

# LUNG FUNCTION STUDIES. VIII. ANALYSIS OF ALVEOLAR VENTILATION BY PULMONARY N<sub>2</sub> CLEARANCE CURVES<sup>1,2</sup>

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(Submitted for publication July 3, 1951; accepted October 15, 1951)

A comprehensive analysis of pulmonary function must include measurements of pulmonary ventilation, diffusion, and circulation. An accurate measurement of alveolar ventilation, independent of diffusion and circulation, is desirable. To date, no method has been wholly satisfactory (3). One approach has been by study of the time course of equilibration of alveolar gas with a "foreign" inspired gas, such as H<sub>2</sub> (4), He (5-7) or pure O<sub>2</sub> (8-15). A principal difficulty has been to differentiate between the effects of an enlarged respiratory dead space and of uneven alveolar ventilation, both of which can retard the completion of equilibration.

The development by Lilly and Hervey of the N<sub>2</sub> meter, for continuous analysis of N<sub>2</sub> concentration of respired gas, permits an automatic breath-by-breath analysis of gas expired during and after the change from breathing air to uninterrupted breathing of O<sub>2</sub>. The ensuring progressive elimination of pulmonary N<sub>2</sub> represents the process of equilibration with a N<sub>2</sub>-free gas, and may be analyzed in terms of alveolar ventilation. This paper presents the pulmonary N<sub>2</sub> clearance curves obtained from healthy persons and patients with cardiorespiratory disease, and a method for analysis of these curves which yields a comprehensive picture of the volume and time characteristics of alveolar ventilation. The lungs of healthy subjects, to a small degree, and of persons with cardiorespiratory disease to a greater degree, are ventilated unevenly; *i.e.*, certain regions appear to be ventilated more rapidly than other regions. The respective volumes and ventilation rates of these several

regions can be determined, as well as the volume and average ventilation rate of the lungs as a whole. The extent of uneven ventilation can be measured quantitatively; this measurement is uninfluenced by the magnitude of the respiratory dead space.

Although this method is laborious at present, it should be useful for investigation of pulmonary physiology, and has served as a standard for simpler methods of studying the uniformity of alveolar ventilation.

## THEORETICAL CONSIDERATIONS

Most simply, the lungs could be represented by a bellows which is uniformly ventilated, *i.e.*, inspired gas is distributed evenly to and mixed instantly with all the gas previously present in the bellows. For simplicity, it will be assumed for the moment that inspired gas contains no N<sub>2</sub>, and that there is no transfer of N<sub>2</sub> from blood and tissue. The basic equation presented by Darling, Cournand and Richards (9) to describe the progressive reduction of alveolar N<sub>2</sub> concentration during the breathing of a N<sub>2</sub>-free gas (O<sub>2</sub>) in such a system is:<sup>4</sup>

$$F_{A_n} = F_{A_0} w^n, \quad (1)$$

where

F = fractional gas concentration. Throughout this paper it refers to N<sub>2</sub>.

F<sub>A<sub>0</sub></sub> = alveolar N<sub>2</sub> concentration before O<sub>2</sub> inhalation. This is assumed to be 80% during breathing of air.

F<sub>A<sub>n</sub></sub> = alveolar N<sub>2</sub> concentration after n breaths of pure O<sub>2</sub>.

w =  $\frac{V_L}{V_L + (V_T - V_D)}$ . This will be called the alveolar dilution factor.

V<sub>L</sub> = volume in which the N<sub>2</sub> is contained at the end of expiration = functional residual capacity = volume of alveolar spaces + volume of respiratory dead space.

V<sub>T</sub> = tidal volume.

V<sub>D</sub> = volume of respiratory dead space.

Equation (1) requires values for alveolar N<sub>2</sub> concentration. These were obtained by Darling from the terminal part of forced-expiration alveolar gas samples. However, recent studies have shown that the N<sub>2</sub> concentration of alveolar

<sup>4</sup> The symbols used are those recently proposed to achieve standardization of respiratory terminology (16).

<sup>1</sup> Presented in part before the Physiological Society of Philadelphia (1) and the American Physiological Society (2).

<sup>2</sup> Supported in part by a research grant from the National Institutes of Health, Public Health Service and in part by a grant from the Commonwealth Fund.

<sup>3</sup> Part of this work was done during tenure of a National Institutes of Health Postdoctorate Fellowship.

gas expired after O<sub>2</sub> inhalation varies even during one exhalation, especially in subjects with pulmonary disease (17, 18). Thus one is faced with a variety of different alveolar N<sub>2</sub> concentrations, none of which is necessarily correct for use in equation (1). However, the mean N<sub>2</sub> concentration of any single expiration has only one value and is therefore preferable for measurement. It is related to the alveolar concentration as follows:

$$\bar{F}_{EVT} = \bar{F}_A (V_T - V_D) + F_D V_D, \quad (2)$$

where

$\bar{F}_E$  = mean expired N<sub>2</sub> concentration.

$F_D$  = N<sub>2</sub> concentration in the dead space gas at end-inspiration.

$\bar{F}_A$  = mean N<sub>2</sub> concentration of expired alveolar gas. In a uniformly ventilated system, this equals end-inspiratory alveolar concentration,  $F_A$  in equation (1). Because  $F_D$  during O<sub>2</sub> inhalation is practically zero,  $F_D V_D$  equals zero.

Rearranging,

$$\bar{F}_E = \bar{F}_A \frac{V_T - V_D}{V_T}. \quad (3)$$

Let  $\frac{V_T - V_D}{V_T}$  equal  $r$  or the dead space dilution factor.

