THE EFFECT OF ANEMIA ON THE ALVEOLAR-CAPILLARY EXCHANGE OF CARBON MONOXIDE IN MAN

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Research Article

THE EFFECT OF ANEMIA ON THE ALVEOLAR–CAPILLARY EXCHANGE OF CARBON MONOXIDE IN MAN *

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Previous work has demonstrated that the exchange of CO between alveolar gas and pulmonary capillary blood is at least partially limited by the rate at which it can combine reversibly with intracellular hemoglobin. The relative importance of the rate of gas diffusion across the pulmonary membrane and the rate of gas uptake by the red cells in determining the over-all rate of alveolar capillary gas exchange has been expressed by the relation (1):

$$1/D_L = 1/D_M + 1/\theta V_c \qquad [1]$$

In this equation D_L is the over-all diffusing capacity of the lungs and D_M is that of the pulmonary membrane alone, both given in milliliters of gas per minute per millimeter Hg; V_c is the average volume of blood in the pulmonary capillary bed and θ is the rate at which 1 ml of this blood combines with CO in milliliters of gas reacting per minute per millimeter CO tension; θ equals the product of the number of grams of hemoglobin per milliliter of blood and the gas uptake rate per gram of hemoglobin. By analogy, the movement of gas between the alveoli and the red cell interior may be compared with the flow of electricity through two resistances in series where $1/D_L$ is the total resistance, $1/D_M$ is that of the membrane alone and $1/\theta V_c$ is that of the average total mass of red cells in the pulmonary capillary bed at any instant; θ decreases as capillary O_2 tension rises, because O_2 competes with CO for intracellular hemoglobin, in effect lowering the chemical reaction rate. By measuring D_L at two or more dif-

ferent capillary O_2 tensions for which corresponding values of θ are known, the data can be obtained for the solution of Equation 1 for both D_M and V_c.

When the concentration of red cells in the pulmonary capillary blood is decreased, without any remarkable changes in the gas uptake rate of the individual cell, θ also decreases and the formula predicts that D_L will decrease as well. In order to determine the physiological effects of anemia on gas exchange and also to confirm the validity of Equation 1, we have measured D_L, D_M, and V_c in five patients with severe iron-deficiency anemia without significant pulmonary disease, both before and after therapy.

METHODS AND SUBJECTS

The pulmonary diffusing capacity was determined by a modification of the Krogh breath-holding technique (2), in which the seated resting subject makes a maximal inspiration from residual volume of a gas mixture containing approximately 0.3 per cent CO, 10 per cent He, and the remainder O_2 and N_2. An alveolar sample is obtained from the expirate after a 10-second period of breath-holding. The expired alveolar sample was dried and analyzed on an infrared analyzer for CO, and on a continuously-sampling mass spectrometer for He, O_2 and CO_2. Appropriate corrections were applied for the slight sensitivity of the instrument to CO_2; 4 per cent CO_2 gave a response equivalent to 0.001 per cent CO.

Measurements of D_L were repeated at several alveolar oxygen tensions from about 100 to approximately 600 mm Hg. The alveolar oxygen tension during the measurement of D_L was varied *a*) by having the subject inspire gas mixtures containing different concentrations of oxygen during the actual measurement of D_L; and *b*) by having the subject breathe 99.5 per cent oxygen or air for several minutes prior to the measurement.

Knowing D_L for several different oxygen tensions, Equation 1 was solved graphically for D_M and V_c (3); θ was obtained from the data of Roughton and Forster (1) who use a value of 2.5 for the ratio of the permeability of the red cell membrane to that of the interior of the cell; θ is proportional to the concentration of hemoglobin (or of normal red cells) in the blood. The values of θ

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were derived for an assumed blood hemoglobin concentration of 14.9 g per 100 ml (equivalent to an O_2 or CO combining capacity of 20 ml per 100 ml). When the pulmonary capillary hemoglobin concentration does not equal this value, θ may be obtained by direct proportion.

