THE EFFECT OF CHANGES IN VENTILATION AND PULMONARY BLOOD FLOW ON THE DIFFUSING CAPACITY OF THE LUNG*†

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The "pulmonary diffusing capacity" for carbon monoxide (D_{LCO}) is of interest as a measure of the extent and permeability of the alveolar-capillary interface. However, its use for this purpose is subject to three major types of error: *1*) undetected influences of other physiologic factors, such as changes in pulmonary blood flow, the volume of air in the lungs and the distribution of inspired air; *2*) disregarded characteristics of the test substance, such as altered rates of chemical combination of carbon monoxide with hemoglobin at different oxygen tensions; and *3*) artifacts due to the test procedure itself, such as those introduced by deliberate respiratory maneuvers.

These factors assume different proportions in different methods of measurement.

For the single breath technique, some of these factors, such as the volume of air in the lungs (1–3) and the rate of combination of hemoglobin with carbon monoxide, have been extensively studied (4, 5). For the steady state methods, many remain to be assessed.

Before applying a steady state method to a variety of physiological problems, it seemed pertinent to us to delineate some factors which could affect the D_{LCO}.

The present study considers specifically the effect of minute ventilation and pulmonary blood flow on the diffusing capacity for carbon monoxide determined by a steady state method.

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GENERAL PRINCIPLES

The diffusing capacity of the lung for carbon monoxide, the pulmonary blood flow and the minute ventilation all increase during exercise. In order to determine if the change in minute ventilation or the change in pulmonary blood flow or both, influence D_{LCO}, three different approaches were used: *1*) Minute ventilation was increased more than pulmonary blood flow by exercising subjects with only a limited capacity to augment cardiac output; *2*) minute ventilation was again increased in excess of a change in pulmonary blood flow by having subjects undergo voluntary hyperpnea; and *3*) blood flow through each lung was varied simultaneously in such a way that blood flow increased in one and decreased in the other while minute ventilation remained virtually unchanged.

SUBJECTS AND METHODS

Rest and exercise. Thirteen subjects with mitral stenosis on the basis of rheumatic heart disease were studied both at rest and during exercise. For the sake of comparison, D_{LCO} was also measured in 21 normal subjects at rest (Table I) and an additional 15 normal subjects were studied both at rest and during exercise (Table II).

These studies involved the simultaneous measurement of minute ventilation, cardiac output and D_{LCO}. Cardiac output was measured by the Fick principle, using oxygen as the test gas and entailed: *1*) open circuits for the administration of inspired gas as well as for the collection and sampling of expired gas; *2*) cardiac catheterization for sampling of pulmonary arterial blood; and *3*) cannulation of a brachial artery for the sampling of mixed arterial blood. For the estimation of D_{LCO}, 0.1 per cent carbon monoxide in air was substituted for ambient air for four to six minutes of the test periods at rest and during exercise.

Exercise was performed in the supine position using a special pedal-pulley device attached to the fluoroscopic table. In all subjects but four, a single level of exercise was used; in these four, exercise was continued for a second period at a greater intensity. Midway through the gas collection period, samples of systemic and pulmonary

arterial blood were drawn for the measurements of oxygen contents, as well as carbon dioxide and carbon monoxide tensions.

The steady state method for measuring D_{LCO} proposed by Filley, MacIntosh and Wright (6) was modified in two respects: *1*) The carbon monoxide tension of expired gas was measured by an infrared physical analyzer[1] and *2*) the carbon monoxide content of arterial blood was measured by the method of Allen and Root (7); this value was used to calculate the tension of carbon monoxide in arterial blood by means of the Haldane relationship (8). For this calculation, it was assumed that in normal subjects, the mean difference in oxygen tension between alveolar gas and arterial blood is approximately 10 mm. Hg. Since the removal of CO from physical solution may continue after blood has left the pulmonary capillary, it is clear that arterial pCO can only underestimate the mean back pressure of carbon monoxide in the pulmonary capillary (4). In this study, therefore, arterial pCO is used as a minimal estimate of mean capillary pressure for carbon monoxide.

The pCO_2 of arterial blood was determined from the line charts of Van Slyke and Sendroy (9). For this measurement, the blood CO_2 content and oxyhemoglobin saturation were determined by the method of Van Slyke and Neill (10) and pH by the MacInnes-Belcher glass electrode. The oxygen and carbon dioxide contents of expired gas were measured in a micro-Scholander apparatus (11).

To relate pulmonary arterial pressures to D_{LCO}, blood pressures were recorded by means of Statham transducers coupled with a multichannel oscilloscope recording apparatus.[2]

Voluntary hyperpnea. In 10 of the normal subjects and four of the patients with rheumatic heart disease, the observations at rest and during exercise were supplemented by similar measurements during a period of voluntary hyperpnea. The level of ventilation during hyperpnea was set to correspond to that which was reached spontaneously during exercise. In order to avoid depletion of carbon dioxide and to preserve a steady state, 3 or 5 per cent CO_2 was added to the inspired mixture in accord with the level of minute ventilation. The actual sequence was as follows: After measurements at rest and during exercise, the subjects underwent a final period of hyperpnea which consisted of breathing 3 to 5 per cent CO_2 in air for 14 minutes followed by an additional four minutes of the same inspired mixture, plus 0.1 per cent CO. During the last two minutes, blood and expired gas samples were collected in the usual way for the measurement of pulmonary blood flow and D_{LCO}.

Unilateral occlusion of one pulmonary artery. In six subjects with either a normal cardiorespiratory system or

[1] Liston-Becker Division of Beckman Instrument Co., Stamford, Conn.

[2] Electronics for Medicine, White Plains, N. Y.

TABLE I

*The pulmonary diffusing capacity in 21 normal subjects at rest**

Patient	Age	Sex	BSA	f	V_T	$\dot{V}_{O_2}$	R_E	Pa_{CO_2}	$\dot{V}_{CO}$	$\bar{P}_{ACO}$	Pa_{CO}	V_D/V_T ×100	CO_F ×100	D_{LCO}
			M.²	*per min.*	*ml.*	*ml./min.*		*mm. Hg*	*ml./min.*	*mm. Hg*	*mm. Hg*	%	%	*ml./min./ mm. Hg*
R. L.	17	M	1.75	18.5	390	257	0.83	41	3.05	0.153	0.003	21	60	20.3
J. P.	17	M	1.95	22.5	427	296	0.76	41	3.16	0.181	0.013	35	45	18.8
J. R.	36	M	1.96	18.5	516	310	0.82	41	3.54	0.155	0.003	32	51	23.3
S. B.	59	M	2.10	17.5	594	296	0.83	36	3.32	0.230		33	40	14.4
O. B.	31	M	1.78	9.5	561	222	0.71	41	2.05	0.210	0.018	27	48	10.7
J. P.	40	M	2.09	17.5	508	295	0.77	38	3.03	0.261	0.004	27	44	11.8
C. B.	41	M	1.69	14.5	487	236	0.78	39	2.50	0.213		28	45	11.7
H. S.	35	M	1.91	16.0	548	257	0.97	39	3.00	0.271	0.012	26	46	11.5
E. R.	49	M	1.74	15.5	472	226	0.85	40	2.79	0.208		30	48	13.4
M. O.	28	M	1.98	15.0	530	298	0.72	39	3.22	0.213	0.001	28	50	15.2
T. M.	17	M	1.96	14.5	543	291	0.82	38	3.71	0.159	0.003	21	54	23.7
C. R.	24	M	1.80	14.0	377	189	0.85	41	2.22	0.186	0.024	20	55	13.7
A. A.	48	M	2.01	14.5	484	222	0.78	42	2.55	0.186	0.002	38	47	13.8
M. H.	36	M	1.85	15.0	514	246	0.89	41	2.88	0.236	0.020	29	46	13.3
J. L.	39	M	1.96	18.5	440	238	0.74	36	2.41	0.246	0.047	35	38	12.0
M. I.	30	M	1.68	17.5	392	225	0.79	38	2.63	0.206	0.004	26	50	13.0
E. G.	61	M	1.93	18.0	532	311	0.78	40	3.10	0.221	0.001	39	40	14.0
P. G.	56	M	1.34	22.0	389	202	0.75	42	2.05	0.201	0.009	40	36	10.7
D. O'D.	44	F	1.62	19.0	412	214	0.86	40	2.57	0.280	0.039	35	41	10.7
M. M.	62	F	1.52	20.0	393	266	0.67	43	1.74	0.203	0.019	34	43	9.0
L. D.	55	F	1.60	15.0	366	218	0.74	42	1.49	0.157	0.021	38	44	11.0

* Symbols: BSA = body surface area, square meters; f = respiratory frequency, breaths per minute; V_T = tidal volume, ml. BTPS; $\dot{V}_{O_2}$ = oxygen consumption, ml. per minute STPD; R_E = respiratory exchange ratio, expired air; Pa_{CO_2} = tension of carbon dioxide in arterial blood, mm. Hg; V_{CO} = uptake of carbon monoxide, ml. per minute STPD; $\bar{P}_{ACO}$ = mean alveolar carbon monoxide tension, mm. Hg; Pa_{CO} = tension of carbon monoxide in arterial blood, mm. Hg; $V_D/V_T \times 100$ = ratio of personal dead space (total dead space minus the instrument dead space) to tidal volume, per cent; $CO_F \times 100$ = ratio of the uptake of carbon monoxide to the volume of carbon monoxide inspired, per cent; and D_{LCO} = diffusing capacity of the lung for carbon monoxide, ml. per minute per mm. Hg.

