Quantitative computed tomography measurement of cross-sectional area of small pulmonary vessels in asthmatic patients

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Abstract

Background: Cross-sectional area (CSA) for small pulmonary vessels is considered a parameter of pulmonary vessel alterations in patients with chronic obstructive pulmonary disease. This study was to evaluate the correlation of CSA with airflow obstruction parameters in asthma. Furthermore, we aimed to measure the difference in vascular alteration between asthma phenotypes and evaluate its relation with cytokine levels.

Methods: We consecutively enrolled 20 adult asthmatic patients (13 women: age range, 26–80 years) and 20 healthy controls (8 women: age range, 23–61 years) from Peking University Third Hospital. Total CSA <5 mm² (CSA<5) was measured with 64-slice spiral computed tomography, and the percentage CSA <5 for the lung area (%CSA<5) was calculated. Data were corrected for body surface area to obtain sixth-generation airway luminal diameter (LDcor), luminal area (Aicor), and airway wall thickness, and airway wall area percentage (WA%) was calculated. Enzyme-linked immunosorbent assay was used to detect the expression of leptin, total immunoglobulin E, periostin, and transforming growth factor β1 in serum and matrix metalloproteinase 9 in induced sputum supernatant of asthmatic patients. The differences in %CSA<5 between subgroups were assessed by independent samples Student’s t test, and Spearman correlation analysis was used to analyze the correlation of %CSA<5 with clinical indexes and inflammatory cytokine levels.

Results: Patients with asthma and controls did not differ in %CSA<5. In asthma patients, %CSA<5 was lower with initial onset age ≤12 years old, airflow restriction and uncontrolled Global Initiative for Asthma classification (all P < 0.05). Moreover, it was positively correlated with forced vital capacity ratio in 1 s (FEV1%) and forced expiratory volume ratio, FEV1%, LDcor, Aicor, and serum leptin level (all P < 0.05) and negatively with total lung WA% (P = 0.007).

Conclusions: %CSA<5 of pulmonary small vessels was well correlated with airflow limitation indexes and sixth-generation airway parameters. It has certain significance in predicting the clinical control of asthma.

Keywords: Asthma; Computed tomography; Airway remodeling

Introduction

Bronchial asthma is one of the common respiratory diseases with increasing incidence and prevalence worldwide. It is a chronic inflammatory condition involving various inflammatory cell and cytokines. Small pulmonary vascular alteration is a characteristic of chronic airway diseases including asthma, although the underling mechanism is still unclear. As a heterogeneous disease, asthma features different airway inflammation types, clinical manifestations, predisposing factors, severity of illness, and response to anti-inflammatory treatment. This heterogeneity leads to different phenotypes. In recent years, researchers have observed and summarized a variety of clinical and inflammatory phenotypes.

Several radiologic examinations used in asthma include ventilation or perfusion scintigraphy, thin-section computed tomography (CT), magnetic resonance imaging with hyperpolarized noble gas, and even dual-energy imaging. CT is the most commonly used technique for clinically detecting airways and peripheral pulmonary vessels. Several studies have shown that the cross-sectional area (CSA) of small pulmonary vessels, which can be quantitatively measured on chest CT, is reliable for in vivo evaluation of vascular changes in small pulmonary vessels. Matsuoka et al proposed the use of CSA for small pulmonary vessels as a parameter of pulmonary vessel alterations in patients with chronic obstructive pulmonary disease (COPD). The CSA of small pulmonary vessels <5 mm² at sub-subsegmental level
(CSA < 5) was measured and the percentage of total CSA < 5 for the lung area (%CSA < 5) was calculated. In individuals with COPD, %CSA < 5 was positively correlated with forced expiratory volume in 1 s/forced vital capacity ratio (FEV1/FVC), even in non-smokers without airflow limitation. However, similar researches in asthma are few.

From previous reports, we hypothesized a similar correlation between reduction in %CSA < 5 and decline in airflow obstruction in people with asthma. To test this hypothesis, we measured the CSA < 5 of pulmonary vessels by CT and evaluated the correlation of %CSA < 5 with airflow obstruction parameters. Furthermore, we measured the expression of several inflammatory cytokines to measure the difference in vascular alteration between asthma phenotypes and evaluate their relation with cytokine levels.

Methods

Ethical approval

This study was performed with the approval of the Ethics Committee of Peking University Third Hospital (2014071). All participants consented to be included in the study.

