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Aerosol deposition predictions in computed tomography-derived skeletons from severe asthmatics: a feasibility study

Shinjiro Miyawaki^{1,7}, Eric A. Hoffman^{2,3,4}, Sally E. Wenzel⁶, and Ching-Long Lin^{1,4,5,*}

¹IIHR-Hydrosience & Engineering, The University of Iowa, Iowa City, Iowa 52242, USA

²Department of Biomedical Engineering, The University of Iowa, Iowa City, Iowa 52242, USA

³Department of Medicine, The University of Iowa, Iowa City, Iowa 52242, USA

⁴Department of Radiology, The University of Iowa, Iowa City, Iowa 52242, USA

⁵Department of Mechanical and Industrial Engineering, The University of Iowa, Iowa City, Iowa 52242, USA

⁶Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA 15260, USA

Abstract

Background—The authors numerically investigated the correlation between airway skeletons of severe asthmatic human subjects and predicted aerosol deposition to shed light on the effect of environmental factors on asthma risk. We hypothesized that there are asthmatic subjects whose airway skeletal structure can expose the subject to a risk of higher local aerosol deposition compared to subjects with a more common/normal branching pattern.

Methods—From a population of severe asthmatics studied at total lung capacity via computed tomography we randomly selected 8 subjects whose Forced Expiratory Volume in 1 sec, percent predicted fell below 45% predicted. To simulate aerosol motion in the human lungs, we employed in-house three-dimensional eddy-resolving computational fluid dynamics and particle tracking models utilizing 3 of the 8 severe asthmatic subjects. One of the 3 subjects was found to have a distinct, localized airway narrowing chosen for further investigation. In the simulation, we controlled flow rate and luminal area, i.e., Reynolds and Stokes numbers, in each branch of the computed tomography-derived airway skeletons.

Findings—We found a distinct enhancement of aerosol deposition associated with the narrowed branches of one subject even when the luminal area was numerically adjusted from its narrowed state to that of a non-asthmatic subject. The branching angle, freed of luminal narrowing persisted

*Corresponding author: Ching-Long Lin, ching-long-lin@uiowa.edu.

⁷Currently at CH2M, 1100 NE Circle Blvd., Suite 300, Corvallis, OR 97330, USA

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Conflict of Interest

Shinjiro Miyawaki, Sally E. Wenzel, and Ching-Long Lin declare that they have no conflict of interest.

in demonstrating a marginally significant increase in local particle deposition compared with the two subjects without the initial constriction.

Interpretation—These results demonstrate the possibility that inherent airway structure may influence localized constriction found in severe asthmatics.

Keywords

subject-specific; geometric airway model; numerical aerosol model; luminal area; branching angle

Introduction

More than 200 million people in the world suffer from asthma according to an estimate by the World Health Organization (WHO) in 2011 (WHO2011). Asthma is caused by both genetic and environmental factors, and the former and latter explain 30–80% and 20–70% of asthma risk, respectively (Institute of Medicine (US) (2000)). Environmental factor consists of exposure to biological and chemical aerosols, e.g., house dust mites, pollen, NO_x, and environmental tobacco smoke (ETS). Asthma causes airway narrowing mainly because of muscle constriction, airway inflammation, and excessive mucus secretion (Jeffery (2001)). An improved understanding of the cause relationship between airway structure and asthma risk would lead to a better investigation of environmental contributions to this disease.

The exposure to aerosols can be investigated in detail by using numerical (*in silico*) models. The spatial resolution of *in vivo* experiments continues to limit the ability to link deposition to specific airway branches (Hofmann (2011)). The numerical models based on three-dimensional (3-D) computational fluid dynamics (CFD) can predict aerosol deposition in each branch using first principles (mainly Navier-Stokes equation and equation of particle motion) (e.g., Miyawaki et al. (2012)). Furthermore, subject-specific modeling is crucial to the investigation of asthmatic lungs because of large inter-subject variability and heterogeneity in lung function and structure (Jarjour et al. (2012), Wongviriyawong et al. (2013)). Thus, a numerical model can estimate aerosol deposition in a subject-specific manner by using individual airway geometry and regional ventilation.

