Convective flow dominates aerosol delivery to the lung segments

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Submitted 15 July 2010; accepted in final form 5 April 2011

Darquenne C, van Erbruggen C, Prisk GK. Convective flow dominates aerosol delivery to the lung segments. J Appl Physiol 111: 48–54, 2011. First published April 7, 2011; doi:10.1152/japplphysiol.00796.2010.—Most previous computational studies on aerosol transport in models of the central airways of the human lung have focused on deposition, rather than transport of particles through these airways to the subtended lung regions. Using a model of the bronchial tree extending from the trachea to the segmental bronchi (J Appl Physiol 98: 970–980, 2005), we predicted aerosol delivery to the lung segments. Transport of 0.5- to 10-μm-diameter particles was computed at various gravity levels (0–1.6 G) during steady inspiration (100–500 ml/s). For each condition, the normalized aerosol distribution among the lung segments was compared with the normalized flow distribution by calculating the ratio (Ri) of the number of particles exiting each segmental bronchus i to the flow. When Ri = 1, particle transport was directly proportional to segmental flow. Flow and particle characteristics were represented by the Stokes number (Stk) in the trachea. For Stk < 0.01, Ri values were close to 1 and were unaffected by gravity. For Stk > 0.01, Ri varied greatly among the different outlets (Ri = 0.30–1.93 in normal gravity for 10-μm particles at 500 ml/s) and was affected by gravity and inertia. These data suggest that, for Stk < 0.01, ventilation defines the delivery of aerosol to lung segments and that the use of aerosol tracers is a valid technique to visualize ventilation in different parts of the lung. At higher Stokes numbers, inertia, but not gravitational sedimentation, is the second major factor affecting the transport of large particles in the lung.

aerosol transport; computational fluid dynamics; gravity; inertia

useful in better understanding the distribution of inhaled drugs. Such knowledge would also allow assessment of the validity of using aerosols as a tracer in studies of ventilation distribution. Indeed, aerosols labeled with radioactive tracers (e.g., 99mTc) are often used in such studies, as they allow more time for scintigraphic measurements (26) than do radioactive gases with shorter half-lives (37).

The main goal of the present study was to determine the mechanisms responsible for the spatial distribution of inhaled aerosols within the human lung. Unlike previous studies that focused on the deposition of aerosol in the central airways (22, 25, 36), this study focuses on the transport of particles through these airways and their subsequent delivery to the lung periphery. We used a model of human airways developed by van Erbruggen et al. (36). Using computational fluid dynamics (CFD), we predicted the distribution of inhaled aerosols delivered to the lung segments for various flow rates, particle sizes, and gravity levels in an attempt to identify the most significant factors affecting aerosol transport to the lung periphery.

METHODS

Model and simulations. The model used in the simulations is described in detail elsewhere (36). Briefly, the geometric model is based on the morphometric data of Horsfield et al. (13) for branch length, diameter, and branching angles and on bronchoscopic and computer tomography images for spatial orientation of the airways. The model extends from the trachea down to the segmental bronchi and comprises a total of 17 bifurcations (Fig. 1, left panel). Each bifurcation is discretized with a structured butterfly mesh using a multiblock meshing approach. The total number of computational nodes is 2,300,000, with an average of 100,000–150,000 nodes for each bifurcation unit making up the model. To ensure accurate predictions of particle transport and deposition, particular attention was given to the quality of the mesh: the orthogonality of 99.99% of the cells having an expansion ratio 10.220.33.4 on October 15, 2017 http://jap.physiology.org/ Downloaded from http://jap.physiology.org/ by 10.220.33.4 on October 15, 2017 Copyright © 2011 the American Physiological Society http://www.jap.org
order explicit Runge-Kutta scheme was used for time discretization (36). Because the exit branches are relatively short, flow was never fully developed in the exit sections. To avoid any influence of the boundary conditions on the computed flow field, each segmental branch was artificially lengthened with a straight tube, the length of which ensured that the exiting flow was fully developed. The artificially lengthened regions were only used for the flow simulations, not for the computation of particle transport. The use of a mean flow approach was chosen on the basis of its ability to correctly predict particle deposition in the large conducting airways (22).

