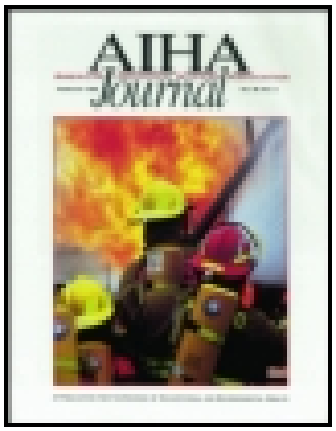

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Development of an Aerosol Dispersion Test to Detect Early Changes in Lung Function

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The dispersion of a 0.5 μm aerosol bolus during tidal breathing differs significantly ($p < 0.0001$) between a group of smokers (with ~20 pack-years average exposure) and a comparable group of nonsmokers. Their mean differences in standard respiratory function indexes from spirometry [forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), mean forced expiratory flow during the middle half of the FVC (FEF_{25-75})] were smaller and not statistically significant. The test is simple to perform and may be done as quickly as spirometry but without using a forced exhalation. Comparison of the coefficients of variation for the dispersion test and FEV_1 indicate that the aerosol dispersion test may be useful in epidemiologic investigations either by reducing the required population size or increasing the level of confidence.

Introduction

Early changes in the lung function of subjects who smoke are thought to occur predominantly in the small airways.[1-3] In the lungs of healthy subjects, however, these small airways contribute only 10% to 30% of the total flow resistance of the tracheobronchial region.[4] Since only a fraction of the small airways are likely to be involved in the initial stages of airway disease, their influence on flow resistance will be even less. Spirometry, as a consequence, is relatively insensitive to small airways disease. Obstruction in the small airways does affect greatly the distribution of ventilation, however, as shown by the frequency dependence of compliance measurements.[5] Measurement of an index of the regional convective ventilation rates in the lung, therefore, may provide useful information on early changes in lung function.

Studies of regional ventilation have shown that there are different regional ventilation patterns between healthy nonsmoking subjects and bronchitic or emphysematic subjects.[6-9] These differences in regional convective ventilation rates were attributed to differences in regional time constants.[9] These regional time constants are a product of the resistance and compliance of the lung units comprising that region. Therefore, an index of the variability of convective ventilation rates of those lung units could supply information on the severity of obstruction.

It has been shown that a bolus of submicrometer-size aerosol may be used as a tracer of convective air movement in the lungs.[10] In comparison to gases, there is relatively little diffusion of such particles during the time period of a normal breath. There also is very little deposition caused by sedimentation and impaction at breathing rates used for quiet breathing, especially if no pause is taken between inhalation and exhalation.[11] It should be possible, therefore, to use aerosols as tracers in studies of the effect of more variable, regional convective ventilation rates. The greater the variability of ventilation rates, the more widely dispersed would be an aerosol pulse because of the wider variation of flow into and out of partially obstructed lung regions.

Background

The aerosol techniques employed by other investigators have involved determinations of the profile of aerosol concentration change with change in breathing volume at the subject's mouth. The aerosol may be injected during the entire inhalation or in a pulse during a portion of the cycle. Analysis of the subsequent mixing or dispersion of the aerosol may then take several forms.

The shape of the exhalation profile has been discussed as a qualitative means of grouping subjects' responses in analyzing the output from aerosol inhaled during the entire inspiration.[12] It was pointed out that the mixing caused by turbulence or nonsequential ventilation should result in a decline in the concentration of aerosol in the tidal air and a corresponding rise in the concentration in the expiratory reserve air. This is reflected, in part, in the concave shape of the exhalation profile from subjects with airways obstruction. Further investigations[13] indicated that the exhalation profile shape seemed to be associated with increased aerosol deposition and smoking status in coal workers.

For calculating the dispersion of inspired pulses of aerosol, the ratio of the half-width (the difference between volumes at which the concentration is half maximum) to the volume at which the peak concentration occurred has been recommended.[10] It also was noted that the amount of aerosol exhaled after the peak concentration should be greater than that exhaled before the peak occurs. This could be accounted for by diffusive transport from alveoli to alveolar ducts during expiration. The peak exhaled concentration expressed as a percent of the peak inspired was suggested as

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an index of dispersion.[14] This same work also noted the asymmetrical appearance of the exhaled concentration profile. In interpreting findings concerning the mixture of an aerosol bolus between the tidal and reserve air, dispersion has been described by the volume difference between the tidal volume and the expiration volume at which the concentration is 1% of the peak inhaled concentration.[15]

None of the previously cited aerosol bolus research was concerned with the use of aerosol dispersion as an index of lung obstruction. It has been pointed out,[14] however, that the bolus technique is virtually the same as using two, single whole-breath aerosol inspirations whose tidal volumes differ by the volume of the bolus of interest. Therefore, indications that a whole-breath aerosol inhalation maneuver may provide a sensitive index of lung obstruction may be extended to include an aerosol bolus test as well.

Work also has been done using an aerosol bolus to study the change in mixing following varying doses of methacholine, a bronchoconstrictor.[16] While no use was made of an index of dispersion in the paper, it was clearly demonstrated in the figures that as the dose of methacholine was increased, the bolus became more disperse. The figures also showed that the differences became more pronounced as the depth of penetration of the bolus was increased. Also, as the dose increased, the volume at which the peak concentration occurred shifted to occur earlier in the exhalation.