The 3-D CFD-based numerical models have been used to study aerosol deposition in asthmatic lungs (e.g., Sbirlea-Apiou et al. (2004), Longest et al. (2006), and Inthavong et al. (2010)). In most numerical studies related to asthma, the effect of narrowed branches on aerosol deposition have been investigated to link higher aerosol deposition to larger pressure drops in narrowed branches when regional ventilation is held constant in healthy lungs. Asthma can change not only airway luminal area (LA), but also regional ventilation (e.g., Orphanidou et al. (1986) and Choi et al. (2013)). Thus, the boundary conditions that are responsible for regional ventilation need to be more realistic in the numerical models for asthmatic lungs. Nonetheless, the previous studies have not investigated the effect of airway skeletons of asthmatic subjects on aerosol deposition, independent of airway narrowing.

The inter-subject variability in airway skeletons (the inherent structure of the bronchial tree) may be related to individual subject susceptibility to asthma and/or to the severity of the disease. It is well known that high density of aerosol particles in air increases the risk of

asthma (Institute of Medicine (US) (2000)), but this alone may not fully explain why one person will develop asthma or enhanced asthma reactions but another will not in similar environmental conditions. It is possible that the lungs of the two people have independently different structure and function, resulting in higher response to a fixed exposure to aerosols due to differences in deposition patterns. In large (proximal) airways, aerosol particles deposit mainly due to inertial impaction, so smaller diameter, larger flow rate, and larger curvature of airflow streamline can cause higher aerosol deposition. The curvature of streamlines can be determined by the airway skeleton (independent of luminal geometry), especially in regards to differences in branching angles (BA), which can be defined as the difference between the directions of parent and child branches (e.g., Horsfield et al. (1971) and Lee et al. (2011)). Cluster analyses have been performed to find the phenotypes of severe asthma (e.g., Jarjour et al. (2012)), but the variables related to airway skeleton were not considered. Thus, the objective of the present study is to investigate the effect of skeleton on aerosol deposition in asthmatic lungs using in-house subject-specific 3-D CFD-based numerical models. We hypothesize that there are asthmatic subjects whose airway skeletons can cause higher aerosol deposition compared to healthy subjects.

The relationship between airway skeletons and the environmental factors of asthma can be investigated numerically. In this study, we focus on the cause of localized narrowing of bronchial segments in the tree of asthmatic subjects. To investigate the environmental factor of asthma, the geometry of branches before development of asthma (branches with healthy LA) is required, but only the geometry after development of asthma (narrow branch) is usually available. Therefore, we have to predict the geometry before development of asthma. Montaudon et al. (2009) found that LA of branches with fourth or higher generation in asthmatic lungs is significantly smaller than that in healthy lungs. Computed tomography (CT) can resolve fourth generation branches, so the LA of branches before development of asthma can be predicted based on the average LA of healthy lungs. We assume that the skeletons of asthmatic lungs reflect the structure of the lung as it existed prior to the emergence of the airway remodeling associated with severe asthma. We can create the airway geometry with average healthy LA and subject-specific skeletons from asthmatic subjects using the geometric model developed by Miyawaki et al. (2016).

The remainder of the paper is organized as follows. First, we describe the method to create the airway geometry before the onset of asthma. Second, we present the results from the numerical simulations for the skeleton and aerosol deposition in asthmatic lungs before the onset of asthma. Finally, we discuss the effect of skeleton on aerosol deposition in asthmatic lungs.

Methods

We utilized a set of CT scans obtained under IRB approval as part of the Severe Asthma Program (SARP) carried out at the University of Pittsburgh (Wenzel et al. (2007)). From these CT data sets (obtained at both total lung capacity (TLC) and functional residual capacity (FRC)) we selected TLC images for 8 severe asthmatics (SA) with FEV1 percent predicted (FEV1pp) falling below 45. This selection criteria was based upon an observation that amongst the CT-resolved bronchial branches in SA lungs segments were not

significantly narrower than healthy lungs if FEV1pp is higher than 45%. In addition to the SA group, we selected 8 healthy non-asthmatic subjects also studied at Pittsburgh under the SARP protocol. We analyzed the geometry in the central branches of all of the selected healthy and SA subjects including the dimensions of central branches. For CFD simulation in the subset of 3 normal subjects and 3 SA subjects we generated “normal” airway trees based upon the skeletal structure of individual airways and the average segment diameters found in the non-asthmatic subjects using an in-house image-based geometric airway model (Miyawaki et al. (2016, 2017)). Finally, we simulated aerosol motion in the airways using in-house CFD and particle tracking models (Miyawaki et al. (2012, 2017)).

