Journal of Biomechanics ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

Aerosols in healthy and emphysematous in silico pulmonary acinar rat models

Jessica M. Oakes [a,b,c,1], Philipp Hofemeier [d,1], Irene E. Vignon-Clementel [b,c], Josué Sznitman [d,*]

[a] Department of Mechanical Engineering, University of California Berkeley, Berkeley, CA 94709,USA
[b] INRIA Paris-Rocquencourt, 78153 Le Chesnay Cedex, France
[c] Sorbonne Universités, UPMC Univ Paris 6, Laboratoire Jacques-Louis Lions, 75252 Paris, France
[d] Department of Biomedical Engineering, Technion - Israel Institute of Technology, Haifa 32000, Israel

ARTICLE INFO

Article history:
Accepted 21 November 2015

Keywords:
Computational fluid dynamics (CFD)
Emphysema
Particle deposition
Disease modelling
Alveoli

ABSTRACT

There has been relatively little attention given on predicting particle deposition in the respiratory zone of the diseased lungs despite the high prevalence of chronic obstructive pulmonary disease (COPD). Increased alveolar volume and deterioration of alveolar septum, characteristic of emphysema, may alter the amount and location of particle deposition compared to healthy lungs, which is particularly important for toxic or therapeutic aerosols. In an attempt to shed new light on aerosol transport and deposition in emphysematous lungs, we performed numerical simulations in models of healthy and emphysematous acini motivated by recent experimental lobar-level data in rats (Oakes et al., 2014a). Compared to healthy acinar structures, models of emphysematous subacini were created by removing inter-septal alveolar walls and enhancing the alveolar volume in either a homogeneous or heterogeneous fashion. Flow waveforms and particle properties were implemented to match the experimental data. The occurrence of flow separation and recirculation within alveolar cavities was found in proximal generations of the healthy zones, in contrast to the radial-like airflows observed in the diseased regions. In agreement with experimental data, simulations point to particle deposition concentrations that are more heterogeneously distributed in the diseased models compared with the healthy one. Yet, simulations predicted less deposition in the emphysematous models in contrast to some experimental studies, a likely consequence due to the shallower penetration depths and modified flow topologies in disease compared to health. These spatial-temporal particle transport simulations provide new insight on deposition in the emphysematous acini and shed light on experimental observations.

1. Introduction

While computational models that describe the behavior of inhaled particles in the respiratory acinar regions of the healthy lung have attracted broad attention (Ma and Darquenne, 2011; Hofemeier and Sznitman, 2015; Harding and Robinson, 2010; Kumar et al., 2009; Khajeh-Hosseini-Dalasm and Longest, 2015), little focus has yet been made on modelling the transport of aerosols in the diseased pulmonary acinus. To the best of our knowledge, no 3D in silico acinar models have attempted to address the fate of inhaled micron-sized aerosols in the context of pulmonary conditions such as emphysema. Emphysema is a progressively severe heterogeneous obstructive disease caused by inhalation of toxic gases and particles over a long period of time (Hogg, 2004). The disease is characterized by alveolar airspace enlargement caused by deterioration of the pulmonary tissue leading to a loss of interalveolar septa (Thurlbeck and Muller, 1994). At its earliest stages the diseased lesions are heterogeneously distributed in the lung; however, as the disease progresses inflammation, protease activity, and remodelling lead to a more severe and widespread distribution of damaged tissue (Suki and Parameswaran, 2014; Suki et al., 2003). Due to the increased resistance of the small airways and tissue compliance, the lung takes a longer time to empty (Hogg, 2004), which may lead to ventilation asymmetry (Oakes et al., 2015), air trapping (Jacob et al., 2013), and ventilation deficiency (Emami et al., 2011). As aerosol medications are increasingly used to either treat pulmonary or systemic diseases, it is imperative to understand deposition in both healthy and diseased lungs. While

* Corresponding author.
E-mail address: sznitman@bm.technion.ac.il (J. Sznitman).
[1] Authors contributed equally.

http://dx.doi.org/10.1016/j.jbiomech.2015.11.026
0021-9290/

effective treatment of emphysema is still unavailable, recent animal studies have suggested that biphosphonate (alendronate) inhalation, commonly used to treat osteoporosis, may have therapeutic potential by blunting the inflammatory response of alveolar macrophages (Ueno et al., 2015).

