Enhancement of particle deposition by flow-limiting segments in humans

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SMALDONE, GERALD C., AND MATTHEW S. MESSINA. *Enhancement of particle deposition by flow-limiting segments in humans.* J. Appl. Physiol. 59(2): 509–514, 1985.—Severe chronic obstructive pulmonary disease is associated with central deposition of inhaled aerosols. This pattern may be due to functional narrowing of the large airways during expiration at flow-limiting segments (FLS). Using a gamma camera and 2.5-μm particles, we compared the pattern of aerosol deposition following quiet breathing with that after a controlled forced expiration (cough) when FLS are known to form in central airways. Lung size measurement by ^{133}Xe allowed construction of regions of interest over the central airways and lung periphery. Deposition in these regions was normalized for area and lung thickness and expressed as a central-to-peripheral (C/P) ratio. In addition, using right-angle light scattering, the fraction of inhaled particles deposited with each breath (DF) was determined. During control studies, airflow and tidal volume were continuously monitored to insure that tidal loops were well below the maximum expiratory flow-volume (MEFV) curve. To create dynamic compression, cough was used to generate a partial MEFV curve, while inspiratory flow, tidal volume, and functional residual capacity were maintained close to quiet breathing. With cough, C/P ratios increased markedly from 1.04 ± 0.18 to 2.21 ± 0.61 ($P < 0.01$, $n = 6$). DF for the lung and airways did not significantly change (0.43 ± 0.11 to 0.45 ± 0.09, P = NS). The greater enhancement of regional deposition in the central airways with deposition unchanged over the whole lung demonstrates that, during cough, peripheral deposition is actually reduced when compared with quiet breathing. We conclude that dynamic compression at FLS can be an important factor in the central deposition of inhaled particles.

expiratory aerosol deposition; cough; choke points

DURING A COUGH or forced expiration, the central airways of normal humans narrow and form discrete flow-limiting segments (FLS) (9, 16). In obstructive lung disease, flow limitation can occur even during quiet breathing when tidal loops are superimposed on maximal expiratory flow-volume (MEFV) curves (17). In these obstructed patients, inhaled radioactive particles (1–3 μm) deposit primarily in the central perihilar regions of the lung (4, 11) in contrast to the uniform peripheral pattern seen in normal subjects. At FLS, local airflow velocities increase and may influence the deposition of airborne particles. If so, the perihilar deposition seen in obstructive disease may be explained by expiratory flow limitation at FLS. In an animal preparation, we demonstrated that particles can pass through the large airways during a quiet inspiration and rapid but passive expiration without significant deposition (14). When expiration was forced, there was a significant increase in deposition just downstream to the tracheal site of flow limitation. This study suggested that FLS impart sufficient inertia to small particles to cause local impaction to dominate over clearance mechanisms and result in net deposition. We found that the pattern of deposition in the dog was similar to particle deposition in tubes containing a narrow constriction, i.e., a flow-limited orifice. In these models, particles are accelerated as they enter the constricted region and impact just downstream from the narrowed airway (6, 7). The amount of aerosol that deposits in the downstream tube is determined by the size of the particles, the geometry of the tube, and the properties of the carrier gas. The purpose of the present paper is to quantitate this effect in humans.

In normal and chronically obstructed human subjects, FLS generally remain fixed in central airways. To isolate their influence on aerosol deposition, the pattern of deposition should be studied in the presence and absence of FLS with other factors controlled. Because of the irreversible nature of chronic obstructive pulmonary disease (COPD), it is not possible to move patients off their MEFV curve. Therefore, we chose subjects who were not flow limited at rest and induced flow limitation with a controlled forced expiration. In addition to observing the influence of FLS on the pattern of deposition, we quantitated deposition over the whole lung to measure the importance of FLS relative to other well-known mechanisms of particle deposition.

In an accompanying article, similar measurements were made in groups of chronically flow-limited and non-flow-limited human subjects as a quantitative comparison of regional and total aerosol deposition between patients and the subjects of the present study.