The transport of 0.5- to 10-μm-diameter particles was computed using a Lagrangian approach for flow rates of 100–500 ml/s and for gravity levels ranging from zero (0 G) to 1.6 times normal gravity (1.6 G). When a particle encountered a wall of the structure, it was presumed to be deposited, and the particle was no longer considered in the simulation. The distribution of the aerosol exiting each outlet, i.e., the delivery of aerosol to each segment of the lung, was then determined. For the range of particle sizes considered here, Brownian diffusion was negligible (1, 9), and the main forces acting on the particles were the drag force and the gravitational force. Aerosol concentrations were dilute enough (volume fraction of particles <10%) that particle interactions were negligible, and, as such, the presence of particles had no effect on the flow. Therefore, all particle simulations were performed using the postprocessor of the CFD package. This approach is similar to that previously used (36).

**Data analysis.** For each combination of flow rate (Q), particle size \(d_p\), and gravity level (G), the normalized aerosol distribution \(N_{AE,i}\) among the lung segments was calculated by dividing the number of particles exiting each segmental bronchus by the total number of particles exiting the model, i.e., in each lung segment \(i\):

\[
N_{AE,i} = \frac{n_{AE,i}}{\sum_j n_{AE,j}} \quad (1)
\]

where \(n_{AE,i}\) is the number of particles exiting the segmental bronchus \(i\). The normalized aerosol distribution was then compared with normalized flow distribution \(N_{Q,i}\):

\[
N_{Q,i} = \frac{Q_i}{\sum_j Q_i} \quad (2)
\]

where \(Q_i\) is the flow exiting the segmental bronchus \(i\), by calculating the ratio

\[
R_i = \frac{N_{AE,i}}{N_{Q,i}} \quad (3)
\]

When \(R = 1\), particle transport is directly proportional to the flow, and, in that circumstance, the sole determinant of particle transport is convective flow. When \(R\) differs from 1, aerosol transport is relatively greater (\(R > 1\)) or smaller (\(R < 1\)) than gas flow. The distribution of \(R\) was characterized by relative dispersion (RD; SD/mean): the higher the RD, the less the proportionality exists between aerosol transport and airflow. By definition, the average of \(R\) over all outlets is 1; therefore, RD is equal to the SD of the distribution.

Each path leading to an outlet of the model was characterized by a path length \(L_i\) and a cumulative angle \(\theta\). These parameters are listed in (Fig. 1, right panel). \(L_i\) was defined as the sum of the length of each airway from the entrance of the model to the outlet \(i\) and, thus, characterizes the total length particles must travel to reach a lung segment. The cumulative angle \(\theta\) was defined as the sum of the branching and the rotational angle of each bifurcation between the entrance of the model and the outlet \(i\). The branching angle was defined as the angle between coplanar parent and daughter branches. The rotational angle was defined as the angle between two successive bifurcation planes. Therefore \(\theta\) characterizes the total turning angle particles experience leading to a lung segment.

Statistical analysis was performed using Systat version 5.03 (Systat, Evanston, IL). Data were grouped in different independent variables such as G level (0, 1, and 1.6 G), particle size \(d_p\) (0.5, 1, 2, and 10 μm), and flow rate \(Q = 100, 300, \text{ and } 500 \text{ ml/s}\). A one-way analysis of variance for correlated samples was performed to test for differences between the chosen independent variables \(d_p\), G, and Q). Post hoc testing using Bonferroni’s adjustment was performed for tests showing significant F ratios. Significant differences were accepted at \(P < 0.05\).

**RESULTS**

**Effect of gravity.** A first series of simulations was performed for 0.5-, 1-, 2-, and 10-μm-diameter particles for conditions representative of light exercise at a mouth flow rate of 500 ml/s. For each particle size \(d_p\), simulations were performed at different gravity levels, i.e., 0, 1, and 1.6 G, corresponding to levels previously studied experimentally in parabolic flights, to study the effect of gravity (6, 8, 9). Data obtained for 0.5- and

