Aerosol Deposition as a Function of Airway Disease: Cystic Fibrosis

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A mathematical model of aerosol deposition has been developed for drug delivery protocols and used successfully to simulate inhalation exposure tests with human subjects. Therefore, we have used the validated model to address the delivery of inhaled pharmaceuticals as a function of disease-induced changes in airway structure. Clinical data from the literature had suggested that progressive lung disease associated with cystic fibrosis (CF) could compromise the successful administration of pharmacologic drugs used in its treatment, hence it was studied. We described the lungs of patients inflicted with CF by different morphologies (representing the processes of airway obstruction, infection and inflammation) than healthy (control) subjects. Affected ventilatory parameters were also examined to demonstrate their effects upon drug disposition. Particle distributions were computed on a generation-by-generation basis. Deposition patterns were dramatically affected by CF-produced alterations in dimensions. The reduced airway caliber in CF enhanced the total dose delivered to the tracheobronchial compartment by 200-300% relative to controls. The spatial distributions of aerosols were completely different in CF patients, being selectively deposited within congested airways. In medical practice the model can be tailored to any specific airway disease. Regarding targeted delivery, the results have relevance to (1) site-specific acting pharmaceuticals in tracheobronchial airways and (2) drugs designed for systemic delivery via deposition in alveolated airways.

KEY WORDS: aerosol therapy; inhaled drugs; cystic fibrosis; targeted delivery.

INTRODUCTION

A mathematical model describing the airborne behavior and deposition characteristics of inhaled pharmacologic drugs has been developed (1). The model has been *validated* by comparisons of calculated deposition patterns with data from inhalation exposures using volunteer human subjects (2).

Clinical investigations have established causal relationships between sites of deposition of pharmacologic drugs and patient response in the treatment and prophylaxis of respiratory tract diseases, for example, asthma. Recently, computer simulations of aerosol deposition in such medical trials have been successfully performed (2-3) using the aforementioned model. The predicted deposition patterns agreed with those observed in the medical arena.

The systematic modeling efforts (1-3) suggest that the selective distributions of medicines within the lung may directly lead to aerosol therapy protocols that are more effective and efficient. The protocols would be more effective because drugs could be targeted to appropriate sites to elicit optimum therapeutic effects, and more efficient because large quantities of drugs would no longer have to be disseminated throughout the lung to deliver required quantities to desired locations. In a real sense, preferential deposition may be regarded as improving the efficacy of an existing pharmaceutical.

We believe that targeted delivery may be a valuable technique to be explored in the treatment of airway diseases. Therefore, we have used the aforementioned mathematical model to determine (i) the role of ventilatory parameters and (ii) and the effect of changes in airway dimensions upon drug deposition patterns within cystic fibrosis (CF) patients.

All CF patients will eventually develop chronic obstructive lung disease (COLD) regardless of the initial sites of disease manifestation including the pancreas, gastrointestinal tract, hepatobiliary system, and genitourinary system (4). Indeed, lung disease accounts for over 90% of CF mortality (5). From this perspective, it may be regarded as the most common and important manifestation of CF.

The research of Anderson et al. (6), Turpin and Knowles (7) and Kavanaugh et al. (8) has suggested that COLD could have a considerable influence on the successful administration of pharmacologic drugs used in treatment. Anderson et al. (6) studied the distribution patterns of discrete, well-defined volumes (i.e., boluses) of inhaled *monodisperse aerosols* in CF patients. They wrote: "We conclude that bolus spreading and deposition are increased in proportion to the severity of obstructive lung disease such as cystic fibrosis." By using the validated model of Martonen (1) to elucidate which factors affect deposition, and quantitating their effects, we suggest that drugs may be administered more effectively and efficiently in the treatment of CF. That is, if the efficacies of inhaled pharmacologic drugs can be improved by delivering them to appropriate sites (e.g., receptors and sensitive cells) then it is important to identify the effects of disease states per se upon deposition.

