Cluster-guided Image Matching Analysis of Multiscale Lung Response to Bronchial Thermoplasty

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ABSTRACT

RATIONALE: The purpose of this study is to assess the use of quantitative computed tomography (QCT) features for analyzing response to bronchial thermoplasty (BT) in asthma. Recently, four QCT-based clusters were identified from the Severe Asthma Research Program (SARP) cohort. We sought to assess the effect of enlarging a local constricted airway in cluster-4 subjects on inhaled aerosol deposition using computational fluid dynamics (CFD) and identify QCT features differentiating patients clinically responsive to BT.

METHODS: CT image data at TLC and FRC, clinical data, and combined precise QCT/CFD image-based airway models were acquired for imaging-based cluster-4 subjects identified from SARP and for seven patients from the BT response study (BTR). For two cluster-4 subjects, the constricted branch in the left lower lobe (LLL) was virtually dilated (VD) to mimic BT-induced luminal expansion. CFD simulations of airflow and 1-8 μm particles transport during slow-deep inhalation were performed for pre- and post-VD airway models. For BTR patients, imaging-based structural and functional alterations pre- and post-BT were analyzed together with clinical data at baseline and 1-year follow-up, using bi-serial correlation analysis.

RESULTS: CFD demonstrated that constriction-induced high-speed flow would create deposition hot spots at the downstream bifurcation (**Figure 4a and c**). After the virtual luminal expansion, they disappeared (**Figure 4b and d**). The particle deposition fraction in the proximal airways in LLL decreased by 20%-35%, and more particles entered the peripheral region. The airway resistance dropped by 80% and 68% with a 50% and 33% VD airway diameter, respectively. As for the BTR patients, they were classified into two groups: one group (subjects 1-3) positively responding to BT treatment (PR) and the other group (subject 4-6) marginally or not responding (MR) (see **Table 1**). Subject 7 was treated as an outlier because of her declined lung function post BT. The two groups were statistically different by age, ACT and FEV1. The PR subjects were either cluster 1 or 2 subjects. The most significant pre-BT QCT features differentiating the two groups included lobar air volume change fraction between TLC and FRC (ΔV_{air}^{F}), airway circularity (Cr), anisotropic deformation index (ADI), Jacobian (J) and airway diameter (Dh*).

CONCLUSION: The preliminary study suggests that luminal expansion of a constricted airway in cluster-4 subjects could substantially reduce airway resistance. Nonetheless, the clinical data suggested that cluster-1 and 2 subjects with QCT features of greater Dh*, Cr and J are more positively responsive to BT treatment.

Virtual Dilation (VD) of Constricted Airway

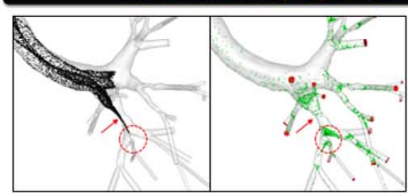

Fig. 1. Formation of particle deposition hot spot through constricted proximal airway

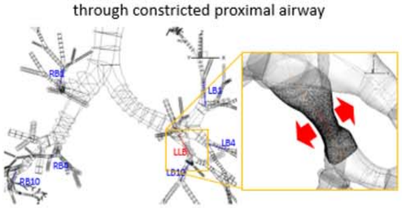

Fig. 2. Virtual dilation of constricted airway geometry

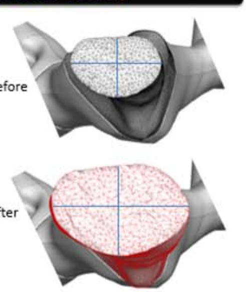

Fig. 3. Cross section comparison in the left lower lobe bronchus (LLB) before and after virtual dilation.

Luminal average diameters at LLB of two severe asthmatic subjects (SARP) were increased with 50% and 33%, respectively.

CFD simulations of slow and deep inhalation corresponding to MDI were performed with 200,000 particles of 1, 2, 4, and 8 μm diameters released in supraglottal inlet of CT-based airway models. Subject-specific flow rate distribution remained the same before and after VD.

Air Flow and Particle Deposition CFD Simulations

Constriction induced high-speed flow and created deposition hot spots at the downstream bifurcation (**Fig. 4a and c**). After the virtual luminal expansion, they disappeared (**Fig. 4b and d**). Deposition fraction (DF) in LLL and local deposition density were decreased by 20-35% .

