Regional deposition of inhaled particles in human lungs: comparison between men and women

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Kim, Chong S., and S. C. Hu. Regional deposition of inhaled particles in human lungs: comparison between men and women, J. Appl. Physiol. 84(6): 1834–1844, 1998.—We measured detailed regional deposition patterns of inhaled particles in healthy adult male (n = 11; 25 ± 4 yr of age) and female (n = 11; 25 ± 3 yr of age) subjects by means of a serial bolus aerosol delivery technique for monodisperse fine [particle diameter (Dp) = 1 µm] and coarse aerosols (Dp = 3 and 5 µm). The bolus aerosol (40 ml half-width) was delivered to a specific volumetric depth (Vp) of the lung ranging from 100 to 500 ml with a 50-ml increment, and local deposition fraction (LDF) was assessed for each of the 10 local volumetric regions. In all subjects, the deposition distribution pattern was very uneven with respect to Vp, showing characteristic unimodal curves with respect to particle size and flow rate. However, the unevenness was more pronounced in women. LDF tended to be greater in all regions of the lung in women than in men for Dp = 1 µm. For Dp = 3 and 5 µm, LDF showed a marked enhancement in the shallow region of Vp ≤ 200 ml in women compared with men (P < 0.05). LDF in women was comparable to or smaller than those of men in deep lung regions of Vp > 200 ml. Total lung deposition was comparable between men and women for fine particles but was consistently greater in women than men for coarse particles regardless of flow rates used: the difference ranged from 9 to 31% and was greater with higher flow rates (P < 0.05). The results indicate that 1) particle deposition characteristics differ between healthy men and women under controlled breathing conditions and 2) deposition in women is greater than that in men.

DEPOSITION SITE AND DOSE of inhaled particles within the lung vary widely depending on particle size, breathing pattern, and lung structure. Generally, particles deposit more in the proximal airways with an increase in particle size and breathing rates, whereas enhanced pulmonary deposition takes place with small-size particles and slow breathing rates (9, 10, 30). Within the bronchial airways, particle deposition tends to localize at and near the carina, particularly with particles >1 µm in diameter (17, 19). In patients with obstructive airway disease, deposition patterns are very heterogeneous and marked by a pronounced deposition in the central airways and various focal “hot” spots in different regions of the lung (22, 26, 29). Overall lung deposition has also been shown to increase in the lungs with obstructed airways and abnormal geometry (15, 20). Therefore, regional deposition dose, or local tissue burdens, can be significantly different among individuals, even if total lung deposition values are comparable. It is also possible that particle burdens could reach the threshold limits at local lung regions under exposure conditions that are normally acceptable, particularly in individuals with compromised lungs. This may have significant implications in health risk assessment of pollutant particulates and in identifying subpopulations prone to overexposure to particulate matter.

Previous studies investigated regional lung deposition primarily by inhalation of radiolabeled aerosols and subsequent measurements of radioactivity in the lung by either a gamma camera or whole body counter. The results have been reported for three large lung compartments, e.g., extrathoracic (larynx and above), tracheobronchial (TB), and alveolar regions (AL) (23, 27, 28). Because these measurements are closely linked to particle clearance from the TB airways, the results have been instrumental for estimating a short- and long-term retention of particles in the lung. However, the three lung compartments are not detailed enough to assess local variations of deposition dose in the lung and to differentiate deposition characteristics among individuals. The reported data were also based largely on measurements in healthy male adults, and it is not warranted for these data to be applied to population groups with different ages and genders.

There are many differences in the anatomy of the lung between men and women. For instance, the size of the lung is smaller in women compared with men, particularly in the upper airways (UA; pharynx and larynx) and the large conducting airways (7, 24). The dynamics of the larynx and vocal cord are also different, as evidenced by different pitches in sound that result partly from different tissue densities and muscle tension. These anatomic and dynamic differences can be significant factors for altering deposition characteristics in the lung. However, how these factors affect deposition characteristics in women and the potential impact of the results in health risk assessment have not been investigated thoroughly. Earlier studies showed that total lung deposition values are comparable between men and women (2, 21, 25) or slightly greater in women than men, depending on breathing patterns (2). However, Pritchard et al. (25) found that deposition distribution within the lung was more proximal in women than men under various breathing conditions and suggested that there is a potential for excessive deposition in the UA regions in women. Presently, there are no systematic data available about the magnitude and specific lung regions of the potential dose difference between genders.