2.1 Healthy and severe asthmatic subjects

Airways in CT images become more difficult to identify if the body mass index (BMI) is too large, so we did not include the subjects with BMI larger than 35. Table 1 shows that there is no significant difference in BMI and total lung capacity (TLC) between the two groups, while FEV1pp is significantly different.

Table 2 shows characteristics of the 6 subjects selected to represent the healthy (1–3) and SA (4–6) subjects. Our large eddy simulation (LES)-based model is more accurate than Reynolds-Averaged Navier-Stokes (RANS)-based model (Miyawaki et al. (2012)). For example, RANS-based models can inaccurately predict the transition from laminar to turbulent flow and overestimate particle deposition. However, our model is still computationally too expensive to simulate aerosol motion for 16 subjects used in the geometric analysis. The effect of turbulent diffusion on aerosol deposition was controlled by selecting the subjects with similar lung size measured by TLC: mean 5.30 (SD 0.16) L and mean 5.31 (SD 0.29) L for healthy and SA subjects, respectively, and by using the same flow rate for all subjects. Given the same flow rate, smaller lung would result in larger Reynolds number (Re) and Stokes number (Stk). Re and Stk are defined as

$$Re = \frac{UD}{\nu} \text{ and } (1)$$

$$Stk = \frac{U\rho_p d^2}{18\mu D}, \quad (2)$$

where U is the average air velocity in a branch, D is the average branch diameter, ν is the kinematic viscosity of air, ρ_p is the particle density, d is the particle diameter, and μ is the dynamic viscosity of air. In other words, we controlled both Re and Stk by controlling the lung size and flow rate. Subjects 4 and 5 developed asthma as adult, so we can use their data to discuss the environmental factor of asthma. We used the data of the three SA subjects to study the skeletal-based effects on aerosol deposition in relation to observed airway narrowing in this sub-group.

2.2 Geometry of healthy airways

We created the geometry of airways with average healthy LA and subject-specific skeletons using the curved-centerline (CL) geometric model (Miyawaki et al. (2016)) by following these nine steps:

1. We manually improved the segmentation of CT images after running automatic segmentation on a commercial segmentation program Apollo (VIDA Diagnostics, Coralville, Iowa).
2. We extracted the branches corresponding to the central branches 0–38 used by Horsfield et al. (1971) (Fig. 1). To compare the dimensions of the airways up to the fourth generation with published data, we assured that the airway tree included branches up to and including the fourth generation. The added branches were not considered when analyzing aerosol deposition.
3. We obtained the LA and BA of each branch using the curved-CL geometric model (Miyawaki et al. (2016)). We estimated the inner diameter of an airway lumen by averaging the radii in four directions that are perpendicular to each other, and we used the diameter to estimate the LA with the assumption of a circular lumen (Fig. 2 a). Most aerosol particles deposit near the carina (bifurcation point between parent and child branches). Thus, the branch angles we consider, as shown in Fig. 2 are based upon the branch angle defined as the angle emanating from the branch point localized to the region of the carina, ignoring curvatures in the child branches at a distance from the carina. The curved-CL geometric model splits a long branch into sub-branches whose aspect ratios are about one, where aspect ratio is the ratio of the length to diameter of a (sub-) branch. We computed the BA using the parent and child sub-branches directly connected to the carina (Fig. 2 b).
4. We normalized the LA with TLC to eliminate the inter-subject variability in LA due to lung size:

$$LA_{b,s}^* = LA_{b,s} / TLC_s^{2/3} \quad (3)$$

where b is branch index and s is subject index. This normalization is reasonable because the TLC of the asthmatic lungs is about 100% predicted value (Table 1), and small normalized LA means that the airway is narrow compared to the capacity of the lung, resulting in small FEV1pp.

