Evaluation of the Effect of Lung Morphometry on the Deposition of Inhaled Particles

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Introduction: The human respiratory tract is a complex, asymmetrical, tree-like system of tubular structures, optimized for the transport and distribution of respiratory gases. The objective of this study is to use a computerized lung model to study the effect of lung morphometry on the airway deposition of inhaled particles.
Material and methods: We used a stochastic lung model to simulate the total and regional deposition of 0.01–10 μm particles through oral breathing in sitting condition. The effect of lung morphometry was examined using the same model with a modified algorithm to create a fully symmetrical lung geometry.
Results: Total deposition curves show similar deposition trends for the two models, the symmetric model returning slightly lower deposition values for all particle sizes. In the bronchial region deposited fractions are highly similar, the symmetric model predicting deposition values that are 2.1–4.6% higher for particles in the 0.01–0.1 μm size range. In the acinar region deposition values are up to 27.6% lower in the case of 0.2 μm particles.
Conclusions: Our study suggests that the deposition of inhaled particles is dependent mainly on particle size, and to a smaller extent on the lung geometry the models are built on. Deposition fractions yielded by the two models are highly similar, although there is a shift in the deposition of inhaled particles from the acinar region towards the bronchial region in the symmetric model.

Keywords: airways, morphometry, modelling, stochastic, symmetric

Received: 21 August 2012

Introduction

The human respiratory tract can be described as a complex system of cylindrical tubes, optimized for the transport of respiratory gases. From a geometrical point of view, the airways assume a tree-like structure, with branches that try to fill efficiently the space they are in, i.e. the thoracic cavity. The way the respiratory tract is optimized for gas transport, while respecting a set of biological, physiological and physical rules, represents a careful balance of design and function. One of the most interesting characteristic of this tree-like structure is its asymmetry: each branch gives birth to two (or sometimes more) daughter branches with different lengths, diameters and branching angles.

The deposition of inhaled particles in the human airways has great implications in the assessment of risks associated with the exposure to infectious agents, toxic, radioactive or allergenic substances from the ambient air, but also in the refinement of therapeutic aerosols used in the treatment of chronic respiratory diseases.

Due to the fact that because of ethical considerations and technical limitations experimental data is limited, currently the most widespread method to study the airway deposition of inhaled particles is to use computerized lung models, which can simulate the transport and deposition characteristics of a wide range of particles in a large number of respiratory conditions.

Lung models are currently used to assess the health risks associated with the inhalation of toxic, radioactive or allergenic substances from the ambient air [1,2,3,4], playing an important role also in cancer related research, where they have the potential to clarify why certain types of cancer develop predominantly in certain areas of the airways [5,6]. Simulation models are also used to evaluate the efficiency of aerosols in the treatment of chronic respiratory diseases such as asthma bronchiale [1], but also in systemic diseases such as diabetes [7] or cancer [8,9,10].

The main differences between the current models concern the lung geometry and the modelling technique used to carry out the simulations. Many of the models imply an idealized, symmetrical lung structure, to reduce computational resources [11,12], but their simplicity also means that they cannot be used for the prediction of realistic deposition patterns in asymmetric and variable lung structures [13]. Numerical models on the other hand involve computational fluid and particle dynamics (CFPD) calculations, using realistic three-dimensional geometries, but their high computational needs limit them to only a several consecutive airway generations, therefore these models can only be used on a local scale [14,15,16,17].

The objective of this study is to use a computerized lung model to study the effect of lung morphometry on the airway deposition of inhaled particles.

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Material and methods

The deposition of inhaled particles was modelled using the current version of the stochastic lung model developed by Koblinger and Hofmann [18,19], Hofmann and Koblinger [20,21], and Hofmann [22,23]. Since the detailed description of the stochastic lung model and its further developments can be found in the aforementioned publications, here we will only present its main features. The model uses a stochastic asymmetric lung structure, where the airways are modelled by a sequence of Y-shaped bifurcation units, consisting of a parent tube and two asymmetrically dividing daughter airways. Extrathoracic deposition is simulated by formulas provided by Yu et al. [24] and Stahlhofen et al. [25]. The tracheobronchial and acinar depositions are computed by the application of analytical deposition formulas in a network of tubular airways reconstructed on the basis of Lovelace database [26] and in the pulmonary acinus structure described by Haefeli-Bleuer and Weibel [27]. The geometric properties of the daughter branches (diameter, length, branching angle, gravity angle) and particle trajectories are selected randomly for each airway segment, thus all paths of the inhaled particles are different from each other.