Previously, our laboratory has reported a new method that can measure detailed regional lung deposition by
means of serial bolus delivery technique and have shown distinctive deposition patterns in young adults (18). In the present study, we measured regional lung deposition in each of 10 equally divided volumetric compartments in healthy male and female adults and compared the results with respect to different particle sizes and breathing patterns. The purpose of this study was to verify the potential effects of gender on deposition characteristics of inhaled particles and to obtain accurate exposure-dose relationships that can be used to develop improved health risk assessment models for inhaled particulate.

**METHODS**

Subjects. Healthy young subjects, both men and women in equal number (n = 11 in each group), were recruited locally. Ages of the subjects ranged from 21 to 32 yr and were matched between men and women. The subjects had no history of smoking, 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. Those who passed the initial screening had their basic lung functions measured by both spirometry and body plethysmography. All subjects under went a screening procedure that included a complete medical history, physical examination, SMA-20 blood chemistry screen, and complete blood count with differential. Those who passed the initial screening had their basic lung functions measured by both 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 at Chapel Hill. Subject characteristics and lung function test results are given in Table 1.

Table 1. Subject characteristics and lung function test results

<table>
<thead>
<tr>
<th>Group</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>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>25 ± 4</td>
<td>181 ± 5</td>
<td>5,419 ± 757</td>
<td>4,484 ± 617</td>
<td>0.83 ± 0.06</td>
<td>3,378 ± 647</td>
<td>1.15 ± 0.59</td>
</tr>
<tr>
<td>Women</td>
<td>25 ± 3</td>
<td>167 ± 5</td>
<td>4,008 ± 584</td>
<td>3,204 ± 520</td>
<td>0.80 ± 0.06</td>
<td>2,955 ± 681</td>
<td>1.79 ± 0.68</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 11 men and 11 women. FVC, forced vital capacity; FEV₁, forced expiratory volume at 1 s; TGV, thoracic gas volume; Raw, airway resistance.

Fig. 1. Illustration of calculation procedures for deposition efficiency in jth compartment (xᵢ) and deposition fraction in local lung regions in a serial compartment lung model. Top: 3-compartment model (j = 1–3). Aerosol recovery (RC) and bolus deposition fraction in each compartment (BDFᵢ) are shown for each sequential bolus inhalation (i = 1–3). Values of xᵢ were assumed to be same on inspiration and expiration. Expressions for inspiratory and expiratory BDF are shown on right of each diagram. Nᵢn and Nᵢex total no. of particles inhaled and exhaled, respectively. Right: expressions for RC. Expressions for both RC and BDF are shown as a fraction of inhaled aerosol entering the mouth.
entering the same compartment. Once $\chi$ 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, where the subscript $i$ represents the number of sequential bolus inhalations. The local deposition fraction in the $j$th compartment (LDF$_j$) can then be obtained by

$$LDF_j = \frac{1}{n} \sum_{i=1}^{n} BDF_{ij}$$

and subsequently TDF of the entire $V_T$ aerosol can be obtained by the summation of LDF$_j$, 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 RC values of aerosols from a series of bolus inhalations. The method is illustrated schematically in Fig. 1.

Generation of test aerosols. Monodisperse DES (di-2-ethylhexyl sebacate) oil aerosols were generated by an evaporation-condensation-type aerosol generator (MAGE, Lavoro E Ambiante, Bologna, Italy). The performance characteristics of the MAGE generator have been described previously (11). 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 lbs./in.$^2$). Liquid aerosols generated initially were passed through a drying column filled with silica gel, and the resulting dry nuclei aerosols were passed at a rate of 1–3 l/min through a “boiler” in which DES oil was heated and vaporized at temperatures of 170–250°C. The mixture of nuclei and DES oil vapor from the boiler was passed through a reheater 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 using 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 (APS 3310, TSI, St. Paul, MN) equipped with an online aerosol diluter (1:100 ratio, model 3302, TSI). Concentration of aerosols was maintained at a level of $2 \times 10^3$ to $40 \times 10^3$ particles/cm$^2$, depending on particle size, with 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 bolus (half-width = 45 ml) by activating a solenoid valve in the bolus injection module. When the valve was open, an aerosol was ejected into the inspiratory airstream via four narrow slits (1.6 mm wide and 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 cmH$_2$O) to help inject the aerosol. The multiphase 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 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 the range of 0–10 V with a current amplifier (model 427, Keithly 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 cmH$_2$O 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 a rate of up to 27 kHz (DT2801A, Data Translation, Marlboro, MA). Both 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 online data acquisition, both 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 of the controls for bolus inhalation, data acquisition, and analysis were programmed with ASYST software (ASYST Software Technologies, Rochester, NY).

