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Application of Both a Physical Theory and Statistical Procedure
in the Analyses of an *In Vivo* Study of Aerosol Deposition

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ABSTRACT

Regional deposition of inhaled aerosols in the respiratory tract is a significant factor in assessing the biological effects from exposure to a variety of environmental particles. Understanding the deposition efficiency of inhaled aerosol particles in the nasal and oral (extrathoracic) airways provides important information for evaluating doses to the extrathoracic region as well as to the lung. Dose extrapolation from laboratory animals to humans has been questioned due to significant physiological and anatomical variations across different animal species. Although human studies are considered as the ideal for obtaining the *in vivo* toxicity information fundamentally important in risk assessment, the number of subjects in the study is often small compared to those used in epidemiological and animal studies. A well-designed experimental protocol is necessary to obtain useful information from a small-scale human study.

The purpose of the present study was to measure *in vivo* the nasal airway dimensions and the extrathoracic deposition of ultrafine aerosols in 10 normal adult males. Both measurements demonstrated significant variabilities among individuals. The nasal geometry of each individual was well characterized at a resolution of 3 mm using magnetic resonance imaging (MRI) and acoustic rhinometry (AR). The turbulent diffusion theory was used to describe the nonlinear nature of extrathoracic aerosol deposition. To determine what dimensional features of the nasal airway were responsible for the marked differences in particle deposition, the MIXed-effects NonLINEar Regression (MIXNLIN) procedure was used to account for the random effect of repeated measurements on the same subject. Using both the turbulent diffusion theory and MIXNLIN, the ultrafine particle deposition is correlated with the nasal dimensions measured by the surface area, minimum cross-sectional area, and complexity of the airway shape. The combination of MRI and AR is useful for characterizing both detailed nasal dimensions and temporal changes in nasal patency. We conclude that a suitable statistical procedure incorporated with existing physical theories must be used in data analyses for experimental studies of aerosol deposition that involve a relatively small number of human subjects.

Keywords: human study, ultrafine aerosols, nasal dimensions

INTRODUCTION

Many naturally or anthropogenic aerosols that may impose potential health effects are commonly present in our living environments: the ambient atmosphere, indoor residences and offices, and industrial workplaces. The biological response caused by inhaled particles depends on the mechanism of interaction with the target tissue and on the site where the particles are deposited in the respiratory system. Therefore, it is necessary to determine the distribution of particle deposition within the human respiratory tract for a proper evaluation of the health risks resulting from the aerosol intake. Of the many factors considered in assessing the health effects from inhaled aerosol, particle size, respiratory flow rate, and airway morphometry are the three most important parameters for characterizing the behavior of inhaled aerosols in the human respiratory airways.

Most data on the filtration efficiency of ultrafine particles in the human nasal and oral airways have been obtained from studies with physical replicate models (Yamada et al., 1988; Cheng, Y. S. et al., 1991, 1993; Swift et al., 1994). The physical replicate models used in these studies were constructed either from postmortem casts using a rubber injection technique, or from *in vivo* morphometric data using MRI. Due to tissue shrinkage in the postmortem condition, the postmortem casts are likely to represent relatively dilated airways. Although the MRI models are regarded as accurate in rendering the physical shape and configuration of the nasal airway in living individuals, the rigid and dry nature of these plastic models makes them difficult to simulate the physiological state of human airways during normal breathing. Little information is available regarding *in vivo* measurements of the deposition of ultrafine particles in the nasal and oral airways. Results obtained from humans are fundamentally essential for a comparison with the findings from deposition measurements using replicate models.

We have measured *in vivo* the nasal and oral deposition of ultrafine particles ranging from 4 to 150 nm in 10 normal adult males during inspiration and expiration. The nasal geometry of each human subject was characterized using AR and MRI techniques. The AR technique, which measures the cross-sectional areas along the nasal passage at 0.35 cm intervals, was used to determine the nasal patency at the time that subjects were actually challenged with test aerosols. The MRI measurements that were taken for each subject prior to the aerosol exposure provided contiguous coronal images in 0.3 cm thickness for the entire length of the nasal airway. Both measurements of aerosol deposition and nasal dimensions demonstrate significant variability among individuals. Based on these experimental data, this paper describes in detail the methodology used for data analysis. A statistical procedure, MIXed-effects NonLINear regression procedure (MIXNLIN), incorporated with the turbulent diffusion theory was used to model dimensional parameters of the nasal airway responsible for the biological variability in aerosol deposition.

