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Research Article

VARIATIONS IN THE PULMONARY CAPILLARY BLOOD VOLUME AND MEMBRANE DIFFUSION COMPONENT IN HEALTH AND DISEASE *

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Forster, Roughton and their colleagues (1, 2) have reported a method of subdividing the components of the pulmonary diffusing capacity by measurement of the apparent diffusing capacity at different alveolar oxygen tensions. This development followed preparatory work by the same authors (3, 4) in which the kinetic factors involved in CO and hemoglobin combination were reported. The principles underlying the measurements have been fully discussed by Forster in a recent review (5).

Lewis, Lin, Noe and Komisaruk (6) reported on the measurement of pulmonary capillary blood volume in normal subjects, using the single breath method of determining the pulmonary diffusing capacity. They found average values of 65 ml for the pulmonary capillary blood volume at rest and 98 ml CO per minute per mm Hg for the membrane diffusion component. In four subjects both of these quantities increased somewhat during exercise. They did not report any results on patients. McNeill, Rankin and Forster (7), using a similar technique of measuring the pulmonary diffusing capacity by a single breath method, found similar values at rest for the pulmonary capillary blood volume, but a lower value for the membrane component, which was about 63.5 ml CO per minute per mm Hg in normal subjects at rest. These authors reported the results of this measurement in five patients with various types of pulmonary fibrosis, two with pulmonary hypertension, two with pulmonary congestion, and three with chronic obstructive emphysema. The most significant findings were the decrease in membrane diffusion component in patients with pulmonary fibrosis, and the increase generally found in pulmonary capillary blood volume in patients with increased pressure in the lesser circulation.

The present study reports the measurement of these two components of the pulmonary diffusing capacity by a steady state method during exercise in 14 normal subjects and in a group of 22 patients. This work was undertaken to study the reliability of the results obtainable with this technique, and to explore its usefulness in investigative work.

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METHODS

The apparatus used in this work has recently been described in full (8). A steady state measurement of diffusing capacity (D_L) is made, the mean alveolar CO tension being calculated from an assumed value of respiratory dead space. Technical details and a study of the errors of this method have been presented previously (8). The determination of pulmonary capillary blood volume (V_c) and membrane diffusion component (D_M) involves the measurement of the pulmonary diffusing capacity at two different oxygen tensions. Each experiment whether on a normal subject or a patient consisted in the measurement of the diffusing capacity on either 60 or 100 per cent oxygen, followed by its determination on air. All estimates were made during moderate or light exercise.

In a typical determination, the subject attained a steady state on the exercise treadmill for 5 minutes, and was then switched into either 60 or 100 per cent oxygen for a further period of about 5 minutes. At the end of this time, without interruption of the exercise, he was connected to the inspiratory bag which contained the same oxygen concentration as he had been breathing, with the addition of approximately 0.20 per cent CO. The inspired and expired gases were monitored in the manner described previously, and a careful note was made of the total time during which the subject breathed CO. The subject then rested on a chair, and during this time a sample of venous blood was drawn for the measurement of carboxyhemoglobin (COHb) by the technique of Lawther and Apthorp (9). With the treadmill in the same position and at the same speed, the subject then resumed his exercise, the sequence of events being timed as before, but on this occasion he was switched into a mixture of air containing about 0.12 per cent CO. Following the determinations of the inspired and mixed expired CO concentrations, the oxygen uptake was calculated using the monitored mixed expired CO_2 and oxygen in the manner previously described (8). The total experiment

with the two measurements of diffusing capacity took about 25 minutes. Values for D_L at each oxygen tension were not "pooled"; each experiment consisted in the double determination of D_L followed by the calculation of V_c and D_M values from these two points. This procedure was followed so that the standard deviation of repeat determinations would provide an indication of the likely error of a single determination of V_c and D_M based on one determination of D_L at each oxygen tension. A higher inspired CO concentration was used during the 100 per cent oxygen determination to lower the proportionate effect of "back pressure" of CO in relation to alveolar CO concentration.

CALCULATIONS

The pulmonary diffusing capacity was calculated from the $D_{CO_{IA}}$ as previously described (8) except that the COHb correction was slightly modified. Early experience with the method showed that the calculated values of V_c and D_M were very sensitive to this correction, and it was found necessary to calculate the mean COHb during the exercise run, rather than to use the COHb level measured at the end of exercise as the pertinent value. This change alters the calculated D_L by not more than one unit, but this is sufficient to affect the calculated V_c.

The corrected D_L was calculated as previously described by Linderholm's method (10). The circulating blood volume of the subject was calculated from the formulas: 32.18 cc per lb in males and 32.14 cc per lb in females.

The alveolar oxygen tension ($P_{A_{O_2}}$) was calculated from the Bohr alveolar gas equation using a mixed expired oxygen percentage of $(100 - F_{E_{CO_2}})$ or $(60 - F_{E_{CO_2}})$ depending on which oxygen mixture had been used. During the air diffusing capacity determination the measured mixed expired oxygen concentration was used in this calculation. Previous work from this laboratory (8) has supported the view of Asmussen and Neilsen (11) that the alveolar oxygen so calculated during exercise in normal subjects is reasonably accurate. The mean capillary oxygen tension ($\bar{P}_{C_{O_2}}$) was then calculated by the method described by Linderholm (10). A "λ value" of 2.5 (2, 3, 5) was assumed for all subjects. The function $1/\theta$ was calculated from the formula,

$$1/\theta = [(0.0057 \times \bar{P}_{C_{O_2}})] + 0.75,$$

which was derived from Figure 1 (2).

