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Research Article

A method for appraising the distribution of diffusing capacity of the lungs (D_L) in relationship to pulmonary capillary blood flow ([unk]Q_C) in normal human subjects was derived from measurements of oxygen diffusing capacity ($D_{L_{O_2}}$) and carbon monoxide diffusing capacity ($D_{L_{CO}}$) performed during breath holding. This method utilizes the fact that the observed $D_{L_{O_2}}$ is considerably reduced in value if uneven distribution of D_L with respect to [unk]Q_C (uneven D_L/[unk]Q_C) is present. In contrast, $D_{L_{CO}}$ is barely affected by uneven D_L/[unk]Q_C, and from its measured value one can calculate the value $D_{L_{O_2}}$ would have if no uneven D_L/[unk]Q_C were present (true $D_{L_{O_2}}$). Once observed $D_{L_{O_2}}$ and true $D_{L_{O_2}}$ are known, the degree of uneven D_L/[unk]Q_C in the lung can be calculated.

In five normal, resting, sitting subjects average values for true $D_{L_{O_2}}$ were 57 ml per (minute × mm Hg), and the directly measured $D_{L_{O_2}}$ was 33 ml per (minute × mm Hg). These values could be explained if one-half of total [unk]Q_C were distributed to approximately 15% of total D_L.

These measurements did not permit the determination of the alveolar to end capillary O_2 gradient, but calculations demonstrate that an important factor in determining its size may be the pattern of uneven D_L/[unk]Q_C present in the lungs. Estimations of the alveolar-end capillary O_2 gradient from measurements of $D_{L_{CO}}$ or $D_{L_{O_2}}$ […]

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Determination of Distribution of Diffusing Capacity in Relation to Blood Flow in the Human Lung *

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Summary. A method for appraising the distribution of diffusing capacity of the lungs (DL) in relationship to pulmonary capillary blood flow ($\dot{Q}$c) in normal human subjects was derived from measurements of oxygen diffusing capacity ($D_{L_{O_2}}$) and carbon monoxide diffusing capacity ($D_{L_{CO}}$) performed during breath holding. This method utilizes the fact that the observed $D_{L_{O_2}}$ is considerably reduced in value if uneven distribution of DL with respect to $\dot{Q}$c (uneven DL/$\dot{Q}$c) is present. In contrast, $D_{L_{CO}}$ is barely affected by uneven DL/$\dot{Q}$c, and from its measured value one can calculate the value $D_{L_{O_2}}$ would have if no uneven DL/$\dot{Q}$c were present (true $D_{L_{O_2}}$). Once observed $D_{L_{O_2}}$ and true $D_{L_{O_2}}$ are known, the degree of uneven DL/$\dot{Q}$c in the lung can be calculated.

In five normal, resting, sitting subjects average values for true $D_{L_{O_2}}$ were 57 ml per (minute × mm Hg), and the directly measured $D_{L_{O_2}}$ was 33 ml per (minute × mm Hg). These values could be explained if one-half of total $\dot{Q}$c were distributed to approximately 15% of total DL.

These measurements did not permit the determination of the alveolar to end capillary O_2 gradient, but calculations demonstrate that an important factor in determining its size may be the pattern of uneven DL/$\dot{Q}$c present in the lungs. Estimations of the alveolar–end capillary O_2 gradient from measurements of $D_{L_{CO}}$ or $D_{L_{O_2}}$ that do not take into account uneven DL/$\dot{Q}$c may underestimate its size.

Introduction

Although the distribution of ventilation with respect to perfusion in the lungs has been extensively investigated, little attention has been given to the distribution of diffusing capacity in relation to blood flow (1–4). Recently a breath–holding method for the determination of $D_{L_{O_2}}$ has been developed that permits the simultaneous measurement of $D_{L_{O_2}}$ and $D_{L_{CO}}$ (5). The numerical value of $D_{L_{O_2}}$ was found on a theoretical basis to be quite sensitive to uneven distribution of diffusing capacity with respect to blood flow (uneven DL/$\dot{Q}$c), whereas $D_{L_{CO}}$ was relatively insensitive. By comparing the numerical values of $D_{L_{O_2}}$ and $D_{L_{CO}}$, we can evaluate the degree of uneven DL/$\dot{Q}$c in the lungs. The present work uses this approach to study the diffusion–blood flow relationships in the lungs of five normal resting subjects.

Methods

Theory

Both steady state and breath–holding methods for measuring O_2 diffusing capacity of the lungs require the assumptions of even distribution of diffusing capacity (DL),

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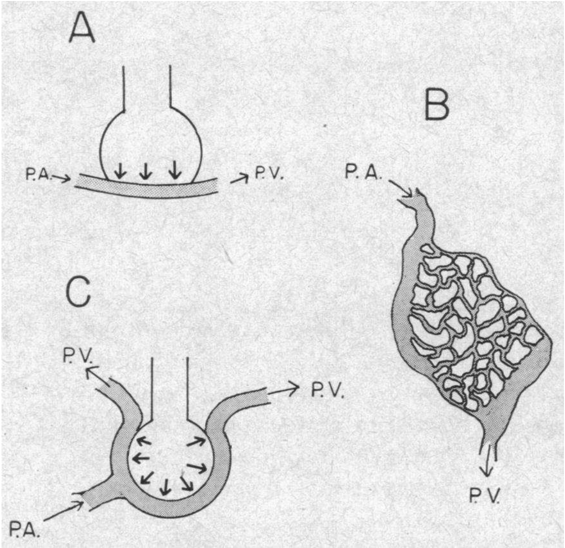

FIG. 1. DIAGRAMS OF THE PULMONARY CAPILLARY BED. Diagram A illustrates the model of the lung and its pulmonary capillary bed that must be assumed for the determination of oxygen diffusing capacity ($D_{L_{O_2}}$) by either the breath-holding method with $^{34}O_2$ or by the steady state method. Diffusing capacity, capillary blood flow, $\dot{Q}_c$, lung volume, and ventilation are assumed to be distributed evenly. This assumption makes the capillary transit time (T_L) from the pulmonary arterioles (labeled P.A.) to the pulmonary veins (labeled P.V.) constant and the end capillary oxygen pressure (P_{O_2} or $P^{34}O_2$) constant throughout the lung. Diagram B, adapted from Von Hayek (9), represents a more anatomically correct view of the pulmonary capillary bed, and since it is likely that some of the blood travels from P.A. to P.V. at different speeds, uneven distribution of diffusing capacity to capillary blood flow (uneven $D_L/\dot{Q}_c$) is a distinct possibility. Diagram C is the lung model used in this paper. Each alveolus is considered to be perfused by two capillaries that may have different lengths and receive different amounts of $\dot{Q}_c$. Unlike diagram A, in this model uneven $D_L/\dot{Q}_c$ may be present depending on the values chosen for the length of the two capillaries and their respective $\dot{Q}_c$.

pulmonary capillary blood flow ($\dot{Q}_c$), and pulmonary capillary blood volume (V_c) along the capillaries. These assumptions are made in order to have a constant alveolar–end capillary gradient for O_2 (6) or O_2 isotope throughout the lungs (5). A number of anatomical observations *in vivo* and *in vitro* indicate that the pulmonary capillary bed is in fact a meshwork of capillaries along the wall of each alveolus (7, 8). It is therefore likely that as blood moves from the pulmonary arterioles to the pulmonary veins, some capillary pathways will be longer than others. In comparison to the shorter ones, these long capillaries have a greater surface area and thereby a larger D_L. If blood flow is not distributed to the different capillary pathways in proportion to their respective lengths (7), uneven distribution of D_L with respect to $\dot{Q}_c$ will result (see Figure 1). Since each alveolus has many capillary pathways of varying length, there is the possibility of a large number of different $D_L/\dot{Q}_c$ compartments within each gas exchange unit.

