NON-UNIFORM PULMONARY DIFFUSION AS DEMONSTRATED BY THE CARBON MONOXIDE EQUILIBRATION TECHNIQUE: EXPERIMENTAL RESULTS IN MAN*

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Available evidence indicates that pulmonary diffusion is distributed in a non-uniform manner throughout the lung; the pertinent literature was reviewed briefly in the preceding paper of this series (1). Conventional methods for measuring the pulmonary diffusing capacity do not allow a quantitative assessment of this non-uniformity, and, in the presence of uneven diffusion, may yield erroneous values for total D_L.[1] This problem has been reviewed recently by Forster (2). The magnitude of the error in D_L induced by non-uniformity of diffusion has not been assessed; in some instances, even its direction cannot be predicted with certainty. Since the phenomenon of uneven diffusion is interesting per se (perhaps relating to the distribution of blood flow within the lung), and since accurate D_L determinations require an assessment of the degree of non-uniformity of diffusion, it would seem important to attempt to quantify this phenomenon.

In the preceding paper of this series a method was described for calculating pulmonary diffusing capacity in the presence of non-uniform D_L/V_A ratios. This method utilizes data obtained during wash-in and washout of helium and carbon monoxide from the lung, a technique previously described in this laboratory and hereafter called the equilibration method (3). To describe non-uniform diffusion, a lung model was assumed, and D_L/V_A variations were determined in terms of pulmonary compartments, each compartment having uniform ventilatory and diffusing characteristics. The suitability of the simple model utilized in these calculations must be demonstrated by its applicability to experimental results. Determined compartments are not intended to represent actual subdivisions of the lung; these compartments have meaning only as indices of the degree of non-uniformity of diffusion which may actually exist.

In the present report, data obtained during equilibration tests on several normal and ab-

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[1] Definition of symbols used in this report:

D_L = pulmonary diffusing capacity
V_A = alveolar volume
$\dot{V}_A$ = alveolar ventilation per unit time
$\dot{Q}_C$ = pulmonary capillary blood flow
V_{TA} = alveolar tidal volume
V_{FRC} = end expiratory alveolar volume
V_C = blood volume of the pulmonary capillary bed
D_M = true diffusing capacity of the pulmonary membrane
t = any time interval
tb = time for a single breath cycle
f = respiratory frequency (f = 1/tb)
P_B = barometric pressure corrected for water vapor
Y and Z = symbols for compartments of the lung, applied as subscripts (e.g., V_{AZ} and so forth)
F_{AX} = fractional concentration of any gas X in alveolar gas
F_{IX} = fractional concentration of any gas X in inspired gas
F_{ETX} = fractional concentration of any gas X in end tidal gas
F_{EIX} = fractional concentration of any gas X in alveolar gas at the end of inspiration
$F\dot{V}_Y$ = fraction of $\dot{V}_A$ to compartment Y
$F\dot{V}_Z$ = fraction of $\dot{V}_A$ to compartment Z
K_{N_2} = a constant indicative of the rate of inert gas washout
K_{CO} = a constant indicative of the total rate of carbon monoxide disappearance from alveolar gas due to diffusion plus ventilation
K_D = a constant indicative of the rate of carbon monoxide disappearance from alveolar gas due to diffusion alone ($K_D = P_B D_L/V_A$)
W = the dilution factor for a uniform lung during washout, such that

$$W = V_{FRC}/(V_{FRC} + V_{TA})$$

Subscript t = at time t
Subscript 0 = at onset of time interval t
Subscript ∞ = after complete equilibration with an inhaled gas.

normal subjects are analyzed by the methods described in the preceding paper. In addition to testing the applicability of the methods, these techniques yield an estimate of DL/VA variability under physiological conditions. A few animal experiments are also reported which confirm the ability of the equilibration test to reflect DL/VA non-uniformity and show its applicability to animal experimentation and its reproducibility when ventilatory characteristics are fully controlled.

METHODS

A diagram of the apparatus is shown in Figure 1. The apparatus has been modified since previous reports (3) to allow incorporation of a rapid helium analyzer. Thus, simultaneous recording of the washout of the inert gas (helium) and the diffusible gas (carbon monoxide) may be obtained. In previous experiments it had been necessary to induce nitrogen washout after completion of the carbon monoxide washout curve.

