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Functional Significance of a Low Pulmonary Diffusing Capacity for Carbon Monoxide *

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Diffusing capacity of the lungs imposes a theoretical limit to oxygen consumption, causing oxygen saturation of arterial blood to fall sharply if this limit is approached (1). The diffusing surface of the normal lung is so large, however, that at sea level oxygen capacity of the blood and the cardiac output rather than diffusing capacity create the major bottleneck to oxygen transport (2). Diffusion becomes an important limit only at high altitudes (3) or when diffusing capacity is reduced sufficiently by disease to cause alveolar capillary block (4).

Diffusing capacity of the lungs usually is measured with respect to CO ($D_{L_{CO}}$) rather than oxygen ($D_{L_{O_2}}$). Yet little information exists regarding how low $D_{L_{CO}}$ must be before alveolar capillary block is manifest. Recent work of Roughton and Forster (5) and of Staub, Bishop, and Forster (6) defines the theoretical relationship between $D_{L_{CO}}$ and $D_{L_{O_2}}$ allowing translation of CO diffusing capacity into terms of oxygen transport. Thus we should be able to state more explicitly the functional significance of a low CO diffusing capacity. Our purpose has been to predict the restriction in maximal oxygen transport implied by a low $D_{L_{CO}}$ and then to check the prediction by experimental measurement.

Methods

Theory. The reciprocals of $D_{L_{CO}}$ and $D_{L_{O_2}}$ are specific resistances in millimeters Hg per milliliter per minute to CO and oxygen transfer into pulmonary capillary blood. The red cell as well as the pulmonary membrane offers resistance to CO and oxygen transfer into blood (5, 6); the total resistance ($1/D_L$) is the sum of the membrane and red cell resistances:

$$1/D_L = 1/D_M + 1/(\theta V_c), \quad [1]$$

TABLE I

Time (Δt) required for the oxygen saturation of hemoglobin in lung capillaries to rise from 1% saturation toward equilibrium with an alveolar oxygen tension of 110 mm Hg

Oxygen saturation (S_c)	$K^* \times \left[\frac{12}{1.23}\int_{1.0}^{S_c}\frac{dS_c}{(P_A-P_c)}\right]^\dagger + \left[12\int_{1.0}^{S_c}\frac{dS_c}{\theta(P_A-P_c)}\right] = \Delta t$			
3.0	K ×	.00180	+	0.00081	=
5.0	K ×	.00364	+	0.00164	=
7.0	K ×	.00550	+	0.00248	=
9.0	K ×	.00738	+	0.00333	=
11.0	K ×	.00929	+	0.00419	=
13.0	K ×	.01123	+	0.00506	=
15.0	K ×	.01318	+	0.00594	=
17.0	K ×	.01516	+	0.00683	=
19.0	K ×	.01715	+	0.00773	=
21.0	K ×	.01916	+	0.00864	=
23.0	K ×	.02120	+	0.00956	=
25.0	K ×	.02325	+	0.01048	=
85.0	K ×	.09741	+	0.04392	=
86.0	K ×	.09911	+	0.04491	=
87.0	K ×	.10087	+	0.04576	=
88.0	K ×	.10267	+	0.04670	=
89.0	K ×	.10456	+	0.04776	=
90.0	K ×	.10652	+	0.04897	=
91.0	K ×	.10860	+	0.05038	=
92.0	K ×	.11079	+	0.05203	=
93.0	K ×	.11311	+	0.05400	=
94.0	K ×	.11563	+	0.05644	=
95.0	K ×	.11853	+	0.05972	=
95.2	K ×	.11921	+	0.06063	=
95.4	K ×	.11993	+	0.06166	=
95.6	K ×	.12070	+	0.06278	=
95.8	K ×	.12151	+	0.06402	=
96.0	K ×	.12237	+	0.06541	=
96.2	K ×	.14643	+	0.08326	=
96.4	K ×	.14856	+	0.08705	=
96.6	K ×	.15132	+	0.09226	=
96.8	K ×	.15554	+	0.10069	=
97.0	K ×	.16637	+	0.12372	=

* $K = \frac{(\text{oxygen capacity in ml of oxygen/ml of blood}) \times (V_c \text{ in ml})}{0.2 \times [D_{M_{CO}} \text{ in ml/(min/mm Hg)}]}$.
V_c = capillary blood volume; $D_{M_{CO}}$ = membrane diffusing capacity.
† P_A = alveolar oxygen tension; P_c = oxygen tension exerted by the oxyhemoglobin in the capillary red cell.

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i.e.,

$$\text{Total resistance} = \text{Membrane resistance} + \text{Red cell resistance},$$

where D_L = apparent diffusing capacity of the lung in milliliters per minute × millimeters Hg, D_M = membrane diffusing capacity in milliliters per minute × millimeters Hg, θ = specific rate of CO or oxygen uptake by red cells in milliliters per (minute × millimeters Hg) per milliliter blood, assuming an O_2 combining capacity of 0.2 ml per ml blood, and Vc = pulmonary capillary blood volume in milliliters.

Since oxygen and CO compete for intracellular hemoglobin (7), increasing the alveolar oxygen tension causes the apparent CO diffusing capacity of the lung (D_{LCO}) to fall owing to the slower rate of CO uptake by red cells. Roughton and Forster (5) estimated the true membrane diffusing capacity for CO (D_{MCO}) and the pulmonary capillary blood volume (Vc) from measurements of D_{LCO} at more than one alveolar oxygen tension. Recently, Staub, Bishop, and Forster (8) measured the kinetics of oxygen uptake by red cells making it possible to predict from measurements of D_{MCO} and Vc how fast blood entering lung capillaries is oxygenated:

$$\Delta_t = \frac{(Cap)}{0.2} \cdot \frac{Vc}{D_{MCO}} \cdot \left[\frac{12}{1.23} \int_{S_{\bar{v}}}^{S_c} \frac{dS_c}{(P_A - P_c)} \right] + \left[12 \int_{S_{\bar{v}}}^{S_c} \frac{dS_c}{\theta (P_A - P_c)} \right] \qquad [2]$$