Bolus aerosol 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) after a prescribed breathing pattern displayed on the computer screen. The subject then activated the data-acquisition mode by pressing a handheld switch displayed on the computer screen. The subject then activated the inspiratory stream by opening an aerosol valve for a prescribed duration (Q˙

determined duration of time. The duration of valve opening was adjusted between 50 and 250 ms, depending on Q˙, to deliver an aerosol bolus more deeply into lung and vice versa. After the exhaled air volume was maintained between 6 and 9 V; the voltage level of 1 V was equivalent to 5,000 particles/cm³ for 1-µm-diameter particles. The bolus was delivered to a lung depth ranging from 100 to 500 ml in 50-ml increments. This procedure was repeated with monodisperse aerosols of three different particle sizes (1-, 3-, and 5-µm diameter), and for each particle size three different Q˙ (150, 250, and 500 ml/s) were used. In all tests the same Q˙ was used for both 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.

Data analysis. For each breath the total number of particles inhaled (Nᵢ) and exhaled (Nₑ) were calculated by integrating the product of aerosol number concentration, C(t), and volumetric flow rate, Q(t), over the inspiratory (Ti) and expiratory (Te) period, respectively. In the calculation the baseline concentration was set at a level of 3% of the peak value of the exhaled bolus and was subtracted from the acquired signal. RC of bolus aerosol (i.e., RCᵢ) was plotted as a function of penetration depth (Vp), where Vp 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 Vp values starting from 50 to 500 ml with an interval of 50 ml. RC values (means ± SD) for each Vp were obtained by averaging all RC data falling within Vp of ± 25 ml. Volumetric lung regions (Vᵢ; j = 1–10) were defined by the regions confined between two adjacent Vp values. For example, V₁ is the region between Vp = 0 and 50 ml, V₂ is the region between Vp = 50 and 100 ml, and so on. The mean RC vs. Vp data were used to calculate values of local deposition efficiency (x or LDE) and LDF for each volumetric region by Eqs. 4 and 5, respectively.

For the purpose of comparison with the conventional regional lung deposition studies, deposition fractions in three lung compartments were obtained: the volume region of 0–50 ml for UA, the volume region of 50–150 ml for TB, and the volume region of 150–500 ml for AL. Deposition values in each of the regions were obtained by adding up LDF values of all Vᵢ, composing the corresponding regions. TDF was obtained by adding up LDF values of all Vᵢ compartments. Differences in RC and deposition values between men and women were tested by using Student’s t-test, and the differences were considered to be significant if P < 0.05.

RESULTS

Bolus aerosol RC. Typical bolus RC data from one male subject are shown in Fig. 4 for three different particle sizes with a fixed Q˙ of 250 ml/s, and the summary of all subject data for men and women is shown in Fig. 5 for three different values of particle diameter (Dᵢ; 1, 3, and 5 µm) and Q˙ (150, 250, and 500 ml/s). RC values were very repeatable and consistent in a given subject, as shown in Fig. 4, and the intersubject variability was small, as indicated by small error bars shown in Fig. 5. RC decreased monotonically with increasing Vp for each particle size and Q˙ used, but the decrease of RC was greater with particles of larger size in both men and women. Figure 5 also shows that RC values were smaller with lower Q˙ (i.e., longer residence time) for a given value of Dᵢ. This flow effect was consistent for all regions of Vp except for very shallow
regions, \(V_p < 100\) ml, in which the effect of \(Q\) was small or negligible. It is also noted that the flow effect was smaller with \(D_p = 5\) µm than with \(D_p = 1\) and 3 µm, and the effect was minimal particularly in the group of women.