From equation (1), one can substitute for  $\bar{F}_A$  in equation (3).

$$\bar{F}_{E_n} = F_{A_0} w^n r \text{ or } \log \bar{F}_{E_n} = \log r F_{A_0} + n \log w. \quad (4)$$

Thus  $\log \bar{F}_{E_n}$  plotted against  $n$  yields a straight line, the value of which at  $n = 0$  equals  $\log r F_{A_0}$ , and the slope of which equals  $\log w$ . Knowing  $F_{A_0}$ ,  $\bar{F}_{E_0}$ , and  $V_T$ , one obtains  $(V_T - V_D)$  from equation (3); from the value and definition of  $w$ , and the value of  $(V_T - V_D)$ , the value of  $V_L$  is obtained. Thus all the ventilatory factors can be determined from measurements which are relatively easily and accurately made, *viz.*,  $F_{A_0}$ ,  $V_T$ ,  $n$  and  $\bar{F}_{E_n}$ . However, equation (4), describing the ventilation of a single bellows, was found to be inadequate for experimental use in almost all cases, principally because the lungs, even in normal subjects, were not evenly ventilated. Its derivation above is presented to clarify further equations for combinations of several single bellows, ventilated synchronously, which were found to fit the experimental data satisfactorily.

Since uneven ventilation is probably largely of a regional nature (19), equations were developed in terms of several independent lung regions or phases, within each of which ventilation is uniform (though not necessarily equal to that of other regions), and from which the separate expired tidal volumes are combined. Such equations will fit the experimental data.

For a two-phase system, the expired N<sub>2</sub> is represented by:

$$\bar{F}_E = \frac{V_{T_1} \bar{F}_{E_1} + V_{T_2} \bar{F}_{E_2}}{V_T} \quad (5)$$

in which the arabic subscripts 1, 2, etc. denote different phases; when the number of respirations is also designated, it is given by either  $n$  or  $o$ , placed as a sub-subscript; and  $V_{T_1}$ ,  $V_{T_2}$  = tidal volumes of respective phases or regions.  $\bar{F}_{E_1}$ ,  $\bar{F}_{E_2}$  = mean expired N<sub>2</sub> concentrations of  $V_{T_1}$  and  $V_{T_2}$ , respectively.

From equation (4),  $\bar{F}_{E_{1n}} = F_{A_{10}} w_1^n \frac{V_{T_1} - V_{D_1}}{V_{T_1}}$ , in which

$w_1 = \frac{V_{L_1}}{V_{L_1} + (V_{T_1} - V_{D_1})}$  and similarly for  $\bar{F}_{E_2}$ , then

$$\bar{F}_{E_n} = F_{A_{10}} w_1^n \frac{V_{T_1} - V_{D_1}}{V_T} + F_{A_{20}} w_2^n \frac{V_{T_2} - V_{D_2}}{V_T}. \quad (6)$$

Let  $\frac{V_{T_1} - V_{D_1}}{V_T} = r_1$  and  $\frac{V_{T_2} - V_{D_2}}{V_T} = r_2$ , then

$$\bar{F}_{E_n} = F_{A_{10}} w_1^n r_1 + F_{A_{20}} w_2^n r_2 \quad (7)$$

or

$$\log \bar{F}_{E_n} = \log (F_{A_{10}} w_1^n r_1 + F_{A_{20}} w_2^n r_2). \quad (8)$$

For a system of three regions or phases

$$\log \bar{F}_{E_n} = \log (F_{A_{10}} w_1^n r_1 + F_{A_{20}} w_2^n r_2 + F_{A_{30}} w_3^n r_3). \quad (9)$$

It will be remembered that  $w$  is a fractional value; hence  $F_{A_0} w^n r$  approaches zero as  $n$  increases. If  $w_3 < w_2 < w_1$ ,  $\log \bar{F}_{E_n}$  will, as  $n$  increases, successively reflect the three components, then only the latter two, and finally only  $F_{A_{10}} w_1^n r_1$ , after which time  $\log \bar{F}_{E_n}$  plotted against  $n$  is linear.

To this point, it was assumed that inspired gas was 100% O<sub>2</sub> and that there was no transfer of N<sub>2</sub> from blood and tissue. When the concentration of N<sub>2</sub> in inspired gas is  $F_I$ , equation (7), for example, becomes

$$\bar{F}_{E_n} = (F_{A_{10}} - F_I) w_1^n r_1 + (F_{A_{20}} - F_I) w_2^n r_2 + F_I. \quad (10)$$

As the N<sub>2</sub> tension of alveolar gas is lowered, N<sub>2</sub> from blood and tissues enters the alveoli and is eliminated in the expired gas. The exact modification of equation (10) which is required to include this N<sub>2</sub> is not known. However, the rate of elimination of blood and tissue N<sub>2</sub> must start at zero, increase and later decrease. It is probable that a maximum occurs during the later part of pulmonary N<sub>2</sub> elimination, several minutes after the start of O<sub>2</sub> inhalation (20). However, the quantities of blood and tissue N<sub>2</sub> eliminated are small, being about 200–300 ml. in a seven minute period of O<sub>2</sub> inhalation (21). We have assumed for purposes of calculation that this is eliminated at a constant rate so that equation (10) becomes

$$\bar{F}_{E_n} = (F_{A_{10}} - F_I) w_1^n r_1 + (F_{A_{20}} - F_I) w_2^n r_2 + F_I + F_b, \quad (11)$$

where  $F_b$  represents the correction for blood and tissue N<sub>2</sub> appearing in the expired gas. The total amount of N<sub>2</sub> eliminated in seven minutes is estimated by the formula of Cournaud (21), and  $F_b$  is calculated as follows:

$$F_b = \frac{\text{Total N}_2 \text{ eliminated in 7 min.}}{\text{No. of breaths in 7 min.} \times V_T}$$

Errors in this correction are of negligible importance early in the procedure. Later, as alveolar N<sub>2</sub> concentration becomes low, it may be incorrect and of some importance, as noted later.

