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Maximal Diffusing Capacity of the Lung for Carbon Monoxide *

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During exercise pulmonary diffusing capacity for carbon monoxide and oxygen increases because the pulmonary capillary bed expands (1). It seems reasonable that there should be an upper limit to this expansion at which the diffusing capacity reaches maximum. The apparent oxygen diffusing capacity (D_{LO_2}) has been noted to approach a plateau or upper limit as the work load increases (2, 3), but a similar plateau for CO diffusing capacity has never been clearly demonstrated (1, 4) perhaps because it has not been measured at heavy enough work loads. Thus our purpose was to determine how high CO diffusing capacity can go as exercise work load increases and to see whether it reaches a plateau before the maximal tolerated work load is achieved.

To accomplish this we measured apparent CO diffusing capacity (D_{LCO}) and pulmonary blood flow simultaneously in five normal adults, five normal children, and in three adult patients with mitral stenosis. Measurements were made at rest and at increasing treadmill work loads up to and beyond that causing maximal oxygen consumption. At rest and at maximal oxygen consumption the true membrane diffusing capacity for CO (D_{MCO}) and the pulmonary capillary blood volume (Vc) were estimated by the Roughton-Forster method (5).

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Methods

First we determined the maximal work load that each subject could tolerate on a motor-driven treadmill. We tried to push each subject beyond that work load, which resulted in the maximal oxygen consumption as defined by Mitchell, Sproule, and Chapman (6). Expired air was collected for measuring oxygen consumption between 1½ and 2½ minutes after starting exercise. The mixed expirate was analyzed with a Pauling oxygen analyzer and an infrared CO_2 analyzer calibrated before each analysis with standard mixtures of oxygen, nitrogen, and CO_2. Heart rates were recorded by EKG on a Grass recorder.

D_{LCO} and pulmonary capillary blood flow ($\dot{Q}c$) were measured simultaneously from the uptake of CO and C_2H_2 during breath holding as previously described in detail by Johnson, Spicer, Bishop, and Forster (1). The method combines the breath-holding technique of Ogilvie, Forster, Blakemore, and Morton for D_{LCO} (4) with that of Cander and Forster for Qc (7). A gas chromatograph was used to perform the gas analyses as described by Lawson and Johnson (8).

D_{LCO}, $\dot{Q}c$, and pulmonary tissue volume were estimated at rest from the line best fitting the exponential disappearance of CO and acetylene during separate breath-holding intervals of approximately 3, 7, 10, and 15 seconds. D_{LCO} and $\dot{Q}c$ at exercise are averages of three or more single breath measurements (5 to 10 seconds of breath holding); $\dot{Q}c$ was calculated assuming that pulmonary tissue volume was the same during exercise as it was at rest. Measurements were duplicated at a high and at a low alveolar oxygen tension (i.e., at approximately 140 and 620 mm Hg) so that both Vc and D_{MCO} could be estimated by the method of Roughton and Forster (5). The latter authors have indicated that the following relationship exists between D_{LCO} and D_{MCO}:

$$1/D_{LCO} = 1/D_{MCO} + 1/\theta_{CO}Vc$$

$$\left(\begin{matrix}\text{total}\\ \text{resistance}\end{matrix} = \begin{matrix}\text{membrane}\\ \text{resistance}\end{matrix} + \begin{matrix}\text{red cell}\\ \text{resistance}\end{matrix}\right),$$

where θ_{CO} = the specific rate in milliliters per minute times millimeters Hg at which CO dissolved in plasma can be absorbed by the red cells in 1 ml of whole blood if the blood has an oxygen capacity of 20 ml of oxygen per 100 ml of blood. Since CO and oxygen compete for the intracorpuscular hemoglobin, the red cell resistance to CO uptake increases as the oxygen tension within the