5. We computed the average normalized healthy LA and BA for each central branch:

$$LA_{h,b}^* = (1/N_h) \sum_{s=1}^{N_h} LA_{b,s}^* \quad \text{and} \quad (4)$$

$$BA_{h,b} = (1/N_h) \sum_{s=1}^{N_h} BA_{b,s}, \text{ respectively,} \quad (5)$$

where N_h is the number of healthy subjects.

6. We further normalized LA and BA with average healthy values:

$$LA_{b,s}^{**} = LA_{b,s}^* / LA_{h,b}^* \text{ and} \quad (6)$$

$$BA_{b,s}^* = BA_{b,s} / BA_{h,b}. \quad (7)$$

For simplicity, we may use Area* and Angle* to denote $LA_{b,s}^{**}$ and $BA_{b,s}^*$ hereafter, respectively. In this study a diseased branch is defined as a branch with low Area* because it is well known that luminal area of asthmatic branches is smaller than that of healthy branches due to airway remodeling.

7. We computed average normalized LA for each subject (LA_s^{**}) to evaluate overall degree of disease:

$$LA_s^{**} = (1/N_b) \sum_{b=1}^{N_b} LA_{b,s}^{**}, \quad (8)$$

where N_b is the number of branches. Hereafter, we may use μ_{Area^*} to denote LA_s^{**} .

8. We computed the average healthy LA for each branch in each subject ($LA_{h,b,s}$) using their TLC and the average normalized healthy LA:

$$LA_{h,b,s} = LA_{h,b}^* \cdot TLC_s^{2/3}. \quad (9)$$

We selected subjects with similar TLC, so $LA_{h,b,s}$ does not vary with subject.

9. We created the CFD mesh of airways with average healthy LA ($LA_{h,b,s}$) and subject-specific skeleton using the curved-CL geometric model (Miyawaki et al. (2017)). Each branch in the resulting CFD mesh has circular cross-section and curved centerline (Fig. 3). The CT-image of the airway above trachea was not available, so we attached the laryngeal model developed by Miyawaki et al. (2017) to the trachea.

2.3 Numerical aerosol simulations

To reproduce 3-D turbulent air flow field in the airways, we used the 3-D CFD model developed and validated by Lin et al. (2005) and Choi et al. (2010). In central branches, air flow is turbulent (e.g., Dekker (1961) and Miyawaki et al. (2012)), so the model is based on LES to resolve large scale eddies. We considered the steady inhalation with a flow rate of 20 L/min to simulate breathing in a resting condition, and the corresponding local Reynolds number in the trachea (Re_t) is 1600. We imposed turbulent flow at the inlet (proximal to glottis) using a synthetic eddy method (SEM) (Jarrin et al. (2009)) as in the simulations by Miyawaki et al. (2017). To control the effect of regional ventilation on aerosol deposition, we applied the flow rate outlet boundary condition proposed by Horsfield et al. (1971) to every subject. This means that the local Re and Stokes number (Stk) in a branch of a subject are similar (difference < 5%) to those of another subject because the averaged healthy LAs are similar.

To compute the particle trajectories in airways, we used Lagrangian particle tracking model developed and validated by Kumar et al. (2011) and Miyawaki et al. (2012). The CFD simulation is much more computationally expensive than aerosol simulation, so we computed the particle trajectories as a post process of the CFD simulation. The Re_t is similar to the Re_t used in the simulation of air by Miyawaki et al. (2012), so we updated the unsteady flow field every 0.006 sec in this study as well to resolve large eddies. We evaluated aerosol deposition in a branch using deposition efficiency (DE), which is defined as

$$DE_b = N_{p,b}/M_{p,b}, \quad (10)$$

where $M_{p,b}$ and $N_{p,b}$ are numbers of aerosol particles entered and deposited in branch b , respectively. Average healthy DE and normalized DE are defined as

$$DE_{h,b} = (1/N_{h,s}) \sum_{s=1}^{N_{h,s}} DE_{b,s} \text{ and } \quad (11)$$

$$DE_{b,s}^* = DE_{b,s}/DE_{h,b}, \quad (12)$$

respectively, where $DE_{b,s}$ is DE_b in Equation (10) for subject s . For simplicity, we may use $Ptcl^*$ to mean $DE_{b,s}^*$ hereafter. $Ptcl^*$ was computed from the CFD airway model based on average healthy luminal area and subject-specific skeleton, while $Area^*$ was based on the airway geometry segmented from CT image. Since subject-specific skeleton was used for the CFD airway model, $Angle^*$ was the same in both CFD model and CT-based geometry.