Experimentally, the mean expired N<sub>2</sub> concentration of various expirations is measured. From these values the combined correction for inspired N<sub>2</sub> and N<sub>2</sub> eliminated from the blood, about 0.5–0.9%, is subtracted. The corrected values are then plotted on semi-logarithmic paper, the log of  $\bar{F}_{E_n}$  being plotted against  $n$ . Such a curve is given in Figure 1, and the analysis into the exponential components by graphic methods is illustrated. The graphic

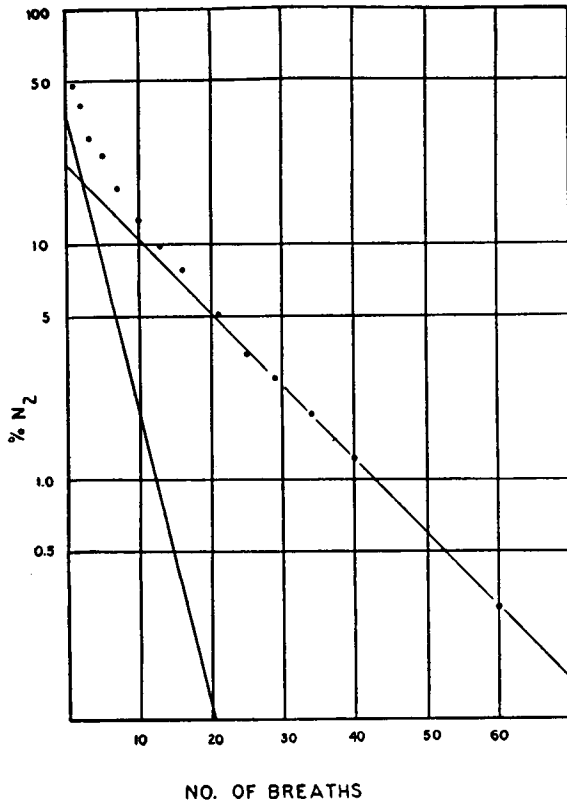


FIG. 1. GRAPHIC ANALYSIS OF DATA FROM HEALTHY ELDERLY SUBJECT T. H., ILLUSTRATING A TWO-PHASE CURVE.

The dots are mean expired  $N_2$  concentration minus correction (0.6%) for inspired and blood  $N_2$ . A curve through all dots represents the sum of the two components. One component is determined by the less steep straight line, or  $(FA_{10} - FI)w_1r_1$ ; the difference between this line and the dots is represented by the steeper straight line,  $(FA_{20} - FI)w_2r_2$ . See text.

analysis of the clearance curve is somewhat subjective. However, satisfactory precision is indicated by the reproducibility of measurements, and the magnitude of the derived dead space values, noted below. With large values of  $w$ , it is both necessary and possible to determine its magnitude to three figures. With small values of  $w$ , both the precision of determination and the effect of errors therein decrease. The analysis of the data by means of the preceding equations yields values of  $V_L$ ,  $w$ , and  $(V_T - V_D)$  for the respective components.

It is also important to know the ventilation rate of the lungs as a whole, the magnitude of uneven ventilation, and to make a ready comparison of these between individuals. This information can be obtained as follows from the data for the several components. Robertson and associates pointed out the relationship between the turnover rate and the average time a molecule remains in a continuously ventilated system (12). This approach can be applied to a cyclically ventilated system such as the lungs. The

basic value is that of  $w$ . However, on first acquaintance, some difficulty may be experienced in its interpretation. There is a derived number by which the ventilation can be characterized, and which is perhaps more easily comprehended. This is the average number of breaths the  $N_2$  molecules remain in a system, from which the  $N_2$  is being completely washed out.<sup>5</sup> This, as defined in the footnote, can be shown to equal  $\frac{1}{1-w}$ , when  $w = \frac{V_L}{V_L + (V_T - V_D)}$ .

The average number of breaths  $N_2$  molecules remain is small in a "deeply" ventilated system ( $w$  is small), and large if "shallowly" ventilated ( $w$  approaches unity).

The average number of breaths  $N_2$  molecules remain in a system having several components, each with different values of  $w$  ( $w_1, w_2, w_3$ ) and in which the decimal fractions of the total lung volume ( $V_L$ ) occupied by the partial lung volumes ( $V_{L1}, V_{L2}, V_{L3}$ ) are, respectively,  $f_1, f_2, f_3$ , equals  $\frac{f_1}{1-w_1} + \frac{f_2}{1-w_2} + \frac{f_3}{1-w_3}$ ; this value hereafter is called the *actual* average breath number.

The magnitude of uneven ventilation can be derived as follows. For a system having certain values for  $V_L$  and  $(V_T - V_D)$ , the average number of breaths  $N_2$  molecules remain can be shown to be minimal when the whole system is ventilated evenly.

If the effective tidal volume ( $V_T - V_D$ ) is *unevenly* distributed to various subdivisions of the total lung volume, the average number of breaths the  $N_2$  molecules remain is increased. However, one can determine what this number would be if ventilation *were uniform*, i.e., the *ideal* average breath number, and thereby acquire a standard for comparison with the *actual* average breath number.

It can be shown that  $\frac{f_1}{w_1} + \frac{f_2}{w_2} + \frac{f_3}{w_3} = \frac{1}{W}$  in which  $f_1$  and  $w_1$ , etc., are as above and  $W =$  the value of the alveolar dilution factor which would obtain in a uniformly ventilated system having the same total  $V_L$  and  $(V_T - V_D)$  as the components. The average number of breaths the  $N_2$  molecules would remain in this uniformly ventilated system or the *ideal* average breath number is  $\frac{1}{1-W}$ .

If uneven ventilation exists, its extent is given by the delay in  $N_2$  elimination produced thereby, expressed as a percentage of the ideal situation.

Pulmonary  $N_2$  clearance delay (%)

$$= \frac{\text{Actual average breath no.} - \text{Ideal average breath no.}}{\text{Ideal average breath no.}} \times 100.$$

The *time* intervals, in minutes, which correspond to the *actual* and *ideal* average breath numbers equal, respectively,

$$\frac{\text{Actual average breath no.}}{\text{Resp. frequency}} \text{ and } \frac{\text{Ideal average breath no.}}{\text{Resp. frequency}}$$

<sup>5</sup> The average number of breaths the  $N_2$  molecules remain =  $\frac{\sum_{i=1}^n i \times M_i}{n}$ , where  $i =$  number of breaths;  $M =$  number of molecules remaining for  $i$  breaths;  $n =$  total number of molecules.