An analysis that takes into consideration many $D_L/\dot{Q}_c$ compartments, although probably more representative of the lungs *in vivo*, makes calculations extremely tedious. We, therefore, assumed a two compartment system representing two capillaries of different length coursing along the alveolar wall (see Figure 1C). In addition, we assumed that all the capillaries have the same cross-sectional area and capillary wall thickness (even distribution of diffusing capacity with respect to pulmonary capillary blood volume). The $D_L/\dot{Q}_c$ ratio of different capillary pathways can then be expressed in terms of capillary transit time (T_L).[1] For instance, pathways with a low $D_L/\dot{Q}_c$ ratio will have a relatively short T_L, and capillaries with a high $D_L/\dot{Q}_c$ ratio will have a relatively long T_L. It should be noted that this model places uneven $D_L/\dot{Q}_c$ within each gas exchange unit rather than in gross regions of the lungs such as lobes or segments.

Effect of uneven $D_L/\dot{Q}_c$ *on* $D_{L_{O_2}}$. The measurement of $D_{L_{O_2}}$ with $^{34}O_2$ requires breath holding after the inspiration of a gas mixture enriched with the stable O_2 isotope of mass 34 ($^{34}O_2$). The partial pressure of $^{34}O_2$ ($P^{34}O_2$) is very low in the blood at the start of the capillary and then progressively increases until at the end of the capillary its mean value determined experimentally is approximately 70% of the alveolar $P^{34}O_2$ (5). However, if uneven $D_L/\dot{Q}_c$ is present, in those capillaries with a long T_L (or high $D_L/\dot{Q}_c$), the alveolar $P^{34}O_2$ and capillary $P^{34}O_2$ will have sufficient time to come almost into equilibrium before reaching the end of the capillary. Once equilibrium is approached, minimal $^{34}O_2$ uptake takes place along that portion of the capillary. Because $^{34}O_2$ uptake is slight at the end of those capillaries with a long T_L, the $^{34}O_2$ uptake for any given alveolar $P^{34}O_2$ is reduced. This reduction results in a decrease in calculated $D_{L_{O_2}}$. Therefore if uneven $D_L/\dot{Q}_c$ is present, the observed diffusing capacity will be lower than if $D_L/\dot{Q}_c$ is evenly distributed (see Figure 2).

Effect of uneven $D_L/\dot{Q}_c$ *on* $D_{L_{CO}}$. In the determination of $D_{L_{CO}}$ alveolar CO is so low (approximately 1.5 mm Hg) that only a small amount of CO diffuses into the blood in the pulmonary capillaries. Because the CO entering the capillary blood is such a small fraction of its total capacity for CO, unlike the case for $^{34}O_2$ described above, there is little change in capillary P_{CO} during breath holding. Even if in some of the capillaries T_L is considerably longer than the mean T_L, there is only a slight increase in capillary

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[1] The assumption of even distribution of diffusing capacity with respect to V_c is not essential, but seems reasonable on the basis of both anatomical and physiological considerations (8, 10). If this assumption is granted, V_c is proportional to D_L, and the T_L for any capillary or group of capillaries can be calculated from the following relationship: $T_L = V_c/\dot{Q}_c$. This equation permits the analysis of uneven $D_L/\dot{Q}_c$ in terms of T_L, which is synonymous with the terms alveolar–capillary contact time (11) or time along the capillary (12) used by others.

P_{CO} as blood moves along the pulmonary capillaries. Because there is little increase in capillary P_{CO}, total CO uptake and calculated $D_{L_{CO}}$ are relatively insensitive to uneven DL/$\dot{Q}$c compared to $D_{L_{O_2}}$. For instance, if in 80% of the capillary bed the transit time increased from a normal value of about 0.8 second to 5 seconds, the end capillary P_{CO} would only rise to about 0.14 mm Hg, which is less than 10% of the alveolar P_{CO}.[2] Such an increase in end capillary P_{CO} would result in a fall of $D_{L_{CO}}$ of less than 5%.[3] However, with the same increase in TL, $D_{L_{O_2}}$ would

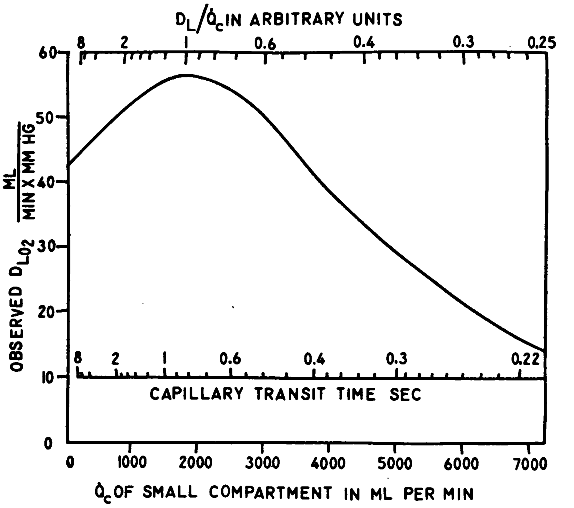

FIG. 2. CHANGE IN MEASURED $D_{L_{O_2}}$ (OBSERVED $D_{L_{O_2}}$) PRODUCED BY DIFFERENT AMOUNTS OF $\dot{Q}$C GOING THROUGH 25% OF THE LUNG'S DIFFUSING CAPACITY. A hypothetical lung is considered to have two compartments containing 25% and 75% of the total diffusing capacity. Total or true $D_{L_{O_2}}$ is given a value of 57 ml per (minute × mm Hg), $\dot{Q}$c a value of 7,200 ml per minute, and pulmonary capillary blood volume (Vc) a value of 100 ml. Observed $D_{L_{O_2}}$, the value of $D_{L_{O_2}}$ that would be determined by using the breath–holding isotope method (5), according to the mathematical methods derived in the text will only equal true $D_{L_{O_2}}$ when the ratio of diffusing capacity to $\dot{Q}$c of each compartment is 57 to 7,200 (even DL/$\dot{Q}$c and indicated by 1 arbitrary unit on the upper horizontal axis). If DL/$\dot{Q}$c is uneven (25% of the diffusing capacity receives either more or less than 25% of total $\dot{Q}$c), observed $D_{L_{O_2}}$ will be less than its maximal value of 57 ml per (minute × mm Hg). Note that the greater the abnormality in DL/$\dot{Q}$c, the greater is the fall in observed $D_{L_{O_2}}$. Capillary transit time for the small compartment was calculated by the method described in the first footnote.