$$\begin{matrix}\text{Time for blood } O_2 \\ \text{sat. to rise from } S_{\bar{v}} \text{ to } S_c\end{matrix} = \text{Time if the pulmonary membrane were the only resistance to } O_2 \text{ uptake} + \text{Additional time due to red cell resistance}$$

where Δt = time interval in seconds; Pc = oxygen tension exerted by the oxyhemoglobin in the capillary red cell in millimeters Hg; P_A = alveolar oxygen tension in millimeters Hg; Sc = oxygen saturation of capillary blood, expressed as a fraction of the oxygen capacity; $S\bar{v}$ = oxygen saturation of mixed venous blood, expressed as a fraction of the oxygen capacity; θ = specific rate of O_2 uptake by red cells at body temperature in minutes^{-1} × millimeters Hg^{-1}, assuming an O_2 capacity of 0.2 ml per ml blood; (Cap) = oxygen capacity of blood in milliliters per milliliter blood; 12 = 0.2 × 60, 0.2 being the normal O_2 capacity of blood in milliliters per milliliter blood and 60 converting Δt from minutes to seconds; 1.23 = the diffusivity of oxygen relative to that of CO in water. The integral in heavy type is the one originally evaluated by Bohr (9) to estimate mean oxygen tension difference from alveoli into capillary red cells.

Equation 2 was integrated numerically (10) for alveolar oxygen tensions ranging from 40 through 140 mm Hg at 10 mm Hg intervals, using the oxygen dissociation curve at pH 7.40 (11). Table I is an example. Most measurements of θ for oxygen uptake by red cells have been made near pH 7.40; however, assuming that θ at a given blood oxygen saturation does not change when pH changes (7), the tables may be corrected to any pH by dividing each of the integrals by the appropriate P_{O_2} multiplier from the Severinghaus nomogram. However, this not only alters the table to account for the Bohr shift in the oxygen-hemoglobin dissociation curve but also changes the alveolar oxygen tension for which the table is valid as follows: alveolar oxygen tension for which the table is valid at pH 7.40 × P_{O_2} multiplier = alveolar oxygen tension for which the table is valid at the new pH. For example, to estimate how fast pulmonary capillary blood would be oxygenated if the alveolar oxygen tension were 110 mm Hg, Vc/D_{MCO} were 2.0, blood oxygen capacity were 0.2 ml per ml, and capillary blood pH were 7.20, proceed as follows. Since the P_{O_2} multiplier for pH 7.20 is 1.22, select the table constructed for an alveolar oxygen tension of 90 mm Hg at pH 7.40 (90 × 1.22 = 110 mm Hg at pH 7.20). Multiply the numbers in column 2 of the table (see Table I) by K = 2.0, adding the products to the adjacent numbers in column 3; divide the resulting sums by the P_{O_2} multiplier (1.22) to give Δt. To estimate the time interval required for oxygen saturation of capillary blood to rise from that of mixed venous blood ($S\bar{v}$) to any saturation Sc, subtract the Δt obtained from the table for $S\bar{v}$ from that obtained for Sc. We have not considered the changing pH as blood traverses lung capillaries nor the associated problem of how fast the Bohr shift occurs; however, the pH change between mixed venous and arterial blood generally is less than 0.1 pH unit even at heavy exercise. Failure to consider this changing pH can cause no more than a 5% error in predicting the upper limits to oxygen consumption imposed by diffusion.

The following formula can be used with the tables described above to estimate the relationship between oxygen consumption and oxygen saturation of blood leaving lung capillaries:

$$\dot{V}_{O_2} = [60\ Vc/\Delta t][(Sc' - S\bar{v}) \times (Cap)] \qquad [3]$$

(i.e., oxygen consumption = [blood flow] × [pulmonary a-v O_2 difference]), where Δt now represents the mean red cell transit time through lung capillaries, Sc is the saturation of blood leaving lung capillaries expressed as a fraction

of the O_2 capacity, and the remaining symbols are the same as for Equation 2. If any two of the quantities Sc′, $S\bar{v}$, or Δt in Equation 3 are known, the third can be estimated from Equation 2. Therefore, if we measure or assume appropriate pulmonary a-v oxygen differences (Sc′ − $S\bar{v}$) and if D_{MCO}, Vc, blood oxygen capacity, and alveolar oxygen tension are known, Equations 2 and 3 may be solved simultaneously with the help of the above tables to give the limiting relationship between oxygen consumption ($\dot{V}O_2$) and oxygen saturation of blood leaving lung capillaries (Sc′). Assuming that the peripheral tissues can extract a maximum of 75% of the oxygen delivered at peak work loads (2) and assuming that there is no venous admixture, Equation 3 simplifies to

$$\dot{V}O_2 = [60\,Vc/\Delta t][Sc' \times 0.75 \times (Cap)] \quad [4]$$

(i.e., oxygen consumption = [blood flow] × [the assumed pulmonary a-v O_2 difference]).

Patient material. The patients selected for exercise studies had low resting diffusing capacities and lung disorders that should limit exercise owing to alveolar capillary block. All had diffuse interstitial infiltrates with the exception of one who had extensive lung resection for pulmonary tuberculosis, leaving apparently normal lung behind.

Measurement. Lung volumes were measured with the patient sitting upright or standing. Forced expiratory volumes were measured with a Stead-Wells spirometer. Functional residual capacities were measured by open circuit nitrogen washout (12). The alveolar mixing index was measured by the single breath technique of Fowler (13).