The measurements of D_L were corrected for the presence of significant amounts of COHb in the mixed venous blood by subtracting the equilibrated CO tension owing to this compound. After washing out most of the nitrogen in the lungs by breathing approximately 100 per cent O_2 beforehand, which resulted in an alveolar O_2 tension of about 600 mm Hg, the equilibrated CO tension was obtained by breath-holding for 1.5 minutes. Estimates of equilibrated blood CO tension were obtained in this manner before and after a group of measurements of D_L, and the correct value for the individual measurement obtained by interpolation and proportioned to the appropriate O_2 tension (4). The calculations are not precise for alveolar O_2 tensions of much less than 200 mm Hg, but are adequate for the present purposes.

Residual volume was measured by the open circuit nitrogen washout method of Darling, Cournand and Richards (5). Maximal expiratory and inspiratory flow rates were calculated by the method of Cander and Comroe (6). The evenness of distribution of inspired gas was measured in four of the five patients by the single-breath O_2 method (7).

We desired subjects for this investigation who had physiologically normal lungs and cardiovascular systems,

and who could be studied a) at a time when their blood hemoglobin was very low, and later b) when it had been raised by therapy. The most common condition in which these circumstances prevail is a previously undiagnosed anemia resulting from acute or chronic blood loss, immediately prior to and after blood transfusion. We were able to study only five patients fulfilling these criteria over a period of more than a year. Their vital statistics, pulmonary function tests and primary diagnoses are given in Table I. Pulmonary function tests were repeated only in Patient 5, whose average results are given. None of these patients had any history, physical signs, or indications by X-ray examination of respiratory disease. Since it is desirable to treat any patient with a markedly low hematocrit as soon as possible, it was difficult to obtain complete pulmonary function studies (particularly arterial blood analyses) on each patient while he was in his most anemic state, but this was largely accomplished, save in Patient 1.

He had a large hiatus hernia with gastrointestinal bleeding and this was considered the major cause of his anemia, although some of the blood findings were not wholly explicable on this basis. Owing to his condition, it was necessary to perform all studies while he was supine.

Patient 2 had large myofibromata of the uterus with considerable vaginal bleeding She also gave a history suggesting heart disease some 20 years earlier. The day before the first measurements of D_L, the patient devel-

TABLE I

Vital statistics and results of pulmonary function tests *

Patient diagnosis	Age	Sex	BSA	VC	RV	TLC	RV/TLC	MIFR	MEFR	MBC	N_2 uniformity
			m^2	ml	ml	ml	$\%$	L/min	L/min	L/min	$\%N_2$
1 Hiatus hernia	44	♂	1.80	4,650 (3,850)	3,450 (1,180)	8,100 (5,030)	42	270	590		1.7
2 Uterine fibromata	38	♀	1.56	2,730 (2,890)	1,690 (880)	4,420 (3,700)	38	226	259		1.2
3 Uterine fibromata	40.	♀	1.78	3,570 (2,800)	1,828 (855)	5,398 (3,655)	34	280	253	84	0.5†
4 Carcinoma of cervix	52	♀	1.51	2,760 (2,630)	2,365 (800)	5,365 (3,430)	44	270	485		0.7
5 Carcinoma of cervix	53	♀	1.70	2,380 (2,670)	1,792 (810)	4,172 (3,480)	43	230	260	80	0

* Diagnosis refers to the condition producing the anemia via chronic blood loss. VC is vital capacity, RV residual volume, TLC total lung capacity (all in ml BTPS). Predicted normal values (8) are given in the parentheses. MIFR and MEFR are maximal inspiratory and expiratory flow rates in liters BTPS/min. The normal values are between 200 and 600 L/min. MBC is the maximal voluntary ventilation in liters BTPS/min. The normal values are given in parentheses (9). N_2 uniformity [single breath N_2 test (7)] is the change in expired alveolar $N_2\%$ between 750 and 1,250 ml of expirate. The normal value is 2% or less. The first study on Patient 1 had to be done supine. Pulmonary function studies were repeated about 1 week after treatment in Patient 5; average values are given. There were no significant changes.

