

Targeting Aerosolized Drugs to the Conducting Airways Using Very Large Particles and Extremely Slow Inhalations

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Abstract

Background: The site of deposition in the respiratory tract for aerosolized, inhaled therapeutic drugs depends on both the particles' aerodynamic size and the patient's breathing pattern.

Methods: In 21 healthy subjects with normal lung function, we evaluated an extremely slow inhalation of a large 9.5- μm MMAD particle aerosol (ESI-9) for its ability to enhance the delivery of radiolabeled particles ($^{99\text{m}}\text{Tc}$ -labeled sulfur colloid) to the conducting airways. The regional deposition of the large particles (modified Pari-Boy jet nebulizer), inhaled at the extremely low rate of 0.080 Lps for 10 sec, was compared to the deposition of 5- μm MMAD particles inhaled during cyclic resting tidal breathing (TVB-5-) (mean 0.44 L and 0.46 Lps). Gamma scintigraphy gave an estimate of conducting airway deposition (% CAD) as a fraction of all deposited particles by multiplying the percent of activity in both lungs immediately postdeposition relative to the total deposition (i.e., lungs + mouth + esophagus + stomach) times the percent of activity cleared from the lungs over 24 h.

Results: % CAD for healthy subjects for the ESI-9 and TVB-5 maneuvers was 35% ($\pm 8\%$) and 27% ($\pm 11\%$), respectively, $p = 0.004$. The amount deposited within the oropharynx was 26% ($\pm 7\%$) and 37% ($\pm 11\%$), respectively, $p < 0.001$.

Conclusions: Higher therapeutic value of a medication delivered to the conducting airways where the primary defect is associated with many diseases, and with fewer losses to the extrathoracic surfaces, may be obtained by using an "extremely slow inhalation and large particle" routine when compared to a normal tidal volume breathing associated with typical nebulizers.

Key words: extremely slow inhalation, nebulizers, deposition, mucociliary clearance, gamma camera imaging

Introduction

MANY ORALLY INHALED, THERAPEUTIC DRUGS have their site of action in the large and/or small conducting airways,⁽¹⁾ for example, anti-inflammatory corticosteroids in asthma and chronic obstructive pulmonary disease (COPD), and hypertonic saline in cystic fibrosis (CF). New inhalable therapies for inflammatory and immune conditions include RNA interference molecules,⁽²⁾ and other emerging therapies for respiratory diseases.⁽³⁾ Recent developments of viral and liposomal vectors for DNA transfer to airway epithelial cells in CF may require targeted delivery to the bronchial airways where the defect in epithelial Cl^- ion transport (CFTR) is manifested.⁽⁴⁾ Nebulizers and inhalers designed for the delivery of therapeutic agents maximize respiratory deposition

as "inhalable" aerosol particles. Particles, however, may deposit elsewhere in the respiratory tract, predominately in the upper respiratory tract or peripheral airspaces, resulting in unwanted side effects and waste. Deposition of these molecules and vectors in the lung periphery, besides being ineffective in this region,^(2,4) may also enhance innate immune response to the deposited therapy.

The quantity and location of particle deposition in the respiratory tract depends on both the particles' aerodynamic size and the patient's flow patterns during inhalation. For spontaneous, resting inhalations during nebulizer use, for example, 0.4-L tidal volume and a mean flow rate of 0.4 Lps, particles greater than 9 μm (MMAD) impact predominately onto surfaces within the oropharynx and are considered "not inhalable." Those smaller than 5 μm may also impact in the

oropharynx, larger airways, and also penetrate deeper into the lung to settle in the alveolar spaces. Under these tidal breathing conditions, minimal deposition occurs in the smaller conducting airways, usually the preferred site for action for many of the inhaled therapeutic agents. Most respiratory devices marketed for delivery of therapeutic agents for spontaneous, resting breathing patterns are designed to provide particles in the respirable range of 1 to 5 μm , with the understanding that there may be considerable oropharyngeal and alveolar surface exposure to the drug.