## PROCEDURE

Details of apparatus have been presented previously (22, 23). In brief, the method consists of continuous analysis and photographic recording of (1) expiratory volume flow and (2)  $N_2$  concentration of respired gases during and after the change from breathing room air to breathing oxygen, the  $N_2$  content of which, 0.25% to 0.4%, was measured for each cylinder with the Van Slyke manometric apparatus. The accuracy of our  $N_2$  meter as used here with reference values ( $O_2$ ) recorded on each inspiration, is about  $\pm 2\%$   $N_2$  at high concentrations,  $\pm 1\%$   $N_2$  from about 30% to 10%  $N_2$ , and  $\pm 0.5\%$   $N_2$  at lower concentrations. Inspired  $O_2$  was delivered from a demand regulator, expired gas was passed through a flow meter, 30 inches of flexible rubber tubing (2 cm. I.D.) and the expiratory valve to a 120 L. compensating recording Tissot spirometer. The tubing-spirometer system was flushed previously with  $O_2$ ; the gas expired into the spirometer during a seven minute period of breathing  $O_2$  permitted measurement of functional residual capacity (FRC) by the method of Darling (24). Tidal volume and respiratory frequency were recorded spirometrically.

The subjects, after semireclining in bed with the trunk and head elevated 50–60° for at least 10 minutes, breathed  $O_2$  quietly for seven minutes. Continuous recordings of  $N_2$  concentration and volume flow of expired gas were made during the first two minutes of  $O_2$  inhalation, and for one or two breaths at the end of each succeeding minute for seven minutes. The mean expired  $N_2$  concentration of each breath was determined by replotting the simultaneous  $N_2$  and flow curves as %  $N_2$  versus volume instead of each versus time, as recorded. The area under this curve is quantity of  $N_2$  expired, and the mean height equals mean  $N_2$  concentration. This was determined graphically for 10–20 separate expirations.<sup>6</sup> Since accuracy of this procedure becomes less as  $N_2$  concentrations decrease, a different procedure was used to measure later breaths in which alveolar (end-tidal)  $N_2$  concentration was less than 5%  $N_2$ . Mean expired  $N_2$  concentration was calculated as end-tidal concentration times the average value of  $\frac{\text{mean \% } N_2}{\text{end-tidal \% } N_2}$  as determined by graphic integration of several prior breaths of similar volume. This calculation is strictly correct only when inspired gas contains no  $N_2$ ; however, as used here, the error is negligible. Measurements were continued until the mean expired  $N_2$  concentration was about 1%  $N_2$ . The tidal volumes during the period of  $N_2$  measurements were corrected to BTPS and average values were used in calculation.

## RESULTS

*Healthy adults*

Table I presents the results on 10 healthy young adults (seven male and three female) and

<sup>6</sup>The graphic integration procedure requires several hours for each subject's record. Attempts, as yet not completely successful, have been made to devise an automatic integration apparatus which would reduce the measurement time to several minutes.

on seven elderly male hospital patients, in whom the history, physical and radiological examinations gave no evidence of cardiorespiratory disease. The majority of the clearance curves could be described by an equation for two phases, each having different volumes and ventilation rates. The value of  $w$ , the alveolar dilution factor, is a measure of the effective ventilation per breath; as  $w$  becomes smaller, the effective ventilation increases, *i.e.*, greater dilution of alveolar gas occurs. The alveolar dilution factor of the major part, average about 80%, of the lung volume appeared to be of a moderate magnitude, having values of about 0.9. This is of the order to be expected from customary values of functional residual capacity, tidal and dead space volumes. However, a smaller part, about 20% of the lung volume, was relatively hyper-ventilated, having  $w$  values between about 0.5 and 0.85.

For the younger subjects, the average number of breaths  $N_2$  molecules remained in the lungs (actual average breath number) varied from 5.9 to 9.7; the mean was 7.63 breaths, or 0.60 minutes. If alveolar ventilation had been uniform,  $N_2$  molecules would have remained 6.38 breaths, or 0.50 minutes. Uneven ventilation was of moderate extent, producing an average pulmonary  $N_2$  clearance delay of 21.1%, S.D.  $\pm 11.9\%$ .

The older subjects differed from the younger in several respects. The effective ventilation per breath of the major part of the lung volume tended to be less. The mean of the actual number of breaths  $N_2$  molecules remained in the whole lung, 11.14 breaths, was significantly greater ( $p < 0.01$ ) than for the younger subjects. This was a result of two factors. First, the average extent of uneven ventilation, shown by an average pulmonary  $N_2$  clearance delay of 45.9%, was significantly larger ( $p < 0.05$ ). Second,  $N_2$  molecules would have remained a significantly greater ( $p < 0.05$ ) number of breaths even if ventilation had been uniform, as shown by the average ideal breath number of 7.77. This is because the enlargement of functional residual capacity (VL) was not accompanied by a corresponding increase in effective tidal volume ( $V_T - V_D$ ). However, the average time  $N_2$  molecules remained in the lungs, about 40 seconds, was not significantly prolonged in

the older subjects because of their greater respiratory frequency.

*Subjects with cardiorespiratory abnormality*

Table II presents the results on 19 patients. These subjects were selected to present a wide variety of pulmonary disorders, both in nature and severity. Of four subjects with clinically varying severity of asthma, three had abnormally uneven ventilation, shown by pulmonary N<sub>2</sub> clearance delay values of 52, 95, and 190%. In the two most severe cases, the average number of breaths N<sub>2</sub> molecules actually remained was more than three times the normal values. One patient (V. J.) with clinically mild asthma (no symptoms or physical signs at the time of the examination) exhibited an abnormally small effective ventilation per breath, as shown by the large actual and ideal breath numbers, although the uniformity of ventilation was not abnormal (13% pulmonary N<sub>2</sub> clearance delay).

All five subjects with chronic pulmonary emphysema showed findings similar to each other. The effective ventilation per breath of the major part of the alveolar gas was very small, with w values exceeding 0.98. Even if ventilation had been uniform, the effective ventilation per breath would have been small, as shown by the abnormally great ideal breath numbers. This is the result of enlargement of the functional residual capacity. Pulmonary N<sub>2</sub> clearance delay was marked, ranging from 115 to 248%. These combined to produce a very slow average ventilation, the average time N<sub>2</sub> molecules actually remained amounting to several minutes.