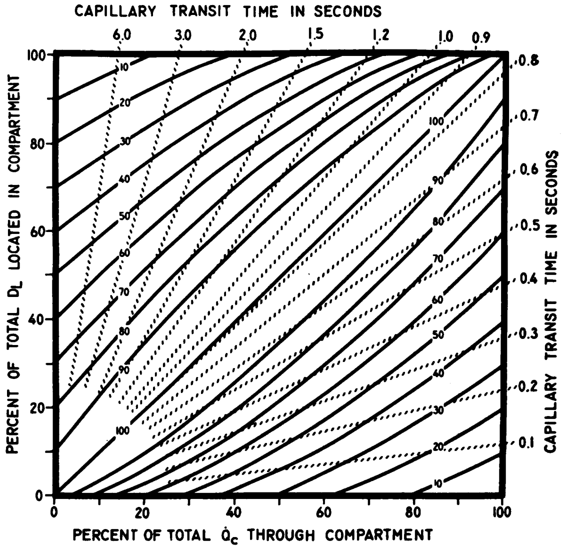

FIG. 3. GRAPHICAL SOLUTION OF EQUATION 4 IN TEXT. This chart permits the determination of the dimensions of DL and $\dot{Q}$c in a lung with two compartments that might have different values for DL and $\dot{Q}$c. Numerical constants used are representative values for our subjects, namely true $D_{L_{O_2}}$ = 57 ml per (minute × mm Hg), total $\dot{Q}$c = 7,200 ml per minute, the Bunsen solubility coefficient for total O_2 in blood (αb_{O_2}) = 2.5, and Vc = 100 ml. The diagonal solid slightly curved lines are isopleths of observed $D_{L_{O_2}}$ as a percentage of true $D_{L_{O_2}}$. The broken lines are isopleths of TL in seconds. As an example, assume that one compartment contains 20% of DL and observed $D_{L_{O_2}}$ is 60% of true $D_{L_{O_2}}$. One then reads across from the 20% point on the upright axis to the diagonal solid line labeled 60. At this point the corresponding point on the horizontal axis is 56%, which is the per cent of the total $\dot{Q}$c passing through the compartment. Since the interrupted line labeled 0.3 passes through the same point, TL for this compartment is 0.3 second. The other compartment must then contain 80% of DL and 44% of $\dot{Q}$c, and its TL determined from the chart would be 1.5 seconds. At the present time we have no method of determining which of the solutions lying along the isopleths of observed $D_{L_{O_2}}$ as a percentage of true $D_{L_{O_2}}$ represents the correct answer (or answers), and since the lung is most likely composed of a large number of DL–$\dot{Q}$c compartments, a two compartment model can only be a rough approximation of the situation present *in vivo*.

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[2] The end capillary P_{CO} of 0.14 mm Hg was obtained by the following calculation: In a subject with a $D_{L_{CO}}$ of 35 ml per (minute × mm Hg), at an average alveolar P_{CO} of 1.5 mm Hg the amount of CO entering 80% of the capillary bed in 5 seconds would be 0.8 × 35 × 1.5 × (5/60) or 3.5 ml. If the Vc were 100 ml and the hemoglobin concentration 15 g per 100 ml, then the total CO capacity of the blood in 80% of Vc would be 0.8 × 100 × 1.34 × (15/100) or 16 ml. The per cent carboxyhemoglobin saturation at the end of these capillaries would be (3.5/16) × 100 or 22%. From the Haldane relationship (13) with a value of 240 for the relative affinity of hemoglobin for CO as compared with O_2 (M) and 120 mm Hg for intracapillary P_{O_2}, end capillary P_{CO} = (120 × 22)/[(240)(99 − 22)] or 0.14 mm Hg.

[3] Even though the end capillary P_{CO} is 0.14 mm Hg in the capillaries with a TL of 5 seconds, from multiple deter-

fall to less than one-third of the value it would have if $\mathrm{DL}/\dot{Q}c$ were evenly distributed.[4]

Determination of value of $\mathrm{DL_{O_2}}$ *if* DL *and* $\dot{Q}c$ *are evenly distributed* (*true* $\mathrm{DL_{O_2}}$). Since uneven $\mathrm{DL}/\dot{Q}c$ may decrease the numerical value of $\mathrm{DL_{O_2}}$ measured with $^{34}O_2$, $\mathrm{DL_{O_2}}$ measured by this technique was called the "observed $\mathrm{DL_{O_2}}$." The degree of unevenness of $\mathrm{DL}/\dot{Q}c$ was calculated by determining the difference between the observed $\mathrm{DL_{O_2}}$ and the true $\mathrm{DL_{O_2}}$. By "true $\mathrm{DL_{O_2}}$" we mean the value of $\mathrm{DL_{O_2}}$ that would be present if diffusing capacity and $\dot{Q}c$ were evenly distributed. Since $\mathrm{DL_{CO}}$ is barely affected by uneven $\mathrm{DL}/\dot{Q}c$, true $\mathrm{DL_{O_2}}$ was determined indirectly from measurements of the pulmonary capillary blood volume (Vc) and diffusing capacity of the alveolar–capillary membrane for CO ($\mathrm{DM_{CO}}$) calculated by measuring $\mathrm{DL_{CO}}$ at alveolar O_2 tensions of approximately 150 mm Hg and 600 mm Hg (14). The following formula was then used to calculate true $\mathrm{DL_{O_2}}$:

$$\frac{1}{\text{true }\mathrm{DL_{O_2}}} = \frac{1}{\mathrm{DM_{^{34}O_2}}} + \frac{1}{(\mathrm{Vc})(\theta O_2)} = \frac{1}{(1.19)(\mathrm{DM_{CO}})} + \frac{1}{(\mathrm{Vc})(\theta O_2)}. \quad [1]$$

The two right-hand terms of the above equation equal, respectively, the resistance to diffusion from the alveolus through the alveolar–capillary membrane into the plasma in the capillaries ($1/\mathrm{DM_{^{34}O_2}}$) and the resistance to diffusion from the plasma into the interior of the red blood cells [$1/(\mathrm{Vc} \times \theta O_2)$]. Their sum, which is the left-hand term (1/true $\mathrm{DL_{O_2}}$), equals the total resistance to diffusion. θO_2 is the diffusing capacity of the red blood cell for O_2 expressed in milliliters per (minute × millimeters Hg × milliliters), and the values reported by Staub, Bishop, and Forster were used (15). $\mathrm{DM_{O_2}}$, the diffusing capacity of the alveolar–capillary membrane for $^{34}O_2$, expressed in milliliters per (minute × millimeters Hg), was considered to be equal to $\mathrm{DM_{CO}}$ multiplied by 1.19 on the basis of Graham's law of diffusivity of gases.[5] The derivation of an expression similar to Equation 1 is described by Roughton and Forster (14).

Quantitative analysis of uneven $\mathrm{DL}/\dot{Q}c$. Observed $\mathrm{DL_{O_2}}$ is calculated by the following formula, whose derivation is given in detail elsewhere (5):

$$\text{observed }\mathrm{DL_{O_2}} = \frac{\dot{Q}c(\alpha b_{O_2})}{760} \ln\left(\frac{1}{K}\right), \quad [2]$$

where $\dot{Q}c$ is the pulmonary capillary blood flow in milliliters per minute measured by the acetylene breath-holding method (16), and αb_{O_2} is the Bunsen solubility coefficient for total O_2 in the blood in milliliters per milliliter per standard atmosphere calculated from the capillary P_{O_2} present during breath holding and the O_2 capacity of the subject's blood. K is a constant and is defined in the following manner:

$$K = \frac{\text{alveolar } P^{34}O_2 - \text{end capillary } P^{34}O_2}{\text{alveolar } P^{34}O_2 - \text{mixed venous } P^{34}O_2}. \quad [3]$$

K is determined from the rate of disappearance of $^{34}O_2$ during breath holding and has a numerical value of about 0.3 in normal subjects. If the lung is divided into two compartments with different $\mathrm{DL}/\dot{Q}c$ ratios such as illustrated in Figure 1C, the relationship between observed $\mathrm{DL_{O_2}}$ and true $\mathrm{DL_{O_2}}$ will be the following:

$$\text{observed }\mathrm{DL_{O_2}} = \frac{\dot{Q}c(\alpha b_{O_2})}{760} \ln\left[\frac{\dot{Q}c}{(\dot{Q}c_1)e^{[-\mathrm{DL_1}(760)/\dot{Q}c_1(\alpha b_{O_2})]} + (\dot{Q}c_2)e^{[-\mathrm{DL_2}(760)/\dot{Q}c_2(\alpha b_{O_2})]}}\right]. \quad [4]$$

$\dot{Q}c_1$ and $\dot{Q}c_2$ are the respective blood flows through the two compartments, and their sum equals $\dot{Q}c$. $\mathrm{DL_1}$ and $\mathrm{DL_2}$ are the respective diffusing capacities of the two compartments, and their sum equals true $\mathrm{DL_{O_2}}$. The detailed derivation of Equation 4 is given in the Appendix. Figure 3 is a graphical solution of Equation 4 that permits the determination of the dimensions of the two diffusing capacity–blood flow compartments for any given value of observed $\mathrm{DL_{O_2}}$ expressed as a percentage of true $\mathrm{DL_{O_2}}$. Numerical constants used are given in the legend to the Figure.