The pulmonary midcapacity during exercise was calculated by adding half the tidal volume to the measured resting functional residual capacity (FRC), a technique shown to give a reasonably accurate estimate of this figure during exercise (8).

The V_c and the D_M were then calculated by solving the equation $1/D_{L_{CO}} = 1/\theta V_c + 1/D_M$ for the two determinations of pulmonary diffusing capacity at the two oxygen tensions. It will be appreciated that this calculation necessarily involves the assumption that the switch

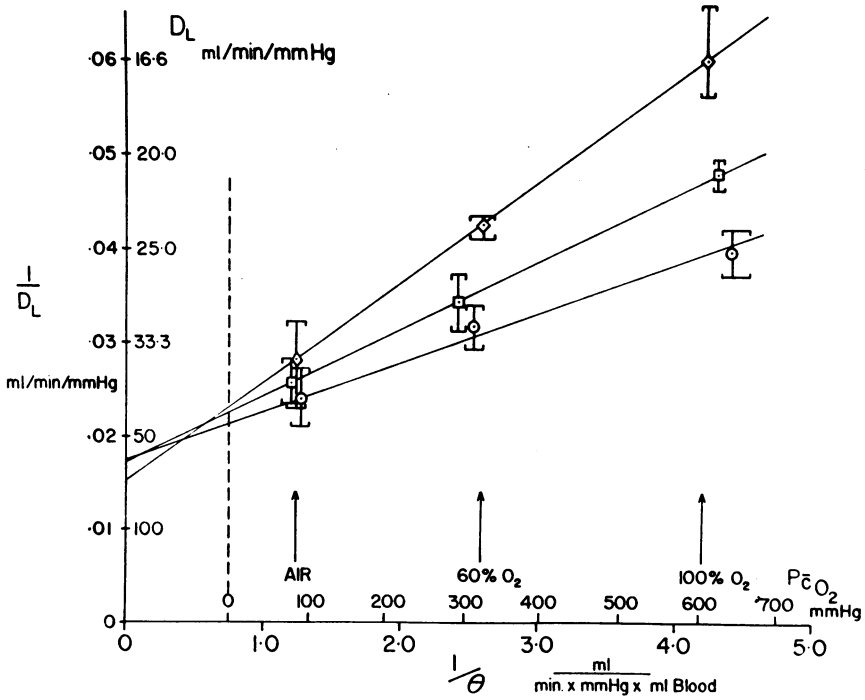

FIG. 1. RELATIONSHIP BETWEEN $1/D_L$ AND MEAN ALVEOLAR CAPILLARY OXYGEN TENSION ($\bar{P}_{C_{O_2}}$) IN SUBJECTS RED ⊡, CJV ⊙, and DVB ◇. The lines about the mean values represent the actual ranges of the observation of D_L and $\bar{P}_{C_{O_2}}$ in these subjects, all of whom were exercising at 3 mph on a flat surface.

from air to oxygen has not changed the pulmonary capillary bed significantly, nor altered the nature or area of the pulmonary membrane.

Very accurate determinations of D_L are required if variability in the calculated pulmonary capillary blood volumes and membrane components is to be avoided. An important precaution is the avoidance of contaminated CO mixtures as mentioned previously (8), and accuracy in the determination of COHb. The correction due to this factor becomes considerable if a heavy smoker is studied, and is more significant when he is breathing oxygen than air. We have found that the calculated back tension of CO must not be allowed to exceed more than 15 per cent of the alveolar CO pressure if considerable errors in the determined value of V_c are to be avoided. When heavy smokers are studied, the inspired CO percentage may have to be increased to 0.30 per cent during the 100 per cent oxygen determination to keep the calculated back CO tension less than 15 per cent of the alveolar CO tension.

RESULTS

Normal subjects. The results are shown in Tables I through VIII, and in Figure 1. In Table I are shown the physical characteristics of the 14 normal subjects studied, together with the results of resting pulmonary function tests. The ages of these subjects varied from 24 to 46. The resting pulmonary function tests were all within predicted limits. In Table II are shown the results of determinations of pulmonary capillary blood volumes and membrane diffusion components in four of these subjects. At a speed of 3 mph with the treadmill flat, a total of 20 determinations was made on these four subjects, all on different days, and four observations were made on Subject DVB at 3 mph on a 10 per cent treadmill grade. The ranges of variation together with the mean values are shown in this table and below each column are the standard deviations of the observations. The extreme right-hand column of this table shows the number of estimations done on 100 or 60 per cent oxygen on each individual. The most variable results were in the determination of V_c in Subject RED. One determination was double another at approximately the same oxygen uptake and this led to the finding of a high standard deviation for the five observations recorded. If this single result be omitted, the standard deviations are less than $\pm$ 12.5 for the determination of V_c on these four subjects. It is clear from the data that there are significant differences in the mean values of V_c between different normal subjects, those, for instance, in LSB being uniformly and significantly lower than those in CJV or RED. There is less variability and rather less variation between individuals in the measured D_M, and the differences in this component disappear when it is related to lung volume (D_M/MC). The V_c is still significantly different after this correction, however (V_c/MC). In Subject DVB, an increase in exercise resulted in a significant increase in the over-all D_L on air (D_L/air), and in V_c, but there was no change in D_M. This suggests that the increased D_L on exercise is mainly accounted for by an increase in V_c, though this conclusion might not necessarily be applicable to the transition from rest to exercise.