The group of subjects with congestive heart failure, all with mitral valvular disease, exhibited varied patterns of ventilation. In three of the five, ventilation was abnormally uneven, with clearance delay values from 60 to 102%. The other two cases, despite similar normal values for N<sub>2</sub> clearance delay, showed certain differences. One case (J. P.) with a clinically minimal

TABLE I  
*Respiratory and pulmonary N<sub>2</sub> clearance data for young and old healthy subjects*  
(See text for explanation of headings)

Subj.	Sex	Age (yrs.)	Tidal vol. (ml.)	Resp. (per min.)	Ventilatory components						Average interval N <sub>2</sub> molecules remained				Pul. N <sub>2</sub> clearance delay (%)	FRC (ml.)	
					Phase 1		Phase 2		Phase 3		No. of breaths		Minutes			Darling	Σ Vt
					f <sub>1</sub>	w <sub>1</sub>	f <sub>2</sub>	w <sub>2</sub>	f <sub>3</sub>	w <sub>3</sub>	Actual	Ideal	Actual	Ideal			
H. B.	M	30	740	15	.94	.865	.06	.588	—	—	7.08	6.25	.47	.42	13	—	2,910
R. W.	M	26	700	10	.66	.864	.34	.680	—	—	5.92	4.76	.59	.48	24	—	1,930
S. K.	M	34	620	12	.74	.879	.26	.657	—	—	6.87	5.20	.57	.43	32	—	1,910
B. K.	M	30	557	15	.84	.886	.16	.758	—	—	7.98	7.25	.53	.48	10	2,310	2,370
H. K.	M	27	467	14	.88	.853	.12	.500	—	—	6.24	4.73	.45	.34	32	1,520	1,270
L. H.	M	30	558	18	.68	.896	.32	.722	—	—	7.66	5.86	.43	.33	31	2,240	2,380
C. W.	M	35	514	10	.85	.903	.13	.865	.03	.524	9.69	8.40	.97	.84	15	2,500	2,670
M. N.	F	28	453	13	1.00	.869	—	—	—	—	7.63	7.63	.59	.59	0	—	2,210
I. M.	F	22	510	12	.96	.893	.04	.537	—	—	9.00	7.70	.75	.64	17	2,760	2,560
D. R.	F	22	481	13	.84	.893	.16	.621	—	—	8.27	6.06	.64	.47	37	1,800	1,790
Mean		25.4	560	13.2	.84	.880	—	—	—	—	7.63	6.38	.60	.50	21.1	2,188	2,200
S.D. ±											1.18	1.30	.16	.15	11.9		
T. H.	M	53	466	20	.74	.931	.26	.751	—	—	11.80	8.15	.59	.45	45	1,930	2,400
F. M.	M	56	330	21	1.00	.888	—	—	—	—	8.92	8.92	.43	.43	0	1,570	1,360
C. W.	M	61	550	11	.82	.899	.18	.613	—	—	8.49	5.82	.77	.53	46	3,510	3,270
G. R.	M	65	643	14	.72	.924	.23	.838	.05	.375	11.03	6.50	.80	.46	70	3,130	3,010
M. G.	M	65	464	15	.42	.929	.58	.864	—	—	10.17	9.10	.68	.61	12	1,940	2,350
J. F.	M	61	577	21	.69	.951	.26	.819	.05	.486	15.50	7.70	.74	.37	101	4,090	2,640
H. S.	M	81	620	16	.93	.922	.07	.554	—	—	12.06	8.20	.76	.51	47	3,250	3,390
Mean		64	521	16.9	.76	.921					11.14*	7.77*	.68	.48	45.9*	2,774	2,631
S.D. ±											2.35	1.21	.13	.08	33.9		

\* Mean value differs significantly by small sample method from mean value for young subjects.

TABLE II

*Respiratory and pulmonary N<sub>2</sub> clearance data for subjects with cardiorespiratory disease*

Subj.	Diagnosis	Sex	Age (yrs.)	Tidal vol. (ml.)	Resp. (per min.)	Ventilatory components						Average interval N <sub>2</sub> molecules remained				Pul. N <sub>2</sub> clearance delay (%)	FRC (ml.)	
						Phase 1		Phase 2		Phase 3		No. breaths		Minutes			Darling	Σ VL
						f <sub>1</sub>	w <sub>1</sub>	f <sub>2</sub>	w <sub>2</sub>	f <sub>3</sub>	w <sub>3</sub>	Actual	Ideal	Actual	Ideal			
E. R.	Asthma mild	F	34	710	17	.46	.911	.54	.694	—	—	6.87	4.51	.41	.27	52	2,530	1,910
V. J.	mild	F	33	364	25	.71	.936	.29	.870	—	—	13.3	11.8	.53	.47	13	2,060	2,310
L. S.	moderate	M	16	525	22	.54	.979	.38	.950	.08	.722	33.5	17.2	1.5	.78	95	3,970	4,720
J. K.	severe	M	41	482	20	.53	.987	.47	.882	—	—	44.5	15.4	2.2	.77	190	3,250	3,750
G. D.	Emphysema moderate	M	70	437	17	.79	.980	.21	.844	—	—	40.7	18.9	2.4	1.1	115	4,600	4,370
N. R.	severe	M	58	312	22	.87	.990	.13	.820	—	—	87.5	27.8	4.0	1.3	215	4,680	3,710
J. C.	severe	M	59	395	20	.72	.991	.25	.926	.03	.622	83.4	24.4	4.2	1.2	240	4,670	4,600
W. A.	severe—asthma	M	60	497	16	.72	.981	.20	.862	.08	.603	39.7	11.4	2.6	0.74	248	3,880	3,440
S. F.	severe—asthma	M	66	467	19	.82	.981	.16	.858	.02	.418	44.5	16.7	2.3	0.88	166	4,250	4,180
J. P.	Congestive heart failure minimal	M	40	307	26	.86	.934	.14	.779	—	—	13.7	10.9	.53	.42	25	2,070	1,730
J. B.	moderate	M	39	574	13	.48	.953	.52	.771	—	—	12.5	6.67	.96	.52	89	2,400	2,170
G. B.	severe	F	39	451	30	.61	.847	.39	.626	—	—	5.0	3.90	.17	.13	29	1,580	1,030
E. W.	severe	F	36	320	32	.45	.972	.48	.926	.07	.752	23.4	14.7	.73	.46	60	2,330	2,700
G. W.	severe—with (?) silicosis	M	56	492	27	.78	.976	.22	.841	—	—	33.7	16.7	1.25	.62	102	4,570	5,560
B. T.	Bronchiectasis, L. lower lobectomy, 8 mos. pregnant	F	22	670	14	.17	.966	.75	.810	.08	.304	9.05	3.73	.65	.27	143	1,660	1,390
E. T.	Sarcoid-pulmonary cyst	F	26	400	31	.69	.973	.31	.850	—	—	27.6	14.3	.90	.46	93	3,330	2,640
T. C.	Pulmonary fibrosis	M	34	392	21	.48	.980	.47	.938	.05	.393	31.6	9.51	1.51	.45	233	2,620	2,760
L. W.	3 mos. post-pneumectomy	M	65	430	23	.48	.961	.37	.892	.15	.635	16.1	7.75	.70	.34	108	1,850	1,750
A. G.	2 wks. post-pneumectomy	M	54	556	24	.55	.952	.37	.885	.08	.498	14.5	7.40	.61	.31	97	2,700	2,040

