R00226

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TERMINAL PROGRESS REPORT

OH-00317 (Formerly EC-00227)

"STUDY OF LUNG STRUCTURE AND FUNCTION WITH AEROSOLS"

Edward D. Palmes - Principal Investigator

a. Period covered by report:

October 1, 1966 through March 31, 1972

b. Summary

The purpose of the studies outlined in this project was to adapt aerosol techniques developed at this laboratory for use as diagnostic tools in the studies of lung diseases, principally emphysema. The rationale of the approach is that aerosols should be deposited more rapidly in smaller than in larger spaces. To this end apparatus and procedures were developed for allowing subjects to hold their breath for various times after inhalation and before exhalation of aerosol. The crude original apparatus was modified to permit its use on patients, as well as normal subjects, and preliminary runs were made on patients with emphysema and/or bronchitis at Bellevue Hospital. The initial studies gave interesting, although limited, results; these have been published. Some of the apparatus was moved to the Public Health Service, Appalachian Laboratory for Occupational Respiratory Diseases (ALFORD), in West Virginia, in June 1970; it was used to collect data on normal subjects and on coal miners. Theoretical treatments of intrapulmonary behavior of aerosols have been made and show some significant correlations with the experimental results.

c. Detailed report:

Introduction

This project had as its primary goal the use of aerosols to measure the dimensions of the air spaces in the lung. It was hoped that the investigation would lead to development of diagnostic procedures which would be useful in characterizing chronic obstructive pulmonary disease (COPD); this is a very widespread disease in occupational groups as well as in the general population. COPD is a general term which includes chronic bronchitis and emphysema either singly or, usually, both together. It is difficult to assess by clinical procedures, including pulmonary function studies and radiography, the relative contributions of airway obstruction, (e.g. chronic bronchitis) and of alveolar wall destruction, (e.g. emphysema). The final diagnosis is made at the post mortem examination and the predictive value of prior clinical appraisal has not been great. It is for this reason that the attempt was made to use aerosols to aid in the diagnosis.

The rationale for the approach is based on the concept that a particle of known size and shape will be deposited in a shorter time if it is confined in a smaller space than in a larger space. Thus, the average time required for an aerosol particle of known size to be deposited should provide an index of the size of the air space in which it is confined. In emphysema there is enlargement of air spaces and it would be expected that persistence (remaining airborne, not being deposited) of aerosol would be increased in this disease.

The procedures and apparatus employed have undergone considerable refinement during the project period, but the basic approaches had been developed by the time of the first proposal. It had been shown by Palmes, et.al. (1) that a monodisperse aerosol of triphenylphosphate is lost during breath holding at a rate which is proportional to the quantity of aero ol in the lungs at the particular time. This implies an exponential decrease in quantity of airborne aerosol with time of breath holding. It had been shown with many normal subjects that quantity of aerosol exhaled by a forced exhalation of at least twice the volume of inhaled aerosol plotted as a straight line on a logarithmic scale against time plotted on a linear scale. The slope of this line, expressed as a half-life, $t_{1/2}$, depends on the size of the pulmonary spaces during breath holding. It should be pointed out that the loss of aerosol during inhalation and exhalation should not influence the slope of this curve since the same maneuver (e.g. one liter of aerosol inhaled, breath held, two liters exhaled) was performed on each breath in the series. There are three probabilities involved: 1) probability of a particle's not being deposited during inspiration p_{in}, 2) probability of not being deposited during breath holding, p_h, and 3) probability of not being deposited during exhalation, p_{ex}. The product $p_{in} \times p_h \times p_{ex}$ would give the probability of not being deposited, P, also called persistence. Since p_{in} and p_{ex} are common to all breaths, persistence, P, is the product of a constant and p_h.

Since the conducting airways are filled with aerosol during breath holding, their size would influence the rate of deposition. For this reason as large a breath as feasible was indicated to minimize the contribution of this 150-200 ml of larger tubing making up the airways. In normals a one liter inhalation followed by a two liter exhalation was adopted since such a maneuver insured at least 80% of the inhaled aerosols being in the parenchyma during breath holding.

