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THE PULMONARY DIFFUSING CAPACITY IN NORMAL SUBJECTS

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The measurement of the pulmonary diffusing capacity has recently been the subject of renewed interest, largely stimulated by the development by Lilienthal (Lilienthal, Riley, Proemmel & Franke, 1946) and Riley (Riley, Lilienthal, Proemmel & Franke, 1946; Riley & Cournand, 1951; Riley, Shepard, Cohn, Carroll & Armstrong, 1954) of a new technique for measuring it. In 1910, August & Marie Krogh described the measurement of the diffusing capacity of the lungs during continuous breathing of carbon monoxide, and also during a period of breath holding. They realized that the first of these methods was made unreliable by the difficulty of calculating the alveolar ventilation, from which the mean tension of CO in the alveoli was derived. This is a critical measurement in the calculation of diffusing capacity since this mean tension is the denominator of the fraction which constitutes it. Riley's method circumvents this difficulty since the mean alveolar O_2 gradient is calculated without direct dependence on the dead space. However, difficulty is encountered when the tidal volume exceeds about $1\frac{1}{2}$ l., since in these circumstances a small error in the measured arterial pCO_2 leads to a very considerable change in calculated effective dead space. In a recent paper Riley (Riley *et al.* 1954) notes this difficulty, and as he finds that the dead space so calculated is often obviously erroneous, he prefers to substitute a more likely value during estimations on exercise, thus in effect 'correcting' the arterial pCO_2. It should be noted that this difficulty observed by Riley operates reciprocally so that during exercise with increasing ventilation, the assumed value of the respiratory dead space influences the calculated mean alveolar CO tension to a smaller and smaller extent. It will be shown later that very different values for respiratory dead space may be assumed during exercise, without these

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producing much difference in the calculated diffusing capacity. At rest, as noted by Krogh & Krogh (1910), the situation is quite different, and the actual value of dead space is critical in determining the diffusing capacity. Filley, MacIntosh & Wright (1954), have ingeniously devised a method of calculating the mean alveolar CO tension from the measured arterial CO_2 tension. This method is simpler than Riley's technique, and also, unlike the latter, enables the diffusing capacity of the lung to be calculated without hypoxia, the effect of which on the lung diffusing capacity is not precisely known.

The theoretical aspects of CO transfer in the lung have recently been reviewed by Forster, Fowler, Bates & van Lingen (1954). It has been shown that there are difficulties in the interpretation of the results of breath-holding experiments, and any method involving breath holding is difficult to use during exercise.

The purpose of this investigation was to study the estimation of the pulmonary diffusing capacity by measurement of the inspired, mixed expired, and end tidal concentrations of carbon monoxide during rest and exercise, and to determine whether this technique was sufficiently accurate and reliable for use in clinical research. In particular it was desired to avoid the necessity of arterial blood sampling, and to decide whether an indirectly calculated value of the mean alveolar CO tension was sufficiently accurate in normal subjects to use in the calculation of the diffusing capacity.

METHODS

Fig. 1 shows the design of the breathing circuit used; certain details of this require explanation. The mouthpiece (M) contains eight rubber flap valves, four on the inspiratory and four on the expiratory side. Its dead space, including the flexible attachment to the mouth, was 75 ml. Beyond the expiratory valves, a mixing chamber (N) of 3½ l. capacity contains an induction motor driving four propeller blades. Switching of the sampling circuits is done by solenoid valves (S) in appropriate places in the circuit. Gas analysis was by infrared analyser of the type described previously (Lawther & Bates, 1953). This was calibrated on two scales, 0–0·15% CO and 0–0·05% CO. The accuracy of this type of instrument is about 3% of scale reading. Gas was drawn through this by a small electric air pump (R), at a rate of 2 l./min, measured by a rotameter (U). Sampling could be instantly stopped by closing the solenoid S_1, which was energized through a relay circuit connected to a contact breaker (K), so that, if required, gas was sampled from just beyond the expiratory valve only during inspiration. All exercise was performed on a motor-driven treadmill, the gradient of which was adjustable. When 'flat' it actually sloped at a grade of 1:50. At '½ slope' the grade was 1:10·7. All tubing in the direct breathing parts of the circuit was 5·1 cm. in internal diameter and the three-way taps (E to J), had a minimum diameter internally of 3·8 c.m During studies on maximum exercise with ventilation rates of up to 90 l./min, the gas meter was disconnected from the circuit and the minute volume measured from the volume of gas collected in the expiratory bag. The pressure swing at the mouthpiece in these circumstances was from $-2·6$ to $+3·4$ cm H_2O.

Two initial 'calibrating' experiments were performed. The first set of observations consisted of attaching a hand-operated pump of constant stroke volume to the mouthpiece and checking that the gas displaced from the bag containing inspired gas (A or B) into bag C, corresponded with the volume recorded by the gas meter. This volume was measured by wet drum flowmeter, the gas being expressed by positive pressure on the tank at W. The second set of observations compared the mixed expired CO concentration as measured by continuously sampling gas from P, with that of the simultaneously collected expired gas in bag D. For seventeen such experiments, the bag gas concentration averaged 0·002 % CO less than the continuous readings. This is just outside the reading error of the meter, and was presumed to result from incomplete bag emptying before the experiment began. Since, however, this error is less than 2 % of the average mixed expired CO, it has been disregarded in subsequent experiments. The experiments were performed at different rates of breathing, and at all times the CO meter gave a steady reading on continuous sampling from P; it can be assumed that the box N ensures complete homogeneity of mixed expired gas during these experiments.