Diffusing capacity of the lung (D_{LCO}) and pulmonary capillary blood flow ($\dot{Q}c$) were measured by a modified breath-holding technique (14, 15). The patient exhaled to near residual lung volume and then inspired a measured volume of gas mixture containing approximately 0.5% neon, 0.3% CO, and 0.5% acetylene in a balance of oxygen and nitrogen. The breath was held 3 to 15 seconds at or near full inspiration after which an alveolar sample was collected; the concentrations of neon, CO, acetylene, and oxygen in the sample were measured by gas chromatography. Neon, being insoluble and inert, is not absorbed during breath holding but provides a reference from which disappearance of CO and acetylene can be measured. At rest the falls in alveolar concentration of CO and acetylene were measured after approximately 3, 7, 10, and 15 seconds of breath holding. The slopes of the fall in log concentration of these gases with time were determined by plotting the results on semilogarithmic graph paper. D_{LCO} equals the exponential slope of CO disappearance multiplied by the alveolar volume. $\dot{Q}c$ equals the exponential slope of acetylene disappearance multiplied by (alveolar volume plus the equivalent tissue volume).[1] Alveolar volume was estimated from the single breath neon dilution (16).[2] Lung tissue volume was estimated from the intercept obtained by extrapolating acetylene disappearance back to the start of breath holding (14). If lung tissue volume is known, $\dot{Q}c$ can be estimated from a single breath measurement of acetylene disappearance. Thus during exercise D_{LCO} and $\dot{Q}c$ were calculated from single breath measurements (5 to 10 seconds of breath holding), assuming that lung tissue volume was the same during exercise as at rest. Exercise measurements of D_{LCO} and $\dot{Q}c$ were repeated 3 or more times and averaged. Measurements of D_{LCO} and $\dot{Q}c$ were duplicated at a high and at a low alveolar oxygen tension (i.e., at approximately 130 and 600 mm Hg) so that both pulmonary capillary blood volume (Vc) and membrane diffusing capacity (D_{MCO}) could be estimated by the method of Roughton and Forster (5).

The relationship betwen θCO and oxygen tension in the red cell is uncertain because the ratio (λ) of the permeability of the red cell membrane to that of the red cell interior is uncertain. We estimated D_{MCO} for three different assumed values of λ as was done by Roughton and Forster (5):

$$1/\theta CO = 0.33 + 0.0058\,P_{O_2} \quad (\lambda = \infty) \quad [5]$$

$$1/\theta CO = 0.73 + 0.0058\,P_{O_2} \quad (\lambda = 2.5) \quad [6]$$

$$1/\theta CO = 1.00 + 0.0058\,P_{O_2} \quad (\lambda = 1.5) \quad [7]$$

As a first approximation D_{MCO} was estimated with Equation 1 assuming that mean oxygen tension in capillary red cells is the same as that in alveolar air. But θCO depends upon oxygen tension in the red cell rather than that in alveolar air. Assuming that the mean difference between alveolar and capillary blood oxygen tension is $\dot{V}O_2/(1.23 \times D_{MCO})$, we corrected the first approximation to membrane diffusing capacity as follows:

$$\text{Corrected } D_{MCO} = [1 - (\dot{V}O_2 \times 0.0058)/1.23\,Vc] \times [D_{MCO} \text{ by first approximation}], \quad [8]$$

where $\dot{V}O_2$ = the oxygen consumption in milliliters per minute at the level of exercise at which the measurement was made, Vc = pulmonary capillary blood volume in milliliters, 1.23 = the factor by which D_{MO_2} is greater than D_{MCO}, 0.0058 = the error in estimating $1/\theta$ per millimeter Hg error in estimating capillary blood oxygen tension (see Equations 5 to 7), and 0.0058/Vc = the error in estimating total red cell resistance per millimeter Hg error in capillary blood oxygen tension. This correction neglects the additional oxygen tension gradient from the plasma into the red cell.

Each patient was exercised at increasing work loads on a motor driven treadmill to determine the highest load tolerated and the maximal oxygen consumption achieved. Exercise was sustained for 3½ minutes at each load, allow-

[1] Equivalent tissue volume is the septal tissue volume of the lung multiplied by the Bunsen solubility coefficient of acetylene in lung tissues. These septal tissues act as a reservoir for the acetylene just as alveolar volume does.

[2] In the original method alveolar volume was estimated as inspired volume plus residual volume. However, patients often find it difficult to exhale fully during exercise; also we could not be certain whether the patients were holding their breaths at full inspiration. Thus we calculated alveolar volume during breath holding by dividing the inspired volume of gas mixture by the neon dilution in the alveolar sample.

ing 30 minutes of rest between increments of work load. Oxygen consumptions were measured from the expired air collected during the last minute of exercise. Oxygen and CO_2 concentrations in the mixed expirate were measured with a Beckman paramagnetic oxygen analyzer and a Beckman infrared CO_2 analyzer. Diffusing capacity and pulmonary capillary blood flow were measured 1½ minutes after starting treadmill exercise. After completing the above measurements arterial blood gases were measured at rest and at exercise up to the peak work load. Arterial blood was collected simultaneously with collection of expired air during the last minute of exericse. Arterial oxygen saturation was measured either by Van Slyke manometric determinations of oxygen capacity and oxygen content or by an American Optical oximeter, the accuracy of which had been verified by Van Slyke determinations. Arterial pH, P_{CO_2}, and P_{O_2} were measured with a Beckman GS pH meter, a Severinghaus P_{CO_2} electrode, and a Clark P_{O_2} electrode, respectively, heated in a water bath to 37.5° C.

