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Distribution of aerosolized particles in healthy and emphysematous rat lungs: Comparison between experimental and numerical studies

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ABSTRACT

In silico models of airflow and particle deposition in the lungs are increasingly used to determine the therapeutic or toxic effects of inhaled aerosols. While computational methods have advanced significantly, relatively few studies have directly compared model predictions to experimental data. Furthermore, few prior studies have examined the influence of emphysema on particle deposition. In this work we performed airflow and particle simulations to compare numerical predictions to data from our previous aerosol exposure experiments. Employing an image-based 3D rat airway geometry, we first compared steady flow simulations to coupled 3D–0D unsteady simulations in the healthy rat lung. Then, in 3D–0D simulations, the influence of emphysema was investigated by matching disease location to the experimental study. In both the healthy unsteady and steady simulations, good agreement was found between numerical predictions of aerosol delivery and experimental deposition data. However, deposition patterns in the 3D geometry differed between the unsteady and steady cases. On the contrary, satisfactory agreement was not found between the numerical predictions and experimental data for the emphysematous lungs. This indicates that the deposition rate downstream of the 3D geometry is likely proportional to airflow delivery in the healthy lungs, but not in the emphysematous lungs. Including small airway collapse, variations in downstream airway size and tissue properties, and tracking particles throughout expiration may result in a more favorable agreement in future studies.

1. Introduction

Computational fluid and particle dynamics simulations provide detailed spatial and temporal distributions of airflow and particles in healthy and diseased lungs. However, to increase confidence in these models, results must be validated against *in vivo* experimental data. While several groups have shown good agreement between three-dimensional (3D) flow (de Rochefort et al., 2007; Mylavarapu et al., 2009) and particle-based (Longest et al., 2012; Ma and Lutchen, 2009; Ma et al., 2009; Zhang and Kleinstreuer, 2001; van Ertbruggen et al., 2009) models with *in vitro* experiments, these comparisons are not sufficient for validation of *in vivo* conditions. While one-dimensional (1D) particle transport models have relatively well predicted *in vivo* data of total and regional deposition in the human (Darquenne and Paiva, 1994; Asgharian et al., 2006; Katz et al., 2013) and rat lung (Schmid et al. (2008), Anjilvel and Asgharian (1995)), they do not provide detailed spatial information. Recently, Minard et al. (2012) showed promising agreement between *in silico* predictions and *in vivo* magnetic resonance (MR) derived flow fields in rat lungs. While these previous studies have advanced the validity of computational models, none of them compared multi-scale simulations to regional particle deposition data in both healthy and diseased lungs.

Emphysema, a disease characterized by increased tissue compliance, expanded acinar volume, and decreased small airway diameter compared to normal (Thurlbeck and Muller (1994)), has been shown to impact particle deposition in the lungs (Oakes et al., 2014; Sweeney et al., 1987; Brand et al., 2009). To study the influence of emphysema-like morphometric changes on particle deposition, we previously (Oakes et al., 2014) employed MR methods (Oakes et al., 2013) to determine lobar deposition in elastase-treated and healthy rat lungs. Results showed, for rats ventilated with the same breathing parameters, that particle concentration was higher in the elastase-treated lungs, compared to the healthy lungs. However, the distribution of particles to the

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lobes was the same in the healthy and emphysematous rats (Oakes et al., 2014) despite the MR and histological measurements suggesting heterogeneous distribution of emphysema-like structures in several lobes of the emphysematous group.

Recently, we developed a 3D–0D coupled numerical model to study airflow and particle deposition in healthy and emphysematous rat lungs (Oakes et al., 2014) that were parameterized from the experimental data of Oakes et al. (2014). The goal of the current study was to extend this previous 3D geometric model (Oakes et al., 2012) and to compare regional deposition predictions to experimental data (Oakes et al., 2014). These simulations required matching the numerical model as closely as possible to the experimental conditions and comparing the predicted distribution of inhaled particles to the experimental lobar deposition. Using this *in silico* model, we explored the influence of flow conditions (unsteady versus steady) and initial particle spatial distribution on deposition and lobar delivery.

