Assessment of regional deposition of inhaled particles in human lungs by serial bolus delivery method

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Kim, Chong S., S. C. Hu, P. DeWitt, and T. R. Gerrity. Assessment of regional deposition of inhaled particles in human lungs by serial bolus delivery technique. J. Appl. Physiol. 81(5): 2203–2213, 1996.—Detailed regional deposition of inhaled particles was investigated in young adults (n = 11) by use of a serial bolus aerosol delivery technique. A small bolus (45 ml half-width) of monodisperse aerosols [1-, 3-, and 5-µm particle diameter (Dp)] was delivered sequentially to a specific volumetric depth of the lung (100–500 ml in 50-ml increments), while the subject inhaled clean air via a laser aerosol photometer (25-ml dead volume) with a constant flow rate (Q˙ = 150, 250, and 500 ml/s) and exhaled with the same Q without a pause to the residual volume. Deposition efficiency (LDE) and deposition fraction in 10 local volumetric regions and total deposition fraction of the lung were obtained. LDE increased monotonically with increasing lung depth for all three Dp. LDE was greater with smaller Q values in all lung regions. Deposition was distributed fairly evenly throughout the lung regions with a tendency for an enhancement in the distal lung regions for Dp = 1 µm. Deposition distribution was highly uneven for Dp = 3 and 5 µm, and the region of the peak deposition shifted toward the proximal regions with increasing Dp. Surface dose was 1–5 times greater in the small airway regions and 2–17 times greater in the large airway regions than in the alveolar regions. The results suggest that local or regional enhancement of deposition occurs in healthy subjects and that the local enhancement can be an important factor in health risk assessment of inhaled particles.

aerosols; respiratory airways; inhalation

DEPOSITION DOSE AND SITE of inhaled particles within the lung are key determinants in health risk assessment of particulate pollutants. Previous lung deposition studies have dealt largely with total lung deposition measurement, and a body of data has been reported for normal subjects with respect to particle size and the mode of inhalation (4, 12, 15, 30). Those studies have shown that total lung deposition varies widely, depending on particle size and breathing pattern, namely, the larger the particle size for particles >0.5 µm diameter or the smaller the particle size for particles <0.5 µm diameter, the greater the lung deposition. However, because particle deposition does not take place uniformly throughout the lung, there exist local regions of the lung at which deposition dose exceeds the average lung dose (20, 22). It is also anticipated that local deposition varies to a much greater extent than total lung deposition, which may result in incidents of extreme dose enhancement at local regions. This may have significant implications in health risk assessment, because a high local dose may cause tissue injuries or initiate a disease process (27), whereas the average lung dose is still in the acceptable range. Information on detailed regional lung deposition is lacking. Traditionally, regional lung deposition has been assessed by inhalation of aerosols labeled with a γ-emitting radionuclide and subsequent lung scanning with a gamma camera over a 24-h period (23, 28). This method is based on the premise that particles deposited in the ciliated airways are cleared out of the lung within 24 h so that the lung deposition can be obtained for two regions, the tracheobronchial (ciliated) and alveolar (nonciliated) regions, by time-series measurements of particle activity in the lung. With head deposition data obtained from the initial scan, deposition values in the three respiratory compartments are determined. However, the method is laborious and cumbersome, involving radiolabeled aerosols and a long study time. Furthermore, recent studies of Gehret et al. (8) suggested that particle clearance from the ciliated airways may take much longer than 24 h, complicating the premise of the clearance method. The scintigraphic lung scan image by a gamma camera provides a direct visual record of deposition distribution within the lung and a means of quantitative analysis for regional deposition to a certain extent (6, 7, 21). However, it is difficult to link the lung scan image to specific anatomic sites of the lung, and the method remains largely qualitative. Because of versatility, mathematical and computer models have been frequently used to estimate regional lung deposition (16, 24, 33). However, these models are based on many assumptions of airway geometry and flow conditions. Model predictions may not be warranted until they have been validated by experimental data. We have developed a novel method to measure regional lung deposition in situ. By delivering a series of inert aerosol boluses to specific target lung regions, deposition values were obtained for 10 different regions with varying volumetric depth. The method is noninvasive, is easy to use, and does not require radioactive labeling of aerosol. The purpose of this study was to obtain the detailed regional deposition data in humans that can be used to develop improved deposition models and to reduce the uncertainty in health risk assessment of inhaled particles.

METHOD

Theoretical Analysis

When a monodisperse aerosol is inhaled with a tidal volume of VT, deposition fraction (DF) of the aerosol in the
Lung can be obtained by measuring the number of aerosol particles inhaled \((N_{in})\) and exhaled \((N_{ex})\) breath by breath as follows:

\[
DF = 1 - \frac{N_{ex}}{N_{in}}
\]  

Here, the aerosol fills the entire volume of \(V_T\), and deposition takes place throughout the lung regions where \(V_T\) communicates. \(DF\) in this case is also defined as total lung deposition fraction (TDF). This traditional aerosol inhalation mode may be divided into a series of aerosol bolus inhalations: the volume \(V_T\) is divided into a number of smaller compartments with equal volume, and a series of inhalations is performed with the same \(V_T\) in which the aerosol fills only one volumetric compartment in each inhalation, as shown in Fig. 1. TDF will then be obtained by

\[
TDF = \frac{1}{n} \sum_{i=1}^{n} (1 - RC_i)
\]  

where \(n\) is the total number of volumetric compartments and \(RC_i = \frac{N_{ex}}{N_{in}}\) is the recovery of bolus aerosol from the \(i\)th compartment.