METHODS

The experimental apparatus is diagrammed in Fig. 1. A subject sits in front of a gamma camera (Picker Dynacamera, low-energy parallel-hole collimator) initially peaked for ^{133}Xe. While quietly breathing at functional residual capacity, an equilibrium xenon scan was obtained to position the subject's lungs over the camera and determine lung volume. Then, the camera was ad-

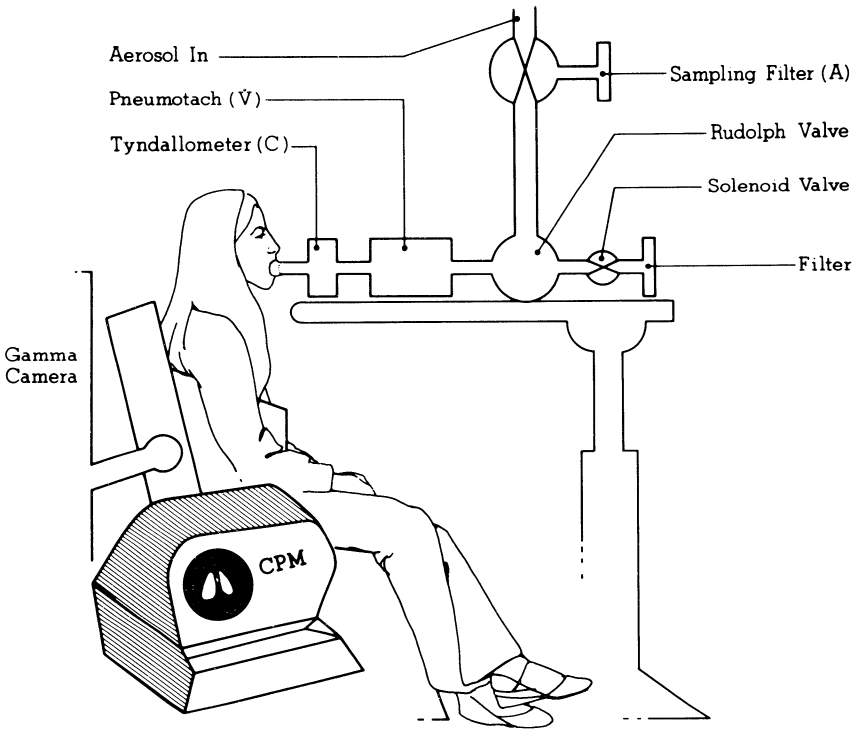

FIG. 1. Experimental apparatus and glossary of terms. During aerosol deposition, subject inhales through Tyndallometer (C) connected in series with pneumotachograph (V̇). Using analog circuitry during quiet breathing, instantaneous product of C and V̇ is integrated with time to yield N, relative number of particles inhaled or exhaled for each breath. Then DF is easily calculated.

C = Concentration (from Tyndallometer)

$\dot{V}$ = Flow (L/min)

V = Volume inhaled (L) (integrated from $\dot{V}$, determined by pneumotach)

A = Activity of inhaled aerosol (μ Ci/L)

N_{in} = Aerosol Inhaled

N_{ex} = Aerosol Exhaled

AV = Total μ Ci inhaled

$$N = \int (C \cdot \dot{V})\, dt$$

$$\text{Deposition Fraction (D.F.)} = \frac{\Sigma N_{in} - \Sigma N_{ex}}{\Sigma N_{in}} \quad \text{for all breaths}$$

justed for ^{99m}Tc, and the subject inhaled radioactive monodisperse aerosol. The aerosol (2.5 μm, geometric SD 1.1) was generated by condensation of bis(2-ethylhexyl) sebacate vapor on nuclei of ^{99m}Tc-labeled human serum albumin (13).

Flow (Fleisch no. 1 pneumotachograph), tidal volume (integrated flow), and aerosol concentration (Tyndallometer) were continuously monitored. The subjects inhaled through a Hans-Rudolph valve and exhaled via a solenoid valve into a filter.

Deposition was measured first during forced expiration. To create dynamic compression, the subjects exhaled against a closed solenoid, and pleural pressure increased until sufficient pressure was attained to insure flow limitation. When the set pressure was reached, the valve opened and a partial flow-volume maneuver was obtained (Fig. 2). With training, this maneuver could be performed at a normal respiratory rate, tidal volume, and inspiratory airflow. After ~20 breaths, the lungs were scanned for 5 min. Following the forced expirations, sufficient time was allowed for clearance of central airways (30–60 min), and the experiment was repeated with normal relaxed expirations. The radioactivity deposited for each maneuver was determined by subtracting the previous background image. Mucociliary clearance was negligible and did not affect the background of the quiet