For many inhaled agents, this design strategy may be sufficient. However, for those drugs that are extremely costly, or have significant, unwanted side effects, an improved delivery regimen may be warranted. One strategy is to enlarge the particle size for a given inhalation flow rate to increase the impaction in more proximal airways, and consequently, reduce the number of particles reaching the peripheral airspaces. For example, Usmani et al.⁽⁵⁾ enhanced the efficacy of albuterol in mild-moderate asthmatics by increasing the particle size from 1.5 to 3 to 6 μm in 1-L boli at 0.5–1 Lps inspiratory flow while keeping the delivered dose constant. Increasing the flow for 6- μm particles to greater than 1.0 Lps, however, reduced the efficacy in half while increasing oropharyngeal deposition by more than 50%. Thus, the strategy of increasing both particle size and flow rate may shift deposition away from the alveolar region but also increases unwanted deposition within the oropharynx.⁽⁶⁾

Anderson et al.⁽⁷⁾ suggested a novel strategy to enhance deposition on the airways by using a larger particle size of 6 μm while restricting the inhalation to extremely low flow rates. Their extremely slow inhalation (ESI) method has been proposed for targeting the particles of an aerosol for deposition in the small airways of the human lung. They reasoned from aerodynamic arguments that by reducing the inhaled flow to very low values, 0.05 Lps, an aerosol with particle size of 6 μm would deposit preferentially in the small airways. At these low flows, deposition by impaction in the extrathoracic and oropharyngeal surfaces is reduced, and within the small airways, the transit time of the particle becomes longer than the gravitational settling time for the airway diameter, thereby increasing deposition in this region. For healthy subjects inhaling 6 μm monodisperse Teflon particles at 0.036 Lps, they found enhanced tracheobronchial deposition to be 50% of total respiratory tract deposition, when compared to their expected value of 30% if the same particles were inhaled at a typical flow rate of 0.5 Lps.⁽⁷⁾ They also concluded that oropharyngeal deposition decreased to 20% from an expected value of 40%.⁽⁸⁾ Alveolar deposition measured with the low flow rate was not different, measured to be the same as the 28% expected for the inhalation flow of 0.5 Lps. They further demonstrated relevant pharmacologic effects of enhanced airway deposition using ESI methods by measuring increases in airway resistance with histamine inhalation for a low inhalation flow of 0.055 Lps compared to a more standard flow of 0.5 Lps.⁽⁹⁾

The encouraging results of that pioneering study, and subsequent investigations into ESI,^(10–12) supported the hypothesis of the current study described here: by increasing the size of the particles to around 9 μm , with a higher airway deposition efficiency concomitant with their faster settling time, alveolar deposition may be further reduced with extremely slow inhalations. Furthermore, to be relevant to the

type of aerosols that might be generated for drug delivery, the ESI-9 method was tested with polydisperse particles corresponding to those delivered by available aqueous nebulizers. The large particle/extremely slow inhalation flow method (ESI-9, 9.5- μm particles inhaled for 10 sec at 0.08 Lps) was compared to a cyclic breathing pattern with volume and flow similar to that associated with spontaneous breathing on jet nebulizers (TVB-5, 5- μm particles, 0.4 L tidal volume of mean flow 0.4 Lps). Finally, unlike the data and conclusions derived from the previous studies of the ESI methodology, we analyzed regional deposition with the higher spatial resolution provided by gamma camera imaging. This study assessed regional deposition within the respiratory tract of a group of healthy adult subjects.

Materials and Methods

Subjects

Twenty-one nonsmoking volunteers (16 male, 5 female) aged 18–41 years, mean 25 were recruited to participate in the study.

All subjects received a medical exam on a separate screening day prior to beginning the study, were free of upper or lower respiratory tract infections for 4–6 weeks prior to beginning the study, and had a forced expiratory volume in 1 sec (FEV₁) greater than 80% of predicted values, average 101 \pm 14% (Pulmo-Screen IIE System, model VRS2000, S&M Instrument Company, Doylestown, PA, USA). The study protocol was approved by the University of North Carolina's Committee on the Protection of Rights of Human Subjects and informed consent was obtained from each subject.

Radioaerosol inhalation

After the initial screening and evaluation visit, the subjects returned for two separate experimental visits. On all of the first visits, a Xenon 133 equilibrium gamma camera (MiE America LFOV, Chicago, IL, USA) scan (rebreathing approximately 1–2 mCi/L) was obtained prior to radiolabeled aerosol inhalation to determine the lung outline and lung thickness correction for characterizing regional deposition in the lung.⁽¹³⁾ Background images (for the ^{99m}Tc energy window) of the subject were taken prior to and immediately following the xenon scans. Sulfur colloid particles radiolabeled with technetium (^{99m}Tc -SC) were prepared from TechneScan Sulfur Colloid Kits (CIS-Sulfur Colloid, CIS-US, Inc., Bedford, MA, USA) following the procedure provided by the manufacturer. The binding of ^{99m}Tc to SC was always greater than 99% determined by paper chromatography. The submicrometer (0.22 μm , gsd 1.75) ^{99m}Tc sulfur colloid particles⁽¹⁴⁾ are insoluble and suspended in a normal saline solution for delivery by the jet nebulizers. For all visits, breathing patterns during aerosol inhalation were controlled after training the subjects to follow feedback signals.

