

Variability in the size of airspaces in normal human lungs as estimated by aerosols

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Lapp, N. L., Hankinson, J. L., Amandus, H., and Palmes, E. D. (1975). *Thorax*, 30, 293–299. **Variability in the size of airspaces in normal human lungs as estimated by aerosols.** Measurement of persistence, expressed as half-life ($t_{1/2}$), of a monodisperse aerosol during breath holding was interpreted as an indirect estimate of the size of intrapulmonary airspaces in healthy subjects. Within subject variation of $t_{1/2}$ measured over a period of nearly two years was small (coefficient of variation 7.7 to 11.5%). Mean effective airspace diameters were calculated from the aerosol $t_{1/2}$ values using the settling term from the equation of Landahl (1950). Calculated mean airspace diameters ranged from 0.30 to 0.79 mm for 36 males and from 0.40 to 0.62 mm for 12 females. Airspace diameters correlated poorly with age, height, weight, and lung volumes. These results suggest marked differences in airways geometry in subjects with similar heights and lung volumes.

Previous work has shown that the persistence expressed as half-life ($t_{1/2}$) of aerosol in the human respiratory tract during breath holding can be interpreted as an indirect method of estimating the size of the airspaces containing the aerosol during breath holding (Palmes, Altshuler, and Nelson, 1967; Palmes, 1973; Palmes *et al.*, 1973). Efforts have also been made to employ aerosols in this manner as a diagnostic test for emphysema. Preliminary studies (Palmes *et al.*, 1971) in this area were encouraging, and it was decided to employ the same apparatus and procedures on a larger population of normal subjects in order (a) to establish reproducibility of the aerosol results on individuals tested at various times, and (b) to determine the range of half-lives in a normal population.

It was also planned to measure a number of pulmonary function indices that incorporate estimates of lung size and volume as well as can be determined during life, in order to see which, if any, of these correlated with the aerosol half-lives.

There has been relatively little work on inhalation of homogeneous aerosols by man, and most of this has been done under steady state breathing

conditions in order to estimate total or regional deposition as a function of particle size. Measurement of aerosol persistence during breath holding may be interpreted as an index of the lung airspace sizes. The rationale is that a particle, having been transported into the lung, will remain airborne until it has traversed a distance necessary to strike a wall. If the particles are all of the same size the mean displacement per unit time by a combination of Brownian motion and sedimentation is constant. It follows, therefore, that the larger the airspace the longer the time required to strike a wall. The effect of lung volume and indirectly the size of the airspace on aerosol persistence was demonstrated in three normal subjects by measuring the rate of disappearance when the breath was held at several different volumes (Palmes *et al.*, 1971); the half-life decreased linearly with lung volume.

METHODS¹

Procedures for generation, characterization, and breathing of aerosols have been described in detail

¹Mention of commercial products or brand names does not constitute endorsement by the Public Health Service

elsewhere (Palmes and Wang, 1971). Briefly, a homogeneous aerosol of triphenylphosphate at about 10^6 particles per millilitre is inhaled as part of a respiratory manoeuvre programmed in the breathing apparatus as shown in Figure 1. The total manoeuvre involves several normal breaths followed by an inhalation to total lung capacity (TLC) at which point the programmed sequence begins. The subject exhales 1.2 litres, inhales 1.0 litre, holds his breath for 0–30 seconds, and then exhales 2 litres. Inhalation and exhalation concentrations are measured by light scattering, and the quantity of aerosol exhaled is divided by the quantity inhaled to give the persistence for the time the breath was held. Since the persistence decreases exponentially with the time of breath holding (Palmes *et al.*, 1967), it can be expressed in terms of a half-life.