Regarding the administration of pharmaceuticals via inhalation, we will investigate whether the *sites* of deposition within lungs vary with morphology and breathing, and whether the *quantities* deposited differ notably.

METHODS

The new approaches for the medical treatment of CF via inhaled particles include: gene therapy, amiloride aerosol, anti-inflammatory drugs, and DNAase aerosol (7). Herein, we shall focus upon how to employ mathematical modeling techniques to assist the physician in targeting the delivery of

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inhaled pharmaceuticals. Agnew (9) has explored the use of modeling to study aerosol deposition and respiratory disease, including CF. We have expanded on that work to systematically examine effects of morphology and ventilation.

Simulation of Cystic Fibrosis

In the lung, the most obvious feature of CF is the hypersecretion of very viscous mucus which congests airways. Thereafter, the characteristic cycle of obstruction, infection and inflammation begins. Konstan and Berger (10) observed that once the "vicious cycle" becomes established, even gene therapy may not stop progressive damage to the lung. Indeed, persistence of infection and inflammation may culminate in bronchiectasis (destruction and permanent ectasia of the tracheobronchial airways) which progresses to respiratory failure and death (7). Therefore, recognition of interactions between infection and inflammation would be crucial components of medical protocols, such as antimicrobial therapy.

A decrease in airway caliber may be attributed to an increased mucus layer, airway infection or airway inflammation, or a combination of these factors, as discussed previously. The contributing authors of *Cystic Fibrosis* (11) consistently reported that airways can eventually become "clogged" or "plugged" with CF. This would obviously indicate that in the extreme, airways are closed. We will consider airways that are at least partially open and thereby permit the delivery of inhaled drugs. In future endeavors, as data become available which describe the closure of such airways and their locations, the effects could be modeled.

In Table I the way in which cystic fibrosis is simulated by mucus, infection or inflammation-induced changes in airway diameters is identified. For brevity only three cases are presented: a control and reductions of TB tree diameters by 20% and 40%. Other reductions in airway caliber (e.g., 5, 10, and 30%) were examined in this work; the calculated particle deposition patterns were intermediate to the aforementioned cases.

Effects of Mucus on Airflow

Medical issues specifically related to the production, properties and function of mucus have been the foci of manuscripts (12-16). However, surprisingly little has been reported concerning the absolute dimensions of mucus layers in healthy or diseased states such as CF. Likewise, the effects of infection and inflammation in CF upon airway caliber have not been systematically examined and quantitated. Although the dimensions of mucus layers within individual airways and the variation of mucus thickness with position in the lung has been measured in certain surrogate laboratory animals, not much is known about conditions in the human lung (17). King et al. (18) suggested that the ratio of mucus thickness to airway radius will seldom exceed 0.20 even for cases of hypersecretion. We are not aware of analogous data which quantitate effects of either infection or inflammation upon airway caliber.

In surrogates, the effects of an increased thickness in the mucus layer (conversely, a reduction in the lumen of an airway) upon resistance to airflow has been investigated under various conditions. Clarke et al. (19) and Clarke (20) studied steady flows in laboratory systems consisting of glass tubes lined with sputum or mucus simulants (i.e., polymer solutions). King et al. (18) examined steady and pulsatile flows in plastic tubes lined with gels having rheological properties comparable to mucus. The results of the laboratory tests were quite remarkable. When either the volumetric flow rate for steady motion was small, or the amplitude of oscillatory motion was small, the resistance to airflow with increasing depths of the surrogate mucus layers was as to be anticipated for simple constrictions in airway diameters. But, at certain higher steady-flow and oscillatory-flow values the resistance increased markedly beyond that expected for a reduction in airway lumen. This increase was of an enormous magnitude and was demonstrated to be due to the creation of "standing waves" in the surrogate mucus layers.