After a baseline period, breathing room air, subjects were allowed to inspire, in succession, a 30 per cent helium mixture, a 30 per cent helium–0.25 per cent carbon monoxide mixture, and room air. All gas mixtures contained 20 per cent oxygen. Expired gas passed through a breathe-through type infrared cell for carbon monoxide analysis (Liston-Becker model A-15) and past the sampling orifice of a rapid helium analyzer (Godart katapherometer). Expired helium and carbon monoxide concentrations were recorded continuously on a Grass polygraph instrument. A diagrammatic representation of the type of record obtained is shown in Figure 1; note the more rapid disappearance of carbon monoxide than of helium during their washout periods. This is due to a combination of diffusion and ventilation effects in the case of CO, while helium disappearance is due solely to ventilation. Further details of the technique are included in a previous report (3).

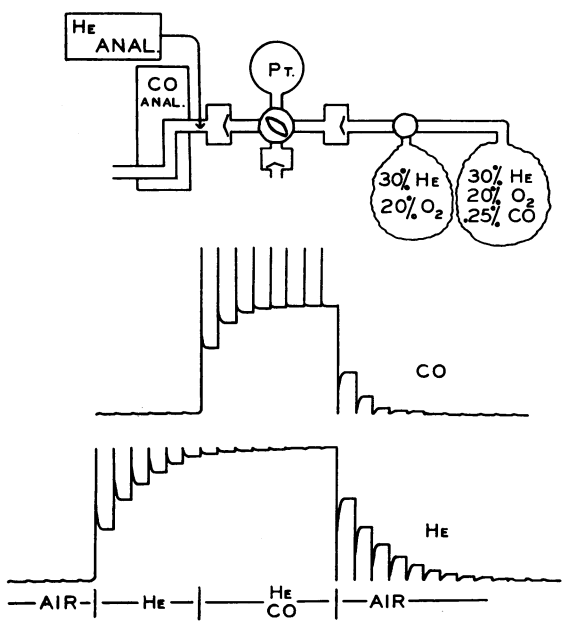

FIG. 1. SCHEMATIC REPRESENTATION OF APPARATUS, ABOVE, AND DIAGRAMMATIC REPRESENTATION OF DATA OBTAINED BY THE "EQUILIBRATION" METHOD, BELOW. In actual tests, the gain is increased during the washout period to record more accurately low concentrations of helium and carbon monoxide.

Subjects were trained to breathe regularly with tidal volumes of approximately 1,000 cc. These large volumes were considered desirable to insure flushing of the dead space of the subject and apparatus with each expiration. Tests were performed with subjects in a standing position.

Calculation of compartments varying in their DL/VA ratios was carried out as described in the preceding paper of this series (1). In each instance, theoretical curves for the calculated compartments were drawn and compared with obtained experimental data. "Total DL" was determined by addition of the DL's of the various compartments.

DL's were also estimated from 10-second intervals of washout during equilibration tests, a procedure which assumes uniform DL/VA and $\dot{V}A/VA$ ratios. This estimate of DL was made as follows:

$$DL = 60VA \times \ln [(FET_{He10\,sec.}/FET_{He0})FET_{CO0}/FET_{CO10\,sec.}]/10PB.$$

Standard breath-holding tests were carried out by the method of Forster, Fowler, Bates and van Lingen (4).

RESULTS

Non-uniformity of diffusion in normal subjects. Equilibration records on five normal subjects in the resting state have been analyzed in terms of multiple compartment systems. None of the tests was compatible with a uniformly diffusing lung. However, in all instances but one, obtained data could be explained by two-compartment models, the theoretical curves for such models conforming well with actual experimental points, as shown in Figure 2. In one instance (Subject 5), it was necessary to utilize a three-compartment system. In this subject, a small, almost nondiffusing region was calculated. Results are summarized in Table I in which the sizes, relative ventilations, and diffusing characteristics of the calculated compartments are indicated. In these normal subjects, calculated variability of DL/VA is two- to fourfold and regions with high DL/VA ratios are small in volume, representing 6 to 18 per cent of the lung volume.