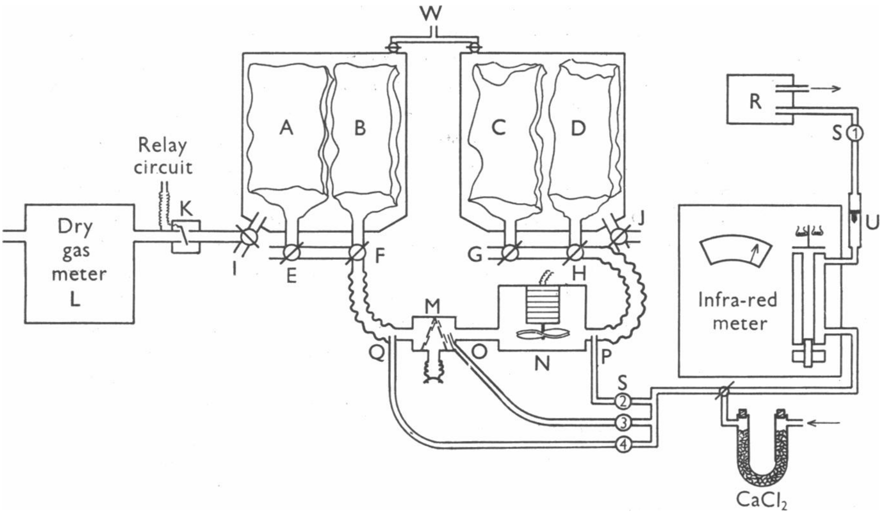

Fig. 1. Circuit Diagram. A,B, bags containing gas to be inspired; C,D, expiratory bags; E,F,G,H,I,J, wide bore control taps; K, contact breaker; L, bellows type dry gas meter; M, mouthpiece valve box containing eight rubber flap valves, total dead space 75 ml.; N, 3½ l. mixing chamber containing four-bladed propeller; O,P,Q, sampling outlets; R, electric air pump; gas from this can be returned to the circuit if desired; $S_{1, 2, 3, 4}$, solenoid valves controlling sampling circuit; U, flow control rotameter; W, pressure line to empty bags.

Before each experiment, the infrared meter was set to zero on dry air and its sensitivity checked against a standard cylinder of 0·04 % CO. As described later, a zero correction was made during each experiment for 'interference' due to water vapour and expired CO_2. The deflexion produced by these factors varies with state of 'decay' of the detector of the instrument and must be constantly checked.

The procedure followed in using this circuit varied slightly in different experiments. In those of which the results are shown in Table 2, the subject sat quietly at rest in a chair for 5 min. He was then connected to the circuit, the taps being adjusted so that he breathed room air. With the fan N in operation and the solenoids S_1 and S_2 open so that the meter is sampling continuously from P, a zero reading (Z) is taken on the CO meter. Solenoid S_2 is then closed and solenoid S_4 is opened, and the subject is switched into 0·14 % CO in air contained in bags A and B. The inspired gas concentration (F_I) is read on the meter. S_4 is closed and S_2 again opened, and the mixed expired CO concentration is noted. This usually becomes steady in 1 min or less, but may vary either due to the fact that an equilibrium state has not been reached or due to variations in ventilation. The next stage in the experiment is delayed until a steady mixed expired concentration is being recorded. The fan N is now switched off, and solenoid S_2 is closed and S_3 is opened. Solenoid S_1 is connected to the relay circuit actuated by K. Tap I is now turned so that the gas meter is connected to the inspired gas tank containing bags A and B. At the same moment tap G is turned so that all expired gas is collected in bag C; this gas is analysed for CO_2 and O_2 so that the appropriate R.Q. correction can be applied. For the next minute (timed by stopwatch) the gas meter will read the minute volume, and the meter will sample from O during each inspiration only. Initial experiments showed that during normal respirations, end tidal samples taken from O produced a stable reading on the meter after about seven respirations. The volume required to flush the meter and produce a stable reading was about 700 ml. Approximately the last 100 ml. of each expiration was being sampled. The exact volume taken into the meter on each 'snatch' will depend on the respiratory rate, but this disadvantage is more than offset in practice by the relative ease with which the samples can be obtained by some such device as this. The standard Rahn-Otis sampler is incapable of delivering samples of sufficient volume except over a relatively long period of time. The contact device (K) worked well when the tidal volume was large, but on some resting experiments the sampling relay circuit had to be actuated by a push button switch pressed by an operator who was observing the subject's respirations. The respiratory rate was counted either by a post-office counter actuated from the same relay circuit from K, or by an observer counting the respirations by watching the gas meter, or, in the case of experiments on trained subjects during maximum exercise, by the subject counting his own respirations during the period of expired gas collection. After the period of 1 min of collection, the taps E,F,G,H are turned so that the subject is once again breathing air, and he is then disconnected. A length of 2·5 cm. diameter rubber tubing is now connected between the flexible mouthpiece and the valve box, so that the dead space is increased by 60 ml. The whole procedure is then repeated. In estimations during exercise, no observations were made until the subject had been exercising at the predetermined grade for at least 5 min. During duplicate runs on exercise (Table 3), measurements were made and samples collected within 2 min of each other while the subject continued his exercise.

The subdivisions of lung volume of these subjects were measured on the helium closed circuit apparatus previously described (Bates & Christie, 1950). The evenness of gas distribution was also measured on this circuit by the index of mixing efficiency. In all these subjects, this value was within the previously noted limits for individuals in this age group. This measurement becomes very important in patients, since any gross inequality of distribution of inspired gas will lead to considerable discrepancy between the end tidal gas sample and the mean alveolar gas tension.