We used the most effective aerosol size when analyzing aerosol deposition, and we used the deposition fraction (DF) of the branches of interest to compare the effectiveness of aerosol

size. The DF of a branch is defined as the ratio of the number of aerosol particles deposited in the branch to the number of aerosol particles entered the oral cavity:

$$DF_b = \frac{N_{p,b}}{M_{p,o}} = \frac{M_{p,t}}{M_{p,o}} \frac{N_{p,b}}{M_{p,t}} = \frac{M_{p,o} - N_{p,o}}{M_{p,o}} DF_b' = (1 - DE_o) DF_b' \quad (13)$$

where $N_{p,o}$ is the numbers of aerosol particles deposited in the oral cavity, $M_{p,o}$ and $M_{p,t}$ are numbers of aerosol particles entered the oral cavity and the trachea, respectively, DE_o is the DE in oral cavity, and DF_b' is the DF based on M_b rather than M_o . The DE_o was estimated based on the empirical curve for oral deposition proposed by Grgic et al. (2004) and the length scale of the oral cavity used by Miyawaki et al. (2012).

As will be shown later, the LA of the SA subjects was significantly smaller than that of the healthy subjects in the central branches whose generation number is greater than two, so we considered those branches as the branches of interest when obtaining the effective aerosol size. The total DF of 5, 10, 20, and 40- μ m aerosols in the central branches whose generation number is greater than two, i.e., $\Sigma_{gen>2} DF_b$, were 0.03, 0.10, 0.16, and 0.00, respectively. Therefore, 20- μ m aerosol deposited most in the branches of interest among the four aerosol sizes tested. To minimize the influence of uncertainty in our model, we analyzed the deposition of 20- μ m aerosol below. Cement dust, Coal dust, flour, paint spray, bacteria, and pollen may contain 20- μ m aerosol (Hinds (1982)).

2.4 Statistical tests

We used a two-tailed and one-tailed t -test for the mean with a significance level of 5% to test if one value is “significantly different” from another value and if one value is “significantly smaller” than another value, respectively.

Results

3.1 Aerosol deposition in asthmatic lungs

We found the correlation between the diseased branch and aerosol deposition in one (subject 4) of the three SA subjects, even with the LA converted to a normal dimension for healthy subjects. In Fig. 4, each point represents one branch of subject 4. The correlation coefficient R for Ptcl* vs. Area* (Fig. 4 a) was -0.49 , and the P value of the two-tailed t -test for the slope of linear regression was 0.014. This implies that there is more aerosol deposition in more diseased branches even if the LA is as large as that in healthy branches. The R and P for Angle* vs. Area* (Fig. 4 a) were -0.40 and 0.056 if one branch with very large BA (branch 31) is not considered. This implies that the BA of more diseased branches is larger, although P is slightly larger than 5%. The R and P for Ptcl* vs. Angle* (Fig. 4 b) were 0.42 and 0.042 if one branch with very large BA (branch 31) is treated as an outlier and is not included in statistical analysis. This implies that there is more aerosol deposition in the branches with larger BA.

3.2 Luminal area and branching angle

To compare the LA and BA of central branches individually, we compared Area* and Angle* of the central branches in healthy and SA subjects. The LA of SA subjects was smaller than that of healthy subjects in 31 of 32 (97 %) branches, and the former was significantly smaller than the latter in 12 of 32 (38 %) branches, whose generation number is higher than one (Fig. 5 a–b). The BA of SA subjects was larger than that of healthy subjects in 20 of 31 (65 %) branches, and the former was significantly larger than that in 1 of 31 (31 %) branches (Fig. 5 c–d).