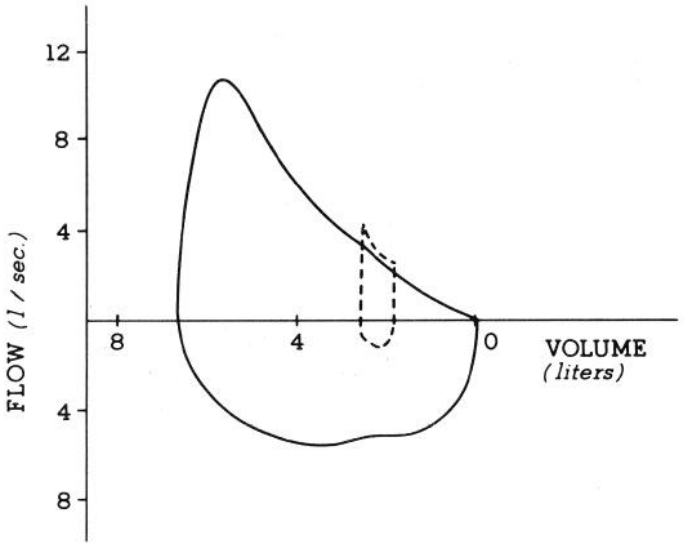

FIG. 2. Partial maximum expiratory flow-volume (MEFV) maneuver superimposed on MEFV curve of *subject 1*.

breaths. However, the flow-limited breaths simulate coughing and could affect the background. Therefore, they were performed first following room background, which was fixed. This allowed the scan following these breaths to represent the actual net deposition of the simulated coughing, since background could not be affected. During quiet and flow-limited breathing, the number of particles inhaled and the number exhaled were calculated for each breath by multiplying the instantaneous aerosol concentration and flow and integrating the product over time. By summing these data for all breaths, the fraction of particles inhaled that actually deposited in the lung, the deposition fraction (DF), was determined (Fig. 1). Further details of the Tyndallometric technique and use of this radioaerosol can be found in previous publications (3, 5, 10, 15).

Regions of interest were drawn over the xenon equilibrium scan to outline parts of the lung that contained most of the central airways vs. the lung periphery (Fig. 3). The central region outlined ~30% of the total lung area. Regional aerosol deposition was reported as a central-to-peripheral (C/P) ratio in which radioactivity deposited in each region was normalized by counts measured in the same region on the xenon scan.

Six subjects were studied, each acting as his own control. All subjects except *subject 3* had normal pulmonary function tests, including diffusion capacity (Table 1). *Subject 3* is a smoker with moderate chronic obstructive lung disease, a normal diffusion capacity, and no response to bronchodilators. Since the purpose of the study was to look at the effects of induced flow limitation on whole lung and regional deposition, the only criteria for inclusion into the study was the absence of flow limitation during quiet breathing. Therefore *subject 3* was included. If flow limitation is a major mechanism of central deposition in flow-limited COPD patients, then a patient with COPD who is not flow limited when breathing aerosol should not have a predominantly central deposition pattern. The tidal loops of all six subjects were well below the MEFV curve.

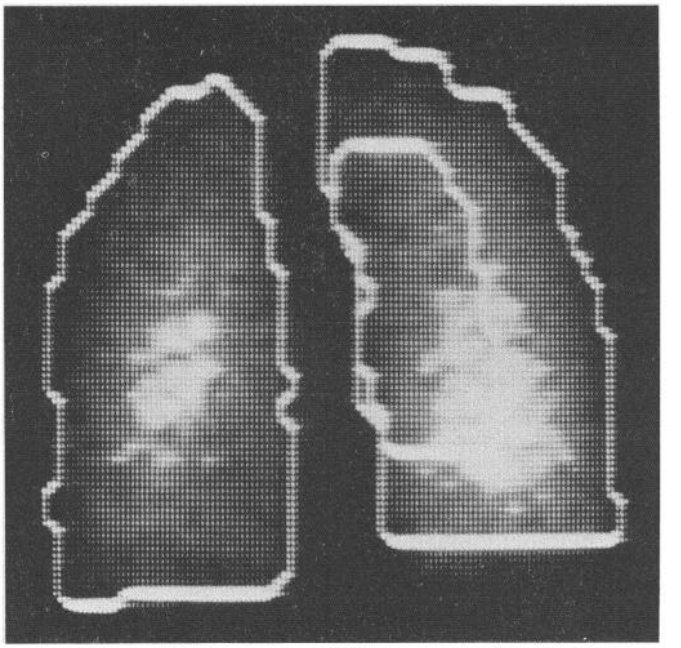

FIG. 3. Equilibrium scan using ^{133}Xe at functional residual capacity in *subject 1*: central and peripheral areas are outlined.