As noted previously, cystic fibrosis is an airway disease characterized by the hypersecretion of mucus. It is important, therefore, that a relative measure of the mucus layer be known. The aforementioned standing waves produced in the mucus lining at high flow rates will serve to further congest the airways beyond the mucus layer-to-airway radius ratio of 0.20 measured by King et al. (18).

Definition of Mathematical Model

A mathematical model has been developed by Martonen (1) in a format specifically designed for easy adaptation into drug delivery protocols. The model has been used successfully to simulate clinical inhalation exposure tests with human subjects and drug trials (2-3).

Although the model is detailed in the cited manuscripts, a few brief comments about it may be prudent at this juncture. The computer code describes the passage of a prescribed volume of aerosolized drug throughout the human lung during a complete breathing cycle of inspiration, pause, expiration, pause. The morphology of the adult human lung is described by the data of Weibel (21). A symmetric morphology has been demonstrated to be a suitable surrogate for particle deposition modeling purposes (22). The actual dimensions (i.e., airway diameter and length) of the morphology may be easily varied on a computer run-by-run basis to allow the physician to address issues related to intersubject variability. Patient respiration is classified by the ventilatory parameters of tidal volume and breathing frequency, which are input data for each simulation. During transport, particles are continuously removed from the inhaled aerosol (i.e., deposited upon airway surfaces) by the mechanisms of sedimentation, inertial impaction and diffusion. The processes have been formulated by Martonen (23). The input data used to characterize the drug particles are size, shape and density. The fluid dynamics patterns within the lung are physiologically realistic, including the depiction of laminar-to-turbulent flow transitions in the upper TB tree and developing velocity profiles in the peripheral airways. The output of the program includes: total deposition in the lung, breakdown of the total on a TB and P compartmental basis, and resolution of deposition on an airway generation-by-generation basis.

In this text deposition within the lung will be normalized to the quantity of aerosol entering the trachea. That is, only particles that have penetrated the extrathoracic (ET) region (contiguous airways of the head, throat and larynx) will be

addressed. We will do so because, as recognized in the review by Stahlhofen et al. (24), most data from inhalation exposure experiments are presented in such a format.

Naturally, in the clinical arena it may be of interest to quantitate aerosol losses in the ET airways. This can be accomplished in a straightforward manner. Various empirical formulas have been presented in the literature (1, 24-26) which permit deposition in the ET region (inclusive of the mouth and nose, their associated pharyngeal passages, and larynx) to be determined as desired. The particle-filtering efficiency can be considerable. According to the work of Martonen (1), cumulative aerosol losses within the oropharyngeal and laryngeal passages for drugs administered via mouth inhalation can easily exceed 70% for either dry powder inhalers (DPIs) or metered dose inhalers (MDIs).

Ventilatory Parameters

Breathing is a key factor to be monitored in an aerosol therapy protocol. The adult conditions (27) we shall simulate are: sedentary (tidal volume = 500 ml, frequency = 14 breaths/min, minute volume = 7 L, inspiratory flow rate = 14 L/min) and light activity (tidal volume = 1291 ml, frequency = 15.5 breaths/min, minute volume = 20 L, inspiratory flow rate = 40 L/min). In the medical arena the parameters may represent intersubject variabilities to be anticipated among a population. For example, the values could indicate situations when different patients are instructed by clinicians to breath in like manner (e.g., to breath "normally" or "slowly and deeply") during drug administration.

Of course, it may not be possible for patients to substantively regulate their breathing parameters because of disease-imposed restrictions upon lung performance. For instance, Turpin and Knowles (7) have observed that CF patients often revert to rapid, shallow breathing patterns. The important point is that our model can actually mimic these real situations observed by physicians.

Aerosol Properties

The particle geometric diameters (D_g) in the simulations will vary from 0.1 to 10 μm. The corresponding aerodynamic diameters of spherical particles of density ρ are: $\rho^{1/2}\ D_g\ C(D_g)$, where the latter term is the particle slip correction factor. These values encompass the size spectrums present in typical polydisperse aerosols (28) produced in the clinical laboratory by nebulizers, MDIs and DPIs.