CALCULATIONS

The following are examples of readings taken during one experiment:

Dry air = 0·0 % CO. Calibration checked at 0·04 % CO.

Mixed expired gas during air breathing (Z) = 0·01 % CO.

Inspired CO (F_I) = 0·137 %. (This value provides a second calibration check at this range.)

Mixed expired CO % = 0·081 %.

Correction of above by subtraction of Z and correction to dry gas (F_{EX}) = 0·074 %.

End tidal CO % = 0·064 %.

Correction of above by subtraction of Z and correction to dry gas (F_{ET}) = 0·056 %.

Minute volume $(M) = 25{\cdot}9$ l./min.

Respiratory rate $(R) = 19$/min.

Hence tidal volume $(V_T) = M/R = 1362$ ml.

Assumed value of subject's dead space plus 75 ml. of instrumental dead space $= V_D$.

By the use of the equations which are set out in the Appendix, the following quantities may be calculated from this information.

(*a*) D_{CO} *I*. The overall pulmonary diffusing capacity may be calculated by dividing the rate of uptake of the gas, by the mean alveolar CO tension calculated from Bohr's equation, the assumed dead space value being used. This value, which is bound to be approximate only, has been guessed from the subject's stature, the values varying from 120 to 150 ml. for men, and from 65 to 110 ml. for women.

(*b*) D_{CO} *II*. The overall diffusing capacity may also be calculated by assuming that the end tidal sample represents the mean alveolar CO tension, and dividing the rate of CO uptake by this. Since the end tidal CO is the lowest likely value of mean alveolar CO concentration, the diffusing capacity so calculated will be the highest likely value.

(*c*) D_{CO} *III*. A maximal likely value for the mean alveolar CO tension may be calculated by a manoeuvre similar to one used by Krogh & Krogh (1910). Knowing the lung volume at the end of a normal expiration (*FRC*) and the concentration of CO it contains (F_{ET}) and knowing the increment added (V_T) and its CO concentration (F_I), the concentration of CO in the lungs at the end of inspiration can be calculated. Recent evidence (Prime, unpublished) indicates that the *FRC* is little changed on exercise. No correction is made for CO disappearing into the blood, and a maximal likely alveolar CO value is taken to be the mean of this 'end inspiration' CO concentration and the measured end tidal sample (F_{ET}). The diffusing capacity calculated from this maximal value of alveolar CO tension will represent a *minimal* likely value for the diffusing capacity.

(*d*) D_{CO} *IV*. This, the mean of D_{CO} II and D_{CO} III, is taken to represent the most likely value of the overall pulmonary diffusing capacity, since D_{CO} II and D_{CO} III set the upper and lower limits respectively.

(*e*) The respiratory dead space can be calculated from Bohr's equation, making the assumption that the end tidal sample (F_{ET}) represents the mean alveolar CO.

Details of these equations are shown in the Appendix.

RESULTS

The physical characteristics of the subjects studied are shown in Table 1. In Table 2 are shown the results of the experiments on them; full protocols of the estimations are not given. Every experiment on every one of these subjects is given in this table. These results can be analysed most conveniently under a number of different headings.

TABLE 1. Details of subjects

Subject	Sex	Age (yr)	Height (in.)	Body surface area (m²)	*VC* (l.)	*FRC* (l.)	Smoking	Athletic activity
AED	M	32	72	1·90	6·0	4·41	0	+ +
DVB	M	32	70	2·01	4·3	2·27	+	0
NGB	F	27	66½	1·65	3·4	2·68	0	0
FLE	M	30	71	1·88	5·4	4·61	+	0
PGB	M	41	74½	2·10	6·0	5·19	+	0
TDC	M	23	69¼	1·85	4·8	3·32	+	+
JHL	M	22	71	1·98	5·4	3·71	+ +	+
RGB	M	23	73	1·90	5·1	2·93	0	+ + +
JE	F	22	62	1·52	3·4	2·06	0	+
PH	M	32	73½	2·14	6·0	4·50	+	+
JW	F	18	64	1·69	3·4	2·72	+	+
RWS	M	35	66	1·76	4·1	1·67	0	0
JFF	F	29	63½	1·64	4·3	2·50	+	0
AW	M	22	74	1·95	6·0	4·78	0	0
JP	M	25	70	1·85	4·8	3·08	0	0
WGH	M	26	71	1·92	4·1	2·93	+	+ +
DHB	M	22	73	1·81	5·5	4·37	+	0
TWF	M	28	71	1·83	4·4	2·59	+ +	0
ASW	M	34	75	2·20	3·7	3·47	+	+ +

The tobacco consumption is graded as follows: 0 = non smoker, + = less than 10 cigarettes/day or 2 oz tobacco/week, + + = any consumption in excess of +. Athletic activity is graded: 0 = no sport within the last 2 years, + = some form of regular competitive sport within last 2 yr, + + = previous high grade competitive sport but not in training, + + + = first class competitive sport and in training. *VC*, vital capacity; *FRC*, functional residual capacity.