During one visit, the subjects followed a shallow cyclic breathing pattern of 0.5 Lps peak flow rate at a frequency of 30 breaths/min, 50% duty cycle, following a lighted graduated flow signal and metronome (tidal volume breathing, TVB-5). Two milliliters of the ^{99m}Tc -SC particle suspension (5 mCi) were placed in a Devilbiss 646 jet nebulizer [aerosol size of 5- μm MMAD, GSD 2.0 by Malvern Mastersizer S (Malvern Instruments USA, Westborough, MA, USA)] for

controlled inhalation by the subjects. The breathing pattern was displayed and recorded from a pneumotachograph attached directly downstream to the nebulizer. Further downstream of the pneumotachograph, a 12-inch tubing was connected to a Spira Electro2 Inhalation Dosimeter (Respiratory Care Center, Hämeenlinna, Finland) dosimeter. Nebulizer operation and display of the flow rate to the subject was provided by the dosimeter. The dosimeter also directed compressor actuation air (Devilbiss Pulmo-Aide, Model 5610D, Somerset, PA, USA) to the nebulizer for a 0.7-sec duration after a 100-mLs delay of onset at the beginning of each 50% duty cyclic breath during TVB. See Figure 1a for a schematic of the equipment.

During the other visit, the subjects inhaled a large particle aerosol [aerosol size of $9.5\text{-}\mu\text{m}$ MMAD, GSD 1.8 by Malvern Mastersizer S (Malvern Instruments)] at extremely slow inhalation flow rates (ESI-9) for 10 sec. The ESI-9 maneuvers were single inhalations from functional residual capacity (FRC) followed by the subject breathing freely (with no aerosol) for a several seconds rest between each breath. The air compressor for the nebulizer was started manually by the investigators during inhalation and turned off during exhalation. The flow rate was equal to the actuation airflow from the compressor through the nebulizer, approximately 0.080 Lps. No other flow was introduced for the subjects, and was ensured by a one-way check valve attached in-line distal to the nebulizer allowing only exhalation. The subject's exhalation was controlled at 0.25 Lps by feedback from a differential pressure gauge (dp gauge) placed across the one-way valve in the subject's breathing line. See Figure 1b for a schematic of this setup. Three milliliters of the $^{99\text{m}}\text{Tc}$ -SC particle suspension (approximately 1.5 mCi) were placed in a Pari jet nebulizer (Pari-Boy; Pari-Werke, Starnberg, Germany). The Pari-Boy was modified by sawing off the lower 2.3 cm of the internal cylindrical baffle.

For both methods, inhalation of the $^{99\text{m}}\text{Tc}$ -SC aerosol proceeded until approximately $40\ \mu\text{Ci}$ of radioactivity had deposited in the subject's lungs (less than approximately 2 min continuous breathing in the case of TVB-5 and 2–8 single breaths for the ESI-9 method over approximately a 2-min period), as measured by a 2-inch single crystal NaI detector placed at the subject's back. The output of the nebulizers was not measured and was not a goal of this study. Experience from previous studies allowed for the adjustment of the curie concentration within the nebulizers to ensure deposition, in a typical subject, of $40\ \mu\text{Ci}$ in approximately 2 min of inhalation breathing time. The doses

inhaled during the two methods were not similar, but for this study, the dose deposited ($40\ \mu\text{Ci}$) was controlled, rather than dose inhaled (not measured). Activity deposited in the mouth was swallowed to the stomach by a small drink of water prior to camera acquisition. This was followed immediately, less than 2-min delay from end of inhalation, by gamma camera scanning (47 sequential 2-min scans) of the subject's lungs for 94 min to measure particle deposition and retention in the lung. Subject's inhalation and imaging were performed seated upright. A laser beam was positioned on the subject's chest to provide a visual cue to help maintain a constant position in the camera field.. Previous studies of unperturbed mucociliary clearance in our laboratory have not detected an order effect (not published), and was not controlled in this study; therefore, the order of the two methods was not randomized. The subjects returned the following day to obtain a single 30-min image of the lungs to measure the long-term particle retention.