† This figure is the percentage of N_2 in the expired alveolar gas after breathing O_2 for 7 minutes. A normal value would be <2.5% (5).

TABLE II

Results of measurements of diffusing capacity of the lung in five patients with anemia *

Patient	Hb	D_L	$D_{L_{120}}$	D_M	V_c	Cell resistance/ membrane resistance	θV_c
	g/100 ml	ml/min ×mm Hg	ml/min ×mm Hg	ml/min ×mm Hg	ml	%	
1 1/20/56†	6.2	22.4	25	∞	66.7		19
1/24/56 Transfused 1 L blood			(27.2)	(51.0)	(82.0)		(57.4)
2/5/56	11.0	23.3	27.8	55.6	105.0	100	53
2/8/56	11.5	26.4	26.7	44.3	109.0	70	58.5
2 3/20/56 Transfused 60 ml; stopped upon reaction							
3/21/56	7.5	14.0	13.7	19.6	91	43	31.7
3/26/56 Hysterectomy; transfused			(22.6)	(42.3)	(68.0)		(47.5)
4/2/56	10.7	16.3	15.4	27.8	79	81	80
3 4/9/56	5.9	13.3	13.2	33.2	80.5	150	45
4/10/56 to Transfused total 2			(26.8)	(50.1)	(81.0)		(56.7)
4/16/56 L blood							
4/25/56	11.4	20.5	20.5	37.0	87.0	127	94
4 6/20/56	4.6	6.6	6.6	8.1	62.5	23	27
Transfused			(21.6)	(40.5)	(65.5)		(45.6)
6/25/56	12.4	17.6	17.4	28.6	65.0	64	76
5 6/30/56	5.9	12.2	10.8	45.5	54.3	320	30
7/2–3/56 Transfused 1.5 L blood			(25.3)	(47.4)	(76.5)		(53.5)
7/3/56	9.2	16.5	15.7	50.0	62.5	220	54

* Hb is blood hemoglobin concentration. D_L is diffusing capacity of the lung as measured using an inspired gas mixture containing about 21% O_2. $D_{L_{120}}$, value of D_L corrected to alveolar O_2 tension of 120 mm Hg according to Equation 1. D_M, diffusing capacity of pulmonary membrane. V_c, volume of blood in pulmonary capillary bed, assuming that hematocrit of this blood equals that in the major vessels. Figures in parentheses are normal predicted values. D_L is predicted according to patient's surface area (2). $V_c = 3.03 \times D_{L_{120}}$; $D_M = 1.87 \times D_{L_{120}}$; and θ (2) at $P_{O_2} = 120$ mm Hg = 0.7 ml/min/ml normal blood/mm Hg CO partial pressure (3). Cell resistance/membrane resistance is ratio of resistance to diffusion of CO within the blood as compared with that across the pulmonary membrane. θV_c = ml CO entering average total red cells in pulmonary capillary bed in 1 second for a pressure gradient of 1 mm Hg.

† This study was performed with the patient supine; in subsequent studies he was sitting.

oped an urticarial reaction, fever, and partial heart block after receiving about 60 ml of a transfusion. Several days after her transfusion reaction she had a hysterectomy and oophorectomy with blood replacement. The measurements of D_L were repeated after the operation.

Patient 3 had large myofibromata of the uterus with severe vaginal bleeding. She was studied before and after blood transfusion in preparation for subsequent hysterectomy.

Patient 4 had carcinoma of the cervix with vaginal bleeding producing a severe anemia. She was studied before and after blood replacement.

Patient 5 had carcinoma of the cervix with extension into the pelvis and her only symptom was severe vaginal bleeding.