In Table III, the subjects who are below 35

TABLE I

*Physical data and results of resting pulmonary function tests in normal subjects**

No.	Subject	Sex	Age	Ht	Wt	VC	FRC	ME%	MMFR
				in	*lbs*	*L*	*L*		*L/sec*
1	RED	M	30	70½	165	4.97	3.18	67	3.92
2	CJV	M	29	71½	195	5.04	2.92	78	4.60
3	FM	M	28	74	205	5.77	3.77	60	6.80
4	GW	M	34	69½	168	4.91	3.54	66	5.90
5	DP	M	24	72½	182	5.04	3.60	71	5.00
6	RF	M	25	65	137	4.40	2.28	71	6.00
7	JE	M	31	71	186	(4.10)	(3.20)		
8	DVB	M	37	70	180	3.33	2.75	92	3.41
9	LSB	M	41	66½	168	3.00	3.26	58	3.50
10	REF	M	39	74	165	(4.40)	(3.50)		
11	WF	M	44	68	163	4.45	2.91	52	2.80
12	JAP	M	42	75	193	4.00	3.21	58	3.90
13	REGP	M	46	66½	173	3.58	1.72	53	3.00
14	JB	M	45	72	211½	4.95	3.02	91	7.00

* VC = vital capacity; FRC = functional residual capacity; ME % = closed circuit helium mixing index; MMFR = maximal midexpiratory flow rate. Results shown in parentheses have been predicted from the subject's height.

TABLE II

*Results of repeated estimates of pulmonary capillary blood volume (V_c) and membrane diffusion component (D_M) in four normal subjects**

Subject	Rate	Grade	Minute vol	V_{O_2}	$\dot{V}_{O_2}/\dot{V}_{air}$	D_{LCO} (air)	V_c	D_M	D_{LCO}/MC	V_c/MC	D_M/MC	No. of estimations
	mph		*l/min*	*l/min*			*ml*					
DVB												
Mean†	3	10%	43.6	1.68	3.42	39.3	122	62.0	9.62	29.6	15.3	100% O_2 × 3
			49.2	1.90	3.86	41.0	131	64.2	10.1	32.3	15.8	60% O_2 × 1
			53.5	2.22	4.17	43.9	135	68.0	11.0	33.9	16.4	Total = 4
SD ±			3.6	0.19	0.31	1.34	5.25	2.36	0.53	1.64	0.5	
			25.7	1.10	3.85	32.5	81	52.2	8.6	20.1	14.5	100% O_2 × 3
Mean	3	Flat	28.4	1.21	4.26	35.3	96	66.5	9.2	25.3	17.4	60% O_2 × 3
			30.2	1.29	4.63	38.6	109	87.0	9.91	30.3	21.5	Total = 6
SD ±			1.45	0.07	0.26	2.34	11.1	11.4	0.40	3.39	2.5	
RED												
			22.8	1.13	5.37	35.3	122	45.3	9.21	31.3	11.9	100% O_2 × 2
Mean	3	Flat	25.3	1.21	4.79	38.8	163	58.2	10.0	42.0	15.0	60% O_2 × 3
			27.4	1.33	4.17	44.0	261	75.7	11.10	67.5	19.1	Total = 5
SD ±			1.53	0.08	0.43	3.0	50.4	11.8	0.65	13.2	2.84	
CJV												
			28.1	1.21	3.17	37.0	182	47.0	9.05	46.8	11.6	100% O_2 × 3
Mean	3	Flat	31.7	1.27	4.01	41.5	200	56.8	10.3	49.4	14.0	60% O_2 × 2
			39.1	1.38	4.42	46.8	214	67.2	11.5	52.7	16.5	Total = 5
SD ±			3.82	0.06	0.46	4.2	12.5	8.1	1.04	2.2	2.1	
LSB												
			21.1	0.98	4.02	20.2	58.0	38.5	6.85	19.7	13.1	100% O_2 × 2
Mean	3	Flat	23.7	1.04	4.39	22.1	68	40.2	7.5	22.9	13.9	60% O_2 × 2
			24.9	1.14	4.80	23.9	80.2	43.1	7.96	26.6	14.4	Total = 4
SD ±			1.21	0.06	0.30	1.6	8.45	1.55	0.43	24.8	5.2	

* Columns 9, 10 and 11 show the values given in the preceding three columns divided by the exercise midcapacity in liters. The final column shows the number of estimates done on air and 100 per cent oxygen, or on air and 60 per cent oxygen on each subject. $\dot{V}_{O_2}$ = oxygen consumption; $\dot{V}_{O_2}/\dot{V}_{air}$ = oxygen consumption per liter ventilation; D_{LCO} = diffusing capacity of the lung for CO; MC = ventilated lung volume.

† Figures above and below the mean value indicate the range of observations.

years of age have been grouped together for convenience so that their data may be compared to those of the normal subjects over 35 years of age shown in Table IV. The difference in D_{LCO} between these two groups, 37.4 in the younger and 30.5 in the older, is significant at the 2 per cent level, confirming work previously reported from this laboratory (8). However, the differences of 20 ml in V_c and 7.9 in D_M are not statistically significant in these small groups of subjects. More work will be required before the cause of the lowered D_L with age can be confidently attributed either to changes in V_c or D_M or both.

Validation of the theoretical considerations underlying this technique requires that the relationship between $1/D_L$ and $1/\theta$ should be linear.