Gamma scintigraphy

Figure 2 is an example of a posterior gamma camera image of the upper body, for one subject, taken less than 2 min following an airway deposition of the $5\text{-}\mu\text{m}$ $^{99\text{m}}\text{Tc}$ -SC particles by TVB-5. Deposited activity is reflected in the image as increasing from dark gray, to gray, and white. The two larger rectangles represent the rectangular outlines of both lungs based on circumscribing an isocontour map of the $^{133}\text{Xenon}$ equilibrium scan (20% of peak values) measured with the subject prior to the study on the first visit day. The central (C) airways region of interest (ROI), smaller rectangle within the whole lung ROI, is shown for the right lung (area = 25% of the whole lung ROI, half-width and half-height aligned to left margin and midvertical). Peripheral (P) activity was calculated from the difference between activities in the whole lung and the activity in C region. The remaining rectangular areas in Figure 2 represents the sum of the outlines of the oropharyngeal, esophageal, and stomach areas, drawn to circumscribe areas with counts at least twice-fold over background. The count density in the left lung ROI that overlaps with the region of the stomach ROI was estimated from the mean count density in the peripheral region of the left lung and proportioned according to the relative ROI area. These estimated counts were added to the left lung peripheral counts and subtracted from the counts measured in the stomach area. Image analysis included background subtraction, decay correction to midpoint of time segment,

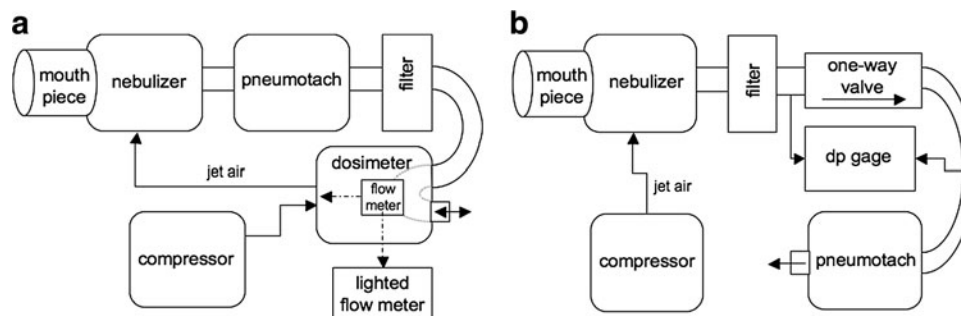


FIG. 1. The experimental arrangement of the nebulizers, control, and instrumentation for inhalation of radioaerosol is shown for the tidal breathing (a), and the extremely slow inhalation (b).

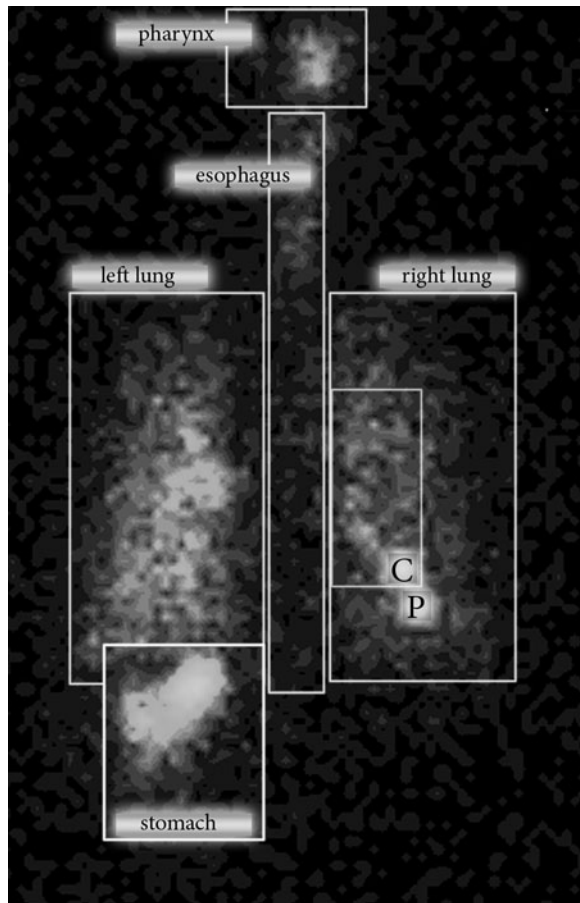


FIG. 2. Initial gamma scintigraphy posterior sample image of deposited sulfur colloid particles labeled with ^{99m}Tc showing the ROIs for the regional analysis. Areas of deposition increase from dark to light. C and P are the central and peripheral regions, respectively, used for C/P analysis.