TABLE II

*The respiration, circulation and pulmonary diffusing capacity in normal subjects at rest, during exercise and voluntary hyperpnea**

Patient, Age, Sex, BSA/M.²	State	f	V_T	$\dot{V}_E$	V_{O_2}	R_E	P_{aCO_2}	V_{CO}	$\bar{P}_{ACO}$	P_{aCO}	V_D/V_T ×100	CO_F ×100	D_{LCO}	$\dot{Q}$
		per min.	*ml.*	*L./min.*	*ml./min.*		*mm. Hg*	*ml./min.*	*mm. Hg*	*mm. Hg*	%	%	*ml./min./ mm. Hg*	*L./min.*
						Rest and exercise								
H. K.	Rest	18.5	542	8.35	260	0.76	40	2.18	0.257	0.011	26	35	8.9	6.7
24, F	Exer.	23	839	16.05	498	0.89	39	4.78	0.279	0.038	29	36	19.8	8.30
1.68	Exer.	26	945	20.42	636	0.99	43	5.31	0.350	0.072	20	29	19.1	8.96
A. S.	Rest	17	439	6.16	284	0.66	32	2.94	0.226	0.018	19	51	14.1	8.6
28, M	Exer.	34	642	18.01	595	0.88	33	6.22	0.330	0.050	27	36	22.2	12.4
1.65	Exer.	40	768	25.30	706	0.95	32	6.66	0.399	0.099	33	27	22.2	13.8
N. L.	Rest	19	362	5.66	216	0.91	40	2.46	0.192	0.015	22	51	14.0	5.02
26, F	Exer.	29	597	14.20	618	0.89	38.5	4.89	0.344	0.028	20	37	15.5	9.50
1.51	Exer.	30	834	20.60	802	0.96	35	6.10	0.393	0.061	22	31	18.4	11.30
	Rest	17	416	5.83	254	0.88	40	2.49	0.185	0.030	23	49	16.0	6.20
C. M.	Rest	19	349	5.39	202	0.78	37	1.85	0.208	0.013	27	44	10.0	
34, F	Exer.	36	585	17.15	554	0.84	36.5	4.08	0.319	0.055	37	28	15.4	
1.58														
D. E.	Rest	13	827	8.79	320	0.82	31	3.47	0.232	0.024	25	47	16.7	
36, M	Exer.	19.5	1,055	16.82	954	0.87	33	6.01	0.280	0.038	28	41	24.8	
2.20	Exer.	21	1,310	22.50	1,051	0.92	39	7.43	0.337	0.054	23	38	26.3	
						Rest, exercise and voluntary hyperpnea†								
A. S.	Rest	12	519	5.07	256	0.74	39.5	2.56	0.191	0.009	22	54	14.1	6.24
24, M	Exer.	21	1,007	17.25	694	1.06	38.5	7.54	0.317	0.032	17	45	26.5	8.47
1.89	Hyper.	20	1,270	20.70	255	1.00	36.5	7.24	0.284	0.050	39	36	30.9	5.67
M. M.	Rest	15.5	506	6.45	230	0.80	33	3.08	0.242	0.005	22	51.3	13.0	6.76
27, F	Exer.	22.0	1,012	18.34	542	1.07	36	6.48	0.335	0.027	31	35.1	21.0	10.04
1.61	Hyper.	20.5	825	15.60	283	0.78	37	5.60	0.368	0.090	31	36.0	20.0	8.09
C. C.	Rest	8	1,045	6.86	254	0.89	35	3.70	0.258	0.023	29	55	15.7	4.38
44, M	Exer.	20	925	15.19	664	0.90	37	5.84	0.312	0.033	30	38	21.0	7.64
1.81	Hyper.	10.5	1,776	15.31	282	0.82	40	5.42	0.298	0.051	35	35	22.0	5.42
	Hyper.	26.0	1,120	23.70	280	0.92	38	6.21	0.382	0.053	46	26	18.0	4.59
L. S.	Rest	10.5	539	4.63	203	0.79	34.5	2.35	0.155	0.006	19	60	15.8	5.34
20, F	Exer.	29.5	905	27.80	704	1.04	35	7.90	0.277	0.027	26	41	31.5	9.38
1.61	Hyper.	22	899	16.20	332	0.51	40	5.92	0.279	0.040	23	42	24.8	6.74
R. G.	Rest	19.5	482	7.80	183	0.80	36	3.72	0.312	0.015	26	49	12.5	
15, M	Exer.	30	611	15.20	591	0.90	38	5.84	0.340	0.025	23	39	18.6	
1.62	Hyper.	15	1,125	14.00	263	1.38	26	5.92	0.313	0.038	23	43	21.6	
J. R.	Rest	12	678	6.55	353	0.71	40	3.03	0.178	0.028	25	45	20.2	
26, M	Exer.	24	1,391	26.90	1,143	0.97	38	8.60	0.361	0.044	20	35	27.1	
2.08	Hyper.	4.3	3,020	10.52	452	0.98	36	5.43	0.206	0.048	17	56	33.7	
	Hyper.	14	3,329	37.50	529	1.77	26	9.00	0.384	0.052	31	26	27.1	
J. J.	Rest	19	356	5.63	251	0.71	40	2.22	0.185	0.028	32	48	14.2	6.4
43, M	Exer.	25	1,077	22.40	934	1.10	40	7.05	0.354	0.047	36	36	23.0	10.74
1.59	Rest	16	436	5.81	245	0.75	40	2.62	0.204	0.046	32	55	16.6	6.8
	Hyper.	25	1,544	31.85	350	0.43	46	7.89	0.340	0.067	32	28	28.9	8.14
E. M.	Rest	17	366	5.17	218	0.75	40	2.04	0.149	0.012	35	47	14.9	6.61
51, M	Exer.	21.5	1,105	19.80	798	1.12	40	5.32	0.264	0.046	42	28	24.4	12.68
1.65	Rest	17.5	380	5.53	240	0.65	40	2.12	0.176	0.056	36	45	17.6	7.50
	Hyper.	22	1,329	24.20	322	0.42	44	7.67	0.351	0.061	22	35	26.6	7.33

* Symbols are the same as in Table I, plus: $\dot{V}_E$ = total ventilation (expired air), L. per minute, STPD and $\dot{Q}$ = pulmonary blood flow, L. per minute.

† During voluntary hyperpnea, Subjects A. S., M. M. and C. C. breathed 3 per cent CO_2 in air; Subjects J. J., E. M., B. K., J. I. and L. S. breathed 5 per cent CO_2 in air; and Subjects R. G. and J. R. breathed ambient air.

TABLE II—*Continued*

Patient, Age, Sex, BSA/M.²	State	f	V_T	$\dot{V}_E$	$\dot{V}_{O_2}$	R_E	Pa_{CO_2}	$\dot{V}_{CO}$	$\bar{P}_{ACO}$	Pa_{CO}	V_D/V_T ×100	CO_F ×100	D_{LCO}	$\dot{Q}$
		per min.	*ml.*	*L./min.*	*ml./min.*		*mm. Hg*	*ml./min.*	*mm. Hg*	*mm. Hg*	%	%	*ml./min./ mm. Hg*	*L./min.*
B. K.	Rest	14	554	6.37	272	0.82	44	2.41	0.190	0.017	32	45	13.9	6.80
41, M	Exer.	28	937	21.58	1,104	1.06	47	7.28	0.306	0.026	25	38	26.1	16.20
1.79	Rest	14	560	6.44	292	0.78	46	2.51	0.180	0.036	32	46	17.4	6.80
	Hyper.	24	1,234	24.00	291	0.80	51	8.57	0.280	0.063	27	40	39.6	7.67
J. I.	Rest	21	370	6.38	259	0.72	43	2.42	0.270	0.015	27	43	9.5	6.8
26, M	Exer.	31	683	17.35	692	0.92	44	5.16	0.331	0.029	35	32	17.1	10.2
1.77	Hyper.	32	720	18.90	370	0.67	42	5.20	0.293	0.056	46	29	21.9	7.88

a unilateral pulmonary lesion (Table III), D_{LCO} and pulmonary blood flow were measured for each lung separately during normal flow and during partial obstruction to flow through one pulmonary artery.

