Respiratory Tract Deposition of Ultrafine Particles in Subjects with Obstructive or Restrictive Lung Disease

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To evaluate the effects of lung disease on deposition of inhaled ultrafine particles (<0.1 μm diameter), we measured total respiratory tract deposition of nonhygroscopic particles of 0.02 to 0.24 μm in five subjects with obstructive lung disease and three subjects with restrictive lung disease and compared it with that in ten normal subjects. Deposition was measured as concentration difference of five size fractions in inhaled and exhaled air using an electrical aerosol analyzer. The data showed that deposition of these ultrafine particles was increased in subjects with obstructive lung disease when compared with normal subjects, while it was unchanged in subjects with restrictive lung disease.

The behavior of inhaled particles in the diseased lung is poorly understood. Only limited measurements have been made of total respiratory tract deposition in subjects with obstructive lung disease (OLD), and to our knowledge, no data exist quantifying deposition in subjects with restrictive lung disease (RLD). This information is valuable because many lung diseases are either initiated or exacerbated by the inhalation of particles, whether they be cigarette smoke particles, microorganisms, dust, toxins, or allergens.1 Also, the characterization of particle deposition in the diseased lung has important implications for the use of therapeutic aerosols.

In OLD, studies to date have consistently found increased central deposition of particles with decreased peripheral deposition, or decreased peripheral penetration of particles.2,3 These studies employed radioactive aerosol particles and scintigraphic scanning, which are effective in characterizing site of deposition but not in quantifying total particle deposition. A few investigators have measured total respiratory tract deposition in smokers and in subjects with OLD and have found it to be increased in both groups.

The increase in deposition in the subjects with obstructive lung disease was significant for particle sizes 0.04 to 0.24 μm. Possible mechanisms for increased deposition in airway obstruction include increased transit time of particles, abnormal expiratory collapse of airways due to flow limitation, and flow perturbations resulting from decreased airway caliber. (Chest 1990; 97:1115-20)

DEHS = di-2-ethylhexyl sebacate; EAA = electrical aerosol analyzer; OLD = obstructive lung disease; and RLD = restrictive lung disease

in comparison to normal subjects.9-13 None of these studies evaluated deposition as a function of particle size in diseased subjects. Limited studies of particle deposition in RLD in humans6 and in animals14 are available, and they suggest decreased total retention and nonuniform deposition of particles. However, no measurements have been made of total respiratory tract deposition in human subjects with RLD.

There are, to our knowledge, no reports of quantitative measurements of the deposition of ultrafine particles (<0.1 μm diameter) in the diseased human lung; all prior investigations have used particle sizes ranging from 0.5 to 5.0 μm in diameter. Particles in the ultrafine size range are ubiquitous, being produced by many industrial processes. Although their contribution to total particulate mass is small, the total surface area available for adsorption of potentially toxic gases is very large. Their small size enhances long residence time in the environment and delivery to the periphery of the lung where they deposit primarily by diffusion. Available data in normal subjects indicate that total respiratory tract deposition of these particles is efficient, increasing as particle size decreases.15-18 Obtaining deposition values for ultrafine particles in subjects with lung disease is important to our understanding of the pathogenesis, exacerbation, and treatment of acute and chronic lung disease. It is also important in that cigarette smoke contains many particles in this size range.20-22 The purpose of this study was to measure total respiratory tract deposition of nonhygroscopic inhaled particles of 0.02 to 0.24 μm diameter in subjects with obstructive and restrictive pulmonary disease and to compare these values with

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data obtained in normal subjects.

METHODS

For these inhalation studies, an aerosol was generated from di-2-ethylhexyl sebacate (DEHS), 0.01 percent in 95 percent alcohol using a condensation generator.16 This aerosol generation system has been previously described.16 Aerosol analysis was performed using an electrical aerosol analyzer (EAA) (TSI model 3030),17 which, in our laboratory,18 and others,19 has been most useful over the size range 0.02 to 0.4 μm. The DEHS aerosol had a count median diameter of 0.04 μm and a geometric SD of 1.7.

The aerosol was directed into a 240-L inhalation chamber that contained three bags and had a microprocessor-controlled valve system at the mouthpiece (Fig 1). The respiratory pattern to be duplicated by the subject was displayed on a dual-beam oscilloscope. The microprocessor was programmed to open or close appropriate inhalation and exhalation valves when the required volume had been exchanged. The respiratory pattern used consisted of a 1-L tidal volume, 12 breaths/minute frequency, 1 L/s constant flow rate, and no end-inspiratory breath hold. All studies were initiated from functional residual capacity. Subjects performed the maneuver while seated and wearing noseclips. A standard pulmonary function test mouthpiece was used on the inhalation chamber.