Agreement between the differently calculated values for the pulmonary diffusing capacity. It will be seen that the highest and lowest likely diffusing capacity values (D_{CO} II and III) fall within fairly narrow limits, and the mean of these two values (D_{CO} IV) seems likely therefore to provide a reasonable estimate of it. Krogh noted the occasionally very high values of D_{CO} obtained when the breathing was shallow, if it was calculated from an assumed value for the respiratory dead space. He found, in an experiment on Marie Krogh, that with a tidal volume of 700 ml., the calculated D_{CO} was 26, but if the tidal volume dropped to 480 ml., a value of 79 was obtained (Krogh & Krogh, 1910). This experiment is repeated in several cases, the estimate on JE providing an almost exact parallel. It will be seen that although D_{CO}I gives a value of 71, D_{CO} IV is only 11·5. It is clear that the resting diffusing capacity cannot be safely determined from an assumed value of dead space if the tidal volume is small. Other subjects (DHB, TWF) show a similar falsely high value for D_{CO} I. No such discrepancy between D_{CO} I and D_{CO} IV occurs during exercise when the tidal volume is large. The false estimates of diffusing capacity that result from assuming a reasonable dead space value when the tidal volume is small, are almost certainly due to the same mechanism that has been shown by Briscoe, Forster & Comroe (1954) to result in some degree of alveolar ventilation when the tidal volume is smaller than the measured anatomical dead space. In the subsequent results to be analysed below, D_{CO} IV will be taken as the best estimate of diffusing capacity.

Effect of 60 *ml. of added dead space.* The addition of this added dead space made no significant difference to the resting D_{CO}.

Repeated estimates of resting diffusing capacity in one individual on different occasions. Experiments on RWS show the relative constancy of the diffusing capacity on different occasions. These results are summarized in Table 3. It will be noted that the diffusing capacity is not dependent on tidal volume, a result to be expected from the work of Forster, Briscoe & Bates (1954).

Constancy of immediately consecutive determinations of D_{CO} on exercise in one individual. Full results of this group of experiments are not given in Table 2, but are summarized in Table 3. One estimate of D_{CO} I was made after 5 min of exercise and repeated 2 min later while the subject continued to exercise at the same rate. These paired observations show a S.D. of 1·9, from which it may be inferred that the likely error of a single determination is in the region of 4·0 if physiological constancy from minute to minute can be assumed.

Resting values of pulmonary diffusing capacity. There are three points of interest in these figures: first, the erroneously high values of diffusing capacity given by D_{CO} I as pointed out by the Kroghs and noted above; secondly, there is considerable individual variation in this value, more than can be ascribed to technical error. This is in agreement with results obtained by Filley *et al.* (1954). It may be that some variation would disappear if all subjects were in a strictly basal state. Thirdly, there appears to be no correlation between the resting D_{CO} and any of the variables in this group of subjects (see Fig. 2*a*).

Moderate exercise in normal subjects. It will be noted that when the tidal volume increases in exercise, the calculated D_{CO} I usually falls between D_{CO} II and D_{CO} III, and hence there is little discrepancy between D_{CO} I and D_{CO} IV. D_{CO} I represents the D_{CO} calculated from an assumed constant dead space, and D_{CO} II that calculated from a measured end tidal sample. Had the dead space been calculated from this sample, it would have had the value shown in the last column in Table 2. It is interesting to see that though there may be considerable discrepancy between the assumed dead space and that calculated from the Bohr equation based on the end tidal CO concentration, there is only small disagreement during exercise between D_{CO} I and D_{CO} II. This reflects the relative unimportance of the actual dead space value in the calculation of the

TABLE 2. Results on normal subjects at rest and exercise

Subject (1)	R/Ex (2)	Tidal vol. (3)	Resp./min (4)	Ass. DS (ml.) (5)	Diffusing capacity (ml./min/mm Hg)				Bohr DS (ml.) (10)
					D_{CO} I (6)	D_{CO} II (7)	D_{CO} III (8)	D_{CO} IV (9)	
AED	R	612	17	215	25·2	24·4	21·2	22·8	212
	Ex 1	1360	19	215	36·9	41·1	35·2	38·1	303
DVB	R	648	15	205	20·2	23·1	19·4	21·3	233
	R*	574	13	265	24·6	16·6	14·0	15·3	226
	Ex 1	1645	15	205	31·2	31·2	22·4	26·8	207
NGB	R	440	23	185	13·6	12·3	11·3	11·8	166
	R*	525	19	245	10·1	10·1	9·1	9·6	244
	Ex 1	988	25	185	25·3	24·3	22·0	23·1	145
FLE	R	1196	11	205	27·9	32·8	24·6	28·7	280
	R*	1245	11	265	24·2	27·8	21·9	24·8	325
	Ex 1	2270	13	205	39·4	45·1	35·1	40·1	451
PGB	R	636	14	225	21·4	22·0	19·2	20·6	230
	R*	696	14	285	20·4	21·9	19·2	20·5	296
	Ex 1	1312	18	225	33·5	37·9	32·8	35·3	316
	Ex 2	2090	20	225	34·9	36·0	32·4	34·2	324
TDC	R	490	16	195	11·5	11·1	10·0	10·5	189
	R*	565	17	255	21·8	13·2	11·9	12·6	167
	Ex 1	1100	19	195	32·2	32·6	27·8	30·2	219
	Ex 2	1575	20	195	30·7	32·3	28·0	30·1	276
JHL	R	533	15	215	29·0	18·5	16·0	17·2	128
	R*	550	13	275	22·7	14·0	12·1	13·1	234
	Ex 1	1885	11	215	31·2	38·3	30·0	34·1	436
	Ex 2	1790	17	215	29·5	31·0	27·0	29·0	302
RGB	R	722	15	225	29·8	28·6	22·5	25·5	218
	Ex 1	988	22	225	44·2	37·3	34·2	35·7	156
	Ex 2	1462	24	225	42·5	45·3	37·8	41·5	285
JE	R	350	13	140	71·0	12·4	10·6	11·5	67
	R*	491	12	200	16·5	13·8	11·0	12·4	182
	Ex 1	1610	10	140	19·4	23·5	18·2	20·9	370
	Ex 2	1522	21	140	24·8	26·8	23·0	24·9	308
PH	R	554	12	215	25·9	14·0	12·6	13·3	125
	Ex 1	1483	15	215	35·6	42·6	34·7	38·6	349
JW	R	494	16	145	23·5	19·4	16·4	17·9	118
	R*	556	16	205	22·8	14·1	12·6	13·3	146
	Ex 1	864	22	145	24·9	26·4	22·9	24·6	138
	Ex 2	1310	27	145	29·0	28·2	25·6	26·9	103
RWS	R	700	10	195	16·3	14·7	12·3	13·5	171
	R*	806	8	265	17·1	15·2	11·9	13·5	240
	R	1165	6	195	14·2	15·9	12·1	14·0	249
	R	1415	6	195	12·6	18·6	13·4	16·0	459
	R*	1300	6	265	13·6	17·5	12·7	15·1	402
	R	682	11	195	29·0	22·5	17·4	19·9	155
	R*	570	10	265	15·9	15·7	11·9	13·8	253
	Ex 1	1320	14	195	19·6	22·6	18·8	20·7	340
	Ex 2	1710	18	195	24·2	25·8	22·4	24·1	335
JFF	R	600	15	175	21·8	21·5	17·8	19·6	173
	R*	724	15	235	20·5	20·6	17·4	19·0	242
	Ex 1	1665	15	175	24·1	27·8	22·9	25·3	393
	Ex 2	1985	19	175	25·5	27·4	23·9	25·6	353
AW	R	490	16	225	21·2	21·8	12·2	17·0	227
	R*	877	15	285	17·1	26·3	18·0	22·1	403
	Ex 1	1566	14	225	39·4	45·3	37·9	41·6	332
	Ex 2	1945	19	225	49·8	46·8	47·3	47·0	118