Procedures

Equation 4 was applied in the following manner: Observed $\mathrm{DL_{O_2}}$ and $\dot{Q}c$ were measured from the rate of disappearance of $^{34}O_2$ and acetylene (C_2H_2) during breath holding (5, 16). The sum of $\mathrm{DL_1}$ plus $\mathrm{DL_2}$, which by definition equals true $\mathrm{DL_{O_2}}$, was determined by the following steps: First the $\mathrm{DL_{CO}}$ was measured at alveolar P_{O_2} of approximately 150 and 600 mm Hg, and then the values for Vc

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minations of the capillary Pco over the 5-second interval, it is apparent that the mean capillary Pco would be less than half this value. Since CO uptake and $\mathrm{DL_{CO}}$ are determined by the alveolar–mean capillary CO gradient, the reduction in calculated $\mathrm{DL_{CO}}$ in this part of the capillary bed would be less than 5%. In addition, in the 20% of the capillary bed with a short TL, the mean capillary Pco would be negligible, so that calculated $\mathrm{DL_{CO}}$ in these capillaries would be unaffected by uneven $\mathrm{DL}/\dot{Q}c$.

[4] See Figure 3 for dimensions of $\mathrm{DL_{O_2}}$, Vc, and $\dot{Q}c$ used. Since 80% of Vc had a TL of 5 seconds, $\dot{Q}c$ of this compartment could be calculated from the relationship $\dot{Q}c = \mathrm{Vc}/\mathrm{TL}$ and was found to be 14% of total $\dot{Q}c$. Since it is assumed that Vc and DL are evenly distributed, a compartment with 80% of total Vc contains 80% of total $\mathrm{DL_{O_2}}$. From Figure 3 it is apparent that if one compartment has 80% of total $\mathrm{DL_{O_2}}$ and 14% of $\dot{Q}c$, the observed $\mathrm{DL_{O_2}}$ is 30% of the true $\mathrm{DL_{O_2}}$ (*vide infra*).

[5] According to Graham's law, the diffusivity of two gases through a liquid is proportional to the ratio of their solubilities and inversely proportional to the ratio of the square root of their molecular weights. If the alveolar–capillary membrane is considered to be essentially water, $\mathrm{DM_{^{34}O_2}} = \mathrm{DM_{CO}}\ (0.244/0.0185)(28/34) = (1.19)(\mathrm{DM_{CO}})$.

and $D_{M_{CO}}$ were calculated (14). These values were then substituted into Equation 1 in order to obtain the value of true $D_{L_{O_2}}$ for each subject. The term D_{L_2} in Equation 4 can then be eliminated by replacing it with true $D_{L_{O_2}}$ − D_{L_1}. Likewise since $\dot{Q}c_1 + \dot{Q}c_2 = \dot{Q}c$, $\dot{Q}c_2$ can be replaced by the term $\dot{Q}c - \dot{Q}c_1$. Because two unknown terms remain in Equation 4, namely D_{L_1} and $\dot{Q}c_1$, these values can be expressed as a locus of possible solutions on a graph. For example, Figure 3 is the graphical solution for Equation 4 in a hypothetical subject with a true $D_{L_{O_2}}$ of 57 ml per (minute × mm Hg), $\dot{Q}c$ of 7,200 ml per minute, and αb_{O_2} of 2.5 ml per ml per standard atmosphere. Note that any point on one of the unbroken curved lines of the Figure represents a possible pair of values for D_{L_1} and $\dot{Q}c_1$ for a particular observed $D_{L_{O_2}}$ expressed as a percentage of true $D_{L_{O_2}}$. Because Equation 4 must be solved by a method of trial and error or with a computer, its graphical solution presented in Figure 3 is helpful in estimating the values of D_{L_1} and $\dot{Q}c_1$ that would satisfy the values of observed $D_{L_{O_2}}$ and true $D_{L_{O_2}}$ obtained in our subjects. With the assistance of this Figure, Equation 4 was solved for each subject, and the solutions were then plotted in Figure 4.

Subjects

Measurements for the determination of uneven $D_L/\dot{Q}c$ were made in five male laboratory personnel, skilled at respiratory maneuvers, in the sitting position. Values for observed $D_{L_{O_2}}$ previously reported were used (5). At the time of the measurements no symptoms of respiratory disease were present. Chest X rays were read as showing no active disease, and vital capacities as well as maximal midexpiratory flow rates were within the normal limits recently published by Bates and Christie (17). Physical characteristics of the subjects are listed in Table I.

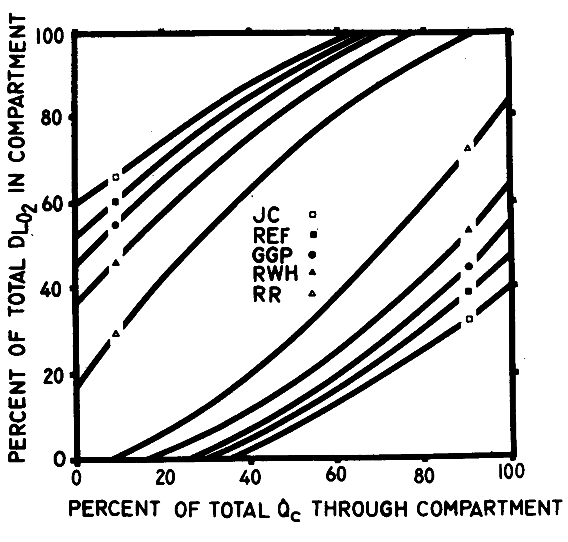

FIG. 4. EXPERIMENTALLY DETERMINED DISTRIBUTION OF $D_{L_{O_2}}$ WITH RESPECT TO $\dot{Q}c$. The curved lines represent the patterns of uneven $D_L/\dot{Q}c$ that would explain the experimental findings for each subject. The two older subjects (JC and REF) have the more uneven $D_L/\dot{Q}c$.

TABLE I

Physical characteristics of experimental subjects

Subject	Age	Height	Weight	Surface area
	years	*inches*	*pounds*	m^2
RR	24	72	175	2.01
GGP	28	73	175	2.03
RWH	34	71	160	1.94
REF	44	74	170	2.02
JC	46	64	132	1.65

Results

The data for determining true $D_{L_{O_2}}$ and observed $D_{L_{O_2}}$ are listed in Table II. For the five subjects the average value for $D_{L_{CO}}$ was 44 ml per (minute × mm Hg), and observed $D_{L_{O_2}}$ measured simultaneously was 33 ml per (minute × mm Hg). The value for Vc calculated from measurements of $D_{L_{CO}}$ at different alveolar P_{O_2} was 104 ml, and $D_{M_{CO}}$ was 61 ml per (minute × mm Hg). From these figures the value for true $D_{L_{O_2}}$ for the five subjects was calculated. The average was 57 ml per (minute × mm Hg), which is considerably greater than the observed $D_{L_{O_2}}$ of 33 ml per (minute × mm Hg).

The pattern of uneven $D_L/\dot{Q}c$ for each subject calculated from Equation 4 is plotted in Figure 4. Unfortunately at the present time we have no method of determining which one of the solutions shown in this Figure represents the correct two compartment model, but it is evident that any of the possible solutions shown represents a fairly marked degree of uneven $D_L/\dot{Q}c$. For instance, if the lung is divided into two compartments with equal amounts of D_L, the amount of blood flowing through the compartment with the lesser amount of $\dot{Q}c$ varied from a low value of 8% of total $\dot{Q}c$ in subject JC to a high value of 28% in subject RR. The median value, represented by subject GGP, was 13%. (If no uneven $D_L/\dot{Q}c$ were present, $\dot{Q}c$ through each compartment would be 50% of total $\dot{Q}c$.)

