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Research Article

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ABSTRACT We measured simultaneously, by single breath methods, pulmonary capillary blood flow ($\dot{Q}_c$), carbon monoxide diffusing capacity (D_{LCO}), and isotopic oxygen ($^{18}O^{18}O$) diffusing capacity ($D_{L^{18}O_2}$) in five normal males during conditions of rest and moderate exercise at mixed venous O_2 tensions (P_{O_2} 33–44 mm Hg). During moderate exercise at a work load of 100 W, pulmonary capillary blood flow increased from 6.9±1.5 to 12.9±3.4 min^{-1} and $D_{L^{18}O_2}$ increased from 25±4 to 43±3 $ml \cdot min^{-1} \cdot mm\ Hg^{-1}$, whereas D_{LCO} showed no significant change (45±5 to 49±10 $ml \cdot min^{-1} \cdot mm\ Hg^{-1}$). $D_{L^{18}O_2}$ increased proportionally to $\dot{Q}_c$ ($r = 0.74$), where D_{LCO} did not ($r = 0.08$). The greater increase in $D_{L^{18}O_2}$ during exercise can be explained by a more homogeneous diffusion/perfusion ($D_{LO_2}/\dot{Q}_c$) distribution in the individual respiratory exchange units during exercise. This improved distribution of $D_{LO_2}/\dot{Q}_c$ acts to help prevent an increase in alveolar-arterial O_2 tension difference from developing despite the decrease in pulmonary erythrocyte transit times that occur during exercise. The insignificant rise in D_{LCO} with exercise under these hypoxic breath-holding conditions may result from pulmonary vasomotor responses to short-term hypoxia or from relative insensitivity of D_{LCO} to moderate levels of exercise.

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INTRODUCTION

Several factors play a significant role in determining the alveolar to pulmonary capillary O_2 tension difference and, hence, the overall effectiveness of pulmonary O_2 exchange. These include ventilation, diffusion, perfusion, and their interrelationship (1–6). In the presence of a normal respiratory apparatus, the lung diffusing capacity for O_2 (D_{LO_2})[1] is sufficiently large that the principal limiting factor for O_2 uptake is pulmonary blood flow during both rest and exercise (7, 8).

The determination of D_{LO_2} depends upon an accurate determination of the "mean" difference between alveolar and pulmonary capillary O_2 tension ($\bar{P}_{AO_2} - \bar{P}_{cO_2}$). At usual alveolar and pulmonary capillary O_2 tensions the alveolar to end-capillary O_2 gradient ($P_{AO_2} - Pc'_{O_2}$) is so small it cannot be calculated accurately (1). Lilienthal, Riley, Proemmel, and Franke (9) devised an ingenious two-level method for measuring D_{LO_2} utilizing determinations of arterial and alveolar P_{O_2} during the breathing of 12–14% O_2 as well as air. The validity of this concept for the measurement of D_{LO_2} has been questioned by a number of investigators (7, 10).

Hyde, Rynes, Power, and Nairn (11) describe a technique for determining D_{LO_2} from the rate of uptake of a stable O_2 isotope, $^{16}O^{18}O$, during periods of breath

[1] *Abbreviations used in this paper:* D_{LCO}, carbon monoxide diffusing capacity; $D_{L^{18}O_2}$, D_{LO_2}, lung diffusing capacity for O_2; D_{MCO}, diffusing capacity of the pulmonary membrane for CO in $ml \cdot min^{-1} \cdot mm\ Hg^{-1}$; $\bar{P}_{AO_2}$, alveolar capillary O_2 tension; P_{cO_2}, pulmonary capillary O_2 tension; $\bar{P}c'_{O_2}$, end-capillary O_2 tension; $\dot{Q}_c$, pulmonary capillary blood flow; θ_{CO}, reaction rate of CO with hemoglobin; V_A, alveolar volume; V_c, pulmonary capillary blood volume in milliliters; Vtis, pulmonary parenchymal tissue volume.

holding. This technique has the advantage of establishing a proportionally larger alveolar to end-capillary gradient for labeled O_2 because the mixed venous P_{O_2} for the isotope is virtually negligible. They found $D_{L_{O_2}}$ measured with the O_2 isotope was approximately 55% of $D_{L_{O_2}}$ estimated from simultaneous measurements of D_{LCO} in five normal resting males. This discrepancy was attributed to uneven distribution of diffusing capacity to blood flow (uneven $D_L/\dot{Q}_c$) within individual gas exchange units of the lung (12). Their theoretical calculations showed that the numerical value of $D_{L_{O_2}}$ would be reduced if there was uneven matching of D_L to pulmonary capillary blood flow ($\dot{Q}_c$). In addition, the relative values of $D_{L_{O_2}}$ and D_{LCO} could be used to determine the degree of uneven $D_L/\dot{Q}_c$ present.