RESULTS AND DISCUSSION

The results of the tests given in Table I show that the pulmonary function of these patients was essentially normal, although they were extremely weak and found it difficult to cooperate in these studies. Patient 1 was unable to sit up, two patients could not be moved to the pulmonary function laboratory before treatment and only limited studies could be done. Vital capacity was within normal limits, while the residual volume and total lung capacity were increased in all patients. The ratio, residual volume/total lung capacity, was above 30 per cent in each patient but less than the expected value if age is considered (8). Other than the general condition of the patients, we have no adequate explanation for the increased residual volume. However, since neither significant airway obstruction nor uneven distribution of inspired gas was indicated by the other tests of pulmonary function, we can rule out any significant

obstructive pulmonary disease. Further, since these patients gave no indication of significant pulmonary disease by history, or by physical or X-ray examination, we inclined to the view that they were as free from pulmonary dysfunction as we could expect under the circumstances pertaining.

A summary of the measurements of the diffusing capacity of the lung at an alveolar O_2 tension of about 100 mm Hg in these patients, before and after blood replacement by transfusion, is given in Table II. More complete data are presented in Figure 1, which is a plot of D_L for all five subjects, at varying alveolar O_2 tension from 100 to about 600 mm Hg before treatment. At the time of the first study, the average blood Hb concentration was 6 g per 100 ml, and after treatment the

average blood Hb concentration was 11 g per 100 ml. Each point in the figure is the average of two or more measurements of D_L. At all three levels of alveolar O_2 tension, D_L in the anemic state was lower than similar data from eight normal subjects at comparable alveolar O_2 tensions (3) (p < 0.01). The value of D_L (corrected to a standard alveolar O_2 tension of 120 mm Hg (D_{L120})) for each patient was less than the value predicted from the body surface area (2) (p < 0.05). With the exception of the case of Patient 1, each measured value of D_{L120} was more than 2 SD (8 ml per minute per mm Hg) below the predicted value at the lower Hb concentration. Except for two data points of Patient 1, all of the D_L measurements were less than the normal data even at the higher Hb concentration. At an av-
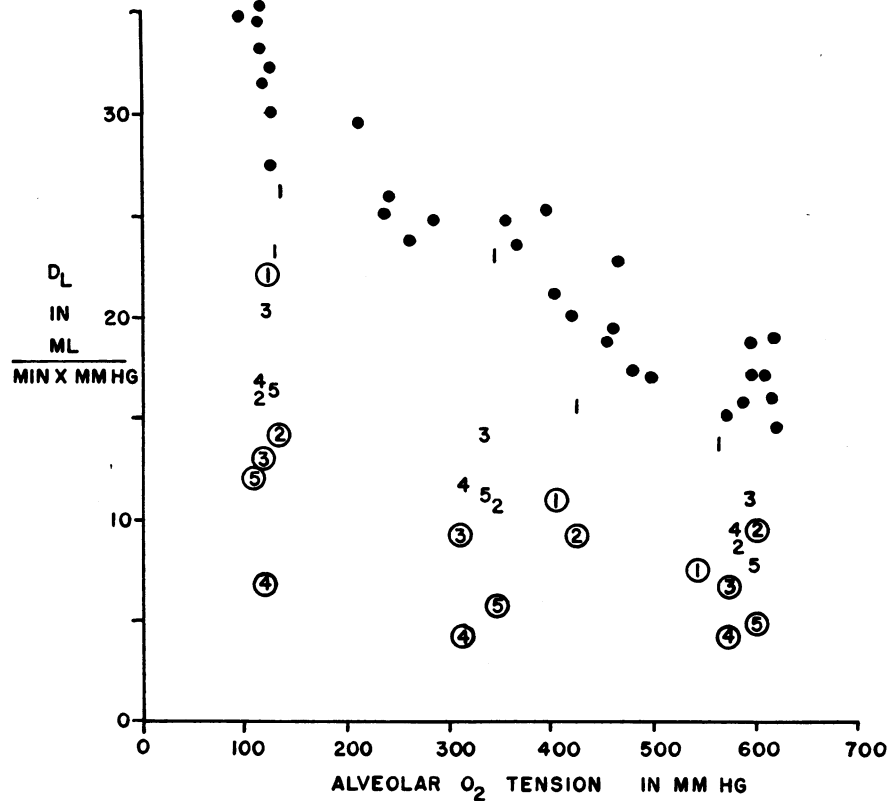

