Temporal Assessment Of Airway Remodeling In Severe Asthma Using Quantitative Computed Tomography

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Research Letter to the Editor

Heterogeneity in asthma is evident at every aspect of the disease process.[1-3] Quantitative computed tomography(QCT) has emerged as a reliable, non-invasive tool for assessment of proximal airway remodeling and air-trapping in asthma.[4] We have recently identified three asthma clusters based on QCT indices using factor and cluster analysis.[3] Subjects in clusters 1 and 3, with more severe asthma had distinct patterns of proximal airway remodeling: cluster 1 showing a dilated right upper lobe apical segmental bronchus(RB1) lumen with wall thickening and cluster 3 had no wall thickening and markedly narrowed lumen. Subjects in cluster 2 had milder asthma and there was lack of proximal airway remodeling. It remains elusive whether airway structural changes reflect cause or effect; namely, are they a consequence of asthma and represent different stages of disease progression or the distinct remodeling changes that are fundamental to pathogenesis of asthma, representing distinct asthma endotypes?[5] Our aim was to assess temporal pattern of proximal airway remodeling in QCT-derived asthma clusters.

Some of the results of this study have been previously reported in the form of an abstract.[6]

Twenty-two patients with severe asthma of mean(SEM) disease duration 28.6(4) years, who were in the placebo arm of a previous study[7] were included in the analysis. All 22 patients had undergone two inspiratory thoracic CT scans to image RB1 and further inspiratory and expiratory full thoracic CT scans as part of research studies at our institute.[3,7] All CT scans were performed after administration of long acting β2-agonist. The mean(range) duration between the first(baseline) and second CT scan was 1.6(0.9–2.7) years and between the second and third was 2.6(1.9–3.7) years.

QCT-derived asthma clusters were determined based on full thoracic paired inspiratory and expiratory CT scans obtained at time point 3.[3] Only inspiratory scans were used for the current analysis. Informed consent was obtained from all subjects and the studies were approved by the Leicestershire, Northamptonshire and Rutland Research Ethics Committee. Fully automated software, VIDA Pulmonary Workstation, version 2.0 [VIDA Diagnostics, Coralville, Iowa] was used for quantitative airway morphometry as described previously.[3]

RB1 wall area(WA)/body surface area(BSA) demonstrated significant increase over time (mean(SEM); first CT, 14.3(0.9); second CT, 14.7(0.9); third CT, 16.5(1.3)mm^2/m^2; repeated measure ANOVA, p=0.008). No significant change was seen in RB1 lumen area(LA)/BSA (mean(SEM); first CT, 9.1(1.0); second CT, 9.6(1.0); third CT, 9.9(0.9); repeated measure ANOVA, p=0.4). There was increase in RB1 length at the time of third CT (mean(SEM); first CT, 11.3(0.8); second CT, 11.0(0.7); third CT, 13.1(0.6)mm; repeated measure ANOVA, p<0.01). The change in RB1 WA/BSA (ΔRB1 WA/BSA =RB1 WA/BSA third CT –RB1 WA/BSA first CT) negatively correlated with change in RB1 length, Pearson correlation, -0.5; p=0.03. When the severe asthma subjects were split into previously described QCT-derived clusters,[3] mean(SEM) change in interval normalized RB1 WA/BSA and LA/BSA respectively was: Cluster 1(n=3), 3.6(0.8) mm^2/m^2/year, 1.7(1.1) mm^2/m^2/year; Cluster 2(n=9), 1.0(0.5) mm^2/m^2/year, -0.02(0.4) mm^2/m^2/year; Cluster 3(n=10), -0.1(0.3) mm^2/m^2/year, 0.1(0.4) mm^2/m^2/year [Figure 1]. A one-way between-groups analysis of covariance (ANCOVA) was performed to compare the differences between clusters (independent variable), of airway mophometry at time of second and third CT (dependent variables) after controlling for the airway morphometry at the

time of first CT (covariate). After adjusting for the airway morphometry (first CT), there were significant differences between the three clusters for RB1 WA/BSA(third CT) [$F(2, 18)=21$, $p<0.001$, partial eta squared=0.70] and for RB1 LA/BSA(third CT) [$F(2, 18)=32$, $p<0.001$, partial eta squared=0.78]. No significant difference was seen between the three clusters for RB1 WA/BSA(second CT) and RB1 LA/BSA(second CT) [data not shown]. Comparison of airway morphometry in healthy controls at time point 3 with airway morphometry in severe asthma clusters at time point 1, 2 and 3 is presented in table 1.