After the inhalation chamber was filled with aerosol, its contents were sampled by the EAA for two consecutive, two-minute periods. Total aerosol concentration in the chamber was adjusted to 10⁴ to 10⁶ particles cm⁻³, which is sufficient for measurement with the EAA. Following this, the subject began the inhalation procedure by practicing the respiratory pattern for a few breaths. Ten equilibration breaths were then executed by inhaling from the chamber and exhaling into the waste bag. The ten subsequent breaths were exhaled into the sample bag, after which analysis of aerosol in the sample bag was performed. The study was concluded by making two more consecutive measurements of aerosol concentration in the chamber. A decay curve for each size fraction was established,20 and from this, the concentration of each size at the time of inhalation was calculated. The difference between concentration in the exhaled air in the sample bag and concentration in the chamber for each particle size during inhalation was calculated as respiratory tract deposition. Deposition was corrected for calibration of the system to account for dilution, dead space entrapment of particles, and particle loss in the system. Three deposition studies were done in each subject. Detailed descriptions of the inhalation system, experimental protocol, and deposition calculation may be found elsewhere.19, 21-23

Studies were done on five subjects with mild to moderate OLD (three men, two women), and three female subjects with mild to moderate RLD as defined by physiologic testing. Pulmonary function tests for the subjects with OLD are shown in Table 1, and those for the subjects with RLD are shown in Table 2. Spirometric testing was consistent with American Thoracic Society recommendations,24 and percent predicted values were calculated using the equations of Crapo and associates.25 Lung volumes were determined using plethysmography, and percent predicted volumes were calculated using the equations of Crapo and coworkers.26

In the group with airway obstruction, three subjects had irreversible obstruction, while two had reversible obstruction for which bronchodilators were being administered at the time of the study. Four of the five subjects were smokers, with a mean history of 62 ± 57 pack-years. The remaining subject with OLD had a clinical diagnosis of asthma and was a lifetime nonsmoker. All of these subjects had stable pulmonary function tests and were feeling well at the time of the aerosol measurements. Peak flow rates were monitored in these subjects before and after the inhalation studies, and they did not change. All three of the subjects with RLD had sarcoidosis, were nonsmokers, and had no evidence of airway obstruction. The group of normal subjects consisted of eight male and two female subjects who were lifetime nonsmokers and had normal spirometric evaluation and lung volumes. Informed consent was obtained from all subjects and the experimental protocol was approved by the Human Research Committee of the University of Arkansas for Medical Sciences.

Data analyses were done using Statistical Analysis System (SAS Institute, Cary, NC) computer programs for calculation of t tests and Pearson correlation coefficients.

RESULTS

Mean (± SEM) deposition fractions for normal,
OLD, and RLD subjects are listed for each particle size in Table 3. Figure 2 displays mean (± SEM) deposition fraction for the OLD group and the normal group as a function of particle size. The results of five of the normal subjects have been reported previously. When differences in breathing patterns are taken into account, these data are comparable to other reports of ultrafine particle deposition in normal subjects. Figure 3 shows mean (± SEM) deposition fraction for the RLD and normal groups for each particle size. The mean deposition fractions for the subjects with OLD were increased for all particle sizes when compared with normal subjects, and significantly so for particle diameters of 0.04 μm (p<0.05), 0.08 μm (p<0.01), 0.13 μm (p<0.001), and 0.24 μm (p<0.0005). For the subjects with RLD, mean deposition fractions did not differ significantly from those of the normal group at any particle size. Mean (± SD) deposition fractions for each individual subject and particle size are given in the appendix for subjects with OLD and RLD. Each value is the average of three deposition studies. The data reveal little intra-subject variation with very reproducible results in each individual. There was some intersubject variation in the subjects with both OLD and RLD, which is also seen among normal subjects. In the subjects with airflow obstruction, no significant correlation was found between deposition values and any spirometric parameter or lung volume measurement.

**Discussion**

These data demonstrate that total respiratory tract deposition of ultrafine particles in subjects with RLD is similar to that of normal subjects, while it is significantly increased in patients with OLD. These findings with ultrafine particles resemble those of previous studies reporting increased deposition of larger-sized particles in subjects with airway obstruction. The mechanisms responsible for particle deposition, however, are distinctly different for ultrafine particles than those for particles with diameters of 0.5 μm or greater. Ultrafine particles are transported onto airspace surfaces as a consequence of collisions with...
gas molecules (Brownian diffusion). Deposition of these particles decreases with particle diameter, is independent of particle density and flow rate, and increases with residence time in the lung. Larger particles are subject to gravitational and inertial forces. Consequently, deposition increases with particle diameter and density, flow rate, and residence time.