Subjects

Between January 2015 and December 2015, we enrolled 20 adult patients with asthma (26–80 years old) and 20 healthy controls (23–61 years old) from Peking University Third Hospital. The diagnosis of asthma met the Global Initiative for Asthma (GINA) definition. Exclusion criteria were acute exacerbations of asthma, COPD, bronchiectasis, interstitial lung disease, pneumonia, cancer, severe cardiovascular disease, or heart failure.

Clinical data including general demographic data, age of onset of asthma, body mass index (BMI), tobacco exposure, asthma control test (ACT) scores, and GINA classification were obtained. For evaluating the difference in %CSA between asthma phenotypes, participants were divided into subgroups by sex, age of onset of asthma ≤ 12 or > 12 years old, BMI < 25 or ≥ 25 kg/m², smoker or never smoker, with or without airflow limitation (FEV1/FVC < 0.7 or ≥ 0.7), ACT well controlled or uncontrolled (ACT score ≥ 20 or < 20), GINA classification controlled/partly controlled or uncontrolled, allergen test positive or negative, and percentage eosinophils in sputum (Eos%) ≥ 3% or < 3%.

Multi-slice CT scanning

We used 64-slice CT (Discovery 750 HD; GE Healthcare, Madison, WI, USA) to measure pulmonary CSA of supine participants at the end of a deep inhalation with no contrast injection and with the following parameters: 120 kV; 125–210 mAs; reconstruction slice thickness, 0.625 mm; slice interval, 0.625 mm. Three CT slices were selected in the CT lung window. The upper cranial slice was taken approximately 1 cm above the upper margin of the aortic arch (the upper lung field), the middle slice was taken approximately 1 cm below the carina (the middle lung field), and the lower slice was taken approximately 1 cm below the right inferior pulmonary vein (the lower lung field).

Image analysis

The CT images were analyzed by using Image J 1.48 (US National Institutes of Health, USA) [Figure 1]. The range of CSA for each vessel was defined as < 5 mm² at the sub-subsegmental level. The CSAs for the three CT slices were summed and %CSA < 5 was calculated. With Airway Analysis software (Thoracic VCAR; GE Healthcare), we measured sixth-generation airway (CT inner diameter < 2 mm) dimensions of three bronchi in the right lung (apical segment of the upper lobe, lateral segment of the middle lobe, and posterior basal segment of the lower lobe) and three bronchi in the left lung (posterior apical segment of the upper lobe, superior lingular segment of the upper lobe, and posterior basal segment of the lower lobe). A representative view of the sixth-generation airway is shown in Figure 2. Values for the six parameters were averaged. We measured airway luminal diameter (LD, mm), inner luminal area (Ai, mm²), and airway wall thickness (WT, mm). The outline of the airway wall was manually adjusted (window width 1000 Hounsfield units [HU]; window level – 600 HU). The percentage wall area (WA%; defined as [wall area/total airway area] × 100) was calculated. After correcting for body surface area, corrected LD (LD_csa), Ai (Ai_csa), and WT (WT_csa) were...
obtained. Two radiologists completed the measurement independently and the mean values were used in the final analysis.

**Pulmonary function tests**

Spirometric examination was performed by lung plethysmography (Elite Series DL; MedGraphics, Vadnais Heights, MN, USA). Spirometric measurements included FVC, FEV1, FEV1 percent predicted (FEV1%), and ratio of FEV1 to FVC (FEV1/FVC).

**Induced sputum cytology**

DL-Dithiothreitol (0.4%) of the same volume was added to induced sputum from asthmatic patients and incubated in 37°C for 30 min. Sputum cells were pelleted by centrifugation at 600 × g for 4 min. Cell differentials were determined by cytospin preparations stained with Wright–Giemsa, and 200 cells were counted. The supernatant was stored at −80°C.

**Allergen and cytokine detection**

Blood samples were centrifuged at 1400 × g for 5 min, and serum samples were separated. Allergen detection tests were performed with EUROLINE Atopy China IgE (EUROIMMUN, Liubeck, Germany). Inflammatory cytokines were detected by enzyme-linked immunosorbent assay. The serum levels of leptin (4A Biotech, Beijing, China), total immunoglobulin E (IgE; EUROIMMUN), periostin (RayBiotech, Norcross, GA, USA), and transforming growth factor β1 (TGF-β1; R&D Systems, Minneapolis, MN, USA) were determined according to the manufacturers’ instructions. Matrix metalloproteinase 9 (MMP-9; R&D Systems) was assayed in sputum according to the manufacturer’s instructions.