In the course of measuring persistence during breath holding it was noted that lung volume had a marked influence on persistence. As expected, the persistence increased with increasing lung volume, but the magnitude of the increase was greater than would have been predicted on the basis of either tubular or spherical models. Preliminary observations on these relationships were reported (2) just prior to the beginning of the project period. The observations were the basis for the present project, since it appeared that aerosols could be used to obtain indices of the size of the intrapulmonary spaces.

Apparatus and Procedures:

The apparatus used on normal subjects in the preliminary studies had been designed and largely constructed and/or assembled by the Principal Investigator. The respiratory maneuver which was adopted is shown in Figure 1 (taken from Ref. 3).

It is seen that the subject must inspire to total lung capacity (TLC), exhale a definite volume, inhale a definite volume of aerosol (fixing lung volume relative to TLC) and after the breath holding interval, exhale a volume twice that inhaled. While the rather crude original apparatus was satisfactory for normal, cooperative subjects, it was tried on hospital patients and found severely wanting. It was decided that the investigators could not reasonably expect most of the patients to do more than perform a completely preset breathing program. This required a complete redesign and construction of the breathing apparatus. The new apparatus (3) incorporates many superior features both in control of the breathing sequence and in aerosol measurement. The main features of the breathing apparatus are: a) a system of solenoid

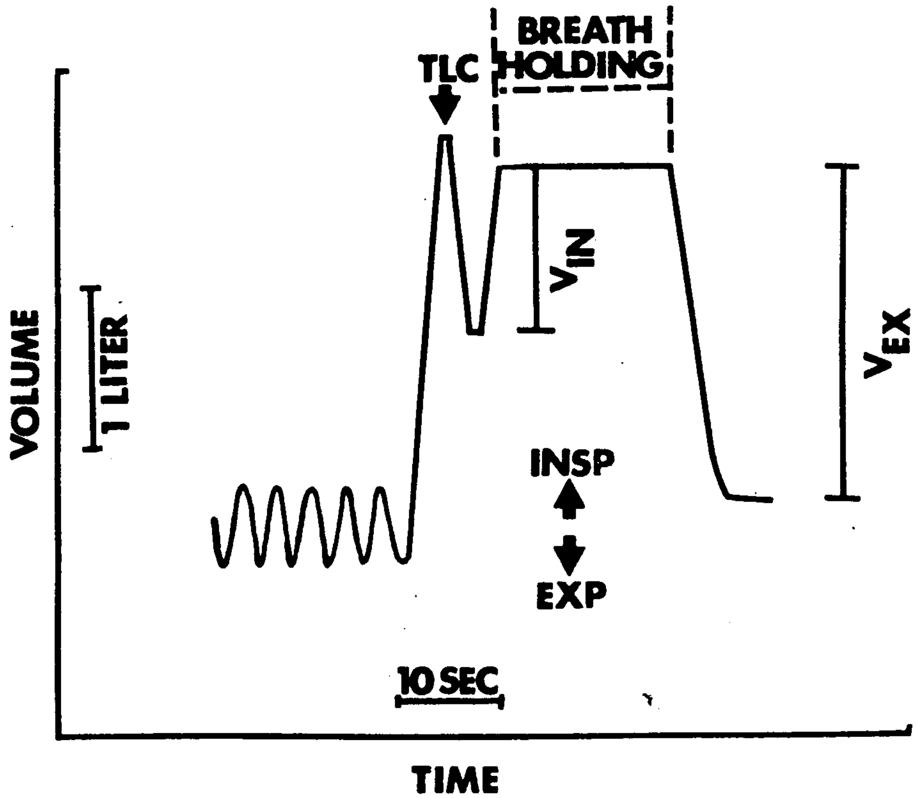

Figure 1 - TYPICAL RESPIRATORY MANEUVER

operated valves which made it possible to switch the subject to either of two bags-in-boxes or to the spirometer, b) a stepping switch to control the solenoids in a preset program and c) triggering devices to advance the stepping switch on the basis of volumes or times set and controlled by the operator. The details are given in Reference 3.