During exercise, a number of investigators have noted that measured values of $D_{L_{O_2}}$ and D_{LCO} increase (1, 9, 13–16). For a given increase in blood flow, the rise in $D_{L_{O_2}}$ is considerably larger than the rise in D_{LCO} (15). This increase in $D_{L_{O_2}}$ with moderate exercise could be due to either an increase in the size of the pulmonary capillary bed or be secondary to the development of a more homogeneous distribution of $D_{L_{O_2}}$ to $\dot{Q}_c$.

In order to evaluate this aspect of the behavior of the diffusing capacity of the lung during exercise, we simultaneously measured $\dot{Q}_c$, $D_{L_{O_2}}$, and D_{LCO} during conditions of rest and moderate exercise in five healthy adult males.

METHODS

Five, male adults familiar with pulmonary laboratory procedures served as subjects (Table I). They had no known active pulmonary disease on the basis of history and physical examination.

The seated subject exhaled to residual volume and then hyperventilated for several breaths from a rubber bag containing approximately 3 liters of a mixture of 8% CO_2 and 92% N_2 in order to nearly equilibrate alveolar P_{O_2} and P_{CO_2} with mixed venous blood tensions. The concentration of O_2 and CO_2 at the mouthpiece was monitored by rapidly responding O_2 and CO_2 analyzers.[2] The volume or concentration of the gas mixture in the rebreathing bag usually had to be readjusted so that alveolar concentration closely approached mixed venous values. After the rebreathing procedure, the subject expired to residual volume and maximally inspired a gas mixture containing 1% acetylene (C_2H_2), 1% neon (Ne), 0.3% carbon monoxide (CO), and 0.2% oxygen of mass 36 ($^{18}O^{18}O$) in a balance of $^{16}O_2$, CO_2, and N_2. The concentration of total O_2 and CO_2 was adjusted for each individual to the mixed venous values determined from the rebreathing procedure. After a predetermined breath-holding period the subject forcefully exhaled. The expired gas was collected in a rubber bag after discarding the initial liter of exhaled gas (17). The experimental procedure was then repeated several times in order to obtain multiple alveolar samples with breath-holding times varying from 3 to 10 s.

[2] Westinghouse O_2 analyzer (Westinghouse Electric Corp., Pittsburgh, Pa.) and Godart CO_2 analyzer (Godart/Statham Instruments, Inc., Oxford, Calif.).

TABLE I
Vital Statistics of Experimental Subjects

Subject	Age	Height	Weight	Body surface area	Hematocrit
	yr	*cm*	*kg*	m^2	
E. W.	22	183	75	1.9	43
R. S.	25	180	79	1.9	43
C. E. C.	33	175	70	1.8	44
R. W. H.	39	180	73	1.9	42
C. C.	42	178	73	1.9	39

For the exercise studies, the seated subjects pedaled a bicycle ergometer with a load of 100 W at 60–70 rpm for 5–10 min before and during the measurements. This exercise level established an oxygen consumption of approximately 1,000 $ml \cdot min^{-1}$ (18). The test gas mixtures were adjusted so that total O_2 and CO_2 concentrations matched those of the respective exercise rebreathing plateau values.

Samples of the collected alveolar gases were transferred into evacuated tonometers and subsequently analyzed with a mass spectrometer for O_2 and its isotopes, C_2H_2, and Ne (19).[3] CO was analyzed by an infrared meter.[4] All gas samples were collected and analyzed in duplicate, and reproducibility in the gas analysis on the mass spectrometer was within 0.5%. Reproducibility of the measurement of CO was within 2%.

Calculations. Alveolar volume (VA) during breath holding was calculated by adding the inspired volume recorded spirometrically to the residual volume determined from the dilution of neon. The alveolar partial pressures of $^{18}O_2$, C_2H_2, and CO at the start of breath holding before any absorption by lung tissues or pulmonary capillary blood were calculated from the inspired test gas concentrations and the neon dilution.[5] The simultaneous disappearance from the alveoli of C_2H_2, CO_2 and $^{18}O_2$ was plotted logarithmically against time of breath holding. The plotted points, representing three or more individual breath holds, were connected by regression lines derived by the method of least mean squares. $\dot{Q}_c$ and pulmonary parenchymal tissue volume (V_{tis}) were determined from the disappearance of C_2H_2 by the method of Cander and Forster (20). D_{LCO} was determined from the slope of the alveolar CO disappearance (17).[6] $D_{L_{O_2}}$ was determined by previously described methods (11).