<table>
<thead>
<tr>
<th>Outlet number</th>
<th>(L_i), mm</th>
<th>(\theta_i), deg</th>
<th>Flow, %</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>153</td>
<td>158</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>156</td>
<td>210</td>
<td>3</td>
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<tr>
<td>3</td>
<td>160</td>
<td>226</td>
<td>10</td>
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<tr>
<td>4</td>
<td>179</td>
<td>318</td>
<td>4.5</td>
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<td>5</td>
<td>179</td>
<td>300</td>
<td>4.5</td>
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<tr>
<td>6</td>
<td>162</td>
<td>246</td>
<td>6.2</td>
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<tr>
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<td>193</td>
<td>353</td>
<td>7.3</td>
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</tbody>
</table>
10-μm-diameter particles are shown in Fig. 2, A and B, respectively, where $R_i$ values are plotted as a function of $L_i$ and $\theta_i$. For 10-μm-diameter particles, there was a significant effect of gravity on $R_i$ ($P < 0.001$, Fig. 2B) unlike for 0.5-μm-diameter particles (Fig. 2A). Similarly, for predictions made with 1- and 2-μm-diameter particles, there was no significant effect of gravity on $R_i$ values only for 10-μm-diameter particles ($P < 0.001$). $d_{p}$, Particle diameter.

![Fig. 2. Effect of gravity on ratios ($R_i$) of normalized aerosol distribution to normalized flow distribution for a mouth flow rate of 500 ml/s. Data are plotted as a function of $L_i$ and $\theta_i$ for 0.5-μm-diameter particles (A) and 10-μm-diameter particles (B). $\bullet$, Data for each outlet $i$ obtained at 0 G; thick vertical line, range of $R_i$ between 0 and 1.6 G. There was a significant effect of gravity on $R_i$ values only for 10-μm-diameter particles ($P < 0.001$). $d_{p}$, Particle diameter.](image)

Table 1. Effect of particle size, gravity level, and flow rate on relative dispersion of $R_i$

<table>
<thead>
<tr>
<th>$d_{p}$, μm</th>
<th>Gravity</th>
<th>Flow Rate, ml/s</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0 G</td>
<td>1 G</td>
</tr>
<tr>
<td>0.5</td>
<td>0.048</td>
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</tr>
<tr>
<td>1</td>
<td>0.049</td>
<td>0.049</td>
</tr>
<tr>
<td>2</td>
<td>0.054</td>
<td>0.054</td>
</tr>
<tr>
<td>10</td>
<td>0.384</td>
<td>0.421*</td>
</tr>
</tbody>
</table>

Simulations were performed at a flow rate of 500 ml/s to determine the effect of gravity and in normal gravity (1 G) to assess the effect of flow rate. $R_i$, ratio of normalized aerosol distribution to normalized flow distribution for bronchus $i$; $d_{p}$, particle diameter. *Significantly different from 0 G ($P < 0.0$). †Significantly different from 100 ml/s ($P < 0.05$). ‡Significantly different from 300 ml/s ($P < 0.05$).

Fig. 3. Effect of flow rate on ratios of normalized aerosol distribution to normalized flow distribution. Data are plotted as a function of $L_i$ and $\theta_i$ for 10-μm-diameter particles in normal gravity (1 G). $\bullet$, Data for each outlet $i$ obtained at flow rate of 500 ml/s; thick vertical line, range of $R_i$ between 100 and 500 ml/s. There was a significant effect of flow rate on these ratios ($P < 0.0001$). The Stokes number is a measure of the importance of inertial effects in determining particle trajectories and is defined for each segmental airway $i$ by

$$\frac{2 \gamma}{\rho d_{p}^{2} u}$$

Effect of gravity. A second series of simulations was performed to determine the effect of gravity on the distribution of aerosol within the lung segments. These simulations were performed in normal gravity (1 G) for 10-μm-diameter particles, the particle size shown to be sensitive to gravity, and for a mouth flow rate of 100–500 ml/s (Fig. 3). There was a significant effect of flow rate on $R_i$ ($P < 0.0001$; Table 1). Relative dispersion increased linearly with increasing flow rate ($R^2 = 0.99$).

Data are also presented in terms of segmental Stokes number (Fig. 4). The Stokes number is a measure of the importance of inertial effects in determining particle trajectories and is defined for each segmental airway $i$ by

$$\frac{2 \gamma}{\rho d_{p}^{2} u}$$

Fig. 4. Data are presented in terms of segmental Stokes number (Fig. 4). The Stokes number is a measure of the importance of inertial effects in determining particle trajectories and is defined for each segmental airway $i$ by $\frac{2 \gamma}{\rho d_{p}^{2} u}$.
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![Fig. 4. Ratios of normalized aerosol distribution to normalized flow distribution to segmental Stokes number (Stk) for mouth flow rates of 100 (•), 300 (○), and 500 (△) ml/s. Data could be approximated by a logarithmic decay, with \( R^2 = 0.64, 0.62, \) and 0.51 for mouth flow rates of 100, 300, and 500 ml/s.](http://jap.physiology.org/)