If particle deposition efficiency in the \(i\)th compartment is defined by \(x_i\) and deposition efficiencies are the same on inspiration and expiration, the deposition amount in each volumetric region as a fraction of inhaled bolus can be calculated as illustrated in Fig. 1, where \(x_i\) is defined by the amount of aerosol depositing in a volumetric compartment divided by the amount entering the compartment. In Fig. 1, expressions for inspiratory and expiratory deposition are shown on the top and bottom of each volumetric compartment, respectively. The fraction of aerosol that is available for exhalation at end inspiration is shown on the right-hand side of each bolus inhalation diagram. Recovery of bolus aerosol from the \(i\)th compartment is then expressed by

\[
RC_i = \prod_{k=1}^{i} (1 - x_k)^2
\]

Values of \(x_i\) can then be obtained from the ratio of \(RC\) values from two adjacent compartments as

\[
RC_i / RC_{i-1} = (1 - x_i)^2
\]

\[
x_i = 1 - (RC_i / RC_{i-1})^{\frac{1}{2}}
\]

Once \(x_i\) values have been obtained, the deposition fraction of a bolus aerosol in each volumetric compartment \((BDF_{ij})\) can be obtained by combining the inspiratory and expiratory deposition in each compartment shown in Fig. 1. The subscript \(j\) represents the number of sequential bolus inhalations. The local deposition fraction \((LDF)\) in the \(i\)th compartment \((LDF_i)\) and TDF of nonbolus \(V_T\) aerosol can then be obtained by

\[
LDF_i = \frac{1}{n} \sum_{j=1}^{n} BDF_{ij}
\]

and

\[
TDF = \frac{1}{n} \sum_{i=1}^{n} LDF_i
\]

where \(n\) is the total number of volumetric compartments of \(V_T\) or the number of sequential bolus inhalations. Therefore, total as well as regional lung deposition can be determined by measuring the recovery of aerosols from a series of bolus inhalations.

**Experimental**

Subjects. Healthy nonsmoking men \((n = 11)\) were recruited locally (age 19–38 yr). The subjects had no history of smoking within 1 yr and no history of hay fever or asthma. All subjects underwent a screening procedure that included a complete medical history, physical examination, SMA-20 blood chemistry screen, and complete blood count with differential. For those who passed the initial screening, their basic lung functions were measured by spirometry and body plethysmography. All subjects were asked to read and sign a consent form.
approved by the Institutional Review Board of the University of North Carolina School of Medicine. Subject characteristics and lung function test results are given in Table 1.

Generation of test aerosols. Monodisperse di-2-ethylhexyl sebacate (DES) oil aerosols were generated by an evaporation-condensation-type aerosol generator (MAGE, Lavoro E Ambiente, Bologna, Italy). The performance characteristics of the MAGE generator have been described previously (18). In the present study the original MAGE generator was modified to improve the quality of aerosols and to generate large-size particles. Briefly, aqueous solutions of NaCl (5–10 mg/l) were nebulized by a Collison-type atomizer that was operated with compressed nitrogen gas (20 psi). Liquid aerosols generated initially were passed through a drying column filled with silica gel, and the resulting dry nuclei aerosols (1–3 l/min) were passed through a "boiler" in which DES oil was heated and vaporized at 170–250°C. The mixture of nuclei and DES oil vapor from the boiler was passed through a reheater that was maintained at 280–320°C and subsequently through a vertical condensation column that was designed to induce condensation of vapor on the surface of nuclei particles. Monodisperse DES aerosols emerging from the condensation column were diluted with clean air (20–100 l/min) by use of a two-stage diluter. By changing the concentration of nuclei and the temperatures of the boiler and the reheater, we generated monodisperse aerosols with 1-, 3-, and 5-µm-diameter (geometric SD < 1.15) particles. Particle size was measured by an aerodynamic particle sizer (model 33B, TSI, St. Paul, MN) equipped with an on-line aerosol diluter (1:100 ratio; model 3302, TSI). Concentration of aerosols was maintained at a level of 2 × 10³–40 × 10³ particles/cm³ depending on particle size: higher concentrations for smaller particle size and vice versa.