Predicting the value of $D_{L_{O_2}}$ from determinations of D_{LCO}. Previous workers have shown that a value for $D_{L_{O_2}}$ derived from D_{LCO} (predicted $D_{L_{O_2}}$) can be calculated using the

[3] Model 21-104 Consolidated Electrodynamics (Bell and Howell Co., Pasadena, Calif.).

[4] Hartmann and Braun Ag, Model Uras-M (Godart/Statham Instruments, Inc., Oxnard, Calif.).

[5] The stable O_2 isotope of mass 36 ($^{18}O^{18}O$) was used in this study. The natural abundance of this isotope is so low that there is an insignificant concentration of isotope in the residual volume or entering the lung in the mixed venous blood. Under these circumstances, the concentration of $^{18}O_2$ at the start of breath holding can be determined from the neon dilution.

[6] The CO back pressure was measured several times on each subject using previously described methods (14). However, at the levels of O_2 and CO tensions used in these studies, the measured CO back pressure was less than 0.001% CO and this correction was insignificant in the calculations of D_{LCO}.

following equations (12, 21):

$$\frac{1}{D_{L_{CO}}} = \frac{1}{D_{M_{CO}}} + \frac{1}{\theta_{CO} Vc} \quad (1\ a)$$

$$\frac{1}{D_{L_{O_2}}} = \frac{1}{D_{M_{O_2}}} + \frac{1}{\theta_{O_2} Vc} = \frac{1}{1.16\ D_{M_{CO}}} + \frac{1}{\theta_{O_2} Vc} \quad (1\ b)$$

where $D_{M_{CO}}$ equals the diffusing capacity of the pulmonary membrane for CO in ml·min^{-1}·mm Hg^{-1} and Vc equals the pulmonary capillary blood volume in milliliters. As all our measurements of DL were made at alveolar O_2 tensions of 33–44 mm Hg, we used an assumed value of 0.98 ml·ml^{-1}·min^{-1}·mm Hg^{-1} for θ_{CO}, the reaction rate of CO with hemoglobin (21). We used the regression equations of Johnson, Spicer, Bishop, and Forster (14) to establish a proportional relationship between DM and Vc. This relationship was approximately 0.6 ml·min^{-1}·mm Hg^{-1}·ml^{-1} and assumed to remain unchanged after exercise because of the small change in $D_{L_{CO}}$. We assumed that the predicted relationship between Vc and DM obtained during normoxia also applies for conditions of short-term alveolar hypoxia. Substituting this ratio and the appropriate experimental $D_{L_{CO}}$ value into equation 1 *a* allowed us to calculate DM and Vc.

In determining predicted $D_{L_{O_2}}$ by equation 1 *b* we used the calculated values for $D_{M_{CO}}$ and Vc established by equation 1 *a*. In substituting for $D_{M_{O_2}}$, $D_{M_{CO}}$ must be multiplied by 1.16 on the basis of Graham's law of diffusibility of gases.

We used the broadly accepted values for θ_{O_2} as determined from data published by Staub, Bishop, and Forster (22). At the P_{O_2} levels used in the present study, θ was approximately constant at about 2.8 ml·ml^{-1}·min^{-1}·mm Hg^{-1}. Recently Rotman, Klocke, and Forster (23) and Mochizuki (24) have suggested that overestimations of θ_{O_2} can occur due to the stagnant layer effects on the membrane of the O_2 electrode in a continuous reaction apparatus. Although the resultant overestimation of θ_{O_2} leads to falsely high values of predicted $D_{L_{O_2}}$, $D_{L_{O_2}}$ is not particularly sensitive to the value of θ_{O_2}. If, at some future date, more accurate methods for calculation of predicted $D_{L_{O_2}}$ become available, the data can be corrected.

Calculation of distribution of diffusing capacity to blood flow. If differences between predicted $D_{L_{O_2}}$ and measured $D_{L_{O_2}}$ are attributed to uneven distribution of diffusing capacity to blood flow, a lung model consisting of an alveolus perfused by two capillaries with different values for $\dot{Q}_c$ and diffusing capacity can be defined (12, 25). The multiple patterns of distribution of $\dot{Q}_c$ to $D_{L_{O_2}}$ consistent with the data are conveniently recorded as a locus of points contained on a curve plotted on a graph of the DL of one of the two compartments and its $\dot{Q}_c$.