In Fig. 5 it is particularly noticeable that RC values are consistently smaller in women than men for all different \(D_p\) and \(Q\) values used (\(P < 0.05\)) except for \(D_p = 1\) µm in shallow regions (\(V_p < 250\) ml). The difference was greater with increasing particle size in all regions of \(V_p\). For example, the women-to-men RC ratio was 0.98, 0.70, and 0.35 for \(D_p = 1, 3,\) and 5 µm, respectively, at \(V_p = 250\) ml with a fixed \(Q\) of 250 ml/s. The ratio tended to increase with increasing \(Q\), although changes were small.

LDE. Figure 6 shows LDE values for each 50-ml volumetric region as a function of \(V_p\) for different particle sizes and \(Q\) values for both men and women. It can be seen that LDE increases consistently with an increase of \(V_p\) for all experimental conditions, with increases seen particularly in men; the larger the \(V_p\), the greater the LDE. However, in female subjects, there was a transient peak in the region of \(V_p = 100\) ml with particles of large \(D_p\) or high \(Q\) values. LDE increased with an increase in \(D_p\) or a decrease in \(Q\) in all \(V_p\) regions in both male and female subjects.

LDE was comparable between men and women for \(D_p = 1\) µm for all \(V_p\) and \(Q\) values used [\(P = \text{not significant (NS)}\)] except for \(V_p = 350\) ml at a \(Q\) of 500 ml/s, for which LDE was greater in women than men (\(P < 0.05\)). For \(D_p = 3\) and 5 µm, LDE was greater in women than men in all regions of \(V_p\) and at all \(Q\) values studied (\(P < 0.05\)) except for two \(V_p\) regions (\(P = \text{NS}\)), as shown in Fig. 6. There was a particularly marked difference between men and women in shallow regions of the lung (e.g., \(V_p = 100\) ml) with \(D_p = 3\) and 5 µm at high \(Q\) values.

LDF. Deposition values in each 50-ml volumetric region are shown in Figs. 7 and 8, in which the effects of \(D_p\) and \(Q\) are illustrated for both male and female subjects. The aforementioned figures show a wide variation of LDF with \(V_p\); LDF increased with increasing \(V_p\) initially, reached a peak value, and then de-
increased with a further increase in $V_p$. For $D_p = 1 \mu m$, the regional variation of LDF was small and the peak deposition was found in the middle to distal regions of the lung. However, with an increase in $D_p$, the peak height increased rapidly and the region of the peak deposition shifted proximally regardless of $Q$. (Fig. 7). For men, peak deposition was found in the $V_p = 300-ml$ region for $D_p = 1 \mu m$, $V_p = 200-ml$ region for $D_p = 3 \mu m$, and $V_p = 100-150-ml$ region for $D_p = 5 \mu m$. For women, the pattern was similar to that in men, but the peak height was greater and the region of the peak deposition was more proximal than those in men.

Figure 7 also shows that in the shallow regions of the lung ($V_p < 250 ml$) LDF increases with an increase in $D_p$ regardless of $Q$ values used ($P < 0.05$). However, in the deeper regions ($V_p > 250 ml$) LDF was greater with $D_p = 3 \mu m$ than with $5 \mu m$ ($P < 0.05$) in both men and women except for $Q = 500 ml/s$, with which the difference was small (e.g., in women) or negligible ($P = NS$ in men). At a low $Q$ of 150 ml/s, LDF was comparable among all three $D_p$ values in the deep lung regions, $V_p > 400 ml$.