TABLE III

*Determinations of pulmonary capillary blood volume and membrane diffusion components on seven normal subjects below the age of 35**

No.	Subject	Minute vol	$\dot{V}_{O_2}$	$\dot{V}_{O_2}/\dot{V}_{air}$	D_{LCO} (air)	D_{LCO} (O_2)	V_c	D_M	D_{LCO}/MC	V_c/MC	D_M/MC
		L	*L/min*				*ml*	*ml CO/min/mmHg*			
1	RED	25.3	1.21	4.79	38.8	21.4	163	58.2	10.0	42.0	15.0
2	CJV	31.7	1.27	4.01	41.4	25.2	200	56.8	10.3	49.5	14.1
3	FM	27.8	1.42	4.80	45.3	26.7	199	62.3	9.3	40.5	12.7
4	GW	31.9	1.11	3.38	39.7	22.2	152	60.2	9.1	34.7	13.7
5	DP	22.6	1.10	4.70	30.9	18.9	150	41.2	6.9	33.6	9.2
6	RF	25.9	1.01	3.41	29.0	15.9	104	45.0	8.5	30.2	13.1
7	JE	36.2	1.89	4.31	37.0	18.1	105	60.0	8.8	24.9	14.3
		22.6	1.01	3.38	29.0	15.9	104	41.2	6.9	24.9	9.2
	Mean†	28.8	1.29	4.20	37.4	21.2	153	54.8	9.0	36.5	13.2
		36.2	1.89	4.79	45.3	26.7	200	62.3	10.3	49.5	15.0
	SD	±4.35	±0.27	±0.57	±5.32	±3.12	±36.1	±7.7	±1.0	±7.5	±1.76

* All estimates done on exercise at 3 mph on a flat surface. Column headings are as in Table II.

† Figures above and below the mean value indicate the range of observations.

TABLE IV

*Determinations of pulmonary capillary blood and membrane diffusion components in the seven normal subjects above the age of 35**

No.	Subject	Minute vol	$\dot{V}_{O_2}$	$\dot{V}_{O_2}/\dot{V}_{air}$	D_{LCO} (air)	D_{LCO} (O_2)	V_c	D_M	D_{LCO}/MC	V_c/MC	D_M/MC
		L	*L/min*				*ml*	*ml CO/min/mmHg*			
8	DVB	28.4	1.21	4.26	35.2	16.7	96	66.5	9.2	25.3	17.4
9	LSB	23.7	1.04	4.39	22.1	11.9	68	40.2	7.4	22.9	13.7
10	REF	26.8	1.30	4.21	35.3	22.0	180	46.7	8.1	41.2	10.6
11	WF	27.6	1.03	3.51	32.6	17.4	114	51.7	6.9	24.4	11.1
12	JAP	25.8	1.18	4.11	30.2	19.8	176	46.0	7.9	38.2	10.0
13	REGP	29.5	1.17	3.83	22.5	12.5	83	33.1	9.1	33.4	13.4
14	JB	24.7	1.23	4.65	35.5	23.4	214	44.2	9.5	56.9	11.8
		23.7	1.03	3.51	22.1	11.9	68	33.1	7.4	22.9	10.0
	Mean†	26.6	1.17	4.14	30.5	17.6	133	46.9	8.3	34.6	12.6
		29.5	1.30	4.65	35.5	23.4	214	66.5	9.5	56.9	17.4
	SD	±1.89	±0.09	±0.28	±5.2	±4.18	±52	±9.6	±0.92	±11.2	±2.33

* Column headings are as in Table II.
† Figures above and below the mean value indicate the range of observations.

This relationship in Subjects DVB, CJV and RED is shown in Figure 1. The slope of the lines reflects the V_c component, and from the intercept, D_M is calculated. The general linearity of the points in any one individual is clear from this figure. The values of V_c and D_M calculated from these slopes appear in Table II. The data in Figure 1 have been used to predict the D_L at different values of $\bar{P}_{CO_2}$ in the same three normal subjects during hypoxia, during voluntary hyperventilation, and during CO_2 breathing. In Table V are shown the results of measurements of D_L under these conditions in which little deviation could be demonstrated from the values of D_L predicted on the basis of Figure 1. This conclusion is discussed in detail later.

Patients. In Table VI are shown the physical characteristics of the first two groups of patients studied. Group 1 consisted of three patients who had had various parts of the lung removed, with

TABLE V

Effect of hyperventilation and hypoxia during exercise at 3 mph on a flat surface

Subject	Rate and grade	Experiment	Ventilation	Inspired oxygen% F_{IO_2}	Mean capillary O_2 $\bar{P}_{CO_2}$	Measured D_{LCO}	Predicted D_{LCO}*
			L/min			*ml CO/min/mm Hg*	
DVB	3 mph Flat	Hypoxia	44.3	10.7	22.0	41.8	41.2
		Hypoxia	40.5	12.4	30.9	43.5	40.6
		Hypoxia	35.6	12.8	34.9	39.4	39.7
		Hypoxia	32.3	15.0	39.9	32.6	39.3
		Hyperventilation	47.5†	20.8	96.3	36.0	34.8
		5.8% CO_2	48.3†	20.8	106.7	34.5	33.9
RED	3 mph Flat	Hypoxia	37.4	11.0	29.5	52.2	42.5
		Hypoxia	39.6	11.6	30.2	47.4	42.3
		Hyperventilation	51.3†	20.8	102.8	43.8	36.7
		5.8% CO_2	56.1†	20.8	95.5	46.4	37.7
CJV	3 mph Flat	Hypoxia	33.7	10.8	25.0	40.4	44.8
		5.8% CO_2	61.5†	20.8	113.2	45.0	40.7

* This column indicates the D_{LCO} predicted for the individual at the measured $\bar{P}_{CO_2}$ (see Figure 1).
† See Table II for results at normal ventilations in these subjects.