RESULTS

Figs. 1 a and b show the rate of disappearance from the alveoli of C_2H_2, $^{18}O_2$, and CO during breath holding at rest and during exercise in a representative subject. The experimental data for all studies at rest and during exercise are summarized in Table II. At rest, the mixed venous O_2 tension during breath holding was 44±1 mm Hg and fell to 33±3 mm Hg during exercise. $\dot{Q}_c$ increased from 6.9±1.5 liters·min^{-1} to 12.9±3.4 liters·min^{-1} during exercise. $D_{L_{O_2}}$ was 25±4 ml·min^{-1}·mm Hg^{-1} at rest and increased to 43±3 ml·min^{-1}·mm Hg^{-1} during exercise. $D_{L_{CO}}$ only changed from 45±5 ml·min^{-1}·mm Hg^{-1} to 49±10 ml·min^{-1}·mm Hg^{-1}. The individual changes for $D_{L_{CO}}$ and $D_{L_{O_2}}$ are shown in Figs. 2 a and b. The above differences in $P_{A_{O_2}}$ (mixed venous P_{O_2}), Vtis, $\dot{Q}_c$, and $D_{L_{O_2}}$ on changing from rest to exercise were all statistically significant ($P < 0.05$). VA and $D_{L_{CO}}$ showed no significant change ($P > 0.10$). Moreover, the changes in $D_{L_{O_2}}$ showed a significant correlation with changes in $\dot{Q}_c$ ($r = 0.74$, $P < 0.005$), while the changes in $D_{L_{CO}}$ did not ($r = 0.08$, $P > 0.10$).

Change in pattern of distribution of $D_{L_{CO_2}}$ to $\dot{Q}_c$ ($D_{L_{O_2}}/\dot{Q}_c$). The theoretical distribution of $D_{L_{O_2}}$ with respect to $\dot{Q}_c$ derived from the data is shown in Fig. 3. The lung model used consisted of an alveolus

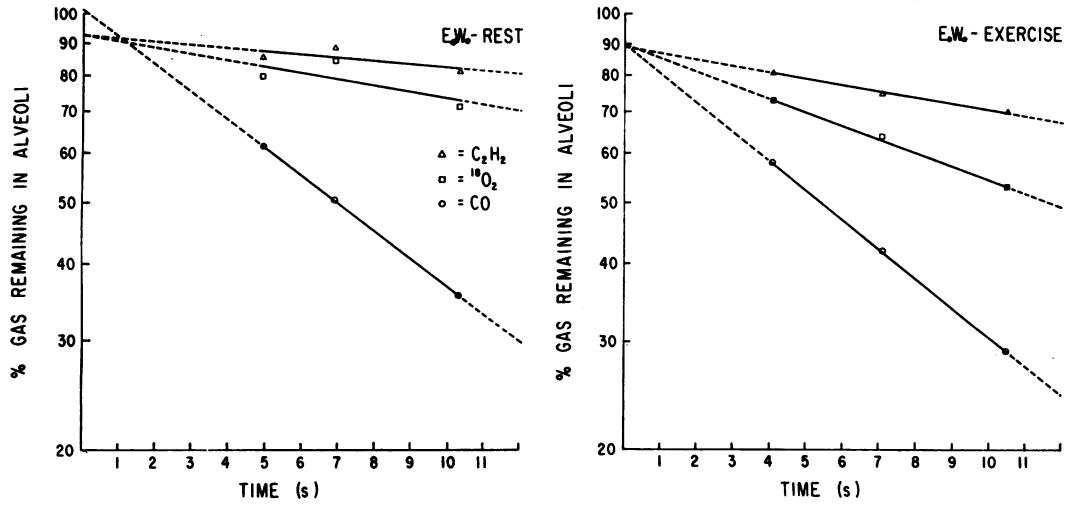

FIGURE 1 Disappearance of C_2H_2, $^{18}O_2$, and CO from the alveolar gas during rest and exercise in subject E. W. The regression lines (—) are calculated by the method of least mean squares and extrapolated (---) to the intercept at ($t = 0$).