Bolus aerosol inhalation system. The core of the system consisted of a laser aerosol photometer, an aerosol bolus injection module, and an on-line data acquisition system (Fig. 2). Test aerosols were introduced into the aerosol photometer as a small pulse (half-width ≈ 45 ml) by activation of a solenoid valve in the bolus injection module. When the valve was open, an aerosol was ejected into the inspiratory airflow via four narrow slits (1.6 mm wide, 18 mm long) positioned across the diameter of the stream. The aerosol chamber upstream of the solenoid valve was maintained at slightly above room pressure (1–5 cmH₂O) to help inject the aerosol. The multiple-slit system was designed to ensure a rapid mixing of aerosol with the inspiratory airflow, thereby producing a well-defined small bolus. In the laser photometer, a laser beam (15 mW He-Ne, Melles Griot, Carlsbad, CA) was expanded into a thin sheet via a cylindrical lens and shone through an aerosol detection cell where the laser beam was

<table>
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<tr>
<th>Subject No.</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>FVC, ml</th>
<th>FEV₁, ml</th>
<th>FEV₁/FVC</th>
<th>TGV, ml</th>
<th>Raw, cmH₂O·l⁻¹·s</th>
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</table>

Mean ± SD 25 ± 4 181 ± 5 5,419 ± 757 4,484 ± 617 0.83 ± 0.06 3,378 ± 647 1.15 ± 0.59

FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; TGV, thoracic gas volume; Raw, airway resistance.
scattered by aerosol particles. The scattered light was collected on a photomultiplier tube (model 9798B, EMI Gencom, Plainview, NY), and the signals from the photomultiplier tube were amplified to 0–10 V with a current amplifier (model 427, Keithley Instruments, Cleveland, OH) and subsequently transmitted to the data acquisition system. The aerosol detection cell was heated to 40°C by an electric resistor imbedded in the metallic block of the cell to prevent moisture condensation on the lens during exhalation. Flow rates through the laser photometer were measured by a pneumotachograph (Fleisch no. 1) in conjunction with a pressure transducer (model 239, ±1.27 cmH₂O range, Setra Systems, Acton, MA) connected directly to the inspiratory inlet of the detector cell. The data acquisition system consisted of a signal modulator and a personal computer (model 326, Dell Computer, Austin, TX) equipped with a high-speed data acquisition board capable of sampling signals at up to 27 kHz (model DT 2801A, Data Translation, Marlboro, MA). Flow and aerosol signals were displayed digitally in the signal modulator in which a built-in integrator circuit provides volume signals for inhaled and exhaled air. The volume signals were used to activate the solenoid valve and to deliver an aerosol bolus to a prescribed lung depth. For on-line data acquisition, flow and aerosol signals were acquired at a rate of 200 Hz, and flow signals were smoothed by passing them through a 50-Hz low-pass filter to eliminate spikes generated by the activation of the solenoid valve. Smoothing of aerosol signals was not necessary. All the controls for bolus inhalation, data acquisition, and analysis were programmed with ASYST software (ASYST Software Technologies, Rochester, NY).

Inhalation procedure. After a few practice breaths, the subject inhaled filtered air via a laser aerosol photometer (25-ml dead space volume) from functional residual capacity (FRC) following a prescribed breathing pattern displayed on the computer screen. The subject then activated the data acquisition mode by pressing a hand-held switch during expiration, inhaled a prescribed volume, and exhaled to residual volume (RV) at a constant flow rate (Fig. 3). During the data acquisition mode, a small aerosol bolus (~45 ml half-width) was introduced into the inspiratory stream by opening an aerosol valve for a predetermined duration of time. The duration of valve opening was adjusted between 50 and 250 ms, depending on flow rate, to maintain a consistent bolus volume: the faster the flow rate, the shorter the duration. The peak concentration of bolus was maintained at 6–9 V; 1 V was equivalent to ~5,000 particles/cm³ for 1-µm-diameter particles. The bolus was delivered to a lung depth (Vₚ) of 100–500 ml in 50-ml increments. Typical bolus signals are shown in Fig. 4. This procedure was repeated with monodisperse aerosols of three different particle sizes [1, 3, and 5 µm diameter (Dₚ)], and for each Dₚ three different flow rates (Q = 150, 250, and 500 ml/s) were used. In all tests the same Q was used for inspiration and expiration, and the inspiratory volume was maintained at 500 ml from FRC. For a given bolus delivery condition, at least five repeated measurements were made. For the purpose of comparison and validation, nonbolus aerosols were also used in a few subjects. The subject inhaled nonbolus aerosols from a 20-liter bag with a single-breath maneuver (inhalation from FRC and exhalation to RV) that was the same maneuver used for bolus aerosols, and TDF values were obtained for several breaths. The same aerosols were then inhaled with a continuous-breathing maneuver (inhalation from FRC and exhalation to FRC) for 1 min, and TDF was obtained breath by breath.

Data analysis. For each breath the total number of particles inhaled (Nᵢ) and exhaled (Nₑ) was calculated by integrating the product of aerosol number concentration, C(t), and volumetric Q(t), over inspiratory and expiratory period, respectively. In the calculation the baseline concentration was set at 3% of the peak value of the exhaled bolus and was subtracted from the acquired signals. Recovery of bolus aerosol (RCᵢ) was plotted as a function of Vₚp, where Vₚp was defined as the inhaled air volume from the mean concentration of the bolus to the end of inspiration. RC data were then grouped for 10 Vₚp values from 50 to 500 ml with an interval of 50 ml. RC values (means ± SD) for each Vₚp were obtained by averaging all RC data falling within Vₚp ± 25 ml. Volumetric lung regions (Vₚ, j = 1–10) were defined by the regions confined between two adjacent Vₚp values. For example, V₁ is the region between Vₚp = 0 and 50 ml; V₂ is the region between Vₚp = 50 and 100 ml, and so on. The mean RC vs. Vₚp data were

![Fig. 3. Schematic diagram depicting an inhalation maneuver for bolus aerosols. Inhalation started at functional residual capacity (FRC) with 500-ml tidal volume, and exhalation was to residual capacity. An aerosol bolus (45 ml half-width) was injected at prescribed time points during inspiration. Conc, concentration.](http://jap.physiology.org/)
used to calculate values of local deposition efficiency (LDE) and LDF for each volumetric region by Eqs. 5 and 6, respectively.