TABLE 2 (*continued*)

Subject (1)	*R*/*Ex* (2)	Tidal vol. (3)	Resp./ min (4)	Ass. DS (ml.) (5)	Diffusing capacity (ml./min/mm Hg)				Bohr DS (ml.) (10)
					D_{CO}I (6)	D_{CO}II (7)	D_{CO}III (8)	D_{CO}IV (9)	
JP	*R*	458	20	205	22·1	15·0	13·8	14·4	162
	*R**	427	20	265	27·4	10·8	9·9	10·3	212
	Ex 1	1041	23	205	29·4	29·0	25·1	27·0	197
	Ex 2	1361	24	205	25·4	25·9	23·7	24·8	317
WGH	*R*	550	14	215	14·1	15·1	12·9	14·0	176
	*R**	634	12	275	23·5	19·8	15·4	17·6	256
	Ex 1	1415	14	215	27·2	30·0	24·5	27·2	306
	Ex 2	2190	15	215	33·9	39·4	32·5	35·9	504
DHB	*R*	768	11	225	27·3	28·6	22·8	25·7	233
	*R**	531	13	285	195·0	21·8	18·0	19·9	230
	Ex 1	2145	11	225	38·4	49·4	37·6	43·5	511
	Ex 2	2175	17	225	38·2	41·5	34·4	37·9	410
TWF	*R*	438	16	215	53·6	13·8	11·9	12·8	132
	*R**	466	15	275	93·0	12·7	10·8	11·7	202
	Ex 1	985	18	215	22·9	24·0	20·4	22·2	244
ASW	*R*	795	15	215	28·8	—	—	—	—
	Ex 1	2130	14	215	36·6	—	—	—	—
	Ex 2	3160	28	215	53·0	—	—	—	—

Column 2. *R* = rest, *R** = rest with 60 ml. added dead space, *Ex* 1 = 3 miles/hr on the flat, *Ex* 2 = 3 miles/hr at grade 1:10·7. Column 5: the figures in this column show the 'guessed' value of respiratory dead space plus 75 ml. of apparatus dead space. Columns 6, 7, 8, 9: see text and Appendix for details of these differently calculated values for the diffusing capacity. D_{CO}IV is considered to be the best estimate on theoretical grounds. Column 10: this shows the value of total dead space calculated by Bohr's equation (see Appendix for details).

diffusing capacity when the tidal volume is large. The average increment in diffusing capacity between rest and walking at 3 miles/hr on the flat was 13·2 ml./min/mm Hg. In most cases there was no further increase, although the rate of working was quadrupled by tilting the treadmill to a slope of 1 in 10·7. This finding is in accord with the 'plateau' of diffusing capacity on effort described by Riley *et al.* (1954) and Filley *et al.* (1954), though it is clear from Table 4 that some subjects do not reach their maximal diffusing capacity at this grade of exercise. For a subject weighing 12 stone, walking at 3 miles/hr on the 'flat' is equivalent to a work load of approximately 140 kg.m/min, with an O_2 consumption of about 1·2 l./min. Equivalent values with the treadmill at a slope of 1 in 10·7 are 620 kg.m/min and 2·2 l. of oxygen per min.

D_{CO} *on maximum effort.* In two subjects, DVB and AED, work was pushed to the limit of tolerance to determine whether any rise in diffusing capacity occurred at these levels of exercise. The results are shown in Table 4. DVB was a non-athletic subject. AED was in fairly good training, and had taken part in competitive athletics, and 4 yr before had been among the ten fastest half milers in the country. The disparity between these two subjects can be seen from the results. The discrepancy between the values for the diffusing capacity increases with progressively severe exercise, reaching finally a stage when the

D_{CO} of AED is nearly double that of DVB. It seems likely that this is related to the relative athletic abilities of the subjects, and is also probably influenced by the larger *FRC* in AED. More work will be required to clarify this point.

