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Effect of depth of inhalation on aerosol persistence during breath holding

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Palmes, E. D., Chiu-sen Wang, Robert M. Goldring, and Bernard Altshuler. *Effect of depth of inhalation on aerosol persistence during breath holding.* J. Appl. Physiol. 34(3): 356–360. 1973.—To determine the effect of depth of inhalation on aerosol persistence in the respiratory tract during breath holding, an aerosol bolus was inhaled, followed by 200–800 ml of clean air to a lung volume slightly below TLC. The breath was then held from 0.5 to 20 sec, after which a forced exhalation was made and aerosol recovery was measured as a fraction of that inhaled. In this way persistence was measured as a function of inhaled volume and of time of breath holding for six normal subjects. The bolus results were then compared with those for complete aerosol inhalations in which persistence was measured in the same way. Results on each subject by the two procedures agreed well, but there were considerable differences between subjects. It was concluded that depth of inhalation has a greater effect on persistence than would be predicted from some current lung models.

aerosol physiology; aerosol bolus; air-space dimensions; lung structure

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EARLIER WORK in this laboratory has shown that, during breath holding following a single inhalation of aerosol, persistence of aerosol (the probability of being exhaled rather than deposited) decreases exponentially with time (5). Such behavior is most simply characterized by a half-life, the time to deposit one-half the airborne aerosol. It was also found that persistence decreased as the lung volume at which the breath was held decreased (6). This was attributed to the intrapulmonary air spaces becoming smaller, on the average, as lung volume is decreased. The relationship between lung volume and half-life of aerosol in the respiratory tract was linear and extrapolated to zero half-life at approximately residual volume.

Because of this observed effect on half-life, the lung volume at which the breath was held was standardized at a volume approximately 200 ml less than total lung capacity to allow a maximum exhaled volume. In all of the previously reported studies the respiratory maneuver started at total lung capacity with exhalation of a preset volume followed by inhalation of a fixed volume of aerosol. At the end of inspiration, the breath was held for times of 0 to approximately 30 sec before exhalation of twice the inhaled volume. It has been found both at this laboratory (1) and by Muir (4) that this maneuver will remove practically all airborne aerosol from the lungs of normal subjects. An apparatus (7) developed for these earlier studies controlled the depth of inhalation, the lung volume relative to total lung capacity at which the breath was held, the time of breath holding, and the volume finally exhaled; it also measured the quantities of inhaled and exhaled aerosol.

The purpose of the present studies was to use these procedures to obtain the dependence of persistence on inhaled volume for selected breath-holding times. This was done in two ways. In the method giving the most detail, a small bolus of aerosol was inhaled and followed by clean air so that the exhalation contains the return of aerosol from a specific inhaled volume element. In the second method, run as a check on the first, the complete inhalation was composed of the test aerosol so that the exhalation contains the sum of the returns from all inhaled volume elements.

APPARATUS AND PROCEDURES

Four male and two female adult subjects were used in each sequence. Total lung capacity, functional residual capacity, residual volume, sex, and cigarette consumption are given in Table 1. All were free of cardiopulmonary abnormalities as indicated by clinical examination and spirometry.

The particle diameter of the monodisperse triphenylphosphate aerosol was between 0.5 and 0.6 μ based on higher order Tyndall spectra obtained in the "Owl." The geometric standard deviation was not measured in these studies, but from earlier work with this generator it was less than 1.2 in all cases.

The apparatus employed for the complete aerosol inhalation studies has been described by Palmes and Wang (7). It had a four-way solenoid controlled valve system which connected a mouthpiece to a spirometer and two anesthesia bags. Each bag was contained in a box which was directly connected to the spirometer to record the change in volume of the bag. To measure the quantity of aerosol, a small tube was used to connect the aerosol photometer inlet to the mouthpiece arm of the valve system. The valve system was programmed to change the connections so that a subject could inhale the aerosol contained in the bag on the left arm of the valve system, hold the breath for a selected time, and then exhale the aerosol to the bag on the right arm. The respiratory maneuver was the same for the complete aerosol inhalations and for the bolus experiments and is shown in Fig. 1. The subject, wearing a noseclip, breathed a few

TABLE 1. *Sex, lung volumes, and cigarette consumption of subjects*

Subj	Sex	TLC, liters	FRC, liters	RV, liters
BA	M	6.0	2.9	1.9
*RG**	F	6.1	2.7	1.4
EDP	M	6.6	3.1	2.0
MS	F	4.8	2.8	1.1
JT	M	9.2	5.1	2.3
CSW	M	5.1	3.0	1.3

* Smoked 20 cigarettes/week; other subjects did not smoke cigarettes.