Discussion

We analyzed the geometry and aerosol deposition of central branches in healthy and SA subjects using our numerical airway geometry and aerosol models, respectively. We aimed to determine if there are any SA subjects whose airway skeletons could cause higher aerosol deposition compared to healthy subjects.

4.1 Aerosol deposition in asthmatic lungs

We found a significant correlation between diseased (narrow) branches and aerosol deposition in the most diseased SA subject (subject 4) among the three SA subjects considered in the analysis of aerosol deposition even if the LA of the diseased branches was healthy. The sign of the correlation coefficient was negative, so there was more aerosol deposition in more diseased (narrower) branches compared to healthy subjects. This correlation could be attributable to BA as explained below. In the analysis of aerosol deposition, LA, breathing pattern, and regional ventilation were controlled (healthy), so two of the most important non-dimensional parameters for aerosol deposition in central branches Re and Stk (e.g., Grgic et al. (2004)) were controlled. The other important parameters in aerosol deposition in central branches include BA and aerosol distribution before entering a branch, which depends on the aerosol motion in the upstream. We found significant correlation between BA and aerosol deposition in this subject. The sign of the correlation coefficient was positive, so there was more aerosol deposition in the branches with larger BA compared to healthy subjects. Larger BA implies that larger curvature of airflow streamlines, resulting in more aerosol deposition due to impaction, so this correlation is reasonable especially when Re and Stk are controlled. Significant correlations between diseased branches vs. aerosol deposition and between aerosol deposition vs. BA imply that the more diseased branches may have larger BA, and we actually found marginally significant ($p < 0.06$) correlation between diseased branches vs. BA.

The results demonstrated the possibility that this subject (subject 4) had central branches with larger BA, and that caused more aerosol deposition, resulting in diseased (narrow) branches. This is based on the assumption that exposure to aerosol does not affect BA as reported by Lee et al. (2011) using rat lungs. While the data presented here is only from 3 SA subjects, the results demonstrate the methodologies potential for exploring whether airway branching structure can influence environmental effects and may help to differentiate those subjects susceptible based upon branching geometry vs. subjects whose airway remodeling is related to other mechanisms (such as in subjects 5 and 6).

We found that 20- μ m aerosol was most effective within the size range of 5- 40- μ m aerosols for the simulating the geometric-susceptible deposition patterns. We recognized that this is larger than particle sizes that would be designed for deeper aerosol delivery. Stahlhofen et al. (1989) discusses an optimal size of 6 μ m for more peripheral delivery.

4.2 Luminal area and branching angle

The LA of central branches in SA subjects was significantly smaller than that in healthy subjects based on a branch-by-branch comparison. The LA of healthy subjects agreed reasonably well with that of the healthy subject studied by Horsfield et al. (1971) (Fig. 5 a), although the TLC of the latter was not available and assumed to be the average TLC of the former (5.43 L). It was unexpected that the LA of SA subjects is significantly smaller than that of healthy subjects even in low-generation branches, e.g., branches 6 and 11. This result suggests that there is a need to further investigate asthma in large airways using CT images even if small airways are not resolved.

BA of central branches in SA subjects was overall larger than that in healthy subjects, but the difference was not significant in most of the branches. The BA of healthy subjects did not agree well with that of the healthy subject studied by Horsfield et al. (1971) (Fig. 8 a). For instance, the main bifurcation (branches 1 and 10) is much more asymmetric in Horsfield et al. than in this current study. This discrepancy may be attributed to that the branching angle was estimated based on the geometry near carina, while Horsfield et al. (1971) may have used the entire branch; in addition to inter-subject variability and possible inflation differences. The difference in BA between healthy and SA subjects was not significant in most of the branches because of inter-subject variability.

4.3 Limitations

Our analysis of aerosol deposition was restricted to three SA subjects due to the computational cost of our LES-based numerical aerosol model, but more subjects may be required to draw general conclusions about SA subjects. Our numerical aerosol model assumed static airway geometry, steady inspiration, isothermal airflow, and no aerosol growth, and those effects may need to be considered for more realistic simulations in the future.