FIG. 1. THE DIFFUSING CAPACITY OF THE LUNG (D_L) FOR EACH OF THE 5 PATIENTS PLOTTED AGAINST ALVEOLAR Po_2 IN MM HG. The circled figures indicate measurements made when the patients were severely anemic, prior to the therapy (average Hb conc. 6 g per 100 ml). The figures without circles indicate measurement made after therapy when the blood hemoglobin concentration had been raised (average Hb conc. 11 g per 100 ml). The numbers refer to the individual patients as in the tables. The solid circles (●) are data from 8 normal subjects (3). Each point is the average of at least two observations.

erage Hb concentration of 6.0 g per 100 ml, D_{L120} was 55 per cent of its predicted value.

In all five patients, after the increase in blood Hb concentration produced by transfusion, D_{L120} was increased (Table II, Figure 2). At an average Hb concentration of 11 g per 100 ml, D_{L120} was 77 per cent of its predicted value. The initial studies in Patient 1 were done with him supine, the later studies, sitting. Since D_L is greater supine than sitting (2), this would tend to displace upward the most leftward point of the graph for Patient 1. Any correction applied for this fact would bring the data on this patient more into line with the remainder. On the average, a 10-day interval occurred between the pre- and post-transfusion studies in a given patient (range 3 to 16 days). Except at the highest alveolar tension in Patient 2, and in spite of variations between individuals, it can be seen (Figure 1) that D_L was greater at the greater blood Hb concentration in all five patients, and at all three alveolar O_2 tension levels. These differences are statistically significant.

Two major questions raised by the present results are: a) Why is D_L less than the predicted normal value in all five patients? b) What is the mechanism of its increase after transfusion?

The five patients studied were of relatively small body size compared with the normal subjects whose data are given in Figure 1—an average surface area of 1.67 m^2 as compared with an average of 2.00 m^2. Under normal circumstances D_L is less the smaller the body size (2) and this might be the explanation for the lower values of D_L in Figure 1 and Table II. However, in four of five patients, the value of D_L (as measured at the lower hemoglobin concentration) was more than 2 SD below the value predicted on the basis of body surface area. Only one patient had a D_L outside these predicted limits after partial restoration of normal hemoglobin concentration. We conclude that the initial low values for D_L are not entirely explicable on the basis of the small body size of the patients.

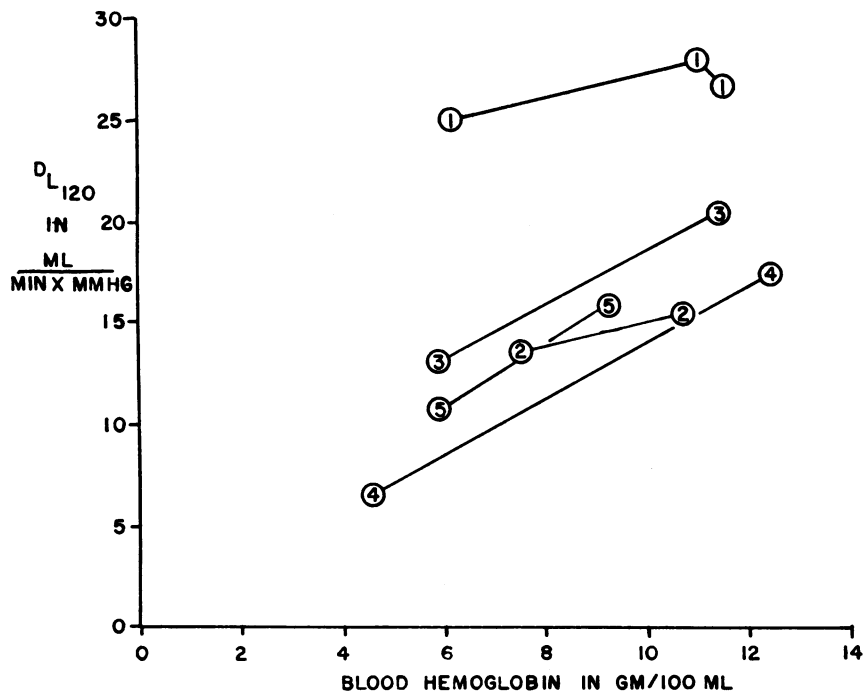The effective surface area of the pulmonary membrane might have been reduced in these pa-