In order to investigate the effect of lung morphometry, we modified the algorithm selecting the morphometric parameters of the airways in which the simulations are carried out, in order to create a symmetrical model. In this model, each tube of an airway generation has identical linear dimensions and branches symmetrically into two identical daughter airways, with a branching angle of 60o.

All simulations were carried out for a healthy, adult male subject, for oral breathing, in sitting condition. The respiratory parameters included a 750 ml tidal volume, a 3300 ml functional residual capacity and a 5 s long symmetrical breathing cycle without breath hold. These specific parameters were obtained from the ICRP66 publication [12].

We modelled the deposition of unit density (1 g/cm3) particles with diameters between 0.01 and 10 μm. The simulations were carried out for one complete breathing cycle, with 100,000 simulations per run. We assumed the particles are inhaled uniformly during inhalation.

Through the simulations the respiratory tract was divided into three distinct regions: the upper airways, or the extrathoracic region (the oral and nasal cavity, the larynx and the pharynx), a bronchial region (generations 0–16) and an acinar region (generations 17–23). The stochastic model calculates the deposition probability of each inhaled particle for each bifurcation unit. Simulation results are presented as deposited fractions (the ratio of deposited particles and the total number of inhaled particles) for total, regional, generational and lobar deposition. Data processing and statistical analysis were performed using Microsoft Excel 2007. We used Student's t test to compare the results, and a p level below 0.05 was considered to be statistically significant.

Results

Total deposition values obtained with the asymmetrical vs. the symmetrical models are depicted in Figure 1. The U-shaped deposition curves show similar deposition trends for the two models, the symmetric model returning slightly lower deposition values for all particle sizes. Although the differences between the deposition fractions are statistically significant for all particle sizes ($p<.001$), these differences are between 2.7%, in the case of 1 μm particles and 13.3% in the case of 5 μm particles.

Extrathoracic deposition values (Figure 2) show the filtering effect of the upper airways for 10 μm particles, with deposition fractions above 60%, while particles in the 0.05–2 μm size range exhibit very low deposition fractions in this region, below 7%. As the morphometric differences between the two models do not affect the extrathoracic region, the fact that the symmetric model yields slightly higher deposition fractions for 0.01–0.1 μm particles can probably be attributed to the differences in the amount of particles deposited during exhalation.

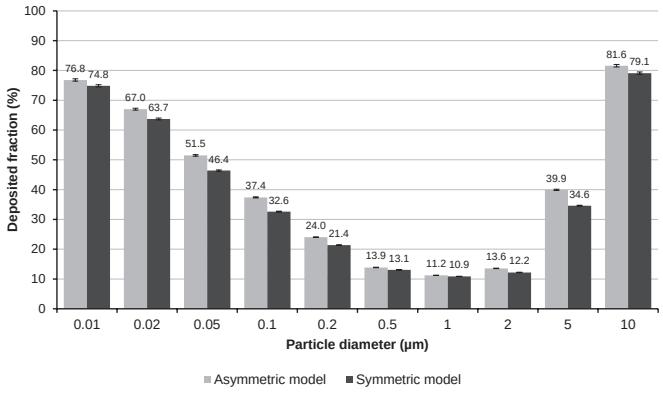

Fig. 1. Comparison of asymmetric vs. symmetric model predictions of total deposition for unit density particles ranging from 0.01 μm to 10 μm under oral sitting breathing conditions. V_T = 750 ml, CRF = 3300 ml, T_{inh} = 2.5 s, T_{exh} = 2.5 s. $p<0.001$ for all comparisons.

