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Poor Symptom Control Is Associated With Reduced CT Scan Segmental Airway Lumen Area in Smokers With Asthma

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BACKGROUND: Cigarette smoking is associated with worse symptoms in asthma and abnormal segmental airways in healthy subjects. We tested the hypothesis that current symptom control in smokers with asthma is associated with altered segmental airway dimensions measured by CT scan.

METHODS: In 93 subjects with mild, moderate, and severe asthma (smokers and never smokers), we recorded Asthma Control Questionnaire-6 (ACQ-6) score, spirometry (FEV_1; forced expiratory flow rate, midexpiratory phase [$FEF_{25\%-75\%}$]), residual volume (RV), total lung capacity (TLC), and CT scan measures of the right bronchial (RB) and left bronchial (LB) segmental airway dimensions (wall thickness, mm; lumen area, mm^2) in the RB3/LB3, RB6/LB6, and RB10/LB10 (smaller) airways.

RESULTS: The CT scan segmental airway (RB10 and LB10) lumen area was reduced in smokers with asthma compared with never smokers with asthma; RB10, 16.6 mm^2 (interquartile range, 12.4-19.2 mm^2) vs 19.6 mm^2 (14.7-24.2 mm^2) ($P = .01$); LB10, 14.8 mm^2 (12.1-19.0 mm^2) vs 19.9 mm^2 (14.5-25.0 mm^2) ($P = .003$), particularly in severe disease, with no differences in wall thickness or in larger airway (RB3 and LB3) dimensions. In smokers with asthma, a reduced lumen area in fifth-generation airways (RB10 or LB10) was associated with poor symptom control (higher ACQ-6 score) (−0.463 [−0.666 to −0.196], $P = .001$, and −0.401 [−0.619 to −0.126], $P = .007$, respectively) and reduced postbronchodilator $FEF_{25\%-75\%}$ (0.521 [0.292-0.694], $P < .001$, and [0.471 [0.236-0.654], $P = .001$, respectively) and higher RV/TLC %.

CONCLUSIONS: The CT scan segmental airway lumen area is reduced in smokers with asthma compared with never smokers with asthma, particularly in severe disease, and is associated with worse current symptom control and small airway dysfunction. CHEST 2015; 147(3):735-744

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ABBREVIATIONS: ACQ-6 = Asthma Control Questionnaire-6; D_{LCO} = diffusing capacity of lung for carbon monoxide; $FEF_{25\%-75\%}$ = forced expiratory flow rate, midexpiratory phase; LB = left bronchial; PC_{20} = provocation concentration methacholine causing a 20% drop in FEV_1; %LAA950 = percentage of lung CT scan voxels below a threshold of −950 Hounsfield units; RB = right bronchial; RV = residual volume; TLC = total lung capacity

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Prevalence rates for active cigarette smoking in asthma range from < 20% to > 35%.[1-4] Adult smokers with asthma have worse symptom control, increased exacerbation rates, and high levels of health-care use compared with never smokers with asthma.[1,3,5,6] In addition, the efficacy of corticosteroids is impaired in smokers with asthma.[1,7-10] The mechanisms accounting for poorly controlled asthma in cigarette smokers are currently unclear,[1,11] including whether alterations to the structure and function of segmental and/or small airways contribute to worse symptoms in smokers with asthma compared with never smokers with asthma.[12,13]

Using CT scanning to measure dimensions of the segmental airways in nonsmokers with asthma, it is found that wall thickness is increased in severe asthma compared with mild asthma,[14-17] that the lumen area is reduced in asthma compared with healthy subjects,[13] and that an increased airway wall area is associated with worse symptoms.[18] Cigarette smoking in healthy subjects is associated with increased CT scan segmental airway wall thickness[19,20] and a reduced lumen area.[20] Dysfunction of the small airways (defined as airways with an internal diameter < 2 mm) is associated with poor current asthma control in nonsmokers with asthma.[21-26]

The combined effects of asthma and cigarette smoke could contribute to poor symptom control and an impaired response to treatment, at least in part as a result of dysfunction of the segmental and/or small airways. We wished to test the hypothesis that impaired symptom control in smokers with asthma compared with never smokers with asthma is associated with narrowed segmental airways, increased wall thickness, or both as measured by CT scan dimensions and/or is associated with abnormal tests of small airway function.