Surface dose in each volumetric region was calculated by dividing LDF by surface area of the region. Weibel's symmetrical lung model (32) adjusted for the lung volume of 3,500 ml (mean FRC of all subjects plus one-half of VT) was used to calculate the surface area. In Weibel's model the lung volume was divided into 50-ml volumetric regions comparable to experimental values, and the surface area of each region was calculated on the basis of the dimensions of individual airway branches.

For the purpose of comparison, deposition fractions in the conventional three-compartment lung regions were determined. Each of the upper airways (UA), tracheobronchial airways (TB), and alveolar regions (AL) was defined by the volumeregion of 0–50, 50–150, and 150–500 ml, respectively. Deposition values in each of the regions were obtained by summing LDF values of \( V_i \) composing the corresponding regions.

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TDF was obtained by summing LDFs of all \( V_i \) compartments. TDF was also obtained by direct integration of RC vs. \( V_p \) curves, inasmuch as

\[
TDF = \int (1 - RC) dV_p \int dV_p
\]

for \( V_p = 0–500 \) ml. The integration was performed for each of 10 \( V_p \) values (50-ml interval) by Simpson's rule, and the results were compared with those obtained by summation of LDFs.

RESULTS

Recovery vs. Penetration Depth With Respect to Particle Size and Flow

Typical recovery data from one subject and the summary of all subject data are shown in Figs. 5 and 6, respectively. RC decreased with increasing \( V_p \) for each

**Fig. 5. Typical bolus aerosol recovery (RC) data from a young normal subject. Data points form compact lines with very little variation.**

**Fig. 6. Bolus recovery as a function of penetration depth for 1- (dashed line), 3- (dashed-dotted line), and 5-µm-diameter (solid line) particles with 3 different flow rates: 150 ( ), 250 ( ), and 500 ( ) ml/s. For clarity, error bars (±SD) are shown only for 250 ml/s flow rate. Magnitude of error for other flow rates is similar to that for 250 ml/s.**

\( D_p \) and \( Q \), but the decrease of RC was greater with particles of larger size. For example, for \( Q = 250 \) ml/s RC decreased from 1.0 to 0.78 for \( D_p = 1.0 \) µm, from 0.99 to 0.05 for \( D_p = 3.0 \) µm, and from 0.94 to 0 for \( D_p = 5.0 \) µm as \( V_p \) increased from 50 to 500 ml. Figures 5 and 6 also show that RC values were smaller with lower \( Q \) values (longer respiratory time) for a given \( D_p \). For example, RC (mean ± SD) was 0.93 ± 0.03, 0.96 ± 0.01, and 0.97 ± 0.01 for \( D_p = 1.0 \) µm; 0.54 ± 0.06, 0.68 ± 0.08, and 0.79 ± 0.04 for \( D_p = 3.0 \) µm; and 0.25 ± 0.06, 0.35 ± 0.05, and 0.40 ± 0.08 for \( D_p = 5.0 \) µm for \( Q = 150, 250, \) and 500 ml/min, respectively, at \( V_p = 200 \) ml. The Q effect was consistent for other values of \( V_p \) as shown in Fig. 6, although the effect was minimal for \( D_p = 5 \) µm, particularly with high \( Q \) values at small \( V_p \) regions. RC values were very repeatable and consistent in a given subject, as shown in Fig. 5, and the intersubject variability was small, as indicated by small error bars in Fig. 6.

Local Deposition Efficiency

Figure 7 shows LDE values for each 50-ml volumetric region as a function of \( V_p \) for different \( D_p \) and \( Q \). LDE increased with an increase of \( V_p \) for each

**Fig. 7. Local deposition efficiency (LDE) in three 50-ml volumetric regions of the lung as a function of \( V_p \) for different \( D_p \) and \( Q \). LDE increased with increasing \( V_p \) for each**

\( D_p \) and \( Q \), but the decrease of RC was greater with particles of larger size. For example, for \( Q = 250 \) ml/s RC decreased from 1.0 to 0.78 for \( D_p = 1.0 \) µm, from 0.99 to 0.05 for \( D_p = 3.0 \) µm, and from 0.94 to 0 for \( D_p = 5.0 \) µm as \( V_p \) increased from 50 to 500 ml. Figures 5 and 6 also show that RC values were smaller with lower \( Q \) values (longer respiratory time) for a given \( D_p \). For example, RC (mean ± SD) was 0.93 ± 0.03, 0.96 ± 0.01, and 0.97 ± 0.01 for \( D_p = 1.0 \) µm; 0.54 ± 0.06, 0.68 ± 0.08, and 0.79 ± 0.04 for \( D_p = 3.0 \) µm; and 0.25 ± 0.06, 0.35 ± 0.05, and 0.40 ± 0.08 for \( D_p = 5.0 \) µm for \( Q = 150, 250, \) and 500 ml/min, respectively, at \( V_p = 200 \) ml. The Q effect was consistent for other values of \( V_p \) as shown in Fig. 6, although the effect was minimal for \( D_p = 5 \) µm, particularly with high \( Q \) values at small \( V_p \) regions. RC values were very repeatable and consistent in a given subject, as shown in Fig. 5, and the intersubject variability was small, as indicated by small error bars in Fig. 6.