METHODS

Mixed-effects Nonlinear Regression Model

The MIXNLIN, a SAS (SAS Institute Inc., Cary, NC) macro program, written by E. F. Vonesh is designed specifically for analysis of nonlinear models involving repeated measurements. The MIXNLIN is a combination of the SAS Base software and the SAS Macro/IML procedure, which computes estimated generalized least square or maximum likelihood to estimate population parameters of a generalized mixed-effects nonlinear regression model (Vonesh, 1992). The main difference of the MIXNLIN from the NLIN (NonLINear

Regression Procedure) is the random effect that takes into account the effects of repeated measurements on estimations of the inter- and intra-subject errors.

In the present study, every subject was repeatedly measured four times for each combination of four particle sizes, two flow rates, and four breathing patterns. The overall data set, including missing values, should be categorized as 128 repeated measurements from each of the 10 human subjects. By recognizing different inter-subject errors among individuals, a subject-specific model of the MIXNLIN was used to estimate the population parameters:

$$Y_i = f(X_i, A_i\beta + B_i b_i) + e_i \quad (1)$$

where Y_i is a vector of repeated measures on the i^{th} subject, X_i is a matrix of independent variables, A_i is the design matrix of fixed effects, β represents the fixed unknown parameters, B_i is the design matrix of random effects, b_i is a vector of inter-subject error of the i^{th} subject, and e_i is a vector of intra-subject error of the i^{th} subject.

Theory of Turbulent Diffusion

The human deposition model of ultrafine aerosols was developed based on the assumption that turbulent diffusion is the dominant mechanism as air flowing through a circular pipe. Using the relationship between the deposition velocity and the pressure drop, Cheng et al. (1993) have derived a theoretical equation for the particle penetration due to turbulent diffusion:

$$Pene = \exp\left[-b \left(\frac{A_s}{A_c}\right)^{1/2} \left(\frac{\Delta P}{\rho u^2}\right)^{1/2} \left(\frac{D}{u}\right)^{1/2}\right] \quad (2)$$

where $Pene$ is the particle penetration fraction, ΔP is the pressure drop, ρ is the density of the fluid, u is the mean flow velocity in the pipe, D is the diffusion coefficient of the particles, and ν is the kinematic viscosity of the fluid. The relationship between the ΔP and u is empirically determined as (Schlichting, 1968)

$$\frac{\Delta P}{\rho u^2} = 0.1582 \left(\frac{L}{d}\right) \left(\frac{ud}{\nu}\right)^{-1/4} \quad (3)$$

where L is the tube length, and d denotes tube diameter. Substituting equation (3) into (2) yields

$$\begin{aligned} Pene &= \exp\left[-b \left(\frac{A_s}{A_c}\right)^{1/2} (0.1582)^{1/2} \left(\frac{L}{d}\right)^{1/2} \left(\frac{ud}{\nu}\right)^{-1/8} \left(\frac{D}{u}\right)^{1/2}\right] \\ &= \exp\left[\frac{-0.3977b}{u^{3/8}} \left(\frac{A_s}{A_c}\right) \left(\frac{A_s}{L}\right)^{1/8} (D)^{1/2} (uA_c)^{-1/8}\right] \\ &= \exp\left[-b' (P_c)^{1/8} \left(\frac{A_s}{A_c}\right) (D)^{1/2} (Q)^{-1/8}\right] \end{aligned} \quad (4)$$

where b' equal to $0.3977b/\nu^{3/8}$ is a constant, P_c is the tube perimeter, and Q is volumetric flow rate in cm^3/sec . The above derived value for b' was valid only in the case of a flow in a circular tube.

Nasal Deposition Modeling

Based on studies of flow dynamics in human replicate nasal models (Swift and Proctor, 1977; Hahn et al., 1993), turbulent diffusion was confirmed to be the dominant mechanism responsible for ultrafine aerosol deposition. Theoretical derivation of turbulent flow in pipes indicated that aerosol penetration through pipes was an exponential function of pipe geometry, particle size, and flow rate. The general model of ultrafine aerosol penetration in the extrathoracic airways was formulated by

$$Pene = \exp[-K_i(A_t)^a(A_n)^b(A_{min})^c(D)^d(Q)^e(\bar{S})^f] \quad (5)$$

where K_i is a pattern-specific constant used to model aerosol deposition in different breathing paths, A_t in cm^2 is the total surface area for both right and left sides of the nose, A_n in cm^2 is the mean nasal cross-sectional area, A_{min} in cm^2 is the nasal minimum cross-sectional area, and $\bar{S}$ is the average airway shape factor (defined as the ratio of the airway perimeter to a reference perimeter calculated from the periphery of the rectangle drawn on the maximum horizontal and vertical boundaries of each 0.3 cm MRI section) for the turbinate region.