degree of failure had an abnormally small effective ventilation per breath (large ideal and actual breath numbers), resulting primarily from a small tidal volume, 307 ml. The other (G. B.), with clinically severe pulmonary and peripheral congestion, had an abnormally great effective ventilation per breath. With a marked polypnea, this produced the most rapid pulmonary N<sub>2</sub> clearance observed.

The two cases examined after pneumonectomy for cancer were selected to see if uneven ventilation could occur in a single lung which was considered pre-operatively to be clinically normal. In both cases, uneven ventilation was marked, the clearance delay values, 108 and 97%, exceeding considerably the average of normal elderly men, 46%. However, these cases cannot be considered as normal single lungs. In both the remaining lung was somewhat overdistended, as indicated by tracheal displacement observed fluoroscopically and by residual volume/total lung capacity ratios of about 55%. Also, in case L. W. emphysematous changes were found at autopsy 13 months later. However, these show that a single lung can be ventilated unevenly.

Abnormally uneven ventilation was also found

in three patients with other varied types of pulmonary disease. Subject B. T. further illustrates the fact that markedly uneven ventilation is not necessarily associated with a long absolute pulmonary clearance time. Uneven ventilation creates a delay beyond the value which would obtain with even ventilation. If the latter is small, because effective minute volume ( $[V_T - V_D] \times \text{resp. per min.}$ ) is large relative to functional residual capacity, the net effect may be a normal average *time* N<sub>2</sub> molecules remain in the lungs.

## DISCUSSION

### *Reproducibility*

The procedure was repeated on five healthy subjects and six patients after a 10–20 minute period of N<sub>2</sub> re-equilibration, breathing air. In five cases, the first and second records were analyzed by different persons, and in six cases by the same person. As shown in Table III, the rapidity of N<sub>2</sub> clearance and the extent of uneven ventilation were similar on both tests. Statistical analysis showed (1) the variation between subjects greatly exceeded the variation between duplicates ( $F = 14.9$ ), and (2) large correlation coefficients between duplicate values,

TABLE III  
Duplicate N<sub>2</sub> clearance measurements

Subject	Average actual breath number		Pulmonary N <sub>2</sub> clearance delay (%)	
	1	2	1	2
M. N.	7.6	7.7	0	5
H. B.	7.1	8.0	13	13
R. W.	5.9	6.8	24	16
M. G.	10.2	9.9	12	33
J. G.	24.9	21.0	50	89
G. R.	11.0	12.7	70	45
H. S.	12.1	14.8	47	43
J. B.	12.5	10.3	87	51
L. W.	16.1	12.0	108	47
G. Y.	42.5	26.0	154	146
N. R.	87.5	75.5	215	164
Mean	21.6	18.6	70.9	59.3

being 0.98 for average actual breath numbers and 0.90 for pulmonary N<sub>2</sub> clearance delay values. More data are required to establish the error of a single determination of pulmonary clearance delay, particularly in patients, since the absolute difference between duplicate measurements appears to vary with the magnitude thereof.

#### Limitations

The accuracy of the mean expired N<sub>2</sub> concentrations was checked by the simultaneous measurement of FRC (1) by the Darling method and (2) by the values (VL<sub>1</sub> + VL<sub>2</sub> + VL<sub>3</sub>) obtained from tidal volume and mean N<sub>2</sub> concentration (Tables I and II). Apparently there was no important systematic error, since the best fitting straight line of regression of FRC<sub>y</sub> (from mean expired N<sub>2</sub> concentration) on FRC<sub>x</sub> (Darling) was

$$FRC_y = 9 + 0.962 (\pm 0.089) FRC_x.$$

However, in certain subjects, particularly the patients, considerable discrepancies occurred. In general, these should probably be attributed to errors in the values calculated from the N<sub>2</sub> clearance curve. The equations assume constancy of tidal, dead space, and lung volumes throughout the procedure. The errors introduced by respiratory changes, if they occur, vary in nature and degree with different types of curves, and also depend on whether the respiratory changes are systematic, such as a progressive increase in tidal volume, and the part of the clearance process in which they occur.

Considerable changes in tidal volume have been observed during the first several minutes of O<sub>2</sub> inhalation, both in normal subjects and in patients. These were probably related to (1) changes in respiratory resistance occurring when the O<sub>2</sub> circuit was attached, and (2) reduction of reflex respiratory stimulation in anoxic subjects by the increased arterial pO<sub>2</sub> associated with O<sub>2</sub> inhalation.<sup>7</sup> In the two healthy subjects showing single phase records (M. N. and L. M.) progressive increases of tidal volume, occurring in the N<sub>2</sub> clearance period, probably obscured some degree of uneven ventilation. One healthy elderly subject showed such marked cyclic changes in tidal volume that the resulting record could not be analyzed. Progressive decreases in tidal volume of the emphysematous subjects probably caused an over-estimate of the extent of uneven ventilation; the prolonged average periods, two to four minutes, during which the N<sub>2</sub> molecules remained in their lungs, were also associated with a reduced minute volume of alveolar ventilation during O<sub>2</sub> inhalation by these anoxic patients (average resting arterial O<sub>2</sub> saturation was 88.7%).