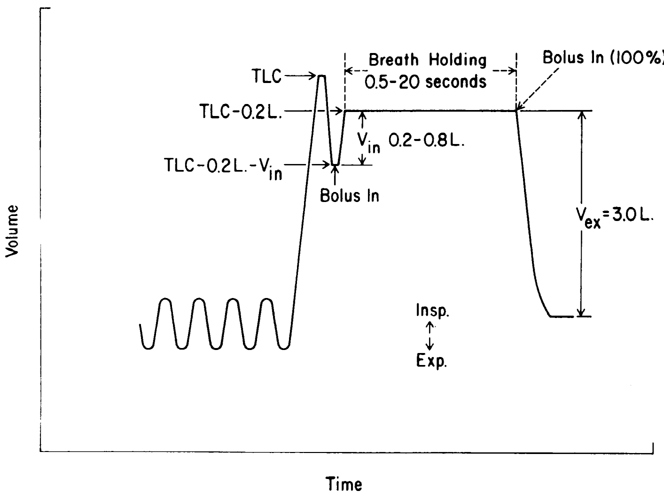

FIG. 1. Respiratory maneuver. Solid arrow—aerosol bolus insertion in inhaled air; dashed arrow—aerosol bolus insertion for calibration.

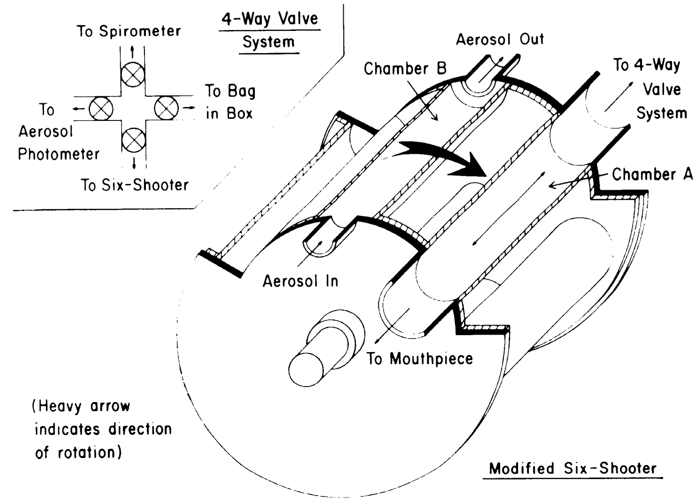

FIG. 2. Modification of breathing apparatus for bolus experiments.

normal breaths while connected directly to the spirometer. He then inhaled to total lung capacity (TLC), exhaled a preset volume (V_{in} + 200 ml), inhaled the preset volume (V_{in}) to the standard lung volume (TLC − 200 ml), and held his breath for 0.5–20 sec. Following the breath holding he exhaled 3 liters (V_{ex}). Exhaled aerosol was collected in an anesthesia bag and immediately drawn through a photometer so that the total scattered light gave a measure of the quantity of aerosol exhaled. This procedure is almost identical to that described by Palmes and Wang (7), except that the exhaled volume was increased to 3 liters to ensure a greater degree of removal of airborne aerosol with the forced exhalation. In the bolus experiment, the first small part of the inhalation consisted of the bolus as described next, whereas for the complete aerosol experiment the entire inhalation (V_{in}) was aerosol.

For the bolus experiments, a modification of the apparatus was made as shown in Fig. 2. In this modification, the bag on the left arm of the valve system was removed, the connection to the aerosol photometer inlet was moved from the mouthpiece arm to the left arm, and a "Six-Shooter" (Med-Science Electronics, St. Louis, Mo.) was inserted between the valve system and the mouthpiece. The subject wearing a noseclip breathed through a mouthpiece and through chamber A of the Six-Shooter. The Six-Shooter was modified by introducing inlet and outlet tubes for aerosol to chamber B. This device makes it possible to insert a 25-ml bolus of aerosol directly and quickly into the inhaled air stream by means of an electrically operated stop whose release causes chamber B to be inserted by spring action into the stream in place of chamber A. For each bolus experiment the subject first breathed through the system, including chamber A of the Six-Shooter, while diluted aerosol from the generator was flowing through chamber B. The subject inhaled to TLC and exhaled until stopped by the apparatus at which time the Six-Shooter was advanced by triggering electrically. This transferred chamber B, filled with aerosol, into the main line as indicated by the solid arrow in Fig. 1. The subject then inhaled the bolus followed by a preset volume of clean air from the spirometer, held his breath for the required time, and exhaled. The exhaled aerosol was collected in the bag-in-box and measured by the photometer. Calibration was accomplished as follows: the 100% value representing the quantity of aerosol inhaled was obtained by manually triggering the Six-Shooter at the start of exhalation (indicated by dashed arrow, Fig. 1) and the reference zero value was obtained by not introducing any aerosol during the entire maneuver. The percentage return of aerosol (aerosol exhaled/aerosol inhaled) was, therefore, expressed on a scale from 100 to 0, fixed by these reference measurements.