\[ \text{Stk}_i = \frac{\rho_p d_i^2 u_i}{18 \mu d_i} \]  

where \( \rho_p \) and \( d_i \) are the particle density and diameter, respectively, \( u_i \) and \( d_i \) are the mean velocity and diameter of outlet \( i \), and \( \mu \) is the dynamic viscosity of air. For each flow rate, data could be approximated by a logarithmic decay (Fig. 4). The lower the mouth flow rate, the tighter was the correlation between \( R_i \) and Stk, and the smaller the deviation of \( R_i \) from unity.

**Particle deposition.** Finally, for validation purposes, particle deposition was computed for all cases performed in normal gravity and compared with experimental data obtained by Zhang and Finlay (41) in an in vitro model of airway bifurcations based on data of Horsfield et al. (13) (comparable to the model used in this study) and with data obtained by Schlesinger and Lippmann (32) in a hollow cast of lung airways. Comparison is shown in Fig. 5, where deposition is plotted as a function of an inertial parameter defined as \( \rho_p d_i^2 Q \), where \( \rho_p \) and \( d_i \) are the particle density and diameter, respectively, and \( Q \) is the mouth flow rate. A good agreement was found between predictions from the present study and data of Zhang and Finlay. Deposition was consistently higher in the study of Schlesinger and Lippmann than in the present study. This would be expected, as the airway cast of Schlesinger and Lippmann included more airway generations (up to 15) than the model used here (up to 7). Finally, comparison between experimental data of generational deposition efficiencies (42) with predictions from this model also showed good agreement (data not shown).

**DISCUSSION**

Particle transport and deposition in realistic lung airway structures have been extensively investigated using CFD techniques (22, 25, 36, 38). The lung models ranged from a simple airway bifurcation to more complex airway trees, including the mouth, larynx, and up to 10 generations of conducting airways (22). Even the most complex of these models of central airways only covered a small portion of the lung in terms of surface area. The lung beyond the airways included in these models represents >90% of the total lung volume and >99% of surface area on which particles may deposit. Therefore, while most of the previous computational analyses have focused on aerosol deposition in the large and medium airways, it is also important to understand the mechanisms by which inhaled aerosols are transported beyond these airways. This is the topic of the present study, in which we determined the delivery of aerosols to the lung segments, i.e., the aerosol distribution at each outlet of our model. Such analysis was done for different flow rates, particle sizes, and gravity levels to identify the main mechanisms that govern the transport of particles in the distal lung.

The particle sizes used in this study spanned the range of inhalable particles, the transport of which is mainly affected by gravity and inertia. The small particles were chosen to reflect the behavior of fine particulate matter (PM2.5), and the 10 μm-diameter particle size was chosen as the upper limit of coarse particulate matter (PM10); these classifications are commonly used to distinguish between fine and coarse airborne particulate matter in epidemiological studies on their effect on a population’s health. Also, the small particle sizes are typical of pharmaceutical drugs delivered to the lung periphery. Previous studies showed that these small particles have an ~80% chance of reaching the lower airways, with 50–60% being deposited in the alveoli (2, 18, 28, 29).

Data show that, for 0.5- to 2-μm particles, \( R \) of normalized aerosol distribution to normalized flow distribution lay in a tight range of 0.85–1.07 for all but two outlets of the model and that these ratios were unaffected by gravity level and particle size (Fig. 2A, Table 1). By definition, \( R = 1 \) means that aerosol transport is proportional to flow. Therefore, our model predictions strongly suggest that aerosol transport closely follows the distribution of ventilation to most lung segments for this particle size range. Furthermore, deposition within the model was not significantly affected by gravity level and was minimal for these particle sizes (<2% in all cases; Fig. 5). These findings support the experimental observations (9) that aerosol deposition and convective mixing as measured by aerosol bolus inhalations are independent of gravity level at shallow lung depth, i.e., in the proximal region of the lung.