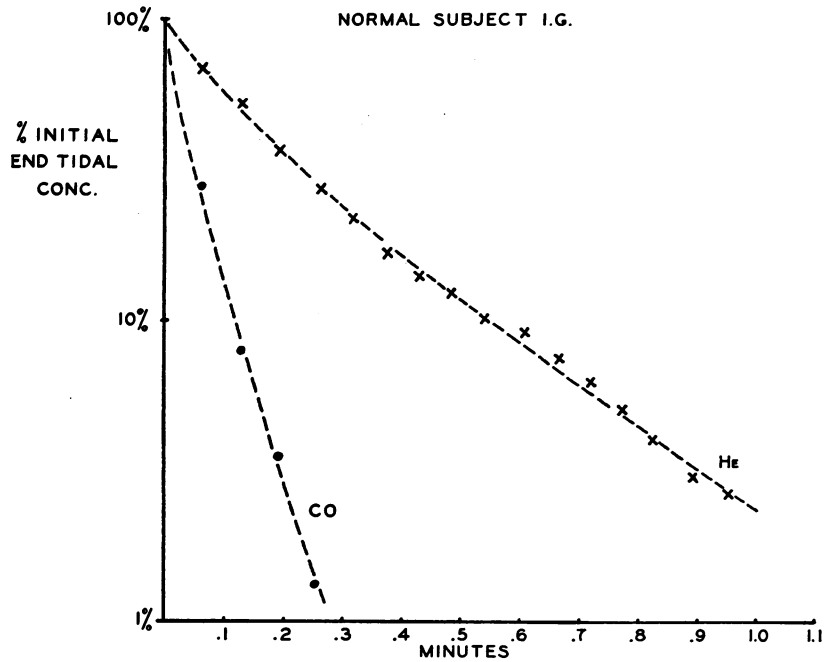

FIG. 2. END TIDAL HELIUM AND CARBON MONOXIDE VALUES OBTAINED DURING THE WASHOUT PERIOD IN SUBJECT 2 (NORMAL) ARE PLOTTED SEMILOGARITHMICALLY AGAINST TIME. Gas concentrations are expressed as per cent of their concentration at zero time, i.e., just prior to changing the inspired gas from carbon monoxide-helium mixture to room air. The broken curves represent the theoretical end tidal values which would be predicted for a lung having the compartments calculated for this subject. Agreement of the calculated broken lines with experimental points indicates how closely the calculated compartments explain obtained data.

Total DL's calculated by the comparmentation method are not significantly different from overall DL's determined by Forster's breath-holding technique, except in Subject 4. However, the breath-holding DL's recorded in Table I were obtained with the lung at full inflation, and are therefore not truly comparable with the equilibration tests which were carried out slightly above the resting lung volume. Because of these differences in lung volume, one would have predicted that breath-holding DL's would be systematically higher than equilibration results (5–7). In Subjects 4 and 5, breath-holding DL's performed at the functional residual capacity (FRC) level were 23 and 27, respectively—values lower than those obtained with the equilibration technique. It would appear that there is a tendency to underestimate the rapidly diffusing areas of lung when breath-holding tests are carried out at 10-second intervals, although the effect is very slight in most subjects. A similar slight underestimate of total DL is noted when the rate of diffusion is estimated from helium and carbon monoxide values at 10 seconds of washout during equilibration tests (last column, Table I).

The gross discrepancy between compartmentation DL and breath-holding or 10-second washout DL's in Subject 4 is due to the large contribution of the rapidly diffusing compartment in this individual. With such a compartment one could predict an underestimate of total DL when diffusion is estimated from carbon monoxide disappearance at a 10-second or longer interval. The results in Subject 4 are of interest, not so much for the absolute values of DL obtained, as for the demonstration of how great an error in DL might result from failure to account for DL/VA variability.

It is difficult to assess the reproducibility of the method under the test conditions applied to the human subject. Alterations in ventilatory rate, tidal volume or FRC would produce a change in the characteristics of the inert gas

washout curve and an alteration in ventilatory compartments. When ventilatory characteristics and lung volume remain perfectly constant (a condition obtained with controlled ventilation in the experimental animal), inert gas and carbon monoxide curves have shown almost no change on successive runs, and there has been no significant alteration in $F_{ET_{CO_\infty}}$. Therefore, under such controlled conditions, calculated compartments would be almost identical on successive tests. Thus far, we have been unable to control ventilation sufficiently in the human (even in trained subjects) to reproduce ventilatory characteristics exactly on successive runs with the large tidal volumes required. For this reason, no statistical evaluation of reproducibility has been attempted. In Subject 2, ventilatory characteristics were closely approximated on successive runs, and the calculated compartments from these two sets of data are indicated in Table I.