TABLE 1. *Pulmonary function, regional deposition, and whole lung deposition during quiet breathing and flow limitation*

Subj No.	PFTS		C/P Ratio		Deposition (DF)	
	FEV_1, % FVC	MMEF, % predicted	Quiet	FL	Quiet	FL
1	72%	82%	0.94	2.00	0.50	0.39
2	77%	62%	0.94	1.80	0.46	0.52
3	58%	25%	1.05	3.33	0.52	0.53
4	85%	139%	0.91	1.60	0.52	0.44
5	86%	106%	1.00	2.38	0.34	0.30
6	77%	61%	1.38	2.17	0.25	0.53
Mean			1.04	2.21	0.43	0.45
±SD			±0.18	±0.61	±0.11	±0.09
P (paired *t* test)			<0.01		NS	

PFTS, pulmonary function; C/P ratio, central-to-periphery ratio of regional deposition; DF, fraction of inhaled particles deposited with each breath; FEV_1, forced expiratory volume at 1 s; FVC, forced vital capacity; MMEF, maximal mid expiratory flow; FL, flow limitation.

RESULTS

Figure 4 qualitatively demonstrates the typical deposition patterns seen for *subject 1* after quiet breathing and forced expiration. When compared with quiet breathing, forced expiration significantly increased perihilar deposition. These observations are quantitated in Table 1. The C/P ratios, deposition fractions, and pulmonary function data are shown for each subject. During quiet breathing, C/P averaged 1.04 ± 0.18, indicating that particle behavior in central lung regions matched that of peripheral regions. With flow limitation, C/P ratios markedly increased in all six subjects to an average of 2.21 ± 0.61 ($P < 0.01$, paired t test), documenting the shift in regional deposition illustrated in Fig. 4. Whole lung deposition for the group did not