FIG. 2. A GRAPH OF D_{L120}, THE VALUE CORRESPONDING TO AN ALVEOLAR O_2 TENSION OF 120 MM HG, AGAINST PERIPHERAL BLOOD HEMOGLOBIN CONCENTRATION FOR THE 5 PATIENTS STUDIED. The numerals inside the circles indicate the patient from whom the datum derives. The lines connect measurements made at different levels of blood hemoglobin concentration on any single patient.
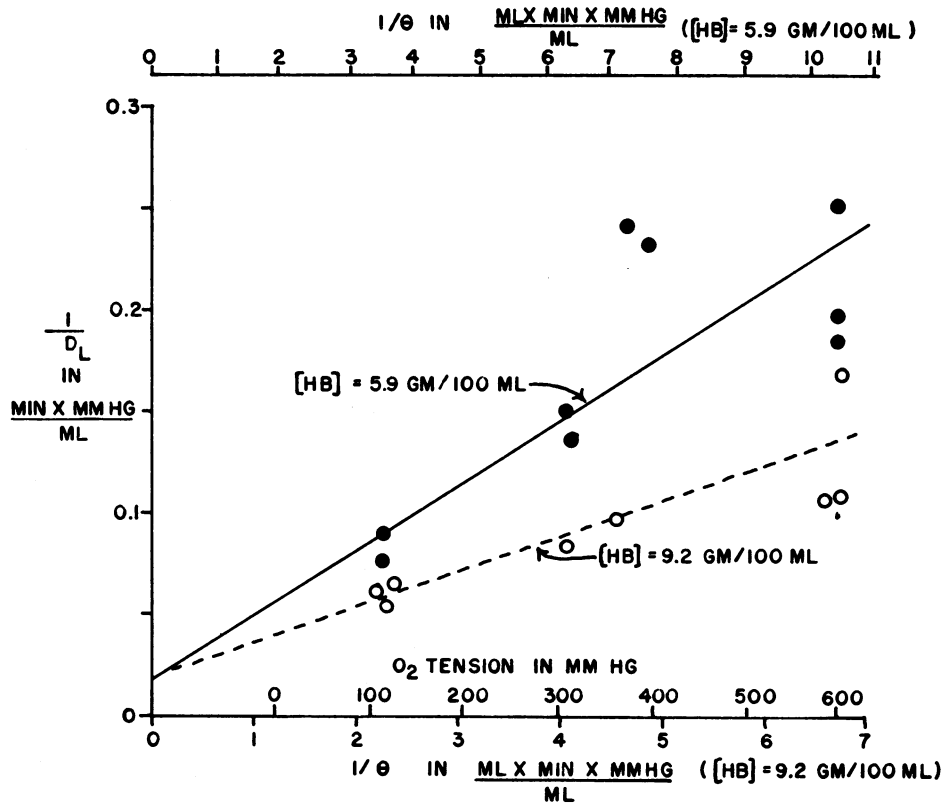
FIG. 3. A GRAPH OF 1/D$_L$ AGAINST 1/θ FOR PATIENT 5, BEFORE AND AFTER TREATMENT OF ANEMIA. Because θ is directly proportional to the blood CO capacity or hemoglobin concentration (1), the scales on the abscissae have to be different for the measurements before and after treatment of the anemia. The solid circles (●) indicate measurements made when the patient's hemoglobin concentration was 5.9 g per 100 ml and the abscissa should be read on the top scale. The open circles (○) refer to measurements made after the patient had been transfused and the hemoglobin concentration in the blood had risen to 9.2 g per 100 ml. These data should be read on the lower scale. The approximate capillary O$_2$ tension is also plotted on the abscissa and refers to either graph. The lines are the least mean squares regression lines for the two groups of data. The intercept on the ordinate equals 1/D$_M$; D$_M$ is 45.5 and 50.0 ml per minute per mm Hg for the upper (more anemic) and lower (post-treatment) cases, respectively. The slopes of the two lines, calculated according to their particular abscissal scale, are proportional to 1/V$_c$. V$_c$ was 54.3 and 62.5 for the anemic and post-treatment measurements, respectively; each point is the mean of at least two observations.