Inhaled volumes used in this study were approximately 200, 400, 600, and 800 ml for both the bolus and total aerosol inhalation experiments. Breath-holding times were approximately 0.5, 10, and 20 sec in the bolus experiments and 0.5 and 15 sec in the total aerosol inhalation experiments. Inspiratory flow rate was not controlled, nor measured with sufficient accuracy to examine its influence; rough estimation suggests an average of 0.7 liter/sec. with a standard deviation of 0.3 liter/sec. There were considerable differences between nominal and actual inhaled volumes because precise control was not possible with a 200 ml/cm spirometer, but the time of breath holding could be much more accurately controlled and measured. The procedure employed for expression of the results is as follows:

First, the primary measurements of fractional return and breath-holding times for each group of breaths with the same nominal inhalation volume were displayed on a semilog grid. By fitting a straight line representing exponential decrease, a single slope for the group was estimated and used to correct the individual measurements of persistence for small differences in time from the nominal breath-holding times, usually not more than 0.5 sec. Persistence for each breath corrected to its intended time of breath holding was then plotted as a function of its actual volume. Thus, the dependence of persistence on inhaled volume was obtained for each of the selected breath-holding times.

RESULTS

The results obtained for the bolus experiments are shown in Fig. 3 with the six subjects identified by their initials. The plots of persistence versus inhaled volumes at the three times of breath holding are shown with smoothed curves through the data; each point represents a single breath with a small timing correction described above. It should be pointed out that the 100% persistence at 0 ml inhaled volume for the 10- and 20-sec curves was assumed rather than measured experimentally. It is seen that the curves show reasonable consistency, particularly at the larger volumes. Since the volume measurements are much less accurate at the smaller inhaled volumes, the greater dispersion makes the fitting of the curve more difficult at these volumes.

From prior studies with whole aerosol inhalations, the rate of loss of aerosol during breath holding (5) had been shown to be exponential; the present values were, therefore, tested for their fit to a single exponential. The goodness of the fit is shown by the solid and dashed lines for the 10-sec curves. The solid line is the direct observation, and the dashed line is the calculated value for 10 sec obtained by interpolating between the 0.5- and 20-sec values and assuming a single exponential decay. It is seen that the fit to a single exponential is quite good and demonstrates that the individual bolus in this respect behaves in very nearly the same manner as does the entire aerosol breaths previously reported (5).

Results for the total aerosol inhalation experiments with 15 sec of breath holding are given by the data points in Fig. 4; the same six subjects are reported in the same relative position as in Fig. 3. To compare the results of the bolus experiments in Fig. 3 with these results requires two steps: first, to calculate an average fractional return for each of the 10- and 20-sec smoothed bolus curves by averaging from zero to the inhalation volume under consideration, and then to interpolate between these 10- and 20-sec values to get the fractional return for 15 sec of breath holding using the exponential time dependence which has been observed for whole aerosol inhalations. The solid curves in Fig. 4 were obtained in this way and represent fractional returns for whole aerosol inhalation predicted by the smoothed curves of Fig. 3. The agreement between the two methods of obtaining persistence at 15 sec was quite close for *subjects BA, EDP, RG,* and *CSW.* It appeared that there was a consistent overestimation by the bolus techniques for both *subjects JT* and *MS.* Even in the latter two cases, however, it appears that the form of the curve resulting from the two techniques was quite similar.