Non-uniformity of diffusion in patients. Five abnormal subjects have been studied by the techniques outlined; results are shown in Table I. Technically satisfactory records were also obtained on one additional patient with emphysema, but these data could not be resolved within the limits of the model described in the first paper of this series. The value for $F_{ET_{CO_\infty}}$ in this patient indicated rates of diffusion much lower than would be compatible with the rate of carbon monoxide disappearance during wash-

TABLE I

Summary of results

Subject	Diagnosis Age, Sex	Comp.	Compartment calculations $F\dot{v}$	V_A	D_L/V_A	D_L	Total D_L	D_L from Forster breath-holding method (10–12 sec)*	Estimate of D_L from 10 sec washout point
				L	*L*				
Normal subjects									
1	24, F	Y	0.37	0.22	31.8	6.9	21.1	23.5	15.3
		Z	0.63	1.69	8.4	14.2			
2	18, M	Y	0.40	0.40	28.0	10.8	37.8		
		Z	0.60	1.82	14.8	27.0			
		Y	0.39	0.35	30.2	10.6	32.1	32.0	37.2
		Z	0.61	2.03	10.6	21.5			
3	23, M	Y	0.20	0.25	16.1	3.9	31.2	32.0	31.0
		Z	0.80	3.82	7.2	27.2			
4	31, M	Y	0.39	0.49	44.8	22.1	48.3	31.3	26.0
		Z	0.61	2.32	11.3	26.2			
5	24 M	X	0.34	0.49	10.4	5.1			
		Y	0.60	2.74	9.1	24.9	30.3	30.0	24.7
		Z	0.06	0.26	1.1	0.3			
Patients									
6	Emphysema	X	0.09	0.14	0	0			
	52, M	Y	0.61	1.01	7.4	7.5	17.4	10.9	21.4
		Z	0.30	3.85	2.6	9.9			
7	Alv. cell carc.	Y	0.43	0.31	8.6	2.6	16.2	18.0	18.9
	59, M	Z	0.57	2.41	5.7	13.6			
8	Berylliosis	Y	0.31	0.27	5.7	1.5	9.9	13.2	10.2
	39, M	Z	0.69	2.05	4.1	8.4			
9	Sarcoidosis	Y	0.74	1.22	13.8	16.8	17.6	6.9	7.8
	32, M	Z	0.26	0.43	1.8	0.8			
10	Lung cyst	Y	0.64	1.36	8.5	11.6	16.9	19.5	14.3
	43, F	Z	0.36	2.38	2.2	5.3			

* Values represent an average of two to five determinations.