Protocol

In their experiments the authors measured indexes of the dispersion of an aerosol bolus in both current smokers and in age- and gender-matched nonsmokers and compared the results of the aerosol tests with spirometric indexes. Both aerosol dispersion and spirometry are approximately equal in the speed with which the tests may be done, and spirometry is currently the primary means of determining pulmonary function in epidemiologic investigations.[17] The aerosol bolus dispersion technique does not require a forced exhalation, which also makes it attractive in terms of obtaining subject cooperation. The authors' primary objective, however, was to determine whether an aerosol dispersion test might provide a more sensitive means than spirometry of detecting early pulmonary function changes, which presumably occur in the small airways, and, therefore, prove useful for epidemiologic investigations and clinical screening.

The regional distribution of inspired air has been shown to depend on the preinspiratory lung volume, tidal volume, body position and inspiratory flow rate.[7,18-20] The aerosol protocol, therefore, was designed to control the volume and flow factors in erect, seated subjects. This was done through subject cooperation and instrument design.

Materials and Methods

The aerosol used for inhalation was tri-phenyl phosphate (TPP), which has been used as an inert, nonhygroscopic aerosol at New York University for over 25 years with no adverse effects. In animal studies[21] TPP at high concentrations is a cholinesterase inhibitor and has an 8-hour time-weighted average, threshold limit value of 3 mg/m^3.[22] The TPP was generated at a concentration of 2 mg/m^3 using an aerosol generator in which a 20% ethyl alcohol–TPP solution passed through a 6-jet Collison nebulizer (BGI, Inc., Waltham, Mass.) and then through an evaporation/condensation column.[23] The alcohol vapor was eliminated by passing the aerosol stream through a column of granulated, activated carbon. The TPP particles were nonhygroscopic and had a count median diameter of 0.4 μm (aerodynamic diameter 0.5 μm), with a geometric standard deviation of less than 1.2 as measured by a differential electrical mobility analyzer (Thermo Systems, Inc., Minneapolis, Minn.).

The aerosol was inhaled through an in-line Sinclair-Phoenix (Virtis Co., Gardiner, N.Y.) aerosol photometer with a logarithmic output on a panel meter and a strip-chart recorder (Linear, Inc., Irvine, Calif.) (Figure 1). Strip-chart recordings for several subjects were compared to data electronically recorded simultaneously at a rate exceeding 1 MHz. Peak values were not significantly different, assuring that strip chart peak-value readings were accurate for the flows used in this study. Prior to this, the airflow traveled through a Fleisch pneumotachograph (Instrumentation Associates, Inc., New York, N.Y.) attached to a Validyne Model MP 45-871 (Validyne, Inc., Northridge, Calif.) flow transducer which was connected to Validyne Model CD14-871 carrier demodulator and Validyne Model FV 156-871 respiratory flow integrator. This transformed flow to volume, and displayed the volume as an electronic signal on a voltmeter.

A solenoid valve allowed either a stream of particle-free air or an aerosol stream to be breathed. A Validyne Model

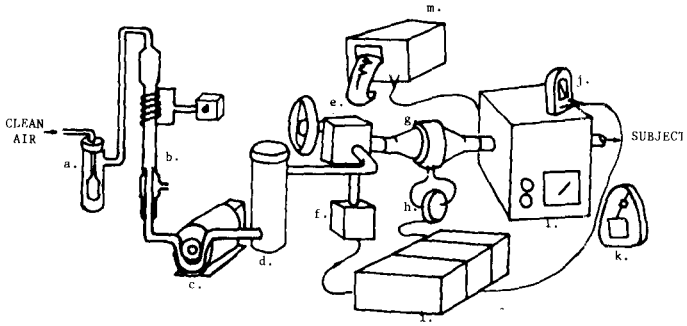

Figure 1—Aerosol bolus dispersion device. Clean air enters the collison nebulizer (a) filled with 20% TPP/ethanol. The 0.5 μm particles are formed by evaporation and condensation in (b) and then pumped (c) through a charcoal canister (d) to remove the ethanol vapors. The subject breathes fresh air through a HEPA filter (e) until a solenoid valve (f) is triggered electronically at a preset volume. The volume is measured using a pneumotachograph (g) attached through a pressure transducer (h) to a volume measurement device (i) which converts the signal from the transducer into volume and triggers the solenoid. Output from volume measurement device also is displayed for the subject on a volt meter (j). The subject then is able to maintain the proper breathing rate and volume by watching the volt meter while listening to the signal from a metronome (k). Aerosol introduced into the subject's breath is monitored by an in-line photometer (l) whose output is displayed on a strip-chart recorder (m).