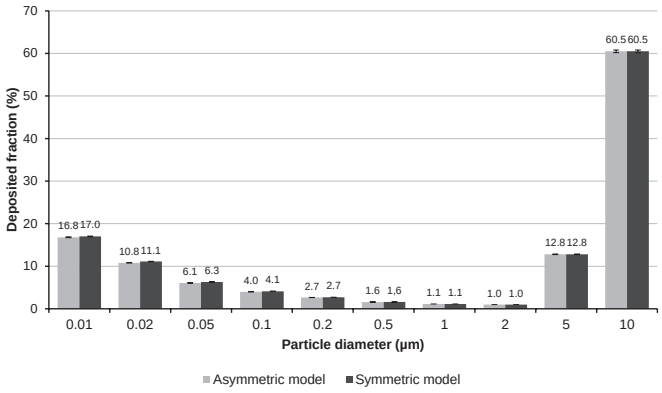

Fig. 2. Comparison of asymmetric vs. symmetric model predictions of extrathoracic deposition for unit density particles ranging from 0.01 μm to 10 μm under oral sitting breathing conditions. V_T = 750 ml, CRF = 3300 ml, T_{inh} = 2.5 s, T_{exh} = 2.5 s. $p<0.001$ for all comparisons where the values are different.

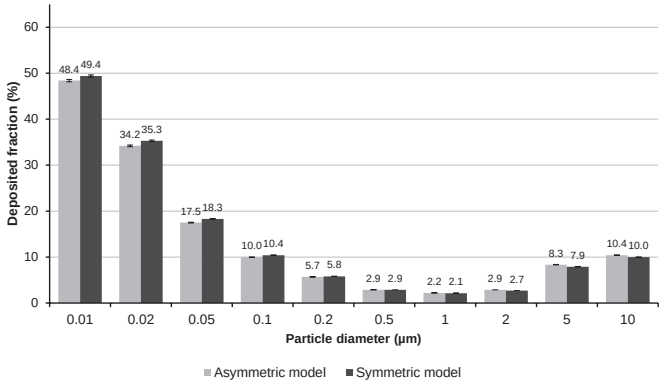

Fig. 3. Comparison of asymmetric vs. symmetric model predictions of bronchial deposition for unit density particles ranging from 0.01 µm to 10 µm under oral sitting breathing conditions. V_T = 750 ml, CRF = 3300 ml, T_{inh} = 2.5 s, T_{exh} = 2.5 s. p<0.001 for all comparisons where the values are different.

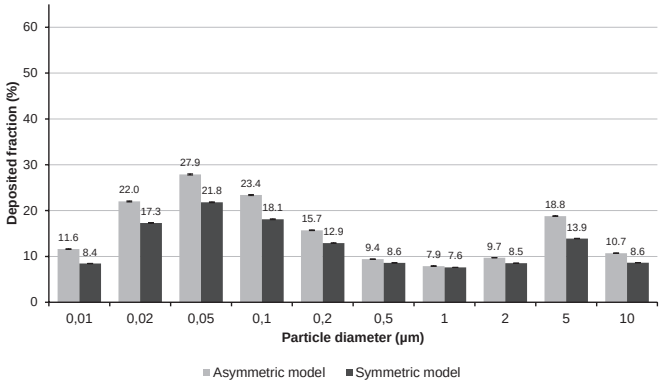

Fig. 4. Comparison of asymmetric vs. symmetric model predictions of acinar deposition for unit density particles ranging from 0.01 µm to 10 µm under oral sitting breathing conditions. V_T = 750 ml, CRF = 3300 ml, T_{inh} = 2.5 s, T_{exh} = 2.5 s. p<0.001 for all comparisons.

The effect of airway geometry on regional deposition becomes visible in the bronchial and acinar regions. Bronchial deposition values (Figure 3) are highly similar between the models, somewhat larger differences can be observed in the case of particles in the 0.01–0.1 µm size range, with the symmetric model predicting higher values, but these differences only amount to 2.1–4.6%. Deposition in this area is representative mostly for particles smaller than 0.05 microns, while particle in the 0.2–2 µm range continue to yield deposition fractions below 6%.

In the acinar region (Figure 4) both deposition curves assume a saddle-like shape with two peaks, at 0.05 µm and 5 µm particles. In contrast to the bronchial region, in the acinar region deposition fractions predicted by the symmetric model are lower for all particle sizes (p<0.001), especially for particles smaller than 0.2 µm, where deposition fractions are smaller with 17.8–27.6%, probably due to the higher deposition of these particles in the bronchial region.