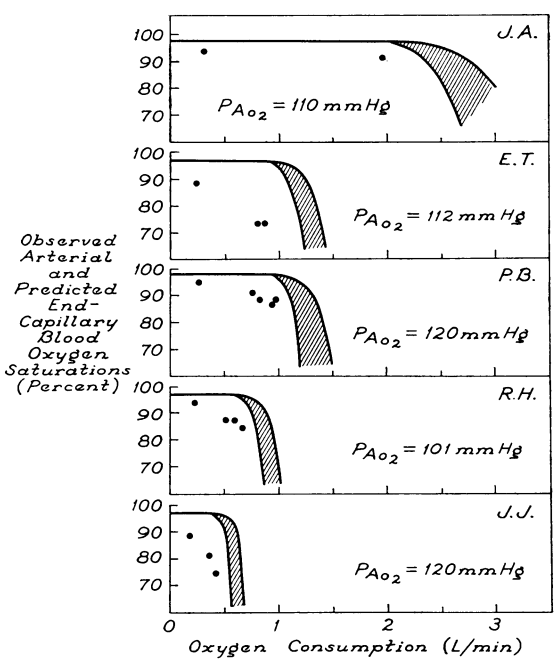

FIG. 1. RELATIONSHIP BETWEEN OXYGEN CONSUMPTION AND THE OXYGEN SATURATION OF ARTERIAL BLOOD, MEASURED AND PREDICTED. The experimental measurements are closed circles. The theoretical range of oxygen consumptions within which the arterial oxygen saturation should fall as work load increases (crosshatched area) was predicted from Equations 2 and 3 (Methods), using the alveolar oxygen tension, pulmonary arteriovenous (a-v) oxygen difference, capillary blood volume, and the maximal and minimal membrane diffusing capacities estimated at or near peak work load. Ventilation, blood flow, and alveolar volume were assumed to be distributed uniformly with respect to the diffusing surface. $P_{A_{O_2}}$ = alveolar oxygen tension.

Results

The patients had predominantly restrictive ventilatory defects although some had mild obstructive ventilatory defects also (Table II). Distribution of inspired air was less uniform than normal in most patients.

Three patients (JA, PB, and JJ) appeared to achieve a true maximal oxygen consumption (Table III) suggesting that the maximal cardiac output had been reached. Pulmonary capillary blood volume and membrane diffusing capacity increased less than normal during exercise due to the low cardiac outputs and perhaps in part to a less distensible capillary bed. Although maximal cardiac outputs were low in most patients, none had signs of congestive heart failure (i.e., elevated venous pressure at rest or salt retention).

The oxygen saturation of arterial blood (Table IV) always started to fall at lower oxygen consumptions and fell less sharply than we predicted from the CO diffusing capacity (Figure 1). Nevertheless, a clear relationship can be seen between the predicted and observed results. The lower the predicted limit for the relationship between oxygen consumption and arterial oxygen saturation, the sharper was the fall in arterial oxygen saturation as work load increased. This suggests that the low diffusing capacity was an important factor in causing oxygen saturation to fall. In no instance could the fall in arterial blood oxygen saturation during exercise be explained by anatomical shunts of mixed venous blood into the systemic circulation (Table V); however, the possibility is not eliminated that relative shunts of mixed venous blood through poorly ventilated lung contributed to the fall.

The maximal oxygen intake, maximal pulmonary capillary blood volume, and membrane diffusing capacity normally expected for each patient at heavy exercise are given in Table VI accompanied by an account of how they were estimated.

Discussion

Prediction vs. measurement. Efficient arterialization of mixed venous blood requires uniform distribution of blood flow and ventilation with respect to the pulmonary diffusing surface. On the other hand, the measurement of $D_{L_{CO}}$ during

TABLE II

Physical description and lung volumes of the patients

Patient	Sex	Age	Height	Weight	Total lung capacity		Forced vital capacity		Forced expiratory volume in 0.5 sec		Alveolar mixing	Diagnosis
			m	*kg*	*ml*	%*	*ml*	%†	*ml*	%†	% N_2 rise	
CMcD	M	18	1.75	59.1	4,410	70	3,220	64	2,340	68	1.2	Sarcoidosis
JA	M	18	1.80	61.0	3,550	52	2,650	48	1,630	44	2.9	Sarcoidosis
ET	M	69	1.73	84.0	3,793	61	2,620	68	1,770	68	3.5	Interstitial fibrosis
PB	M	44	1.70	59.1			2,954	66	1,666	55	3.8	Interstitial fibrosis
RH	F	47	1.52	59.5	1,939	49	1,313	44	643	32		66% lung resection
JJ	F	32	1.50	41.0	3,620	94	2,020	70	1,200	61	5.5	Sarcoidosis

* Per cent of predicted based on data of Needham, Rogan, and McDonald (17).
† Per cent of predicted based on data of Miller, Johnson, and Wu (18).

TABLE III

Alveolar capillary blood flow ($\dot{Q}_c$), capillary blood volume (V_c), and membrane diffusing capacity ($D_{M_{CO}}$) at rest and exercise

Patient	Work load		Alveolar volume*	Heart rate	Oxygen consumption	$\dot{Q}_c$	D_{LCO}†	Vc	D_{MCO}‡		
									$\lambda = \infty$	$\lambda = 2.5$	$\lambda = 1.5$
	mph	*grade*	*ml*	*beats/min*	*ml/min*	*L/min*	*ml/min/mm Hg*	*ml*			
CMcD	Rest		4,657		225	7.07	20.5	73	33	40	48
	4	12½	4,094		1,402	15.1	31.2	152	35	42	45
	5	12½	4,424		1,732	16.8	30.5	147	39	44	48
	6	12½	4,429		2,252	19.8	36.8	155	44	50	55
	7	12½	3,638		2,247	19.8	36.8	164	42	47	51
JA	Rest		3,310	92	306	8.67	19.6	77	27	31	35
	4	12½	3,100	178	1,483	13.8					
	5	12½	3,090	186	1,589	15.7	25.4	86	31	36	38
	6	12½	3,130	188	1,773	15.3	27.4	87	32	37	42
	7	12½	3,050	192	1,960	16.8	24.3	100	28	32	35
ET	Rest		4,021	72	240	3.93	9.9	45	12.9	14.6	16.0
	2	0		120	754						
	2½	0	3,904	137	831	5.90	10.4	45	12.7	14.2	15.4
	3	0		135	921	6.30					
PB	Rest		4,900		256	5.71	7.8	42	9.6	10.6	11.4
	2	0		90	759	7.50					
	3	0		121	828						
	3½	0	4,763	133	956	7.74	8.7	29	11.3	13.4	15.3
	4	0		140	947						
RH	Rest		1,937	90	225	3.29	5.8	17	9.2	11.7	14.3
	1½	0		112	608						
	2½	0		114	641						
	3	0	1,978	122	703	6.52					
	3½	0	2,072	124	737	7.46	8.1	34	10.1	11.4	12.5
	4	0		122	801						
JJ	Rest		3,242	76	161	3.00	4.0	14	5.7	6.8	7.8
	1	0		107	300						
	2	0		128	457	2.92					
	2½	0		126	441						
	3	0	3,332	132	441	2.80	4.3	16	5.2	6.0	6.6
	4	0		140	396	2.66					