Local Deposition Efficiency

Figure 7 shows LDE values for each 50-ml volumetric region as a function of \( V_p \) for different \( D_p \) and \( Q \). LDE increased with an increase of \( V_p \) for each experimental conditions. For each condition, LDE was greater with larger \( D_p \) or lower \( Q \) in all volumetric regions of the lung. For example, for \( Q = 250 \) ml/s, LDE increased from 0.005 to 0.022 for \( D_p = 1.0 \) µm, from 0.0045 to 0.29 for \( D_p = 3.0 \) µm, and from 0.03 to 0.38 for \( D_p = 5.0 \) µm as \( V_p \) increased from 50 to 500 ml. With a decrease of \( Q \) from 250 to 150 ml/s, LDE increased by 65–184, 9–76, and 6–68% for \( D_p = 1, 3, \) and 5 µm, respectively, depending on \( V_p \). The increase was more pronounced with \( D_p = 1 \) µm than \( D_p = 3 \) or 5 µm in all regions of the lung, but the difference was particularly noticeable for \( V_p > 250 \) ml. A smaller but consistent increase was found in most of the lung regions with \( D_p = 3 \) and 5 µm.
When $Q^{\prime}$ was increased from 250 to 500 ml/s, LDE decreased, averaging across lung regions, by 54 ± 17, 45 ± 4, and 17 ± 15% for $D_{p} = 1, 3,$ and 5 µm, respectively. The percent decrease was consistent in the deep regions of the lung ($V_{p} \leq 250$ ml) for each $D_{p}$, but considerable variation was found in the small $V_{p}$ regions. Overall, LDE varied more with small-size particles and with low $Q^{\prime}$ values.

### Local Deposition Fraction

Deposition values in each 50-ml volumetric region are shown in Fig. 8. LDF varied widely with $V_{p}$, ranging from −0 to 0.028 for $D_{p} = 1$ µm, from 0.004 to 0.11 for $D_{p} = 3$ µm, and from 0.04 to 0.16 for $D_{p} = 5$ µm for $Q^{\prime}$ values used. LDF increased with increasing $V_{p}$ initially, reached a peak value, and then decreased with a further increase of $V_{p}$. The peak value was found at $V_{p} = 300–350$ ml for $D_{p} = 1$ µm, but the peak region was shifted proximally to $V_{p} = 200–250$ ml for $D_{p} = 3$ µm and to $V_{p} = 100–150$ ml for $D_{p} = 5$ µm (Fig. 9). LDF increased with a decrease in $Q^{\prime}$ in all regions of $V_{p}$, but particularly in the regions of large $V_{p}$ for $D_{p} = 1$ µm. However, for $D_{p} = 3$ and 5 µm the effect of $Q^{\prime}$ was minimal in the regions of large $V_{p}$. The Q effect was small in all regions of $V_{p}$ for $D_{p} = 5$ µm. In the shallow regions of the lung ($V_{p} < 250$ ml) LDF increased with an increase of $D_{p}$ regardless of $Q$. However, in the deeper regions ($V_{p} > 250$ ml) the effect of $D_{p}$ was small and LDF was comparable between $D_{p} = 3$ and 5 µm.

### Surface Dose in Local Lung Regions (LDF/Regional Surface Area)

The results of surface dose in local lung regions are summarized in Table 2 and illustrated in Fig. 9 for $Q^{\prime} = 250$ ml/s. Because of difficulties in estimating the surface area of the upper airways ($V_{p} < 50$ ml), the surface dose was obtained for $V_{p} > 50$ ml. Surface dose was much greater in the shallow airway region ($V_{p} < 200$ ml) than in the deeper alveolar region ($V_{p} > 200$ ml). The difference was more pronounced with larger particles. Surface dose was greater in the most proximal regions of the lung ($V_{p} > 250$ ml).
mal region of the lung ($V_p = 50–100$ ml) than at $V_p = 150–200$ and $100–150$ ml, regardless of $D_p$ and $Q$. Surface dose was 2–17 times greater in the shallow airway region of $V_p = 50–100$ ml and 1–5 times greater in the region of $V_p = 150–200$ ml than in the region of $V_p = 250–350$ ml, which represents mainly the alveolar region, for all three $D_p$ and $Q$ values. The value was greater with larger $D_p$ but did not vary much with $Q$.

Upper Airway, Tracheobronchial, and Alveolar Deposition

Three-compartment regional lung deposition results are summarized in Fig. 10. With a standard breathing pattern of $V_T = 500$ ml and frequency of 15 breaths/min ($Q = 250$ ml/s), UA deposition (oropharyngeal + laryngeal) was $0.7 \pm 0.7$ and $4.1 \pm 3\%$ for $D_p = 3$ and $5$ µm, respectively. UA deposition was negligible for $D_p = 1$ µm. TB deposition was $1.7 \pm 0.8, 10.7 \pm 3.9$, and $26.3 \pm 4.3\%$ and AV deposition was $7.4 \pm 1.5, 39.7 \pm 1.7$, and $39.0 \pm 4.0\%$ for $D_p = 1, 3$, and $5$ µm, respectively.