The measurement of blood flow through each lung separately was done as previously described (12). In brief, the techniques included: *1*) bronchospirometry for the administration of different inspired mixtures to each lung, as well as the collection of expired gas from each lung separately; *2*) cardiac catheterization with a triple lumen catheter to allow sampling and injection proximal and distal to the occlusive balloon; and *3*) arterial cannulation.

The rate of blood flow through each lung was changed by inflating the balloon in one pulmonary artery. Blood flow was thus diminished to one lung and correspondingly increased in the opposite one.

The lung with the occluded pulmonary artery breathed 25 per cent O_2, while the contralateral lung breathed 21 per cent O_2. Following a 15 minute period of equilibration, each lung continued to breathe its own inspired mixture plus 0.1 per cent CO for an additional four minutes. Blood and gas samples for the calculation of O_2 uptake, CO uptake, cardiac output and arterial blood pCO_2 were collected during the last two minutes of the four minute period.

By this protocol, *total* blood flow may be calculated by dividing O_2 uptake of both lungs by the corresponding arteriovenous difference for O_2. The blood flow through the lung receiving 25 per cent O_2 is calculated from its O_2 uptake and the arteriovenous O_2 difference across that lung, on the assumption that the pulmonary venous blood from that lung is 98 per cent saturated. The flow through the contralateral lung is measured as the difference between the total blood flow and the flow through the lung receiving the 25 per cent O_2. For these measurements, it is assumed on the basis of previous studies in this laboratory that during occlusion of one pulmonary artery, there is no significant bronchial collateral circulation (13) to the compromised side.

For the calculation of the D_{LCO} for each lung separately, during both the control and test periods, separate estimates of pulmonary dead space were required: During the control period, dead space was calculated for each lung by the Bohr formula on the assumption that the arterial tension of carbon dioxide is equal to the alveolar tension of carbon dioxide. During the period of partial occlusion, the calculation was more indirect: a total dead space for both lungs was calculated by the Bohr relationship using the tidal volume, the fraction of CO_2 in expired gas from both lungs and the arterial pCO_2. The dead space of the lung through which flow was increased was similarly calculated from the arterial pCO_2 and the expired fraction of CO_2 from that lung. The dead space of the remaining lung was calculated as the difference between these two. Where occlusion of a pulmonary artery was complete, as in J. M., no estimate of physiologic dead space in that lung was possible; in this case, the control dead space was used in the calculations of D_{LCO}.

CALCULATIONS

In addition to the measurement of the diffusing capacity of the lung for carbon monoxide (D_{LCO}), the uptake of CO by the lung per minute ($\dot{V}_{CO}$), and the ratio of the uptake of CO to the volume of CO inspired (CO_F) have been used as indices of the diffusing capacity.

The pulmonary diffusing capacity is calculated according to the following expression of Fick's law of diffusion:

$$D_{LCO} = \frac{\dot{V}_{CO}}{\bar{P}_{ACO} - \bar{P}_{CCO}},$$

where

D_{LCO} = diffusing capacity of the lung for carbon monoxide in ml. per minute per mm. Hg,

$\dot{V}_{CO}$ = uptake of carbon monoxide, ml. per minute,

$\bar{P}_{ACO}$ = mean alveolar carbon monoxide tension, mm. Hg and

$\bar{P}_{CCO}$ = mean tension of carbon monoxide in pulmonary capillary blood, mm. Hg.

The uptake of CO is calculated from an analysis of inspired and expired fractions of CO using a nitrogen correction for metabolic gas exchange:

$$\dot{V}_{CO} = \dot{V}_E \left(\frac{F_{E_{N_2}}}{F_{I_{N_2}}} F_{ICO} - F_{ECO} \right),$$

where

$\dot{V}_E$ = total minute ventilation, L. per minute, STPD,

$F_{E_{N_2}}$ = fraction of nitrogen in expired gas,

$F_{I_{N_2}}$ = fraction of nitrogen in inspired gas,

F_{ICO} = fraction of carbon monoxide in inspired gas and

F_{ECO} = fraction of carbon monoxide in expired gas.

TABLE III

The ventilation, circulation and pulmonary diffusing capacity of each lung separately *

Patients, Age, Diagnosis, BSA/M.²	State†	Lung‡	$\dot{V}_E$	$\dot{V}_{O_2}$	R_E each lung	R_E both lungs	V_D/V_T ×100	$\dot{V}_{CO}$	CO_F ×100	$\bar{P}_{ACO} - \bar{P}_{aCO}$	D_{LCO}	$\dot{Q}$	$\frac{\Delta D_{LCO}}{\Delta}$‖ ×100	$\frac{\Delta \dot{V}_{CO}}{\Delta}$‖ ×100	$\frac{\Delta \dot{Q}}{\Delta}$‖ ×100
			L./min.	*ml./min.*			%	*ml./min.*	%	*mm. Hg*	*ml./min./ mm. Hg*	*L./min.*	%	%	%
C. L. 57, 1.67, Infiltrates RLL; RML	Control	R	4.01	128	0.61	0.72	43	1.20	30	0.350	3.4	5.52			
		L	5.00	136	0.82		39	1.32	28	0.313	4.2	3.58			
	LPA occluded	R	4.00	150	0.69	0.83	32	1.16	29	0.372	3.1	7.96	− 6	− 3	+ 44
		L	5.11	86	1.08		51	1.09	22	0.290	3.8	2.20	−10	−17	− 38
	Control	R	4.87	123	0.91	0.98	38	1.12	23	0.368	3.0	6.06			
		L	5.37	119	1.06		39	1.23	24	0.316	3.9	2.90			
	LPA occluded	R	3.95	153	0.66	0.77	29	1.13	29	0.383	2.9	6.58	− 3	+ 1	+ 9
		L	4.74	89	0.97		48	0.97	21	0.311	3.1	2.05	−20	−29	− 21
J. C. 54, 1.71, Bronchiectasis RML; RLL	Control	R	6.83	189	0.71	0.71	46	2.67	39	0.238	11.2	4.02			
		L	3.91	163	0.71		25	2.41	62	0.250	9.7	2.75			
	RPA occluded	R	5.99	32	1.53	0.69	75	1.40	23	0.370	3.8	0.43	−66	−48	− 89
		L	3.51	228	0.58		20	2.16	63	0.263	8.2	9.18	−15	−10	+230
	RPA occluded	R	6.81	12	3.00	0.73	77	1.04	15	0.459	2.3	0.21	−80	−61	− 94
		L	3.96	235	0.61		24	2.12	55	0.260	8.2	7.49	−15	−12	+170
J. Mc. 55, 1.95, Carcinoma left hilum	Control	R	5.38	169	0.84	0.87	39	2.45	46	0.222	11.0	5.11			
		L	4.68	75	0.94		61	0.94	20	0.180	5.2	1.66			
	LPA occluded	R	8.57	251	0.94		36	2.75	32	0.287	9.6	7.18	−15	+12	+ 40
		L	5.20	0			55¶	0.43	8	0.420	1.0	0	−80	−53	−100
		R	8.24	241	0.94		35	2.76	33	0.280	9.9	6.9	−13	+13	+ 35
		L	5.79	0			50¶	0.50	8	0.380	1.3	0	−73	−47	−100
A. J. 51, 1.74, Bilateral apical infiltration	Control	R	6.50	150	0.91	1.10	42	1.70	26	0.300	5.7	2.98			
		L	7.88	124	1.33		44	1.86	24	0.298	6.2	2.06			
	RPA occluded	R	4.92	89	1.08	0.97	46	1.23	25	0.328	3.7	1.97	−35	−28	− 34
		L	6.50	183	0.92		30	1.91	30	0.351	5.4	4.07	−13	+ 3	+ 98
E. W. 48, 1.85, Normal lungs	Control	R	6.54	163	0.88	0.95	45	1.63	26	0.300	5.5	3.80			
		L	4.31	110	1.05		29	1.40	27	0.282	5.0	3.03			
	RPA occluded	R	4.90	89	0.82	0.73	62	0.82	17	0.219	3.7	1.6	−15	−50	− 58
		L	3.40	148	0.68		31	1.43	43	0.246	5.6	4.48	+12	+ 2	+ 48
	RPA occluded	R	4.52	36	2.01	0.92	59	0.84	19	0.229	3.7	0.74	−31	−48	− 80
		L	3.90	167	0.68		33	1.41	37	0.250	5.6	4.91	+ 2	+ 1	+ 62
T. G. 52, 1.80, Carcinoma right lung	Control	R	4.46	87	0.84	0.72	59	0.95	22	0.226	4.2**	3.73			
		L	4.97	214	0.66		38	1.42	30	0.374	3.8**	4.20			
	RPA occluded	R	5.65	48	0.95	0.63	76	0.66	12	0.183	3.6	2.91	−14	−31	− 22
		L	5.50	288	0.57		34	1.49	28	0.383	3.9	4.24	+ 3	+ 5	+ 1

* Symbols as in Table I.
† The lung with the occluded pulmonary artery breathed 25 per cent O_2 while the contralateral lung breathed 21 per cent O_2. The same mixtures, plus 0.1 per cent CO, were used to measure D_{LCO}.
‡ R refers to right lung; L to left lung.
‖ Represents $\frac{\text{final value} - \text{initial value}}{\text{initial value}}$.
¶ Same dead space as in control period.
** The D_{LCO} of both lungs, measured two days later without bronchospirometry, was 8.2 ml. per minute per mm. Hg.