**Statistical analysis**

SPSS 13.0 (IBM, Amund, NY, USA) was used for analysis. Data are expressed as mean ± standard deviation (SD) or median (interquartile range). Differences between subgroups were compared by independent-samples Student’s t test. Spearman correlation analysis was used to analyze the correlation between %CSA < 5 and inflammatory cytokine levels. A value of P < 0.05 was considered statistically significant.

**Results**

**Participant characteristics and parameters**

A total of 40 participants (20 with asthma and 20 healthy controls) were enrolled. The characteristics of the participants are summarized in Table 1. The age of

| Characteristics                  | Asthma (n = 20) | Control (n = 20) | t      | P     |
|----------------------------------|----------------|-----------------|--------|-------|
| Age (years)                      | 54.1 ± 17.8    | 39.5 ± 12.9     | -5.478 | <0.001|
| Sex (male/female), n             | 7/13           | 12/8            |        |       |
| BMI (kg/m²)                      | 25.7 ± 2.8     | 23.5 ± 3.6      |        |       |
| Duration of disease (years), median (interquartile range) | 9 (4–37.5) | 21.3 ± 4.1     |        |       |
| ACT score                        |                |                 |        |       |
| Pulmonary functions              |                |                 |        |       |
| FEV1%                            | 85.6 ± 12.8    | 106.0 ± 10.7    | -5.478 | <0.001|
| FEV1/FVC                         | 69.3 ± 10.4    | 86.1 ± 5.2      | -6.473 | <0.001|
| %CSA<5                           | 0.9 ± 0.1      | 1.0 ± 0.2       | -1.457 | 0.153 |
| Airway measurement               |                |                 |        |       |
| LD_cor (mm)                      | 1.3 ± 0.1      | 1.5 ± 0.3       | -3.074 | 0.005 |
| Ai_cor (mm²)                     | 1.4 ± 0.3      | 2.0 ± 0.4       | -6.086 | <0.001|
| WT_cor (mm)                      | 1.0 ± 0.1      | 0.7 ± 0.1       | 6.846  | <0.001|
| WA%                              | 83.0 ± 4.2     | 72.0 ± 4.2      | 8.329  | <0.001|

Data are mean ± standard deviation unless otherwise indicated. BMI: Body mass index; ACT: Asthma control test; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; %CSA<5: the percentage of total cross-sectional area <5 mm² for the lung area; LD_cor: Corrected airway lumen diameter; Ai_cor: Corrected inner luminal area; WT_cor: Corrected airway wall thickness; WA: Airway wall area.
asthma onset was from 1 to 70 years old, and the median disease duration was 9.0 years (range 4.0–37.5 years). The mean ACT score was 21.3 ± 4.1. As compared with health controls, asthmatic patients showed decreased pulmonary function based on spirometric testing (P < 0.001). The two groups did not differ in %CSA<5. On sixth-generation airway measurement, LD_{cor} and A_{icor} were lower and WT_{wa} and WA% were higher for asthma patients than controls. Table 2 shows the levels of inflammatory cytokines in serum and sputum of asthmatic patients, as well as sputum cytology.

### Comparison of %CSA<5 among asthmatic subgroups

%CSA<5 was significantly lower with asthma onset ≤12 than >12 years old (n = 4 and n = 16) (0.747 ± 0.050 vs. 0.922 ± 0.134, P = 0.021), with than without airflow limitation (n = 9 and n = 11) (0.793 ± 0.117 vs. 0.964 ± 0.111, P = 0.004) and with uncontrolled than partially/totally controlled GINA classification (n = 7 and n = 13) (0.785 ± 0.105 vs. 0.942 ± 0.128, P = 0.012) [Table 3].

### Correlation of %CSA<5 with clinical data and inflammatory cytokines

%CSA<5 was positively correlated with FEV_{1}/FVC (r = 0.560, P = 0.010) and with FEV_{1}%, LD_{cor}, A_{icor}, and serum leptin level (P = 0.001, 0.004, 0.002, and 0.008, respectively) and negatively with WA% (r = −0.579, P = 0.007) [Table 4].

### Discussion

In this study, we detected CSA from 20 asthmatic individuals and 20 healthy controls, as well as sixth-generation airway parameters and pulmonary function.