In Fig. 8 the effects of $Q$ on LDF are shown for each of three $D_p$ studied. The value of peak deposition de-
creased gradually with an increase in Q from 150 to 500 ml/s (P < 0.05) for Dₚ = 1 and 3 µm in both men and women, but the decrease was small and negligible (P = NS) for Dₚ = 5 µm. The region of the peak deposition was shifted gradually toward the mouth as Q increased from 150 to 250 and 250 to 500 ml/s for Dₚ = 1 µm, but there was virtually no shift in the region of peak deposition for Dₚ = 5 µm in the range of Q tested. For Dₚ = 3 µm, the peak region shifted distally with an increase in Q from 150 to 250 ml/s but shifted back to the proximal region with a further increase in Q from 250 to 500 ml/s. Overall patterns of distribution of LDF as a function of Q were similar between men and women. However, the peak height was greater, particularly for Dₚ = 3 and 5 µm (P < 0.05, but P = NS for Dₚ = 1 µm), and peak deposition tended to be more localized in a smaller-size region in women than men. Figure 8 also shows that for both men and women, LDF increased with a decrease in Q in all regions of Vp for Dₚ = 1 µm, particularly in the deep lung regions: P < 0.05 for Vp > 150 ml, but P = NS for Vp ≤ 150 ml. However, for Dₚ = 3 µm, LDF increased primarily in the middle region of the lung (Vp = 100–300 ml) with lower values of Q, and changes in LDF were small or negligible in the shallow and deep lung regions. The flow effect was practically negligible in all regions of Vp for Dₚ = 5 µm in both men and women, indicating that breathing patterns may not be a significant factor for deposition distribution of this particular size particles.

In Fig. 9, direct comparisons between men and women are shown for each of the Dₚ and Q values used. For Dₚ = 1 µm, LDF tended to be greater in female than in male subjects in all regions of Vp. The difference was particularly noticeable in the middle lung regions, Vp = 150–300 ml, with low Q values, although the difference was not significant (P = NS). However, the difference was significant in larger Vp regions, ≥400 ml, with a high Q of 500 ml/s (P < 0.05). For Dₚ = 3 and 5 µm, LDF was enhanced markedly in the shallow Vp regions, <150 ml depth, in women compared with men (P < 0.05). For example, the LDF of women was 1.7–3.4 times greater than that of men at Vp = 100 ml for all three Q values tested; the difference tended to be greater at higher Q values. However, in deep lung regions (Vp > 200–250 ml) LDF was greater in men than women, particularly for Dₚ = 5 µm (P < 0.05), although the differences were small.

Three-compartment regional deposition. Three-compartment regional lung deposition values are summarized in Table 2, in which percent deposition in the UA, TB, and AL regions as well as in the total lung (TDF) are compared between men and women for Dₚ = 1, 3, and 5 µm and Q = 150, 250, and 500 ml/s. In women, UA deposition was in the range from 1.8 to 3.3 and 8.6 to 9.3% for Dₚ = 3 and 5 µm, respectively, and these values were greater than those in men (P < 0.05). UA deposition was negligible for Dₚ = 1 µm. TB deposition ranged from 15.1 to 24.8% for Dₚ = 3 µm and from 40.8 to 42.8% for Dₚ = 5 µm within the range of Q used, and these TB values were greater by 62–104% and 41–69%, respectively, compared with those in male subjects (P < 0.05). For Dₚ = 1 µm, TB values were small in both men and women, but the values tended to be greater in women than men (P = NS). AL deposition was in the range from 4.3 to 16.3% for Dₚ = 1 µm, 30.1 to 40.6% for Dₚ = 3 µm, and 28.1 to 31.6% for Dₚ = 5 µm in women. Compared with values in men, in women these values were greater by 11–23% for Dₚ = 1 µm (P = NS) but smaller by 21% for Dₚ = 5 µm (P < 0.05). TDF values were greater in women than men by 14–31% for Dₚ = 3 µm and 9–20% for Dₚ = 5 µm with Q = 150–500 ml/s (P < 0.05), and, for a given Dₚ, the difference in men vs. women was greater with an increase in Q. For Dₚ = 1 µm, TDF tended to be greater (9–28%) in women than men, but the difference was not significant.

DISCUSSION

We compared regional deposition of inhaled particles in young adult men and women in situ under controlled
Three-compartment regional lung deposition of inhaled particles in men and women

