Characteristics of Inhaled Particle Deposition in the Lungs of Imaging-based Asthma Clusters: a Numerical Study

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ABSTRACT

RATIONALE: Recently, four imaging-based asthma clusters were identified in association with the Severe Asthma Research Program (SARP), showing close correlation with distinctive clinical and demographic characteristics. In this study, we have sought to understand regional deposition patterns of inhaled particulate in association with imaging-based subtypes, employing computational fluid dynamics (CFD) to simulate air flow and inhaled particle distribution. We computed the regional particle flow and deposition patterns in the representative members of the four asthma clusters and healthy subjects.

METHODS: Three-dimensional (3-D) CFD simulations of air flow and 1-8 μm particle transport were performed using computed-tomography (CT)-based airway models. Four representative asthma clusters and two healthy (one male and one female) subjects were selected for analysis. Subject-specific air flow boundary conditions for CFD were generated by registering CT volumetric images acquired at total lung capacity (TLC) and functional residual capacity (FRC) and adjusting in association with airway resistance and peripheral compliance. Inspiratory breathing profile imposed at the tracheal inlet was characterized as a "slow and deep" breathing pattern.

RESULTS: Regional particle distribution characteristics such as lobar particle flow fraction, lobar deposition fraction, and lobar and generational deposition efficiency were found different between the representative subjects ($p<0.05$), attributable to combined effects of subject-specific regional air flow characteristics and particle size. One severe (cluster 4) and one non-severe (cluster 2) asthmatic cluster, characterized by airway constriction, had an increased deposition efficiency in generations 4 through 6, even in comparison with the other severe asthmatic cluster which was characterized by airway wall thickening but not constriction (cluster 3) (**Figure 1**). Flows passing through constricted airway regions impinged on distal bifurcations at a high speed, resulting in depositional hot spots. A reduced branching angle at the right main bronchus (cluster 4) resulted in reduced penetration of particles to the right upper lobe. The effect of airway structural metrics on particle deposition in the central airways increased with increasing particle size.

CONCLUSION: Particle deposition characteristics were associated with imaging-based structural metrics, such as airway constriction, characterizing some asthma clusters. The results suggest that relief of the proximal airway narrowing may facilitate peripheral delivery of inhaled particulates, possibly influencing the recent success of bronchial thermoplasty. The results also demonstrated the potential of using imaging-based cluster-guided CFD analysis for tailoring pharmaceutical drug treatment.

Introduction

While aerosolized bronchodilator and corticosteroid inhalations are common treatments for asthma, the delivery to the peripheral lung regions using current methods are limited in part by inter-subject variability of lung structure and function. A recent study (Choi et al. J Allergy Clin Immunol 2017;S0091-6749(17):30146-X) performed multiscale imaging-based cluster analysis (MICA) using local/global structural and functional variables, and established four distinctive clusters that are correlated with clinical phenotypes and demographic features from Severe Asthma Research Program (SARP) cohort. We have sought to cluster-specific characteristics in inhaled particle deposition patterns, using computational fluid dynamics (CFD) simulations of subject-specific air flow and particle transport.

Methods

We selected one subject from each of the clusters (C1-C4), representative of the remarkable anatomic distinctions of their cluster, and one healthy non-asthmatic male (HM) and female (HF). 200,000 particles were released in supraglottal inlet of CT-based airway models for CFD.

Table 1. Key features for subject selection, analysis, and CFD (Parenthesis: Average in cluster).