The subjects did not show any significant change in post bronchodilator forced expiratory volume in 1 second(FEV_1) %predicted [mean(SEM) change from baseline, -1.8(2.7); paired sample t-test, p=0.5], post bronchodilator FEV_1/forced vital capacity(FVC) (%) [mean(SEM) change from baseline, -0.7(1.3); paired sample t-test, p=0.6], asthma quality of life questionnaire(AQLQ) score [mean(SEM) change from baseline, 0.07(1.3); paired sample t-test, p=0.7] and sputum neutrophils [mean(SEM) change from baseline, 5.4(7.1); paired sample t-test, p=0.5] at the time of third CT scan compared to baseline. There was a statistically significant increase in the asthma control questionnaire(ACQ) [mean(SEM) change from baseline, 0.4(0.2); paired sample t-test, p=0.03]. The change in RB1 QCT indices (LA/BSA, WA/BSA and length) between third and first CT did not show any significant correlation with change in post bronchodilator FEV_1 %predicted, post bronchodilator FEV_1/FVC%, ACQ and AQLQ.

Previous longitudinal studies have demonstrated a significant decrease in proximal airway wall dimensions after use of inhaled corticosteroids(ICS),[8,9] ICS/ long acting

beta-2 agonist(LABA) combination[10] and anti-IgE treatment.[11] In contrast, Brillet *et al.* found no change in CT assessed airway dimensions in poorly controlled asthmatics treated for 12 weeks with inhaled LABA and ICS despite improvement in physiological measures of airway obstruction and air trapping.[12] A follow-up of asthma subjects on ICS from a previous study[8] for a mean duration of 4.2 years did not show any significant change in airway dimensions with reported mean(SEM) change in interval-normalised RB1 WA/BSA of -0.27 (0.59) mm^2/m^2/year.[13] We have previously shown a decrease in RB1 WA/BSA in severe asthma subjects after one-year treatment with anti-IL-5 compared to placebo with approximately 10% between-group change.[7] In the current analysis severe asthma subjects demonstrate small, albeit significant temporal increase in RB1 WA/BSA but no change in the RB1 LA/BSA. These varied patterns of airway remodeling exhibited by asthma subjects may be explained by heterogeneous nature of the disease, differences in patient selection and duration of treatment and/or follow up. A recent longitudinal study in severe asthma subjects has demonstrated that in a multivariate regression model baseline %WA was a predictor of subsequent airway remodeling.[14] In our analysis after adjusting for the RB1dimensions at time of first CT, significant differences were found in RB1 dimensions between severe asthma QCT-derived clusters at the time of third CT but not at the time of second CT. Severe asthma patients when grouped based on QCT-derived clusters, show a differential temporal pattern of airway remodeling, particularly patients in cluster 3, where no significant change in airway wall or lumen dimensions was demonstrated over a period of 2.6 years. This suggests that the mechanism of lumen narrowing in this asthma phenotype may be due to decreased compliance of the airway wall or alteration between intrinsic and extrinsic airway wall properties,[15] rather than thickened airway wall encroaching upon the

lumen. Mathematical modelling studies[16,17] have also shown that thickening of the adventitia can uncouple the airway smooth muscle(ASM) from the lung's elastic recoil forces abating the airway-parenchymal interdependence. QCT based phenotyping could thus help us unravel novel asthma subtypes which may have distinct pathophysiological mechanisms. The inverse correlation between the change in RB1 WA/BSA and RB1 length suggests that despite bronchodilation, ASM shortening resulting in shortening in airway length may contribute to QCT assessed airway wall thickening.

We acknowledge that QCT-derived clusters were determined based on full thoracic paired inspiratory (third CT in the current analysis) and expiratory CT scans as part of a recent study[3] and temporal CT (first and second CT in the current analysis) data was obtained from retrospective scans. We therefore are unable to assess the stability of CT derived phenotypes. Moreover, there is lack of data in current literature on temporal stability of airway morphometry in healthy subjects. Temporal assessment was only possible in small number of subjects in each cluster with only 3 subjects in cluster 1, therefore further verification of these findings is required by large longitudinal studies. Despite this limitation, temporal analysis may provide useful insight into natural history of airway remodeling.

Figure Legend

Figure 1: Temporal assessment of airway remodeling in asthma clusters

Asthma clusters were determined based on data from third CT. Retrospective scans were available for temporal assessment of RB1 remodeling. Airway dimensions of 30 healthy controls determined as part of our previous study[3] are included on the figure for reference. The data for healthy control subjects is plotted only at time point 3 as longitudinal data is not available.

Table 1: RB1 dimensions of severe asthma and healthy subjects

	Cluster 1 (n= 3)	**Cluster 2 (n= 9)**	**Cluster 3 (n= 10)**	**Healthy Controls (n= 30)**	**Significance (p value)**
First CT					
Wall Area/BSA (mm^2/m^2)	17.6 (2.6)	16.9 (1.0)	10.9 (1.0)		<0.001∞^
Lumen Area/BSA (mm^2/m^2)	13.0 (3.7)	11.6 (1.3)	5.6 (0.8)		<0.001∞^
Second CT					
Wall Area/BSA (mm^2/m^2)	18.4 (0.9)	17.2 (1.0)	11.3 (1.0)		0.001∞^
Lumen Area/BSA (mm^2/m^2)	14.4 (1.5)	11.8 (1.5)	6.2 (0.9)		0.001^
Third CT					
Wall Area/BSA (mm^2/m^2)	25.8 (1.4)	19.5 (1.0)	10.9 (0.7)	18.7 (1.0)	<0.001Δ∞^§
Lumen Area/BSA (mm^2/m^2)	17.2 (1.2)	11.8 (0.6)	5.9 (0.5)	13.7 (1.0)	<0.001Δ∞^