* The alveolar lung volume estimated from the alveolar dilution of neon during breath-holding measurements.
† D_{LCO} = diffusing capacity of the lungs. Mean alveolar oxygen tension at the termination of breath holding was on the average 153 mm Hg at rest and 134 mm Hg at peak work loads.
‡ D_{MCO} has been calculated for different assumed values of λ (i.e., the ratio of permeability of the red cell membrane for CO to the permeability of the red cell interior) in order to indicate the range of uncertainty involved in estimates of D_{MCO}.

TABLE IV

Arterial blood gases when breathing air at rest and exercise

Patient	Work load		Oxygen consumption	RQ	Arterial blood				Alveolar P_{O_2}
					P_{CO_2}	pH	Oxygen capacity	Oxygen saturation	
	mph	*grade*	*ml/min*		*mm Hg*		*vol/100 ml*	%	*mm Hg*
CMcD	Rest		225	0.82	40	7.46	18.32	97.0	102
JA	Rest		306	0.85	38		19.88	94.0	105
	7	12½	1,966	1.09	39		20.74	91.5	112
ET	Rest		240	0.79	39	7.44	19.77	88.5	101
	2½	0	822	0.96	36	7.45	21.18	73.5	112
	3	0	860	1.05	37	7.47		73.5	111
PB	Rest		256	0.85	29	7.52	19.30	95.0	114
	2	0	759	0.90	30	7.45		91.0	114
	3	0	828	0.89	29	7.48	19.76	89.0	115
	3½	0	956	0.93	28	7.48		88.0	117
	4	0	947	1.07	26			87.0	122
RH	Rest		237	0.74	35	7.49	20.32	94.0	97
	1½	0	580	0.77	35	7.48		87.0	97
	3	0	514	0.89	39	7.45	21.32	87.0	100
	3½	0	673	0.90	37	7.48		84.0	103
JJ	Rest		184	0.74	32	7.45	19.43	89.0	108
	2	0	344	0.87	31	7.49		81.5	113
	3	0	441	1.02	29	7.48	20.78	75.0	118

a single breath is independent of how inspired air and blood flow are distributed if diffusing capacity per unit lung volume (D_L/V_A) is uniform (23). Thus conditions in the lung requisite for accurate measurement of D_{LCO} are not necessarily the same conditions requisite for efficient oxygen transfer into mixed venous blood. Assuming that theory concerning the relationship between D_{LCO} and D_{LO_2} is correct, nonuniformity of ventilation, blood flow, and diffusing capacity

TABLE V

Alveolar-arterial oxygen tension gradients when breathing 100% oxygen as estimates of the true venous admixture or anatomical shunt at rest and exercise

Patient	Work load		Alveolar P_{O_2}	Arterial P_{O_2}	Anatomical shunt*	Difference between $S_c'_{O_2}$ and Sa_{O_2}, breathing air, attributable to the anatomical shunt†
	mph	*grade*	*mm Hg*	*mm Hg*	%	%
CMcD	Rest		667	637	2.8	0.5
JA	Rest		671	617	4.8	0.9
	7	12½	664	591	2.0	1.2
ET	Rest		665	607	2.9	0.9
	2½	0	659	594	1.4	0.9
PB	Rest		677	676	0.0	0.0
	3½	0	676	631	1.1	0.7
RH	Rest		670	556	5.1	1.7
	3	0	666	541	3.9	1.8
JJ	Rest		676	538	8.0	2.1
	3	0	675	518	3.1	2.4

* Estimated from the formula of Berggren (19) (i.e., % shunt = [Sendroy factor × (PA_{O_2} − Pa_{O_2}) × 100]/[pulmonary a-v oxygen difference]) using the ratio, oxygen consumption/$\dot{Q}_c$, to estimate pulmonary a-v oxygen difference.

† It was assumed that the pulmonary a-v oxygen difference and the per cent shunt are the same whether breathing air or 100% oxygen (20). Sc'_{O_2} = end-capillary blood oxygen saturation; Sa_{O_2} = arterial blood oxygen saturation.

with respect to lung volume would be the major potential sources of error in translating D_{LCO} into terms of O_2 transport.

The predictions of how arterial oxygen saturation should fall as oxygen consumption increases (Figure 1) were made from measurements of diffusing capacity at full inspiration and at maximal oxygen consumption, assuming that D_{LCO} is not altered by breath holding, that D_L/V_A is uniform, and that ventilation and capillary blood flow are uniform with respect to diffusing capacity. These conditions are optimal for the transfer of both oxygen and CO into capillary blood, and only if these conditions are fulfilled would we expect arterial oxygen saturation to fall exactly as predicted with respect to oxygen consumption. If diffusing capacity per unit lung volume (D_L/V_A) is not uniform, D_{MCO} or Vc might be estimated too high or too low depending on how representative the alveolar samples are when measuring D_{LCO}. Lewis, Lin, Noe, and Hayford-Welsing (24) compared D_{LCO} measured by the single breath technique with that measured by a rebreathing method designed to obviate the breath-holding maneuver and to keep alveolar air well mixed while measuring CO disappearance; by the latter method they minimized errors due to nonuniformity of D_L/V_A. The close correlation that they found between the rebreathing and single breath measurements of D_{LCO} in normal subjects and in patients with diffuse lung disease suggests that neither breath holding per se nor nonuniformity of D_L/V_A causes appreciable systematic errors in D_{LCO}. However, D_{LCO} is larger at full inspiration than at normal operational lung volumes (25–27); therefore, single breath measurements may be systematically too high on this account. Assuming that our measurements of CO diffusing capacity at full inspiration are correct, the deviations from optimal conditions that most likely account for the premature fall in arterial blood oxygen saturation (Figure 1) are as follows:

1) Diffusing capacity measured at full inspiration rather than at operational lung volume will predict the limits in Figure 1 to be too high.