Experimental:

Bellevue Hospital Studies:

The apparatus was set up in Bellevue Hospital and the patients brought into the laboratory for the runs. The diagnoses were based on clinical and radiological findings including spirometry. The results obtained on normal subjects and on patients were presented at the Third International Symposium on Inhaled Particles (4) and are shown in Table I from this paper. It should be stated at the outset that the one liter inspiration, two liter expiration was not possible for the great majority of the bronchitic and emphysematous patients. It is seen also that those 5 patients characterized as emphysematous but not bronchitic were capable of the one liter-two liter maneuver. It is very interesting that two of the patients in this group of five showed remarkably long half-lives. Primarily because of Dr. Wang's departure, it was not feasible to continue the data collection at Bellevue after these pilot runs, but as it is pointed out below studies on patients and normal subjects were continued at ALFORD. The Bellevue studies yielded some interesting leads and gave promise that aerosols might be used effectively to distinguish large spaces ventilated mostly by convection from large spaces ventilated mostly by diffusion.

Studies on Normal Subjects:

In addition to the work on patients, the effect of lung volume on $t_{1/2}$ in normal subjects was greatly expanded; this is also reported in Reference 4. As shown in Figure 2, taken from Reference 4, the half-life for the three normal subjects studied decreases linearly with lung volume and, interestingly, extrapolates to zero at approximately residual volume (RV) for the two subjects measured. This makes attractive an hypothesis that the lung is ventilated primarily by changing dimensions of the alveolar ducts rather than those of the alveoli; this area is discussed in the manuscript and allusion will be made to it below under the