Uneven $D_L/\dot{Q}c$ showed a tendency to be more marked with increasing age, for in the two subjects over 40 years old 50% of D_L received on the average 9% of the total $\dot{Q}c$, whereas in the three subjects under 40, 50% of D_L received 20% of total $\dot{Q}c$. Measurements in more subjects over a wider age range would be needed to confirm this suggestion of progressively severe uneven $D_L/\dot{Q}c$ with advancing age.

TABLE II

Data for determination of uneven DL/Qc *in five subjects**

Subject	$\dot{Q}c$	Vc	DL$_{CO}$†	DM$_{CO}$‡	DM$_{^{34}O_2}$§	Alveolar PO$_2$‖	αbO$_2$¶	θO$_2$¶	True DL$_{O_2}$	Observed DL$_{O_2}$	Observed DL$_{O_2}$ as per cent of true DL$_{O_2}$
	L/min	*ml*	*ml/(min × mm Hg)*	*ml/(min × mm Hg)*	*ml/(min × mm Hg)*	*mm Hg*	*ml/ml*	*ml/(min × mm Hg × ml)*	*ml/(min × mm Hg)*	*ml/(min × mm Hg)*	%
RR	8.2	98	44	59	70	36.0	2.49	2.8	56	46	82
GGP	8.0	106	51	72	86	41.5	2.71	2.8	62	34	55
RWH	7.1	112	44	57	68	42.0	2.62	2.7	55	35	64
REF	6.2	80	40	53	63	49.0	2.60	2.5	48	23	48
JC	6.3	123	43	66	79	43.5	2.46	2.7	64	26	41
Average	7.2	104	44	61	73	42.0	2.58	2.7	57	33	58

* $\dot{Q}c$ = pulmonary capillary blood flow; Vc = pulmonary capillary blood volume; DL$_{CO}$ and DL$_{O_2}$ = carbon monoxide and oxygen diffusing capacity of the lungs; DM$_{CO}$ and DM$_{^{34}O_2}$ = carbon monoxide and oxygen diffusing capacity of the pulmonary membrane; PO$_2$ = oxygen tension; αbO$_2$ = Bunsen solubility coefficient for total O$_2$ in blood; θO$_2$ = diffusing capacity of red blood cells for oxygen.

† DL$_{CO}$ measured at alveolar PO$_2$ listed in the sixth column of figures.

‡ DM$_{CO}$ calculated from measurements of DL$_{CO}$ performed at alveolar PO$_2$ of approximately 15 mm Hg and 600 mm Hg.

§ DM$_{^{34}O_2}$ calculated by multiplying DM$_{CO}$ by 1.19 on basis of Graham's law (see text).

‖ Alveolar PO$_2$ present during the determination of observed DL$_{O_2}$.

¶ αbO$_2$ and θO$_2$ for alveolar PO$_2$ present during determination of observed DL$_{O_2}$.

Discussion

The above results indicate that a considerable degree of uneven distribution of diffusing capacity (DL) with respect to pulmonary capillary blood flow ($\dot{Q}c$) is present in normal resting human subjects. Among the alternative explanations for the data is the possibility that the DL/$\dot{Q}c$ patterns determined are an artifact due to inaccuracies in the measured quantities of either observed DL$_{O_2}$ or true DL$_{O_2}$.

Accuracy of observed DL$_{O_2}$. Sources of error in the measurement of observed DL$_{O_2}$ have been described in detail elsewhere (5). It was concluded that the error in the measurement is less than ± 15%, which is not sufficient to alter dramatically the degree of uneven DL/$\dot{Q}c$ calculated for our subjects.

Accuracy of true DL$_{O_2}$. Appraisal of the accuracy of true DL$_{O_2}$ is more complex because its value depends on the terms from which it is calculated in Equation 1, namely Vc, DM$_{CO}$, θO$_2$, and the factor 1.19 used to convert DM$_{CO}$ into DM$_{^{34}O_2}$. Errors in the determination of Vc and DM$_{CO}$ by performing DL$_{CO}$ at different alveolar PO$_2$ have been discussed previously (14, 18). It should be noted that for the subjects in this report errors in Vc and θO$_2$ produce only one-third the error in true DL$_{O_2}$. Therefore it seems unlikely that those measurements would be sufficiently inaccurate to alter markedly true DL$_{O_2}$. Errors in DM$_{CO}$, however, produce almost the same per cent change in true DL$_{O_2}$, but fortunately a lower limit for the value of DM$_{CO}$ can be calculated in the following manner: DL$_{CO}$ was measured simultaneously with observed DL$_{O_2}$. The average value of DL$_{CO}$ for the five subjects was 44 ml per (minute × mm Hg), which theoretically represents the minimal value possible for DM$_{CO}$ under the conditions of the experiment. Even if DM$_{CO}$ were this minimal value, the average value for true DL$_{O_2}$ calculated by Equation 1 would be 43 ml per (minute × mm Hg), which is still considerably greater than 33 ml per (minute × mm Hg), the average value of observed DL$_{O_2}$. The factor 1.19, used to convert DM$_{CO}$ into DM$_{^{34}O_2}$, was calculated on the basis of Graham's law and the assumption that the solubilities of CO and $^{34}O_2$ in the alveolar–capillary membrane are similar to their respective solubilities in water. Though the alveolar–capillary membrane is predominantly water, it contains proteins and lipid membranes that might alter the solubilities of these two gases. Experimentally it has been shown that the relative solubility of O$_2$ of mass 32 compared to CO is changed from 1.25 to 0.78 if the measurement is made in a solution containing equal quantities of glycerol and buffer solution instead of buffer alone (19). If in these experiments the conversion factor used should have been 0.78 instead of 1.19, the average value of true DL_{O_2} would fall from 57 ml per (minute × mm Hg) to 40 ml per (minute × mm Hg). This value is still greater than 33 ml per (minute × mm Hg), the average value of observed DL_{O_2}, so that even if there is an appreciable error in the factor used to convert DM_{CO} into DM_{O_2}, there will still be a considerable degree of uneven $DL/\dot{Q}c$ in the lungs.

In addition to errors in observed DL_{O_2} and true DL_{O_2} several other factors might influence the determination of uneven $DL/\dot{Q}c$, namely the artificiality of constructing a two compartment lung, pulsatile pulmonary capillary blood flow, and the upright posture of the subjects.

Errors arising from the assumption of a two compartment lung. Equation 4 is listed in a form that is applicable to a lung with only two $DL/\dot{Q}c$ compartments, but by adding to the denominator inside the large bracket terms of the form, $\dot{Q}c_n e^{[-DL_n(760)]/[\dot{Q}c_n(\alpha b O_2)]}$, the equation can be used to construct a lung with many compartments. Although at the present time we have no measurements available that justify the complexity of constructing more than two compartments, it seems likely that the lung may have many capillary pathways with different patterns of $DL/\dot{Q}c$ distribution. Although a knowledge of the dimensions of a greater number of compartments would be expected to give a more exact picture, a multicompartment model must still take into account the experimental finding of a large difference between true DL_{O_2} and observed DL_{O_2}. A multicompartment model of the lungs would therefore not invalidate the existence of uneven $DL/\dot{Q}c$. It would, however, demonstrate the pattern of distribution of uneven $DL/\dot{Q}c$ more clearly.