TABLE I

Normal subjects

Subject	Sex	Age	Height	Weight	Total lung capacity*	Maximal oxygen consumption	Maximal heart rate
		years	*m*	*kg*	*L* (BTPS†)	*ml/min/kg*	*beats/min*
SD	F	8	1.33	30.9	2.53	47.2	202
TE	M	9	1.33	29.5		51.9	200
RB	F	10	1.48	35.0	4.19	48.3	212
JH	F	12	1.48	43.6	4.56	47.2	
LM	F	15	1.67	48.6		41.8	
WH	M	18	1.73	74.1	6.16	49.3	175
JH	M	20	1.70	60.0	5.15	45.7	185
JV	M	21	1.63	59.1	4.85	44.7	168
ES	M	23	1.80	74.5	6.18	44.8	182
HL	M	27	1.82	73.6	5.91	47.0	
PC	F	28	1.70	61.8	5.39	32.0	

* Measured by open-circuit nitrogen washout.
† Body temperature, pressure, saturated with water.

red cell increases; thus at high alveolar oxygen tensions D_{Lco} becomes less. If the relationship between P_{O_2} and $1/\theta_{co}$ is known, it is possible to estimate D_{Mco} and Vc from measurements of D_{Lco} at two or more alveolar oxygen tensions. The relationship between $1/\theta_{co}$ and oxygen tension has been measured *in vitro* and lies within the following range of uncertainty (5): $1/\theta_{co} = 0.33 + 0.0058\ P_{O_2}$, and $1/\theta_{co} = 1.00 + 0.0058\ P_{O_2}$. To estimate D_{Mco} and Vc we have assumed an intermediate relationship between $1/\theta_{co}$ and P_{O_2} (i.e., $1/\theta_{co} = 0.73 + 0.0058\ P_{O_2}$) (1).

D_{Lco} changes with changes in pulmonary blood flow under certain conditions (1); therefore, whenever pulmonary capillary blood flow measured while the subject was breathing air differed from that while he was breathing oxygen by more than 10% of the higher blood flow, membrane diffusing capacity and capillary blood volume were not calculated. This precaution helps to insure that measurements of D_{Lco} made at different oxygen tensions are comparable. D_{Lco} was corrected for the accumulation of carboxyhemoglobin in mixed venous blood as previously described (1, 9).

Vital capacities were measured with a Stead-Wells spirometer, and functional residual volume was estimated from the nitrogen washed out of the lungs during 7 minutes of oxygen breathing. Breath-holding measurements were made at or near total lung capacity.

Results

Table I describes the normal subjects and gives the maximal oxygen consumption of each in milliliters per minute per kilogram of body weight. Maximal oxygen consumption was achieved by each subject according to the criteria of Mitchell, Sproule, and Chapman (6).

Table II provides a description of the patients with mitral stenosis. In two of these patients the diagnosis was established by cardiac catheterization and confirmed at surgery. In the remaining patient the diagnosis had to be made on clinical grounds since the patient refused catheterization. Maximal oxygen consumptions of these patients were significantly lower than those predicted.

The essential results are given in Figure 1 and

TABLE II

Patients with

Patient	Sex	Age	Height	Weight	Total lung capacity		Maximal oxygen consumption	
			m	*kg*	*L*	*% pred.*†	*L/min/kg*	*% pred.*‡
1	F	25	1.65	57.3	5.90	119	19.4	53
2	F	33	1.65	66.4	5.08	103	19.6	57
3	F	25	1.57	49.5	3.54	83	13.7	38

* MS = mitral stenosis; MI = mitral insufficiency.
† Predicted from the formula of Needham, Rogan, and McDonald (10).
‡ Predicted from Andersen's data (11).

in Tables III and IV and may be summarized as follows:

1) At maximal oxygen consumption the average arterial-venous difference in oxygen content (15.5 ± 1.7) estimated indirectly from pulmonary capillary blood flow during breath holding (Table III) is not significantly different from the a-v oxygen difference at maximal oxygen consumption (14.3 ± 2.5) measured by Mitchell, Sproule, and Chapman (6) during normal breathing ($p \sim 0.1$). This is evidence that the breath-holding maneuver used for our measurements did not significantly alter pulmonary capillary circulation at heavy exercise.

2) In normal subjects D_{LCO} increased as the work load increased and reached a plateau at approximately the same work load at which blood flow and oxygen consumption reached peak levels (Figure 1).