tients by a chronic abnormality, such as pulmonary fibrosis, or a more acute process, such as pulmonary edema. However, save possibly in Patient 2 (who may have had some cardiopulmonary dysfunction following her transfusion reaction), there were no indications of abnormalities in the lungs by the usual clinical, radiological, or functional tests. Since, after transfusion, D$_{L120}$ increased an average of 58 per cent in from 3 to 16 days, any abnormalities in the pulmonary membrane would have had to be rapidly reversible to explain the changes in D$_L$ found.

The values of the diffusing capacity of the pulmonary membrane and the pulmonary capillary blood volume presented in Table II were obtained from graphical solutions of Equation 1, by the data in Figure 1. This graphical solution for the case of Patient 5 is given in Figure 3. The initial measurements of D$_L$ were made when the patient's peripheral venous blood had a Hb concentration of 5.9 g per 100 ml. After transfusion this rose to 9.2 g per 100 ml at the time of the second measurements of D$_L$; θ, the rate of combination of CO with the blood, is proportional to Hb

concentration. Therefore, two scales are given on the abscissa, corresponding to the two blood Hb concentrations. The data were fitted to Equation 1 by the method of least squares. It should be noted that the two lines are plotted against different scales for $1/\theta$ on the abscissa and that in actuality their slopes $(1/V_c)$ are approximately equal.

A reduction in D_L in anemia can be predicted from Equation 1 because of the increase in the intravascular diffusion resistance, $1/\theta V_c$, secondary to the decrease in the rate at which 1 ml of blood in the pulmonary capillaries can take up CO per mm Hg of plasma CO tension. θV_c could be considered the "diffusing capacity" of the red cells in the capillary bed at any instant.

If the only change in the pulmonary capillary bed in anemia were a decrease in the hematocrit of the pulmonary capillary blood, one would expect D_M and V_c (which are dependent mainly upon the dimensions of this bed) to be normal and remain relatively unchanged by therapy. Also one would expect the measured value of θV_c in anemia to be less than normal and to rise with an increase in the hematocrit. As seen in Table II, D_M was less than normal prior to therapy and increased after therapy in four of five patients, but these changes are not statistically significant. It should be remarked that D_M is obtained by extrapolation (see Figure 3) and that $1/D_M$ lies near the origin except in severe pulmonary capillary block. Slight errors in the measured values of D_L can lead to large proportional changes in D_M, making it theoretically a more variable measure than V_c. For example, the initial value of D_M in Patient 1 was infinity. In addition, unusually large variations in D_L were found, particularly at high alveolar O_2 tensions, because, when D_L is reduced (as it was in these patients), the relative change in alveolar CO concentration during 10 seconds of breath-holding becomes small, and small analytical errors produce large changes in the calculated value of D_L. For example, in Patient 4 prior to treatment, the alveolar CO concentration fell between 10 and 25 per cent in 10 seconds. An analytical error of 3 per cent (which is not unrealistic) would produce an error in D_L of between 14 and 30 per cent. V_c tended to be closer to the predicted values than did D_M, and rose in four of five patients, but again these