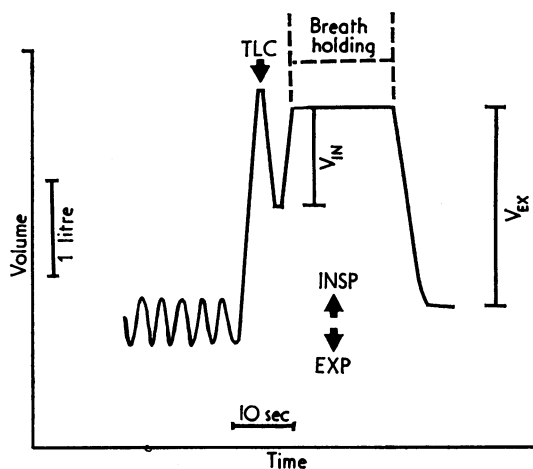


FIG. 1. Typical aerosol inhalation and breath holding manoeuvre. (Reprinted by permission of the editor from: Palmes, E. D. and Wang, C. S. (1971). *American Industrial Hygiene Association Journal*, 32, 43.)

This half-life can be used to calculate for a tubular model the average or 'effective' diameter of the space in which the aerosol is confined. The rationale is that particles randomly distributed in randomly orientated tubes of infinite length, as treated by Landahl (1950), will be deposited at an exponential rate, the exponent being determined by the diameter of the tubing and by the physical properties of the particles. As discussed in an earlier publication (Palmes *et al.*, 1973), the equation derived from Landahl can be simplified in

dealing with triphenylphosphate aerosol particles of approximately 0.55 micra diameter. The persistence of the aerosol can then be based completely on the sedimentation rate of particles during breath holding. The justification for disregarding Brownian motion is derived from the work of Wang, Altshuler, and Palmes (1968), who showed that for particles suspended between parallel plates the larger of the separate effects of settling and Brownian motion is generally a better approximation than that which treats the separate probabilities of deposition independently. In the present studies the simplified equation is:

$$\text{Airspace diameter} = 0.027 \text{ mm/sec} \times t^{\frac{1}{2}} \text{ (sec)}$$

The constant 0.027 mm/sec is the rate of gravitational settling for the subject particles in air; thus the half-life gives a direct index of the size of the airspaces. This size is defined as that diameter tubing which, if of infinite length and randomly orientated, would show the same aerosol persistence or half-life as that observed in the human subject.

It should be noted that with a 1-litre inhalation most of the aerosol should still be airborne and located within the small airspaces within the parenchyma during breath holding since the 1-litre breath is considerably larger than the anatomical deadspace. Each sequence involves 6–10 breaths, breath holding ranging from 0 to 30 seconds. The results for the series of breaths were used to determine the slope of the persistence curve by a least squares procedure. It was then possible to determine the half-life, intercept for zero breath holding time, and the 95% confidence limits for the half-life.

The study population includes 36 men and 12 women. All were members of the professional and technical staff of the Appalachian Laboratory, the West Virginia University Medical Center, or New York University Medical Center. Twenty-two of the men and eight of the women had never smoked. Twelve men were former smokers. Two men and four women were cigarette smokers at the time of the study.

Spirometry was performed using a high-fidelity waterless electronic spirometer (Ohio Medical Products, Madison, Wisconsin, Model 800) equipped with temperature probe (Yellow Springs Instrument Co., Yellow Springs, Ohio, Model 405) and time-pulse generator (Hankinson and Lapp, 1970). Total lung capacity and airways resistance were measured in a constant volume body plethysmograph (Warren E. Collins, Inc., Braintree, Mass.) using the methods of Dubois *et al.* (1956a) and Dubois, Botelho, and Comroe

(1956b). The predicted values for total lung capacity were calculated from the short formulae of Needham, Rogan, and McDonald (1954), and those for forced vital capacity were obtained from Kory *et al.* (1961) and Kory, Smith, and Callahan (1966).

Diffusing capacity for carbon monoxide was measured by the single breath technique (Ogilvie *et al.*, 1957) modified by using residual volume obtained in the plethysmograph and analysing the gases in a gas chromatograph (Beckman Co., Fullerton, California, Model GC5A). Values obtained in 20 healthy men and 30 healthy women subjects in the ALFORD laboratory were used to predict the normal diffusing capacity in these subjects (Seaton, 1972; Seaton, Lapp, and Morgan, 1972).