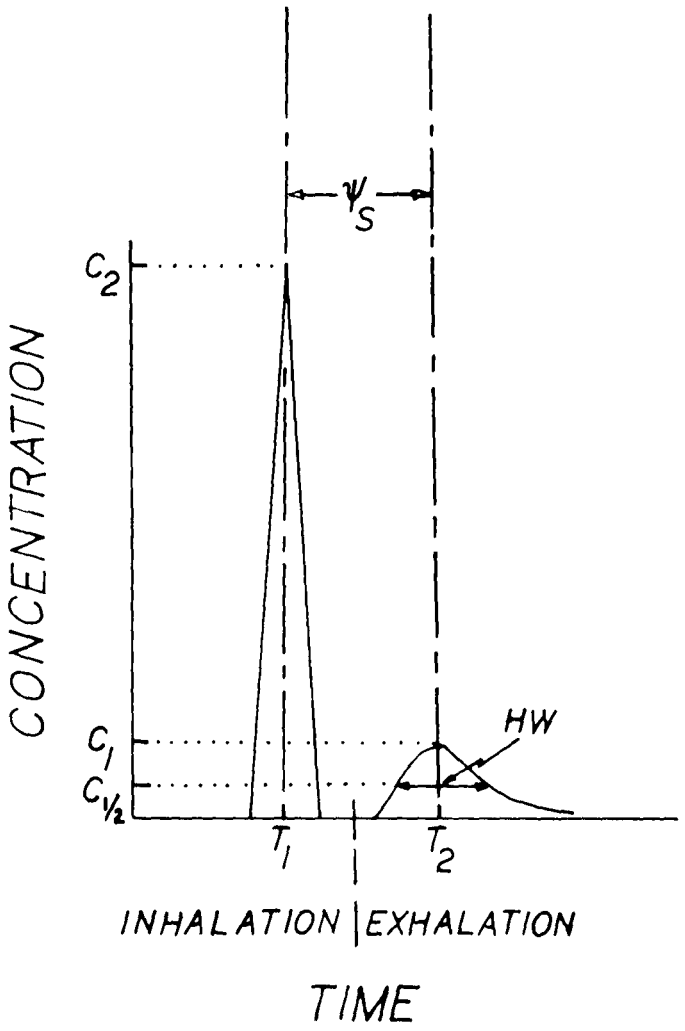

Figure 2—Idealized profile of the inhaled and exhaled bolus, where the three indexes of dispersion are defined as 1) $100(C_2/C_1) = \psi_p$; 2) $T_2-T_1 = \psi_s$; and 3) $HW = \psi_h$; where C_2 is the peak inhaled concentration, C_1 is the peak exhaled concentration, T_1 is the time at which the peak inhaled concentration occurred, T_2 is the time at which the peak exhaled concentration occurred, and HW is the time difference at which one-half the peak exhaled concentrations ($C_{1/2}$) occurred.

AL 64 alarm-controller unit connected to the flow integrator was preset to alternately switch the solenoid on and off at the desired volumes, thus creating a pulse of aerosol during a 0.25 L portion of the inhalation at any point during the inhalation.

Spirometry was performed using an Ohio 822 spirometer (Sensormedics, Inc., Anaheim, Calif.). Data were derived from a time-volume plot on a chart recorder attached to the spirometer. For each subject, a minimum of 3 acceptable forced vital capacity (FVC) maneuvers were performed. The largest FVC and forced expiratory volume in one second (FEV_1) were taken, regardless of the curves on which they occurred. The mean forced expiratory flow during the middle half of the FVC (FEF_{25-75}) was taken from the test maneuver having the greatest sum of FVC and FEV_1.

With the exception of the series of volume versus dispersion index measurements, which were done with the subjects breathing from residual volume (RV), all breathing maneuvers were begun using the subjects' functional residual capacity (FRC) as a reference point. The FRC was determined by having the subject breathe deeply, sigh and then take several breaths at a quiet breathing rate. FRC was the volume at which inspiration began after the series of quiet breaths had been taken. Subjects listening to a metronome and watching the volume display thereby could control their own breathing rate by breathing in the required volume within the required time period. Subjects were coached both before and during the experiment, and their breathing rate constantly was monitored to assure that a steady flow rate was maintained.

Indexes of dispersion were obtained for each of ten sequential breaths after FRC was established. The indexes all were averaged, and the average indexes of dispersion are reported for each subject. Three different indexes of dispersion were calculated (Figure 2) in the following ways: 1) by expressing the peak exhaled concentration as a percentage of the peak inhaled concentration ($\psi_p = C_1/C_2 \times 100$); 2) by measuring the time between the peak inhaled and peak exhaled concentrations ($\psi_s = T_2 - T_1$); or 3) by measuring the width of the exhaled pulse at half the maximum concentration (ψ_h = HW) with a constant input pulse width. The median depth of penetration (V_m) was the volume difference between the midpoint of the 0.25 L bolus and the end of inspiration.

Selection of Test Parameters

The initial tests with the aerosol dispersion system employed a population of five smokers and five nonsmokers to attempt to optimize the testing procedure to be used subsequently with a larger population. The test consisted of aerosol dispersion measurements at three penetration depths and three different inspiratory flow rates. In these first trials, only peak heights were utilized as an index of dispersion. The concentration baseline shifted after the first inhalation (because approximately 1% of the input pulse of aerosol was left in the 250 cc dead space of the photometer) but generally remained constant after the first breath. For tests in which ψ_p was measured for a series of breaths, the initial peaks were not used. Where only a single breath was taken, as when performing the maneuver from residual volume, the value of the peak-dispersion index, therefore, was slightly higher because the residual aerosol added to the first exhaled peak but not to the inhaled peak.

Table I shows the results of these exploratory tests. Lower flow rates did not decrease the peak-height index, as would have occurred had sedimentation deposition increased. It appears that there was decreased dispersion at lower flow rates and/or lesser deposition losses. Subsequent analyses showed that there was very little deposition, as will be discussed later.