3) D_{LCO} increased owing to a twofold increase in Vc and a 20% increase in D_{MCO} (Table III). Vc does not appear to expand further when the work load exceeds that causing maximal oxygen consumption and maximal cardiac output (Table IV).

4) In the patients with mitral stenosis Vc was larger than normal at rest (Figure 2), presumably owing to higher pulmonary capillary pressures; during exercise Vc did not increase much above that at rest, and in no instance did Vc exceed the normal upper limit (Figure 2).

Discussion

Our results confirm those of Newman, Smalley, and Thomson (13) that D_{LCO} continues to increase with increasing work load until maximal oxygen consumption is reached. However, as exercise work load increases beyond that causing maximal oxygen consumption, neither D_{LCO} nor Vc increases further. This does not mean necessarily that the maximal potential volume of the pulmonary capillary bed has been reached. The capillary bed might expand further if pulmonary blood flow could go higher or if capillary blood pressure could be increased by some other means. Left atrial pressure is an important determinant of capillary pressure in the lungs, and if the capillary bed were capable of further expansion, an abnormally high left atrial pressure should cause Vc to exceed the peak volume measured in normal subjects during exercise (14–17). However, in the present investigation the pulmonary capillary blood volumes were no greater in three patients with mitral stenosis working at full capacity than in normal subjects exercising (Figure 2), and the results obtained by other investigators who have measured Vc in patients with pulmonary congestion (15–17) are in essential agreement with our own (Figure 3). Furthermore, it has not been possible artificially to induce pulmonary congestion in normal subjects severe enough to make the pulmonary capillary bed expand more than it normally does at heavy exercise. Ross, Maddock, and Ley (18) have induced pulmonary congestion in normal subjects by G-suit inflation. Lewis, McElroy, Hayford-Welsing, and Samberg (19) have done the same by intravenous infusions of norepinephrine in normal subjects both upright and supine. The largest increase in pulmonary capillary blood volume reported from these latter two studies was 1.9 times the control value, which is about the same increase as that normally observed from rest to peak exercise. The findings

TABLE II

mitral stenosis

Maximal heart rate	Cardiac catheterization at rest				Diagnosis*	Clinical grade
		Pulmonary arterial pressure				
	Cardiac output	Systolic/ Diastolic	Mean	Wedge		
	L/min		*mm Hg*			
144	7.20	43/24	31		MS	II
220					MS	III
175	3.08	99/48	64	35	MS and MI	IV

TABLE III

Pulmonary capillary blood flow ($\dot{Q}c$), volume (Vc), and membrane diffusing capacity (DM_{CO})

Subject	At rest				At maximal O_2 consumption			
	VA*	$\dot{Q}c$	Vc	DMco	VA*	$\dot{Q}c$	Vc	DMco
	L	*L/min*	*ml*	*ml/min / mm Hg*	*L*	*L/min*	*ml*	*ml/min / mm Hg*
SD	2.01	4.6	42	34	2.41	11.1	101	37
TE	2.48	3.1	48	30	2.27	10.2	81	41
RB	3.58	4.4	82	37	3.86	10.8	112	60
JH	3.95	5.8	87	59	3.70	12.0	173	48
LM	3.72	5.8	71	47	3.86	12.9	128	59
WH	6.10	6.8	110	72	6.11	21.1	182	116
JH	5.23	5.7	80	72	5.11	20.4	170	84
JV	5.20	5.4	63	59	4.65	16.6	131	73
ES	6.27	6.7	77	85	5.65	24.2	215	79
HL					5.91	18.6	200	97
PC	5.11	4.7	86	64	4.89	13.8	175	87
Average								
Normal	4.36	5.3	75	56	4.40	15.6	167	71
Patient 1	5.91	7.6	136	53	5.70	10.9	177	57
Patient 2	4.26	6.5	170	31	4.75	7.9	172	37
Patient 3	3.58	4.6	111	26	3.66	5.4	131	25

* VA = alveolar volume measured from the single-breath neon dilution.

suggest that the normal pulmonary capillary bed may be approaching or may have reached the upper limit of distensibility at peak exercise. This conclusion is further substantiated by the anatomical estimates of pulmonary capillary blood volume made by Weibel (20).