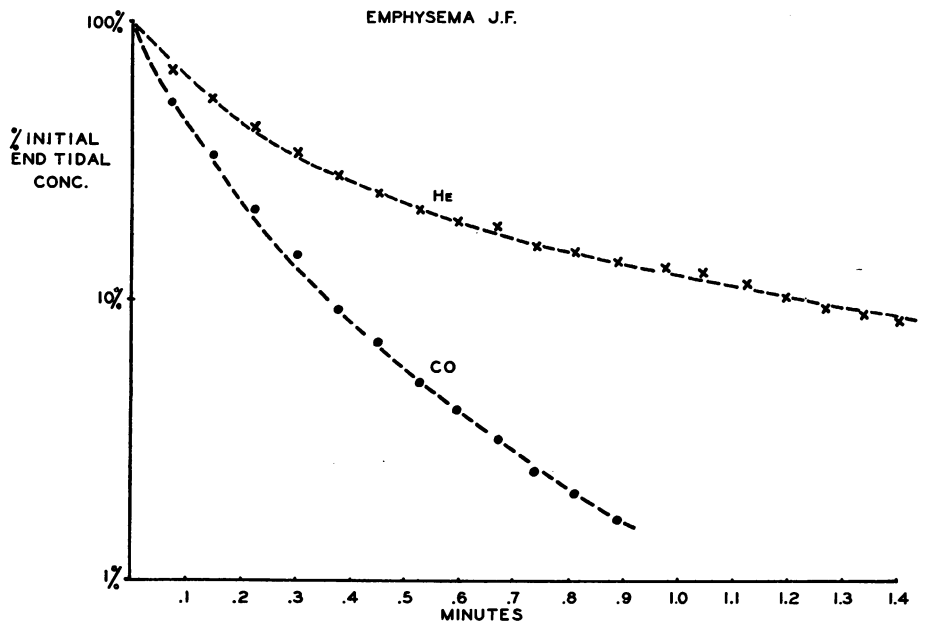

FIG. 3. END TIDAL HELIUM AND CARBON MONOXIDE VALUES OBTAINED DURING THE WASHOUT PERIOD IN PATIENT 6 (EMPHYSEMA) ARE PLOTTED SEMILOGARITHMICALLY AGAINST TIME. Gas concentrations are expressed as per cent of their concentration at zero time. The broken curves represent the theoretical end tidal values which would be predicted for a lung having the compartments calculated for this subject. Agreement of the calculated broken lines with experimental points indicates how closely calculated compartments explain obtained data.

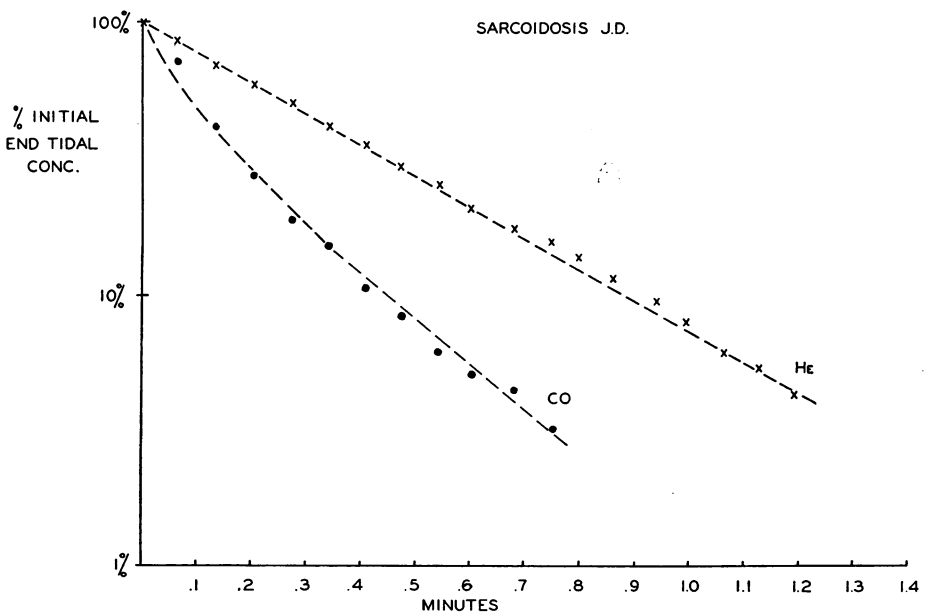

FIG. 4. END TIDAL HELIUM AND CARBON MONOXIDE VALUES OBTAINED DURING THE WASHOUT PERIOD IN PATIENT 9 (SARCOIDOSIS). Plotted as in Figures 2 and 3.

out. This result has not been adequately explained.

There is considerable variability in the results obtained in the remaining patients. In one case of berylliosis and in one of diffuse alveolar cell carcinoma there are only very slight calculated DL/VA variabilities. In these two patients there is reasonable agreement between DL's determined by equilibration and by breath-holding methods.

Case 6, with chronic obstructive emphysema, reveals marked variability in DL/VA, and data are explained by calculating a small, nondiffusing area of lung. In this subject, the breath-holding method yields a value for DL well below that from compartmental calculations. It is of interest that estimation of DL from 10 seconds of carbon monoxide washout yields an erroneously high DL. In Figure 3 carbon monoxide washout data for this subject are compared with theoretical washout points for his calculated compartments.

A patient with a lung cyst (Subject 10) revealed a large, poorly ventilated compartment with relatively poor diffusion. In this patient, breath-holding DL exceeds that from compartment calculations.