As noted before, the constant correction factor used for N<sub>2</sub> eliminated from blood and tissues is somewhat inaccurate. However, it has been used because its error is exceeded by that of determining the mean expired N<sub>2</sub> concentration, and the exact correction, at present unknown, must await knowledge of the relative blood flow through the various ventilatory regions of the lungs. The limited accuracy of our method at low N<sub>2</sub> concentrations precluded the attempt to obtain information about blood and tissue N<sub>2</sub> elimination by a more prolonged procedure. The multiphasic shape of the corrected clearance curves could be possibly attributed to an underestimate of the correction factor in only four of 36 cases.

However, we believe the magnitudes of uneven ventilation indicated by the values of pulmonary N<sub>2</sub> clearance delay are valid in general. Twenty-seven of these subjects (nine normals and 18 patients) were also examined with another method of estimating the magnitude of uneven

<sup>7</sup> A preliminary period of breathing compressed air from a demand regulator similar to that used for O<sub>2</sub> delivery, and the use of another N<sub>2</sub>-free gas, such as 80% helium—20% O<sub>2</sub>, might reduce the inconstancy of tidal volume.

ventilation, which is based on the variation in  $N_2$  concentration of alveolar gas expired after a single maximal inspiration of  $O_2$  (18, 19). Although this latter method is, at least theoretically, not a perfect and direct index, it is independent of the sources of error affecting the analysis of the  $N_2$  clearance curves. There was general agreement between the two methods, as indicated by a highly significant, and fairly strong, correlation ( $r = +0.76$ ).

One can obtain the total effective tidal volume ( $V_T - V_D$ ) from analysis of the clearance curves. This obviously permits a measurement of respiratory dead space, which, if of unreasonable magnitude, indicates errors arising from (1) inconstancy of the respiratory volumes during the clearance process and/or (2) inaccuracies in the graphic analysis procedure. The average dead space value, corrected for apparatus dead space, for all male subjects (Tables I and II) was 137 ml., and for all female subjects, 127 ml. These are quite reasonable values and support the validity of the method. However, we do not recommend this method for measurement of respiratory dead space. It is unduly liable to errors arising from slight variations in determination of slope and position of the function describing the ventilation of hyperventilated areas. The direct method described previously (22, 23) is superior.

#### *Comparison of methods*

The "single breath" method for estimating uniformity of alveolar ventilation, noted above, requires only a single deep breath for its execution and only a few minutes for measurement. Theoretically, however, the variation in  $N_2$  concentration of expired alveolar gas depends both on uneven end-inspiratory distribution of inspired  $O_2$ , and also on the change during expiration of proportion of gas expired from various lung areas (18, 19). The correlation noted above between the "single breath" results and the  $N_2$  clearance analyses supports the general validity of the "single breath" test. Comparison was made to see if those patients judged to be abnormal by the single breath test were also abnormal by the values of pulmonary clearance delay. The appropriate mean plus 2 S.D. was used as the upper limit of normality. The results were identical in 15 of 18 patients, including

all the cases of asthma, emphysema, bronchiectasis, sarcoid, and pulmonary fibrosis. The discrepancies occurred in two cases of congestive heart failure and one subject after pneumonectomy. The latter, however, probably merely indicates the inadequacy of the current data, based on only seven elderly subjects, to define clearly the normal variation of clearance delay values. Therefore, it currently appears that an abnormal "single breath" test is a reliable sign of abnormally uneven ventilation in subjects with this type of primary pulmonary disease. Further validation of the single breath test would be desirable in other types of patients, such as those with congestive heart failure, and in testing of uneven ventilation before and after therapy. Of the two tests, the single breath test, being rapidly and easily executed and measured, is preferable for the routine clinical detection of abnormally uneven ventilation.

However, the analysis of the pulmonary  $N_2$  clearance curves yields much more information. First, the value of pulmonary  $N_2$  clearance delay is a quantitative measurement of the extent of uneven ventilation. Its theoretical advantages recommend it for investigative use, particularly in the measurement of changes in the extent of uneven ventilation, such as might occur with therapy. Second, a rather comprehensive and quantitative picture of the volume and time characteristics of alveolar ventilation are obtained, both for the lungs as a whole and for its ventilatory subdivisions. Alveolar ventilation is the first step in the process of pulmonary gas-blood exchange. Further studies of alveolar diffusion and perfusion are possible when alveolar ventilation can be independently described.

#### *Accuracy of the Darling method for measurement of functional residual capacity*

This method requires knowledge of the change in the mean  $N_2$  concentration of alveolar gas occurring in a seven minute period of  $O_2$  inhalation. An estimate of the final alveolar  $N_2$  concentration is obtained by analysis of the terminal portion of a forceful expiration, delivered at the end of seven minutes. The question whether such a sample accurately represents the mean alveolar  $N_2$  concentration, particularly in subjects with uneven and delayed alveolar ventilation, has



been considered both by Darling and others (25). In the subjects above, continuous analysis of this forceful expiration was made. The  $N_2$  concentration of the terminal part was abnormally high ( $>2\%$ ) in the five cases with emphysema and the two cases of severe asthma (average  $4.6\%$ ). However, alveolar gas expired earlier in the same expirations had lower  $N_2$  concentrations. The  $N_2$  concentration of the unexpired residual gas was of course not directly measurable.