and attenuation correction for different organs/regions according to the estimates of Pitcairn and Newman.⁽¹⁵⁾ Attenuation values were 2.3 for head and esophagus, 2.2 for lungs and 3.4 for stomach.

Clearance kinetics and regional deposition

The whole lung ROI bordering the right lung was used to determine, by computer analysis of remaining counts in the ROI, the whole lung clearance kinetics of the activity as a fraction of the initial counts throughout the gamma camera scanning period of 94 min (R_t), where t = time point in minutes, and also for a single 30-min image collected the next day at nearly 24 h postinhalation (R_{24}). Regional deposition was calculated from the clearance kinetics as described in the following.^(16,17) The fraction of activity remaining in the right lung after 24 h subsequent to radioisotope dosing (R_{24}) was used to estimate alveolar deposition, assuming negligible alveolar clearance through the first 24 h. The clearance of ^{99m}Tc -SC through 60 min posttracer deposition ($C_{60} = 1 - R_{60}$) served as the primary index of cilia-dependent clearance from the large airways. The difference between the alveolar deposition, R_{24} , and large airway deposition, C_{60} , was assumed to be indicative of deposition in the interme-

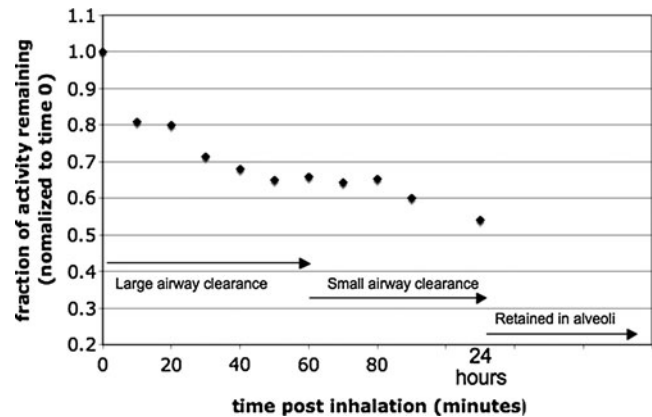


FIG. 3. Clearance of labeled particles from the respiratory surfaces over time is used to calculate the amount of particles in the region where the particles had deposited during inhalation. A retention value is the fraction of activity remaining within the right lung at a time point after inhalation and relative to the initial activity deposited within the right lung.

diate and small airways. Figure 3 graphically illustrates the relationships between the clearance kinetics and regional deposition, using a typical retention curve from one subject. Conducting airway deposition as a percentage of total deposition (% CAD) was calculated by multiplying the percent of activity cleared from the right lung ROI over 24 h, by the lung deposition as a fraction of total deposition measured in all respiratory pathways [i.e., lung (both left and right) + mouth + esophagus + stomach].

To assess central versus peripheral airway deposition within the lung, a central to peripheral (C/P) ratio of ^{99m}Tc activity was calculated for the initial deposition scan following the ^{99m}Tc -SC aerosol inhalation, and normalized to the C/P of the ^{133}Xe equilibrium scan.⁽¹³⁾ Comparison of data sets between groups was performed using functions within Excel 2004 for Macintosh for paired two-sided t -tests with a p -value ≤ 0.05 accepted as significant, unless otherwise stated. Values are given as mean with standard deviation unless otherwise indicated.

Results

Inhalation of 5- μm MMAD particles using tidal volume breathing (TVB-5) was accomplished with a mean flow rate of 0.46 ± 0.05 Lps and mean tidal volume 0.44 ± 0.06 L; and inhalation of larger 9.5- μm MMAD particles with a larger tidal volume and extremely slow inhalation flow rate (ESI-9) was achieved with a mean flow rate 0.08 ± 0.01 Lps and mean inhaled volume 0.8 ± 0.1 L.