TABLE II

Results of Experimental Data during Rest and Exercise

		V_A	$P_{A_{O_2}}$	Vtis	$\dot{Q}_{C_{C_2H_2}}$	$D_{L_{CO}}$	$D_{L^{18}O_{2(meas)}}$	$D_{L^{18}O_{2(pred)}}$	$\frac{D_{L^{18}O_{2(meas)}}}{D_{L^{18}O_{2(pred)}}}$
		*liter**	*mm Hg*	*ml*	$l \cdot min^{-1}$	$ml \cdot min^{-1} \cdot mm\ Hg^{-1}$	$ml \cdot min^{-1} \cdot mm\ Hg^{-1}$	$ml \cdot min^{-1} \cdot mm\ Hg^{-1}$	%
E. W.	Rest	5.82	43	635	5.7	49	18	74	24
	Exercise	5.82	30	997	13.1	53	40	79	51
R. S.	Rest	4.72	43	373	7.1	44	26	66	39
	Exercise	5.33	37	847	14.2	34	40	51	78
C. E. C.	Rest	4.76	44	135	9.4	50	27	75	36
	Exercise	4.79	33	503	17.8	44	44	66	67
R. W. H.	Rest	5.93	46	589	6.2	46	24	69	35
	Exercise	6.14	33	771	10.0	60	48	90	53
C. C.	Rest	5.16	43	624	5.9	38	28	57	49
	Exercise	5.82	30	1119	9.5	53	42	79	53
	Rest-Mean	5.28	44	471	6.9	45	25	68	37
	SD	0.57	1	216	1.5	5	4	7	9
	Exercise-Mean	5.58	33	847	12.9	49	43	73	60
	SD	0.53	3	235	3.4	10	3	15	12
	Significance Level	NS	$P < 0.0005$	$P < 0.05$	$P < 0.005$	NS	$P < 0.0005$	NS	$P < 0.005$

Abbreviations: V_A, alveolar volume; $P_{A_{O_2}}$, alveolar oxygen pressure; Vtis, calculated pulmonary tissue volume; $\dot{Q}_{C_{C_2H_2}}$, pulmonary capillary blood flow; $D_{L_{CO}}$, measured single breath CO diffusing capacity; $D_{L^{18}O_{2(meas)}}$ and $D_{L^{18}O_{2(pred)}}$, measured and predicted single breath $^{18}O_2$ diffusing capacities, respectively.

* Standard temperature and pressure, dry.

with two perfusion pathways (12, 25). Our results showed a considerable degree of uneven distribution of $D_{L_{O_2}}$ with respect to $\dot{Q}_c$ at rest. In all subjects, more even $D_L/\dot{Q}_c$ was present during exercise. However, there was considerable individual variation in the amount of improvement (Fig. 3). These variations may, in part, be due to different cardiac outputs during exercise. For instance, in subject R. S., who demonstrated considerable improvement in $D_L/\dot{Q}_c$ distribution, $\dot{Q}_c$ increased 7.1 liters$\cdot$min^{-1}, while in subject R. W. H., whose blood flow increased only 3.8 liters$\cdot$min^{-1}, a less dramatic change in $D_L/\dot{Q}_c$ distribution occurred. Another factor which may play a part is age. The oldest subject C. C. (age 42) showed very little improvement, while one of the younger subjects (R. S.) showed appreciably more change. Measurements in a much larger number of subjects with a wider range in age would be required in order to establish a relationship between age and degree of uneven $D_L/\dot{Q}_c$.

In the upper left half of Fig. 3, we have recorded the possible patterns of uneven $D_L/\dot{Q}_c$ distributions based on the mean values in Table II and compatible with reported values of alveolar-arterial O_2 gradients (9, 10, 25). For example, one possible solution shows that approximately 60% of the blood flow perfuses 10% of the diffusion surfaces at rest and 18% of the diffusion surfaces during conditions of mild exercise. This inhomogeneity could account for alveolar-arterial O_2 gradients of approximately 5 mm Hg at rest and 10 mm Hg during mild exercise (7).

To determine the possible influences of different D_M/Vc ratios on the distribution of $D_L/\dot{Q}_c$, the mean data were recalculated for a D_M/Vc ratio of 1.5 ml$\cdot$min^{-1} $\cdot$mm Hg$^{-1}\cdot$ml^{-1}, the ratios found by Lewis, Lin, Noe, and Komisaruk (26). The resulting levels of uncertainty are depicted by the shaded area in Fig. 3 and suggest that even with changes in D_M/Vc between 0.6 and 1.5 ml$\cdot$min$^{-1}\cdot$mm Hg$^{-1}\cdot$ml^{-1}, there remain substantial improvements in $D_L/\dot{Q}_c$ ratios with mild exercise.