Weibel has counted the number of capillaries in representative parts of inflated and fume-fixed

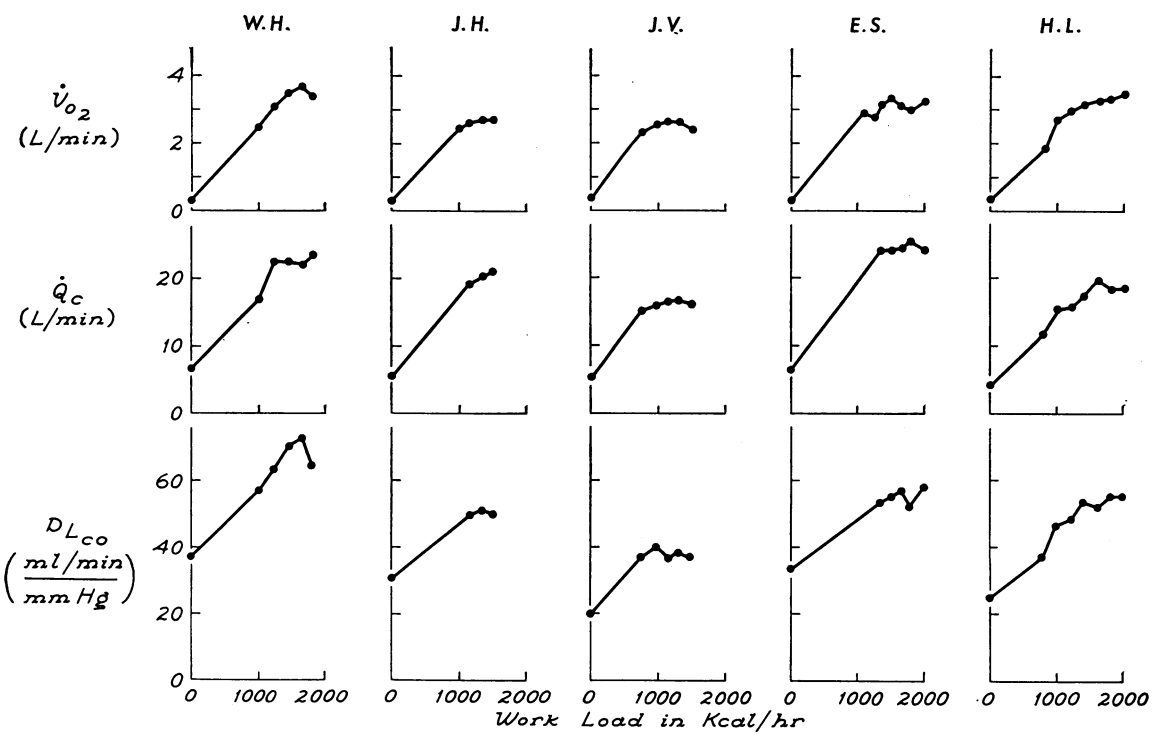

FIG. 1. THE RISE IN OXYGEN CONSUMPTION ($\dot{V}O_2$), PULMONARY CAPILLARY BLOOD FLOW ($\dot{Q}c$), AND DIFFUSING CAPACITY (DL_{CO}) WITH INCREASING WORK LOADS. All three tend to approach peak levels at the same work loads.

TABLE IV

Pulmonary capillary blood flow ($\dot{Q}c$), volume (Vc), and membrane diffusing capacity (D_{MCO}) at maximal oxygen consumption and at a heavier work load

Subject	At maximal oxygen consumption					Beyond maximal oxygen consumption				
	Load*	$\dot{V}o_2$†	$\dot{Q}c$	Vc	D_{MCO}	Load*	$\dot{V}o_2$†	$\dot{Q}c$	Vc	D_{MCO}
	kcal/hr	*L/min*	*L/min*	*ml*	*ml/min mm Hg*	*kcal/hr*	*L/min*	*L/min*	*ml*	*ml/min mm Hg*
TE	620	1.58	10.2	81	41	679	1.43	9.6	74	40
JH	1,326	2.72	20.4	170	84	1,482	2.62	21.1	198	76
JV	1,294	2.62	16.6	131	73	1,460	2.41	16.2	133	71
ES	1,490	3.33	24.2	215	79	1,996	3.28	24.2	198	86
Average	1,182	2.56	17.8	149	69	1,404	2.44	17.8	151	68

* Work loads were estimated from the grade and speed at which the subject ran using the nomogram of Margaria Cerretelli, Aghemo, and Sassi (12).