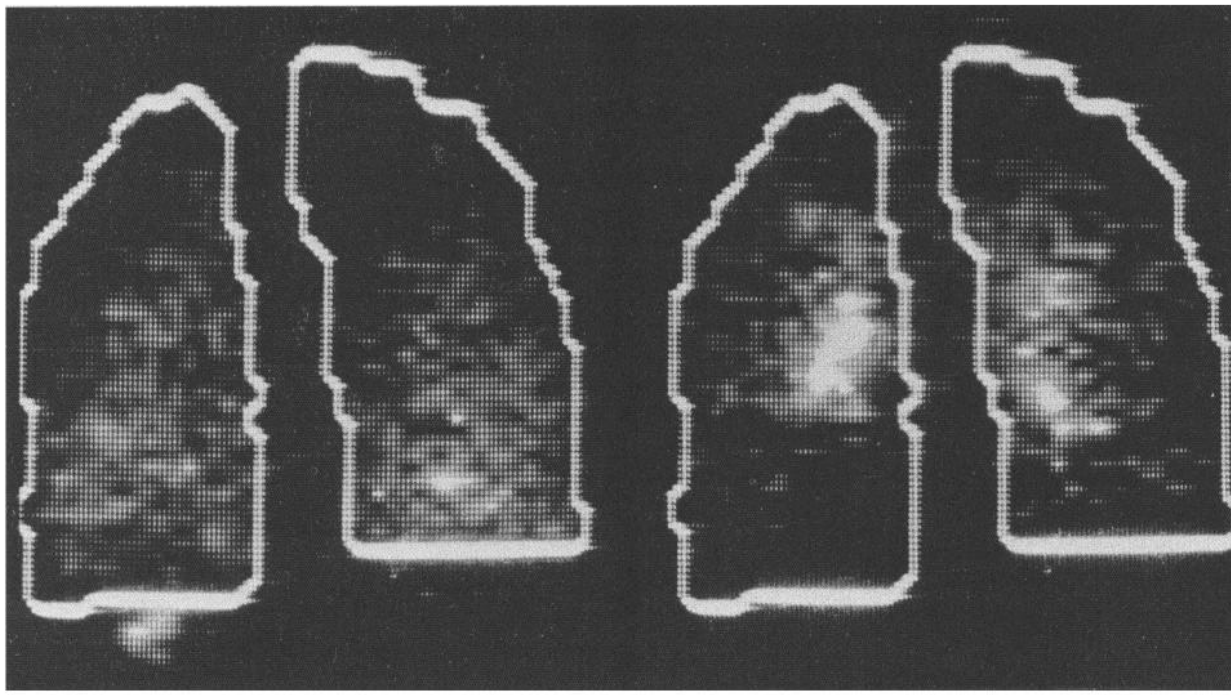

FIG. 4. Net deposition of ^{99m}Tc aerosol in *subject 1* (posterior view): quiet breathing (*left*); flow limitation (*right*). These images were obtained by subtracting appropriate background images and normalizing each image to same number of counts. Overall lung outline was obtained via xenon scan. Activity just below outline of left lung is in stomach and represents clearance from previous inhalation. It was not eliminated during subtraction because stomach activity moved during interval between background and deposition scans (7–8 min).

significantly change (0.43 ± 0.11 to 0.45 ± 0.09).

Other parameters that can influence deposition are listed in Table 2: tidal volume, the major determinant of aerosol penetrance into small airways; peak inspiratory flow, an index of forces influencing inspiratory impaction; and aerosol residence time during inspiration and expiration, a major factor governing the number of particles that deposit in airways by mechanisms of settling and diffusion (3, 18). Each factor is analyzed using the paired *t* test. Tidal volume, peak inspiratory flow, and inspiratory residence time were not significantly different during induced flow limitation when compared with quiet breathing. Expiratory residence time was significantly shorter, however, ($P < 0.05$) since expiratory flows were higher.

TABLE 2. *Tidal volume, inspiratory flow, inspiratory residence time, and expiratory residence time during quiet breathing and flow limitation*

Subj No.	Tidal Volume, ml		Inspiratory Flow, l/s		TI, s		TE, s	
	Quiet	FL	Quiet	FL	Quiet	FL	Quiet	FL
1	508	490	1.06	1.53	1.2	1.4	1.4	1.3
2	537	615	1.14	1.22	1.8	2.0	2.5	1.4
3	268	490	1.88	1.49	1.1	1.0	1.4	0.8
4	1,021	1,114	1.25	1.20	1.8	2.4	3.1	2.4
5	765	825	1.33	1.38	1.5	1.3	2.8	1.3
6	855	1,176	1.57	2.25	1.2	1.2	1.3	1.1
Mean	659	785	1.37	1.51	1.4	1.6	2.1	1.2
±SD	±272	±305	±0.30	±0.39	±0.3	±0.5	±0.8	±0.2
P (*t* test)	NS		NS		NS		<0.05	

TI, inspiratory residence time; TE, expiratory residence time; FL, flow limitation.

DISCUSSION

This study demonstrates that subjects who normally deposit inhaled aerosol uniformly throughout the lung shift deposition to the central airways with changes in their ventilatory pattern confined to expiration. As illustrated in Fig. 4, the flow-limited deposition appears maximal in the region of the airways known to form FLS. These regional observations could not be explained by changes in inspiratory events, i.e., tidal volume, which can affect penetration of aerosols, and inspiratory flow, which influences inspiratory impaction. Although tidal volume and peak inspiratory flow varied from subject to subject, there was little intrasubject variation and differences in the data by paired analysis are not significant. There was a trend in some individuals to increase tidal volume (especially *subject 3*). An increase in tidal volume would tend to reduce C/P ratios, since penetration into small airways would be greater (18). In two subjects (*1* and *6*), peak inspiratory flows were higher during flow limitation, and some of the shift in deposition may have been related to these increases. However, in another study where we studied regional lung deposition of the same aerosol during quiet breathing and exercise, we were able to estimate the influence of increases in peak inspiratory flow on central airways deposition in the absence of expiratory flow limitation (1). In that study C/P ratios were 1.02 ± 0.07 during quiet breathing (5 subjects), the same distribution found in the present

study. During exercise, the C/P ratios increased to only 1.29 ± 0.10 much less than the average value in the flow-limited subjects of the present study (2.21 ± 0.61). In the exercise study, peak inspiratory flows averaged 2.09 ± 0.36 l/s, higher than the average of the present study (1.51 ± 0.39) and similar to our subject with the highest inspiratory flow (*subject 6*). Thus, in *subjects 1* and *6*, changes in inspiratory flow cannot account for the increase in central airway deposition seen with flow limitation.