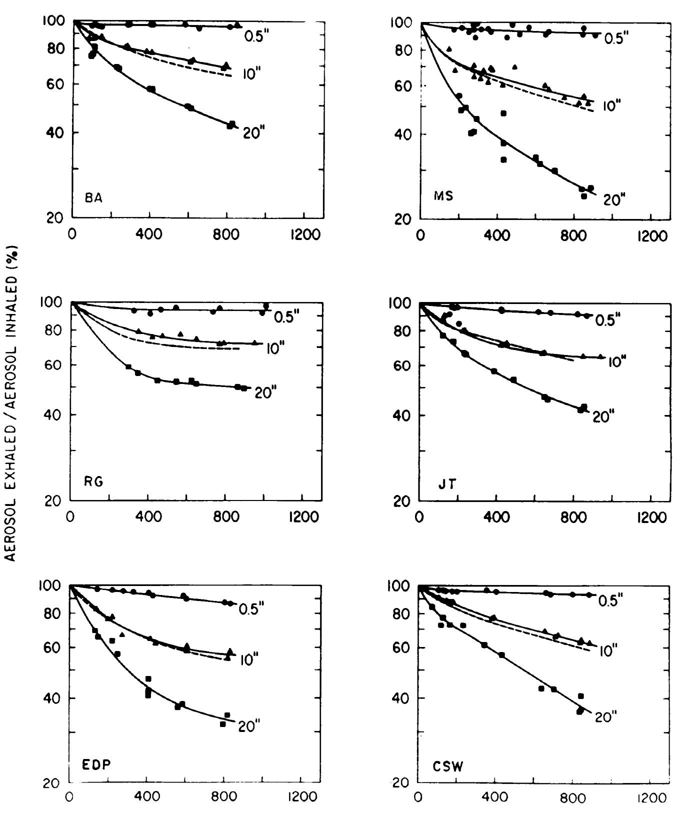

FIG. 3. Aerosol persistence as function of depth of inhalation of bolus and time of breath holding.

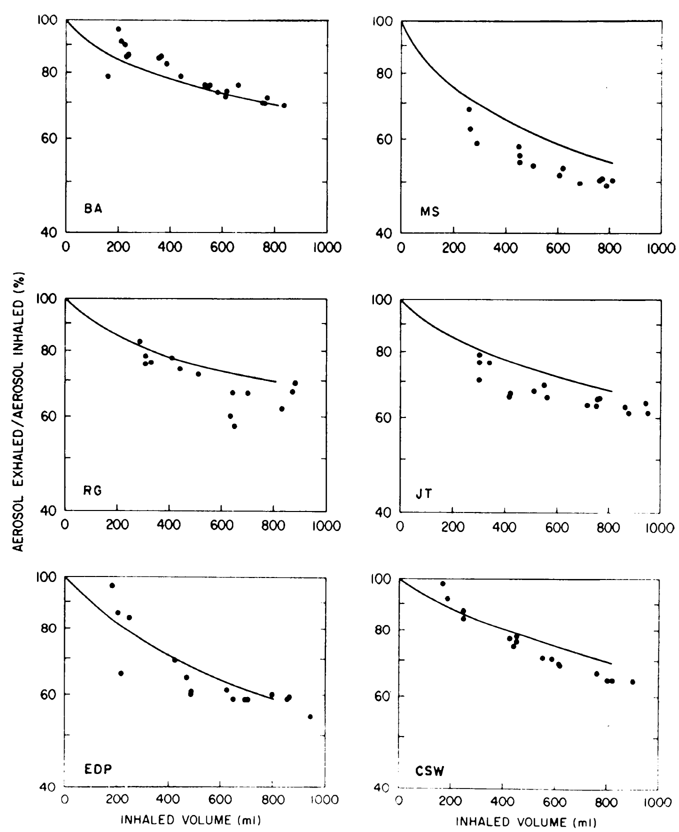

FIG. 4. Comparison of complete aerosol inhalation data with curve predicted from bolus inhalations.

DISCUSSION

Deposition of aerosol contained in the various elements of the inhaled volume, as specified by the bolus approach, provides improved experimental data which serve as a means of checking accuracy of lung models for aerosol deposition. All of these models are based on certain assumptions as to aerosol distribution and on the assignment of anatomical dimensions to the various participating elements of the respiratory tract. Direct anatomical interpretation based on aerosol deposition must be undertaken with great caution as there are serious divergences between the simple theoretical assumptions of the models and the actual complex situation (1). The more important of these for the interpretation of the aerosol deposition data are: *1*) the axial dispersion of the bolus, *2*) the nonuniformity of aerosol concentration in cross section at the end of inspiration, *3*) the relatively short length of the passageways which become stubbier with increasing depth, and *4*) the irregularity of the branching and regional distribution of flow. Thus actual persistence is a weighted average over many branching tubes of different depths and sizes and the averaging procedure is not well understood.