Anatomical deadspace at functional residual capacity was estimated in 21 of the men and 11 of the women by the method of Fowler (1948).

RESULTS

Values for the half-life of aerosol persistence obtained in seven subjects (five men and two women) measured on at least five different occasions over a period of nearly two years are shown in Table I. The within subject variation for $t_{\frac{1}{2}}$ was relatively constant, as indicated by the coefficient of variation $((SD/Mean) \times 100)$ which ranged from 7.7% to 11.5%.

Values for the various indices of pulmonary function and $t_{\frac{1}{2}}$ of aerosol persistence within the respiratory airspaces during breath holding for the study subjects are available from the authors upon request. The mean values and standard deviations for the pulmonary function indices, aerosol $t_{\frac{1}{2}}$, and average airspace diameter are grouped by sex and smoking status in Table II. The women were shorter, not as heavy, and on average somewhat younger than the men. Within the male group the nonsmokers and current smokers were also shorter, younger, and lighter than their exsmoking counterparts.

Total lung capacity expressed as a percent of predicted value averaged about 90% of predicted for all groups. However, there were no differences between the subjects in each of the smoking categories in regard to TLC.

Forced vital capacity (FVC), which in nonobstructed subjects is approximately the same as vital capacity, averaged slightly greater than predicted overall, but there were no significant differences between the mean values for each smoking category.

Diffusing capacity for carbon monoxide (DLCO) averaged about 100% of the predicted value for the men but averaged approximately 90% for the women.

In those subjects in whom it was measured, the mean values for anatomical deadspace (VD) were found to be somewhat lower than the expected value of approximately 1 ml per pound (0.45 kg) of body weight (Radford, 1955).

It is well known that lung volumes tend to be reasonably closely related to height and that airways resistance and diffusing capacity for carbon monoxide are largely related to lung volume. We therefore sought similar relationships of estimated airspace diameters to height and lung volumes. Among the male subjects correlation coefficients between estimated airspace diameters and height, age, TLC, FVC, DLCO, and VD, were $r = -0.46$, $r = -0.46$, $r = -0.38$, $r = -0.25$, $r = -0.14$, and $r = -0.40$, respectively. The highest correlation coefficients found among the female subjects were between estimated airspace diameters and FVC ($r = 0.74$) and VD ($r = 0.71$). The correlation coefficients between estimated airspace diameters and height, age, TLC, and DLCO for the women were $r = 0.20$, $r = -0.21$, $r = 0.50$, and $r = 0.13$, respectively.

The mean calculated airspace diameters for nonsmoking males were similar to those obtained for both nonsmoking and smoking females; whereas, the values for exsmoking males were significantly larger. These differences might be a consequence of the difference in age between the

TABLE I
REPRODUCIBILITY OF MEASUREMENT OF HALF-LIFE

Subject No.	Half-life						Mean \bar{X}	Standard Deviation S	Coefficient of Variation S/ \bar{X}
	19.4	15.8	17.0	21.2	19.2	—			
6	19.4	15.8	17.0	21.2	19.2	—	18.5	2.13	11.5
16	22.9	22.9	22.0	22.2	28.3	—	23.7	2.62	11.0
18	10.0	12.2	11.3	10.6	11.6	—	11.1	0.86	7.7
22	20.4	19.9	23.4	21.3	25.2	20.1	21.7	2.13	9.8
31	26.1	24.3	29.4	25.3	24.5	28.4	26.3	2.11	8.0
39	20.3	19.9	19.6	22.6	25.5	—	21.6	2.49	11.5
44	18.9	21.2	19.6	20.4	23.7	—	20.8	1.85	8.9