	HF	HM	C1	C2	C3	C4
Demography						
Gender	Female	Male	Female	Male	Female	Male
Age (yrs.)	29	28	20	52	49	51
Weight (kg.)	61.5	99.0	58.6	111.8	85.1	103.0
Asthma Severity	N/A	N/A	Non-severe	Non-severe	Severe	Severe
Features for Presented Subject (Sub-population Average)						
D_h^* (sLLL)	0.35 (0.34)	0.38 (0.33)	0.37 (0.34)	0.24 (0.27)	0.43 (0.34)	0.23 (0.28)
J	2.0 (2.0)	2.4 (2.1)	3.3 (2.5)	1.8 (1.7)	1.9 (1.9)	1.4 (1.5)
IC (Liters)	2.5 (2.2)	3.4 (3.1)	3.0 (3.2)	2.5 (1.8)	2.7 (2.0)	1.8 (2.1)
ϑ_{RMB} (º)	90.0	90.0	94.8	74.8	91.3	67.9
CFD Flow Inlet Conditions at Peak Inspiration (PI)						
Q_{PI} (L/min)	50.2	66.7	60.2	50.5	53.3	35.8
D_h^* (Trachea)	1.17	0.99	0.88	0.94	1.23	0.97
Re	4364	5364	6647	3905	3894	2742

D_h^*, hydraulic diameter normalized predicted tracheal diameter; sLLL, left lower lobe subset; *J*, Jacobian determinant; *IC*, inspiratory capacity computed from volumetric CT images at TLC and FRC; Q_{PI}, peak inspiratory flow rate; *Re*, Reynolds number based on Q_{PI} and the tracheal diameter.

Results: Regional Particle Deposition

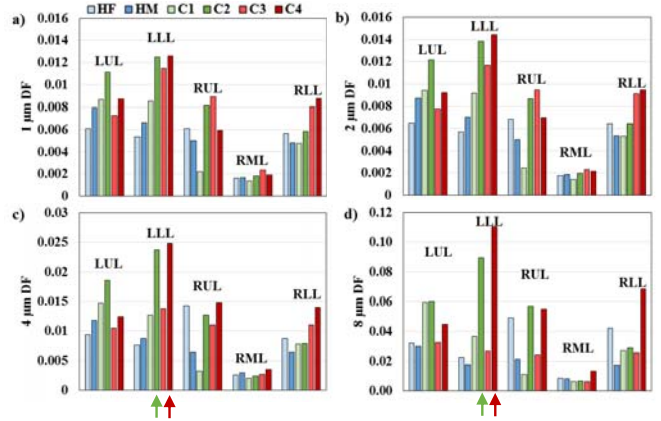

Figure 4. Lobar deposition fractions (DF) of (a) 1-μm, (b) 2-μm, (c) 4-μm, and (d) 8-μm particles. DF in LLL is greater in the C2 and C4 subjects than in the others, and the relative difference increases as the particle size increases, as indicated by green and red arrows.

Deposition efficiency in lobar to sub-segmental branches also increased in the C2 and C4 subjects for 4-μm and 8-μm particles, compared to others.