DISCUSSION

These data indicate that in normal subjects there is an impressive discrepancy between experimentally measured and predicted $D_{L_{O_2}}$ which decreases with exercise. A likely explanation is the maldistribution of

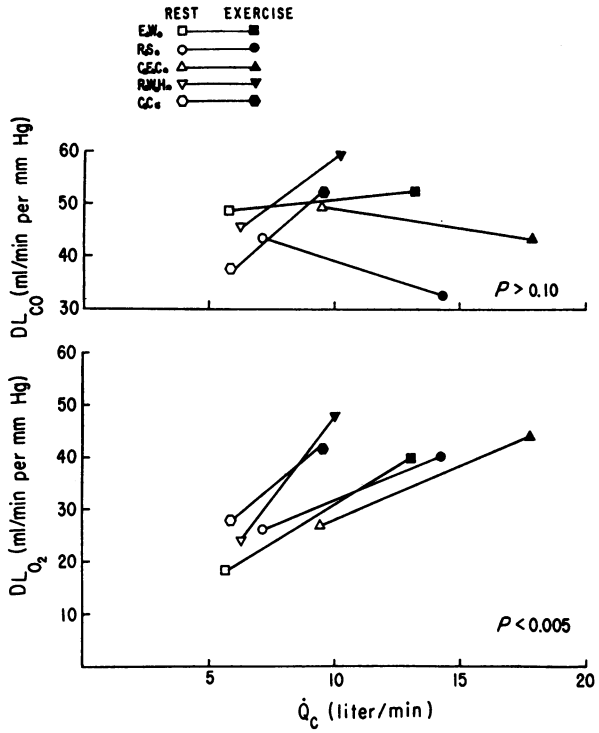

FIGURE 2 Changes in diffusion capacity for CO (D_{LCO}) and for O_2 (D_{LO_2}) with respect to simultaneously determined Q_c.

perfusion ($\dot{Q}_c$) to the lung's diffusion surfaces (D_L) (2, 5, 6, 12, 25).

Sources if nonuniform distribution of D_L to $\dot{Q}_c$ at rest

Heterogeneity of $D_L/\dot{Q}_c$ ratios in these experiments may result from: (*a*) topographical variations in $\dot{Q}_c$ due to gravitational forces; (*b*) stratified inhomogeneity of $\dot{Q}_c$ within gas exchange units; (*c*) heterogeneity of $\dot{Q}_c$ in individual gas exchange units scattered throughout the lungs; (*d*) pulsatile pulmonary capillary blood flow; (*e*) the 15–20 s of severe hypoxia required by the method, and; (*f*) the breath holding maneuver used in the experimental technique.

(*a*) *Gravitational variations.* Gravitational variations in $\dot{Q}_c$ are present in the normal lung (27) and potentially account for $D_L/\dot{Q}_c$ inhomogeneity. Glazier, Hughes, Malone, and West (28) have shown that areas of the lung characterized by a low $\dot{Q}_c$ (top of the upright lung, zone 1) have a reduced capillary blood volume (Vc). This would tend to lessen the effect of this variation. However, of interest are the recently reported findings of Hyde, Fisher, Marin, and Sonnemann (29) and Michaelson, Sackner, and Johnson (30) demonstrating that $D_L/\dot{Q}_c$ ratios are the lowest in dependent regions of the lung and highest in superior portions of the lung. This finding suggests that the superior portions of the lung contain a relatively more stagnant portion of Vc. However, theoretical calculations by a number of workers have shown that topographical heterogeneity of $D_L/\dot{Q}_c$ cannot fully account for the total $D_L/\dot{Q}_c$ inhomogeneity (12, 25). Further, the hypoxia of the present studies may have lessened the gravitational variation of $\dot{Q}_c$ (31, 32).

(*b*) *Stratified inhomogeneity.* Stratified inhomogeneity of gas exchange units may likewise contribute to overall heterogeneity of $D_L/\dot{Q}_c$ ratios. It is possible that at rest the relatively poorly ventilated peripheral gas exchange units have less perfusion than the more proximal (central) gas exchange units in order to maintain a relatively even distribution of ventilation to perfusion (33). When a deep inspiration is taken to measure D_{LCO} and D_{LO_2}, the sluggish blood flow in the distal parts of the airway would significantly contribute to D_{LCO} but at the same time remove little labeled $^{18}O_2$ and thereby not contribute to D_{LO_2}. The quantitative importance of this phenomena has yet to be established in man (34).

(*c*) *Heterogeneity with respect to individual gas exchange units.* Random heterogeneity of $\dot{Q}_c$ in individual gas exchange units may be caused by anatomical variation in lengths of capillary pathways (35). However, at the present time there is no experimental basis for assessing the magnitude of this unevenness. Anatomical studies indicate that pulmonary capillary pathways may vary from 60–250 μm (36). Recent evidence suggests that this heterogeneity may be within alveolar units (capillaries) and not within arteriolar units (37). This type of random inhomogeneity could account for the bulk of the $D_L/\dot{Q}_c$ unevenness observed in the present studies.