Martonen and Katz (3) have specifically addressed the effects of polydispersity upon deposition and demonstrated the relative significance of the mechanisms of diffusion, inertial impaction and sedimentation in aerosol therapy protocols. The respective deposition processes are usually most effective in notably different regions of the lung under quite different breathing conditions. For instance, diffusion is efficient in the alveoli, sedimentation is efficient in the peripheral airways during slow deep breathing, and inertial impaction is efficient in the large TB passages during rapid breathing. Naturally, overall deposition in the lung is a complex interplay of these mechanisms.

At this juncture, it must be emphasized that monodisperse aerosols are routinely produced in research laboratories when inhalation studies are performed with human test subjects. Numerous experiments have been itemized in the review work of Stahlhofen et al. (24) and more recently by Martonen and Katz (2,3). It is important to note that monodisperse aerosols are produced by commercial instrumentation which operate on vastly different physical principles, such as the spinning top and condensation generators, which can be tailored to particular laboratory needs. Such instrumentation, therefore, is adaptable to the clinical environment. Indeed, the medical team of Anderson et al. (6) *have used monodisperse aerosols with CF patients.*

Use of monodisperse aerosols eliminates experimental artifacts arising from polydispersity (perhaps the most salient being nonuniform dispersion within the lung) a priori. Thus the site of drug deposition can be related to a patient's therapeutic response in a straight-forward manner. Obviously, this is a very important consideration since human subject inhalation exposures, drug testing and clinical trials are time consuming, closely regulated and expensive.

RESULTS AND DISCUSSION

To support the applicability of our work in the medical arena, we consulted physicians directly and inquired how they would like us to describe disease-induced airway changes in their patients. Accordingly, we simulated both highly localized and widely dispersed cases of CF by introducing appropriate modifications to our control algorithm (i.e., AC = 1.0 in the next paragraph) for lung morphology. We conducted an extensive and systematic examination encompassing three fundamental patterns of spatial changes in lung dimensions. (1) We *blocked* airflow to prescribed regions (e.g., designated lobes) by completely closing airways selected by some physicians. (2) We *restricted* airflow to regions identified by other physicians by reducing proximal (i.e., upstream) airway diameters. (3) Certain physicians requested that we *regulate* airflow within the whole, contiguous TB tree. During the review process it was recommended that, for brevity, we limit our discussion to case (3).

The validated mathematical model (1-3) will now be used in a systematic fashion to examine the behavior of inhaled pharmacologic drugs as functions of both the degree of airway disease and a patient's commensurate ability to regulate breathing. The lung of a healthy subject will be defined by Weibel's (21) morphology; it will be the control case in our computations. That is, the effects of disease—as manifest in altered airway dimensions—upon deposition patterns will be evaluated relative to the normal lung.

In Figures 1-2 deposition is presented as a function of inhaled drug size for a prescribed range of respiratory intensities. Since the lung has different clearance mechanisms, the TB and P compartments are separated in Panels A and B. The ordinates of the figures are normalized to the aerosol quantity entering the trachea. The term "AC" denotes "airway coefficient", see Table I. The AC curves signify that Weibel (21) diameters have been multiplied by those respective values. For instance, an airway caliber change of −20% is represented by AC = 0.80. The ventilatory parameters were defined previously.