Subject 9, with widespread fibrosis due to pulmonary sarcoidosis, revealed a markedly impaired DL both by the breath-holding test and by the carbon monoxide fall-off at 10 seconds of washout. However, total DL from compartment calculations is 2.5 times as high as the breath-holding value. In this subject, a relatively small, poorly diffusing area of lung is apparently grossly overemphasized by the 10-second breath-holding test. Data on this subject are indicated in Figure 4.

Induction of non-uniformity of diffusion in the dog. In several experiments on thoracotomized anesthetized mongrel dogs whose respiration was controlled by a Harvard respirator pump, temporary occlusion of a main or lobar pulmonary artery by external compression produced a definite deflection in the carbon monoxide washout curve; concomitantly, there was a change in the end tidal carbon monoxide concentration achieved after equilibration with an inspired CO mixture ($FET_{CO\infty}$). With ventilation fully controlled, no change was noted in inert gas washout

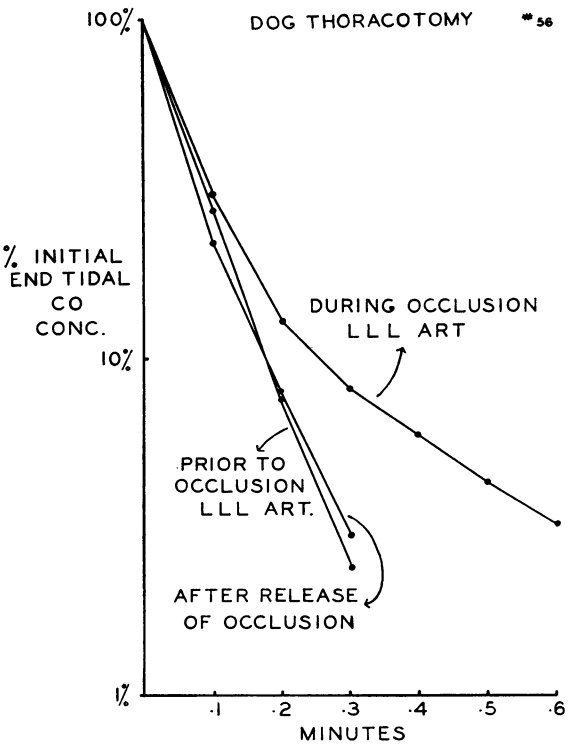

FIG. 5. CARBON MONOXIDE WASHOUT CURVES OBTAINED BEFORE, DURING AND AFTER TEMPORARY OCCLUSION OF THE PULMONARY ARTERY TO THE LEFT LOWER LOBE. Successive end tidal carbon monoxide concentrations are plotted semilogarithmically against time and are expressed as per cent of end tidal carbon monoxide concentration at zero time.

during these experiments, and the alterations in carbon monoxide could be interpreted directly in terms of changes in pulmonary diffusion. Under these circumstances, the linearity of successive end tidal carbon monoxide values plotted semilogarithmically against time is directly indicative of the uniformity of DL/VA throughout the lung. As noted in Figure 5, discernible non-uniformity of DL/VA was induced by temporary occlusion of a lobar artery; the effect was promptly reversed on release of the occlusion. The alterations induced by occlusion of a main pulmonary artery were more marked than were those with occlusion of a lobar vessel. From the data obtained, it seems likely that much smaller degrees of DL/VA non-uniformity than those induced by lobar artery occlusion would not be detected by the equilibration test, at least with present techniques.

DISCUSSION

The present investigations confirmed previous reports of D_L/V_A non-uniformity in the normal lung (4, 5, 7). Failure to demonstrate uneven diffusion by the equilibration test as originally employed (3) was probably due to technical limitations of the method and failure to obtain a regular breathing pattern with sufficiently large tidal volumes; with improved technique, D_L/V_A variability has been consistently noted. In our experience, a similar degree of non-uniformity of diffusion is noted with the equilibration test and Forster's breath-holding test when lung volume is controlled (7). It is possible to explain this unevenness of diffusion on the basis of poor perfusion of the superior portions of the lung due to hydrostatic effects, but further studies are needed to determine what other factors might be involved.

