Measurement of Pulmonary Air Spaces Using Aerosols

Edward D. Palmes, PhD, New York

During investigation of the relationship of aerosol persistence in the human respiratory tract to the dimensions of the air spaces, procedures were developed in which the subject inhaled a fixed volume of aerosol and held his breath at known lung volumes for a series of times prior to exhalation. With appropriate correcting, the persistence of aerosol could be measured as a function of time of breath holding. The distance that particles must be moved during breath holding by sedimentation or diffusion to reach a wall of the respiratory tract is determined by the size of the air spaces; the time required to reach the wall also depends on this distance. The persistence of aerosol, therefore, provides an index of the size of the air spaces containing aerosol during breath holding.

The purpose of this investigation is to summarize the background, rationale, and present status of work on the use of monodisperse aerosols as tools for estimating the linear dimensions of the lung air spaces. The long-term goal of the studies is to develop a diagnostic test for pulmonary diseases involving alterations in lung spaces. Thus, such a test would be appropriate to emphysema on the assumption that destruction of alveolar walls would result in larger-than-normal air spaces. The experimental basis of this approach is the dependence of aerosol deposition rate on the dimensions of the space in which it is confined. This dependence is quantitated by measurement of the rate of loss of aerosol during breath holding. Persistence (aerosol exhaled/aerosol inhaled) was measured by light scattering techniques after breath holding from 0 to usually 20 or 30 seconds. The work is still in its early stages but has received a preliminary clinical trial.

All reports on aerosol desposition during breath holding have come

Received for publication May 25, 1972; accepted June 13.
From the Institute of Environmental Medicine, New York University Medical Center, New York.
Reprint requests to 550 First Ave, New York 10016 (Dr. Palmes).

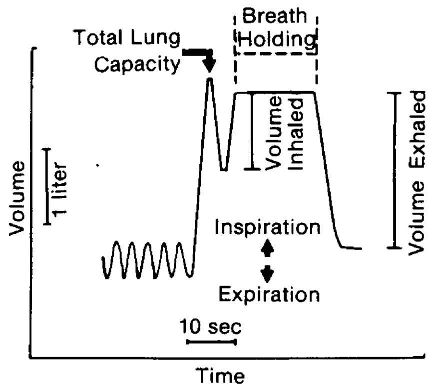

Fig 1.—Typical respiratory maneuver. (From Palmes and Wang[3])