2) Distribution of inspired air was not uniform (Table II), nor would we expect capillary perfusion to be uniform with respect to diffusing capacity: these abnormalities would cause inefficient utilization of the available diffusing surface (28).

TABLE VI

*Predicted values for maximal oxygen intake ($\dot{V}_{O_2}$), maximal pulmonary capillary blood volume (V_c), and maximal membrane diffusing capacity (D_{MCO})**

Patient	$\dot{V}_{O_2}$	V_c	D_{MCO}
	L/min	*ml*	*ml/min/mm Hg*
CMcD	2,659	200	98
JA	2,740	217	107
ET	3,784	200	98
PB	2,660	195	95
RH	2,082	131	60
JJ	1,432	127	58

* Maximal oxygen consumption was predicted to be 45 ml per kg of body weight for males and 35 ml per kg for females based upon the data of Andersen for young adults (21). The maximal pulmonary capillary blood volume and membrane diffusing capacity for CO were predicted from the following formulas (22): Vc = 30.5 × predicted total lung capacity (TLC) + 9.4; D_{MCO} = 16.7 × predicted TLC − 6.8, where λ is assumed to be 2.5 (Equation 6). Age regressions have not been taken into account in predicting either the maximal oxygen consumption or the diffusing capacity.

Membrane diffusing capacity at resting functional residual capacity (FRC) is approximately 70% of that measured at full inspiration in normal subjects (25). If mean lung volume during heavy exercise were midway between resting FRC and full inspiration and if the same relationships hold for patients as for normal subjects, the predicted upper limits in Figure 1 would be about 15% too high.

Figure 2 exemplifies the effect of unequal red cell transit times or uneven blood flow through lung capillaries on the oxygen saturation of blood leaving the lung. Red cell transit times can be unequal without gross regional differences in blood flow or diffusing capacity. For instance, pulsatile blood flow may carry some red cells through the capillary bed faster than others (29). Also the pulmonary capillary bed, a labyrinth of interconnecting capillaries, presents many alternative paths of different length from artery to vein requiring different times for red cell transit. A fixed unevenness of red cell transit or of capillary perfusion with respect to diffusing capacity will cause arterial blood oxygen saturation to start falling at lower oxygen consumptions than predicted; uneven ventilation with respect to per-

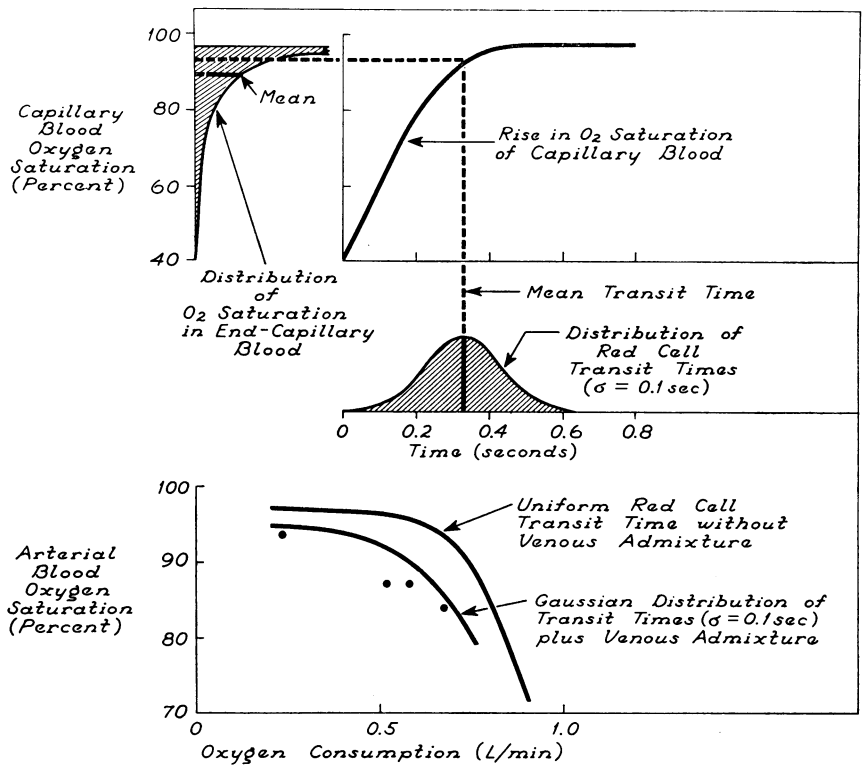

FIG. 2. EFFECT OF UNEVEN RED CELL TRANSIT THROUGH LUNG CAPILLARIES UPON THE OXYGEN SATURATION OF MIXED END-CAPILLARY BLOOD. If the time required for red cells to traverse the lung capillaries varies as illustrated above by the normal frequency distribution, the distribution of end-capillary blood oxygen saturations will be such that the mixture of blood leaving the lung will contain less oxygen than that predicted assuming a uniform transit time. The lower part of this figure shows how taking into account the measured anatomical shunt and assuming a fixed nonuniformity of red cell transit times brings the predicted fall in arterial blood oxygen saturation during exercise into closer agreement with the measured data from patient RH.

fusion also may cause arterial oxygen saturation to fall prematurely with respect to our predictions. In either case, as work load increases, the relationship between arterial oxygen saturation and oxygen consumption will approach but never reach the upper limits predicted assuming uniform capillary perfusion, diffusing capacity, and ventilation.

For the above reasons our predictions of the relationship between arterial oxygen saturation and oxygen consumption based upon measurements of $D_{M_{CO}}$ and Vc must be considered upper limits that can be reached only under ideal conditions.