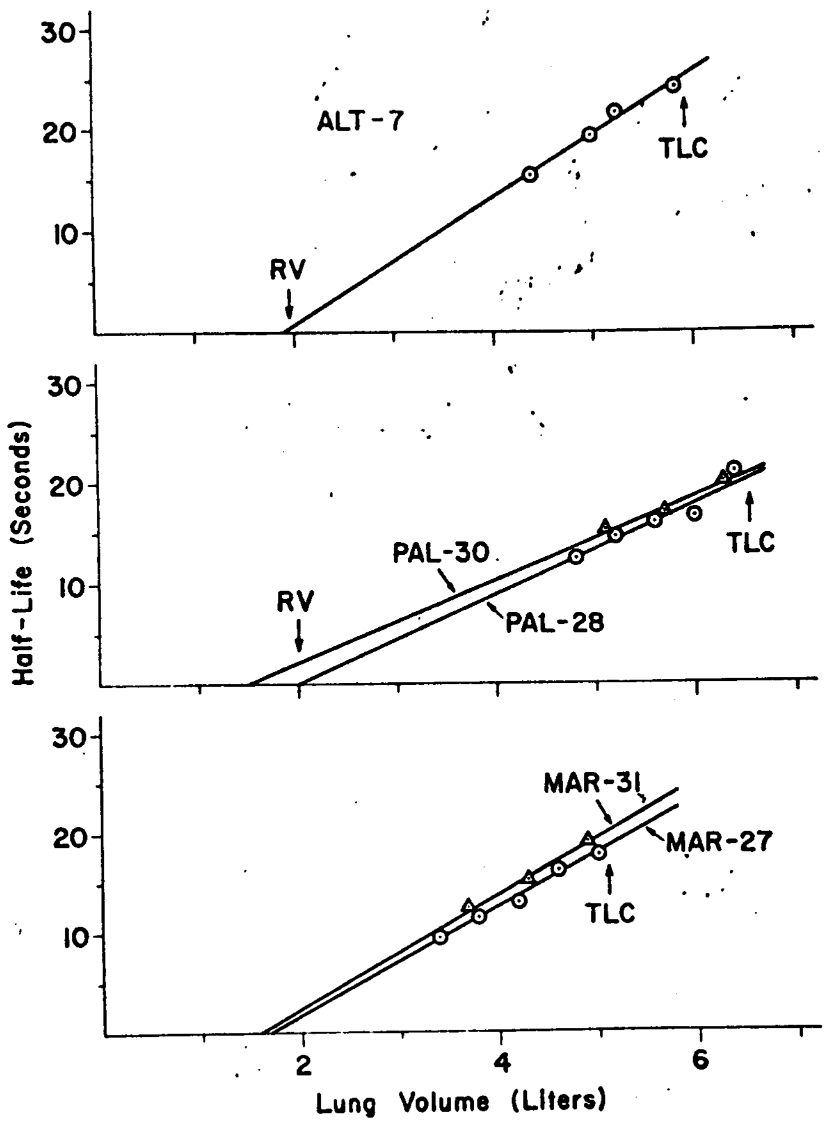

FIGURE 2. Effect of Lung Volume on Aerosol Persistence

Table 1

Spirometry, Nitrogen Washout and Aerosol Handling

Name	VC ml	VC % Pred	FeV$_1$ ml	FeV$_1$ % VC	RV Vol	RV % Pred	TLC ml	TLC % Pred	N_2 Washout End-tidal N_2 3 min.	N_2 Washout End-tidal N_2 7 min.	N_2 Washout Alv. N_2 7 min.	P at 0 Sec %	$t_{1/2}$ Sec.	Aer. Inh. ml
NORMAL SUBJECTS														
Alt	4010	102	3790	94	1940	117	5950	106	1.5	0.4	0.6	93	23.2	1000
Pal	4560	117	3740	82	2000	121	6560	118	2.1	0.9	-	86	23.5	1000
Wan	3760	95	3210	85	1280	98	5040	96	-	-	-	92	22.3	1000
Blo	4000	93	3430	85	1900	104	5900	97	-	-	-	89	25.2	1000
BRONCHITIS WITH EMPHYSEMA														
Gar	1200	33	420	34	4310	260	5572	116	-	-	-	65	17.2	500
Sie	2100	67	1310	62	4107	300	6207	138	-	-	-	75	18.2	750
Roc	2960	86	2210	74	1914	129	4871	97	-	-	-	91	28.1	950
Rod	2620	63	730	28	3627	235	6131	120	24.0	9.5*	6	76	26.4	900
Rap	1770	53	650	37	4370	290	6138	126	8.5	4.0	10.7	89	53.4	500
Gib	2650	72	1480	56	4510	290	7160	138	-	-	-	74	52.2	800
Coo	1330	53	490	36	3345	320	4675	128	-	-	-	70	38.0	500
Sol	2420	60	970	40	2084	206	4500	102	6.0	2.6	9.8	81	20.4	550
McG	1980	51	1130	54	3507	210	5550	101	-	-	-	75	21.5	550
EMPHYSEMA WITHOUT BRONCHITIS														
Viv	3500	127	2400	55	3900	263	7400	150	4.9	1.4	-	85	23.2	1000
Sch	4000	99	2000	50	2500	185	6500	122	-	-	-	85	23.4	1000
McF	3450	95	1260	37	3800	242	7250	138	11.5	4.0	4.0	83	23.6	1000
Lyn	3990	104	2320	58	3170	134	7160	129	-	-	-	80	50.4	1000
Dun	3010	90	1550	51	3003	200	5820	124	3.0	0.9	1.4	76	43.1	1000

* 4 minutes

heading "Theoretical".

Six normal subjects were examined by a bolus procedure, and a paper based on the data has been accepted for publication (5). In these experiments the subject inhaled a 25 ml bolus of aerosol followed by nominal volumes of 200, 400, 600 or 800 ml of clean air. After inhalation the breath was held for 0, 10 or 20 seconds, and the subject then exhaled three liters, a volume expected to remove virtually all airborne particles from the respiratory tract in the exhaled gas. The subject went through the above procedure for each volume and each time with at least two breaths at each volume at each time. It was then possible to construct curves showing the effect of depth of inhalation of the bolus and of time of breath holding. The smoothed curves for each subject from zero to 800 ml can be used to estimate the fraction of aerosol deposited, or not deposited, at 0, 10 and 20 seconds. Similarly the persistence at any volume up to 800 ml can be interpolated for times up to 20 seconds. From the data it is also possible to estimate the fraction of a total aerosol breath up to 800 which would be returned after some particular time of breath holding. To examine this point, the 6 subjects took inhalations of 200, 400, 600 and 800 ml, used breath holding times of zero and 15 seconds and exhaled three liters. A comparison of values by the two procedures showed excellent agreement for all subjects when one considers the very great differences in the two approaches. This paper also points out similarities (and differences) between size of lung spaces estimated by direct measurement and by persistence of aerosol. Another paper (6) discussing the broad implications of the aerosol approach to measurement of lung air spaces is in press.