TABLE VI

*Physical characteristics and resting pulmonary function tests in Groups 1 and 2 of the patients studied**

No.	Subject	Sex	Age	Ht	Wt	VC	FRC	ME%	MMFR	Diagnosis
				in.	*lbs*	*L*	*L*		*L/sec*	
	Group 1									
15	M FEN	F	50	65½	133	1.98	1.27	39	1.80	Pneumonect. L
16	J COT	M	41	69½	157½	2.12	1.87	47	1.50	Pneumonect. R
17	V RIC	F	27	68½	96½	1.41	2.13	33	0.52	Use of only rt. upper lobe
	Group 2									
18	A MAD	F	38	65	122					Thyrotoxicosis
19	G KOS	F	32	65½	120					Thyrotoxicosis
20	F BOU	M	35	64¼	132	2.80	2.72	64	1.31	Atr. sept. defect
21	I GAL	F	22	63	78	2.20	2.42	60	2.70	Atr. sept. defect
22	F ATK	F	30	63¼	100½	2.35	2.42	64	2.25	Pat. duct. art.
23	T NAD	M	20	69	155					Pat. duct. art.
24	A McC	M	37	71	152	1.65	3.32	34	1.10	Pat. duct. art.
25	H WAH	M	25	71½	149	2.96	2.78	67	1.30	Tric. atresia

* See Table I for details of column headings.

a reduction in FRC as a consequence. Group 2 consisted of a group of eight patients in all of whom there was reason to suppose that the pulmonary blood flow was abnormal; two of these patients had untreated thyrotoxicosis, two had atrial septal defects with high pulmonary blood flows, three had a patent ductus arteriosus with considerable increase in pulmonary flow in each case, and the last patient had tricuspid atresia with a reduction in cardiac output at rest as shown by cardiac catheterization. The results of determinations of V_c and D_M on these patients are shown in Table VII. In each case the exercise managed by the patient is shown in the second column and the minute volume and oxygen uptake are adjacent. The two patients who have had a pneumonectomy showed considerable variation in pulmonary capillary blood volume, though both values may be considered to be within half the approximate normal range. The membrane components are very constant and again are about half the predicted normal values for these subjects. The membrane component in relation to ventilated lung volume is slightly below the predicted values in these patients and the V_c in relation to lung volume appears to be normal in the first two patients and definitely reduced in the third (Patient 17). These findings are of some interest since

TABLE VII

*Results of determinations of pulmonary capillary blood volume and membrane diffusion components in patients in Groups 1 and 2**

Subject	Diagnosis	Rate†	Minute vol	$\dot{V}_{O_2}$	$\dot{V}_{O_2}/V_{air}$	D_{LCO} (air)	D_{LCO} (O_2)	V_c	D_M	D_{LCO}/MC	V_c/MC	D_M/MC
		mph	*L/min*	*L/min*				*ml*				
Group 1												
15 M FEN	Pneumonect. L.	1.5	19.90	0.80	4.00	12.3	6.5	47	14.9	6.3	24.0	7.6
16 J COT	Pneumonect. R.	2	21.60	1.05	4.85	16.7	11.1	103	19.3	7.3	44.0	8.4
17 V RIC	Use of only rt. upper lobe	1.5	15.67	0.53	3.38	11.5	6.0	38	18.3	4.7	15.3	7.5
Approx normal		3	21–31	1.0–1.9	3.5–4.8	22–45	12–27	68–200	33–66	6.9–10.5	24–56	9–17
Group 2												
18 A MAD	Thyrotoxicosis	1.5	18.65	0.73	3.91	17.3	11.6	111	21.2	6.9	44.3	8.5
19 G KOS	Thyrotoxicosis	2	20.50	0.88	4.29	19.5	11.0	79	27.6	7.1	28.9	10.1
20 F BOU	Atr. sept. defect	1.5	21.60	0.60	2.78	31.0	19.6	164	41.7	9.9	52.4	13.3
21 I GAL	Atr. sept. defect	2	22.65	0.55	2.43	30.2	18.6	150	41.7	10.4	51.5	14.4
22 F ATK	Pat. duct. art.	1.5	17.30	0.54	3.12	21.5	13.2	112	27.6	7.6	39.7	9.8
23 T NAD	Pat. duct. art.	2	24.85	0.97	3.90	22.7	14.1	113	30.0	6.8	34.0	9.0
24 A McC	Pat. duct. art.	1.75	35.60	1.09	3.06	21.9	13.7	109	29.0	5.5	36.3	7.5
25 H WAH	Tric. atresia	2	34.10	0.62	1.82	23.9	12.7	83	40.0	7.0	24.3	11.7

* See previous tables for details of column headings.
† All estimates done on exercise at rate shown on a flat surface.