Subjects could perform the test beginning at RV (Table II). This produced differences between the smoking and nonsmoking groups. These differences were not as great as those produced when breathing from FRC, however. Part of the reason may have been that only a single breath was taken from RV while multiple breaths from FRC could be taken and averaged together. The subjects could regulate their

TABLE I
Relative Peak Heights (ψ_p) for 2 Liter Inhalation from Functional Residual Capacity (FRC)

Subject	V_m (L)[A] RATE (L/s)	0.13			0.25			0.37		
		1.0	0.67	0.50	1.0	0.67	0.50	1.0	0.67	0.50
Nonsmokers										
FNCD		28.9	26.6	31.0	25.7	26.7	25.1	24.9	29.5	21.9
FNLP		21.7	26.2	27.4	12.5	15.1	13.6	-	25.3	12.2
FNMS		21.4	28.6	32.3	26.9	29.9	35.9	25.9	29.6	28.2
MNPM		16.6	29.6	36.4	14.9	24.7	26.4	11.2	20.7	17.8
MNMM		23.3	29.8	32.4	21.9	27.2	28.4	21.4	22.2	21.7
Mean		21.38	26.96	31.90	20.36	24.72	25.88	20.85	25.46	20.36
Std. Dev.		2.87	3.99	3.23	6.43	5.65	8.03	6.71	4.09	5.89
Smokers										
FSNS		20.7	25.9	27.6	23.4	23.7	21.3	18.8	14.9	17.3
FSCB		26.2	34.8	45.8	21.3	40.0	39.0	20.8	22.3	34.8
MSDL		24.9	36.1	35.6	19.4	33.7	19.3	16.1	15.1	22.2
MSCC		14.9	16.9	23.6	16.6	-	24.0	15.2	16.8	21.9
MSJC		9.4	8.5	15.4	7.1	9.3	8.4	8.3	6.4	9.5
Mean		19.22	24.64	29.60	17.56	26.68	22.40	15.84	15.10	21.14
Std. Dev.		7.04	11.46	11.60	6.36	13.39	11.01	4.76	5.71	9.20
p[B]		NS[C]	NS	NS	NS	NS	NS	NS	<0.01	NS

[A] V_m = median depth of penetration
[B] p = probability determined by t-test comparison of smokers to nonsmokers
[C] NS = not significant at 0.05 level

breathing more easily over the course of multiple breaths, and greater statistical confidence could be assured by using the average. In addition, the subjects found breathing from FRC to be more comfortable.

Only one combination of breathing frequency and penetration depth yielded highly significant differences between the two groups using a two-tailed t-test ($p<0.01$) because of both relatively large mean differences and a relatively low order of variability. Since there was a highly significant difference between the smoking and nonsmoking groups for the combination of a flow rate of 0.67 L/sec and median penetration volume of 0.38 L, testing to further optimize the bolus delivery was considered unnecessary. These values were used for all further testing unless otherwise noted.

To test the effect on dispersion of a change in the lung volume, a nonsmoking subject inhaled boluses to varying depths for tidal volumes of 1.0, 1.5 and 2.0 L. There was no significant difference in the regression lines for values of the dispersion index plotted against the same penetration depths (Figure 3). Therefore, neither the tidal volume nor the preinspiratory lung volume appeared to affect the dispersion of the bolus to any measurable extent.

Smoking Versus Nonsmoking Subjects

To simulate the application of an aerosol dispersion test in an epidemiologic study of the effects of chronic exposure to air contaminants, a group of "healthy" smokers were chosen to be the exposed population. A matched group of healthy nonsmokers were chosen as the control group. The groups were matched on the basis of average age and average height and were divided on the basis of gender. There were 12 males and 7 females in each group. There was no significant difference in either average age or height between the smoking or nonsmoking groups at the 95% confidence level. The average cumulative exposure index for the smoking population was 20 pack-years. There were no complaints of chronic cough or shortness of breath in either group nor did any of the subjects work for extended periods of time in jobs that were associated with obstructive lung disease. Both groups were recruited from workers at a laboratory which does occupational safety and health research. A number of subjects in both groups were practicing industrial hygienists but exposure to potential lung irritants during field work was limited to only several weeks per year. Subjects were tested randomly over the course of a working day during a 1-yr period.

Tables III and IV present the results of the comparison between spirometry and aerosol dispersion for nonsmoking and smoking subjects. Not all subjects consented to perform the spirometry; thus, comparison of the two types of tests were done with fewer subjects. The conclusions, however, remain the same. Significant differences were noted using a one-tailed t-test to test the hypothesis that the smoking subjects had an exhaled concentration profile that was more dispersed than the nonsmoking subjects. The level of signifi-

TABLE II
Relative Peak Heights (ψ_p) for a 3 Liter Breath from Residual Volume (RV) at 0.67 Liters/Second