Several mechanisms may be postulated to explain increased ultrafine particle deposition in the subjects with OLD. The first question to be addressed is the ability of the subjects with OLD to follow the breathing pattern compared with that of the normal subjects. Respiratory tracings were made of representative subjects with OLD and normal subjects during actual deposition studies. The subjects with OLD were noted to have prolongation of the final portion of the expiratory phase when compared with normal subjects, which would increase the residence time of particles in the lung. Since particles in this size range deposit primarily by Brownian diffusion, which is time-dependent, deposition would be increased by increased particle residence time. Figure 4 displays tracings of two breaths from a representative subject with OLD and a normal subject that have been superimposed to facilitate comparison. The tracing of the subject with OLD exhibits prolongation of the expiratory phase of each breath, so that the total duration of one breathing cycle is approximately 1 s greater than that of the normal subject. Can this increase in residence time in the subject with OLD account for the measured increase in deposition fraction? Using calculations described by Heyder et al. for total deposition of particles in the thermodynamic domain, the percent increase in deposition of a 0.08-μm particle, for example, when the breathing cycle period is increased from 2 to 3 s is approximately 16 percent. However, the measured deposition fraction for the 0.08-μm particle in the subject with OLD depicted in Figure 4 was 0.53 compared with 0.31 for the normal subject shown, which is an increase of 71 percent. Thus, other factors must contribute to the increase in particle deposition seen in the subjects with OLD.

Perhaps a more important mechanism implicated by these volume-time curves is the onset of flow limitation in these subjects attempting to achieve 1 L/s flow rates. Figure 5 shows tracings of maximal flow-volume loops for the five subjects with OLD. In attempting 1 L/s flow rates during deposition studies, all of these subjects would be flow limited during the majority of, or at least the final portion of, the expiratory phase. This could result in abnormal expiratory collapse of airways with increased deposition during expiration at flow-limiting segments. This mechanism has been shown to increase deposition of larger-sized particles and may also influence

Figure 3. Mean (± SEM) deposition fraction for the subjects with restrictive lung disease and the normal subjects as a function of particle size. No significant difference was found between the groups.

Figure 4. Tracings of two breaths from a subject with obstructive lung disease (OLD) and a normal subject recorded during actual deposition maneuvers and superimposed for comparison. The breathing cycle duration is approximately 1 s greater in the subject with OLD than in the normal subject due to prolongation of the expiratory phase.
ultrafine particle deposition. It is possible that turbulent forces and eddies in the area downstream of flow-limiting segments bring particles closer to airway walls, increasing the likelihood of deposition by diffusion. The 0.2-μm particle may be more susceptible to these forces, resulting in a relatively greater increase in deposition than that seen with the 0.02-μm particle.

Another proposed mechanism for increased deposition in the subjects with OLD is decreased airway caliber, that would result in increases in linear velocity and local turbulence. Transition from laminar to turbulent flow in these regions might cause displacement of particles toward airway walls and result in increased collection efficiency. Excessive airway secretions could also increase deposition, either by increasing airway narrowing or as a result of two-phase gas-liquid interaction.\textsuperscript{35,36} Two of the subjects with OLD had a clinical diagnosis of chronic bronchitis and two others had a diagnosis of asthma, either of which may increase the amount of secretions in the airways. Both of these conditions may also be associated with acute bronchospasm, which could increase deposition, but monitoring of peak flow rates revealed no change in the degree of obstruction during performance of the studies. Further studies are necessary to elucidate which mechanism plays the greatest role in increasing deposition of ultrafine particles in airway obstruction. It would be helpful to collect further data from normal and obstructed subjects with strict control and matching of particle residence time, and also to vary flow rates to observe the effect of flow limitation on deposition.

Deposition in the subjects with RLD was not different from that in normal subjects and this may reflect relatively normal airway diameters and flow profiles, with absence of abnormal airway closure or increased secretions. These subjects do have marked reductions in FRC, which should serve to decrease airway diameters and cause deposition to increase. However, very little is known about airway caliber in RLD or about the effect of the fibrosing process on airway size. The observed respiratory time in these subjects was comparable to that in normal subjects, so this variable can be eliminated as a factor affecting

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**Appendix**

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<th>Deposition Fraction (± SD) for Subjects with Obstructive Lung Disease</th>
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the deposition data. These data were taken from only three subjects, all of whom had sarcoidosis, so it is difficult to know if they are representative of all patients with RLD.

To our knowledge, these are the only available measurements to date of deposition amount in subjects with RLD. The information concerning deposition quantity in subjects with OLD is scant well, and the present study constitutes the only data available for ultrafine particle deposition in these subjects. These findings have important implications for the patient with OLD who continues to smoke cigarettes or who inhaled irritants, toxins, microorganisms, or therapeutic aerosols.

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REFERENCES

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