The *mean* alveolar  $N_2$  was estimated from the  $N_2$  clearance curves of the seven cases noted above as follows. The fractional changes of alveolar  $N_2$  concentration per breath in the various lung areas are given by  $w_1, w_2,$  and  $w_3$ . The initial  $N_2$  concentration in all areas was about  $80\%$ . After seven minutes, the  $N_2$  concentration in the more rapidly ventilated phases 2 and 3 is practically equal to the inspired concentration. The alveolar  $N_2$  concentration in phase 1 equals  $(80 - FI) w_1^n + FI$ , where  $n$  equals resp. per min.  $\times 7$ . Since the fractional values of the total volume occupied by the various phases are known, the mean alveolar concentration is readily calculated.<sup>8</sup>

Mean values of the seven cases were, for the forced expiration alveolar sample,  $4.6\%$ ; for the calculated *mean* alveolar  $N_2$  concentration,  $8.2\%$ ; for the alveolar concentration of phase 1,  $11.0\%$ . That is, the alveolar sample in subjects such as these with small expiratory reserve/residual capacity ratios, comes predominantly from relatively hyperventilated areas. Calculations using the expired alveolar sample concentration, therefore, yielded FRC values which, in these cases, were about  $5\%$  too small. Practically, this is unimportant. In fact this demonstration that the error is small in these extreme cases increases our confidence in the Darling method. In clinical usage, calculations based on the expired alveolar sample concentration are satisfactory. As a method for measurement of functional residual capacity, the Darling method is preferable to the analysis of pulmonary  $N_2$  clearance curves, on the basis of apparatus simplicity, and rapidity and accuracy of measurement.

<sup>8</sup> The Darling FRC values given for these seven subjects in Table II were calculated by using this value rather than the  $N_2$  concentration of the alveolar sample.

#### Other data

Robertson, Siri, and Jones have recently reported findings similar to those given in Tables I and II, based on multiphasic analysis of pulmonary  $N_2$  elimination rates (12). However, we prefer to treat alveolar ventilation as a discontinuous rather than as a continuous process, as they have done. This permits the derivation of the pulmonary  $N_2$  clearance delay, which is determined by the extent of uneven ventilation. Robertson and associates use a measure "E" of the efficiency of ventilation, which is dependent not only on the extent of uneven ventilation, but also on the dead space/tidal volume ratio, and, with certain methods of calculation, the respiratory frequency.

Bateman, in a recent study of pulmonary  $N_2$  clearance of normal subjects, concluded that the behavior of the normal lung is compatible with a single chamber model (10). This is in contrast with data obtained by continuous analysis reported here and by Robertson, Siri, and Jones (12). However, one of several requirements upon which experiments were rejected or accepted was the "definiteness of linear relationship between  $y$  and  $n$ "; that is, the definiteness with which the clearance process could be described by a single value of  $w$ . As Robertson points out, analysis of multiphasic pulmonary clearance or equilibration curves with equations containing only one exponential term (4, 6, 10) is inadequate and may lead to ambiguous or at times incorrect interpretation of the nature of ventilatory inefficiency (23, 26). Bates and Christie (6) have achieved a clear cut separation of the ventilatory efficiency of certain types of subjects, quite in accordance with our results. However, their method, based on the  $90\%$  equilibration value, is at least theoretically incapable of demonstrating certain patterns of abnormally uneven ventilation which may exist in pulmonary diseases other than those reported.

#### INTERPRETATION

It is not clear why the lungs, either both or one (after pneumonectomy), with many anatomical subdivisions, appear to be ventilated as if they consisted of only two or three regions. Although this is of course possible, it seems more likely

that (a) technical inadequacies limit the resolution of the curves, and (b) the curves reflect patterns of the distribution of ventilation rates among the many regions. The measured curves were satisfactorily described in terms of regional inequalities of ventilation. However, we do not consider that this establishes the total or partial degree to which uneven ventilation is regional in nature. The possible mechanisms of uneven ventilation, which have been discussed elsewhere (19), and the spatial locations involved require further study.

#### SUMMARY

Measurements were made on successive breaths, during the elimination of pulmonary  $N_2$  while breathing 99.6%  $O_2$ , of (a) the mean expired  $N_2$  concentration, (b) number of breaths and (c) tidal volume. Equations with which the data have been described and analyzed are presented. The equations assume that uneven alveolar ventilation is of a regional nature.

The lungs, both in healthy young and old subjects and in patients with cardiorespiratory disease, are, in varying degrees, ventilated unevenly, *i.e.* certain regions appear to be ventilated more rapidly than other regions. The volumes and respective ventilation rates of these several regions can be determined, as well as the volume and average ventilation rate of the lungs as a whole. The extent of uneven ventilation can be measured quantitatively by the resulting delay in pulmonary  $N_2$  clearance. This is determined relative to the rate of  $N_2$  clearance which the subject would have achieved, breathing in the same manner, if alveolar ventilation had been uniform throughout the lungs. This measurement is uninfluenced by the magnitude of the respiratory dead space. In effect, a control and test procedure are done simultaneously for each subject.

In 10 healthy young adults, breathing quietly in the semi-reclining position,  $N_2$  molecules remained in the lungs an average of 7.6 breaths or 36 seconds. This was 20% longer than if ventilation had been uniform. In seven elderly subjects  $N_2$  molecules remained an average of 11.1 breaths, or 41 seconds. The increase in the average number of breaths was due to a smaller effective ventilation per breath and to a greater extent of uneven ventilation.

Abnormally uneven ventilation was found in almost all of 19 patients with cardiorespiratory diseases, including asthma, emphysema, congestive heart failure and others. The delaying effect of uneven ventilation can be overcome if the total minute volume of alveolar ventilation is large in relation to the functional residual capacity.

Twenty-seven of the subjects were also examined by another method of estimating the magnitude of uneven ventilation, which is based on the variation in  $N_2$  concentration of alveolar gas expired after a single maximal inspiration of  $O_2$ . There was general agreement between the two methods, the relative utility of which is discussed.

The functional residual capacity, measured from the pulmonary  $N_2$  clearance curves, agreed satisfactorily with simultaneous measurements by the method of Darling and coworkers. Analysis of the  $N_2$  clearance curves permitted an estimate of the error of the Darling method. This amounted to about a 5% systematic underestimate in emphysematous subjects, resulting from the failure of the terminal alveolar gas sample to represent accurately the mean alveolar  $N_2$  concentration.

Although the method presented permits an improved description of alveolar ventilation, a final interpretation of such data must await further study of the spatial distribution and the controlling mechanisms involved in alveolar ventilation.

#### ACKNOWLEDGMENTS

The authors wish to thank Dr. J. H. Comroe, Jr. for valuable advice and Dr. R. E. Forster, II, Doris Raneiri, and Carol Kimball for assistance.

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