TABLE 3. Analysis of results

	No. of obs.	ml./min/ mm Hg mean	Range	S.D.
Resting values of D_{CO}IV	18	17·6	10·5–28·7	±5·0
Resting values of D_{CO}IV with 60 ml. added dead space	15	15·8	9·6–24·8	±4·4
Repeated estimations of D_{CO}IV in one individual (RWS) at rest	7	15·0	13·5–19·9	±2·5
Difference between consecutive estimates of D_{CO}I in one subject on exercise	28	—	0·2–4·5	±1·9
Exercise D_{CO}IV at 3 miles/hr, flat (*Ex* 1)	18	30·8	20·7–43·4	±6·3
Exercise D_{CO}IV at 3 miles/hr, ½ slope, grade 1:10·7 (*Ex* 2)	12	31·9	24·1–47·0	±7·1
Increment of D_{CO}IV between rest and 3 miles/hr flat (*Ex* 1)	18	13·2	5·5–25·3	±5·5
Dead space increment (60 ml.) as estimated by Bohr equation	15	+61 ml.	+176 to −22	±57

TABLE 4. Comparison between two subjects

	Rest		Mild exercise		Maximum effort	
	AED	DVB	AED	DVB	AED	DVB
Speed, miles/hr	—	—	3	3	4·2	4·0
Slope	—	—	Nil	Nil	1 in 5·3	1 in 5·3
Work in kg.m/min	—	—	143	139	1830	1680
Minute vol., l./min	10·4	9·7	25·9	24·6	136	107
Resp./min.	17	15	19	15	36	52
Oxygen uptake, l./min	—	—	1·6	1·2	4·76	3·68
D_{CO}, ml./min/mm Hg	25·2	20·2	36·9	31·2	73·5	41·5

Accuracy of dead space measurement from the Bohr equation. Since the actual volume of the respiratory dead space in these subjects is not known, no direct comparison can be made. The experiments with a 60 ml. added dead space, however, enable this value to be compared with the increment shown by the Bohr equation. The variability of the Bohr calculated figures is evident, although the mean value for the added dead space is 61 ml. It is of interest to note that the calculated Bohr value of the dead space increases on exercise, as noted by many other workers using different gases—most recently by Bannister, Cunningham & Douglas (1954). It is to be expected that the end tidal sample will become less representative of the mean alveolar CO tension if the duration of expiration is prolonged. This fact, and the additional factor of the increased rate of gas exchange on exercise, probably account for the difference. Bannister & Cunningham (1954) prefer to ascribe it to relative over-ventilation of underperfused alveoli on exercise, and it is not yet possible to say definitely how likely a factor this is.

Relationship of diffusing capacity to individual variables. In Table 1 are shown the physical characteristics of the subjects studied, together with an assessment of their athletic ability and smoking habits. With so many possible factors to influence the diffusing capacity, a very large number of subjects would have to be studied before a formal statistical multiple correlation could be attempted between these variables and the diffusing capacity. A preliminary study of the results indicated, however, a striking relationship between the functional residual capacity (*FRC*) and the diffusing capacity on exercise. There is no similar relationship at rest. These findings are illustrated in the two parts of Fig. 2. Since the *FRC* is fairly closely correlated with height, there is a similar—but less exact—relationship between the exercise diffusing capacity and the height. Since the vital capacity (*VC*) is also related to height, this too is related very indirectly to the level of diffusing capacity found on exercise. It seems likely that the *FRC* is the determining factor among these relationships, and Fig. 2 has been plotted with this as the abscissa. In the two parts of this figure, the sex, tobacco consumption, and athletic ability of each subject is indicated by an appropriate identification. It seems clear that the women have generally lower values of diffusing capacity by virtue of their smaller functional residual capacities. There is no evident relationship to smoking. Although in the majority of subjects, athletic activity does not seem an important factor, yet it should be noted that the only + + + athlete (RGB) had a somewhat higher diffusing capacity at this moderate grade off exercise than would have been predicted from his *FRC*. Cohn, Carroll, Armstrong, Shepard & Riley (1954) have noted the influence of age on the maximal diffusing capacity, and their equation for the prediction of this value is based on the age and height of the subject. The age range in this group of subjects is small, but there appears to be no close relationship to diffusion capacity in these subjects. The only pointer in this direction is that the diffusing capacity of the oldest subject (PGB) was rather lower than might have been predicted from his *FRC*. It seems, therefore, that the most significant correlation in this small group of subjects at this grade of exercise is between the exercise diffusing capacity and the *FRC*. It might be objected that those of larger stature, being heavier, were doing more work at this grade than smaller people. While this is true, the difference is not large, and it seems unlikely to have influenced the results; since the increment of diffusing capacity between 3 miles/hr on the flat and 3 miles/hr at a slope of 1 in 10·7 was negligible (see Table 3). The explanation of this correlation is probably that in those with a larger *FRC*, there is a greater total quantity and surface area of blood exposed to the gas per 'unit' of ventilation. Forster, Briscoe & Bates (1954) have found that the pulmonary diffusing capacity at rest is unaffected by the general level of breathing being altered by varying the *FRC*. This finding probably means that this manoeuvre does not change the pulmonary capillary blood volume in one individual, and the observation is therefore not at variance with the findings reported here.