In order to assess the degree of non-uniformity of diffusion which may exist in the normal human lung, data obtained during carbon monoxide equilibration tests have been analyzed in terms of a lung model containing compartments which differ in their ventilatory and diffusing characteristics. The nature of the model is such that calculated D_L/V_A variability is minimized, a fact that must be considered in interpreting quantitative results. Also, the compartments calculated are not a unique solution to the data obtained and are mathematical concepts rather than representations of actual anatomical divisions of the lung. Within these limitations, the results in five normal subjects indicate that the lung behaves as though 6 to 18 per cent of its volume contained 12 to 46 per cent of its diffusing capacity, with D_L/V_A variations ranging from two- to fourfold. All results were obtained with subjects in a standing position.

It has been recognized that non-uniformity of D_L/V_A ratios throughout the lung might result in considerable error in the estimate of overall D_L by some of the conventional diffusion techniques (2). Comparing total D_L's determined by the compartment method with overall D_L's determined by the breath-holding method of Forster and colleagues (4), it would appear that the latter technique underestimates total diffusing capacity very slightly in most normal subjects when breath-holding periods of 10 seconds or longer are utilized. Except in one instance, this apparent underestimate was too small to be of practical significance. The one exception demonstrates that a sizable error might result even in a normal lung, the 10-second breath-holding test yielding a result 35 per cent lower than that of compartmentation calculations. A similar degree of underestimation of D_L resulted when equilibration data were analyzed by considering the carbon monoxide disappearance at 10 seconds of washout. Utilization of time intervals as long as 10 seconds causes an underestimate of the small, rapidly diffusing regions of lung—areas which could be of great importance in normal gas exchange.

Studies in patients reveal considerably more variation than those in normal subjects. Two patients (with diffuse alveolar cell carcinoma and berylliosis) showed almost uniform D_L/V_A ratios throughout the lung. Hydrostatic pressure differences throughout the lung, which may be of importance in producing D_L/V_A non-uniformity, may have been minimized in these subjects by a complicating pulmonary hypertension. However, this is speculation.

A patient with sarcoidosis and one with chronic obstructive emphysema revealed marked non-uniformity of D_L/V_A. In the case of sarcoidosis, a small, poorly diffusing portion of lung appears to have resulted in a gross underestimate of total D_L when carbon monoxide disappearance at 10 seconds was used as a basis for calculation. In the patient with emphysema, overall D_L was also seemingly underestimated by the breath-holding test. These examples serve to corroborate the theoretical considerations reviewed by Forster (2) concerning the possible errors in total D_L when there is marked non-uniformity of diffusion. One might seriously question the meaning of a conventionally determined diffusing capacity under these circumstances, since it is impossible to know whether one is obtaining an index of the best diffusing region or of the most poorly diffusing region of lung in an individual patient. Apparent changes in D_L with therapy or with altered physiological state could represent only a variation in emphasis of different lung regions rather than a true alteration in total pulmonary diffusing capacity.

In the patient with chronic obstructive emphysema, a small nondiffusing lung region was determined. Ventilation to this region may be equated with physiological dead space, exemplifying the interrelationship of measurements of ventilation, perfusion, and diffusion functions.

A patient with a lung cyst revealed a large, slowly diffusing compartment. Although it is tempting to correlate this with the radiologically demonstrable cyst, there is no proof of identity between the calculated compartment and any anatomical division of the lung.

It is important to consider the effect of D_L/V_A variability on certain applications of the breath-holding diffusing technique. Aside from the error induced in the absolute value for D_L, the phenomenon might lead to systematic errors in the relationship of D_L's obtained under various physiological states. For example, if carbon monoxide diffusion was slowed proportionally in all compartments when a high oxygen mixture was being inhaled, one would expect to decrease the underestimate of total D_L by the breath-holding method. This is due to the sampling of a relatively earlier and faster portion of the oxygen-slowed carbon monoxide disappearance curve when CO disappearance at 10 seconds is being considered. At the same time interval, the slower compartments would be more heavily represented if overall diffusion was rapid, as occurs while room air is breathed. The effect would be noted to some extent at almost any time interval employed and would lead to a systematic underestimate of the difference in D_L's at various oxygen tensions. When applied to the method of Forster and associates (8) and Roughton and Forster (9), this would lead to an underestimate of the membrane component of diffusion (D_M) and an overestimate of the effective pulmonary capillary blood volume (V_C).[2] This same phenomenon may also be of importance in comparing D_L's obtained under various conditions of ventilation or exercise.