Previous in vivo (Brand et al., 2009; Oakes et al., 2014a; Sweeney et al., 1987) and in vitro studies (Oakes et al., 2010; Berg and Robinson, 2011) have attempted to uncover the behavior of inhaled particles in the emphysematous lung. However, likely due to the progressive nature of the disease, there remains a lack of agreement on whether there are more or less particles depositing in the emphysematous lung compared to a healthy one. For example, Oakes et al. (2014a) found enhanced deposition in elastase-treated rat lungs compared to healthy ones measured with Magnetic Resonance Imaging (MRI), in contrast to earlier measurements obtained in elastase-treated hamsters where a decreased deposition was measured (Sweeney et al., 1987). Yet, both animal studies (Oakes et al., 2014a; Sweeney et al., 1987) agreed on the enhanced heterogeneity in the distribution of aerosol deposition patterns in the diseased lungs. In 3D scaled-up in vitro studies, Oakes et al. (2010) and Berg and Robinson (2011) determined a decrease in penetration depth in an emphysematous alveolar sac and acinar model compared to healthy ones and hypothesized that this would result in a decrease in deposition in the diseased models. This finding agrees with deceased deposition in emphysema, compared to healthy lungs, found in a stochastic model of various types of emphysema (Sturm and Hofmann, 2004).

The advantage of numerically modelling the lung lies in the ability to investigate particle transport and deposition at temporal and spatial resolutions that are currently beyond reach with current state-of-the-art imaging modalities. Motivated by such shortcomings and available aerosol deposition data in rats (Oakes et al., 2014a), a computational framework has been recently developed to model airflow and particle transport in anatomically reconstructed conducting airways of rats (Oakes et al., 2014b). While deposition predictions between in vivo and in silico agreed well in healthy rats, similar agreement was not found for the emphysematous animals (Oakes et al., 2015). As this in silico model did not include the small airways and acinar region of the lung, the behavior of particles once they reach the distal regions of the lung remains widely unknown. It is hypothesized that the enlarged airspaces and deterioration of the alveolar septa, characteristic of emphysema, will lead to noticeable differences in total and spatial distribution patterns of particles.

The main aims of this study were to numerically investigate the deposition patterns in healthy and diseased acini and to shed light on the transport mechanisms behind the enhanced deposition in emphysema found experimentally (Oakes et al., 2015). For such purpose, we adapted a numerical acinar framework recently developed (Hofemeier and Sznitman, 2015) and compared deposition predictions between a healthy rat acinar model and two emphysematous cases. The emphysema models were created by enlarging airspaces and removing connecting alveolar septa in either a homogeneous or heterogeneous fashion. To facilitate comparison between our predictions and experimental data, both the ventilation (i.e. breathing patterns) and particle properties were chosen to match the conditions implemented in Oakes et al. (2014a). By assessing the differences between healthy and diseased acini, our efforts aim to advance the knowledge of inhaled particles in the deep regions of the diseased lung and pinpoint the mechanisms responsible for the deposition differences between the healthy and emphysematous rats.

2. Methods

2.1. Rat acinar geometry

Three distinct multi-generational rat acinar domains were designed following a space-filling model of 3D polyhedral units (Fung, 1988; Sznitman, 2009). A healthy (H), heterogeneous emphysematous (E_{Het}) and homogeneous emphysematous (E_{Hom}) models were created (Fig. 1a–c), where each acinar network consists of up to six airway generations with a maximum of 277 polyhedral alveoli (Table 1). The resulting sub-acini capture sufficiently well realistic full acinar structures (Khajeh-Hosseini-Dalasm and Longest, 2015). A healthy human acinar model (Hofemeier and Sznitman, 2015) was scaled down by 15% to match dimensions of a rat acinus (Rodriguez et al., 1987) at functional residual capacity (FRC) since interspecies differences are overall minor (see limitations below for further discussion). The outer airway sleeve diameter, including the ducts and surrounding alveoli, was held constant at 86 μm with a characteristic alveolar diameter of 35 μm. Airway ducts spanned a length of 56–85 μm, depending on generation.