	Median Depth of Penetration (V_m)									
Subjects	**2.37**	**2.13**	**1.87**	**1.63**	**1.37**	**1.13**	**0.87**	**0.63**	**0.37**	**0.13**
Nonsmokers										
FNSG	4.5	8.6	11.0	12.1	13.3	20.9	16.3	19.2	27.0	22.1
FNRH	4.5	3.5	4.5	5.4	6.9	8.3	8.1	11.4	16.6	-
FNKM	5.9	8.0	6.6	9.1	8.6	10.6	-	15.1	21.2	15.3
MNMM	-	4.9	5.5	9.2	8.8	9.3	12.8	11.8	18.0	18.0
MNGP	8.1	7.8	8.2	10.0	15.6	12.0	12.0	11.5	14.6	
Mean	5.8	6.6	7.2	9.2	10.6	12.2	12.3	13.8	19.5	18.5
Std. Dev.	1.7	2.2	2.6	2.4	3.7	5.1	3.4	3.4	4.8	3.4
Smokers										
FSTG	3.5	4.8	4.7	5.7	7.3	7.3	6.3	14.9	13.2	10.8
FSJM	4.0	6.6	4.5	4.9	7.6	8.5	10.5	13.5	14.8	-
FSNS	4.3	5.6	6.6	5.0	7.9	8.7	10.8	15.2	12.9	-
MSGT	2.5	4.0	5.7	5.5	8.1	4.8	7.9	8.6	-	-
MSJF	4.7	7.3	7.3	5.6	5.8	6.5	6.1	6.7	9.4	12.0
MSDL	1.7	3.4	3.5	3.7	4.7	5.5	10.8	9.2	11.7	16.3
MSFH	3.4	3.5	3.9	4.3	4.5	6.3	7.4	7.9	976	10.7
MSKB	4.2	8.3	6.9	6.2	9.2	12.2	11.9	10.7	14.9	9.3
MSAM	2.6	3.0	2.8	3.1	4.9	5.3	6.1	8.9	15.1	16.4
MSJB	4.3	4.4	4.4	5.1	6.6	7.9	11.2	11.5	11.9	19.6
Mean	3.5	5.1	5.0	4.9	6.7	7.8	8.9	10.7	12.4	13.6
Std. Dev.	1.0	1.8	1.5	1.0	1.6	2.2	2.4	3.0	2.6	3.8
p[A]	<0.01	NS[B]	NS	<0.001	<0.02	<0.02	<0.05	NS	<0.01	NS

[A]p = probability determined by t-test comparison of smokers to nonsmokers
[B]NS = not significant at 0.05 level

cance considered sufficient was an alpha level of 0.05. Significance was obtained for differences in 2 of the dispersion indexes, ψ_p and ψ_s. No significant difference was noted between the half-widths, ψ_h, of the 2 groups. Only 1 nonsmoker had a value of ψ_p that was below 19%, while 2 subjects in the smoking group had values of ψ_p that were above 19%, so that, in addition to a high level of confidence in the separation of the means, there was little overlap between the groups. The range of the intrasubject (breath to breath) coefficient of variation was approximately the same in both nonsmoking and smoking groups for the indexes of dispersion; ranging from 0.04 to 0.37 in the nonsmoking group and from 0.09 to 0.43 in the smoking group. The range was approximately the same regardless of the index of dispersion as well.

Of the spirometric values measured for the two groups, only the differences between female smokers and nonsmokers were significant. Regression analysis of the data in Tables II and III showed that there was no correlation between the spirometric indexes or pack-years and any of the dispersion indexes for smokers and only moderate (<0.5) correlation between the spirometric indexes (FEV_1, FVC, and FEF_{25-75}) and aerosol dispersion. Adjusting the spirometric values by the square of the individual's height did not improve the correlation in either group.

Digitization of the strip-chart data allowed conversion of the concentration profiles to a linear scale. Linearization made it possible to replot and integrate the inhaled and exhaled peaks so that the percent deposition could be calcu-

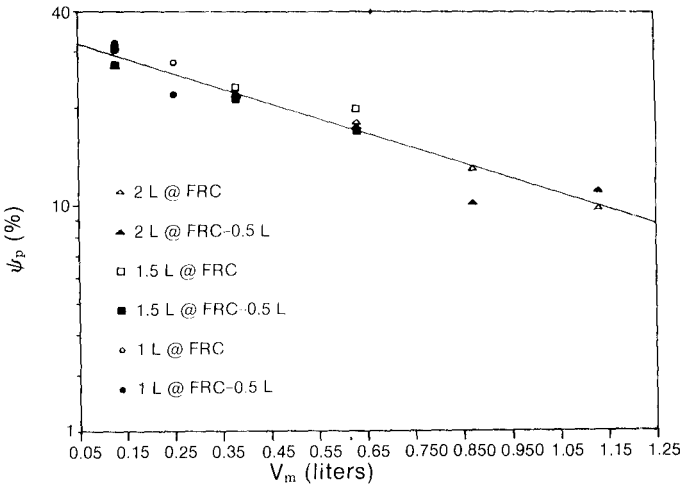

Figure 3—A linear regression plot of the penetration volume (V_m) versus the peak dispersion index (ψ_p) showing no effect of changing tidal volume or preinspiratory volume when breathing from FRC or 0.5 L below FRC. Dispersion values are the average of 10 consecutive breaths at each point.

lated. The small difference between the mean percent deposition for the smokers (mean = 6%, standard deviation = 10%) and nonsmokers (mean = 5%, standard deviation = 10%) was not significant at the 0.05 level.

Results from the repetition of the peak dispersion measurement for 5 nonsmoking subjects are given in Table IV. These repeat measurements were done several months apart for each of the subjects, with the 4 measurements for Subject 4 done over the course of 18 months. Note that the repeat values for these nonsmoking subjects remain well above the values for the smoking group.

Another series of tests was done with a different group of subjects. The dispersion index ψ_p was determined starting at the subjects' residual volume (RV) for a single tidal breath of 3L (Figure 4). The bolus was inserted in subsequent breaths at volumes beginning after the first 0.5 L and continuing every 0.25 L up to 2.75 L after the initiation of the 3.0 L breath. Because the reserve volume of most of the subjects would be expected to vary between approximately 0.75 and 1.25 L, the 3.0 L tidal volume inhaled from RV roughly was equivalent to the 2.0 L tidal volume inhaled from FRC. This single breath measurement at 10 different penetration depths was performed in 5 nonsmokers and 10 smokers. The slopes of the lines were approximately parallel, with no significant difference from each other at the 95% confidence level using the general linear models procedure (GLM). The GLM procedure developed by SAS[24] (SAS Inc., Carey, N.C.) uses the method of least squares to fit general linear models. The model used to compare the two lines was the following:

$$\text{Log}(\psi_p) = V_m + \text{Group} + V_m * \text{Group} + \text{Subject(Group)} + V_m * \text{Group(Subject)} \quad (1)$$

where group = smokers or nonsmokers,
subject = individual subjects,
and an * denotes interactive effects,
and ( ) denotes nested effects.