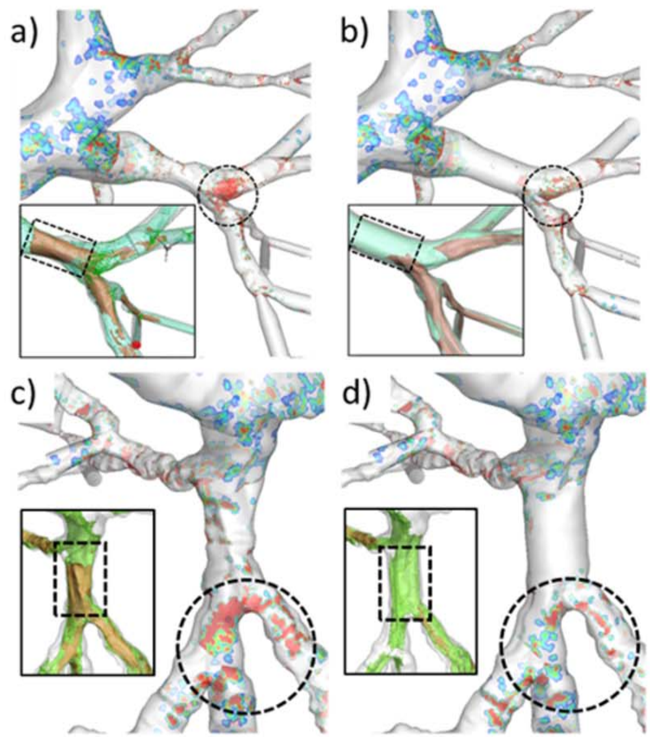

Fig. 4. CFD-predicted air flow (inserts) and particle deposition density (DD) of 4 μm particles in LLL before (a, c) and after (b, d) luminal expansion of two cluster 4 subjects. DD presented as number of particles per mm2. Subset figures show iso-surfaces of airspeed at 2.5 m/s (green) and 5 m/s (brown). (a) was adapted from **Figure 4** of Choi et al. (2019 J Aerosol Med Pulm Drug Deliv. doi: 10.1089/jamp.2018.1487).

Pre- and Post-Bronchial Thermoplasty (BT)

We analyzed pre- and post-BT total lung capacity (TLC) and functional residual capacity (FRC) images of 7 patients treated by BT on segmental airways.

One subject belonged to cluster 4, which is characterized by airway constriction and significant air trapping.

Relatively large segmental airways such as LB10 was enlarged and air trapping was decreased after BT, however clinical response remained marginal.

In all patients, imaging-based functional improvements were found (**Fig. 6**).

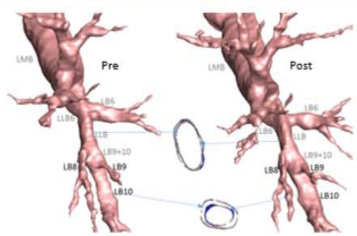

Fig. 5. Pre- and post-BT luminal area comparison in a BT-treated segmental airway branch in LLL (LB10) and non-treated LLB.

BT-induced Functional Changes

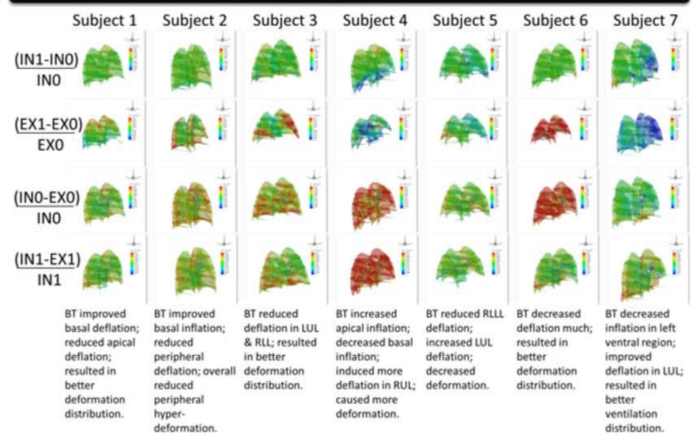

Fig. 6. Demonstration of imaging-based regional lung function response (local expansion) map in 7 severe asthma patients treated by BT:

(1) Pre- to post-BT change on TLC: blue shows decrease in inflation.
(2) Pre- to post-BT change on FRC: red and blue show decreased and increased deflation.
(3) pre-BT TLC-FRC inflation: red shows greater ventilation.
(4) post-BT TLC-FRC inflation (bottom): red shows greater ventilation.

Discussion: Clinical, Imaging, and CFD features

We analyzed association of 57 imaging-based structural and functional variables with clinical response to the BT treatment comparing baseline and 1 year after three BT treatments.

Bi-serial correlation analysis suggested five pre-BT imaging variables are associated with positive clinical response: ventilation fraction in the right middle lobe (RML), circularity of airway lumen in LLL segmental branches, anisotropic deformation, average local volume expansion in the right upper lobe, and average normalized diameter of segmental airways in the right lower lobe (RLL).

In addition, ventilation fraction in the right middle lobe (RML) and normalized wall thickness in segmental airways of RLL are also associated variables. Air trapping improvement in RLL is also associated.

Table 1. Imaging metrics associated with clinical response

Pre-BT	Post-BT
ΔVair% (RML) (p=0.03)	ΔVair% (RML) (p=0.097)
Cr (sLLL) (p=0.023)	WT* (sRLL) (p=0.09)
ADI_LLL (p=0.052)	**Pre- vs Post-BT**
J (RUL) (p=0.08)	AirT% (RLL) (p=0.043)
Dh* (sRLL) (p=0.005)	

Summary

We utilized imaging-based asthma cluster membership in conjunction with lung CFD to assess the sole effect of constricted airway dilation in severe asthmatic patients selected by imaging-based cluster membership. Dilation of LLB reduced proximal deposition hot spots and improved deliver of the particles to the small airways. Luminal expansion of a constricted airway in cluster-4 subjects substantially reduced airway resistance. Nonetheless, the clinical data suggested that cluster-1 and 2 subjects with QCT features of greater Dh*, Cr and J are more positively responsive to BT treatment. Results may suggest to treating BT on LLB for cluster 4 patients, since LLB constriction still limits air flows and drug delivery to the distal small airways even though the segmental airways such as LB8, LB9, and LB10 are improved.

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