TABLE VIII

*Physical data and resting pulmonary function tests in patients in Groups 3 and 4**

No.	Subject	Sex	Age	Ht	Wt	VC	FRC	ME%	MMFR	Diagnosis
				in.	*lbs*	*L*	*L*		*L/sec*	
	Group 3									
26	M LED	F	31	63	150					MS
27	H LAP	F	42	59½	79	1.95	2.34	40	1.27	MS
28	E MOF	F	34	57¾	102	2.50	2.37	67	3.50	MS
29	M HEA	F	46	62	104	2.16	2.51	59	2.20	MS
30	P MOL	M	19	70	155	3.94	2.83	50	5.70	MS + I
	Group 4									
31	E RYL	F	50	61	117½	1.45	1.58	48	1.40	DIF
32	E St.L	M	50	65	170	3.42	3.26	43	1.20	DIF
33	V AYB	F	48	64	140	1.87	1.41	59	2.40	DIF
34	S ARN	F	64	65	162	1.43	1.75	59	0.75	DIF
35	T LAV	F	46	63	113	1.70	2.38	52	2.50	BS
36	D BOU	F	15	67	116	2.75	3.07	63	2.70	BS

* See Table I for details of column headings. MS = mitral stenosis; MS + I = mitral stenosis + insufficiency; DIF = diffuse interstitial fibrosis; BS = Boeck sarcoid.

there is no evidence that the V_c of the remaining lung approximates that of the two lungs, although presumably it has a high pulmonary blood flow. The membrane components have been universally lowered by removal of one lung, as would be expected. Patients 18 to 24 may be presumed to have an increased pulmonary flow. The cardiac output is known to be much increased in untreated thyrotoxicosis during exercise (12), and a high resting pulmonary flow had been confirmed by cardiac catheterization in Patients 20 to 24. Patient 25 with tricuspid atresia was found at cardiac catheterization to have a cardiac index of half the predicted value. Consideration of the results in Group 2 as a whole shows that there is no evidence that an abnormally high or low pulmonary blood flow during exercise causes a change in V_c since all measurements of V_c in this group are within the predicted range. It is perhaps of interest that the membrane diffusing components (D_M/MC) were somewhat lower than expected in Patients 18 and 24, which might suggest that in some of these conditions there is an impairment of diffusion across the membrane resulting from the persistent high blood flow. In Table VIII are shown the physical characteristics and results of resting pulmonary function tests in patients in Group 3 and 4. Group 3 consists of four pa-

TABLE IX

*Results of determinations of pulmonary capillary blood volume and membrane diffusion component in patients in Groups 3 and 4**

Subject	Diagnosis	Rate†	Minute vol	$\dot{V}_{O_2}$	$\dot{V}_{O_2}/\dot{V}_{air}$	D_{LCO} (air)	$D\dot{V}_{CO}$ (O_2)	V_c	D_M	D_{LCO}/MC	V_c/MC	D_M/MC
		mph	*L/min*	*L/min*				*ml*				
Group 3												
26 M LED	MS	1.5	19.80	0.82	4.12	26.9	17.4	152	34.8	10.0	56.4	12.9
27 H LAP	MS	2	18.80	0.53	2.82	12.9	11.3	293	13.7	4.8	110.0	5.1
28 E MOF	MS	1.5	20.16	0.64	3.17	18.7	15.4	275	20.5	6.9	101.5	7.6
28 E MOF	MS post op.	1.5	13.63	0.60	4.36	21.3	11.9	84	31.3	8.1	31.1	11.5
29 M HEA	MS	1	26.60	0.53	2.00	14.3	7.7	50	23.0	4.8	16.9	7.7
30 P MOL	MS, MI	2	22.35	0.94	4.19	25.6	13.8	93	38.7	7.7	28.3	11.8
Approx normal		3	21–31	1.0–1.9	3.5–4.8	22–45	12–27	68–200	33–66	6.9–10.5	24–56	9–17
Group 4												
31 E RYL	CDIF	1.5	15.20	0.61	4.01	8.9	7.8	21	9.4	6.0	13.7	6.3
32 E St.L	CDIF	1.75	27.80	1.13	4.07	15.2	11.4	140	17.2	3.8	35.0	4.3
33 V AYB	CDIF	2	30.00	0.69	2.30	7.9	4.8	36	10.4	4.4	19.6	5.7
35 S ARN	CDIF	0.75	24.50	0.59	2.41	6.8	3.5	20	10.4	3.3	9.8	5.0
35 T LAV	BS	1.5	20.40	0.72	3.53	17.8	6.8	36	45.9	6.4	13.0	16.5
36 D BOU	BS	2	16.55	0.77	4.66	21.1	12.0	84	30.0	8.6	34.3	12.3

* See previous tables for details of column headings. MS = mitral stenosis; CDIF = chronic diffuse interstitial fibrosis; BS = Boeck sarcoid.
† All estimates done on exercise at rate shown on a flat surface, except those for Subject 36 who exercised on a surface with a 5 per cent slope.

tients with mitral stenosis and one with mitral stenosis with predominant mitral insufficiency. In Group 4 are four patients with chronic diffuse interstitial pulmonary fibrosis (in whom the diagnosis has been confirmed by lung biopsy in three), and two patients with sarcoid of the lung (in both of whom the diagnosis has been confirmed by lung biopsy). Table IX shows the results of determination of V_c and membrane components in these patients. In Patients 27 and 28, both of whom represented typical examples of tight mitral stenosis with considerable dyspnea and a reduced pulmonary compliance, the values of V_c are high, and those for the D_M are low. Patient 28 was studied three weeks after a successful valvotomy, at which a very tight valve was found. On each occasion the level of exercise was the same, and there was an increase in $\dot{V}o_2/\dot{V}_{air}$ after surgery from 3.17 to 4.36, in conformity with the observations of Cotes (13), and MacIntosh, Sinnott, Milne and Reid (14). There was a slight increase in over-all D_L from 18.7 to 21.3, but this small change masks considerable alterations in V_c and D_M. The V_c fell from 275 to 85 ml after surgery, and the membrane component rose from 20.5 to 31.3. Patient 29 had the murmur of mitral stenosis, but was judged to be so little incapacitated that surgery was not indicated. The pulmonary compliance in this patient was within normal limits (0.190 L per cm H_2O). It is of particular interest, therefore, that the V_c was normal, although there was a slight reduction in D_M. In Patient 30, who had predominant mitral incompetence, the values for V_c and D_M were within normal limits.