Significance was determined using an F-test on the output data from GLM. To compare the slopes, an F-value was derived as follows:

$$F = \frac{SS_A/df_A}{SS_B/df_B} \quad (2)$$

where SS_A = type I sum of squares for x*group,
df_A = degrees of freedom for x*group,
SS_B = type I sum of squares for x*group (subject), and
df_B = degrees of freedom for x*group (subject).

TABLE III
Comparison of Aerosol Bolus Dispersion Test Parameters[A]

		Age (yr)	Height (cm)	Deposition (%)	ψ_p[B] (%)	ψ_s[C] (sec)	ψ_h[D] (sec)
12 Male	Mean	31.2	181.4	7	22.4	1.3	0.42
Nonsmokers	Std. Dev.	5.6	4.4	10	3.5	0.3	0.20
12 Male	Mean	34.7	180.8	5	13.7	1.7	0.53
Smokers	Std. Dev.	9.3	6.5	10	5.7	0.4	0.14
19.9 pack-yr	p[E]			N.S.[F]	<0.0005	<.01	N.S.
7 Female	Mean	29.1	164.1	2	25.7	1.3	0.47
Nonsmokers	Std. Dev.	6.2	6.2	9	3.7	0.1	0.16
7 Female	Mean	35.4	160.7	9	14.5	1.7	0.38
Smokers	Std. Dev.	5.0	5.6	12	4.6	0.5	0.09
18.0 pack-yr	p[E]			N.S.	<0.0005	<.05	N.S.
19 Total	Mean	30.4	174.6	5	23.4	1.3	0.44
Nonsmokers	Std. Dev.	5.7	9.7	10	3.8	0.3	0.18
19 Total	Mean	35.0	173.4	6	14.0	1.7	0.47
Smokers	Std. Dev.	7.8	11.7	11	5.2	0.4	0.14
19.2 pack-yr	p[E]			N.S.	<0.00001	<.001	N.S.

[A]Inhalation volume = 2.0 L; flow rate = 0.67 L/sec; bolus injected at 1.50 L; and volume of bolus 0.25 L.

[B]ψ_p = aerosol dispersion index: maximum concentration of aerosol in exhaled air as a percentage of bolus concentration.

[C]ψ_s = aerosol dispersion index: time between peak inhaled and peak exhaled concentration.

[D]ψ_h = aerosol dispersion index: width of exhaled aerosol pulse at half the maximum concentration (half-width).

[E]p = significance of differences (one-tailed t-test) between nonsmoking and smoking groups.

[F]N.S. = not significant

TABLE IV
Results for Respiratory Function and Aerosol Bolus Dispersion Tests

		Age (yr)	Height (cm)	FVC[A] (L)	FEV_1[B] (L)	FEF_{25-75}[C] (L/Sec)	ψ_p[D] (%)
11 Males	Mean	31.6	181.4	5.40	4.41	4.22	22.4
Nonsmokers	Std. Dev.	5.6	4.5	0.76	0.71	1.52	3.7
9 Male	Mean	32.6	180.8	5.04	4.18	4.52	14.1
Smokers	Std. Dev.	7.1	7.2	0.95	0.47	1.63	6.5
20.1 pack-yr	p[E]			N.S.[F]	N.S.	N.S.	<0.0025
4 Female	Mean	31.0	163.3	4.21	3.55	3.95	25.1
Nonsmokers	Std. Dev.	8.0	4.0	0.52	0.49	0.93	4.6
4 Female	Mean	36.0	164.0	3.51	2.58	2.22	15.1
Smokers	Std. Dev.	6.6	4.2	0.19	0.49	1.16	6.1
22.3 pack-yr	p[E]			<0.025	<0.025	<0.050	<0.010
15 Total	Mean	31.5	176.3	5.03	4.14	4.21	23.1
Nonsmokers	Std. Dev.	6.0	9.0	0.88	0.76	1.39	4.0
13 Total	Mean	33.6	175.6	4.60	3.72	3.81	14.4
Smokers	Std. Dev.	6.9	10.2	1.07	0.88	1.83	6.1
20.8 pack-yr	p[E]			N.S.	N.S.	N.S.	<0.0001

[A]FVC = forced vital capacity

[B]FEV_1 = forced expiratory volume in one second

[C]FEF_{25-75} = mean forced expiratory flow during the middle half of the FVC

[D]ψ_p = aerosol dispersion index: maximum concentration of aerosol in exhaled air as a percentage of peak inhaled concentration.

[E]p = significance of difference (one-tailed t-test) between nonsmoking and smoking groups.

[F]N.S. = not significant

The same procedure was used to determine that there was a significant difference in the intercepts at the 99.6% confidence level by comparing group with subject (group).

Discussion

As a tracer of convective motion in the lung, an aerosol should show the effect of longer time constants in diseased regions of the lung. Aerosol entering regions with greater time constants should make the round trip into and out of the lung more slowly. Thus, subjects with longer time constants caused by disease of the lungs should have aerosol exiting over a longer period or at later times.