It is possible to determine the non-uniformity of diffusing capacity to ventilation ($D_L/\dot{V}_A$) ratios as well as diffusing capacity to lung volume (D_L/V_A) ratios from the compartments calculated in the present report. This aspect has not been emphasized since the model on which calculations are based was not designed to demonstrate unevenness of $D_L/\dot{V}_A$. In assuming identity of the slowly ventilating compartment with the compartment having the lowest sum of ventilation and diffusion effects, the model reduces calculated $D_L/\dot{V}_A$ variations to a minimum possible value. As determined, unevenness of $D_L/\dot{V}_A$ varies from almost uniform ratios to threefold variations in normal subjects and from nearly uniform ratios to almost eightfold variations in the five patients studied. Four of five normal subjects showed *less* than 1.8-fold differences in $D_L/\dot{V}_A$ in different compartments, while four of five patients studied showed *greater* than 2.3-fold variations in $D_L/\dot{V}_A$ ratios. Unevenness of $D_L/\dot{V}_A$ ratios would be expected to produce a systematic underestimate of total D_L by the oxygen or carbon monoxide steady state techniques (2). Unfortunately, we have no steady state data on our subjects and therefore cannot directly assess the actual error in steady state D_L determinations due to this effect.

Considerable practical difficulty has been encountered in use of the equilibration technique in patients. The need for large tidal volumes and an absolutely regular breathing pattern has proved a decided disadvantage. Failure to obtain these ends produces an unsteady equilibration value for $F_{ET_{CO}}$ and makes calculations unreliable. It is partly for this reason that a larger series of patients has not been included in this report and that tests are difficult to reproduce in a given individual. In addition, the complexity of the calculations by the present

[2] In an attempt to assess the importance of the effect, carbon monoxide disappearance curves were obtained in several normal subjects at different oxygen tensions, using both equilibration tests and breath-holding tests at various time intervals. D_L's were then determined at each oxygen tension using a uniform percentile fall in alveolar carbon monoxide rather than a uniform time interval. This procedure should minimize any error in Vc due to D_L/V_A non-uniformity. In the normal subjects tested, Vc by this technique was not significantly smaller than that obtained by the conventional methods. Failure to observe the predicted difference is most likely due to the relatively slight D_L/V_A variability in most normal subjects and the relative crudeness of the measurements. Also, it is probable that diffusion is not affected proportionally by high O_2 tensions in the variously diffusing lung regions, causing an unpredictable error in Vc measurements. The phenomenon might be more apparent in the abnormal lung.

method makes the determination of compartments impractical as a routine clinical laboratory procedure. However, despite the limitations of the methods, the ability to analyze carbon monoxide data in terms of a non-uniformly diffusing lung should prove important in future studies of pulmonary diffusion. In theory, such an approach might reveal localized abnormalities in the alveolar-capillary membrane or pulmonary capillary bed before significant changes could be detected in overall DL. Also, such methods may add to the accuracy of total DL determinations. It seems likely that improvements in technique and mathematical approach can increase the sensitivity and accuracy of the methods described and add to their applicability.

Many of the difficulties noted in clinical application of the equilibration test may be circumvented in animal experiments, in which ventilation and lung volume are fully controlled. Under these circumstances, alterations in the degree of DL/VA non-uniformity are reflected directly in carbon monoxide washout curves, and data are highly reproducible on successive tests. For these reasons the method should prove useful in certain types of physiological experimentation.

SUMMARY

1. Data obtained during carbon monoxide equilibration tests are indicative of non-uniformity of diffusion throughout the lung, i.e., variable diffusing capacity to lung volume ratios.

2. Using an assumed lung model, diffusion has been quantified in terms of compartments which vary in their diffusing characteristics. In normal subjects, the lung behaves as though 6 to 18 per cent of its volume contained 12 to 46 per cent of its diffusing capacity. In four of five subjects, total diffusing capacity calculated by compartmentation methods was not significantly different from that calculated by the conventional breath-holding technique. In one normal subject, the breath-holding test may have markedly underestimated a rapidly diffusing area of lung.

3. In patients, variable degrees of diffusing capacity/lung volume non-uniformity were noted. This phenomenon appeared to produce an unpredictable error in the breath-holding method in abnormal subjects. It is believed that true overall diffusing capacity cannot be accurately assessed by conventional techniques in patients with marked pulmonary abnormalities.

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