<table>
<thead>
<tr>
<th>Lung Regions</th>
<th>$D_p=1,\mu m$</th>
<th>$D_p=3,\mu m$</th>
<th>$D_p=5,\mu m$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>150</td>
<td>250</td>
<td>500</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>0.3±0.2</td>
<td>0.1±0.1</td>
<td>0.04±0.03</td>
</tr>
<tr>
<td>TB</td>
<td>2.7±0.5</td>
<td>1.5±0.2</td>
<td>1.1±0.2</td>
</tr>
<tr>
<td>AL</td>
<td>14.7±1.2</td>
<td>7.7±0.5</td>
<td>3.6±0.3</td>
</tr>
<tr>
<td>TDF</td>
<td>17.9±1.2</td>
<td>9.3±0.5</td>
<td>4.6±0.3</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>0.1±0.1</td>
<td>0.1±0.1</td>
<td>0.1±0.1</td>
</tr>
<tr>
<td>TB</td>
<td>2.9±0.6</td>
<td>1.9±0.2</td>
<td>1.5±0.3</td>
</tr>
<tr>
<td>AL</td>
<td>16.3±1.3</td>
<td>9.3±0.9</td>
<td>4.3±0.6</td>
</tr>
<tr>
<td>TDF</td>
<td>19.3±1.7</td>
<td>11.3±1.1</td>
<td>5.9±0.8</td>
</tr>
</tbody>
</table>

Deposition values (means ± SE; n = 11 in each group) are percentages of aerosol inhaled with a tidal volume of 500 ml. $D_p$, particle diameter ($\mu m$); UA, upper airways region; TB, tracheobronchial region; AL, alveolar region; TDF, total deposition fraction (sum of UA, TB, and AL); 150, 250, and 500: respiratory flow rate in ml/s. *P < 0.05 vs. men.

breathing conditions by using a serial bolus aerosol delivery method. This was the first study to investigate the effects of gender on detailed dose distribution of inhaled particles within the lung. The results demonstrate that 1) deposition distribution within human lungs is highly uneven along the volumetric depth of the lung; and 2) there are distinct differences in deposition distribution within the lung between men and women, namely, a greater deposition in the proximal airways in women than men.

We used a bolus aerosol method to assess regional lung deposition in situ with inert aerosols. Because the method does not require radiolabeled aerosols and aerosol monitoring can be achieved on-line continuously during inhalation, a large number of repeated measurements can be achieved with varying inhalation conditions in a short period of time. However, with the method regional deposition is inferred on the basis of the delivery depth of bolus aerosol and, as such, certain limitations are applied to the method, as discussed in a previous report (18). Briefly, one of the key factors affecting the accuracy of the bolus aerosol method is the distribution pattern of bolus aerosol within the lung as the aerosol flows in and out of the lung. If the aerosol flow is not distributed evenly within the lung, the actual anatomic regions to which bolus aerosol is delivered may not be determined accurately by the inhaled volume of air. This would also result in a wide variation of bolus RC or deposition data expressed by Vp because uneven distribution patterns are not likely to be consistent among different subjects, or even in the same subjects, inhaling aerosols with different breathing patterns at different times. However, many ventilation distribution or imaging studies indicate that ventilation patterns in normal subjects are even and reversible (4, 13). In our preliminary study using radiolabeled bolus aerosol, the deposition pattern was found to be fairly even between the right and left lung in healthy persons when the bolus was inhaled from the near-FRC level (1). In the present study bolus RC data are very consistent with respect to lung depth, as shown in Fig. 4. In every set of measurements in all subjects, RC values decreased monotonically with an increase in Vp, indicating that a series of bolus aerosols was indeed delivered to regions of successively greater depth in an orderly fashion. The present results may prove useful within their limitations for assessing regional distribution of lung deposition in healthy adults.