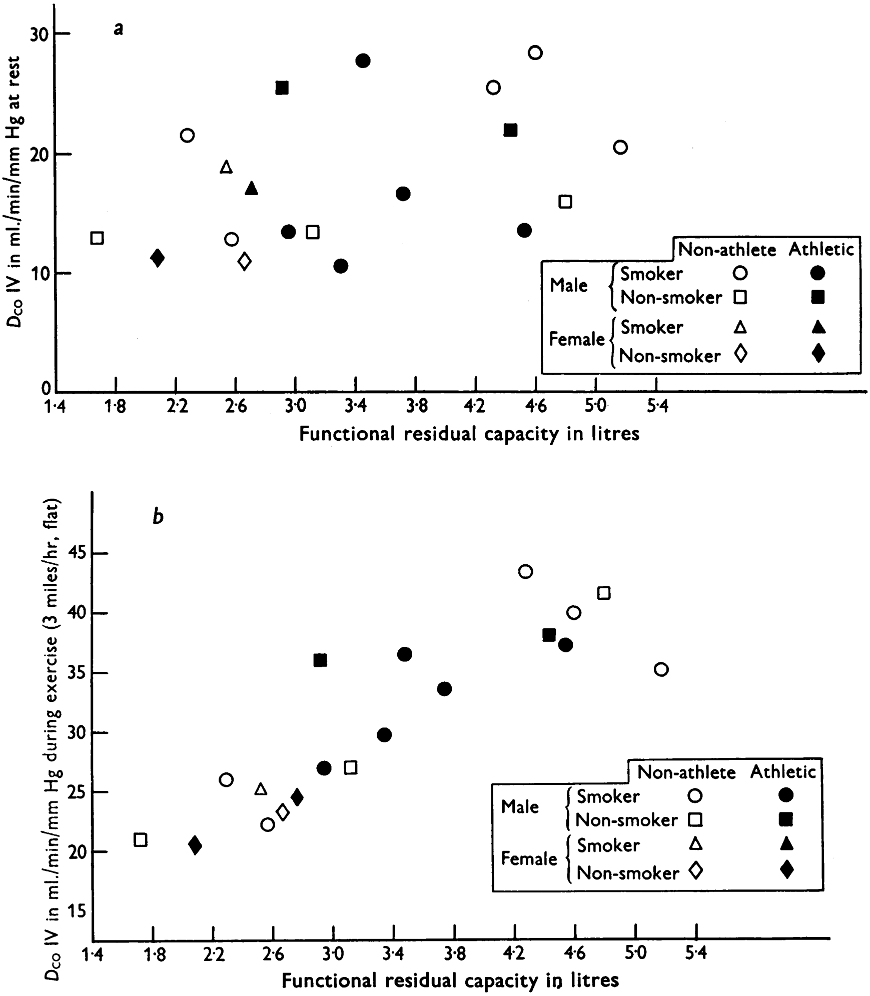

Fig. 2. (*a*) The value of the resting D_{CO} does not bear any relationship either to the functional residual capacity or to any of the individual variables indicated. (*b*) The exercise D_{CO} is related to the functional residual capacity. It does not appear to be influenced by the other individual variables indicated. It is of interest that the rather high D_{CO} at an *FRC* of 2·9 l. is that of the most athletic subject (RGB), and the point furthest to the right which is somewhat lower than the others of equivalent *FRC*, is that of the oldest subject in the series (PGB).

DISCUSSION

In Table 5 the results of estimates of the pulmonary diffusing capacity with this technique are compared with those of other workers. In view of the varying levels of exercise used, and the wide individual variation, there is a generally satisfactory agreement between these figures. The close agreement between Filley's results (Filley *et al.* 1954) and those in this series lends support to the conclusion that a good estimate of the overall diffusing capacity can be made during a continuous breathing experiment without blood gas analysis. The method therefore is particularly suitable for use in clinical research.

TABLE 5. Comparison with other estimates of D_{CO}

Author	Age range	At rest	'Moderate' exercise*
M. Krogh (1915)	20–50	18–40	—
Bøje (1934)	25–60	18–35	32–46
Lilienthal *et al.* (1946)	28–36	9·8–29·2†	40–61*
Riley *et al.* (1954)	17–40	14†	34–63*
Filley *et al.* (1954)	20–45	13–30	23–55
Present authors	18–41	10·5–29	21–43·5

* It will be realized that there is considerable variation in the level of exercise used by different authors.

† *Note*: values converted from D_{O_2} to D_{CO} by dividing by 1·23 (Krogh & Krogh, 1910).

Recently Forster, Fowler & Bates (1954) have analysed the theory of carbon monoxide transfer in the lungs, and their work points to several general conclusions of importance in the interpretation of the results of the present study. The overall D_{CO} measured by any steady state technique is dependent on the balance between ventilation and diffusion within the lung. Interference with this balance (by impairing the evenness of gas distribution without a parallel change in diffusion for instance) will lead to a lower figure for the overall diffusing capacity, without there necessarily being any defect in diffusion in any part of the lung. It has been suggested that all such overall indices of diffusing capacity should therefore be prefixed 'apparent'. This suggestion has not been adopted here, partly for convenience, and partly because the estimate of diffusing capacity during a breath-holding experiment is also 'apparent' in the sense that it is dependent to some extent on the balance between contained gas volume and diffusion within the lung. Since both are 'apparent' in two different senses, the term may be dropped provided that the limitations of each are remembered. Apart from this qualification, the pulmonary diffusing capacity is influenced by a wide variety of factors. The kinetics of COHb formation, and the actual volume of pulmonary capillary blood at any one time, both play important parts in determining its value, in addition to the effect exerted by the pulmonary 'membrane'. It has been pointed out by Roughton (1945*a*) that under certain kinetic conditions, the assumption of a zero back pressure of plasma CO may be erroneous, and this will affect the value found for the diffusing capacity. Further work on this important aspect is required before the matter can be taken further. The inter-relation of diffusing capacity, kinetics, and the pulmonary capillary blood volume was used by Roughton (1945*b*) in his most ingenious calculation of the latter value. It is likely that the increased pulmonary diffusing capacity of exercise is to be explained by an increase in pulmonary capillary blood volume, though it is important to realize that this volume is not directly nor necessarily dependent on the rate of blood flow through the lungs. Whether in the case of those (such as AED in this series) capable of a much greater increase in diffusing capacity than others, the whole explanation lies in such an increased pulmonary capillary blood volume is not so certain. It may well be that the permeability of pulmonary epithelium and capillary play some part. Future work on the kinetics of the reactions of CO with haemoglobin may enable these effects to be separated. It is intriguing to speculate whether a man is athletic because he is capable of a great increase in diffusing capacity, or whether he improves his diffusing capacity as a result of athletic activity. No solution to this problem is provided by the figures in this study, which are only adequate to suggest that there may be some relationship between athletic ability and the pulmonary diffusing capacity.