2. Methods

2.1. Multi-scale numerical airflow framework

The numerical framework has been previously described in Oakes et al. (2014). The 3D geometry was created with a custom version of the open source software, SimVascular (simvascular.org) (Schmidt et al., 2008) and includes up to 16 airway generations, with 81 terminal airways (Fig. 1) (Oakes et al., 2012). Airflow was simulated with an open source stabilized finite element Navier–Stokes solver, assuming rigid walls and incompressible Newtonian flow (density $= 1.2 \times 10^{-6}$ g/mm^3, viscosity $= 1.81 \times 10^{-5}$ g/mm s). A custom linear solver was employed, incorporating resistance-based preconditioning with a combination of GMRES and conjugate gradient methods (Esmaily Moghadam et al., 2013). Three respiratory cycles were simulated with six Newton iterations of the linear system within each time step of 10^{-4} s. Anisotropic mesh adaptation based on the Hessian of the velocity field was employed to ensure mesh convergence of the solution (Müller et al., 2005) using meshsim (Simmetrix, Troy, NY). Mesh convergence was confirmed for both the flow field and particle deposition.

A no-slip boundary condition was assigned at the airway walls, the experimentally measured time-varying pressure ($P_H(t)$ or $P_E(t)$, H: healthy, E: Emphysema) (Oakes et al., 2014) was applied at the trachea face (Fig. 1A) and 0D resistance ($R_{i,j}$) and compliance ($C_{i,j}$) models (Bates and Suki, 2008) were implemented at each distal face by implicitly coupling the 0D models to the 3D model (Esmaily Moghadam et al., 2013). A representative healthy and emphysematous rat were chosen to match the rat-specific global parameters with its pressure curve. The 0D model is governed by the following equation:

$$R_{i,j}\frac{dV_{i,j}(t)}{dt}+\frac{V_{i,j}(t)}{C_{i,j}}=P_{i,j}(t)-P_{peep}, \tag{1}$$

where $V_{i,j}$ is the inspired volume, $P_{i,j}(t)$ is the pressure at each distal face and the j and i indices identify the distal faces, with lobe j and assigned airway number i. P_{peep} is the constant pressure of 1 cm H_2O (Oakes et al., 2014). Note that the distal pressure P_D in Fig. 1 does not appear in this equation as it describes the evolution of the inspired, not the total volume (Oakes et al., 2014). To prevent numerical instability a convective stabilization scheme (Esmaily Moghadam et al., 2011) was imposed at all faces with $\beta=0.1$. The resulting resistance in the 3D geometry was calculated at the time of maximum inspiration ($R_{3D,insp}$) and expiration ($R_{3D,ex}$) by dividing the average pressure drop in the 3D geometry by the flow rate at the trachea.

In the next two paragraphs, the parameters $R_{i,j}$ and $C_{i,j}$ were derived using a combination of the experimental measures and a purely 0D model (e.g. Fig. 1C). With this formulation, it was assumed that the 3D resistance did not influence the average flow repartition in the distal branches of the 3D tree. Therefore, the driving pressures, $P_H(t)$ or $P_E(t)$ (Fig. 1A) remained the relevant $P(t)_{i,j}$ for these solely 0D models. This assumption was tested and its validity is confirmed in the discussion section.