The mean alveolar tension of CO is calculated from the Bohr dead space assuming that $V_{D_{CO_2}} = V_{D_{CO}}$, so that:

$$\bar{P}_{A_{CO}} = \frac{V_T(P_{E_{CO}}) - V_{D_{CO_2}}(P_{I_{CO}})}{V_T - V_{D_{CO_2}}},$$

where

$V_{D_{CO_2}}$ = dead space for carbon dioxide based on arterial blood pCO_2,

$V_{D_{CO}}$ = dead space for carbon monoxide and

V_T = tidal volume, BTPS.

The fraction of CO taken up from inspired gas was calculated according to Filley, MacIntosh and Wright (6) as follows:

$$CO_F = \frac{\dot{V}_{CO}}{V_E\left(\frac{F_{E_{N_2}}}{F_{I_{N_2}}} F_{I_{CO}}\right)} - V_D \text{ (instrument) (f)} + (F_{I_{CO}} - F_{A_{CO}}),$$

where

CO_F = ratio of the uptake of carbon monoxide to the volume of carbon monoxide inspired, per cent,

$F_{A_{CO}}$ = fraction of carbon monoxide in alveolar gas and

f = respiratory frequency, breaths per minute.

The arterial tension of CO was calculated from the Haldane relationship (8):

$$P_{a_{CO}} = \frac{P_{a_{O_2}} \cdot (COHb)}{210 \cdot (O_2Hb)},$$

where

$P_{a_{CO}}$ = tension of carbon monoxide in arterial blood, mm. Hg,

$P_{a_{O_2}}$ = tension of oxygen in arterial blood, mm. Hg,

(COHb) = content of carboxyhemoglobin in arterial blood, volumes per cent,

(O_2Hb) = content of oxyhemoglobin in arterial blood, volumes per cent and

210 = relative affinity constant for carbon monoxide and oxygen in blood.

RESULTS

Rest and exercise

The $D_{L_{CO}}$ was measured at rest in 36 normal subjects. These individual measurements and the data from which they were derived appear in Tables I and II. The average resting $D_{L_{CO}}$ for this entire group was 14.1 ml. per minute per mm. Hg.

The corresponding values for patients with rheumatic heart disease appear in Table IV. The average resting $D_{L_{CO}}$ for this group of subjects is 14.6 ml. per minute per mm. Hg, which is not significantly different ($p > 0.05$) from the normal subjects.

An analysis of the resting $D_{L_{CO}}$ according to sex, for both normal subjects and patients with rheumatic heart disease, is included in Table V. It may be seen that the mean resting value for the normal males (14.8) is higher than the mean resting value for normal females (11.5). This difference is only of suggestive statistical significance ($p < 0.05$).

It is of interest, that the mean $D_{L_{CO}}$ of the three male subjects in the rheumatic group is higher than the value in the normal subjects. However, the number of subjects is obviously too few for statistical comparison.

The diffusing capacity during exercise and the data from which they were derived are shown in Table II for normal subjects and in Table IV for subjects with rheumatic heart disease. It may be seen that each subject experienced an increase in diffusing capacity during exercise.

As is shown in Table V, the mean $D_{L_{CO}}$ during exercise in normal subjects is slightly greater (22.1 ml. per minute per mm. Hg) than the mean exercise $D_{L_{CO}}$ in subjects with rheumatic heart disease (20 ml. per minute per mm. Hg). However, Table V also indicates that the normal subjects achieved a higher level of exercise (mean O_2 uptake of 430 ml. per minute per $M.^2$) than did subjects with rheumatic heart disease (mean O_2 uptake of 320 ml. per minute per $M.^2$). When this difference in level of exercise is taken into account by expressing the increase in $D_{L_{CO}}$ as per 100 ml. increase in oxygen uptake, both groups demonstrate an average increase in $D_{L_{CO}}$ of 1.9 ml. per minute per mm. Hg per 100 ml. increase in O_2 uptake.

In Figure 1, the $D_{L_{CO}}$ is related to minute ventilation and to pulmonary blood flow for both groups of subjects at rest and during exercise. It may be seen, in Figure 1A, that there is a good statistical correlation ($p < 0.001$) between $D_{L_{CO}}$ and the minute ventilation, at rest and during exercise; on the other hand, as seen in Figure 1B, the correlation between $D_{L_{CO}}$ and pulmonary blood flow is poorer ($p = 0.01$). Figure 1 emphasizes that during exercise, $D_{L_{CO}}$ increases in subjects with mitral stenosis in the face of abnormally low increments in pulmonary blood flow.

Figure 2 substitutes CO uptake for $D_{L_{CO}}$ and shows a similar type of relationship with minute ventilation and pulmonary blood flow.

TABLE IV

The ventilation, circulation and pulmonary diffusing capacity in patients with rheumatic heart disease at rest, during exercise and voluntary hyperpnea *

Patients, Age, Sex, BSA/M.²	State	f	V_T	$\dot{V}_{O_2}$	R_E	P_{aCO_2}	$\dot{V}_{CO}$	$\bar{P}_{ACO}$	P_{aCO}	D_{LCO}	CO_F ×100	V_D/V_T ×100	$\dot{Q}$	P.A. pressure S	D	M
		per min.	*ml.*	*ml./min.*		*mm. Hg*	*ml./min.*	*mm. Hg*	*mm. Hg*	*ml./min./ mm. Hg*	*%*	*%*	*L./min.*	*mm. Hg*		
							Rest and exercise									
F. R.	Rest	10	597	277	0.72	43	2.36	0.096	0.009	27.1	59	28	3.60	34	19	29
40, M	Exer.	25.5	1,444	1,023	1.02	42	10.56	0.286	0.031	41.5	39	38	6.80	76	50	60
1.85																
C. M.	Rest	17	460	170	0.91	37	2.23	0.210	0.013	11.4	45	30	3.54	42	22	31
51, F	Exer.	40	788	634	1.01	30	5.90	0.359	0.045	18.8	26	36	8.93	55	32	43
1.51																
P. B.	Rest	16.5	514	145	0.79	37	2.07	0.201	0.011	10.9	45	25	5.00	40	16	27
37, F	Exer.	28.0	596	417	0.96	36	4.25	0.230	0.041	22.5	41	35	7.74	65	28	41
1.37																
F. L.	Rest	25.5	457	216	0.72	32	2.68	0.181	0.019	16.6	49	25	4.80	28	15	18
31, F	Exer.	26	602	300	0.87	38	3.18	0.221	0.038	17.3	33	33	5.10	37	20	29
1.23																
L. D.	Rest	15.5	583	275	0.75	31	2.59	0.306	0.021	9.1	38	26	5.85	61	25	37
43, F	Exer.	30	964	648	1.06	30	5.33	0.454	0.044	13.0	24	26	5.89	97	55	74
1.57																
G. A.	Rest	16	529	235	0.84	31	3.29	0.178	0.015	20.2	54	23	4.52	40	18	26
56, F	Exer.	25	740	480	0.90	33	5.31	0.228	0.031	27.0	38	33	5.16	72	44	58
1.66																
M. I.	Rest	20	385	231	0.83	40.5	2.42	0.238	0.011	10.7	43	31	5.02	67	34	45
31, F	Exer.	29.5	556	423	0.97	40	4.22	0.343	0.029	13.4	33	35	6.32	110	47	67
1.59																
H. K.	Rest	10.0	653	270	0.77	42	2.79	0.178	0.011	16.8	53	29	4.66	60	24	38
40, M	Exer.	20.0	760	496	0.89	41.5	5.28	0.239	0.029	25.1	45	32	5.76	84	32	52
1.93																
R. D.	Rest	13.5	480	267	0.74	39	2.47	0.211	0.021	13.0	50	25	4.31	41	18	28
34, M	Exer.	22	881	422	0.97	40	5.40	0.330	0.046	19.0	35	22	4.26	75	38	55
1.61																
							Rest, exercise and voluntary hyperpnea †									
S. C.	Rest	14	602	202	0.75	31.5	2.40	0.275	0.016	9.3	37	35	4.04	61	23	36
51, F	Exer.	18	839	454	0.93	31	4.77	0.373	0.027	13.8	25	43	5.82	105	48	70
1.47	Hyper.	24	713	233	0.75	42	3.72	0.324	0.040	13.1	27	46	4.68	61	21	36
V. W.	Rest	13.5	385	172	0.74	35	1.97	0.184	0.003	10.9	52	23	3.19	60	31	41
34, F	Exer.	22	567	357	0.93	36	3.99	0.292	0.019	14.6	41	25	3.40	114	66	86
1.36	Hyper.	21	638	‡		35	3.63	0.253	0.049	17.7	35	24		72	36	47‖
L. L.	Rest	11	417	215	0.62	40	2.14	0.099	0.004	22.6	63	23	5.52	40	23	33
33, F	Exer.	24	752	570	1.00	41	6.29	0.251	0.021	27.2	42	26	7.70	82	43	60
1.63	Hyper.	20	1,420	250	0.95	35	6.88	0.254	0.028	30.4	29	50	6.24	33	15	24
I. R.	Rest	16	318	185	0.73	43	1.72	0.177	0.012	10.4	50	31	4.52	20	5	13
32, F	Exer.	25.5	484	275	1.00	40	3.16	0.278	0.041	13.3	35	40	4.67	24	8	16
1.43	Hyper.	18	750	220	0.50	42	4.13	0.246	0.052	21.3	41	37	4.68	19	8	12