In Group 4 the changes are those one would expect to find in patients whose main difficulty is the transfer of oxygen across the pulmonary membrane. The D_M is reduced in all patients in the pure pulmonary fibrosis group (Patients 31 to 34), and the extent of this reduction can be seen from comparison of D_M in relation to ventilated lung volume in the last column. The values found in these four patients vary between 4.3 and 6.3 for this figure (D_M/MC) whereas the normal range is from 9 to 17, approximately. Patients 35 and 36, with sarcoidosis, show considerable variation, the former having a normal D_M but a low value of V_c, and the latter having a normal V_c and a nearly normal D_M. These variations in this condition are to be expected, and the low V_c found in Patient 35 may reflect the fact that the main brunt of the lesion has been perivascular, as has been suggested by a number of authors (15, 16) for this condition. It is of interest, however, that the considerable difference in V_c between these two patients is not reflected by much difference in the over-all D_L.

DISCUSSION

The data so far reported on the subdivision of the pulmonary diffusing capacity into its two components have been obtained by use of a single breath method (5–7). Apart from the objection that the holding of a deep breath may modify the quantities it is desired to measure, the single breath is difficult to manage during exercise. It is now generally recognized that the mean alveolar CO tension may be reliably measured during exercise in a steady state experiment, at least in subjects with normal gas distribution (8).

The present studies show that the components of pulmonary diffusion capacity may be reliably measured by this technique during steady state exercise, and the theoretical work of Forster and his colleagues has been confirmed by the demonstration under these conditions of a linear relationship between $1/D_L$ and $1/\theta$ (see Figure 1). It seems likely that the differences in the rate of gas diffusion between individuals at the same rate of exercise are mainly attributable to variations in the V_c. The D_M, when expressed in relation to the volume of lung being ventilated, appears to be relatively constant in normal subjects at the same exercise level. The relative importance of these two factors is well illustrated by comparison of normal Subjects 2 and 6 in Table III. At the same exercise rate, the over-all D_L was 12 units greater in Subject CJV; V_c in CJV was approximately twice that in Subject 6, yet the D_M expressed in relation to lung volume was only 1 unit different between these two subjects. There was a large difference in V_c expressed in relation to the ventilated lung volume illustrating that the principal difference between these two subjects lay in this component rather than in the membrane component. Although these two subjects were the same age (see Table I), there was a 6 inch difference in height and a 60 pound difference in weight between them. There was only a 600 ml difference in vital capacity and a 700 ml difference in

FRC. The constancy of the results obtained in duplicate estimates of V_c and membrane components in the present study (Table II) may be compared to that reported by Lewis and associates (6) using the single breath technique. His data show less variation in V_c on repeat determinations, but the D_M showed more variation than that found in the present study. The reason for these differences is not altogether clear, but may reside in the errors inherent in the two techniques.

It may be pointed out, however, that provided the tidal volume is comparable during the two determinations of D_L, the value assumed for the respiratory dead space exerts no effect on the calculated V_c. Consequently, with a steady state technique of the type used, this subdivision of the D_L may be more reliably measured than the calculated D_M, which is affected by the value assumed for the dead space.

Ross, Frayser and Hickam (17), using the Filley method of calculating the mean alveolar CO tension, reported large increases in D_{LCO} with hyperventilation. These authors also suggested that much of the increase in D_{LCO} on exercise is to be attributed directly to the ventilation change. The data in Table V indicate that the observed values of D_{LCO} under conditions of hypoxia, voluntary hyperventilation, or CO_2 breathing, differ little from those that would be predicted for the individual concerned at the particular alveolar oxygen tension obtaining during the experiments. In only one subject (RED) did the observed values fall consistently above the predicted figures. No effect was demonstrable in the other two subjects. These results suggest that during exercise, neither hypoxia nor an increase in ventilation per se, causes any consistent or considerable alteration in the state of the pulmonary bed. The discrepancy between these observations and those of Ross and co-workers (17) and Turino, Brandfonbrener and Fishman (18), are not readily explained. Both authors reported striking increases in D_L during hyperventilation when the alveolar CO tension was computed from the measured arterial CO_2 tension. Such increases are not found if the end tidal CO is directly measured or if the mean alveolar CO is calculated, using a predicted value of respiratory dead space.

Forster (5) considered that anoxia might well change the pulmonary capillary bed, but if this were the case, the observed D_{LCO} in Table V under these conditions might be measurably greater than that predicted on the basis of the linear relationship shown in Figure 1. The precision of the data in Figure 1 in respect to these three normal subjects suggests that the line of observed relationship between $1/D_L$ and $1/\theta$ can be extrapolated confidently to cover low oxygen tensions, though θ values may not be reliable at capillary oxygen tensions below 150 mm Hg (2). The finding of little discrepancy between observed and predicted figures indicates that the effect of anoxia is probably slight, at least in short-term experiments on exercise, but more precise conclusions cannot be drawn from the data at this stage.

The study of the 22 patients in the present series leads to the following general conclusions.

1. When portions of the lungs are removed, D_M is proportionately reduced. The V_c of the remaining lung seems variable. The general result is that the over-all D_L is about that predicted for one lung, as was found in previous studies of McIlroy and Bates (19) and Linderholm (20). There does not appear to be any considerable increase in the V_c of the remaining lung in relation to its gas volume, although presumably the pulmonary blood flow through the lung is substantially increased.