Unlike the situation for small (0.5- to 2-μm) particles, \( R \) varied greatly between outlets for 10-μm-diameter particles.
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For a flow rate of 500 ml/s, R was 0.30–1.93 in normal gravity (Fig. 2B), suggesting that the intrinsic mobility of these large particles has a significant effect on their distribution among the outlets of the model. Particle intrinsic motions result from diffusion, sedimentation, and inertia. For 10-μm-diameter particles, diffusion is negligible; therefore, only gravity and inertia affect R. The effect of gravity is shown in Fig. 2B, where predictions were obtained for different gravity levels (0–1.6 G) at a flow rate of 500 ml/s. The effect of inertia is displayed in Fig. 3, where R was predicted at each outlet of the model in normal gravity for flow rates of 100–500 ml/s. Data show that the smaller the flow rate and, consequently, the smaller the inertial effects, the smaller is the deviation of R from 1. While gravitational and inertial effects were statistically significant, inertia clearly had the largest effect on R, as evidenced by the very much larger difference between flow rates (Fig. 3) than between gravity levels (Fig. 2B).

One limitation of the model used in this study is that it did not incorporate the upper airway, i.e., the orolaryngeal path, and, more particularly, the glottic constriction. Previous studies (14, 22, 31, 38) have shown that flow and particle trajectories are very complex in the upper airway, including the development of turbulence that, while decaying, can be transported downstream over several generations of conducting airways (34). Choi et al. (4) studied intersubject variability of airflows in human lungs in models of the upper airways and up to seven generations of conducting airways. They showed that, depending on subject-specific airway morphology, the laryngeal jet could impinge on the tracheal wall at different locations and in different directions (i.e., toward the rear or the front wall of the trachea). They also showed that, provided a uniform velocity profile was imposed at the inlet of a simplified upper airway model that only included the larynx, most flow characteristics predicted in the complete upper airway model could be reproduced. Xi et al. (38) used a simplified model of the upper airway with a forward-sloped larynx and a rearward-sloped trachea and predicted a laryngeal jet that was skewed toward the right of the trachea, in agreement with the in vitro measurements of Corcoran and Chigier (5) on a cadaver-based throat cast. In another study, Lambert et al. (19) predicted a laryngeal jet that was skewed toward the left and rear of the tracheal wall. These studies highlight the fact that while upper airway geometry can affect flow distributions, the effect is variable, subject-specific, and, as such, not generalizable.

However, the amount of flow in each airway is not driven by flow patterns in the upper airway but, rather, by the downstream conditions, i.e., by lobar expansion. De Backer et al. (10) showed that turbulence has a negligible influence on the flow distribution between the right and left lung and that the distribution was mainly determined by the downstream lung expansion, i.e., the downstream flow partition, as assumed in flow computations performed in this study. Longest and Vinchurkar (21) showed the importance of correctly approximating inlet velocity and particle profiles in regional models of the respiratory tract. In a model of three successive generations of conducting airways, they showed that laminar and turbulent (low Reynolds number κ-ω) flow models provided good local quantitative estimation of particle deposition, provided the correct initial particle profile was specified. We performed simulations with an idealized mouth-larynx geometry connected to the trachea of the model used in this study. In this idealized upper airway geometry, the mouth was approximated by a horizontal 60-mm-long 16-mm-diameter circular tube; the pharynx was approximated by a 90° bend with a 30-mm curvature radius connected to a 20-mm-long vertical tube for a total pharyngeal length of 65 mm, consistent with average dimensions used by Stapleton et al. (33); and the larynx was based on the geometries of Katz et al. (15, 16), where the glottis was modeled by a quasi-triangular opening, the area of which was 45% of the tracheal cross-sectional area. Deposition obtained in this expanded model was similar to that obtained in the tracheobronchial tree with no upper airway when a uniform initial profile of particles was applied at the entrance of the trachea (i.e., the initial particle profile used in the present study). Such a uniform profile better approximates the blunt axial velocity profile that develops downstream of the glottis (17). Predicted deposition was systematically higher when a parabolic profile of particles was used at the inlet of the trachea than when the uniform profile was used. Therefore, even though the upper airway was not included in the model, the interpretation of predictions made in this study, where a uniform inlet condition was applied at the inlet of the trachea, should be sound and allow for demonstration of mechanisms of particle transport in subsequent lower airways.