* Symbols are the same as in Table I, plus P.A. pressure, SDM = pressure in the pulmonary artery; systolic, diastolic and mean, mm. Hg.
† During voluntary hyperpnea, Subjects S. C., V. W. and L. L. breathed 3 per cent CO_2 in air; Subject I. R. breathed 5 per cent CO_2 in air.
‡ No gas analyses; V_D assumed.
‖ Pressure unchanged from level just prior to voluntary hyperpnea.

TABLE V

*The diffusing capacity and fractional uptake of carbon monoxide at rest and during moderate exercise**

Subjects Sex	No.	Age	State	$\dot{V}_{O_2}$	D_{LCO}	$CO_F \times 100$
		yrs.		*ml./min./M.²*	*ml./min./mm. Hg*	%
				Normal subjects		
Males	28	(14–61)	Rest	141 (113–172)	14.8 (9.5–23.7) ± 3.48	47 (36–60) ±4.9
Females	8	(20–62)		143 (126–175)	11.5 (9.0–15.8) ± 2.28	45 (34–60) ±8.2
Males	10	(14–44)	Exercise	450 (360–617)	23.3 (17.4–27.1) ± 4.10	36 (27–45) ±4.8
Females	5	(20–44)		391 (296–531)	20.1 (16.0–31.5) ± 5.80	34 (28–41) ±4.0
				Rheumatic heart disease		
Males	3	(34–40)	Rest	151 (140–165)	19.3 (14.0–27.1) ± 5.6	54 (50–59) ±3.3
Females	10	(31–51)		139 (112–176)	13.2 (9.1–22.5) ± 3.3	48 (37–63) ±7.4
Males	3	(34–40)	Exercise	357 (262–552)	27.9 (16.8–41.6) ±10.3	40 (35–45) ±4.7
Females	10	(31–57)		305 (193–420)	17.5 (13.0–27.4) ± 4.4	34 (24–42) ±6.5

* Symbols as in Table I. Mean values are followed by range in parentheses; figures after range indicate standard deviation.

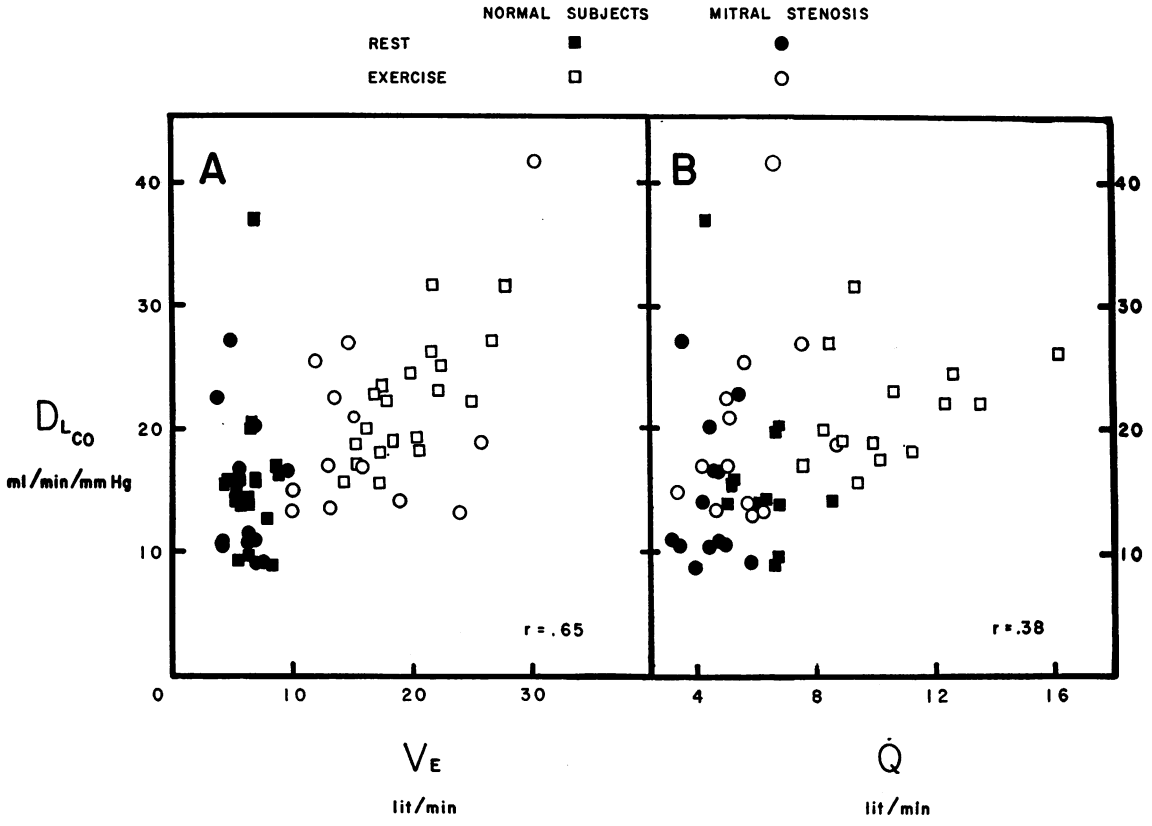

FIG. 1. THE EFFECT OF MINUTE VENTILATION ($\dot{V}_E$) AND PULMONARY BLOOD FLOW ($\dot{Q}$) ON THE DIFFUSING CAPACITY OF THE LUNG FOR CARBON MONOXIDE (D_{LCO}) IN NORMAL SUBJECTS AND IN PATIENTS WITH MITRAL STENOSIS, AT REST AND DURING EXERCISE

Although pulmonary blood flow increased only slightly during exercise in the patients with mitral stenosis, the D_{LCO} increased normally (Table V).

Finally, as may be seen from Table V, the amount of CO removed from inspired air averaged 45 per cent in normal subjects at rest and decreased to 35 per cent during exercise. These mean values for patients with mitral stenosis are not significantly different ($p > 0.05$).

Voluntary hyperpnea

The data concerning minute ventilation, pulmonary blood flow and diffusing capacity during voluntary hyperpnea are listed in Tables II and IV. In all but three instances (M. M., L. S. and R. G.), the minute ventilation during voluntary hyperpnea was the same, or greater, than that during exercise. It may be seen that this deliberate augmentation of ventilation up to levels of 32 L. per minute was associated with increases in cardiac output of only 20 per cent above the resting levels.

Figure 3 illustrates the relationship between D_{LCO} and minute ventilation (Figure 3A) and D_{LCO} and pulmonary blood flow (Figure 3B) in four normal subjects and one subject with mitral stenosis at rest, during exercise and during voluntary hyperpnea. It may be seen from Figure 3A that as ventilation is increased, either by voluntary hyperpnea or exercise, the diffusing capacity also increases. However, as may be seen in Figure 3B, the increases in D_{LCO} during voluntary hyperpnea are independent of increases in pulmonary blood flow since: *1*) In the rheumatic subject, the increases in D_{LCO} were unaccompanied by changes in blood flow either during voluntary hyperpnea or exercise, and *2*) in the normal subjects, the largest increments in D_{LCO} occur during voluntary hyperpnea when blood flow was consistently less than during exercise.