Representative deposition patterns for one subject and each inhalation method are shown in Figure 4. A simple visual inspection of the images illustrates that the TVB-5 method (Fig. 4a) deposits more particles in the oropharyngeal region, with some swallowed to the stomach, and a diffuse distribution throughout the lung, when compared to the ESI-9 method. The ESI-9 method deposited the particles more focally in the central region, as seen in Figure 4b, and comparatively less in the oropharyngeal region, as represented by the decreased mouth and stomach activity,

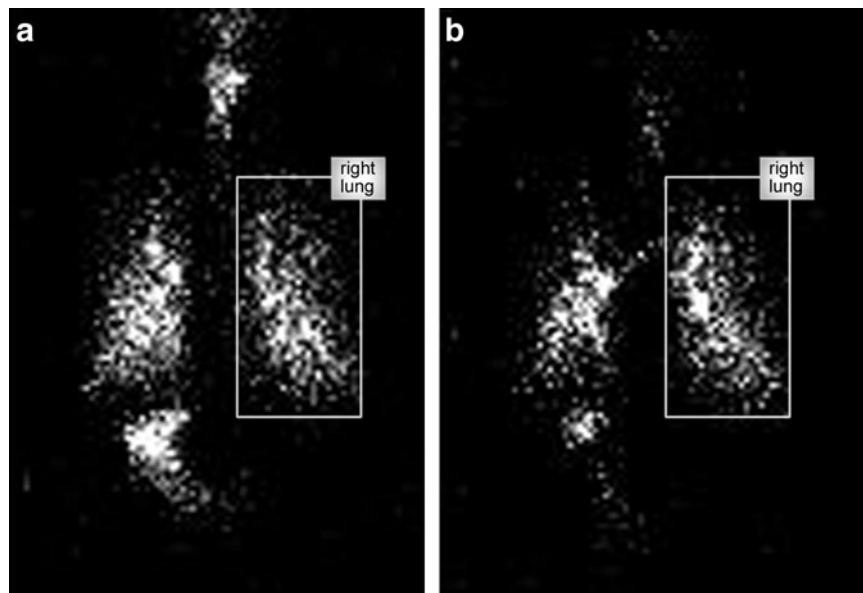


FIG. 4. Representative gamma camera posterior images are shown illustrating the deposition patterns for two inhalation methods. (a) Tidal volume breathing of 5- μm aerosol, 0.44-L inhalation at 0.48 Lps cyclic mean flow, 35% extrathoracic deposition; (b) Large 9.5- μm particle, extremely slow inhalation, 0.80-L inhalation at 0.080 Lps constant flow, 21% extrathoracic deposition. ROIs indicate location of right lung. Images have been gray-scaled to same number of total counts (Subject 41019).

when compared to the TVB-5 method. For illustration purposes, the images have been rescaled to the same number of total counts. A quantitative measure of central airway deposition, C/P, was 1.6 and 1.9, respectively, $p = 0.02$.

Table 1 summarizes the regional deposition data. There was a reduction in extrathoracic deposition and an increase in lung deposition for the ESI-9 method, compared to the TVB-5 method. Furthermore, % CAD and large airway deposition was significantly increased with the ESI-9 method. The lower section of Table 1, “percent of deposition within the lung,” illustrates difference in values obtained for proximal airway deposition by two types of measurements. The large airway deposition, 20% for ESI-9 and 13% for TVB-5, is based on a physiological definition (amount cleared in 1 h) while the central ROI deposition, 40% for ESI-9 and 31% for TVB-5, is based on a planar spatial measurement of the first gamma camera image. Hence, both types of measurements show a greater deposition in the proximal airway generations with the ESI-9 method compared to the TVB-5 method. Alveolar fraction (of total deposition) was significantly different between the two methods, with fewer particles deposited in the alveolar region with the ESI-9 method. However, when considering only the activity deposited within the lungs, alveolar deposition was not significantly different. Intermediate/small airway deposition was not different between the two methods.