(*d*) *Pulsatile flow.* Theoretical considerations have indicated that pulsatile pulmonary capillary blood flow might have a detrimental effect on the efficiency of O_2 gas exchange in the lungs (38) because some erythrocytes would have a relatively brief exposure to alveolar gas during peak flow. However, recent evidence indicates that Vc increases when $\dot{Q}_c$ increases (39), thereby preventing extremely rapid transit times of the erythrocytes during systole. Preliminary measurements in the dog have shown that $D_L/\dot{Q}_c$ imbalances are greater during conditions of decreased pulsatility at the same $\dot{Q}_c$, alveolar pressure and pulmonary venous pressures (40). This finding agrees with the observations that pulsatile blood flow has a beneficial effect upon O_2 exchange in membrane-pump oxygenators (41). Therefore, pulsatility of flow probably does not account for the major share of the inhomogeneity of $D_L/\dot{Q}_c$ distribution.

(*e*) *Effects of short-term hypoxia.* The interpretation of the experiments reported here is complicated

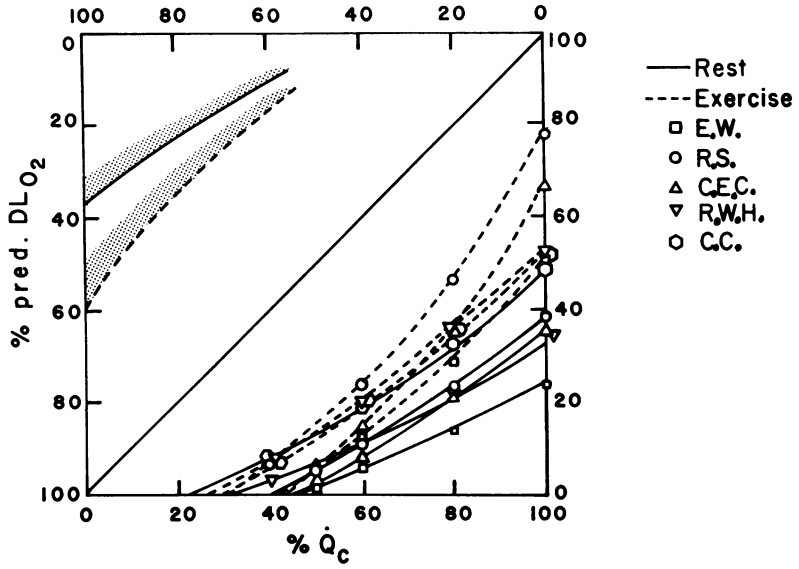

FIGURE 3 Distribution of predicted $D_{L_{O_2}}$ with respect to Qc during rest (—) and exercise (---). The diagonal line through the center of the figure is the line of identity and represents ideal matching of $D_{L_{O_2}}/\dot{Q}c$. The curves in the lower right-hand side of the figure show the individual distributions of $D_{L_{O_2}}/Qc$ in each of our subjects during rest and exercise. The upper left-hand side of the figure shows the solution for the mean values utilizing realistic values for alveolar-pulmonary capillary O_2 gradients (see text). The shaded areas represent DM/Vc ratios from 0.6 to 1.5 (see text).

by the possible effects of measuring DL at a low O_2 tension. This may theoretically contribute to the discrepancy between measured and predicted $D_{L_{O_2}}$ and hence to the magnitude of the $D_L/\dot{Q}_c$ variances found. For example, hypoxia may (*a*) cause precapillary vasoconstriction in some areas resulting in uneven $D_L/\dot{Q}_c$ or, (*b*) alter in an unpredictable manner the comparative reaction rates of O_2 (θ_{O_2}) and CO (θ_{CO}) with hemoglobin in the pulmonary capillaries.

The present experiments were performed at alveolar P_{O_2} levels known to influence pulmonary hemodynamics (42). However, these hemodynamic changes may require 5–10 min "conditioning" periods (43). There is no available data that would indicate how short-term (15–20 s) hypoxia, such as those used in the present studies, might influence $D_L/\dot{Q}_c$ distribution within gas exchange units.

It is also difficult to assess the relative influence θ_{CO} and θ_{O_2} in the ranges of P_{O_2} used in the current study because θ_{CO} has not been measured at these levels of P_{O_2} (44) and because θ_{O_2} used in this study may be overestimated because of technical reasons (23, 24). Thus, it is possible that, because of the method of estimation, θ_{O_2} has been assigned too high a value relative to θ_{CO}. This would lead to an overestimate of the degree of uneven $D_L/\dot{Q}_c$ both at rest and during exercise.