Deposition was greater with $Q = 150$ ml/s and smaller with $Q = 500$ ml/s than with $Q = 250$ ml/s in all three regions for $D_p = 1$ and $3$ µm. With $D_p = 5$ µm, TB deposition increased with a decrease in $Q$ as with $D_p = 1$ and $3$ µm, but the effect of $Q$ was not consistent in UA and AV deposition.

Total Lung Deposition

The bolus data were analyzed by two methods to determine the TDF: 1) summation of LDF values in all local regions, as in Eq. 7, and 2) direct integration of RC vs. $V_p$ curves, as in Eq. 8. TDF values were also obtained with nonbolus aerosols with the same single-breath maneuvers used for bolus aerosols. The results are summarized in Table 3. Also included in Table 3 are TDF values obtained with controlled continuous breathing. Mean TDF values obtained with the LDF method ranged from 4 to 18, 37 to 59, and 66 to 75% for $D_p = 1, 3$, and $5$ µm, respectively, at $Q = 150–500$ ml/s. TDF was greater with smaller $Q$ values for three $D_p$ values. These values were consistent with those obtained with the integration method for all $D_p$ and $Q$ values tested, although values with the LDF method tended to be greater than those with the integration method (P = NS). Because the integration method utilized raw data with no artificial divisions of lung volume, the good

### Table 2. Surface dose of inhaled particles in local regions of healthy human lung during normal breathing

<table>
<thead>
<tr>
<th>Lung Regions, ml</th>
<th>$D_p = 1$ µm</th>
<th>$D_p = 3$ µm</th>
<th>$D_p = 5$ µm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>150 ml/s</td>
<td>250 ml/s</td>
<td>500 ml/s</td>
</tr>
<tr>
<td>50–100</td>
<td>4.78</td>
<td>2.58</td>
<td>14.6</td>
</tr>
<tr>
<td>100–150</td>
<td>3.63</td>
<td>1.70</td>
<td>11.8</td>
</tr>
<tr>
<td>150–200</td>
<td>2.31</td>
<td>1.24</td>
<td>11.3</td>
</tr>
<tr>
<td>200–250</td>
<td>3.33</td>
<td>2.45</td>
<td>3.82</td>
</tr>
<tr>
<td>250–350</td>
<td>4.00</td>
<td>1.71</td>
<td>3.42</td>
</tr>
<tr>
<td>350–500</td>
<td>1.66</td>
<td>1.64</td>
<td>1.45</td>
</tr>
</tbody>
</table>

Values are means of 11 observations; surface dose = local deposition fraction/local surface area (cm²) × 10⁶. Surface area was calculated from Weibel’s symmetrical lung model (32) at a lung volume of 3,500 ml. $D_p$, particle diameter; 150, 250, and 500 ml/s, respiratory flow rate.

### Table 3. Comparison of percent TDF determined by four different methods in young normal subjects

<table>
<thead>
<tr>
<th>$Q$, ml/s</th>
<th>Summation of LDF</th>
<th>RC vs. $V_p$ Integration</th>
<th>Nonbolus Single Breath</th>
<th>Nonbolus Steady-State Breathing</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>$D_p = 1$ µm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>$D_p = 3$ µm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>$D_p = 5$ µm</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD of 11 observations. Tidal volume was 500 ml for all tests. $Q$, respiratory flow rate; TDF, total deposition fraction; LDF, local deposition fraction; RC, recovery; $V_p$, volumetric penetration.
agreement between the two methods indicates that the calculation schemes used for determining LDE and LDF of local lung regions are accurate. Table 3 also shows that TDF values obtained with nonbolus aerosols are comparable to those of the LDF and integration methods, indicating that a series of bolus inhalation is indeed equivalent to inhalation of a single whole-breath aerosol.

TDF values obtained with the single-breath LDE or integration method were comparable to those obtained with controlled continuous breathing for $D_p = 3$ and 5 $\mu$m but much smaller than with continuous breathing for $D_p = 1$ $\mu$m. The results indicate that deposition of particles with $D_p = 3$ and 5 $\mu$m was completed at a level of FRC during exhalation. Therefore, an extended exhalation from FRC to RV could not recover any more particles. However, because of a low deposition efficiency, particles with $D_p = 1$ $\mu$m could remain airborne in the airway space and can be exhaled with reserve air below FRC, resulting in a decrease in deposition with single-breath inhalation.

Comparison With Other Studies

TDF and three-compartment regional deposition results were compared with results from previous studies. Because the majority of the data reported previously was obtained with widely varying breathing patterns (12, 30), two studies were selected for comparison; these studies employed the same breathing pattern used in the present study: one experimental (15) and one theoretical (33). The results of $D_p = 1$ $\mu$m were excluded because of the discrepancy between single-breath and steady-state breathing, as shown above. The results are shown in Fig. 11. The present TDF values are in good agreement with those of two previous studies. However, the regional deposition values were variable among the studies. In the present study, AL deposition was greater but UA deposition was smaller than in the previous studies. The TB deposition values were greater than in previous experiments but smaller than the theoretical predictions.