Discussion

Greater aerosol deposition in the conducting airways, as measured by % CAD, was observed with ESI-9, the large particle/extremely slow inhalation method when compared to a typically sized particle inhaled under tidal breathing, TVB-5. For our healthy subjects, there was an approximate 50% relative increase in deposition onto the conducting airways with the slow inhalation method when compared to

tidal breathing. Although single breaths of aerosol are required for the ESI-9 method compared to continuous tidal breathing for TVB-5, the very high aerosol concentration, that is, there is no diluting air, and large particle size associated with the ESI-9 method resulted in a very efficient delivery of aerosol to the airways. In fact, we needed to reduce to one-fourth the specific radioactivity in the nebulizer for ESI-9 versus TVB-5 because the former was so efficient at delivering comparable radioactivity to the lung. Thus, 2–8

TABLE 1. THE REGIONAL DEPOSITION OF INHALED PARTICLES USING THE EXTREMELY SLOW INHALATION OF 9.5- μm PARTICLES (ESI-9) AND TIDAL VOLUME BREATHING OF 5- μm PARTICLES (TVB-5)

<i>Percent of total deposition</i>	<i>ESI-9</i>	<i>(SD)</i>	<i>TVB-5</i>	<i>(SD)</i>
Lungs ^a	75	(7)	64	(11)
% CAD ^b	35	(8)	27	(11)
Large airways ^c	15	(8)	9	(7)
Alveolar deposition ^a	35	(3)	54	(9)
Extrathoracic ^a	26	(7)	37	(11)
<i>Percent of deposition in the lungs</i>				
large airways ^d	20	(10)	13	(11)
In central ROI ^a	40	(5)	31	(6)
Alveolar n.s.	53	(10)	59	(14)
C/P right lung ^e	1.9	(0.3)	1.6	(0.4)

Differences between ESI-9 and TVB-5 are evaluated by paired *t*-test.

^a $p < 0.001$, ^b $p = 0.004$, ^c $p = 0.009$, ^d $p = 0.04$, ^e $p = 0.02$, n.s. not significant. C/P is planar analysis of deposition in central region compared to the peripheral region.

CAD, conducting airway deposition; ROI, region of interest.

single breaths delivered by ESI-9 deposited roughly the same mass of aerosol particles to the respiratory tract as approximately 2 min of inhalation with TVB-5. This may be an additional advantage in efficiency for the ESI method.

The calculation of % CAD assumed that the cleared activity had resided in the conducting airways, and that all of the activity initially deposited there was removed by mucociliary action through 24 h postinhalation. The fraction of activity deposited on the airways would certainly be underestimated if particles remained on bronchial airway surfaces after 24 h. Further, any particles remaining in the lungs after 24 h were assumed to have deposited in the alveoli, on relatively non-clearing surfaces. This is likely a valid approximation for particles deposited during inhalation by TVB-5^(7,18) in these healthy subjects. However, calculations made by Camner et al.⁽¹⁰⁾ of airway deposition and retention using three mathematical models, indicate that a substantial slow-clearing fraction may remain on the airways after 24 h when deposited during ESI-9. They estimated parameters based on a two-compartment clearance kinetic model for each of the large and small airways, and one very long clearance fraction in the alveoli. For particles in the 10- μm range, the best fit to their experimental data indicated that 16% of the particles were deposited in a slow-clearing small airway compartment, with an indeterminate slow-clearing fraction for the larger airways. Therefore, it is likely that a higher fraction than that calculated here for % CAD was deposited in the small airways, and consequently, less in the alveoli, with ESI-9.

Compared to TVB-5, ESI-9 enhances all conducting airway deposition. As measured by the increased clearance in 1 h, ESI-9 enhances large airway deposition. The lower retention at 24 h postinhalation indicates reduced alveolar deposition. In an early study by Knudson et al.,⁽¹⁹⁾ a similar pattern of regional lung deposition changes were observed in normal lungs comparing a low flow rate inhalation versus a normal flow rate bolus delivery with end-inspiratory breathhold. Although a faster clearance in 1 h was observed for the "bolus with breathhold method," indicating higher deposition in the largest airways, the clearance through 24 h was identical, indicating that the slower flow inhalation method deposited a higher fraction of particles further down the airways into the smaller but clearable airways. A disadvantage of the bolus method for drug delivery purposes is that a large number of aerosol boli would need to be inhaled to deliver sufficient quantities of drug to the airways. On the other hand, with the ESI-9 method a very large mass of aerosol can be delivered with each breath, requiring less time and fewer breaths to achieve similar drug delivery.