In Figure 4A, minute ventilation is plotted against the uptake of carbon monoxide for the subjects of Figure 3. For the sake of reference, the line from Figure 1 relating these values

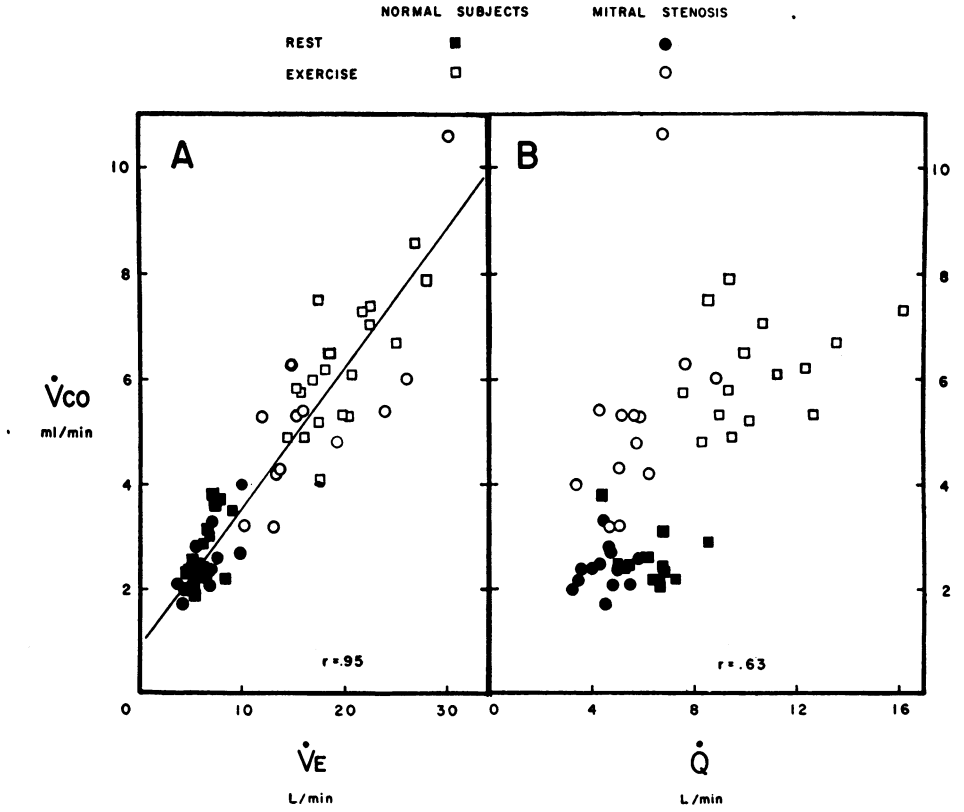

FIG. 2. THE EFFECT OF MINUTE VENTILATION ($\dot{V}_E$) AND PULMONARY BLOOD FLOW (Q) ON THE UPTAKE OF CARBON MONOXIDE ($\dot{V}_{CO}$) IN NORMAL SUBJECTS AND IN PATIENTS WITH MITRAL STENOSIS AT REST AND EXERCISE

during rest and exercise is also included. It may be seen that the relationship between the CO uptake and ventilation during voluntary hyperpnea is the same as that during exercise. As in the case of D_{LCO}, Figure 4B illustrates that these increases in $\dot{V}_{CO}$ during voluntary hyperpnea are also independent of changes in pulmonary blood flow.

The values for the fraction of CO removed from inspired air during voluntary hyperpnea are also included in Tables II and IV. It may be seen that the fraction of CO removed from inspired gas (CO_F) is, in most instances, reciprocally related to the level of ventilation. Thus, when the level of ventilation during voluntary hyperpnea exceeded that during exercise, the CO_F was less than that during exercise. Conversely, when the level of ventilation during hyperpnea was less than that during exercise, the CO_F was higher. However, in three subjects (J. J., E. M. and B. K.), even though minute ventilation during voluntary hyperpnea exceeded that during exercise, the CO_F was higher.

In order to assess the effect of a change in ventilatory pattern on D_{LCO}, the respiratory frequency and tidal volume were varied in two subjects, C. C. and J. R., during two successive periods of voluntary hyperpnea. In both subjects, D_{LCO}, $\dot{V}_{CO}$ and CO_F were higher during breathing patterns of slow frequency and large tidal volume.

Unilateral occlusion of one pulmonary artery

In Table III are listed the data for the calculation of D_{LCO}, $\dot{V}_{CO}$ and pulmonary blood flow ($\dot{Q}$) for each lung separately. These data are also the basis for Figure 5.

The values for oxygen uptake and pulmonary blood flow in Table III indicate that different degrees of occlusion of a pulmonary artery were accomplished in different subjects. Despite these changes in blood flow, minute ventilation in each lung remained relatively unaffected. As may be seen in Figure 5, the increases in blood flow had no appreciable affect on either D_{LCO} or V_{CO}, even when blood flow increased by 230 per cent.

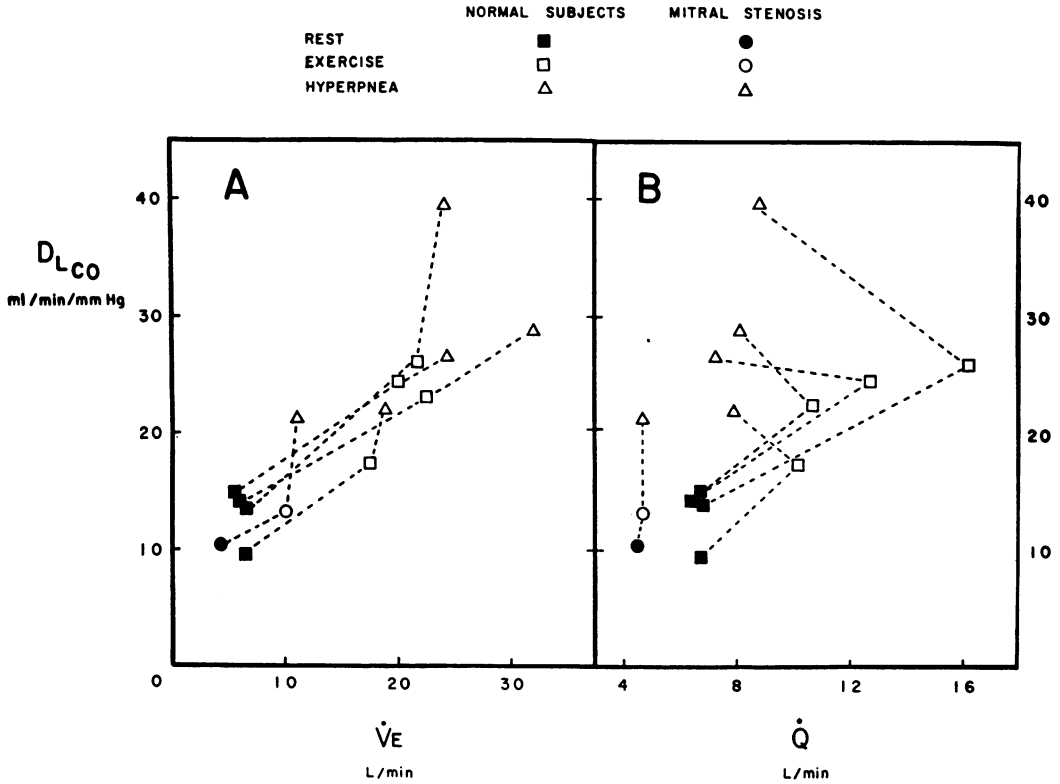

FIG. 3. THE EFFECT OF MINUTE VENTILATION ($\dot{V}_E$) AND PULMONARY BLOOD FLOW (Q) ON THE DIFFUSING CAPACITY OF THE LUNG FOR CARBON MONOXIDE (D_{LCO}) DURING REST, EXERCISE AND VOLUNTARY HYPERPNEA IN FOUR NORMAL SUBJECTS AND ONE PATIENT WITH MITRAL STENOSIS

Only when blood flow was severely curtailed, *i.e.*, to less than 50 per cent of the control value, did a decrease in D_{LCO} and $\dot{V}_{CO}$ become apparent.

Although the fraction of CO removed from inspired air tended to parallel the change in D_{LCO}, individual results are difficult to assess because of unavoidable changes in ventilation between the control and the test periods.

Relation between pulmonary artery pressure and D_{LCO}

In the normal subjects, pulmonary artery pressures averaged 18/7 mm. Hg, with a mean of 12 at rest and increased to 25/11, with a mean of 16 during exercise. In the patients with mitral stenosis (Table IV) pulmonary artery pressure was abnormally high at rest, averaging 46/21 mm. Hg, with a mean of 31; during exercise, the average pulmonary artery pressure rose to 76/39 mm. Hg, with a mean of 50. Both groups of subjects failed to show any change in pulmonary artery pressure during voluntary hyperpnea.

No correlation was demonstrable between the level of pulmonary artery pressure and the D_{LCO} in either group of subjects, either at rest or during exercise.

Effect of correction of tension of CO in arterial blood (P_{aCO}) on D_{LCO}

As expected, the tension of CO in arterial blood increased with the time of exposure to 0.1 per cent CO (14). The effect of this increase in P_{aCO} on calculated D_{LCO} is illustrated in Figure 6. It may be seen that when P_{aCO} is taken into account in the calculation of D_{LCO}, after six minutes of exposure at rest, the D_{LCO} increases by 5 to 10 per cent. The exercise D_{LCO} after 12 minutes of exposure increased by 10 to 15 per cent, and after 18 minutes of exposure D_{LCO} increased by 20 to 30 per cent.