TABLE II
SUMMARY STATISTICS

Subject	Height (in.)	Weight (lb.)	Age (yr.)	TLC % pred.	FVC % pred.	DLco % pred.	RAW ¹ (cmH ₂ O l/sec)	TGV ² (litres)	V _D ³ (ml.)	Half-life (sec.)	Airspace Diam (mm.)
Males, all											
n	36	36	36	36	36	31	36	36	21	36	36
\bar{x}	69.9	165.9	32.9	89.4	105.5	101.3	1.58	3.92	141.8	20.0	0.55
SD	1.9	19.8	10.7	11.0	12.6	10.4	0.44	0.69	27.0	4.4	0.12
Nonsmokers											
n	22	22	22	22	22	21	22	22	15	22	22
\bar{x}	69.8	162.2	29.84	89.4	106.2	101.0	1.48	3.86	141.0	18.8 ⁴	0.51 ⁴
SD	1.82	18.8	8.2	13.4	14.1	10.9	0.37	0.72	27.7	3.9	0.11
Exsmokers											
n	12	12	12	12	12	9	12	12	5	12	12
\bar{x}	70.1	175.7	40.0 ⁴	90.5	105.0	103.0	1.72	4.05	146.0	22.2 ⁴	0.61 ⁴
SD	2.20	18.8	12.4	5.9	10.8	9.5	0.52	0.69	30.0	4.8	0.13
Smokers											
n	2	2	2	2	2	1	2	2	1	2	2
\bar{x}	69.8	148.5	25.0	82.5	100.5	91.0	1.84	3.65	133.0	20.6	0.56
SD	—	—	—	—	—	—	—	—	—	—	—
Females, all											
n	12	12	12	12	12	10	12	12	11	12	12
\bar{x}	64.4	121.8	25.8	89.3	102.5	89.6	2.01	3.04	101.8	18.5	0.51
SD	1.5	14.1	8.6	10.5	14.0	10.0	0.61	0.67	20.2	2.8	0.08
Nonsmokers											
n	8	8	8	8	8	8	8	8	7	8	8
\bar{x}	64.5	119.2	26.1	89.5	103.2	89.0	1.93	3.16	97.1	18.5	0.51
SD	1.12	9.4	10.2	9.62	15.10	11.6	0.44	0.63	22.6	2.9	0.08
Smokers											
n	4	4	4	4	4	2	4	4	4	4	4
\bar{x}	64.0	126.8	25.2	89.2	101.0	91.5	2.18	2.79	110	18.7	0.51
SD	2.1	21.6	5.3	13.6	13.6	—	0.92	0.76	14.3	3.0	0.08

¹RAW = airway resistance.

²TGV = thoracic gas volume.

³V_D = anatomic deadspace.

⁴Denotes significant difference between nonsmokers and exsmokers P < 0.05.

male exsmoking and the other groups or could represent a change related to their smoking habit.

DISCUSSION

It should be stated at the outset that the estimation of the effective diameter of the pulmonary airspaces using aerosols is fundamentally an anatomical measurement. It is hoped that the use of aerosols will permit an indirect measure of airspace dimensions which will not only make possible more realistic estimates of average airspace sizes in normal subjects, but will also allow an estimate of the variability of these sizes within a normal population.

We were somewhat surprised that in so far as aerosol persistence is an estimate of airspace diameter, this size did not correlate well with other predictors of lung size, such as height or lung volumes. We also found no good correlations between effective airspace diameters and age or sex. The observations may be explained partially on the basis of the relatively large dispersion of values for effective diameters that was seen between individuals which might obscure meaningful correlations. On the other hand, Green, Mead, and Turner (1974) found that maximal

expiratory flows which are in part related to the geometry of the airways were also quite variable between different subjects with similar lung volumes. They postulated the concept 'dysanaptic growth' of the two parts of the lungs, the central airways, and the peripheral gas exchange units, as an explanation for their findings.