#### Table 2: Inflammatory cytokine levels and induced sputum cytology for asthma patients (n = 20).

| Items                  | Values                          |
|------------------------|---------------------------------|
| Peripheral blood       |                                 |
| Leptin (µg/L)          | 11,914.24 (7656.49–23,960.21)   |
| Total IgE (IU/mL)      | 122.76 (29.89–319.22)          |
| Periostin (ng/mL)      | 5.33 (4.27–9.82)               |
| TGF-β1 (ng/mL)         | 755.73 (495.12–1013.77)       |
| Induced sputum         |                                 |
| Neutrophils (%)        | 73.60 (57.35–95.60)            |
| Eosinophils (%)        | 1.50 (0–23.85)                 |
| MMP-9 in sputum (ng/µg protein) | 32.84 (18.26–52.21) |

Data are presented as mean (interquartile range). IgE: Immunoglobulin E; TGF-β1: Transforming growth factor β1; MMP-9: Matrix metalloprotease 9.

#### Table 3: Comparison of %CSA<5 among subgroups of asthma.

| Items                          | Number | %CSA<5       | t    | P   |
|-------------------------------|--------|--------------|------|-----|
| Male                          | 7      | 0.805 ± 0.096| −2.086| 0.051|
| Female                        | 13     | 0.931 ± 0.143|      |     |
| Age of asthma onset ≤12 years | 4      | 0.747 ± 0.050| −2.523| 0.021* |
| Age of asthma onset >12 years | 16     | 0.922 ± 0.134|      |     |
| BMI < 25 (kg/m²)              | 7      | 0.893 ± 0.163| 0.136| 0.894 |
| BMI ≥ 25 (kg/m²)              | 13     | 0.884 ± 0.134|      |     |
| Smoker                        | 5      | 0.824 ± 0.163| −1.168| 0.258|
| Never smoker                  | 15     | 0.908 ± 0.131|      |     |
| With airflow limitation       | 9      | 0.793 ± 0.117| −3.346| 0.004†|
| Without airflow limitation    | 11     | 0.964 ± 0.111|      |     |
| ACT well controlled           | 12     | 0.933 ± 0.143| −1.905| 0.073|
| ACT uncontrolled              | 8      | 0.818 ± 0.112|      |     |
| GINA partially/totally       | 13     | 0.942 ± 0.128| −2.781| 0.012†|
| GINA uncontrolled             | 7      | 0.785 ± 0.105|      |     |
| Allergen test positive        | 11     | 0.926 ± 0.150| 0.664| 0.517 |
| Allergen test negative        | 6      | 0.880 ± 0.111|      |     |
| Sputum Eos ≥3%                | 5      | 0.917 ± 0.115| −1.198| 0.259|
| Sputum Eos <3%                | 7      | 0.999 ± 0.118|      |     |

*P < 0.05. †P < 0.01. %CSA<5: the percentage of total cross-sectional area < 5 mm² for the lung area; BMI: Body mass index; ACT: Asthma control test; GINA: Global Initiative for Asthma; Eos: Eosinophils.
Moreover, we examined several inflammatory cytokines in asthma. %CSA<5 was affected by age of asthma onset, airflow limitation, and GINA uncontrolled status. It was correlated with some pulmonary function indexes, airway remodeling indexes and serum leptin level in patients with asthma.

Since CT has been used to detect peripheral pulmonary vessels, studies of the CSA of small pulmonary vessels have focused mainly on COPD and emphysema. Previous reports demonstrated a positive correlation of %CSA<5 with FEV1/FVC. Besides being associated with obstructive ventilatory parameters, %CSA<5 was negatively correlated with thoracic aortic calcification score and pulmonary arterial mean pressure. Recent studies have suggested that CSA is negatively correlated with degree of emphysema and frequency of acute exacerbations in patients with COPD. However, to our knowledge, no study has investigated %CSA<5 for pulmonary small vessels in people with asthma.

Consistent with previous results, we found that %CSA<5 in asthma was also positively correlated with FEV1/FVC and FEV1%. Moreover, %CSA<5 was lower in asthmatic patients with airflow limitation than with normal lung function, which confirmed the correlation between %CSA<5 and airflow obstruction indexes and suggested an association of pulmonary vascular alteration with impaired ventilation. We supposed that the heavier the airflow obstruction, the greater the decrease in pulmonary vascular bed. Meanwhile, %CSA<5 was lower with uncontrolled than totally or partially controlled GINA classification, which indicates that inflammation may destroy small pulmonary vessels. In fact, an article just published reported consistent results, that is, loss of peripheral pulmonary vasculature associated with asthma severity, control, and lung function. Our results further indicate that the CT measurement of small pulmonary vessels has certain clinical significance to predict asthma control.