Constriction Induced Deposition Hot Spots C2 and C4

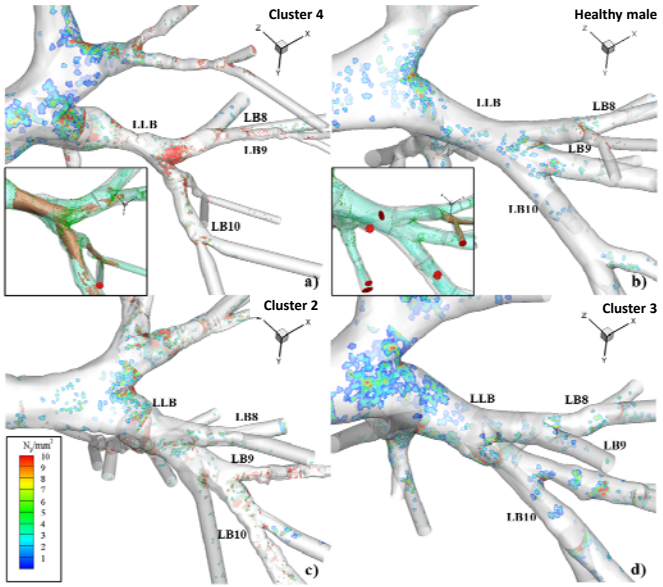

Figure 3. Particle deposition density (DD), the number of 4-μm particles per mm^2, in the left lower lobe (LLL) for (a) cluster 4, (b) healthy male, (c) cluster 2, and (d) cluster (3). In (a) and (b) inserts, green and brown colors denote air flow speed at 2.5 m/s and 5 m/s, respectively. Jet-like high speed flow forms through considerably constricted "LLB" branch in the C4 subject induced remarkable deposition hot spots in the cluster 4 subjects (↑↑). The subject of cluster 2, which was also characterized by airway narrowing in LLL, had increased deposition (↑).

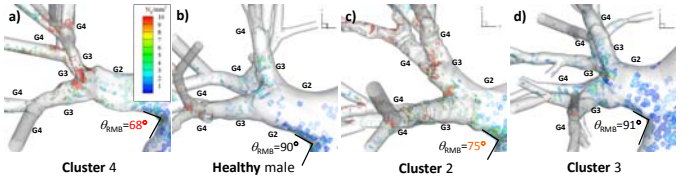

Figure 4. DD of 4-μm particles in RUL of (a) cluster 4, (b) healthy male, (c) cluster 2, and (d) cluster (3). Airway constriction and small branching angle at RMB induced deposition hot spots in C4 (↑↑) and C2 (↑).

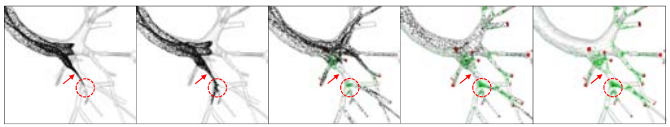

Figure 5. Formation of deposition hot spot passing constricted airway: LLB in cluster 4 subject. Black, green, and red dots indicate active, deposited, and advected particles.

Discussion: Clinical, Imaging, and CFD features

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Clinical Features	•Similar to healthy subjects •Non-severe asthma •Easy to control symptoms	•Little inflammation •Mix of non-severe & severe subjects •Difficult to control symptoms	•Female dominant •Severe asthma •Difficult to control symptoms	•Male dominant •Severe asthma •Difficult to control symptoms
Imaging Features	•Reversible lung function •Increased *J*	•*J* ↓ •θ_{RMB} ↓ •Airway constriction (D_h^* ↓ in LLL, RMB, & bronchus intermedius)	•Airway wall thickening •Reversible lung function •Moderate reduction in *J*	•*J* ↓↓ •Significant air trapping •Airway constriction (D_h^* ↓) •Reduced θ_{RMB}
CFD Features	•Re ↓ •Stk ↑ •Similar to healthy subjects	•Re ↓ •Stk ↑ •LLL DF ↑ •DE ↑ in segmental and sub-segmental airways •DE ↑ distal to θ_{RMB}	•Re ↓ •Stk ↑ •Generational DE similar to healthy subjects •Particle FF ↑ in RUL	•Re ↓ •Stk ↑ •LLL DF ↑ •DE ↑ in segmental and sub-segmental airways •DE ↑ distal to θ_{RMB}

Summary

We utilized imaging-based asthma cluster membership in conjunction with lung CFD to assess the effects of cluster-specific, imaging-based variables on air flow and particle deposition corresponding to MDI inhalation. The CFD analysis from local air flow characteristics and particle DD on airway walls to the lobar and the global lung particle DF and DE showed that airway constriction in C2 and C4 subjects contributed to higher deposition in lobar to sub-segmental airways, while C3 and C4 are severe asthmatic dominant. The results suggest that the use of MICA features may provide guidance in patient selection for pharmaceutical interventions or other treatments to facilitate peripheral delivery of inhaled particulates.

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Disclosure: Eric A. Hoffman - a share holder in VIDA diagnostics which is commercializing lung image analysis software derived by the University of Iowa of Iowa lung imaging group.