We suppose that the standard lung function test that most closely resembles the aerosol test is the single breath carbon monoxide diffusing capacity (transfer factor). Even here, however, there are marked differences between the two measures. First, the gas molecules utilized in the transfer test are approximately 1000 times smaller than the aerosol particles and therefore their root mean square displacement should be approximately 1000 times greater than that of the aerosol particles. Secondly, the volumes inhaled in the two tests are several litres (one vital capacity) for the gas and one litre for the aerosol. Thirdly, the gas is inhaled beginning at residual volume, whereas the aerosol is inhaled beginning at 1.2 litres from total lung capacity. Thus, the gas would be expected to be distributed more or less uniformly throughout the lungs in proportion to their relative regional ventilation, whereas the aerosol, being inhaled near total lung capacity,

should be distributed preferentially to the dependent lung zones that receive most of the latter part of the inspiratory volume (Milic-Emili *et al.*, 1966).

Thus, while the aerosol technique would be expected to be markedly influenced by small differences in airways geometry, the transfer test would not.

The finding of widely different average airspace diameters among healthy subjects with similar lung volumes and, apparently, lung sizes has implications in the area of the pneumoconiosis-producing dusts. Given two subjects with similar lung volumes but one having smaller mean airspace diameters, both working in the same dusty environment, the one with the smaller airspaces might be expected to deposit more particles per unit of alveolar ventilation than the one with larger airspaces. Differences between individuals with regard to deposition during steady state breathing have been reported by a number of investigators at a variety of particle sizes (Altshuler *et al.*, 1957; Lippman and Albert, 1969; Giacomelli-Maltoni *et al.*, 1972). The situation is, however, much more complicated during active respiration than during the breath holding period considered here. This is because during steady state breathing experiments previously cited, much of the intersubject variation in aerosol deposition was accounted for on the basis of the differences in the amount of mixing between inhaled air containing aerosol and lung air. Therefore, the only way in which the effect of size of deep airspaces on deposition during steady state breathing could be determined would be to make both measurements on the same subjects; to our knowledge, this has not been done. It was because of this problem that we chose to use the breath holding method to make our estimates of airspace diameters.

Deposition of particles is only one part of the pneumoconiosis story. Another relates to the rate of clearance of the deposited particles, which has also been shown to have considerable intersubject variability (Albert *et al.*, 1973).

Unfortunately, in many respects our experiments are of the 'black box' variety. The data obtained represent the calculated mean diameters for a considerable fraction of the lung and do not permit precise anatomical localizations. The great bulk of the 1000 ml inhalation of aerosol-containing air would penetrate beyond the conducting airways into the gas exchanging alveolated airspaces. Our measurements are, therefore, weighted in favour of the small intrapulmonary

airspaces where the mean linear distance a particle needs to travel to impact on a wall during breath holding is relatively short.

It should be noted that the volume of the aerosol inhaled was held constant; however the size of the anatomical deadspace varied from subject to subject, in those in whom it was measured. Thus, the relative fraction of the inhaled aerosol present within the small intrapulmonary airspaces varied inversely in relation to the size of the deadspace. This may have contributed to the dispersion of the values of the calculated airspace diameters within our subjects. The relatively high positive correlation between measured airspace diameters and anatomical deadspace found in female subjects ($r=0.71$) appears to support this assumption. On the other hand, the mean relative fractions of inhaled aerosol that penetrated beyond the anatomical deadspace for the men and women were 0.86 and 0.90 respectively. It seems unlikely that a 4% difference between the fractions penetrating into the intrapulmonary airspaces could explain all of the differences found in diameters estimated by aerosol persistence.

The exact location of the aerosol at the beginning of breath holding is not known for another reason. Pathway lengths are not the same to all parts of the respiratory tract; therefore the anatomical region in which the aerosol is suspended may be different. There is bound to be some axial dispersion of the aerosol during inhalation owing to the fact that at these flow rates flow is laminar in most of the respiratory tract. On the other hand, the changes produced in $t\frac{1}{2}$ by increasing inhaled volume beyond 600 ml were relatively small when studied by a bolus technique (Palmes *et al.*, 1973) in six normal subjects. The $t\frac{1}{2}$ of aerosol persistence observed in subjects inhaling 1000 ml would not be expected to be greatly influenced by this axial dispersion.