Effect of pulsatile $\dot{Q}c$ *on uneven* $DL/\dot{Q}c$. Measurements in man of instantaneous $\dot{Q}c$ indicate that $\dot{Q}c$ is pulsatile (20). If some of the red blood cells rapidly traversed the capillaries during systole, whereas others had a prolonged exposure to the alveolar gas during diastole, variation in $DL/\dot{Q}c$ during the cardiac cycle would

TABLE III

Effect of uneven distribution of alveolar volume (V_A), *pulmonary capillary blood flow* ($\dot{Q}c$), *and pulmonary diffusing capacity on measured values of* CO *diffusing capacity* (DL_{CO}), O_2 *diffusing capacity* (DL_{O_2}), *and the alveolar to end capillary* O_2 *gradient* (A-c O_2 *gradient*)*

	Compartment no.	Compartment dimensions					Total A-c O_2 gradient‡	DL_{CO}	Observed DL_{O_2}
		True DL_{O_2}	$\dot{Q}c$	V_A	Capillary transit time	A-c O_2 gradient†			
		ml / (min × mm Hg)	*ml/min*	*ml*	*sec*	*mm Hg*	*mm Hg*	*ml / (min × mm Hg)*	*ml / (min × mm Hg)*
A. Upright posture (ref. 1, 21)	1	9.7	980	1,800	1.04	0			
	2	18.8	2,380	1,800	0.83	0	0	41 (−7%)§	50 (−12%)‖
	3	28.5	3,840	1,800	0.78	0			
B. Anatomical and microscopic data (ref. 7, 9, 22)	1	10.0	3,600	¶	0.29	0.5			
	2	30.0	3,600	¶	0.88	0	0.25	44 (0%)§	27.2 (−52%)‖
	3	17.0	0	¶		0			
C. Pulmonary capillary transit time of 0.1 sec in 5% of capillary channels (ref. 23)	1	1.46	1,530	¶	0.10	16.5			
	2	55.54	5,670	¶	1.03	0	5	44 (0%)§	38.1 (−33%)‖
D. Measurements in anesthetized dogs (ref. 3)	1	1.14	1,200	¶	0.12	12			
	2	55.86	6,000	¶	0.86	0	2	44 (0%)§	40.1 (−30%)‖

* Representative measurements in our subjects were used, namely, DL_{O_2} calculated from the CO data (true DL_{O_2}) = 57 ml per (minute × mm Hg), total $\dot{Q}c$ = 7,200 ml per minute, total V_A = 5,400 ml, DL_{CO} = 44 ml per (minute × mm Hg), and capillary blood volume (Vc) = 100 ml.

† A-c O_2 gradients were taken from Figure 5.

‡ The numbers in this column were calculated from the A-c O_2 gradient of each compartment. Alveolar P_{O_2} was assumed to be 100 mm Hg, and end capillary O_2 content for each compartment was obtained from a standard O_2 dissociation curve at pH of 7.40.

§ Per cent reduction from DL_{CO} of 44 ml per (minute × mm Hg).

‖ Per cent reduction from true DL_{O_2} of 57 ml per (minute × mm Hg).

¶ Uneven $DL/\dot{Q}c$ was considered to be within each gas exchange unit so that all alveoli had the same rate of change of CO and $^{34}O_2$ during breath holding.

result (2). Because this form of uneven $D_L/\dot{Q}_c$ might explain the difference between observed $D_{L_{O_2}}$ and true $D_{L_{O_2}}$ seen in our subjects, we evaluated this possibility by obtaining representative values of pulsatile flow from the data published by Linderholm, Kimbel, Lewis, and DuBois (20) and then calculated an observed $D_{L_{O_2}}$. We used the values of total $\dot{Q}_c$, V_c, and true $D_{L_{O_2}}$ listed in Table III, a pulse rate of 100 per minute, a systole of 0.12 second with a $\dot{Q}_c$ of 300 ml per second, and diastole of 0.48 second with a $\dot{Q}_c$ of 75 ml per second. No significant change in $D_{L_{O_2}}$ was produced by this pattern of $\dot{Q}_c$, but if pulsatile blood flow were combined with uneven $D_L/\dot{Q}_c$ such as illustrated in Figures 1B and 1C, rapid pulsatile flow through capillaries of short length would permit some blood to pass through them during systole and thereby produce a very brief exposure to alveolar gas. Such a condition would decrease observed $D_{L_{O_2}}$ without changing true $D_{L_{O_2}}$. At the present time we have no method of separating uneven $D_L/\dot{Q}_c$ due to pulsatile flow from uneven $D_L/\dot{Q}_c$ from other causes, so that pulsatile flow may be a significant contributing factor to the uneven $D_L/\dot{Q}_c$ observed in our subjects.

Effect of uneven perfusion and diffusion per unit of lung volume secondary to the upright position. Evidence has been presented that in the upright posture the upper zones of the lungs have considerably less $\dot{Q}_c$ and D_L per unit of lung volume (V_A) than is found in the lower zones (21, 24). To establish whether this type of uneven distribution might explain our data, we calculated the changes in $D_{L_{O_2}}$ and $D_{L_{CO}}$ that would result in a subject whose lungs had three zones of equal V_A, but proportionately less amounts of D_L and $\dot{Q}_c$ in the upper zones. Numerical values for total V_A, D_L, and $\dot{Q}_c$ are representative for our subjects, and the dimensions of the three zones were chosen on the basis of observations made by others using regional scanning of the lungs after the inspiration of radioactive CO and CO_2 (1, 21) (see Table III). This model of uneven distribution produced a decrease in $D_{L_{O_2}}$ of 12% and a decrease in $D_{L_{CO}}$ of 7%. Since these changes in part cancel out during the determination of uneven $D_L/\dot{Q}_c$ and also are too small to account for the 18% to 64% difference between observed $D_{L_{O_2}}$ and true $D_{L_{O_2}}$ seen in our subjects, we do not think the sitting position alone explains the uneven $D_L/\dot{Q}_c$ we calculated.

In addition, the effect of uneven distribution of alveolar volume (V_A) with respect to D_L (uneven V_A/D_L) resulting from the upright position was evaluated with compartmental dimensions based on the data reported by Burrows and co-workers (25). These calculations showed that there would be changes in $D_{L_{O_2}}$ and $D_{L_{CO}}$ but insufficient in magnitude or direction to produce significant changes in the calculated values of uneven $D_L/\dot{Q}_c$. We conclude that uneven distribution of D_L with respect to $\dot{Q}_c$ within each gas exchange unit of the lung is the best explanation for our experimental findings. Although it is likely that there is uneven distribution of $D_L/\dot{Q}_c$ and D_L/V_A in gross anatomical zones of the lung, the value of observed $D_{L_{O_2}}$ would be only slightly reduced. The comparison of observed $D_{L_{O_2}}$ to true $D_{L_{O_2}}$ is, therefore, not a good method for investigating this particular type of uneven distribution.

Comparison to other measurements of uneven $D_L/\dot{Q}_c$. Piiper, Haab, and Rahn calculated the degree of uneven $D_L/\dot{Q}_c$ in anesthetized dogs from measurements of the alveolar–arterial O_2 gradient (3). They concluded that diffusion of O_2 into the blood takes place from two functional compartments, namely one small compartment containing 2% of the diffusing capacity and receiving 14% of total $\dot{Q}_c$ and one large compartment containing 98% of the diffusing capacity and receiving 86% of $\dot{Q}_c$.[6] If there were a similar pattern of uneven $D_L/\dot{Q}_c$ in the lungs of our human subjects, it would have no influence on the value of $D_{L_{CO}}$, but $D_{L_{O_2}}$ would decrease from its average "true" value of 57 ml per (minute × mm Hg) to an observed $D_{L_{O_2}}$ of 40.1 ml per (minute × mm Hg), which is slightly greater then the experimentally determined average value of 33 ml per (minute × mm Hg). Preliminary studies in resting man using breath holding with 5% carbon monoxide (26) and the steady state O_2 diffusing capacity method (27)

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[6] These authors reported that a small portion of the perfusion (1.5%) probably behaves like a true shunt ($D_L/\dot{Q}_c = 0$). This compartment was omitted in our analysis because the method of measuring uneven $D_L/\dot{Q}_c$ described in this paper is only influenced by perfusion that comes in contact with alveolar CO, acetylene, and $^{34}O_2$ during the breath–holding maneuver.

indicate that two-thirds of $\dot{Q}$c is delivered to 20% of the diffusing capacity. In the subjects of the present study this pattern of uneven DL/$\dot{Q}$c would result in an observed DL$_{O_2}$ of approximately 30 ml per (minute × mm Hg) (see Figure 3), which is in good agreement with the experimentally determined average value of 33 ml per (minute × mm Hg).

