 [*]	-0.156	-0.289 [*]	0.335 [*]
FEF _{25-75%} pred ^a	-0.091	-0.028	-0.048	-0.211	-0.245	0.193

^{*} $p < 0.001$; ^{*} $p < 0.05$.

^a Pearson's correlation coefficients. Spearman's correlation was analyzed for other variables.

cause perennial and seasonal allergic asthma or rhinitis. Some investigators have researched the difference in diagnostic and therapeutic approaches, epidemiology and the serum levels of interleukin-4, squamous cell carcinoma antigen, immunoglobulin, eosinophil cationic protein and eosinophil of asthma patients depending on different aeroallergen sensitization [13,15,19,20,23]. Relatively there is few studies about the airway remodeling of asthma patients with different allergen allergy. Sears MR et al. reported that persistent asthma (beginning in childhood and continuing into adulthood) is associated with allergy to HDM, and relapse after remission is associated with early onset of childhood asthma as well as allergy to HDM [24]. The airway remodeling exposure to HDM may be onset in cradle. Infant monkeys repeatedly exposed to HDM allergen have a significant increase in the eosinophil content of the central and terminal airways and in mucous cells in central airways [25]. And the total smooth muscle mass and average bundle size of the Infant monkeys were also significantly greater [26]. An increase in the amount of smooth muscle is one of the major contributors to the airway wall thickening characteristic in the lungs of chronic asthmatics. Grainge CL, Lau LC, Ward JA, et al. evaluated the influence of repeated experimentally induced bronchoconstriction on airway structural changes in patients with asthma, they concluded that bronchoconstriction without additional inflammation induces airway remodeling in patients with asthma [27]. Patients with HDM allergy are continuously exposed to antigen stimuli throughout the

year and will suffer daily repeated allergen challenges and would develop more persistent and repeat bronchoconstriction than patients with weed pollen allergy, whose exposure is limited to a certain season and the attacks are relatively fewer. So these may be the reason that the airway wall thickness in patients with HDM allergy will be greater than those with weed pollen allergy.

Niimi A, Matsumoto H et al. concluded that the degree of airway wall thickening may relate to the duration of asthma, but they did not study the relation of airway wall thickening and the duration of rhinitis [6]. Baran H et al. investigated the relationship between the Allergic Rhinitis and its Impact on Asthma classification, they found that there was a statistically significant different Impact between the groups for weed pollen and HDM allergy [28]. But Lee, Mohammadi et al. did not find a difference between the groups for the studied allergens [29,30]. we found in this study that the airway wall thickness of subjects with weed pollen mono-sensitization significantly relative with the duration of rhinitis, but not with the duration of asthma. On the contrary, the airway wall thickness of subjects with HDM mono-sensitization significantly correlated with the duration of asthma, not with the duration of rhinitis. The possible explanation maybe that there may persist minimal inflammation in the airway of rhinitis patients with weed pollen allergy before the presence of classic asthmatic symptoms, and the speculation need to be confirmed in the future study.

Correlations of airway wall thickness with pulmonary function tests have been studied in the past time, but the results are controversial. Our study showed different results depending on different allergens. In the weed pollen group, the FEV₁/FVC, which is the indices of airflow obstruction, has significantly negative correlation with WA %, but it has significantly positive correlation with WA% in the HDM group, and there were statistic significance. This result was novelty and difficult to interpret. WA% may have been affected by the degree of airway narrowing or dilatation. The fact as discussed earlier that WA% was not correlated with the duration and severity of asthma. We tried to give a speculative explanation as like Niimi A [6]. In concise description that HDM-allergic asthmatic patients with absence of "classic bronchiectasis" in this study might have caused airway luminal area to increase with more severe asthma as lung volumes increase [31], which also was supported in this study that there were significantly

Table 5 Correlation coefficients between airway wall thickness and clinical indices in all asthmatic patients.

	WA/BSA (mm ² /m ²)	LA/BSA (mm ² /m ²)	WA (%) (%)
Age (years) ^a	0.228 [*]	0.204	-0.044
Duration of asthma (years)	0.341 [*]	0.303 [*]	-0.159
Duration of Rhinitis (years)	0.164	0.117	-0.029
FEV ₁ %pred ^a	-0.169	0.121	-0.011
FEV ₁ /FVC ^a	-0.251 [*]	-0.187	0.034
FEF _{25-75%} pred ^a	-0.239 [*]	-0.204	0.064

^{*} $p < 0.001$; ^{*} $p < 0.05$.

^a Pearson's correlation coefficients. Spearman's correlation was analyzed for other variables.