In order to capture and integrate some of the emphysema-like morphological changes, the H model was modified according to two characteristics features: (i) removing the inter-alveolar septal walls as highlighted in Fig. 1c (inset) and (ii) increasing the acinar volume of the model by adding additional polyhedral structures in the bifurcation regions (see Table 1). Thus, diseased regions were characterized as enlarged continuous airspaces without distinct alveolar cavities, in contrast to the normal regions (compare Fig. 1a to d). The entire E_{hom} model was defined as diseased and thus the emphysema-like changes were distributed throughout the model (see Fig. 1d and Table 1). The E_{het} model represents a non-uniform distribution of emphysema where two zones were created; a normal zone (N) and a diseased zone (D). The bottom right portion of the model was prescribed as diseased as highlighted in gray in Fig. 1b leaving the rest of the model as normal (Fig. 1c). FRC values for each model, including the two regions of the E_{het} model, are presented in Table 1, showing that FRC increases with emphysema severity. In order to underline the loss of septal walls, the number of alveolar cavities as well as the surface-to-volume ratio S/V are shown in Table 1; here, we find that S/V is approximately decreased by half for the E_{hom} model compared to the healthy condition. Corresponding videos presenting the acinar models and their respective breathing motions are supplied in the Supplementary Material (SM).

2.2. Respiration curves

A self-similar breathing motion was prescribed across the entire acinar domain to simulate cyclic expansion and contraction motion following previous works (Hofemeier and Sznitman, 2014, 2015; Sznitman, 2009). Realistic respiration curves, derived from rat ventilation studies (Oakes et al., 2014a, 2014b), were scaled for each of the acinar models in order to match realistic tidal volumes. Specifically, the time-dependent acinar volumes were defined as $V_{H,A}(t) = \alpha\, V_{H,T}(t)$ and $V_{E,A}(t) = \alpha\, V_{E,T}(t)$ for the H and E_{hom} models, respectively; note that the indices A and T indicate acinar and total lung, respectively. Assuming that the acinar volume fraction of the H and E_{hom} models are identical, α was set to $FRC_{H,A}/FRC_{H,T}$, with $FRC_{H,T} = 4.77$ mL (Rubio et al., 1998).

It is important to note that a straightforward scaling of the time-dependent volume curve is not feasible for the E_{het} model as the tissue mechanics of the normal and diseased zones are different. Following a recent approach (Oakes et al., 2015), we scaled the curves separately for each region based on a lumped model where respiratory resistance (R) and compliance (C) are in series. Assuming that the normal region of the lung correlates with the healthy rat lung, R_N and C_N were set to $R_N = R_{H,T}/\alpha_N$ and $C_N = C_{H,T}{*}\alpha_N$, where $R_{H,T} = 0.098$ cm H_2O-s-cm^{-3} and $C_{H,T} = 0.236$ cm^3 (cm H_2O)$^{-1}$. Here, $\alpha_N = \alpha FRC_{N,A}/FRC_{H,A}$ (Oakes et al., 2015). The respiratory volume curve of the normal region ($V_{N,A}(t)$) was found by directly solving

$$R_N \frac{dV_{N,A}(t)}{dt} + \frac{V_{N,A}(t)}{C_N} = P(t) - P_{peep}, \tag{1}$$

where $P(t)$ is the pressure measured at the trachea of the emphysematous rat during ventilation and P_{peep} is the positive expiratory pressure of 1 cm H_2O (Oakes et al., 2015). The respiratory volume curve of the diseased region ($V_{D,A}(t)$) was calculated as $V_{D,A}(t) = TV_{D,A}^{V_{E,T}(t)} TV_{E,T}$, where the tidal volume of the diseased region is defined as $TV_{D,A} = TV_{E,A} - TV_{N,A}$. The corresponding $V_{N,A}$ and $V_{D,A}$ were prescribed to the normal and diseased regions of the E_{het} model in the 3D flow simulations.

The resulting volume curves (i.e. $V_A(t)$ normalized by FRC_A) and flow rates over the cycles are shown for each acinar model in Fig. 2a and b, respectively. Note that the tidal volumes were the same for each model and were slightly larger in the diseased region compared to the normal region of the E_{het} model (Table 1 and Fig. 2). As shown in Oakes et al. (2015), the decay rates of $V_{E,A}$ and $V_{D,A}$ were slower compared to the corresponding healthy curves (Fig. 2a). This resulted in lower peak flow rates during exhalation (Fig. 2b). Flow rates during inspiration were nearly the same for the H and E_{hom} models because all the rats were ventilated with identical settings (Oakes et al., 2014b). The diseased zone of E_{het} finished filling slightly after the corresponding normal zone, due to the longer time constant of the diseased

Please cite this article as: Oakes, J.M., et al., Aerosols in healthy and emphysematous in silico pulmonary acinar rat models. Journal of Biomechanics (2015), http://dx.doi.org/10.1016/j.jbiomech.2015.11.026