Quantitative computed tomography–derived clusters: Redefining airway remodeling in asthmatic patients☆

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Background: Asthma heterogeneity is multidimensional and requires additional tools to unravel its complexity. Computed tomography (CT)–assessed proximal airway remodeling and air trapping in asthmatic patients might provide new insights into underlying disease mechanisms.

Objectives: The aim of this study was to explore novel, quantitative, CT-determined asthma phenotypes.

Methods: Sixty-five asthmatic patients and 30 healthy subjects underwent detailed clinical, physiologic characterization and quantitative CT analysis. Factor and cluster analysis techniques were used to determine 3 novel, quantitative, CT-based asthma phenotypes.

Results: Patients with severe and mild-to-moderate asthma demonstrated smaller mean right upper lobe apical segmental bronchus (RB1) lumen volume (LV) in comparison with healthy control subjects (272.3 mm^3 [SD, 112.6 mm^3], 259.0 mm^3 [SD, 53.3 mm^3], 366.4 mm^3 [SD, 195.3 mm^3], respectively; $P = .007$) but no difference in RB1 wall volume (WV). Air trapping measured based on mean lung density expiratory/inspiratory ratio was greater in patients with severe and mild-to-moderate asthma compared with that seen in healthy control subjects (0.861 [SD, 0.05)], 0.866 [SD, 0.07], and 0.830 [SD, 0.06], respectively; $P = .04$). The fractal dimension of the segmented airway tree was less in asthmatic patients compared with that seen in control subjects ($P = .007$). Three novel, quantitative, CT-based asthma clusters were identified, all of which demonstrated air trapping. Cluster 1 demonstrates increased RB1 WV and RB1 LV but decreased RB1 percentage WV. On the contrary, cluster 3 subjects have the smallest RB1 WV and LV values but the highest RB1 percentage WV values. There is a lack of proximal airway remodeling in cluster 2 subjects.

Conclusions: Quantitative CT analysis provides a new perspective in asthma phenotyping, which might prove useful in patient selection for novel therapies. (J Allergy Clin Immunol 2014;133:729-38.)

Key words: *Asthma, airway remodeling, distal airway, CT, quantitative imaging, phenotypes, cluster analysis, fractal analysis*

Asthma remains a major health care burden affecting an estimated population of 300 million persons worldwide, with an annual premature fatality of 250,000 persons.[1] Approximately 5% to 10% of patients have severe asthma and do not respond adequately to traditional treatment. These patients have severely impaired quality of life and impose a disproportionately high burden on health care resources because of the high risk of exacerbation, hospitalization, and death.[2] There is increasing recognition that asthma is heterogeneous and comprises distinct phenotypes.[3-5] Statistical techniques, such as factor and cluster analysis, have been used to dissect asthma heterogeneity and identify distinct clinical phenotypes.[4] Although quantitative computed tomography (CT)–based disease phenotyping has been used in patients with chronic obstructive pulmonary disease,[6,7] this has not yet been fully used in asthmatic patients. Quantitative CT techniques[8-10] now enable assessment of the proximal airways,[9] indirect assessment of the small airways,[11] and assessment of the fractal geometry of the tracheobronchial tree.[12]

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Abbreviations used

ATS: American Thoracic Society
BSA: Body surface area
CT: Computed tomography
D_{av}: Averaged fractal dimension
D_e: Most efficient cover fractal dimension
D_{sc}: Slope-corrected fractal dimension
D_{sce}: Slope-corrected most-efficient covering fractal dimension
FRC: Functional residual capacity
HU: Hounsfield units
ICC: Intraclass correlation coefficient
LA: Lumen area
LV: Lumen volume
MLD E/I: Mean lung density expiratory/inspiratory ratio
Pi10: Hypothetical airway with internal perimeter of 10 mm
Po20: Hypothetical airways with outer airway perimeter of 20 mm
RB1: Right upper lobe apical segmental bronchus
ROI: Region of interest
RV: Residual volume
TLC: Total lung capacity
VI: Voxel index
VI_{-850} E-I: VI−850 change on paired inspiratory and expiratory CT scan
$VI_{-850/-950}$ E-I: Voxel index change of percent voxels between −950 and −850 HU on paired inspiratory and expiratory CT scan
WA: Wall area
WV: Wall volume

We hypothesized that asthma phenotypes, as determined by using quantitative CT measures of proximal airway remodeling and air trapping, have distinct clinical and physiologic features. Our study aims were (1) to compare quantitative CT measures of proximal airway remodeling and air trapping from volumetric paired inspiratory and expiratory CT scans between patients with severe asthma, patients with mild-to-moderate asthma, and healthy control subjects; (2) to compare the fractal dimension of segmented airway tree and terminal air space between patients with severe asthma, patients with mild-to-moderate asthma, and healthy control subjects; and (3) to use factor and cluster analysis with quantitative proximal and distal airway CT indices to generate novel asthma phenotypes and compare their clinical and physiologic features.