The variability of the pulmonary diffusing capacity, and the possibility that under conditions of severe hypoxia it may increase greatly beyond the value found in these experiments, indicate that the term 'diffusion constant' should be dropped in describing this measurement. The variability found also suggests that transposition of values for the pulmonary diffusing capacity obtained under one set of circumstances to different conditions may be quite misleading. The difficulty noted by some authors (Barcroft, 1914; Roughton, 1944) in accounting for rates of oxygen uptake at altitudes, on the basis of a predetermined pulmonary diffusing capacity, should be reviewed in the light of this knowledge.

SUMMARY

1. A respiratory technique using carbon monoxide is described for the measurement of the pulmonary diffusing capacity during steady state conditions at rest and exercise.

2. The effect of differently calculated values of mean alveolar CO tension on the diffusing capacity is discussed.

3. It is shown that end tidal sampling is essential for a reliable estimate of resting diffusing capacity. On exercise the value calculated from an assumed value of anatomical dead space agrees well with values calculated from measured end tidal samples. It is concluded that this technique is suitable for the measurement of the pulmonary diffusing capacity, and particularly applicable to clinical research since no blood sampling is required.

4. Nineteen normal subjects have been studied at rest and during exercise on a motor-driven treadmill. The resting diffusing capacity (CO), D_{CO} is not apparently related to age, sex, stature, functional residual capacity of the lungs, smoking habits, or athletic ability. On exercise, however, the D_{CO} is related to the measured functional residual capacity. There was no close correlation with age, but the range of age difference in the group was small. The most athletic subject had a higher D_{CO}, and the oldest member of the series a lower D_{CO} than might have been predicted from their respective lung volumes.

5. The day-to-day variation in resting diffusing capacity in one subject was from 13·5 to 19·9 ml./min/mm Hg. The standard deviation of the difference between immediately consecutive estimates on exercise was 1·9.

6. The mean resting D_{CO} was 17·6 ml./min/mm Hg. At 3 miles/hr on the flat the mean D_{CO} was 30·8, and at the same speed at a grade of 1:10·7 the mean D_{CO} was 31·9

7. Detailed comparisons between one athletic and one non-athletic subject in the series showed a striking difference between the D_{CO} on maximum effort in the two subjects. The athlete reached a D_{CO} of 73·5, and the non-athlete 41·5. There is insufficient evidence as yet to show whether a high grade of athletic ability is dependent on a high D_{CO}.

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APPENDIX

Symbols: D_{CO} = Diffusing capacity (CO) in ml./min/mm Hg
P_b = Barometric pressure, mm Hg
V_T = Tidal volume
R = Respirations per minute
V_A = Functional residual capacity
V_D = Dead space (includes instrumental dead space)

$$\left.\begin{array}{l} F_I = \text{Inspired} \\ F_{EX} = \text{Mixed expired} \\ F_{ET} = \text{End tidal} \end{array}\right\} \text{Carbon monoxide concentration ATPD}$$

(*a*) $D_{\mathrm{CO}}\mathrm{I}$ calculated from an assumed value of the respiratory dead space:

$$D_{\mathrm{CO}}\mathrm{I} = \frac{V_T(V_T - V_D)\times R\times(F_I - F_{EX})}{(F_{EX}V_T - F_IV_D)\times(P_b - 47)}\ \text{ml./min/mm Hg.}$$

(*b*) $D_{\mathrm{CO}}\mathrm{II}$ calculated on the assumption that the end tidal sample represents the mean alveolar tension:

$$D_{\mathrm{CO}}\mathrm{II} = \frac{V_T\times R\times(F_I - F_{EX})}{F_{ET}\times(P_b - 47)}\ \text{ml./min/mm Hg.}$$

Since the end tidal sample represents the lowest likely value for the mean alveolar tension, the D_{CO} calculated from this equation is a *maximal* value.

(*c*) Calculation of maximal mean alveolar tension:

$$\text{max alv. concentration at end of inspiration} = \frac{F_{ET}V_A + V_TF_I}{V_A + V_T}.$$

The maximal likely mean alveolar concentration is taken as the mean between this value and F_{ET}. D_{CO} III is then calculated by substitution of this value for F_{ET} in the equation in section (*b*) above. Since this value of mean alveolar tension is the highest likely, the D_{CO} calculated from it (D_{CO} III) will be the *lowest* likely value.

(*d*) The dead space may be calculated from Bohr's formula, if it is assumed that F_{ET} represents the mean alveolar concentration.

$$V_D = \frac{V_TF_{EX} - V_TF_{ET}}{F_I - F_{ET}}.$$

This is the 'Bohr-calculated' dead space.

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