Asthma is a chronic airway inflammatory process involving many inflammatory cells, mediators, and cytokines. Besides chronic focal inflammation in the airway and lung parenchyma, individuals with asthma also have a systemic inflammatory response. Inflammatory biomarkers exist in the lung and also in blood circulation. Microvascular alteration is one of the known features of chronic inflammatory diseases including asthma. Therefore, we selected several inflammatory cytokines closely related to asthma, including leptin, total IgE, periostin, TGF-β1, and MMP9, to analyze their correlation with %CSA<5. %CSA<5 was positively correlated with serum leptin level (P = 0.008) but not other inflammatory cytokines.

Leptin production has been demonstrated in human peripheral lung tissue, namely bronchial epithelial cells, alveolar type II pneumocytes, and lung macrophages. Numerous studies have shown high expression of serum leptin in asthma and increased with disease exacerbation. Leptin improved serum IgE level and enhanced airway responsiveness in asthmatic mice. Our previous results showed that sex and BMI are important factors affecting serum leptin levels in individuals with asthma. This study suggested that leptin is involved in pulmonary vascular changes of people with asthma. In fact, leptin has a role in vascular remodeling. In the study of leptin-deficient ob/ob mice, exogenous leptin greatly increased neointima formation. Exogenous leptin also enhanced lesion growth and increased cellular proliferation in injured arteries from wild-type mice but had no effect on vessels from leptin receptor–deficient db/db mice, which suggests that leptin promotes neointima formation in a receptor-dependent manner. Experiments in vascular smooth muscle cells suggested that leptin could participate in vascular remodeling and stiffness by extracellular matrix production in the cells via the activation of the oxidative stress–PI3K/Akt pathway and the production of the profibrotic factors TGF-β and connective tissue growth factor. The mechanism of leptin in vascular alteration in asthma needs further studies.

Although quantitative CT measurement is used to check sixth-generation airway and pulmonary vessels, previous studies did not correlate %CSA<5 with airway remodeling indexes. LDcor and Aicor are two parameters that reflect the size of the sixth-generation airway cavity. In this study, they were positively correlated with %CSA<5 of small vessels of the lung: the larger the sixth-generation airway cavity, the larger the CSA of small pulmonary vessels. We presumed that the larger the air chamber, the better the gas exchange and the smaller pulmonary vessels. WA% reflects the airway wall area. A larger airway wall area is associated with more severe airflow obstruction. %CSA<5 was negatively correlated with WA%. We speculate that the thicker the airway wall, the more severe the airflow restriction and the greater the destruction of the small pulmonary vascular bed for therefore smaller CSA of the pulmonary small vessels. These results explained the aforementioned differences between airflow-restricted groups from the anatomic perspective of the airway wall as well as the positive correlation between %CSA<5 and obstructive ventilator indexes. It further supports our hypothesis that pulmonary vascular alteration may reflect the degree of airflow limitation.

In this study, no significant difference in %CSA<5 between asthma patients and controls was found possibly because our patients had mild to moderate asthma, and changes of sixth-generation airway occur earlier and more easily than small vessel changes. Although we did not enroll children with asthma, %CSA<5 was reduced for participants with age of asthma onset ≤12 years old, which implied that long-term persistent inflammation in the lung may damage the pulmonary vasculature of children.

There were several limitations to this study. The major one is low sample size. We recruited 78 asthma patients, but only 20 had complete data, including chest CT scan results, induced sputum, and results of cytokine detection, which may imply selection bias. Second, we excluded acute exacerbations of asthma. Further studies could compare each parameter during all clinical stages in asthma. Third, the CSA measurement might have been affected by the automatic exposure control provided by the scanner.
Finally, we did not measure the CSA of pulmonary vessels histologically, so CSA measured by CT scan and the actual CSA of pulmonary vessels might differ. Further studies are necessary.

In summary, this study demonstrated that %CSA<5 of pulmonary small vessels correlated well with indexes of airflow limitation in asthma and may be a new clinical indicator reflecting the degree of airflow limitation. Moreover, %CSA<5 has potential to predict the clinical control of asthma.

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**Conflicts of interest**

None.

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