Studies at ALFORD:

In June 1970, arrangements were completed for moving some of the breathing apparatus and associated electronic components to the PHS Appalachian Laboratory for Occupational Respiratory Diseases (ALFORD), located at the University of West Virginia Medical School at Morgantown, West Virginia. It had long been considered highly desirable to use the aerosol procedures on normal subjects and patients who had been characterized by sophisticated pulmonary function studies, as well as by the usual clinical procedures. Procedures set up and operating at ALFORD include extensive series of measurements in the body plethysmograph and measurements of diffusion, as well as the more standard clinical and radiological procedures. The joint effort was also planned to include work on miners who are brought in for study. The clinical and physiological aspects are under the direction of Dr. N. LeRoy Lapp at ALFORD and the aerosol studies are supervised by Dr. Palmes with the excellent cooperation of Mr. John Hankinson of ALFORD.

The apparatus was set up by Dr. Palmes in late June 1970 and the ALFORD staff was instructed in its use. It has been used on approximately 65 subjects as of the preparation of this report and there have been remarkably few technical difficulties.

Of the 65 subjects, 44 were normal non-smokers. It was found that half-lives for this group were variable from about 10 to about 30 seconds. It was also shown that the inter-subject variability from one measurement to another was relatively small. In other words, there were consistent differences between normal individuals. The differences did not correlate, however, with any of the following: age, height, weight, sex, lung volumes, lung mechanics or CO diffusing capacity. It was found that the dispersion of the values for the normal population was quite close to that found by Matsuba and Thurlbeck (7) in average airway diameters of 20 normal cadavers. These results were reported (8) at the Fall 1972 meeting of the American Physiological Society, and a manuscript is being prepared for publication.

Theoretical Studies:

In the course of the investigations, a continuing effort has been made to correlate the experimental work with pertinent theoretical considerations concerning the behavior of aerosols in small, confined spaces. Unfortunately, there is no acceptable model for the interaction of aerosol particles with the lung surfaces. There are, as mentioned earlier, two general parts of the respiratory tract, the conducting airways and the parenchyma. Although the model of Weibel (9) is widely used, it must be recognized that it is a highly oversimplified representation of pulmonary architecture. Before Dr. Wang joined the group he had worked during a part of his post-doctoral year at Cal Tech on a problem of "Distribution and Deposition of Particles Suspended Between Parallel Plane Surfaces" (10). Although this treatment was purely theoretical, it is felt that it does have relevance for aerosol behavior in the lungs.

In a publication covering both theoretical and applied aspects, Altshuler (11) discussed the problems involved in reconciling existing models with the actual lung anatomy and physiology and proposed a more realistic model; he utilized data from studies supported by this grant, as well as earlier projects in the same area.

A simple model involving alveolated plates was used by Palmes, et.al. (4) to explain the effect of lung volume on half-life. It is seen in this paper that if certain assumptions are made concerning dependence of half-life on a linear distance which must be traversed by an aerosol particle, that the lung on the average appears to act as a series of parallel alveolated plates. While these results are not considered conclusive, it is felt that additional light is being thrown on some of the mechanisms for pulmonary ventilation and particle behavior which could not be studied by other means.

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d. Publications

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2. Palmes, E.D. Use of aerosols to measure pulmonary dimensions. APCA Journal 18:671, 1968.

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8. Hankinson, J.L., N.L. Lapp, H. Amandus and E.D. Palmes. Behavior of half-micron particles in the normal human lung. Physiologist 15:159, 1972 (Abstract).

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