The curves of Figures 1-2 are almost self-explanatory, however, a few comments may be in order to put the results into perspective. Let us address, in order, the distribution of

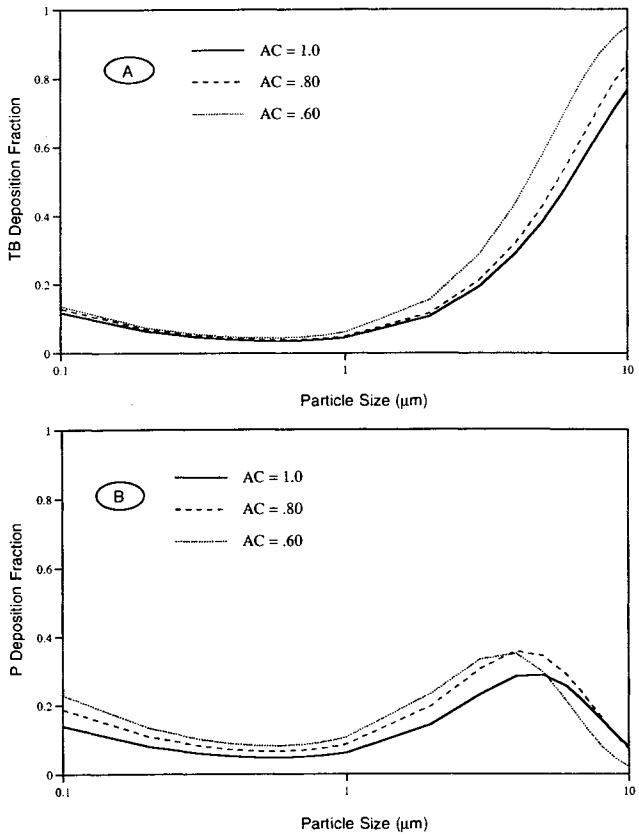

Fig. 1. Effects of airway dimensions upon aerosol deposition in the TB (Panel A) and P (Panel B) compartments of adult human subjects, healthy or with respiratory disease. *Sedentary* breathing conditions are addressed.

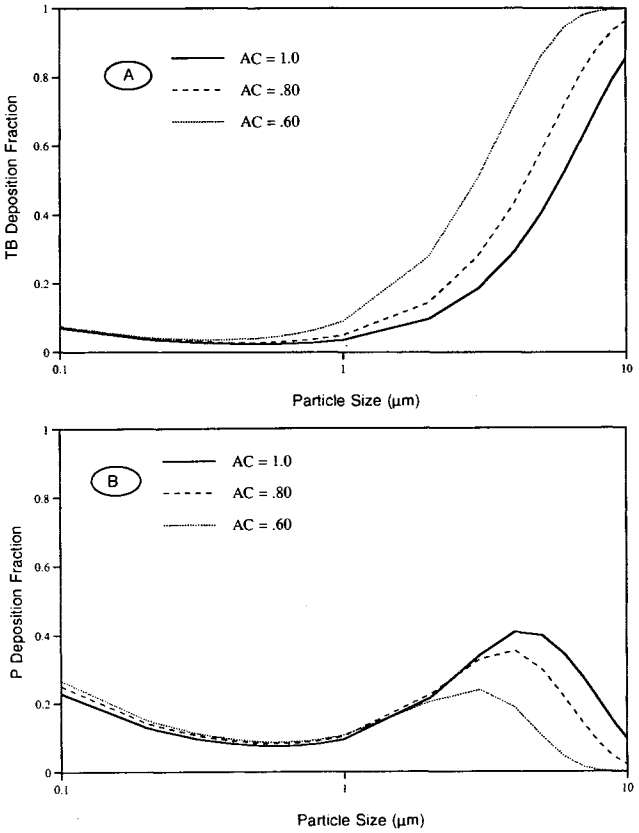

Fig. 2. Effects of airway dimensions upon aerosol deposition in the TB (Panel A) and P (Panel B) compartments of adult human subjects, healthy or with respiratory disease. *Light activity* breathing conditions are addressed.