It has been shown[8] that an index of the aerosol deposition distribution pattern within the lungs of asymptomatic cigarette smokers is a more sensitive indicator of early airways change than is spirometry. That aerosol test, using visual inspection of gamma camera images of radiolabeled aerosol in the lung, appeared to measure large-scale inhomogeneities of ventilation. The authors, therefore, concluded that the small-airways disease in the smokers was related to the inhomogeneities of airflow which resulted in the observed lung deposition pattern.

The results of that study are consistent with previous studies using radioactive xenon gas boluses in bronchitics, emphysematics and smokers.[6,7,9] In those studies, regional inhomogeneities in ventilation were attributed to differences in convection rates. Since the aerosol used for the index of dispersion traces the pattern of convection, it was reasonable to expect that a similar level of discrimination would be found between smokers and nonsmokers as that obtained previously.[8]

Modeling of the exhaled pulse using a gamma function would make it possible to skew the distribution without changing substantially the half-width so that a larger percentage of the aerosol exits in the tail of the distribution. In this case the peak time and the peak height would be changed. As discussed in prior work,[25] this parameter either could increase or decrease, depending upon where the mixing occurred. In the test summarized in Table II, however, the exhaled bolus began so quickly after the completion of the inspired bolus that detection of a significant decrease in ψ_s was not possible with the available equipment. If the half-width were normalized by dividing by the peak exhalation time, as has been suggested,[10] this would result in a difference in the half-width when any change in the distribution took place. The fact that the half-widths were not significantly different between two groups in Tables III and IV indicates that a Gaussian distribution is an inappropriate model for the exhalation profiles. The half-width of a Gaussian distribution would have to change substantially with any change in peak height. The results of this study also indicate that the major change in the distribution must have taken place in the tails of the distribution, lending credence to the hypothesis that the later opening regions are contributors to the observed changes in ψ_p and ψ_s. Other investigators[10,14] have noted an asymmetrical shape to the exhalation profile. The gamma distribution is an expected function in a

stirred vessel and the nonuniform expansion of the alveoli seems to be reasonably represented in that way.

Application

For epidemiologic investigations the availability of a sensitive test of early airway changes would make it possible to reduce the population size required to obtain a specific level of confidence. For example, by comparing the "t" statistic for the peak-height dispersion index differences between smokers and nonsmokers (t_1 = 4.52) with that for FEV_1 between the same groups (t_2 = 1.62), it is possible to estimate the relative population size (n) required to obtain the same level of confidence using a method similar to one previously described:[26]

$$n = 2\left[\frac{t_1 \times S_{p2}}{\Delta\bar{x}_2}\right]^2 \quad (3)$$

where S_{p2} = pooled standard deviation of the FEV_1 test, and
$\Delta_{\bar{x}2}$ = difference in mean FEV_1 between the smokers and nonsmokers.

In this case, n = 107, which means that a population size approximately 7.6 times greater than the population size used in Table III would be required to give the same level of confidence for the FEV_1 as obtained using the aerosol dispersion test (assuming the mean difference and standard deviation were representative of the true mean and standard deviation). In cases where the population size is small and fixed, this also means that significant differences in aerosol dispersion can be detected where only small and nonsignificant changes in spirometry occur.

Part of the reason for the dispersion test's increased sensitivity also can be seen from examination of the coefficient of variation. It is the ability of the aerosol dispersion test to use more than a single "best effort" that decreases its variability and, thus, increases its sensitivity. By using the mean of several measurements as the overall value for any given subject, the uncertainty associated with single values is reduced. The larger the number of values that make up the mean for a given subject, the higher the confidence that the value approaches the "true" value for that subject. The coefficient of variation (COV) reflects that by being a comparison of the standard deviation to the mean for a given number of values. The smaller the COV, the higher the level of confidence in any set of measurements. One way to reduce the coefficient of variation, then, is to increase the number of measurements. Since the coefficient of variation is inversely proportional to the square root of the number of measurements, the benefit diminishes with increasing sample size. When compared to spirometry, however, where the assigned value is that of a single or a few best efforts spread over a 1–5 min period, the benefit of being able to make a multiple series of valid measurements within a short interval readily is apparent.

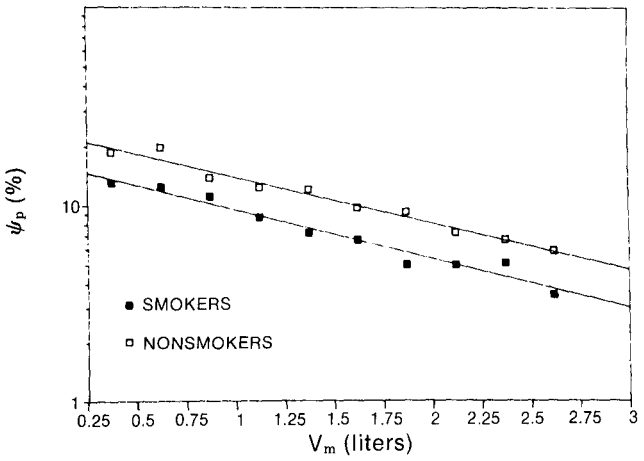

Figure 4—Comparison of the peak aerosol dispersion index (ψ_p) at varying depths of penetration (V_m) for smoking and nonsmoking subjects. Results shown are the average values for the groups.