Sources of error in methods

As may be seen from the equations above, and from the data in Tables I through V, the calcu-

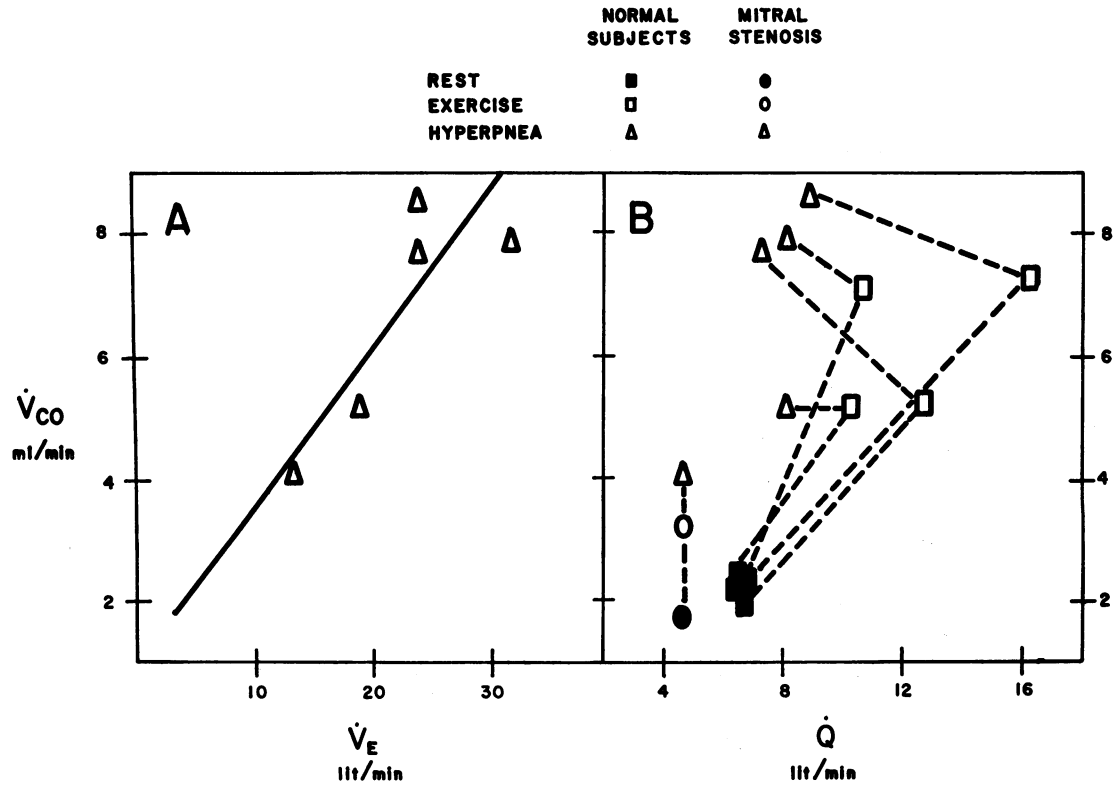

FIG. 4. THE EFFECT OF MINUTE VENTILATION ($\dot{V}_E$) AND PULMONARY BLOOD FLOW ($\dot{Q}$) ON THE UPTAKE OF CARBON MONOXIDE ($\dot{V}_{CO}$) IN THE SUBJECTS OF FIGURE 3 DURING REST, EXERCISE AND VOLUNTARY HYPERPNEA
The diagonal line in Figure 4A is derived from the data of Figure 1A by the method of least squares.

lation of D_{LCO} by the steady state method affords ample opportunity for compounding errors. As indicated by Filley, MacIntosh and Wright (6), the major sources of error are *1*) the measurement of arterial pCO_2 by virtue of its effect on the calculation of the dead space and *2*) the measurement of the expired fraction of carbon monoxide. By the nature of these errors, the estimation of D_{LCO} by the steady state method is more accurate for high, rather than low, tidal volumes. Thus, at rest, where tidal volumes are small, the effect of the dead space volume on the calculation of D_{LCO} is relatively large. An error of 2 mm. in the measurement of arterial pCO_2 may lead to an error of ± 10 per cent in the D_{LCO} by its effect on the dead space measurement. A concordant error in determination of expired CO of 2 per cent of full scale will increase the error in D_{LCO} to ± 25 per cent.

When tidal volumes are large, as during exercise or during voluntary hyperpnea, the effect of changes in dead space volume on the calculation of alveolar pCO are less, so that errors from this source diminish. Also, at high tidal volumes, gross errors in pCO_2 are readily apparent due to the unlikely dead space volumes which result. Assuming tidal volumes in the range of 2,000 ml., the combined effect of a 2 mm. error in Pa_{CO_2} and a concordant 2 per cent error in expired CO lead to a 12 per cent error in D_{LCO}. Similarly, a change in V_D/V_T ratio from 12 to 39 per cent during exercise or voluntary hyperpnea varies the D_{LCO} by approximately 9 per cent.

The use of the Fick principle for the measurement of pulmonary blood flow depends on the maintenance of steady state conditions. Although the performance of voluntary hyperpnea while breathing 3 or 5 per cent CO_2 made the achievement of a steady state difficult, nonetheless, as seen in Tables II and IV, in all but four of the subjects (J. J., N. N., L. S. and I. R.) strict criteria for a steady state were fulfilled. In these four subjects, the respiratory quotient (R.Q.) was low. This low R.Q. presumably reflects a continuation of the unsteady state which obtains at the start of CO_2 breathing when CO_2 output is reduced because of storage of metabolic CO_2 in body tissues (15). Under such circumstances, the O_2 uptake by the lungs calculated from the fractions of O_2 and CO_2 in expired gas is artificially high. The high O_2 uptake leads to an elevation of cardiac output calculated by the Fick principle. Such considerations suggest that in these subjects with a low R.Q. during voluntary hyperpnea, the *actual* increase in cardiac output was even less than indicated in Table V.

DISCUSSION

These different types of experiments are in accord in demonstrating a marked effect of minute ventilation on D_{LCO}. By way of contrast, they indicate that D_{LCO} is little affected by a change in pulmonary blood flow until flow is reduced well below 50 per cent of normal. They also offer some basis for speculation concerning the effect of the pulmonary blood volume on the pulmonary diffusing capacity.

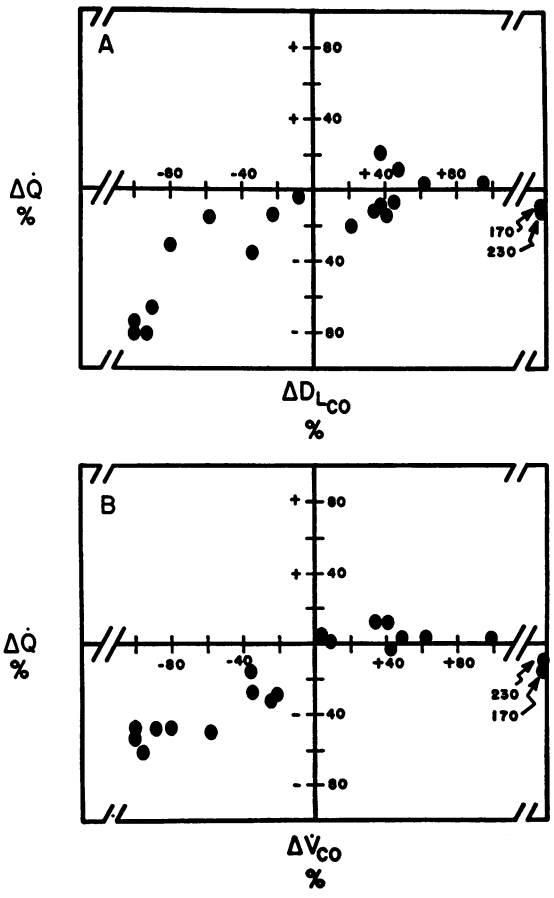

FIG. 5. THE EFFECT OF A CHANGE IN THE BLOOD FLOW THROUGH EACH LUNG (% ΔQ) ON THE CORRESPONDING DIFFUSING CAPACITY FOR CARBON MONOXIDE (% ΔD_{LCO}) (UPPER FIGURE) AND ON THE UPTAKE OF CO (% $\Delta \dot{V}_{CO}$) (LOWER FIGURE)

Ventilation

It is generally believed that during quiet breathing only a fraction of the alveolar surface is used for diffusion. During exercise, as minute ventilation increases, it is likely that the alveolar-capillary membrane is stretched and the area used for diffusion increases.

Previous indirect estimates of D_{LCO}, such as the fractional uptake of CO (16), as well as direct measurements by the single breath technique (3, 17), suggest that the volume of gas in the lung influences the area available for alveolar-capillary gas exchange. Some support for this point of view is brought forth in the present study, where an enlarged *mean* alveolar volume, presumably accomplished by slow deep breathing was associated with values of D_{LCO} greater than with usual breathing patterns.