Functional significance of a low $D_{L_{CO}}$ and $D_{M_{CO}}$. We have predicted the reduction in maximal oxygen consumption implied by a low CO diffusing capacity according to the theoretical considerations discussed under Methods (Figures 3 to 5). According to these calculations at an alveolar oxygen tension of 110 mm Hg diffusing capacity must fall to less than 50% of normal before significantly limiting oxygen transport. This is consistent with the observations of Linderholm (20) that cardiac output rather than diffusing capacity imposes the upper limit to oxygen consumption in subjects with one lung. Also according to our calculations oxygen transport should be impaired to about the same extent whether alveolar capillary block is caused by simple loss of capillaries or by thickening of alveolar capillary membrane. However, we have not considered the possibility that loss of capillaries may cause additional restriction of oxygen trans-

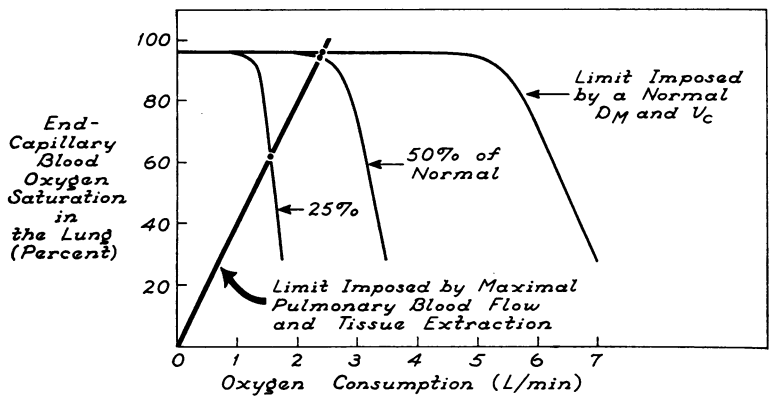

FIG. 3. THEORETICAL UPPER LIMITS TO OXYGEN CONSUMPTION IMPOSED BY ALVEOLAR-CAPILLARY DIFFUSION AND CARDIAC OUTPUT. The theoretical limits imposed by diffusion (curved lines) were predicted from Equations 2 and 4 (Methods), assuming an alveolar oxygen tension of 110 mm Hg and a normal oxygen carrying capacity of blood. The straight line is the maximal oxygen consumption that can be achieved at different oxygen contents of arterial blood at a normal maximal cardiac output (Equation 4 in Methods). The points of intersection are the maximal oxygen consumptions satisfying both the maximal diffusing capacity and maximal cardiac output. The predictions are based upon normal average values for D_{MCO}, Vc, and Qc measured at maximal oxygen consumption in our laboratory (21), D_M = membrane diffusing capacity; V_C = pulmonary capillary blood volume.

port by lowering the maximal pulmonary blood flow. If cardiac output is reduced enough, alveolar capillary block may never become manifest. Experimental data, though closely following the theoretical lines, are displaced to the right indicating that the actual reduction in maximal oxygen consumption is generally greater than that

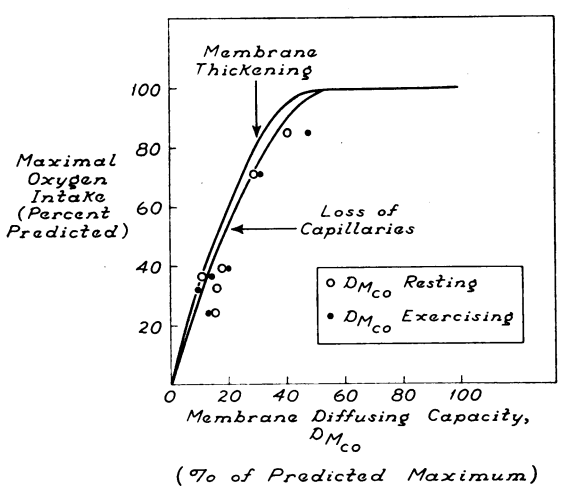

FIG. 4. EXPECTED AND OBSERVED REDUCTION IN MAXIMAL OXYGEN INTAKE ASSOCIATED WITH A LOW MEMBRANE DIFFUSING CAPACITY AT SEA LEVEL. Theoretical predictions (curved lines) were made as shown in Figure 3 assuming an alveolar oxygen tension of 110 mm Hg. One line pertains if the membrane diffusing capacity is reduced simply by loss of capillaries and the other if membrane diffusing capacity is reduced by thickening of the alveolar capillary membrane without loss of capillary blood volume.

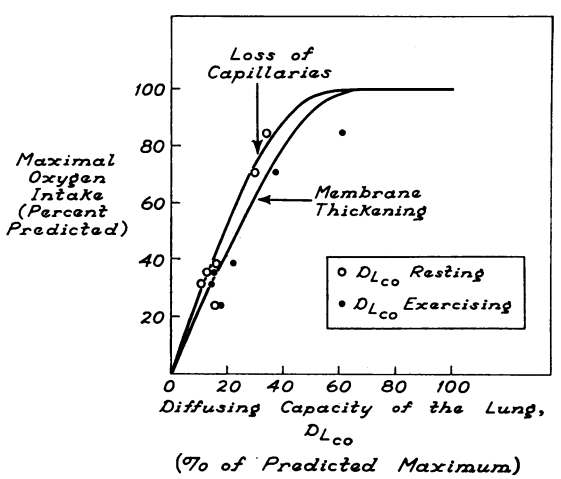

FIG. 5. EXPECTED AND OBSERVED REDUCTION IN MAXIMAL OXYGEN INTAKE ASSOCIATED WITH A LOW APPARENT CO DIFFUSING CAPACITY (D_{LCO}). The curved lines indicate the reduction of maximal oxygen intake expected from a given reduction of D_{LCO} if D_{LCO} is measured at an alveolar oxygen tension of 130 mm Hg. The two theoretical lines, one representing loss of capillaries and the other thickening of the alveolar capillary membrane, are reversed with respect to their positions in Figure 4.