Studies of aerosol transport in the oral extrathoracic region (11, 31) have predicted <2% deposition for 0.5- to 2-μm particles and flow rates <500 ml/s. Our simulations predicted <2% deposition in the large airways for the same small particle sizes (Fig. 5). Therefore, during oral breathing, most of these particles reach the lung segments and do so in accordance with the distribution of ventilation among the segments. This is supported by various aerosol exposure studies showing that small particles do indeed reach the central and peripheral region of the lungs that are ventilated (27, 35, 39). These are important observations when one wishes to determine the potential therapeutic effectiveness of drugs administered by inhalation therapy. Indeed, while the efficacy of drugs will depend primarily on their pharmacology, the site and extent of deposition in the respiratory tract are also key factors (24). For example, it has been shown that aerosolized insulin for diabetest (20) or aerosolized opiates for pain control (23) give better results if they reach the lung periphery.

Fig. 6. Effect of Stokes number in trachea on relative dispersion of R, for the model where the most peripheral outlets (outlets 8, 9, and 10) are pooled into a single outlet. Data suggest that for Stk < 0.01, aerosol and gas flow are distributed similarly, as evidenced by low relative dispersion.
Finally, another important consequence of our findings is that the heterogeneity of ventilation distribution resulting from the intrinsic asymmetry of the lung structure and/or from disease state will dictate aerosol transport in the lung. In other words, for a given set of flow conditions and particle sizes, we have shown that aerosol transport is a good tracer of convective gas transport. This is the case for small (0.5–2 μm) particles at a mouth flow rate of 500 ml/s and for 10-μm-diameter particles at a flow rate of 100 ml/s. It is often useful to characterize these conditions with a single parameter, i.e., the Stokes number at the model inlet. In this study, the Stokes number at the model inlet varied from 1.15 × 10⁻⁴ to 0.046. Our data suggest that, for Stk < 0.01, aerosol and gas flows are distributed in proportion to the lung segments, as shown in Fig. 6, which shows a tight relationship between aerosol transport and airflow, as evidenced by a low relative dispersion of R.4.

Aerosols labeled with fluorescence or radioactive tracers (e.g., ⁹⁹ᵐTc) are often used in ventilation studies. Radiolabeled aerosols allow more time for scintigraphic measurements (half-life on the order of hours) than radioactive gases such as ⁸¹ᵐKr or ¹³³Xe, which have shorter half-lives (13 s and 5 min, respectively) (37). Also, because radiolabeled aerosols deposit in the lungs, they facilitate topographical measurements compared with radiolabeled gases that are cleared much faster. The use of aerosol also provides simultaneous information on deposition patterns that can be useful in the evaluation of efficiency of inhaled drugs. Our study strongly supports the use of aerosol to visualize lung ventilation distribution and quantify heterogeneity of ventilation distribution in different parts of the lung. For example, Robertson and colleagues (30) used 1-μm-diameter fluorescent particles to assess ventilation distribution in the pig lung ventilated at a flow rate averaging 3.3 l/min. If it is assumed that tracheal diameter is 15 mm (40), these experimental conditions lead to a Stokes number in the trachea of 6 x 10⁻⁵, which is well below the upper limit suggested by our data. In another study involving humans, Cabahug et al. (3) measured lung ventilation using ⁹⁹ᵐTc-diethylene triamine pentaacetic acid aerosols with a mass median diameter of 1 μm and a flow rate of up to 1,000 ml/s, resulting in a Stokes number of up to 9 x 10⁻⁴, again well below the upper limit of 0.01 suggested by our study.

In conclusion, using a model of the conducting airways extending from the trachea to the segmental bronchi, we have predicted the distribution of aerosol transport to the lung periphery. Our data show that ventilation defines the delivery of aerosol to lung segments for small (0.5–2 μm) particles. This is also the case for large (10 μm) particles, provided that inhaled flow is kept low (100 ml/s), i.e., that inertia is negligible. At higher flow rates, inertia, but not gravitational sedimentation, is the second major factor affecting the transport of large particles in the lung. Our data suggest that convective flow is the main determinant of aerosol transport in the lung segments when the Stokes number in the trachea is <0.01.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES


GRANTS

This study was supported by National Institute of Environmental Health Sciences Grant ES-01177 and by the National Space Biomedical Research Institute (NSBRI) through National Aeronautics and Space Administration NCC 9-58 as NSBRI Grant TD00701. C. van Erbruggen was a Belgian-American Educational Foundation-Henri Benedictus Fellow of the King Baudouin Foundation, Belgium.

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