METHODS

Detailed methods are available in the Methods section in this article's Online Repository at www.jacionline.org.

Subjects

Adults with asthma (severe asthma, n = 48; mild-to-moderate asthma, n = 17) and healthy control subjects (n = 30) were recruited into a single-center study. Asthma was confirmed by a respiratory physician based on history and supported by evidence of variable airflow obstruction, airway hyperresponsiveness, or both.[13] Severe asthma was defined in accordance with American Thoracic Society (ATS) guidelines.[14] Asthmatic patients who did not meet the ATS severe asthma definition were classified as having mild-to-moderate asthma. All patients with severe asthma (n = 48) had previously taken part in another study.[15] Healthy subjects were asymptomatic and had no known respiratory illness, with normal spirometric results. All subjects underwent clinical characterization, including an extensive history, skin prick tests for common aeroallergens, peripheral blood tests, spirometry, full pulmonary function tests, methacholine challenge tests, and sputum induction.[16] Asthma-related quality of life and asthma control were assessed by using the Asthma Quality of Life Questionnaire[17] and Asthma Control Questionnaire.[18] Informed consent was obtained from all subjects, and the study was approved by the Leicestershire, Northamptonshire, and Rutland Research Ethics Committee.

CT imaging

Volumetric whole-lung scans (Siemens Sensation 16; Siemens, Surrey, United Kingdom) were acquired at full inspiration and at the end of normal expiration. Details of CT acquisition and radiation safety (see Table E1 in this article's Online Repository at www.jacionline.org) are discussed in the Methods section in this article's Online Repository. Fully automated software, the Volumetric Information Display and Analysis (VIDA) Pulmonary Workstation, version 2.0 (PW2 software; VIDA Diagnostics, Coralville, Iowa; http://www.vidadiagnostics.com), was used for quantitative airway morphometry, lung densitometry (see Fig E1 in this article's Online Repository at www.jacionline.org) and calibrated by using density measures of air, blood, and electron density rods (see Fig E2 in this article's Online Repository at www.jacionline.org) and fractal dimension (see Figs E3 and E4 in this article's Online Repository at www.jacionline.org) analysis. The repeatability (see Fig E5 in this article's Online Repository at www.jacionline.org) and accuracy (see Fig E6 in this article's Online Repository at www.jacionline.org) of airway morphometry were assessed. Ninety-five percent CIs of mean lung density expiratory/inspiratory ratio (MLD E/I) among healthy control subjects was considered the normal range for CT air trapping. CT air trapping in asthmatic patients was graded based on MLD E/I values: (1) *severe*, greater than the upper limit of the 99.5% CI of the MLD E/I in healthy control subjects; (2) *moderate*, greater than the upper limit of the 98% CI of the MLD E/I in healthy control subjects; and (3) *mild*, greater than the upper limit of the 95% CI of the MLD E/I in healthy control subjects.

Statistical analysis

Statistical analysis was performed with GraphPad Prism 5.00 (GraphPad Software, San Diego, Calif) and SPSS (SPSS, Chicago, Ill) software. Parametric data were expressed as means (SDs), and nonparametric data were described as medians (interquartile ranges). Log-transformed data are presented as geometric means (95% CIs). The χ^2 and Fisher exact tests were used to compare ratios. One-way ANOVA with the Tukey correction (parametric data) and the Kruskal-Wallis test with the Dunn intergroup comparison (nonparametric data) were used to compare multiple groups. The Pearson correlation coefficient was used to determine airway structure and function relationships. Unsupervised multivariate modeling with principal component and cluster analysis was performed to extract factors that best describe the underlying relationship among the quantitative CT variables and determine cluster membership of all asthmatic patients. A 2-way random-effects model with absolute agreement intraclass correlation coefficients (ICCs) was used to assess single-measure reliability for the (1) lumen area (LA), wall area (WA), and length measurements of Leicester Airway Phantom tubes 4 to 9 by a single observer 2 months apart and (2) LA/WA and length measurements of Leicester Airway Phantom tubes 4 to 9 by using a steromicroscope and Vernier caliper, respectively, compared with PW2 software measurements. A P value of less than .05 was taken as statistically significant.

RESULTS

Baseline demographics and clinical characteristics of patients with severe (n = 48) or mild-to-moderate (n = 17) asthma and healthy control subjects (n = 30) are shown in Table I. Among the 3 groups, no significant differences were found in age, sex, body surface area (BSA), and smoking status.