an inhaled drug among the TB and P compartments. Particle deposition in the TB tree behaves in a very systematic manner. As AC values decrease, signifying that airways have become congested, deposition increases. This behavior is in complete accord with the action of the inertial impaction deposition mechanism as formulated by Martonen (23). That is, as airway diameters decrease the velocity through them will increase (i.e., for a prescribed inspiratory flow rate), and the effectiveness of the impaction process is directly related to the velocity's magnitude. Indeed, as the intensity of breathing increases sequentially from a sedentary state to light activity (i.e., from Figure 1 to 2) the increase of deposition becomes ever more pronounced. For instance, in Figure 2, Panel A, the deposition of a 3 μm particle increases from approximately 15% (AC = 1.00) to 24% (AC = 0.80) to 44% (AC = 0.60). The relevance of these results regarding the targeted delivery of site-specific acting pharmaceuticals to diseased lungs is quite clear: namely, the effect of cystic fibrosis will enhance deposition by about 290% (i.e., a factor of 44/15). In the P compartment deposition is affected because fewer particles penetrate to those alveolated airways, having been filtered by the upstream TB airways. The implication is important for pharmacologic drugs that are designed to enter the circulatory system and then elicit their therapeutic effects. Overall, the deposition of submicron (i.e., < 1 μm) particles is relatively unaffected by AC values when compared to larger particle sizes. This was as expected due to the relatively minor role of diffusion in the overall process of deposition under the examined conditions.

In Figures 3-4 the spatial distributions of drug particles are presented on a generation-by-generation basis for the sedentary and light activity cases, respectively. The TB compartment contains generations $0 \leq I \leq 16$ and the P compartment $17 \leq I \leq 23$. Four particle sizes are considered, each in a separate panel. For brevity, only a few comments will be made to facilitate interpretation of the illustrations. The deposition fraction for each generation I is the aerosol mass deposited therein divided by the aerosol mass entering the trachea. Under sedentary conditions (Figure 3), deposi-

Table I. Identification of the adult human lung morphologies (column 1) selected to simulate the respiratory disease (column 2) with the ailment-caused variations in airway dimensions (column 3) and spatial definitions used to simulate their physical locations (column 4)

Test Morphology	Lung Disease	Airway Caliber	Lung Location
Control	None (healthy)	Weibel (21)	$0 \leq I^a \leq 23$
Patient	cystic fibrosis	−20%	$0 \leq I \leq 16$
"	"	−40%	"

[a] = I denotes lung airway generation according to Weibel (21) morphology.