It is pertinent to note that the relationship between the volume of alveolar gas and the D_{LCO} may involve several less evident physiological adaptations: *1*) a redistribution of blood within the lung so as to preserve CO gradients for diffusion, and *2*) absolute increases in both blood flow (18, 19) and volume (20) incident to respiratory maneuvers which involve deep or prolonged inspirations.

Although these hidden mechanisms cannot be assessed, it is nonetheless clear that methods for determining D_{LCO} which involve increases in the mean alveolar gas volume such as the single breath technique of Forster, Fowler, Bates and

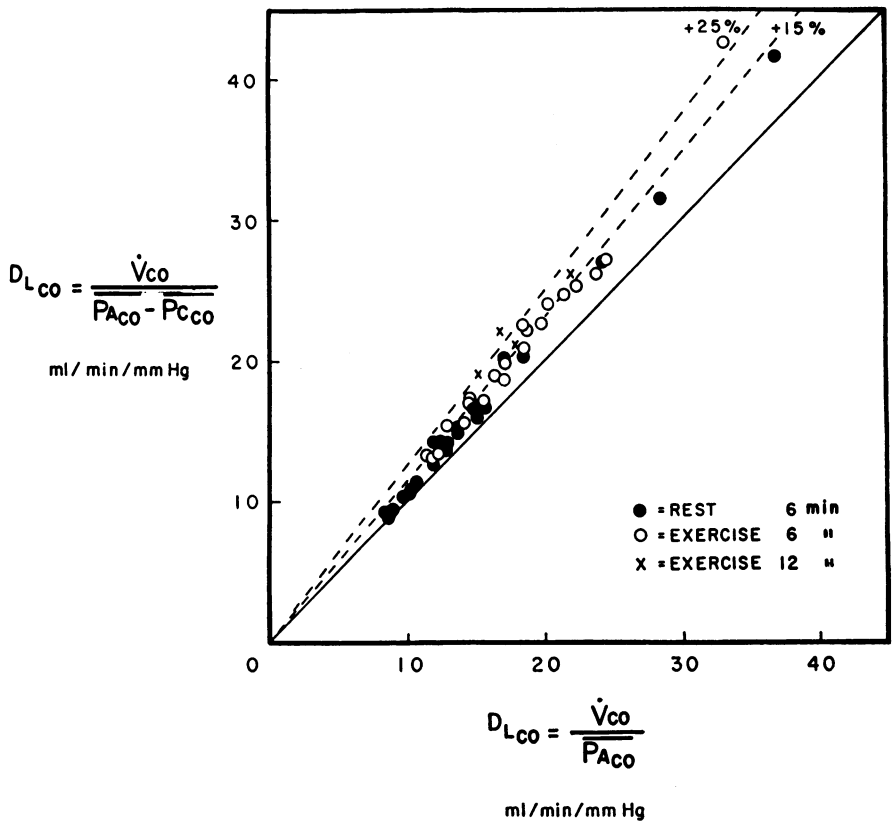

FIG. 6. THE EFFECT OF AN ESTIMATED "BACK PRESSURE" OF CARBON MONOXIDE IN PULMONARY CAPILLARY BLOOD ON THE CALCULATED VALUE FOR DIFFUSING CAPACITY OF THE LUNG

The values on the ordinate are calculated on the assumption that the mean tension of CO in arterial blood equals the mean tension of CO in the pulmonary capillary. The values for the abscissa are calculated on the assumption that the mean tension of CO in the pulmonary capillary is zero.

Van Lingen (21) and the rebreathing technique of Kruhøffer (22) should yield larger values for D_{LCO} at rest than do methods utilizing normal breathing patterns. These differences have been observed (23).

Rate of pulmonary blood flow

On the basis of calculations applied to data on CO uptake determined by Forbes, Sargent and Roughton (24), Hatch (25) concluded that at equilibrium the partition coefficient of CO between blood and air is of such high magnitude, that the rate of pulmonary blood flow should have a negligible effect on the transfer of gas from alveolar air to blood. These theoretical predictions of Hatch are supported by the results of the present study. A similar lack of relationship between uptake and blood flow would be expected for other gases whose partition coefficients are in the same order of magnitude (26). Consequently, these observations emphasize that as long as permeability of the pulmonary capillary membrane remains high, the factors limiting the uptake of such gases are the size of the diffusing surface and the volume of gas brought to it, rather than the rate of pulmonary blood flow.

With respect to the D_{LCO} as a measure of the size of the capillary bed, it is of interest that a doubling of pulmonary blood flow did not appreciably alter D_{LCO}. Several possibilities may account for a lack of increase in capillary area: *1*) that the capillaries were already distended by the supine position to a point where an increase in blood flow could be accommodated with no further increase in luminal size; *2*) that the increased pulmonary blood flow was accommodated by opening of new capillaries which are in contact with poorly ventilated alveoli; or *3*) that the change in D_{LCO} was too small to be detected by these methods. The data do not allow distinction among these possibilities.

It is easier to rationalize a reduction in $\dot{V}_{CO}$ and D_{LCO} when blood flow is severely curtailed to the point of decreasing perfusion pressures and capillary blood volume. This situation exists distal to an occlusive balloon in a pulmonary artery (27) and such reduction in $\dot{V}_{CO}$ and D_{LCO} have been observed. The possibility arises that stagnation of pulmonary blood distal to the balloon may contribute to the reduction in $\dot{V}_{CO}$ and D_{LCO}. That stagnation is of little significance in this regard is suggested by: *1*) the reduction in D_{LCO} during partial occlusion of a pulmonary artery when flow continues at a considerable, though reduced rate and *2*) the insufficient saturation of pulmonary capillary blood with CO during brief complete occlusion of a pulmonary artery. Thus, it can be shown that in a lung with an assumed capillary blood volume of 30 ml. and a measured CO uptake of 0.4 ml. per minute, the critical saturation of approximately 30 per cent would not be reached during the four minutes of CO breathing.

Relationship between D_{LCO} and pulmonary artery pressure

Pulmonary hypertension from mitral stenosis is associated with an elevation of pressure in the pulmonary capillaries (28). As a consequence, the capillaries may be distended and the area available for diffusion increased. It was observed in this study, that subjects with mitral stenosis had a normal diffusing capacity for CO. This normal value may therefore represent a balance between anatomic alteration of the smaller pulmonary vessels and an increase in the pulmonary capillary blood volume.

In contrast to the pulmonary capillary hypertension of mitral stenosis, the experiments involving unilateral occlusion of a pulmonary artery resulted in a lowering of pulmonary vascular pressure and possibly capillary blood volume distal to the occluding balloon. In these experiments, as would be anticipated, the D_{LCO} of the affected lung was decreased.

Pulmonary blood volume

In the absence of any direct measurement of pulmonary capillary blood volume, changes in this variable can only be inferred. There is indirect evidence (29) that the central blood volume increases in the supine position; the pulmonary capillaries may well share in this increase (30). Such a mechanism was invoked by Bates and Pearce (31) to explain the higher resting diffusing capacity in the supine position for both single breath and steady state methods. The supine position has also been shown to effect a more uniform distribution of blood and inspired gas

in the lungs, particularly with regard to the upper lobes (32).

These considerations suggest that the increase in D_{LCO} during voluntary hyperpnea when blood flow remains virtually unchanged may reflect, in part, an increase in alveolar capillary blood volume. They also indicate that even though pulmonary blood flow has little effect on D_{LCO}, the effect of the volume and distribution of blood in the lung may be appreciable.

The increase in D_{LCO} during exercise

Even though an attempt has been made in this study to isolate some of the individual factors which determine the diffusing capacity of the lung, it is apparent that under most physiological circumstances their interplay is so complicated as to make this type of distinction extremely difficult. This is particularly true of studies done during exercise where ventilation, pulmonary blood flow and possibly pulmonary blood volume all are increased. However, the data from this study do indicate that the increase in diffusing capacity for carbon monoxide, observed during mild to moderate exercise, is related to the increase in ventilation rather than to the increase in pulmonary blood flow. This conclusion is supported by the recent observations of others (33).

SUMMARY AND CONCLUSIONS

1. The effect of minute ventilation and pulmonary blood flow on the diffusing capacity of the lung for carbon monoxide was investigated at rest and during exercise by steady state methods.

2. For this purpose, normal subjects were contrasted with patients in whom pulmonary blood flow had been restricted by mitral stenosis.

3. In order to vary ventilation and blood flow independently, special methods, such as voluntary hyperpnea and unilateral occlusion of a pulmonary artery, were also employed.

4. The results indicate that diffusing capacity for carbon monoxide is little affected by changes in pulmonary blood flow until flow is markedly reduced. By way of contrast, increases in ventilation are associated with increases in diffusing capacity, and seem to account for the rise in diffusing capacity observed during moderate exercise.

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