In a comparison of the present results with the conventional three-compartment lung deposition, the three lung regions were determined on the basis of the volume of inhaled air measured from the mouth: 50 ml for UA, from 50 to 150 ml for TB, and >150 ml for AL. Previously, the volume of the oropharyngeal cavity, which represents primarily UA, has been reported variably, but a value of 50 and 40 ml is generally accepted as a representative value for men and women, respectively (12). As for the TB region, Hart et al. (8) measured dead space volume (UA + TB) in a large number of adult subjects and found that it was linearly correlated with body height ($r^2 = 0.84$) regardless of gender. For a person with a height of 174 cm, which was the average for all of the present male and female subjects, the dead space volume was 150 ml, which was the value used to define the TB region in the present study. When our deposition values in these three compartments are compared with conventional results obtained by various investigators (Fig. 10), there is good agreement in each lung region, indicating that the present results are reasonable representations of deposition in these three lung regions. In Fig. 10 it can be seen that our results of AL deposition of $D_p=1\,\mu m$ tend to be lower than the previous results. This was due partly to the fact that the present results were obtained with the single-breath maneuver, consisting of a maximal exhalation to RV. Because particles that remain airborne in the deep lung regions at the end of inhalation can be exhaled by an extended exhalation from FRC to RV, AL deposition tends to be smaller with the single-breath maneuver, particularly for particles with a low deposition efficiency, e.g., $D_p = 1\,\mu m$. However, the effects are negligible for larger size particles, because particle recovery is essentially complete at the level of FRC during exhalation, as indicated in Fig. 5.
It is interesting to note that LDE is greater in women than men throughout the entire region of the lung, particularly for coarse particles. It should be noted that lung deposition is governed primarily by three factors: particle size, breathing pattern, and geometry of the lung. However, because both male and female subjects inhaled the same aerosols by using the same breathing patterns, the different results could be attributed to certain differences in lung anatomy between men and women. Because Vp is measured from the mouth, for a given value of Vp the actual anatomic sites to which a bolus aerosol is delivered may vary depending on an individual’s lung size, i.e., a deeper penetration in smaller-size lungs and vice versa. As a result, RC values would be lower and deposition would be greater in small-size lungs. In the present study the average lung volume was smaller in women than in men, and this could result in a greater LDE in females at a given Vp. However, according to the studies of Hart et al. (8) showing a good correlation between anatomic dead space and body height, the dead space volume of our female subjects could be smaller than that of our male subjects by ~25 ml. When the volume difference was corrected by shifting the female LDE curve to the right by 25 ml in Fig. 6, LDE was still greater in women in most of the Vp regions. In Fig. 6 it can also be seen that the difference will persist even after a shift of the LDE curve to the right by a volume much larger than 25 ml, particularly for D_p = 5 µm. Although the effects of dead space volume may be assessed to a certain extent by normalizing Vp with thoracic gas volume (TGV; e.g., Vp/TGV), the difference in TGV between our male and female subjects was small (3,378 vs. 2,955 ml), and the normalization would result in only a 13% shift of LDE curve to the right, which does not account for the differences in LDE. These analyses suggest that factors other than lung size or dead space volume might have contributed to a great extent to the difference in LDE of coarse particles between men and women.

Our results show a marked variation in regional deposition within a normal lung, which was characterized by a unimodal peak, the location of which was shifted from the peripheral to proximal regions with an increase in D_p. This finding was consistent with theoretical expectations, because large-size particles deposit primarily by inertial impaction in the proximal airways, in which flow velocity is high before aerosol reaches the peripheral regions, whereas small-size particles penetrate more deeply into the peripheral region and deposit there by sedimentation. However, the actual experimental data for humans have never been reported previously in such detail as shown in the present study. It should be noted that our results show a fairly consistent regional deposition pattern with coarse particles (D_p = 3 and 5 µm), particularly for D_p = 5 µm, regardless of respiratory Q˙ values used. This could be expected because two primary deposition mechanisms for coarse particles, inertial impaction (which is governed by the parameter D_p^2/Q and increases with increasing Q) and sedimentation (which is controlled by the parameter D_p/Q and therefore increases with decreasing Q), could act to compensate for each other as Q changed. It is also noted that because deposition of coarse particles is controlled by the second order of Q˙, particle size is expected to have a greater effect on lung deposition than Q. Our results showing a marked increase in deposition, with an increase in D_p, particularly in the shallow regions of the lung (see Fig. 7), are consistent with these theoretical expectations. In contrast, a deposition pattern of fine particles (D_p = 1 µm) was highly variable with respiratory Q; a greater deposition in a deeper region with decreasing Q. This was, in fact, expected, because fine particles deposit mainly by sedimentation, and, with a slow Q, particles remain longer in the lung and deposit more in deeper lung regions, where sedimentation distance is short. These characteristic deposition patterns were similar between men and women, but they were more pronounced in women, showing enhancement of deposition in the peak regions for both fine and coarse particles. In other words, deposition was more localized within the lung in women. In our results it can also be noted that, for coarse particles, regional deposition is dictated primarily by particle size, whereas deposition distribution is greatly modulated by breathing patterns for fine particles. The implications of these results are that local tissue burdens of coarse particles in the proximal airways are greater in women than...
men during normal activities, regardless of breathing patterns. This may result in more incidents of respiratory irritation or illness in women than men in an environment with elevated levels of coarse particle.