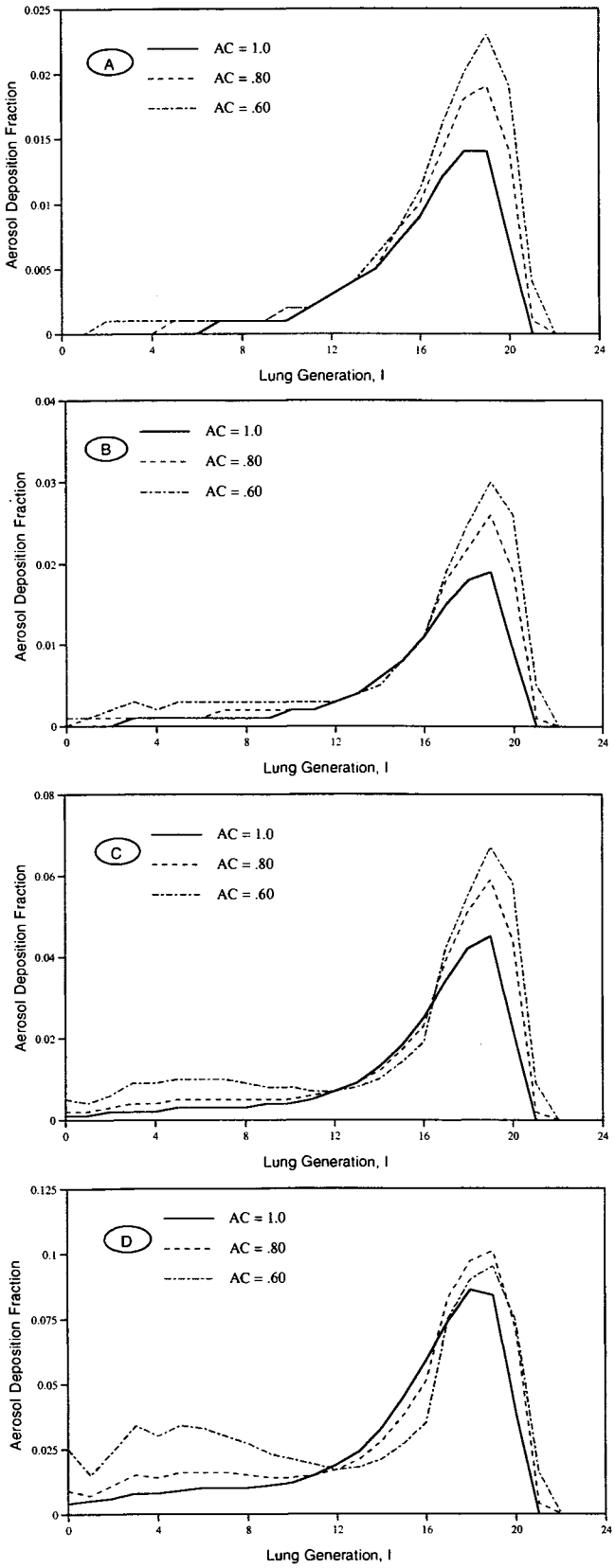

Fig. 3. Aerosol distributions within the lung for *sedentary* breathing conditions. The deposition curves are presented on a generation-by-generation basis for the selected AC values. The particle sizes are Panel A, D_g = 0.5 μm; Panel B, D_g = 1.0 μm; Panel C, D_g = 2.0 μm; and, Panel D, D_g = 4.0 μm.