We believe that the enhanced central airways deposition demonstrated above is the result of expiratory FLS influencing particles that failed to deposit on peripheral airways during inspiration. An alternative explanation is that particles deposited on mucus in peripheral airways are resuspended during flow limitation and redeposited in central airways. Although it is theoretically possible that induced flow limitation or a cough can suspend mucus from small airways into the gas phase and blow it out of the lung (8), there is no published evidence in normal subjects demonstrating that small airways can be cleared of mucus during cough. Studies to date have only shown that in some patients radioactive particles can be cleared from the lung during voluntary coughing (2, 12) but not in normal subjects (2). Unpublished observations in our laboratory suggest that, in normal subjects, particles deposited in peripheral airways are not cleared during induced cough. Regional and whole lung clearance of radiolabeled aerosol from small airways (C/P ratio = 1.0) are no different if the clearance is measured during quiet breathing or induced coughing performed in the same manner as in the current study. Furthermore, even if particles were resuspended in airborne mucus from small airways, their central deposition during forced expiration would have to be explained, and deposition downstream from FLS would be a likely possibility.

The results in the present study parallel the earlier experiments in dogs in that the site of the increased deposition followed the site of the FLS: the trachea in the dogs (14), the segmental and lobar bronchi in humans. It is theoretically possible that the higher expiratory flows alone were responsible for the increased central deposition independent of local distortions of these airways due to FLS. We believe this explanation is unlikely. In the dog study cited above, deposition in the lung, including the segmental airways, did not increase with flow limitation; deposition only increased downstream to the tracheal FLS. In the present study, the maximum increase in central deposition during flow limitation was seen in the obstructed subject who had the smallest increase in expiratory flow.

In addition to the changes in regional deposition, the measurement of DF provides an index of the quantitative importance of flow limitation as a mechanism of deposition. In the absence of airway pathology (e.g., tumors, mucus plugs), the major mechanism of aerosol deposition for 2.5-μm particles during quiet breathing is gravitational settling. In a given subject, with the penetration of aerosol into the lung controlled by fixing tidal volume, the major factor governing the quantity of aerosol deposited is the residence time of the aerosol within the airways (3, 15). Under these conditions, in a uniformly ventilated lung, regional deposition should be uniform with the C/P ratio equal to 1.0. This means that particles have an equal probability of depositing in the small air spaces encompassed by either our central or peripheral lung regions (normalized for volume by the xenon scan). This was the case during quiet breathing with virtually no aerosol depositing in central airways (C/P = 1.04). During flow limitation, C/P ratios increased to 2.21, indicating deposition in central airways. The fraction of particles inhaled that actually deposited was unchanged (Table 1). Analysis of residence times (Table 2) demonstrates that inspiratory settling was unchanged (inspiratory residence time equals 1.4 ± 0.3 s for quiet breathing, 1.6 ± 0.5 for flow limitation; P = NS by paired analysis). Expiratory settling time was significantly reduced (expiratory residence time equals 2.1 ± 0.8 s for quiet breathing, 1.2 ± 0.2 for flow limitation; $P < 0.05$). If gravitational settling remained the major mechanism of deposition during flow limitation, then C/P ratios should have remained near 1.0 and DF should have decreased (i.e., inspiratory deposition unchanged and reduced expiratory deposition). Not only did C/P ratios increase but DF did not decrease. Therefore, deposition over the whole lung did not change in spite of a reduction in peripheral deposition. This suggests that during flow limitation the dominant mechanism of deposition is no longer settling in small airways but expiratory deposition in large airways at FLS. The bulk of the aerosol is deposited in relatively few central airways rather than being distributed evenly throughout the lung.

The demonstration of flow limitation as a mechanism of deposition in humans has important theoretical and clinical implications. Dynamic differences in airway geometry during inspiration and expiration can result in major changes in mechanisms of aerosol deposition, shifting deposition sites and changing the local burden of deposited particles in the airways. Simultaneously, forces at FLS can also interact directly on the same airways to impair mucociliary clearance (14). The early observations in dogs and the present controlled study in humans suggest that events usually confined to lung mechanics and pulmonary function may be major determinants in the lung's ability to act as an environmental defense organ. The accompanying article will attempt to relate some of these possibilities to clinical disease.

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