Many studies have investigated the option of varying the particle size of the nebulized aerosol to enhance total lung deposition (usually without regard to regional deposition within the lung) or to increase inhaled drug efficacy. Most of the studies of this kind have approximated a "typical" nebulizer breathing pattern in the range of 0.5 to 1.0 Lps. One such study⁽²⁰⁾ increased the efficacy of albuterol (increasing FEV₁ and FEF₂₅₋₇₅) by increasing the particle size from 1.5 to 6 μm . However, they recognized that it was not clear if increased efficacy was due to increasing the total lung deposition and/or increasing regional deposition to the airways. Their subsequent study,⁽⁵⁾ emphasizing the regional location of deposition found that increasing particle size from 1.5 to 6 μm , decreased total lung deposition, but also decreased the

penetration of particles into the periphery. The decrease in penetration was accompanied by an increase in oropharyngeal deposition. The intermediate lung region, that is, the airways, received a measurable but insignificant increase in deposited particles. A review of other studies that optimize efficacy by changing particle size can be found in Weda et al.⁽²¹⁾ The general consensus derived from these and modeling studies⁽⁶⁾ is that changing only the particle size shifts particle deposition between the oropharyngeal and alveolar compartments, while leaving the deposition onto airways relatively unchanged. Deposition of polydisperse 6.5- μm particles introduced as a 0.15-Lps aerosol bolus was investigated with a reduced inhalation flow⁽²²⁾ as an attempt to increase lung deposition by reducing losses in the upper airways. Inhalation at 0.13 Lps reduced oropharyngeal deposition from 52 to 29% when compared to an inhalation flow of 0.50 Lps while increasing lung deposition from 48 to 71%. They report an increase in lung deposition, primarily in the peripheral airspaces, however, from 27 to 47%, respectively, as measured by retention at 24 h postinhalation. In this case, the reduced flow allowed the particles to escape deposition in the oropharynx and enter into the lung. However, the particles were not large enough to settle onto the conducting airways in transit and instead settled distally in the alveoli.

The extremely low inhalation flow rate used for enhancing the airway deposition was well tolerated for the group of healthy subjects with normal lung function. It is also expected to be within the capabilities of most respiratory patients to perform. In a small group of five cystic fibrosis patients with mild lung disease (data not published), the disease did not prevent the proper performance of the maneuver. The procedure was easily learned and reproduced, especially because the inhalation flow rate was controlled by the actuating air of the jet nebulizer as the only source of flow to the subject. However, this study used specialized equipment for controlling and monitoring breathing patterns that would not likely be available to patient use. In addition, other nebulizer types that may require a different mechanism for controlling inhaled airflow, for example, vibrating membrane, powder metered dose inhalers (pMDIs), dry powder and fluidized bed, were not tested. For these applications, it may be useful to incorporate "smart" nebulizers with their automatic control of breathing patterns.

The test particle in this study was composed of insoluble submicrometer 0.22 μm and gsd 1.75, sulfur colloid particles⁽¹⁴⁾ labeled with ^{99m}Tc suspended in a normal saline solution. The colloids are suspended in either 5- or 9.5- μm droplets depending on the type of nebulizer. Hence, the tracer is deposited within the respiratory tract as an aerodynamically large particle that then disperses as smaller particles onto the mucous layer upon contact with the airway surface. The determination of the extrathoracic fraction of deposition depends on the initial scintigraphic image and would not be affected by colloidal particle size or low levels of deposited activity. However, the calculation of % CAD depends on clearance through the first 24 h, and it is controversial whether the size of the dispersed colloidal particles influences clearance velocity.⁽²³⁾ Counting accuracy for the lower levels of activity remaining after 24 h was corrected for by increasing the length of frame acquisition time to approach the counting uncertainty of the initial image. Linearity tests on the gamma camera system were

performed to confirm accuracy (<5%) at the low levels of activity used in this study.

The current study reports the results from healthy volunteers with normal lung function, and needs to be extended to include mildly obstructed patients, for example, chronic bronchitic (CB) and CF patients. It is not known what the presence of pathologies, such as severe mucus obstructions in CB and CF, might do to introduce changes in regional lung deposition with the different delivery method.

Conclusions

These data indicate that in the healthy lung, the “very large particle/extremely slow inhalation flow,” ESI-9, protocol deposits the particles preferentially in the larger conducting airways, with reduced extrathoracic deposition, when compared to typical inhalation by tidal breathing with nebulizers producing aerosols of 5- μ m particles or less. Higher therapeutic value of a medication delivered to the airways, with lowered losses to the extrathoracic airways and alveoli, is anticipated and should be investigated by using a “very large particle/extremely slow inhalation” routine when compared to normal tidal breathing.

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Author Disclosure Statement

No conflicts of interest exist.

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