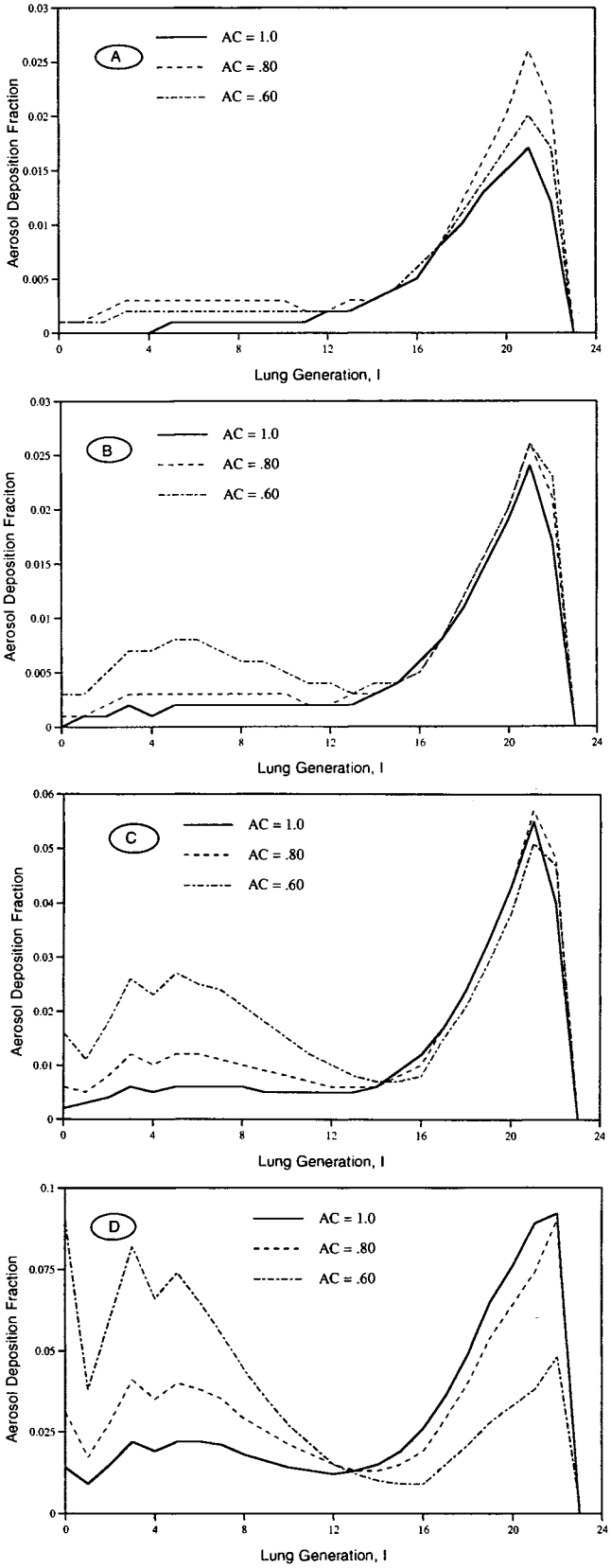

Fig. 4. Aerosol distributions within the lung for *light activity* breathing conditions. The deposition curves are presented on a generation-by-generation basis for the selected AC values. The particle sizes are: Panel A, D_g = 0.5 μm; Panel B, D_g = 1.0 μm; Panel C, D_g = 2.0 μm; and, Panel D, D_g = 4.0 μm.

tion occurs preferentially in the acinar region of the lung. Deposition is inversely related to airway caliber, and in a systematic fashion. For the largest particle size (4 μm, Panel D) examined, deposition is shifted somewhat to upstream airways. For particle sizes >1 μm the shift to proximal airways is much more pronounced as the level of respiratory intensity is increased to light activity conditions (Figure 4). Indeed, for the 4 μm particles the peak of deposition is of equal magnitude in the upper airways when AC = 0.60 as in the lower airways for the control case (AC = 1.0). The implication is obvious to aerosol therapy practice, namely that airway disease can directly cause a completely different deposition pattern within the lung. As AC values decrease, deposition increases in a monotonic manner; this is in accordance with the increased effectiveness of the inertial impaction deposition mechanism. The effect of disease is apparent, as airways become congested the deposition of inhaled drugs will be substantively shifted to the upper TB tree.

As a final demonstration of how the model may be integrated into drug delivery protocols, let us focus on effects of ventilatory parameters. Consider the C Panels (2 μm particles) of Figures 3-4. For a resting patient (i.e., the sedentary level of Figure 3), the 2 μm particles are selectively deposited in the alveolated airways with the distribution reaching a peak at I = 19. For a patient following a regulated breathing pattern mimicking light activity conditions (Figure 4), however, deposition has a maximum in I = 5. The spatial distribution of the drug has been changed completely with the prescribed breathing regimen.

SUMMARY

Experimental data from the medical literature clearly establish that, for a prescribed breathing profile, the deposition pattern of an inhaled drug is a function of particle size. However, most of the data are for healthy (i.e., volunteer) test subjects. Therefore, it is extremely difficult for physicians, nurses, and aerosol therapy technicians to target drugs within diseased lungs. Herein, factors affecting the deposition patterns of inhaled pharmaceuticals were studied using a validated mathematical model. The lungs of patients were simulated by different morphologies than a normal subject and it was shown that dose distributions can be markedly affected by cystic fibrosis induced changes in airway dimensions. Furthermore, different ventilatory parameters were examined to demonstrate the effects of breathing upon the deposition patterns of inhaled drugs. This is a salient issue because instructing a patient how to breath can be a very important factor in targeted drug delivery. Of course, it may not be possible to regulate the breathing of impaired individuals. In Figures 1-4, the effects of morphology and ventilation upon deposition have been systematically expressed in terms of (i) drug quantities delivered to the TB and P compartments of control subjects and CF patients and (ii) spatial distributions of the drugs on a generation-by-generation basis.

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