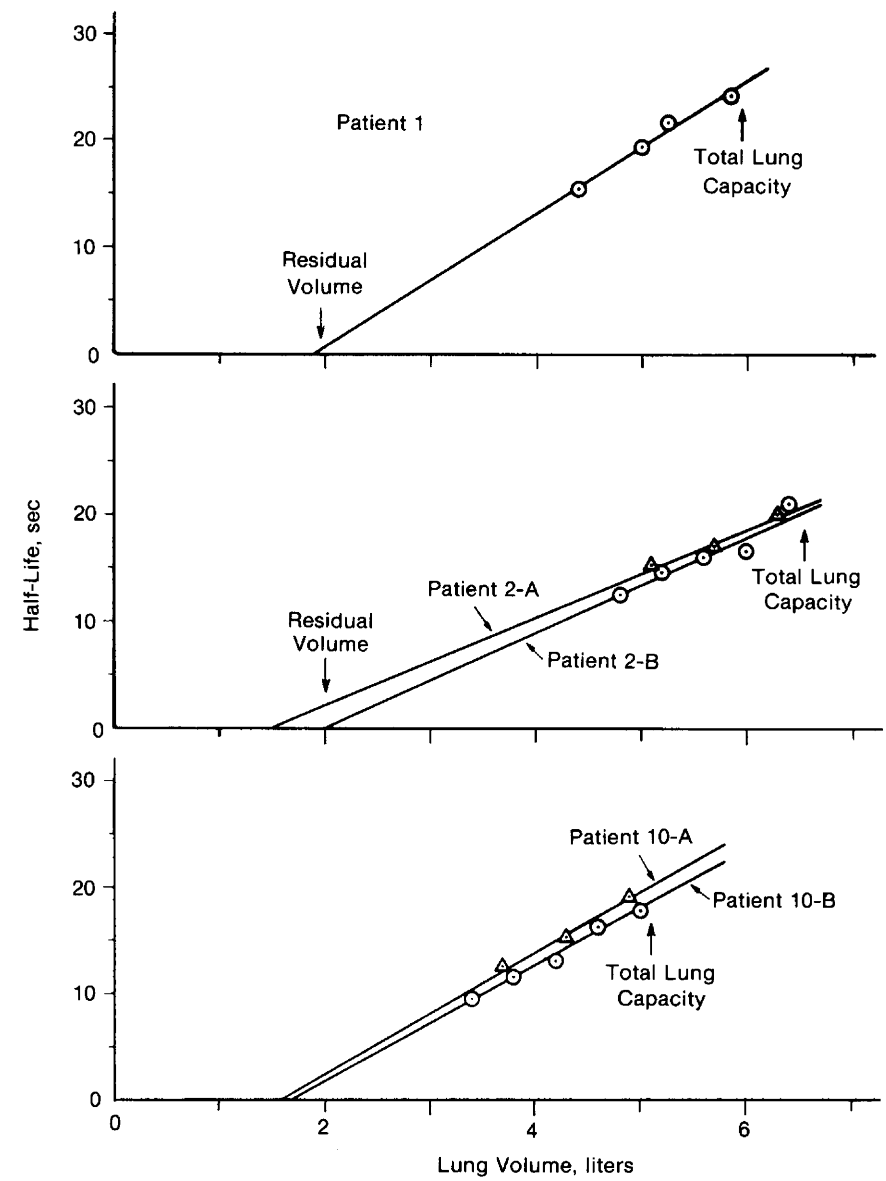

Fig 2.—Effect of lung volume on aerosol persistence. (From Palmes et al[5])

from this laboratory with the exception of an abstract by Cotes et al.[1] This discussion will necessarily, therefore, be almost exclusively concerned with procedures and results from this laboratory.

Measurement of persistence during breath holding makes it possible to separate the contributions of Brownian motion and sedimentation of the particles from other less well-understood factors operating during inhalation and exhalation. These first two types of particle motion have been studied extensively and can be predicted on physical bases for aerosols of the type employed here. Thus, the predicted motion of the particle and its persistence can be used to estimate the size of the space in which it is contained.

Experimental

The aerosol material used in all of the work reported below was triphenyl phosphate, a low-vapor pressure, nonhygroscopic liquid. Median particle size of the uniform droplets (standard geometric deviation less than 1.2) was varied from about 0.1μ to 1.0μ to estimate effect of particle size on deposition, but most of the studies employed 0.5μ to 0.6μ diameter particles, the size of minimum deposition.[2] The procedures for measuring aerosol persistence during breath holding at predetermined lung volumes relative to total lung capacity (TLC) have been described by Palmes and Wang.[3] The spirogram of the most frequently used procedure is shown in Fig 1. After a few quiet breaths the maneuver involves inhalation to TLC, exhalation of approximately 1.2 liters, inhalation of about 1.0 liter, breath holding, and exhalation of 2.0 liters. Thus, the breath is held at a volume of approximately TLC less 200 ml.

A series of times from 0 to 30 seconds are run and the aerosol recovered is plotted as a straight line on a log scale against breath holding time on a linear scale. The slope of this line is expressed as a half-life, ie, the time required for one half of the airborne particles in the lung to be deposited. Changing the volume at which the breath was held without changing the

Spirometry and Aerosol Handling*									
	Vital Capacity		Forced Expiratory Volume, 1 sec		Residual Volume		Total Lung Capacity		
Patient	ml	% Predicted	ml	% Vital Capacity	Volume, ml	% Predicted	ml	% Predicted	Half-Life, sec
Normal Subjects									
1	4,010	102	3,790	94	1,940	117	5,950	106	23.2
2	4,560	117	3,740	82	2,000	121	6,560	118	23.5
3	3,760	95	3,210	85	1,280	98	5,040	96	22.3
4	4,000	93	3,430	85	1,900	104	5,900	97	25.2
Emphysema Without Bronchitis									
5	3,500	127	2,400	55	3,900	263	7,400	150	23.2
6	4,000	99	2,000	50	2,500	185	6,500	122	23.4
7	3,450	95	1,260	37	3,800	242	7,250	138	23.6
8	3,990	104	2,320	58	3,170	184	7,160	129	50.4
9	3,010	90	1,550	51	3,003	200	5,820	124	43.1

* From Palmes et al.[5]

rest of the maneuver could be accomplished by a simple adjustment of the apparatus. This made it possible to measure half-life and relate it to degree of lung inflation during breath holding as described by Palmes et al.[4,5]

It should be pointed out that the earliest studies were carried out with relatively simple apparatus, since it was well within the capabilities of the normal, trained subject to go through even a complicated maneuver without any difficulty. However, in preparation for the second series of experiments involving patients with chronic obstructive pulmonary disease (COPD), it became obvious that both cooperation and pulmonary ability of most of the patients were very poor. It was at this juncture that the apparatus was converted to its present form,[3] permitting complete control over the entire breathing sequence starting with the patient at TLC. This apparatus has been used on a large number of normal subjects and patients over a period of several years in the form reported and appears to be relatively foolproof.