changes are not statistically significant. It would not be unreasonable to expect an increase in the dimensions of the pulmonary capillary bed in anemia in view of the known increase in pulmonary blood flow seen in it (10).

θV_c, which actually equals the "diffusing capacity" of the red cells in the pulmonary capillary bed at any instant, was less than the predicted value and rose after therapy in all five patients; this change was statistically significant (p 0.03). Changes in θV_c can be observed without having to make any assumptions as to the value of θ, since $1/D_L$ can be plotted against mean capillary O_2 tension. These findings are in agreement with the hypothesis that in anemia CO movement within the pulmonary capillary blood is impeded. Since V_c, calculated on the basis of assumed changes in θ, did not change significantly, it is most probable that θV_c was reduced because θ was reduced, and the latter change could have been caused either because the number of red cells in the pulmonary capillary bed was reduced, or because the rate of CO uptake of the individual red cells was reduced. No data are available on the latter point, but there is no evidence to lead us to expect such an abnormality. If there had been an increase in the resistance to gas diffusion through the plasma of the pulmonary capillaries in the anemic state, this should have been interpreted as an increase in D_M, because the "pulmonary membrane" includes the entire path between the surface of the red cells and the alveolar gas according to the analysis. It is not possible to obtain direct experimental measurements of the hemoglobin concentration in the pulmonary capillary blood, so we have assumed it is equal to that in the peripheral venous blood, and it is on this basis that the values of V_c in Table II have been calculated.

Since there appear no other reasonable explanations, it seems permissible to conclude that the initially reduced values of D_L in these patients resulted from an increase in $1/\theta V_c$, and that the increase in D_L, which occurred when the blood hematocrit rose, resulted from a decrease in this intravascular resistance.

Since the rate at which 1 ml of normal whole blood takes up O_2 from the plasma per mm P_{O_2} difference is of the same order as θ for CO (1), we presume that the rate of diffusion of O_2 within the blood is also an important factor in determin-

ing the rate of O_2 exchange in the lungs as well as in the peripheral tissues. In anemia, where the total red cell surface available for O_2 exchange in the capillaries at any instant is decreased, the O_2 gradient would necessarily be increased.

Mochizuki and associates (11) have measured the diffusing capacity for O_2 in anesthetized dogs, in which the red cell concentration was varied from about 2.5 to 6.8×10^9 per ml blood. They estimated the venous admixture percentage (arterial-mixed venous) from O_2 content and alveolar and arterial Po_2 while the animal was breathing a gas mixture enriched with O_2. These authors found that the calculated value of D_L for O_2 increased proportionally to the increase in hematocrit, other conditions remaining constant. This finding is consistent with the data in Figure 2.

SUMMARY

The diffusing capacity of the lung (D_L) was measured by the breath-holding CO technique in five patients with severe chronic anemia, but without evidence of significant lung disease, before and after their blood hemoglobin concentration was increased by transfusion. Simple pulmonary function studies showed an increase in residual volume but no significant airway obstruction or non-uniform distribution of inspired gas.

D_L prior to therapy was less than predicted in all five patients. The average interval between the measurements of D_L in each patient was 9 days, in which time D_L at an average alveolar O_2 tension of 120 mm Hg had increased an average of 54 per cent; at an average alveolar O_2 tension of 250 mm Hg had increased an average of 95 per cent; and at an average alveolar O_2 tension of 590 mm Hg had increased an average of 69 per cent.

ACKNOWLEDGMENTS

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