(*f*) *Effects of breath holding.* The breath-holding maneuver can result in elevated alveolar pressures and, therefore, diminish $\dot{Q}_c$ to the superior portions of the lung (45), potentially altering $D_L/\dot{Q}_c$ distribution. However, preliminary studies utilizing the rebreathing technique so that breathholding at total lung capacity is avoided shows a similar range of $D_L/\dot{Q}_c$ inhomogeneity (46), so that it is unlikely that this respiratory maneuver substantially effected the $D_L/\dot{Q}_c$ distribution.

Causes for a more even distribution of DL to $\dot{Q}_c$ with exercise

The principal finding in the present study was that exercise causes a more homogeneous distribution of DL to $\dot{Q}_c$ (Fig. 3). Increased $\dot{Q}_c$ through the pulmonary capillaries during exercise may result in recruitment of additional pulmonary capillaries (47) or increased blood flow through portions of the pulmonary capillary bed with relatively stagnant blood flow. Both factors could contribute to a more even distribution of DL to $\dot{Q}_c$ and result in the observed increase in $D_{L_{O_2}}$ during exercise. Since D_{LCO} did not substantially increase with moderate exercise in our subjects, a major portion of the increased $D_{L_{O_2}}$ cannot be attributed to recruitment of previously closed capillaries because this even would have been expected to have raised D_{LCO}. The data suggests that the increase in $D_{L_{O_2}}$ with mild exercise

stems primarily from a more even distribution of blood flows through capillaries that are open at rest rather than recruitment of previously closed capillaries.

Comparison with $D_L/\dot{Q}_c$ unevenness found by others

The estimates of $D_L/\dot{Q}_c$ derived from the present data reveal a greater nonuniformity of $D_L/\dot{Q}_c$ then previous extimates (12, 25). For example, at rest, Johnson and Miller (25) calculated D_{LO_2}, as measured by the steady-state method, to be only 48% of predicted D_{LO_2} and Hyde and co-workers (12) found a value of 57% while the current study showed a value of only 39%.

During mild exercise the ratios of observed D_{LO_2} to predicted D_{LO_2} calculated by Johnson and Miller (25) increased to 88%, whereas the present directly measured values rose to only 60%.

Individual variations between subjects and different methods may explain the differences between the previous Hyde data and the current studies. Hyde and co-workers (12) used measured values of D_M and Vc to calculate their predicted D_{LO_2} values whereas the current studies used predicted D_M/Vc ratios from the literature and extrapolated values for θ_{CO}. The current method for calculating D_M and Vc resulted in significantly higher predicted D_{LO_2} values and therefore resulted in a greater degree of $D_L/\dot{Q}_c$ inhomogeneity than that found by Hyde and co-workers (12). Johnson and Miller (25) in their calculations employed data gathered by the steady-state technique which requires the simultaneous measurements of arterial and alveolar O_2 tensions and O_2 consumption and estimates concerning mixed venous O_2 tensions (9, 13, 48). While the D_{LO_2} resting values from the above studies are comparable to the current studies, the exercise values are substantially greater. Maldistribution of $\dot{Q}_c$ resulting from the more severe alveolar hypoxia present in the current studies may have contributed to this discrepancy.

Influence of uneven $D_L/\dot{Q}_c$ on gas exchange

During exercise the improved distribution of D_{LO_2} to $\dot{Q}_c$, coupled with the known increase in the size of the pulmonary capillary bed, may account for the ability of the human to maintain almost complete saturation of the arterial blood during maximal exercise despite a decrease in mean capillary transient time to almost one-third of the resting level (1). In addition, the improvement of the distribution of $D_{LO_2}/\dot{Q}_c$ during exercise may contribute to the observed finding of a rise in arterial P_{O_2} in some subjects going from rest to moderate exercise (49, 50).

Attempts have been made to assess $D_{LO_2}/\dot{Q}_c$ relationships in diseases involving the pulmonary circulation (6, 14, 25, 51, 52). In the presence of diseases involving the pulmonary capillary bed, increases in flow may not be accompanied by improvement in $D_{LO_2}/\dot{Q}_c$ relationships. Such an inability to improve $D_{LO_2}/\dot{Q}_c$ distribution with exercise may contribute to the increase in alveolar-arterial O_2 difference and striking hypoxemia caused by exercise in patients with the "alveolar-capillary block syndrome".

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