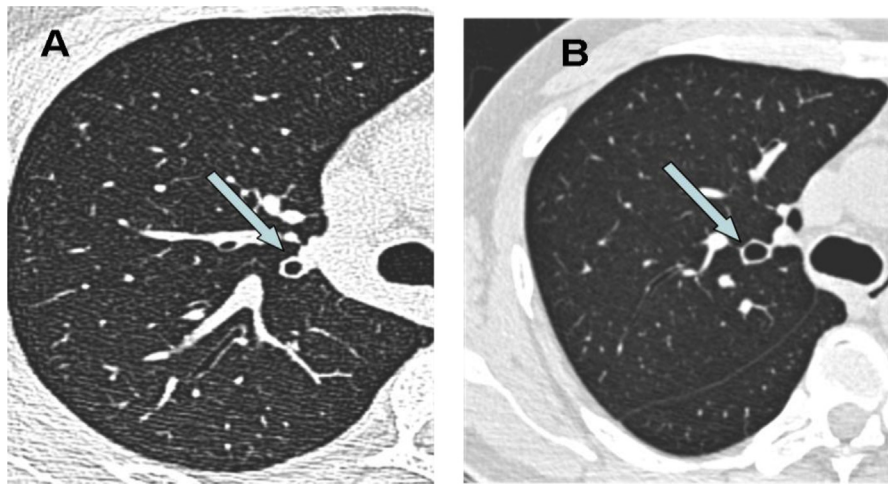


Figure 2 Representative CT images of (A) a patient with weed pollen mono-sensitization and (B) a patient with HDM mono-sensitization. The BSA of the two patients is equal. It clearly depicts that the luminal area of patient with HDM mono-sensitization is greater than that of patient with weed pollen mono-sensitization.

negative relation between the indices of LA/BSA and FEV₁/FVC, and pollen-allergic asthmatic patients whose exposure is intermittent and the asthma attacks is relatively fewer has not developed the larger luminal area, and might have caused airway wall area to increase and the luminal area to decrease with more severe asthma. These also can be shown in Fig. 2. Another possible explanation involves the fact that results are not free from variability and with regarding the method of WT and LA quantification.

The difference between HDM group and weed pollen group of FEF_{25–75%} pred, which is the indices of small airway obstruction, may be related to the causes that pollen allergen grains are larger than the grains of HDM allergens, and which need rainfall, wind, as well as storm to trigger pollen grains to emit respirable particles that can penetrate into the lower airways [32].

Niimi A et al. found that FEV₁ was significantly lower in almost all severity asthma patient than healthy control group [6], however, in our study, there was no difference in FEV₁ between asthma group and health control group, we considered the mainly potential reasons for the phenomena may be that all patients of this study is belong to the most common phenotypes: allergic asthma, which usually respond well to inhaled corticosteroid treatment. Before the patients were enrolled, they had accepted a symptomatic and sufficient anti-inflammatory treatment with a suitable-dose inhaled corticosteroid (ICS) or plus a long-acting inhaled β_2 -agonist (LABA), and have maintained control for at least 6 months, and the pulmonary function also were improved.

In allergic asthma, airway inflammation is triggered by specific (inhalation of allergen such as HDM allergen and pollen spores) or non-specific triggers (such as air pollutants, smoking and viral infection). Pollutant particles from combustion systems, such as motor vehicles, cooking and Tobacco smoking, especially in the countryside of china, have been linked to the incidence of allergic asthma and can increased airways hyperreactivity and inflammation. and Although little is known about the effect of combustion systems on structural changes in asthmatic airways, in

order to reduce the non-specific impacts on airway remodeling, we selected lifetime no smokers and urban residents, which relatively have little effects in cooking.

Boulet, Awadh et al. performed a measurement of wall thickness and outer or luminal diameter at a selected point in each bronchus [33,34], we thought that bronchial contours may present irregularities, especially on diseased bronchi, and the remodeling process is not circumferentially homogenous all around the bronchial wall, the manual method may yield measurement biases, So we quantified the entire airway wall thickness by measuring the airway intraluminal area and the total bronchial area, and did not calculate the luminal diameter and outer diameter as indices of airway wall dimension in the study.

Airway wall thickness can be related to structural changes of remodeling but also to edema and infiltration of inflammatory cells [35]. Therefore, before CT scanning, a sufficient anti-inflammatory treatment is needed. In the study, the asymptomatic asthma patients had maintained control at least 6 months was selected. The effect of ICS on airway remodeling are not defined. There is little evidence that corticosteroids can reverse airway remodeling in asthmatic patients.

Study limitations

There are some limitations to our study. First, this is an observational, descriptive, cross-sectional study, the potential for bias to be introduced by patients and investigators in the assessment of outcomes should be considered. Second, airway measurements of the bronchial wall thickness at the trunk of the apical bronchus of the right upper lobe can not completely represent the small airway where asthma occurs. Third, differences in dose of allergen exposure during the study may influence the results. In spite of these limitations, the findings provide important information that there are differences in airway remodeling depending on the sensitization to different relevant allergens.

Conclusion

This is the first study to compare the differences of severe asthma patients mono-sensitized to weed pollen or HDM, focusing on airway remodeling using high-resolution computed tomography. Our results show that there are differences between asthmatic patients with HDM or weed pollen mono-sensitization, not only in airway wall thickness, but also the indices of small airway obstruction. However, CT is a mono-contrast technique, and there is a lack of specificity. The results need to be confirmed on a larger population of patients in other future studies. Our study explored the different morphometric dimension of airway, the mechanism underlying the differences of airway remodeling according to different sensitization remains to be resolved.

Conflict of interest

We declare that we have no conflict of interest.

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