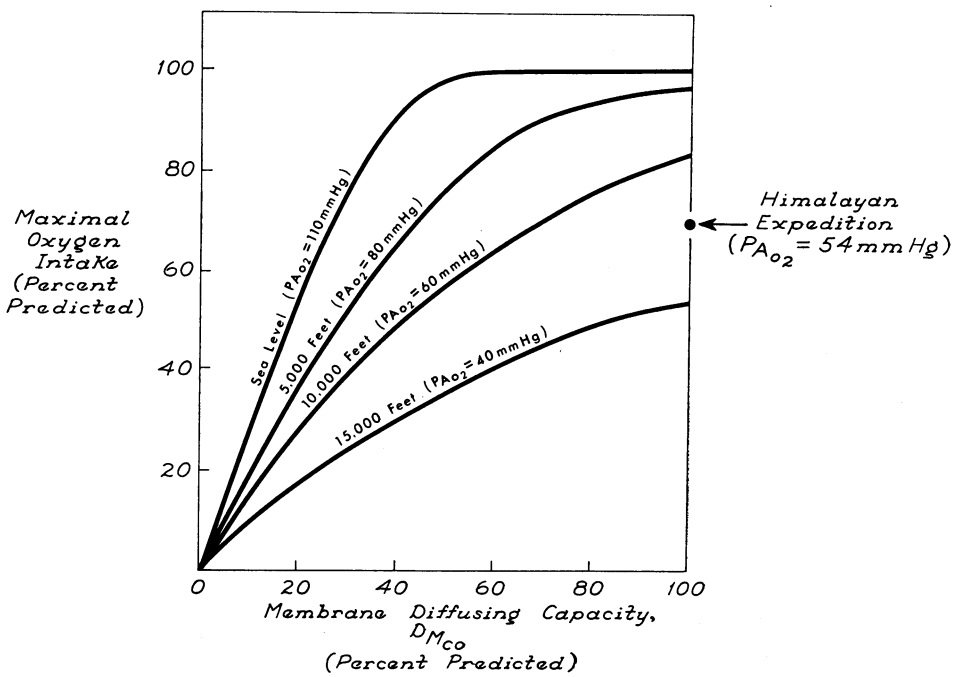

FIG. 6. PREDICTED EFFECT OF ALTITUDE UPON THE RELATIONSHIP BETWEEN MAXIMAL OXYGEN INTAKE AND MEMBRANE DIFFUSING CAPACITY FOR CO. The predictions were made assuming that the alveolar CO_2 tension is 40 mm Hg (i.e., assuming no compensatory hyperventilation) and that the respiratory quotient is 1.0 at heavy exercise. Members of the British Himalayan expedition in 1960 (3) reached maximal oxygen intakes at 19,000 feet that equal those predicted at 12,000 feet because they hyperventilated enough to raise their alveolar oxygen tensions to above 50 mm Hg.

predicted. $D_{M_{CO}}$ measured at rest seems to be as good an index of the restriction imposed upon oxygen consumption as $D_{M_{CO}}$ measured at peak exercise loads; this is true because membrane diffusing capacity increases very little from rest to peak exercise. Thus it is not necessary to measure diffusing capacity during exercise to obtain a good estimate of exercise limitation imposed by diffusion.

Effects of altitude. The measurements and predictions discussed so far pertain to sea level. As normal persons ascend to higher altitudes, their exercise tolerance becomes increasingly limited by diffusion owing to the progressive fall in alveolar oxygen tension. The generalizations concerning the relationships between maximal oxygen consumption and membrane diffusing capacity at sea level also apply to different altitudes (Figure 6). Above 10,000 feet the diffusing capacity should begin to limit oxygen transport in normal persons, and the disability of patients with alveolar capillary block should be greatly accentuated. When ascending from sea level to 10,000 feet the maximal oxygen consumption in a normal person should fall only about 15%. But maximal oxygen consumption may fall more than 50% when a patient with a low diffusing capacity ascends from sea level to 10,000 feet. Furthermore, a patient can have a low diffusing capacity which is not functionally significant at sea level but which is incapacitating at 10,000 feet.

The low inspired oxygen tension at high altitudes may be partially compensated by alveolar hyperventilation. A 20-mm Hg increase in alveolar oxygen tension due to hyperventilation can increase maximal oxygen intake as much as descending 5,000 feet. Thus both ventilatory capacity and diffusing capacity may become important rate limiting steps in oxygen transport at high altitudes.

Summary

If diffusing capacity of the lungs is reduced enough by disease, alveolar capillary block results, causing maximal oxygen consumption to be curtailed by a sharp fall in arterial oxygen saturation. Our purpose was to determine whether measurements of carbon monoxide diffusing capacity can be used in accord with presently accepted theory to predict the limits that a low diffusing capacity imposes on oxygen consumption. In six patients suspected of having alveolar capillary block pulmonary capillary blood flow, capillary blood volume (Vc), and membrane diffusing capacity for CO (D_{MCO}) were measured at full inspiration both at rest and exercise. From these measurements we predicted how oxygen saturation of arterial blood would fall as oxygen consumption increases at a given alveolar oxygen tension. To make these predictions D_{MCO} and Vc were translated into terms of oxygen transport using *in vitro* measurements of Staub, Bishop, and Forster (8) to estimate kinetics of oxygen uptake by capillary red cells; we assumed that D_{MO_2} equals 1.23 D_{MCO} and that lung volume, ventilation, and blood flow were uniformly distributed with respect to diffusing surface. Then the same patients were exercised on a treadmill up to the heaviest load tolerated, and the relationship between oxygen consumption and oxygen saturation of arterial blood was measured. At heavy exercise oxygen consumption approached the upper limits predicted from D_{MCO} and Vc even though arterial oxygen saturation began to fall at a lower oxygen consumption than predicted. Reasons for the latter discrepancy are discussed. The experimental data as well as theory indicate that maximal oxygen intake at sea level should not be limited significantly by diffusion until membrane diffusing capacity is less than 50% of predicted normal. Theory also indicates that above 10,000 feet diffusing capacity should become important as a limit to oxygen consumption even in normal subjects. The latter is supported by the measurements of West and co-workers (3) on subjects exercising at 19,000 feet.

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