† $\dot{V}o_2$ = oxygen consumption.

post-mortem lungs, measured the capillary diameters, and estimated the amount of blood that the capillary bed could hold if all the capillaries were completely filled to the point of being circular cylinders. The normal capillary bed of the lung expands during heavy exercise to about the same volume as that estimated by Weibel for a completely filled capillary bed (Figure 3). The latter observation also suggests that the pulmonary capillary bed expands simply by filling up rather than by capillaries being stretched to larger diameters. As suggested by Cotes, Snidal, and Shepard (21), the lung capillaries may fill from collapsed or elliptical cylinders at rest to circular cylinders during exercise without their walls being stretched and with little or no change in membrane diffusing capacity. Further radial expansion of a capillary beyond this point of complete filling would require stretching of the capillary walls and very likely high distending pressures, since according to the Laplace relationship the elastic recoil in the wall of a small capillary has a considerable mechanical advantage for resisting distention (i.e., tension in the wall of a cylinder = distending pressure × radius). Thus it is possible that Weibel's anatomical estimates of Vc represent the

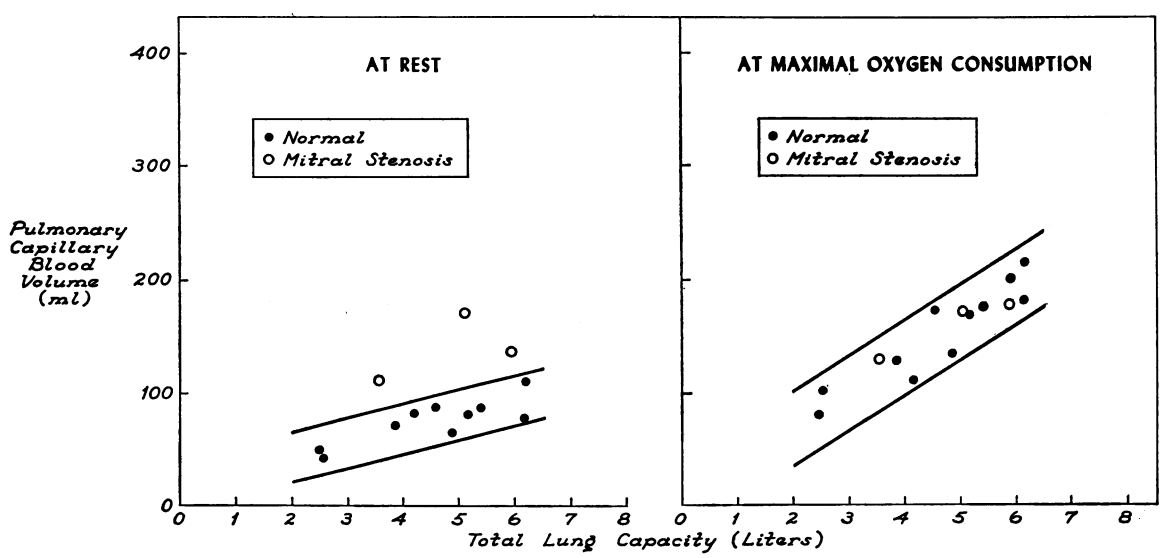

FIG. 2. PULMONARY CAPILLARY BLOOD VOLUME (Vc) IN RESPECT TO TOTAL LUNG CAPACITY AT REST AND AT EXERCISE. The solid lines represent 2 SE on either side of the normal regression line. At rest the pulmonary capillary blood volumes of the patients with mitral stenosis were consistently above normal, presumably as a consequence of the higher capillary pressures in the patients; at peak exercise expansion of the pulmonary capillary bed in the patients did not exceed that found in the normal subjects.