In spite of these difficulties, it is considered worthwhile to compare the results of estimation of tube diameters from aerosol persistence with dimensions obtained on the basis of direct measurement. Measured persistence during breath holding can be interpreted to give an average tube diameter by using the following expression of Landahl (3) for the settling of aerosol which initially fills a randomly oriented infinitely long tube:

$$-\ln(1 - S) = 3.6 \times 10^5 \rho\, d^2 \left(1 + \frac{1.8 \times 10^{-5}}{d}\right) \frac{t}{D}$$

where S is the fraction removed by settling, ρ is density, d is particle diameter (cm), t is settling time (sec), and D is tube diameter (cm). The tube diameters in Fig. 5 were calculated from the 0.5- and 20-sec curves of Fig. 3 using $\rho = 1.31$, $d = 5.5 \times 10^{-5}$ cm, $t = 19.5$ sec, and $1 - S =$ ratio of the fractional returns for 0.5 and 20 sec of breath holding reported in Fig. 3 for inhalation volumes of 200, 400, 600, and 800 ml. The justification for using pure settling without Brownian motion is carried over from the exact treatment of particles suspended between parallel plates by Wang, Altshuler, and Palmes (8), who showed that the larger of the separate effects of settling and Brownian motion is generally a better approximation than that which treats the separate effects as if they were independent probabilities. Also given for reference in Fig. 5 are the anatomical dimensions of the Weibel human airway model "A" for an average lung volume of 4,800 ml at about three-fourths maximal inflation plotted against depth in respiratory tract which is taken to be 40 ml more than depth from entrance of trachea as given by Weibel (9). The qualitative resemblance is striking but the rate of change of diameter with volume is seen to be larger for the experimental values than for the anatomical measurements over the 200- to 800-ml range.

The conclusion obtained from comparison of the calculated average diameters with the Weibel anatomical dimensions, identifying inhalation volume with depth of penetration, is that the measured persistence is more markedly

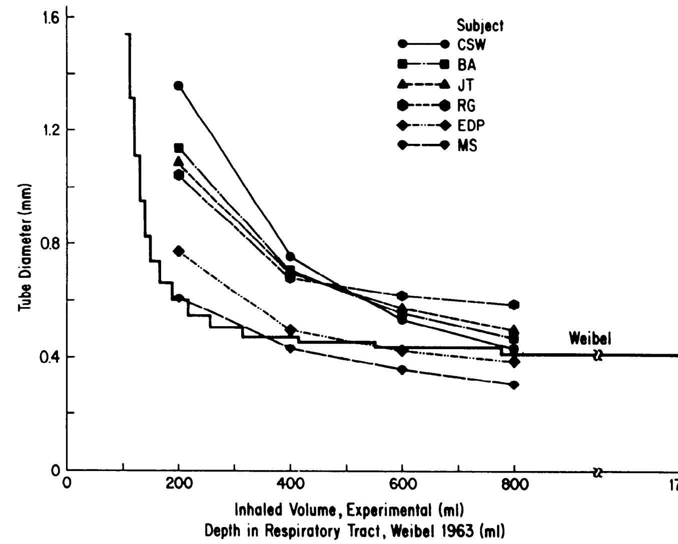

FIG. 5. Equivalent tube diameter as a function of inhaled volume for bolus experiment compared to diameters of the airway model "A" of Weibel (9).

dependent on inhalation volume than is persistence predicted by the Landahl settling expression. The rough agreement between the two methods presents a temptation to reverse the process and associate the diameter calculated from aerosol persistence with a depth of penetration. If this is done it is to be noted that the calculated diameters do not rank in the order of total lung capacities of the subjects as shown in Table 1. For example, although *subject JT* has a considerably larger TLC than the other subjects, he does not have the largest calculated diameter at any of the inhaled volumes.

Some unreported, exploratory experiments suggested that inhaled flow rate in the ranges observed here did not appear to influence persistence. Thus inhaled flow rate was not controlled or measured with sufficient accuracy to examine its influence. A higher inspiratory flow rate will cause more turbulence and a flatter velocity profile in the larger conducting airways and should decrease axial dispersion with two opposing effects on bolus persistence: a decrease because the trailing end penetrates further with less aerosol in larger conducting airways and an increase because the leading end penetrates less with less aerosol in smaller alveolar ducts.

Another difference between experiment and theory was previously reported in the observation that persistence during breath holding is less dependent on particle size than is predicted by existing theory (5).

It should be noted that the persistence of aerosol at 0.5-sec breath holding was very high in all cases, in fact, it was greater than 90% at 800 ml for all but one of the subjects. It should be borne in mind that this very high fractional recovery of inhaled aerosol is based on exhalation of a volume several times that of the inhaled volume and, therefore, does not reflect the marked effect of intrapulmonary mixing on total aerosol deposition with continuous breathing of aerosols previously reported (2).

It is felt that the agreement between the bolus experiments and the whole-breath experiments was quite satisfactory and that the reproducibility of the bolus experiments themselves was excellent in view of the fact that the bolus contains a very small volume of dilute aerosol, approximately 10^5 particles/ml or about 2.5×10^6 particles total.

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