DISCUSSION

We used a serial bolus aerosol delivery method to measure regional deposition of inhaled particles in 10 volumetric regions of the lungs of young adults during normal breathing. This was the first systematic investigation for determining regional deposition in humans in situ with inert aerosols. The results demonstrate that 1) deposition distribution within the lung is highly uneven along the volumetric depth of the lung and that the site of peak deposition shifts from the distal to the proximal region of the lung with an increase of $D_p$, and 2) surface dose was many times greater in the conducting airways than in the alveolar region regardless of $D_p$ and $Q$. The bolus aerosol method has been used previously for a variety of studies: to investigate convective mixing of airway flow (14, 26), to detect small airway obstruction (1, 25), or to measure effective airway dimensions at local regions of the lung (2, 11).

However, the method has not been fully implemented for measuring regional lung deposition during normal breathing. Heyder et al. (13) first proposed the idea of using bolus aerosols to assess regional deposition in the lung. Using a mathematical scheme that was somewhat cumbersome, they calculated deposition efficiencies of 1-$\mu$m-diameter particles in 10 volumetric regions of the lung. The bolus data used for the calculation were obtained in two subjects who inhaled the bolus aerosol with a fixed breathing pattern of $V_r = 1,000$ ml and $Q = 250$ ml/s. In the present study we developed a simple unambiguous mathematical scheme to calculate regional deposition efficiencies; this scheme involved only two consecutive bolus recovery values. The method was thoroughly examined with aerosols with different-size particles ($D_p = 1–5$ $\mu$m) and at different $Q$ (150–500 ml/s) in a large number of subjects.

Theoretical studies suggest that particles in the size range of 1–5 $\mu$m diameter deposit in the lung mainly by inertial impaction and sedimentation (9, 20). Theory predicts that inertial impaction plays a significant role in the large airways where flow velocity is high, whereas sedimentation plays a dominant role in the small peripheral airways. Because the diameter of the airways decreases with increasing depth into the lung, thus reducing the sedimentation distance, deposition becomes more efficient in the distal regions of the lung. Our results showing an increase of LDE with respect to $V_p$ are consistent with theoretical expectations. Also LDE is greater with lower $Q$ in the $D_p$ range tested in all regions of the lung. However, LDE was comparable between low and high $Q$ with particles of larger $D_p$.
particularly in the shallow lung regions. This indicates that particles in this size range deposit in the lung mainly by sedimentation and that inertial impaction plays a significant role only in the regions of small \( V^* \), both of which are consistent with theoretical expectations.

Our results show that deposition sites vary with \( D_p \), shifting the peak deposition site from the peripheral to proximal regions with an increase of \( D_p \) from 1 to 5 \( \mu \)m. This finding was expected, because small-size particles, i.e., \( D_p = 1 \) \( \mu \)m, had little chance of deposition in the proximal regions because of very low LDE and subsequently could penetrate into deep regions of the lung where deposition efficiencies were high. However, because of enhanced losses in the proximal regions, large-size particles could not reach deep lung regions in large quantity. As a result, low values of LDF could be expected in the peripheral regions, despite high values of LDE. Deposition values in the peripheral regions remained fairly constant, despite the wide variation of \( Q^* \), particularly for large-size particles. This result was due to the fact that LDF was determined by the product of the amount of particles available and the value of LDE in the peripheral regions. With low \( Q^* \), LDE was high but the number of particles available was small, resulting in consistent values of LDF. This finding suggests that, for \( D_p > 1 \) \( \mu \)m, regional deposition in the lung is dictated primarily by particle size. \( Q^* \), however, will likely become an important factor for regional deposition for smaller-size particles (i.e., \( D_p \leq 1 \) \( \mu \)m). Because the ratio of surface area to volume of the respiratory airways is approximately proportional to the inverse of airway diameter, surface area is smaller in the proximal than in the peripheral volume regions. This will result in an increase in local surface dose in the proximal volume regions. In the present study the surface dose estimated by using airway dimensions of Weibel's lung model was found to be highest in the 50- to 100-ml (large airway) regions followed by the 150- to 200-ml (small airway) regions, regardless of \( D_p \) and \( Q^* \). Previously, Hofmann et al. (16) showed in their theoretical calculation that surface dose was highest in the large airway regions and decreased monotonically with increasing lung depth beyond the large airway regions. Our results are consistent with this prediction, in that the large airway regions received the greatest surface dose. However, the present results further indicate that the small airway regions are also a major site of pronounced surface dose. We showed previously that, within the bronchial airways, deposition occurs preferentially near the bifurcation ridges, resulting in a manyfold increase in surface dose near the bifurcation compared with straight airway segments (22). The implication of these results is that although the anatomic structure of the bronchial airways (as a first-line host defense) might have been evolved to sustain the insult of inhaled pollutants, the high magnitude of local surface dose could have potential to induce significant health hazard. The finding has relevance to the clinical observations that many lung diseases often originate from the small airways (17).