2.1.1. Healthy 0D parameters

The 0D model parameters for the healthy simulations were defined as

$$C_{i,j}=\frac{A_{i,j}\alpha_j C_{global}}{A_{T_j}} \tag{2}$$

$$R_{i,j}=\frac{R_{global}A_{T_j}}{\alpha_j A_{i,j}}, \tag{3}$$

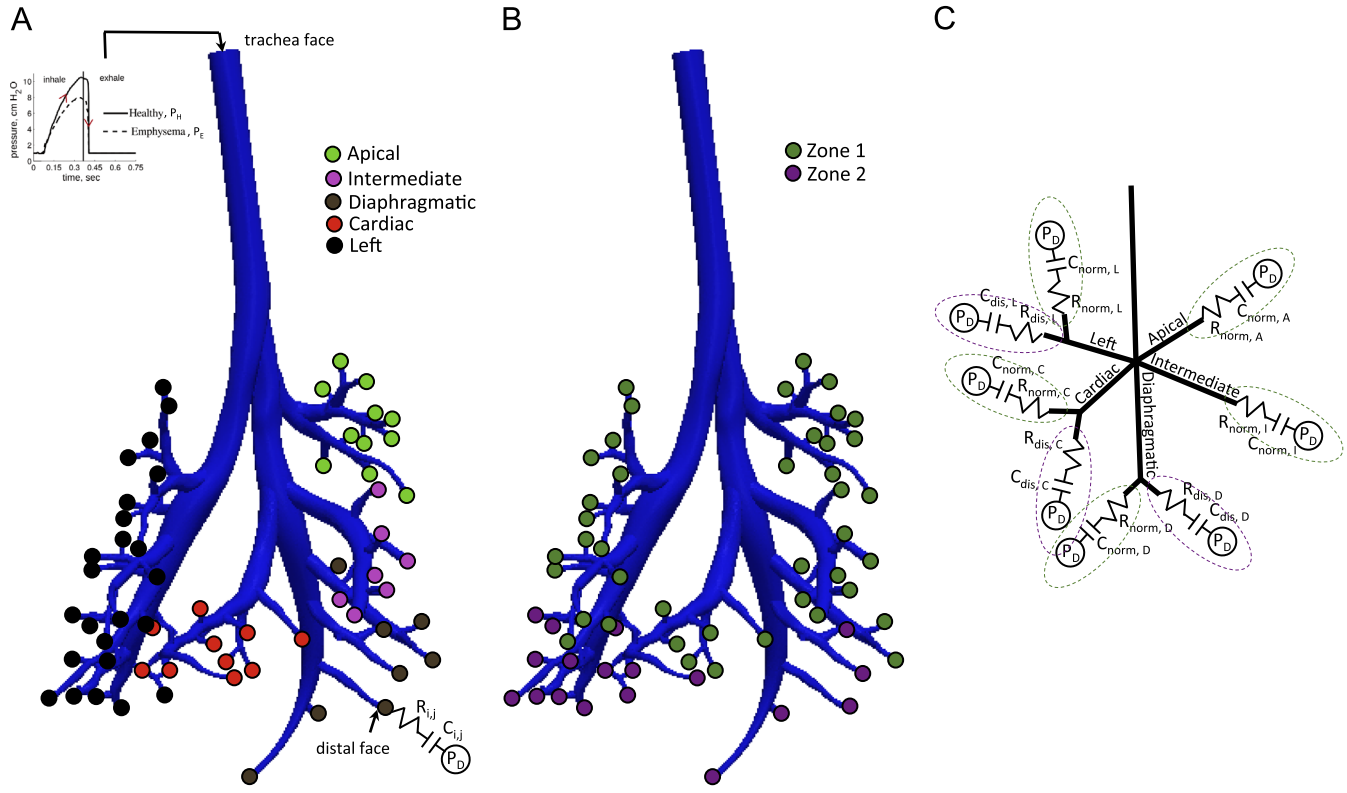

Fig. 1. 3D airway geometry (Oakes et al., 2012) used for all the simulations. Panel A: Identification of the airways leading to the five lobes. Panel B and C: Definition of the zones used for the emphysematous simulations. Zone 2 (diseased region) was set to be at the bottom $\frac{1}{3}$ of the left, cardiac and diaphragmatic lobes. Zone 1 (normal region) was defined as the top $\frac{2}{3}$ of the left, cardiac and diaphragmatic lobes and the entire apical and intermediate lobes. Panel C shows the distribution of the normal (R_{norm} and C_{norm}) and diseased (R_{dis} and C_{dis}) parameters for each zone. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)