Conclusions

This study demonstrated significant correlations between airway remodeling vs. aerosol deposition for one of the three severe asthmatic subjects with $FEV1_{pp} < 45\%$ when luminal dimension as a variable was eliminated, looking just at the effect of branching angle. A marginally significant correlation was shown between remodeled branch vs. branching angle for the same subject. The primary contribution of this study is the demonstration of a framework allowing for the investigation of the relationship between airway remodeling, airway structure, and aerosol depositions using numerical airway models and subject specific CT imaging.

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Eric A. Hoffman is a shareholder in VIDA diagnostics that is commercializing lung image analysis software derived by the University of Iowa lung imaging group. He is also a member of the Siemens CT advisory board.

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Fig. 1.

The branch numbers used by Horsfield et al. (1971). Branch 31 is hidden behind branches 30 and 32, and branch 17 for this subject was very short. The numbers and edges of branches are colored by lobe.

Fig. 2. The definition of the dimensions of branches: (a) the radii in four directions used to estimate luminal area (LA), and (b) the branching angle (BA). r , f , l , b , and c are right, front, left, back, and centerline points in Miyawaki et al. (2016), respectively. The figure shows the BA of right main bronchus (RMB).

Fig. 3.

The red surface shows the airway geometry segmented from CT image and the gray surface shows the CFD airway model based on average healthy luminal area ($LA_{h,b,s}$) and subject-specific skeleton at left lingual bifurcation: (a) subject 1 (healthy, red surface is similar to gray surface) and (b) subject 4 (asthmatic, red surface is thinner than gray surface). The numbers in the figure denote the branch numbers used by Horsfield et al. (1971). The luminal area (LA) of branch 24 in subject 4 is 7% average healthy LA ($LA_{b,s}^{**} = 0.07$).

Fig. 4.

The correlation between normalized luminal area (Area*) (in the airway geometry segmented from CT image), normalized deposition efficiency of 20- μ m aerosol (PtcI*) (in the CFD airway model), and normalized branching angle (Angle*) (same in both CT-based geometry and CFD model) for one (subject 4) of the three SA subjects analyzed. The correlation coefficient r and p -value for PtcI* vs. Area*, Angle* vs. Area*, and PtcI* vs. Angle* were $(-0.49, 0.014)$, $(-0.40, 0.056)$, and $(0.42, 0.042)$, respectively, if one outlier with very large BA is not included.

Fig. 5.

(a) The normalized luminal area ($LA^*_{b,s}$) of central branches in healthy subjects, SA subjects, and the healthy subject studied by Horsfield et al. (1971) (H71); (b) the location of the branches where $LA^*_{b,s}$ of SA subjects is smaller (blue) or significantly smaller (red) than that of healthy subjects; (c) The branching angle ($BA_{b,s}$) of central branches in healthy subjects, SA subjects, and the H71 subject; and (d) the location of the branches where $BA_{b,s}$ of SA is larger (blue) or significantly larger (red) than that of healthy subjects. The TLC of the healthy subject studied by Horsfield et al. (1971) was not available and assumed to be the average TLC (5.43 L) of the healthy subjects in the present study. The signs † indicates significantly smaller values compared to healthy subjects based on one-tailed t -test with significance level of 5%.

Table 1

Clinical characteristics of healthy and severe asthmatic (SA) subjects used for geometric analysis. The data are based on eight subjects for each group, and mean (SD) is presented.

Group	Healthy	SA
Height (cm)	166 (10)	173 (10)
Weight (kg)	68 (16)	84 (25)
BMI	24 (4.7)	28 (5.6)
TLCpp (%)	98 (12)	105 (16)
FEV1pp (%)	96 (10)	37 (5.2) [†]

The sign [†] indicates significantly smaller values compared to healthy lung, based on one-tailed *t*-test with significance level of 5%.

Clinical characteristics of healthy and severe asthmatic (SA) subjects used for aerosol analysis. AAO is age of asthma onset.

Table 2

Group Subject	Healthy			SA		
	1	2	3	4	5	6
AAO	–	–	–	28	24	0
TLC (L)	5.17	5.48	5.24	5.55	4.98	5.39
TLCpp (%)	111	103	101	127	105	88
FEV1pp (%)	102	109	94	40	42	35
μ_{Aveat}^*	0.99	0.99	0.98	0.49	0.75	0.89