Discussion

According to Hofmann, modelling particle deposition in the human lung is an attempt to solve a physical problem in a biological system by applying mathematical methods [13]. Particle deposition is influenced by biological factors, such as lung morphometry or respiratory parameters, but also physical factors, such as fluid dynamics, particle properties or deposition mechanisms. Although it has been proved that the deposition of inhaled particles shows significant variations through various breathing conditions [12,28,29,30,31,32,33], this study focuses on the effect of lung geometry. Nevertheless, as the simulations were carried out for a wide range of particle diameters, and the size of the particles determines the dominant deposition mechanism and the lung regions where deposition occurs, deposition mechanisms will also be discussed.

The magnitude of each of the three deposition mechanisms – Brownian diffusion, gravitational sedimentation and inertial impaction – varies with the parameters of particles, lung morphometry and breathing method [13]. Particles larger than 1 µm deposit in the upper airways and the central airways through impaction, due to their large size, as seen in Figure 2. These particles may also reach the peripheral regions of the airways if the flow velocity is low, explaining the presence of these particles in the acinar region, as seen in Figure 4. Particles in the 0.1–1 µm size range follow the stream of air all the way to the alveoli, yielding low deposition fractions in the extrathoracic and bronchial region, but they are mostly exhaled, as shown by their low total deposition values. Particles smaller than 0.1 µm deposit mainly by diffusion in the bronchial and acinar regions (Figures 2 and 3), but also in the extrathoracic region (Figure 1).

While it is rather difficult to compare the results with similar studies, due to the wide range of models and parameters these studies employ, all studies seem to agree that the deposition curves follow the same trend depending on the size of the particles, regardless of lung geometry and modelling technique. In a study by Hofmann [13], several types of lung models were compared, using the same set of modelling parameters, which were similar to the ones used in our study: particle size between 0.001–10 µm, nose breathing in resting, tidal volume of 750 ml, functional residual capacity of 3300 ml and a 5 second long breathing cycle. This comparative study found that total and regional deposition curves were similar in all cases, and while there were differences in the absolute values, all deposition fractions were within a range of ±10%, similarly to the results of our study.

The same study also reports that deposition calculations using different deposition equations in a given lung model or different morphometric lung models with the same deposition equations indicate that deposition fractions are affected by the selection of a specific lung model and a specific set of deposition equations, but all models predict the same trends as functions of particle diameter and breathing

parameters [13]. However, Hofmann's study compares results obtained with systematically different models, where the methods used in the calculations can also contribute to the differences between deposition fractions, while the two models used in our study differ only in the way they consider the sequence of tubes that make up the airways, thus our results reflect the pure effect of asymmetry vs. symmetry of the airways. At the same time, there are studies which report considerable differences in regional deposition values when comparing results obtained with models using different lung geometries [34,35,36], similarly with our study, which predicts differences as high as 27.6% in the acinar region. It should be noted however that the higher bronchial and lower acinar deposition values predicted by the symmetric model compensate each other when we compare the total deposition values of the two models.

Given these results, the question arises, why should we use a more complex, asymmetric model in favour of a simpler, symmetric one, when the results are so similar? The answer is simple given the higher number of modifiable input parameters, which allow a more realistic simulation and inherently a better description of the processes that take place in the respiratory tract. In addition, modelling individual variability in lung morphometry or quantifying the amount of deposited particles in the different lobes of the lungs are only possible with an asymmetric model. Nevertheless, simple symmetric models may still be used when these issues are not important.

Further studies are needed to assess the effect of other types of lung morphometry modifications (such as the obstruction of the airways during an asthma attack) on the deposition of inhaled particles.

Conclusions

Our study shows that in identical breathing conditions the deposition of inhaled particles is dependent mainly on particle size, and to a smaller extent on the lung geometry the models are built on. Deposition fractions yielded by a symmetric model are highly similar to those obtained with an asymmetric one, the differences amounting to a maximum of 4.6% in the bronchial region, and these differences reach 27.6% in the acinar region only for particles smaller than 0.1 μm, signalling a shift in the deposition of inhaled particles from the acinar region towards the bronchial region.

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