Results

The results, particularly in patients, are still few in number. Nevertheless, the experiments furnish interesting leads although justifying only tentative, and not definite, conclusions. The results in patients and in normal subjects have been reported in detail.[5] and are summarized here. Studies on three normal subjects reported therein give strong support to the rationale of the entire approach. In these experiments the three normal subjects, in five different runs, each performed the breath holding maneuver described using in all cases a 1-liter inhalation and a 2-liter exhalation, but setting lung volume at which the breath holding was done at three to five different values relative to TLC. The results are shown in Fig 2. The half-lives for each lung volume were obtained as described and the entire series was completed within the same day. Hence, all conditions were as close to identical as possible for each of the runs. It is seen that the half-life appears to be a linear function of lung volume. The results bore out the ability of the procedure to demonstrate changes in the average size of the lung air spaces and to provide an index of geometric size of these spaces.

Unfortunately, present theory for calculation of deposition during breath holding is entirely inadequate as discussed earlier by Palmes et al.[6] Landahl[7,8] concluded that half-life should depend on a critical linear dimension, in his case the diameter of a tube. In an infinitely long tubular model, then the estimated linear dimension (the tube radius) as derived from the half-life should vary as the square root of the lung volume. Similarly, a spherical model would require that the estimated linear dimension be proportional to the cube root of the lung volume. Our observed direct proportionality between the linear dimension and lung volume and its extrapolation to zero at about residual volume is consistent with a model in which the alveolar ducts behave like parallel plates rather than tubes or spheres.[5] Thus, in this model the lung expands in an accordion-like manner rather than by increasing the diameters of tubes or spheres.

It has been shown that exhalation of twice the inhaled volume, at least in normal subjects, will remove virtually all of the aerosol that is still airborne.[6,9,10] There is necessarily, however, a contribution of aerosol contained in the larger conducting airways as well as that in the parenchyma. In the studies of Palmes et al[5] the concern was only with the air spaces of the parenchyma, so that an attempt was made to minimize the contribution of the upper airways. It was on this basis that a 1-liter inspiration was chosen in the initial studies. By this choice, a large fraction of patients with advanced COPD was virtually eliminated from the study. Presently under development is a procedure with a small bolus of aerosol that is much less demanding on breathing capabilities. In the early studies it was found that only 5 of 14 patients with a diagnosis of relatively advanced COPD on whom it was possible to get any data (inhalation at least 500 ml, exhalation twice inhalation) were able to complete the prescribed 1 liter-in–2 liters-out maneuver. All five of these patients had a diagnosis of emphysema with little chronic bronchitis, which was based on clinical criteria. The results from these patients along with results on four normal subjects are presented in the Table. It is interesting that three of the patients behaved very similarly to the normal subjects, whereas two showed remarkably long half-lives; patients 8 and 9 are very significantly abnormal in this respect.

Comment

It has been possible, using apparatus and procedures developed especially for the purpose, to measure the persistence of aerosols in the human respiratory tract during periods of breath holding and from this procedure to obtain an index of the dimensions of the lung air spaces. It was found that most of the patients with advanced COPD were incapable of performing the maneuver as originally developed. The reasons for this are apparent. The patient, even though he might have a forced vital capacity (FVC) of 2 liters, might, particularly in the brochitics, require many seconds in order to achieve this volume. Here the time of breath holding during exhalation can become a significant factor.

Two of the patients presented in the table are considered to be significantly different, not only from normals but from the other three patients with the same diagnosis; assuming the diagnoses to be correct, all five emphysematous patients would have enlarged air spaces. A plausible explanation for the finding in these two patients is that their enlarged air spaces are ventilated by convection to a considerably greater degree than are the presumably enlarged air spaces in the other three subjects. By convection is meant the organized flow of gas that carries the aerosol particles along in the stream; it is distinguished from diffusion, the other mechanism for pulmonary ventilation, in that it is accomplished by random motion of gas molecules. Diffusion, or Brownian motion, of a particle or molecule is inversely proportional to its size. Since the aerosol particles are about 1,000 times larger than gas molecules, aerosols are virtually nondiffusing relative to gases. Persistence of aerosol particles can only be influenced by the space in which they reside during breath holding; these are necessarily those spaces ventilated by convection, not diffusion. This is true regardless of the size of other spaces in the lung which are ventilated only by diffusion. In other words, even if a patient has large areas in which there is extensive destruction of alveolar walls, and during tidal respiration the only spaces still ventilated by convection are in a small residue of normal tissue, then the patient, by this aerosol procedure, would appear to be normal. On the other hand, if the enlarged spaces were preferentially ventilated by convection, the abnormality would be detected by this procedure.

This investigation was supported under grant OH00317, National Institute for Occupational Safety and Health, and is part of a center program supported by National Institute of Environmental Health Sciences grant ES 00260.

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