Compared with men, LDF in women is markedly enhanced in the shallow regions of the lung, particularly with large-size particles. This may result from certain structural or geometrical differences in the upper and large conducting airways between men and women. By using an acoustic reflectance method, Martin et al. (24) measured tracheal dimensions in a large number of male and female subjects (age 20–35 yr) and found that the cross-sectional area of the trachea was smaller by ~32% in women than men at the same level of lung volume. These results were consistent with other findings obtained by different methods, including roentgenogram (3) and computed tomography (6). Because a sudden change in dimensions between adjacent airways is unlikely, one may also expect smaller dimensions in the large conducting airways subsequent to the trachea. An increase in inertial impaction and flow turbulence in the small-size airways could, in turn, result in enhancement of particle deposition in the shallow regions of the lung. In fact, in our earlier theoretical studies utilizing Weibel's symmetrical lung model, we found a 50% increase in deposition of particles 3 μm in diameter in the large conducting airway when the diameters of the airways were uniformly reduced by 25% (16). In recent experimental studies using various bifurcating airway models (17), it was found that airway deposition increased with a power function of an impaction parameter, Stokes number, the value of which is inversely proportional to the third power of airway diameter for a given Q. The results suggest that a 30% reduction in airway cross-sectional area could result in a deposition increase in the bifurcating airways by >100%. On the basis of the measurement of radioactivity from the lung after inhalation of radiolabeled aerosols, Pritchard et al. (25) also reported an increase in deposition in the shallow TB regions of the lung in women compared with men. It should also be noted that the size of the larynx is usually smaller in women than men (7). A smaller opening in the larynx could generate a stronger turbulent jet into the trachea and could result in deposition enhancement in the trachea and airways downstream (5). The small size, together with certain differences in geometry and dynamic motion of the larynx, could also lead to deposition enhancement in the larynx itself. The present results are in line with expectations from the earlier studies. However, differences in the structure and function of the upper and large airways between men and women, and the precise role of these differences in particle deposition needs to be investigated further.

Although different methods were used in measuring lung deposition, previous studies showed consistently small or no differences in total lung deposition between men and women. By analyzing the differences between radioactivity collected on the inspiratory and expiratory filters, Pritchard et al. (25) found that total lung deposition was in good agreement between men and women for particles in the size range of 2.5 to 7.5 μm in diameter. In the present study the breathing pattern was not controlled, and the subjects inhaled aerosols spontaneously with their own breathing pattern. However, women usually breathe with smaller Vt than men during spontaneous breathing (2). Therefore, if female subjects inhale the aerosols with the same Vt as that of men, lung deposition may increase in women. Recently, Bennett et al. (2) investigated total lung deposition of particles (Dp = 2.0 μm) under spontaneous as well as a selected fixed breathing condition. They found a greater deposition (~17%) in women than men with a fixed breathing pattern. However, the difference was not significant under the spontaneous breathing condition. In the case of smaller-size particles, a deposition index of 1-μm-diameter particles was measured for a group of young and old normal subjects by using a rebreathing technique, and no significant differences between men and women were found in deposition in both age groups with a controlled breathing pattern (21). The present results, showing no difference in TDF for Dp = 1 μm between men and women, but a greater deposition in women than men for Dp = 3 and 5 μm, are consistent with the earlier studies. This, together with regional deposition enhancement in women, may lead to a greater health risk in women than men. However, the ventilation rate is smaller in women compared with men, e.g., 6.0 vs. 8.6 l/min during normal breathing (2), and daily activity patterns vary widely among individuals in real life. Therefore, these exposure factors need to be incorporated into the present results, which were obtained under carefully controlled breathing conditions, to assess accurately the potential health risk of particulate matter.

In conclusion, we measured detailed regional lung deposition patterns of inhaled particles in young healthy adults and investigated the gender difference. We found marked differences in regional deposition patterns between men and women and enhancement of regional dose in women in varying regions depending on particle size. These findings may have significant implications in health risk assessment concerning inhaled particles on one hand and will be useful for targeted aerosol delivery in pharmaceutical and clinical studies on the other.

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