2. In long-standing conditions in which the pulmonary blood flow is greatly increased, there is no concomitant increase in V_c. This conclusion is somewhat at variance with that of Auchincloss, Gilbert and Eich (21), who used the single breath D_L technique at rest to study patients with congenital and acquired heart disease. These authors found an increased D_L at rest in some patients in the congenital heart disease group, but they did not report any exercise results. Their findings are therefore not necessarily at variance with the present conclusion that the exercise D_M and V_c are not increased in these patients compared with those of normal subjects. The possibility exists that the taking and holding of a single breath by patients with large intracardiac shunts may significantly alter the state of the pulmonary bed. The finding of a lowered D_M in Patients 23 and 24 may well reflect irreversible changes secondary to the pulmonary hypertension, since the two patients with primary pulmonary hypertension studied by McNeill and associates (7) showed a de-

crease both in D_M and in V_c. The pulmonary diffusing capacity in thyrotoxicosis has been noted previously to be normal or lower than normal, even though the pulmonary blood flow is considerably elevated.[1] The two patients with untreated thyrotoxicosis included in the present study illustrate this finding. The predicted D_{LCO} for these two patients at the exercise level they maintained is 27 and 31 ml CO per minute per mm Hg, respectively (8), whereas the measured figures were 17.3 and 19.5. The D_M was reduced in the first of these patients and was clearly limiting the rate of gas diffusion considerably. In the second patient it was just below the approximate normal level. In neither patient was there any increase in V_c. Taken together, the findings in Group 2 in Table VII indicate that the components of pulmonary diffusion are independent of the absolute level of pulmonary blood flow. This supports the animal experimentation reported by Rosenberg and Forster in which the authors arrived at the same conclusion (22).

3. The finding of high values for V_c in mitral stenosis supports the conclusion of McNeill and associates (7). The additional evidence presented above suggests that this may be an important measurement in this condition, since the over-all D_L may alter little after a successful valvotomy and so conceal the fact that the V_c and D_M components have changed considerably in different directions. The variable results noted by others (14, 23, 24) in the over-all D_L in mitral stenosis, may well be explained by the present observation that further subdivision of the D_L is required before the data become meaningful in terms of changes in the pulmonary capillary bed. Further, the present finding of normal values in a patient with little disability, who was known to have a normal pulmonary compliance, certainly suggests that alterations in V_c and membrane diffusion components represent a basic change in the physiopathology of this disease. The demonstration of a marked change in these values only three weeks after a valvotomy (Patient 28, Table IX), is also of considerable interest, since it has proved difficult to correlate the considerable subjective improvement which many such patients have with any measurable physiological variable. It may be that the measured V_c during exercise will prove to be a sensitive indicator of change occurring in the pulmonary bed as a result of valvotomy.

4. In pulmonary fibrosis the measurement of D_M probably represents the most sensitive criterion of normality available. Its expression in terms of the ventilated lung (D_M/MC) increases its sensitivity considerably. This is well illustrated by Patient 32 in Table IX whose pulmonary infiltration was known to have been present for less than three months. The D_M/MC ratio was 4.3 against the predicted value of at least 9.0. The lung biopsy in this patient showed that the alveolar walls were uniformly thickened but only by about one extra layer of cells. Pathologically the section was regarded as representing an extremely early example of Hamman-Rich syndrome. Systematic study of D_M changes in this and other types of pulmonary fibrosis would undoubtedly provide a sensitive indicator of alterations in the pulmonary membrane. In certain diseases such as sarcoidosis, it may be found that the main area of involvement in the lungs can be localized by a study of the relative changes in V_c and D_M. The finding in the present study of an unexpectedly low V_c in a patient with sarcoidosis, as well as in two of the patients with a diffuse interstitial fibrosis, suggests that the involvement of the lung may be quite different in different patterns of these diseases.

SUMMARY

1. The components of the pulmonary diffusing capacity have been studied in 14 normal individuals, and in a group of 22 patients with varying clinical conditions. All the determinations of pulmonary capillary blood volume and membrane diffusing capacity were made during exercise.

2. The results reported show that this determination is sufficiently stable and reliable to permit comparisons to be made between normal subjects and patients.

3. The data suggest that in normal subjects the pulmonary diffusing capacity increases with exercise mainly because the pulmonary capillary blood volume rises. Individual differences in diffusing capacity also seem mainly attributable to variations in this component. Hyperventilation and hypoxia

[1] Bates, D. V. Unpublished observations.

could not be shown to exert much influence on the pulmonary diffusing capacity.

4. Removal of one lung appears to result in a halving of the membrane component.

5. High flow conditions in the lesser circulation are not associated with any increase in pulmonary capillary blood volume. In one patient with a reduced pulmonary flow the pulmonary capillary blood volume was normal.

6. Mitral stenosis may lead to a considerable increase in pulmonary capillary blood volume, and a concomitant reduction in membrane component. In one patient studied before and after a successful valvotomy, the pulmonary capillary blood volume at equivalent exercise had dropped from 275 ml before operation to 85 ml postoperatively and the membrane component rose from 20 to 31 ml CO per minute per mm Hg. This reciprocal change in these two variables resulted in a very similar over-all diffusing capacity before and after operation.

7. In a group of patients with pulmonary fibrosis the main defect was found to be in the membrane diffusion component, the pulmonary capillary blood volume being either normal or reduced.

8. It is concluded that this technique based on the theoretical work of Forster (5) is capable of yielding valuable information in a wide variety of clinical conditions.

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