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.

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 aspect ratio 1.5. It was also shown in an earlier study (36) that the number of nodes used to generate the mesh was sufficient to ensure mesh-independent results. Increasing the number of nodes (and the required computational resources) resulted in velocity profile differences <2%.

Aerosol and gas transport was simulated with the FINE/Turbo software package (version 6.1, Numeca). Flow field was computed previously and is described elsewhere (36). Briefly, velocities within the geometric model were computed for steady inspiration ranging from 100 to 500 ml/s at the mouth. For each inspiratory flow, a uniform velocity profile was imposed at the inlet of the model, and flow at each outlet was assumed to be proportional to subtended lung volumes; i.e., specific ventilation was the same to all lung regions. The flow percentages computed by Horsfield et al. (13) were used to impose mass flow at each outlet of the model (Fig. 1, right panel) but one (where a static level pressure was set to avoid redundancy in the boundary conditions). Flow within the model was then determined using a finite-volume method to solve the mean flow velocities of the Reynolds-averaged Navier-Stokes equations. A central explicit second-order scheme was used for spatial discretization, while a fourth-
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 (dp), and gravity level (G), the normalized aerosol distribution (NAE) 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:

\[
N_{AE,i} = \frac{n_{AE,i}}{\sum_j n_{AE,j}}
\]

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 (NQ,i):

\[
N_{Q,i} = \frac{Q_i}{\sum_i Q_i}
\]

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

\[
R_i = \frac{N_{AE,i}}{N_{Q,i}}
\]

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 \( R_i \) 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 \( R_i \) 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 (Li) and a cumulative angle (θi), These parameters are listed in (Fig. 1, right panel). Li 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 θi 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 θi 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 (\( Q = 100, 300, \) and 500 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, \text{mm} )</th>
<th>( \theta_i, \text{deg} )</th>
<th>Flow, %</th>
</tr>
</thead>
<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>
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<tr>
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<td>160</td>
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</tr>
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<td>4</td>
<td>179</td>
<td>318</td>
<td>4.5</td>
</tr>
<tr>
<td>5</td>
<td>179</td>
<td>300</td>
<td>4.5</td>
</tr>
<tr>
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<td>162</td>
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<tr>
<td>7</td>
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<td>303</td>
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<td>186</td>
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</tr>
<tr>
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<td>180</td>
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<td>175</td>
<td>354</td>
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</tr>
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<tr>
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<tr>
<td>18</td>
<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 $R_i$, which lay in a tight range around $R_i = 1$, except for outlets 8 and 10 (Fig. 1). These outlets are the most distally located in terms of generation numbers (at the level of generations 7 and 8, respectively). The $R_i$ value of these outlets might possibly be a result of their distal location, as each bifurcation presents the potential for the aerosol transport to diverge from the distribution of gas flow. Outlets 8, 9, and 10 were pooled in a single outlet, so that there were a similar number of generations (5 or 6) leading to each outlet used in the comparisons. Relative dispersion of $R_i$ was then calculated and is shown in Table 1 for each particle size and gravity level. For 0.5-, 1-, and 2-μm-diameter particles, there was no difference in relative dispersion at any gravity level and particle size ($P > 0.01$). Only for 10-μm-diameter particles was there a significant change with gravity level ($P < 0.001$), with relative dispersion being increased with increasing gravity level.

**Effect of flow rate.** A second series of simulations was performed to determine the effect of flow rate 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

\[
\frac{d_i}{c} = \frac{d_{\text{p}}}{d_{\text{i}}} \left( \frac{\rho - \rho_{\text{air}}}{\rho_{\text{air}}} \right) \left( \frac{V_{\text{air}}}{V_{\text{p}}} \right) \frac{\Delta \rho}{\rho_{\text{air}}}
\]

where $d_{\text{p}}$ is the particle diameter, $\rho$ is the density of the particle, $\rho_{\text{air}}$ is the density of air, $V_{\text{air}}$ is the air velocity, $V_{\text{p}}$ is the particle velocity, and $\Delta \rho$ is the difference in density between the particle and the air.

**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>0 G $R_i$</th>
<th>1 G $R_i$</th>
<th>1.6 G $R_i$</th>
<th>100 ml/s $R_i$</th>
<th>300 ml/s $R_i$</th>
<th>500 ml/s $R_i$</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.048</td>
<td>0.048</td>
<td>0.048</td>
<td>0.048</td>
<td>0.048</td>
<td>0.048</td>
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<tr>
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<td>0.049</td>
<td>0.049</td>
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<td>0.049</td>
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<tr>
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<td>0.054</td>
<td>0.054</td>
<td>0.054</td>
<td>0.054</td>
<td>0.054</td>
<td>0.054</td>
</tr>
<tr>
<td>10</td>
<td>0.384</td>
<td>0.421*</td>
<td>0.430*</td>
<td>0.074</td>
<td>0.217†</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 ($P < 0.01$). †Significantly different from 100 ml/s ($P < 0.05$). ‡Significantly different from 300 ml/s ($P < 0.05$).
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 (PM_{2.5}), and the 10 μm-diameter particle size was chosen as the upper limit of coarse particulate matter (PM_{10}); 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_{i} 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.

**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.

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Unlike the situation for small (0.5- to 2-μm) particles, R varied greatly between outlets for 10-μm-diameter particles.

![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.](image)

![Fig. 5. Total deposition of particles (DE) as a function of inertial parameter (ρd^2Q). Inertial parameter reflects effect of inertia on particle transport and deposition. Predictions from this study (●, solid line) are compared with experimental data of Zhang and Finlay (41) (○) and data from Schlesinger and Lippmann (32) (△).](image)
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 Stapelton 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 diabetes (20) or aerosolized opiates for pain control (23) give better results if they reach the lung periphery.
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.

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) (26) 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 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.

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-011177 and by the National Space Biomedical Research Institute (NSBRRI) through National Aeronautics and Space Administration NCC 9-58 as NSBRRI Grant TD00701. C. van Erbruggen was a Belgian-American Educational Foundation-Henri Benedictus Fellow of the King Baudouin Foundation, Belgium.