Materials and Methods

Subjects and Study Design

A cross-sectional study was performed in subjects with asthma who were recruited to the Glasgow COPD and Asthma Biomarker study.[27] Clinical, physiologic, and CT scan measurements were taken. Participants with mild, moderate, and severe persistent asthma (GINA [Global Initiative for Asthma] classification)[28] (both current smokers and never smokers) were recruited. Asthma criteria included the following: age range of 18 to 75 years and duration of asthma ≥ 6 months; symptoms of episodic wheezing, chest tightness, and/or dyspnea; objective confirmation by airway hyperactivity determined by a ≥ 20% drop in FEV_1 at a methacholine dose of ≤ 8 mg/mL or when FEV_1 < 60% predicted, by evidence of airflow variability with a ≥ 12% and 200 mL increase in FEV_1 following 2.5 mg nebulized albuterol. All subjects had been taking stable medication for 4 weeks, and had had no exacerbation of disease for 4 weeks. Smokers were defined as those who had smoked for ≥ 10 pack-years and were currently smoking five or more cigarettes per day. The West Glasgow Research Ethics Committee approved the study, and all patients gave written informed consent (MREC approval number 07/SO709/46).

Measurements

Questionnaire: The Asthma Control Questionnaire-6 (ACQ-6) score[29] was obtained.

Lung Function Tests: Spirometry was performed according to American Thoracic Society guidelines[30]; measurements included FEV_1, FVC, reversibility, and forced expiratory flow rate, midexpiratory phase ($FEF_{25\%-75\%}$). Airway hyperresponsiveness to methacholine (provocation concentration methacholine causing a 20% drop in FEV_1 [PC_{20}]) was measured.[31] Lung volumes (residual volume [RV] and total lung capacity [TLC]) and diffusing capacity of lung for carbon monoxide (DLCO) were performed using the body box technique (Zan500 Body Plethysmography; nSpire Health, Inc).

CT Scan of the Chest: Scans were performed at full inspiration using 16-slice Brightspeed and 64-slice Lightspeed scanners (GE CT scanner) with the following parameters: 120 kV; 100 mAs; collimation, 1 mm; reconstruction slice thickness, 0.65 mm; reconstruction slice separation, 0.5 mm; and pitch, 1; the data were reconstructed with a chest (CHST) filter. All scans were evaluated centrally at the University of Edinburgh. Airway dimensions were measured with the software Pulmonary Workstation 2.0 (VIDA Diagnostics, Inc), which plotted an airway path from which airway profiles were generated on cross-sections orthogonal to this airway path. Airway dimensions were measured at 1-mm intervals in the right bronchial (RB) or left bronchial (LB) segment from airway generation 3 (RB3, RB6 or LB3, LB6 larger airways) and airway generation 5 (RB10 or LB10, smaller airway) using the convention of generation number based upon number of branch points from the trachea. The following CT scan airway values were obtained: wall thickness (mm) and lumen area (mm^2). Emphysema was quantified as the percentage of lung CT scan voxels below a threshold of −950 Hounsfield units (%LAA950).

Statistical Analysis

Continuous variables were summarized as median (interquartile range). Comparison between different patient groups was by Student *t* test or one-way analysis of variance for approximately normally distributed variables and by Wilcoxon test or Kruskal-Wallis test for other variables. Categorical variables were summarized by their observed frequencies and percentages within the participant subsets. These values were compared using Fisher exact probability tests including the Freeman-Halton extension for variables with more than two categories. Analyses were considered descriptive or exploratory. Secondary analyses were adjusted for multiple testing (Bonferroni correction). Data were analyzed using R version 2.15 (The R Project for Statistical Computing).[32]

Results

Demographics and Baseline Clinical Characteristics

Smokers with asthma compared with never smokers with asthma had higher ACQ-6 scores (1.87 [1.27-2.67] vs 1.00 [0.46-1.79], $P < .001$) (Table 1). Smokers with asthma and never smokers with asthma were similar in terms of age, sex, duration of asthma, dose of inhaled corticosteroid, body surface area, and PC_{20} (Table 1).