RESULTS AND DISCUSSION

A statistical test was used to determine which cross-sectional area measurement, A_{min} or A_n , was a better index for representing the effects of nasal patency on particle deposition. The best-fitted values of all the parameters in equation (5) were obtained by using the NLIN procedure. Results for parameters b (coefficient for A_n dependence) and c (coefficient for A_{min} dependence) were 0.40 and -0.64, respectively; b was also highly correlated with c . By removing one parameter at a time, the same NLIN procedure was used to fit individual models that included only A_n or A_{min} in the equation. The best-fitted value was 0.08 for b in the A_n -only model and -0.15 for c in the A_{min} -only model. Diffusional deposition of particles is derived as an inverse function of the tube cross-sectional area for a turbulent aerosol flow through a circular pipe, as shown above. From the statistical analysis, including A_{min} in the model reduced more residual than the inclusion of A_n ; that is, statistically A_{min} fits the model better than A_n . Thus, based on both the physical and statistical considerations, A_{min} was selected to represent the nasal patency, and the deposition model of equation (5) was modified as

$$Pene = \exp[-K(A_t)^a(A_{min})^c(D)^d(Q)^e(\bar{S})^f] \quad (6)$$

The MIXNLIN was used to fit the entire experimental data into equation (6). Table I shows the results of the best estimates for each parameter. An important finding from this analysis was that the absolute values of a and c were similar. As shown in equation (4), particle losses to the pipe walls by diffusion from turbulent flow are a function of A_t/A_n . By recognizing both the similarity in deposition mechanism and the difference in geometry between circular pipes and human nasal airways, $(A_t/A_{min})^a$ was used to substitute $(A_t)^a(A_{min})^c$ in equation (6) for the final human deposition model. Also included in the final model was the $\bar{S}_t$. This yields

$$Pene = \exp[-K(\frac{A_t}{A_{min}})^a(Diff)^b(Flow)^c(\bar{S}_t)^d] \quad (7)$$

Table 2 shows the final results of parameter estimates using the format of equation (7). Both coefficients for particle size and flow rate, h and i , were highly significant ($p < 0.001$). The effect of A_i/A_{min} on particle deposition was weaker than that derived from the theory of turbulent pipe flow, and the estimate g was significant at the 95% confidence level ($p < 0.05$). Although only marginally significant ($p = 0.084$), the estimate 1.24 for the $\bar{S}_i$ -dependence had the strongest effect on particle deposition. The large standard deviation of j was probably due to a marked increase of intra-subject variation as a result of considering the random effect of 128 repeated measurements corresponding to only a single $\bar{S}_i$ for each subject. It was not surprising to find an insignificant estimate for K , because the inspiration and expiration data were pooled to determine the common estimates for the dependence of particle size, flow rate, and nasal dimensions. Based on the above analyses, a best fitted geometry-related diffusion parameter was developed as $(A_i/A_{\text{min}})^{0.27}(D)^{0.39}(Q)^{0.28}(\bar{S}_i)^{1.24}$.

CONCLUSIONS

This report describes a methodology for analyzing an in vivo study that involves repeated measurements of aerosol deposition in the human nasal and oral airways. Using both the turbulent diffusion theory and MIXNLIN, the ultrafine particle deposition is correlated with the nasal dimensions measured by the surface area, minimum cross-sectional area, and complexity of the airway shape. We conclude that a suitable statistical procedure incorporated with existing physical theories must be used in data analyses for experimental studies of aerosol deposition that involve a relatively small number of human subjects.

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Table 1 Parameter Estimates for $Pene = \exp[-K(A_e/A_{min})^a(D)^c(Q)^e]$

Parameter	Estimate	Standard Deviation	Lower 95% Limit	Upper 95% Limit	P Value
K	0.58	0.28	0.03	1.13	0.041
a (for A_e)	0.45	0.61	-0.74	1.64	0.460
c (for A_{min})	-0.34	0.09	-0.51	-0.17	< 0.001
d (for D)	0.36	0.01	0.35	0.38	< 0.001
e (for Q)	-0.28	0.03	-0.33	-0.23	< 0.001

Table 2 Parameter Estimates for $Pene = \exp[-K(A_e/A_{min})^g(D)^h(Q)^i(\bar{S}_e)^j]$

Parameter	Estimate	Standard Deviation	Lower 95% Limit	Upper 95% Limit	P Value
K	1.28	0.87	-0.43	2.99	0.142
g (for A_e/A_{min})	0.27	0.08	0.11	0.44	0.001
h (for D)	0.39	0.01	0.37	0.40	< 0.001
i (for Q)	-0.28	0.02	-0.32	-0.23	< 0.001
j (for $\bar{S}_e$)	1.24	0.71	-0.16	2.65	0.084

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