Recently, Engel *et al.* (1972) demonstrated that, due to cardiac churning, there is considerable mixing between alveolar gas and deadspace gas over and above that accounted for by molecular diffusion. If, as these authors suggest, convective mixing associated with nonrandom eddy currents and secondary motions is an important factor contributing to the spread of the gas front, it also could contribute to the dispersion of our aerosol during breath holding. This effect should have been relatively small, however, since the aerosol particles remaining airborne would be carried in the bulk flow of air produced by cardiac churning which, according to Engel's calculations, was

equivalent to a tracheal flow of approximately 100 ml per second.

The most straightforward procedure to establish the relationship between aerosol persistence during breath holding and the size of the airspaces is to study the same lungs using aerosol persistence and morphometric measurements on histological sections. This has obviously not been done on any of our subjects, but recently Matsuba and Thurlbeck (1971) measured the number and average diameters of small (less than 2 mm) nonalveolated airways in the lungs of 20 normal cadavers after carefully controlled inflation, fixation, and sectioning. Figure 2 shows a cumulative frequency diagram comparing the results of Matsuba and Thurlbeck with the aerosol data on estimated airspace diameters. It can be seen that they found an average diameter of 0.68 mm and a coefficient of variation of 24%, while our value for the average effective airspace diameter, as estimated by aerosol persistence, was 0.54 mm with a 21% coefficient of variation. We do not believe that a strict comparison of average sizes by the two methods is justified, because the aerosol method is looking at alveolated airspaces as well. Nevertheless the similarity of the coefficients of variation for the two sets of values, 24% versus 21%, is highly suggestive that there is considerable variability in the average size of similar anatomical units in normal human populations when estimated by either technique.

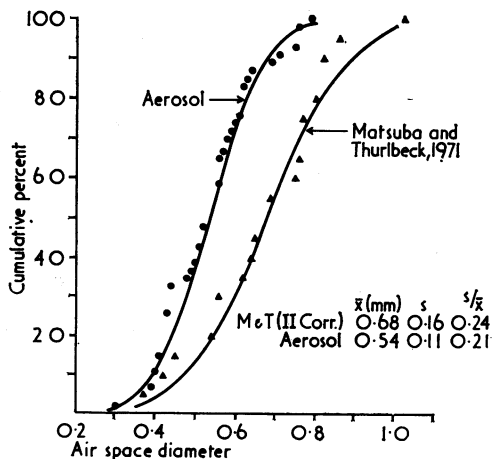


FIG. 2. Distribution of airspace diameters determined by aerosol persistence compared with diameters of small (<2 mm) nonalveolated airways found by Matsuba and Thurlbeck (1971). The ordinate refers to the percent of airspaces less than the stated diameter.

It should also be noted that previous investigations by Thurlbeck (1967), and more recent ones by Angus and Thurlbeck (1972), on the number and dimensions of alveoli in the normal human lung also suggest wide variations between subjects of similar heights. These workers found that although the total number of alveoli and, consequently, lung volume were positively correlated with body length (height), the mean linear intercept (average interalveolar distance) was independent of body length and lung volume.

This type of distribution in normal populations has profound implications for lung models, whether one considers either gas transport and distribution or aerosol distribution and deposition. Treating the airspace diameters as if they were approximately equal for all normal subjects makes it possible to arrive at elegant models for estimating aerodynamic characteristics, but the models fail to take into account variability in airspace size within normal subjects and the difference in aerosol behaviour which would result from this variability. One of the models for aerosol deposition in wide use is that of the International Committee for Radiation Protection (Morrow, 1966). This model is used to estimate total and regional aerosol deposition for each particle size in a single anatomical model made up of tubes of a series of fixed sizes. Similarly, Weibel's regular model of the lung (Weibel, 1973), which is also widely used to explain aerodynamic behaviour, certainly does not suggest such wide variations in the anatomy of the airspaces between subjects as we or Matsuba and Thurlbeck (1971) have detected.

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