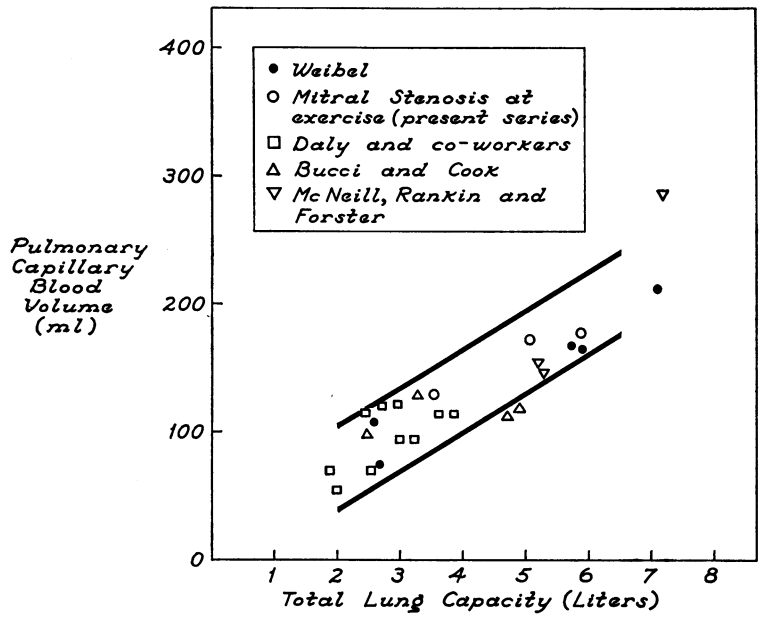

FIG. 3. ANATOMICAL ESTIMATES OF PULMONARY CAPILLARY BLOOD VOLUME (Vc) COMPARED TO PHYSIOLOGIC ESTIMATES IN PATIENTS WITH PULMONARY CONGESTION AND IN NORMAL SUBJECTS AT HEAVY EXERCISE. The solid lines represent 2 SE on either side of the regression line for normal subjects at heavy exercise (Figure 2). The anatomical estimates of Vc are within the same range as those found by physiologic measurements in normal subjects at peak exercise and in patients with pulmonary congestion. The patients with pulmonary congestion studied by Daly and co-workers (14) had mitral stenosis and as a group had an average left atrial pressure of 23 mm Hg. The patients studied by Bucci and Cook had high pulmonary blood flows due to interatrial septal defects plus some associated obstruction to left ventricular filling (15). One of the patients studied by McNeill, Rankin, and Forster (16) had left ventricular failure due to hypertension, one had mitral stenosis, and one an atrial septal defect. The results are compatible with the hypothesis that the pulmonary capillary bed approaches its maximal potential volume at peak exercise and cannot be distended significantly more by higher capillary pressures.

physiologic upper limit of pulmonary capillary blood volume and that the pulmonary capillary bed fills to this volume only at very heavy work loads.

Summary

The purpose of this investigation was to determine how much the apparent CO diffusing capacity (D_{LCO}) increases from rest to peak exercise and whether it reaches a plateau with increasing work load. Pulmonary capillary blood flow and apparent CO diffusing capacity were measured by a breath-holding technique both at rest and during exercise and repeated at two different alveolar oxygen tensions so that the true membrane diffusing capacity (D_{MCO}) and pulmonary capillary blood volume (Vc) could be determined by the Roughton-Forster method.

D_{LCO} kept rising as work load was increased until the pulmonary blood flow and oxygen consumption stopped going up. D_{LCO} increased principally because of a twofold increase in Vc during exercise. D_{MCO} increased only about 20% above the resting value.

In the three patients with mitral stenosis pushed up to their peak work loads, Vc rose to the same level as in normal subjects during exercise but did not exceed the normal upper limit. This suggests that maximal distensibility of the capillary bed in normal subjects is reached or closely approached

at peak work loads. The maximal pulmonary capillary blood volume in the normal subjects as well as in the patients with mitral stenosis agrees closely with the anatomical estimates made by Weibel of the maximal capacity of the pulmonary capillary bed.

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