The present study employed a single-breath inhalation method that involved maximal expiration to RV. Because particles remaining in the airway space at the end of VT expiration would be washed out with continued maximal exhalation, the single-breath inhalation will result in lower deposition than expected with steady-state breathing, particularly for small-size particles with small deposition efficiency. Our results showing lower TDF values with single-breath than with steady-state breathing for \( D_p = 1 \) \( \mu \)m are consistent with the above reasoning. However, our results with \( D_p = 3 \) and 5 \( \mu \)m show comparable TDF values between single-breath and steady-state inhalation, indicating that deposition of these particles is essentially complete within each breath of steady-state breathing. Therefore, for the purpose of comparison with controlled continuous breathing, the present regional deposition data are valid only for these large-size particles.

Although our TDF values are comparable to those of previous studies (15, 32), the regional deposition values are in variance. One of the reasons for the inconsistency might be differences in the actual anatomic regions of the lung involved in the deposition measurements. In the present study the lung regions were determined on the basis of the volume of inhaled air: 50 ml for the UA and 50–150 ml for the TB regions. Previously, the volume of the oropharyngeal cavity has been reported variably, ranging from 35 to 50 ml (5, 11, 30). Hart et al. (10) measured the dead space volume (UA + TB) in a large number of adult subjects and found that the dead space volume was correlated linearly with height. For a man with a height of 180 cm, which was the average height of subjects in the current study, the dead space volume was ~160 ml. Therefore, our values used for the UA and TB regions are consistent with the above reported values. However, the actual delivery of aerosol boluses to these target regions may not be fully warranted for reasons discussed below.

The results of previous regional lung deposition studies were obtained by external scanning of the head (UA deposition) combined with mucociliary clearance measurements (TB deposition). Because of large variability of head deposition (30) and many factors other than just particle deposition affecting measurements of mucociliary clearance rate (31), one may not be certain whether mucociliary clearance measurement truly represents the TB deposition. These factors could have contributed to some of the differences in regional deposition among the present and previous experimental studies. Also the difference between the present results and those of previous theoretical studies is rather small, suggesting that experimental methods may indeed be the major factor for the observed difference.

The accuracy of the present results is limited by how the inhaled bolus flows in and out of intended lung regions. To ensure that inhaled boluses actually fill the intended anatomic sites in an orderly serial fashion, the following conditions may need to be satisfied: 1) an even distribution of inhaled air throughout the lung, 2) an equal time for filling and emptying of different lung
regions, and 3) the reversibility of inspired air, i.e., the first-in last-out principle. Although these conditions may not be warranted in patients with lung disease, many ventilation distribution or imaging studies indicate that ventilation patterns of normal subjects are even and reversible (3, 19). However, there have been some suggestions that bolus aerosols may reach the lung regions deeper than anticipated via preferential flow passages (29). This implies that inhaled air may not be distributed evenly in the normal lungs, and the distribution patterns may vary during inspiration. If this really occurs, the actual anatomic regions may not be identified by serial compartmentalization of inhaled air. However, such an abnormal bolus distribution pattern is unlikely to be consistent among subjects or within a subject who inhales aerosols with different flow rates. This would result in wide inter- and intrasubject variation of bolus recovery or deposition data expressed by lung depth, particularly those in regions of shallow depth. However, our deposition results were very consistent with respect to lung depth for each subject and also among subjects, as shown in Figs. 5 and 6, respectively. In every set of measurements in all subjects, RC values decreased monotonically with an increase of \( V_p \), indicating that a series of bolus aerosols was indeed delivered to regions of successively greater depth in an orderly fashion.

Previous studies suggested that bolus aerosols may penetrate the lung deeper than anticipated because of axial streaming (5, 29). This can take place because flow streams move faster in the central core than near the wall surface of a tube. However, because inhaled particles remain in the central core of the airways during axial streaming, there would be little chance of deposition of those particles in the overpenetrated regions if particles are exhaled immediately without breath holding. Furthermore, in our preliminary studies using a straight-tube model, we found that recovery of bolus aerosols delivered to the exit end of the tube was consistent with predictions based on the mean \( V_p \). Because a particle filter was attached at the exit end of the tube, axial streaming could have resulted in greater particle collection in the filter and subsequently smaller recovery than expected. The results suggest that axial streaming of aerosol may not take place with cyclic flows to the same extent as predicted by the theory of fully developed laminar flow. Therefore, inhaled aerosol boluses would be expected to remain in the intended lung regions, and the present results may be a reasonable representation of regional deposition in normal human lungs. There are no known methods that can measure directly particle deposition sites in the human lung. Invasive animal studies may provide some clues of deposition sites but are unlikely to produce quantitative regional dosimetric data that can be extrapolated to human lungs. The present results may be useful, within their limitation, for assessing regional variation of lung deposition in humans.

In conclusion, we measured regional lung deposition of inhaled particles by means of the serial bolus aerosol delivery method. Deposition in lung regions as small as 50 ml was measured in healthy normal humans. We found remarkable variation in regional deposition dose showing the peak region dose, exceeding many times the average lung dose. These observations may have significant implications in health risk assessment of inhaled pollutant particles and serve as a basis for improved risk assessment models.

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REFERENCES