Influence of uneven DL/$\dot{Q}$c *on the pulmonary alveolar to end capillary* O$_2$ *gradient* (A-c O$_2$ *gradient*). The presence of uneven DL/$\dot{Q}$c within the alveoli of the lungs has considerable bearing on the estimation of the size of the A-c O$_2$ gradient. Previous reports do not agree about the magnitude of this gradient in normal individuals or even in diseased subjects. On the basis of measurements of distribution of ventilation to perfusion, right to left shunting around the alveoli, and the single breath DL$_{CO}$, some authors have stated that even in the so-called alveolar-capillary block syndrome an A-c O$_2$ gradient does not exist (28, 29). On the other hand, more recently Johnson, Taylor, and DeGraff have cited evidence showing that the arterial O$_2$ desaturation seen in certain diffuse restrictive diseases of the lung tissues may in part be explained by an A-c O$_2$ gradient produced by the presence of red blood cell transit times of different duration in the pulmonary capillary bed (30). After a careful analysis of the influence of both uneven DL/$\dot{Q}$c and uneven ventilation-perfusion ratios upon the A-c O$_2$ gradient, Piiper and co-workers concluded that the O$_2$ gradient they measured in anesthetized dogs was principally due to uneven DL/$\dot{Q}$c rather than uneven ventilation-perfusion ratios (3).

Because we have no data that permit the determination of the precise pattern of uneven DL/$\dot{Q}$c present in the lungs of our subjects, its exact contribution to the A-c O$_2$ gradient cannot be calculated at the present time. As an alternative we chose four patterns of uneven DL/$\dot{Q}$c fashioned after reports in the literature and calculated the A-c O$_2$ gradient that would result in a resting subject with values for true DL$_{O_2}$, $\dot{Q}$c, and Vc approximately the same as found in our subjects (see Table III). Using these values together with a mixed venous P$_{O_2}$ of 42.5 mm Hg and an alveolar P$_{O_2}$ of 100 mm Hg, one can calculate the rate at which the P$_{O_2}$ in the red blood cells increases as they traverse the capillaries (12). This calculation is presented graphically in Figure 5, and from it we determined the end capillary P$_{O_2}$ for a DL/$\dot{Q}$c compartment whose capillary transit time (TL) is known.[7]

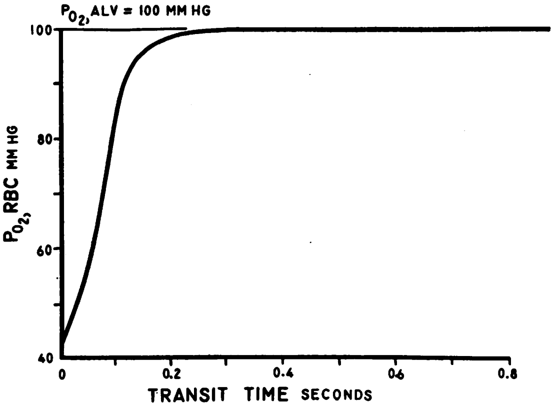

FIG. 5. RATE OF RISE OF P$_{O_2}$ IN A RED BLOOD CELL AS IT TRAVERSES A CAPILLARY IN THE LUNGS OF A SUBJECT WITH A MIXED VENOUS P$_{O_2}$ OF 42.5 MM HG AND AN ALVEOLAR P$_{O_2}$ OF 100 MM HG. Oxygen diffusing capacity of the membrane was considered to be 73 ml per (minute × mm Hg) and Vc 100 ml, which are representative values for our subjects. [For details of the calculation see (12)]. P$_{O_2,RBC}$ is the P$_{O_2}$ in the capillary blood for any particular transit time. Note that when the capillary transit time falls below 0.2 second, a significant alveolar to end capillary O$_2$ gradient develops.

A-c O$_2$ *gradient secondary to the upright posture.* Table IIIA shows the effect of uneven DL/$\dot{Q}$c and uneven VA/$\dot{Q}$c secondary to the upright posture on the A-c O$_2$ gradient. Because the shortest TL for this model is 0.78 second, essentially no A-c O$_2$ gradient is present.

A-c O$_2$ *gradient secondary to the* DL/$\dot{Q}$c *distribution observed in microscopic studies of the pulmonary capillary bed.* Von Hayek (9) and Weibel (22) have pointed out that the capillary pathway from the pulmonary arterioles to the pulmonary veins is a meshwork of vessels whose length may

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[7] Calculation of end capillary P$_{O_2}$ from Figure 5 requires the assumption of even distribution of Vc with respect to membrane diffusing capacity (*vide supra*). Once this assumption is accepted, the per cent of the membrane diffusing capacity of a compartment equals the same percentage of total Vc. TL of the compartment can then be calculated by the following relationship: TL = Vc of compartment/ $\dot{Q}$c of compartment. If Vc is not distributed evenly with respect to membrane diffusing capacity, the end capillary P$_{O_2}$ can still be calculated, but the procedure becomes more laborious.

vary from about 60 μ to 250 μ or longer. It has been postulated from *in vivo* observations that shorter routes stay open whereas longer ones may be intermittently closed off. Blood flow in some capillaries has been seen to stop and even reverse direction (7). On the basis of the above information we constructed a lung model in which, in each gas exchange unit, 50% of the blood flow goes through capillaries 80 μ long, and the other 50% traverses capillaries 240 μ long. In addition, 30% of the capillary blood volume contains blood that is not flowing (see Table IIIB). Although this pattern of uneven $D_L/\dot{Q}_c$ according to Equation 4 would produce an observed $D_{L_{O_2}}$ of 27 ml per (minute × mm Hg) compared to the true $D_{L_{O_2}}$ of 57 ml per (minute × mm Hg) (values similar to those seen in our subjects, the A-c O_2 gradient is barely perceptible (0.25 mm Hg).

A-c O_2 *gradient secondary to the uneven* $D_L/\dot{Q}_c$ *suggested by cinematographic observations of the pulmonary capillary bed in vivo.* Schlosser, Heyse, and Bartels recently developed a method that permits the visualization of the subpleural pulmonary capillaries of rabbit lungs. They reported that the average transit time for a red blood cell through these capillaries is only 0.1 second (23). On the basis of their observations we calculated the observed $D_{L_{O_2}}$ and A-c O_2 gradient that would result if 5% of the capillary channels carrying blood from the pulmonary arteries to the pulmonary veins were 60 μ long and had a transit time of 0.1 second. The remaining 95% of the channels were assumed to be 120 μ long and would receive 79% of the total blood flow (see Table IIIC). According to Equation 4 this pattern of uneven $D_L/\dot{Q}_c$ results in an observed $D_{L_{O_2}}$ of 38 ml per (minute × mm Hg), a value 33% less than the true $D_{L_{O_2}}$ of 57 ml per (minute × mm Hg). In the fast compartment the A-c O_2 gradient would be 16.5 mm Hg, and after mixing with the blood from the slow compartment, the total pulmonary A-c O_2 gradient would be 5 mm Hg. These data suggest that a significant amount of the difference between alveolar and arterial P_{O_2} could be due to uneven $D_L/\dot{Q}_c$.