Data expressed as mean (SEM). Intergroup comparisons: one-way ANOVA with Tukey test to compare all pairs of columns. *p<0.05 Cluster1 vs Cluster 2, ∞p<0.05 Cluster 2 vs Cluster 3, Δp<0.05 Cluster1 vs Cluster 3, ❖p<0.05 healthy controls vs Cluster 1, #p<0.05 healthy control vs cluster 2, ^p<0.05 healthy controls vs Cluster 3, §p=0.06 healthy controls vs Cluster 1. RB1 dimensions for healthy controls subjects were only available at time point 3 and were compared with RB1 dimensions of severe asthma subjects at all three time points.

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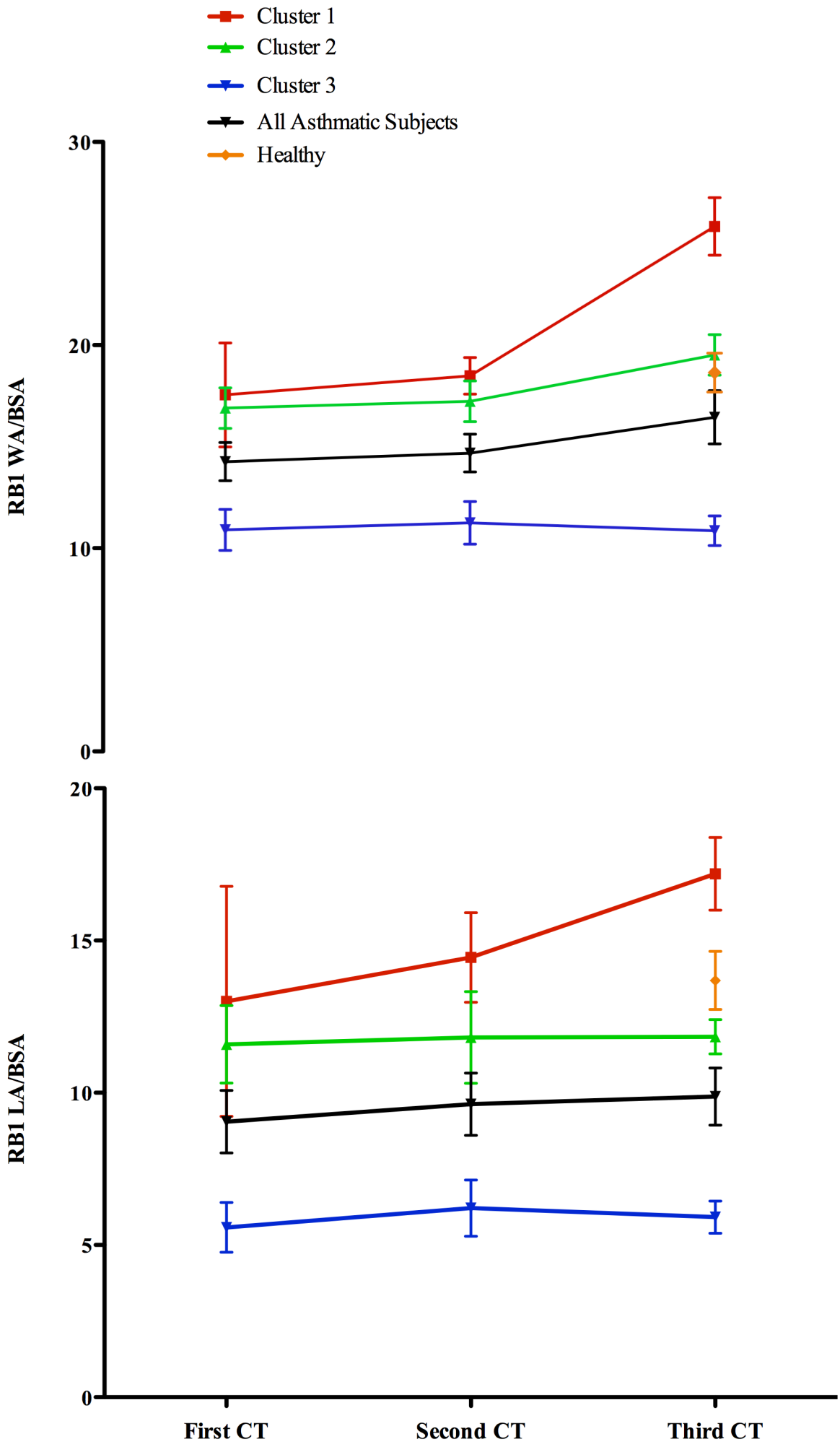
Cluster 1
Cluster 2
Cluster 3
All Asthmatic Subjects
Healthy
RB1 WA/BSA
30
20
10
0
RB1 LA/BSA
20
15
10
5
0
First CT
Second CT
Third CT