In addition, the entire lung volume can be characterized by inserting the bolus at various points within the breath. This method also yielded significant differences between a smoking and nonsmoking group of subjects (Figure 4). Some lung regions appear to have larger involvement than others. This was reflected in the data used to select the best operating parameters (Table I) in which the differences in dispersion were much greater and the variability was much less for one particular combination of penetration volume and flow rate. Depending on the nature of the disease process which alters aerosol dispersion, each subject may show a significant change at a different lung volume. No single penetration depth, however, could be identified in the present study as playing a dominant role in causing the greater dispersion in the smoking group.

Summary and Conclusions

Several indexes or aerosol dispersion were examined in this study, and two were found to yield significant differences between the smoking and nonsmoking groups. Two indexes which showed significant differences were the relative peak height (ψ_p) and the time between inhaled and exhaled peaks (ψ_s). On the other hand, the width of the exhaled peak at half the maximum concentration (ψ_h) was not significantly different between the two groups. Assuming that some of the increased dispersion was due to slower emptying pathways in the lungs with airways obstruction, it should be expected that relatively more aerosol would occur later in the exhalation in the smoking group.

While it appears that a number of penetration depths cause the bolus to disperse to a significantly different degree in the smoking group as compared to the nonsmoking group, the penetration depth used to obtain the data in Tables II and III is the shallowest (*i.e.*, the smallest volume between the midpoint of the bolus and the end of the breath) that gave significant differences. This would be important in studying a large population with a wide range of lung volumes. The smaller the tidal volume necessary for the test, the easier it is to have all members of the population perform the same test. While it may be possible to compensate for varying lung

TABLE V
Variability in Repeat Measurements of Aerosol Dispersion Index

Subject	First Measurement	Repeat Measurement	Percent Changes
1	28.62	29.46	3
2	25.42	21.57	15
3	19.58	20.70	5
4	21.77	22.17, 22.41, 22.86	2, 3, 5
5	23.42	26.62	14

sizes, it appears that the test can work as well at the same penetration depth for all subjects for establishing differences between healthy adult smokers and age- and gender-matched nonsmokers.

Adjustment to a fixed fractional volume appears to have little practical significance for aerosol dispersion testing in adults. No significant difference in the peak-height index was observed in the nonsmoking subjects where there was almost a two-fold difference in the range of forced vital capacities. It would, in fact, tend to make the test more difficult to set up for each individual as well as more time consuming, since a forced vital capacity maneuver would be required. On the other hand, some research should be done to determine if data adjusted for relative lung volumes might be necessary for testing children whose lung volumes will vary considerably with age.

The results indicate that the aerosol dispersion test requires approximately an order of magnitude fewer subjects than does spirometry for comparable sensitivity in detecting early lung changes caused by an inhaled irritant. If utilized, the aerosol dispersion test could make it possible to perform epidemiologic studies on groups which previously were too small to use when only marginal differences in spirometry were expected. The different information obtained from the aerosol dispersion test also may reveal previously undetected effects in small populations. Greater sensitivity may allow earlier diagnosis, treatment, or intervention, yielding a better prognosis than spirometry.

The equipment used for the study was available as off-the-shelf units generally intended for other uses and adapted to the purposes of this study. It resulted in limitations to the type of experiments that could be done and the precision of data that could be collected. While both dispersion and deposition could be determined and the test could be run with minimal delays to the subject, extensive overhaul frequently was necessary. The shortest test, used to derive the values in Tables III and IV, requires 10 breaths over a period of approximately 1 min. Since a forced breathing maneuver was not required, there was no discomfort to the subject in performing the test. The time required to participate in the test also was equal to or less than that required for spirometry.

The lack of correlation between the dispersion test results and the spirometric indexes presents a limitation to a definitive interpretation of the findings of this study. There are several possible reasons for the lack of correlation. The most obvious reason is that the tests are measuring different airway functions under different physiological conditions. Another may be the low signal to noise ratio of the spirometry, which also would account for the lack of significant differences in spirometric indexes between the smoking and nonsmoking groups. A larger population with a wide range of spirometric values might allow determination of the correlation of aerosol dispersion and spirometry for young adult smokers. For subjects with more extensive lung disease, there is an additional problem. The dispersion test will detect only lung areas that are open to convective flow. If a subject has areas that are so diseased as to be closed to convective flow at normal ventilation rates, then the dispersion test as done to construct Table II may not show the expected magnitude of change. Even among individuals with changes that are significantly lower than normal, bronchodilation reveals that there may be areas that remain obscured, as seen in those subjects with increased dispersion changes after bronchodilation.[25]

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NIOSH Technical Report

Safe Maintenance Guidelines for Robotic Workstations

The U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health (NIOSH) has recently issued (March 1988) DDHS (NIOSH) Publication No. 88-108, *Safe Maintenance Guidelines for Robotic Workstations.*

This guide is concerned with robotics technology. Its aim is to help someone who has been given a robotic safety responsibility to learn ways to prevent injuries during tasks which call for personnel to intervene in robot work zones. There are many reasons why personnel enter robot work zones (job set up, repair, programming, inspection). The injuries that have occurred happened most frequently when corrective maintenance was being done. This guide describes the hazards which exist when a worker is in a robot's working area and describes means to minimize or eliminate these hazards. When the safety of a robotic system under development is in question, this guide can be an aid for developing training of personnel, task design, simulation, maintenance-data collection, equipment specification and maintenance instructions. Where safety solutions already have been applied to robot work stations, this guide may be used to evaluate their effectiveness.

A copy of this guide may be obtained from the National Institute for Occupational Safety and Health, Publications Office, 4676 Columbia Parkway, Cincinnati, OH 45226.