A-c *gradient secondary to the pattern of uneven* $D_L/\dot{Q}_c$ *observed in anesthetized dogs.* Piiper and co-workers concluded that in anesthetized dogs diffusion of O_2 in the pulmonary capillary blood takes place from two functional compartments, a smaller one receiving 14% of $\dot{Q}_c$, but containing only 2% of the diffusing capacity, and a larger compartment with 86% of $\dot{Q}_c$ and 98% of the diffusing capacity (*vide supra*). For our human subjects the A-c O_2 gradient for the smaller compartment according to Figure 5 would be 12 mm Hg and after mixing with the blood flowing through the larger compartment would decrease to 2 mm Hg. The comparable figure for the A-c O_2 gradient from both compartments calculated by Piiper and co-workers was 10 mm Hg. This discrepancy can be accounted for by a number of factors, including the larger value of $D_{L_{O_2}}$ in the human subjects [0.8 ml per (minute × mm Hg) per kg vs. 0.3 ml per (minute × mm Hg) per kg in dogs]; the difference in the O_2 dissociation curves used, which is quite critical in the calculation of the A-c O_2 gradient (31); and the fact that the fall in $D_{L_{O_2}}$ with rising intracapillary O_2 recently demonstrated *in vivo* (5) was taken into account in the humans but not in the dogs.

Relationship between D_L *and the size of the* A-c O_2 *gradient.* The data in Table III demonstrate an apparent paradox: A lung model such as IIIB may have a lower observed $D_{L_{O_2}}$ than another model, yet its A-c O_2 gradient may be smaller. Therefore the observed values of $D_{L_{O_2}}$ and $D_{L_{CO}}$ in the presence of uneven $D_L/\dot{Q}_c$ do not necessarily give information relevant to the estimation of the size of the A-c O_2 gradient. The precise pattern of distribution of uneven $D_L/\dot{Q}_c$ may be of greater importance in determining this gradient than the absolute values of diffusing capacity. For example, in the four hypothetical lungs listed in Table III, the A-c O_2 gradient varied from essentially 0 to 5 mm Hg depending more on the pattern of uneven $D_L/\dot{Q}_c$ chosen than on the measured values of $D_{L_{CO}}$ or $D_{L_{O_2}}$.

It has been stated that in normal subjects breathing air at rest or even during heavy exercise, as well as in patients with chronic airway obstruction, no A-c O_2 gradient will be present because of the large size of the diffusing capacity (12, 28, 32). All of these calculations have assumed even distribution of diffusing capacity to blood flow. The data presented in this report indicate that fairly marked degrees of uneven $D_L/\dot{Q}_c$ may be present in resting man, and it is possible for this uneven $D_L/\dot{Q}c$ to be distributed in a manner that produces an appreciable A-c O_2 gradient. In the face of this information we believe it is hazardous to judge the size of the A-c O_2 gradient on the basis of CO diffusing capacities alone. The distribution of diffusing capacity with respect to $\dot{Q}c$ must be taken into account.

Although our results do not permit the calculation of the A-c O_2 gradient, they do suggest that the development of more precise methods for the measurement of the pattern of uneven $D_L/\dot{Q}c$ may permit an accurate estimation of its size.

Appendix

Derivation of Equation 4 in the text, which expresses observed $D_{L_{O_2}}$ *as a function of the distribution of diffusing capacity* (D_L) *with respect to pulmonary capillary blood flow* ($\dot{Q}c$) *in the lung.*

The total $^{34}O_2$ leaving the lungs per minute during breath holding equals the amount leaving via the pulmonary capillaries less the amount arriving in the mixed venous blood, or:

$$\text{total } ^{34}O_2 \text{ leaving lungs per minute in milliliters per minute} = \frac{\dot{Q}c(\alpha b_{O_2})(Pc_{34O_2} - Pmv_{34O_2})}{760}, \quad [5]$$

where $\dot{Q}c$ is expressed in milliliters per minute, Pc_{34O_2} equals the end capillary $P^{34}O_2$ in millimeters Hg, Pmv_{34O_2} is the mixed venous $P^{34}O_2$ in millimeters Hg, and αb_{O_2} is the Bunsen solubility coefficient for total O_2 in the blood in milliliters per milliliter per standard atmosphere calculated from the capillary P_{O_2} present during breath holding and the O_2 capacity of the subject's blood.

If a lung with uneven $D_L/\dot{Q}c$ could be divided into compartments within which diffusing capacity and $\dot{Q}c$ were distributed evenly, then as in Equation 2:

$$D_{L1} = \frac{\dot{Q}c_1(\alpha b_{O_2})}{760} \ln\left(\frac{1}{K_1}\right),$$

$$D_{L2} = \frac{\dot{Q}c_2(\alpha b_{O_2})}{760} \ln\left(\frac{1}{K_2}\right), \quad D_{L3} = \ldots \text{ etc.,} \quad [6]$$

where D_{L1}, D_{L2}, D_{L3} . . . , $\dot{Q}c_1$, $\dot{Q}c_2$ . . . , and K_1, K_2 . . . , are, respectively, the true $D_{L_{O_2}}$, $\dot{Q}c$, and K for each compartment. The amount of $^{34}O_2$ removed from each compartment per minute can be calculated by applying Equation 5, and for example for compartment 1 would equal:

$$\frac{\dot{Q}c_1(\alpha b_{O_2})(^1Pc_{34O_2} - Pmv_{34O_2})}{760}, \quad [7]$$

where $^1Pc_{34O_2}$ equals the end capillary $P^{34}O_2$ in compartment 1.

For a two compartment lung the total milliliters of $^{34}O_2$ leaving the lung per minute during breath holding must equal the sum of the amount leaving the two compartments in the blood less the amount entering, or:

$$\frac{\dot{Q}c(\alpha b_{O_2})(Pc_{34O_2} - Pmv_{34O_2})}{760} = \frac{\dot{Q}c_1(\alpha b_{O_2})(^1Pc_{34O_2} - Pmv_{34O_2})}{760} + \frac{\dot{Q}c_2(\alpha b_{O_2})(^2Pc_{34O_2} - Pmv_{34O_2})}{760}. \quad [8]$$

K for a compartment of the lung can be defined as in Equation 3 and for compartment 1 would be:

$$K_1 = \frac{(\text{alveolar } P^{34}O_2 - {}^1Pc_{34O_2})}{(\text{alveolar } P^{34}O_2 - Pmv_{34O_2})}. \quad [9]$$

The terms Pc_{34O_2}, $^1Pc_{34O_2}$, and $^2Pc_{34O_2}$ can be eliminated from Equation 8 by substituting in their respective values obtained from Equations 3 and 9. The resultant equation simplifies to the following form:

$$\frac{1}{K} = \frac{\dot{Q}c}{\dot{Q}c_1(K_1) + \dot{Q}c_2(K_2)}. \quad [10]$$

Equation 6 can be solved for K_1 and K_2 and then substituted into Equation 10, giving:

$$\frac{1}{K} = \frac{\dot{Q}c}{\dot{Q}c_1 e^{[-D_{L1}(760)/\dot{Q}c_1(\alpha b_{O_2})]} + \dot{Q}c_2 e^{[-D_{L2}(760)/\dot{Q}c_2(\alpha b_{O_2})]}}. \quad [11]$$

Equation 9 can be substituted into Equation 2 so as to eliminate 1/K giving:

$$\text{observed } D_{L_{O_2}} = \frac{\dot{Q}c(\alpha b_{O_2})}{760} \times \ln\left[\frac{\dot{Q}c}{\dot{Q}c_1 e^{[-D_{L1}(760)/\dot{Q}c_1(\alpha b_{O_2})]} + \dot{Q}c_1 e^{[-D_{L2}(760)/\dot{Q}c_2(\alpha b_{O_2})]}}\right]. \quad [12]$$

Acknowledgment

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Addendum

While this paper was in press, we obtained an article by Thews and Witte (33), in which they included a theoretical analysis of the influence of nonuniform distribution of O_2 diffusion on the alveolar to end capillary O_2 gradient. Their calculations showed that if distribution of O_2 diffusing capacity is nonhomogeneous, the "apparent" O_2 diffusing capacity will always be less than the "true" O_2 diffusing capacity, and the end capillary O_2 tension will be lower than if diffusing capacity were uniformly distributed. Their findings, which are in agreement with ours, indicate that the steady state O_2 diffusing capacity is affected by uneven $D_L/\dot{Q}c$ in a manner similar to that described in this report for the single breath O_2 diffusing capacity.

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