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Research Article

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Diffusing Capacities and Ventilation: Perfusion Ratios in Patients with the Clinical Syndrome of Alveolar Capillary Block

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ABSTRACT Studies were performed on 10 patients with the clinical syndrome of alveolar capillary block while each patient was breathing four different inspired oxygen mixtures. The data were interpreted using the principle of the Bohr integral isopleth with which alveolar oxygen tension in the differently ventilated parts of the lung can initially be treated as unknown. It is then possible to determine the distribution of ventilation, of perfusion, of diffusing capacity, of lung volume, and of alveolar and end capillary blood oxygen tension in the variously functioning parts of the lung. In two patients shunts were the major factor interfering with oxygen transfer. In four others inequalities in ventilation: perfusion ratios and in diffusing capacity in different parts of the lung were the factors interfering with oxygen transfer. In four more patients ventilation: perfusion ratios were the same throughout the lung, the only disturbance of oxygen transfer being in the total diffusing capacity or in its distribution between the different parts of the lung.

INTRODUCTION

Recent work employing Bohr integral isopleths has thrown some instructive light on the distribution of diffusing capacity, of ventilation, of perfusion, and of ventilation: perfusion ratios in bronchitis and emphysema (1). The present work deals with the application of this new method of collecting and interpreting data in patients with the clinical syndrome of alveolar capillary block. In conventional considerations of pulmonary oxygen transfer by diffusion, alveolar oxygen tension is considered to have a certain fixed numerical value and is treated during Bohr integration as one of the entities which determines oxygen transfer. The present approach is unusual in treating alveolar oxygen tension as one of the entities which is initially unknown and determined by oxygen transfer (2–5).

METHODS

Patients were selected from the wards of the Chest Service and the Columbia Medical Division of Bellevue Hospital on the grounds that they were believed to have the clinical syndrome of alveolar capillary block (6, 7). The clinical syndrome consists of dyspnea (not due primarily to heart disease nor to obstructive lung disease), hyperventilation, cyanosis on exertion, rales at the bases of the lungs, often a low arterial P_{CO_2}, and a roentgenogram showing widespread involvement of the lungs by any of a wide variety of pathological processes. Table I gives the clinical diagnosis and roentgenographic interpretations in the 10 patients reported on here.

Patients were brought to the laboratory after breakfast and after their usual morning medication. A Cournand needle was inserted into a brachial artery. Studies were performed with the subjects propped up by a back rest on a bed. A mouthpiece was inserted and expired gas was flushed through a Tissot spirometer (Warren E. Collins, Inc., Boston, Mass.) which was used later to measure ventilation. After breathing each inspired gas for a period of 12 min to reach a steady state, expired gas was collected in the Tissot spirometer and arterial blood samples were taken for analysis for carbon dioxide and oxygen by the Van Slyke method and for measurement of pH. When studies during air breathing were completed, similar studies

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were performed while breathing three of the following gas mixtures: 14, 18, 24, 30, and 40% oxygen in nitrogen. Which gas mixtures were selected depended on clinical assessment of what the patient was likely to tolerate. Finally, the procedure was repeated during 100% oxygen breathing, blood analysis in this case being supplemented by measurements using an oxygen electrode. The diffusing capacity for carbon monoxide was determined by the steady-state method of Bates, Boucot, and Dormer (9) using an end tidal sampler (10). A nitrogen washout was performed by the two-balloon method of Emmanuel, Briscoe, and Cournand (11) and interpreted in terms of the volume and ventilation of the well ventilated (fast space) and poorly ventilated (slow space) groups of alveoli. The term "slow space," coined by Hickam, Blair, and Frayser (12) to describe collectively those alveoli which wash out an invert gas, such as nitrogen, slowly when oxygen is breathed, will be used in the present account.

For purposes of interpretation the data needed are numerous and include the arterial oxygen saturations measured while breathing four different inspired oxygen-nitrogen mixtures, the minute ventilations and respiratory rates, the oxygen consumption, and the nitrogen washout curve. The data derived are likewise numerous and include alveolar and end capillary oxygen tensions while breathing each inspired gas, and the ventilation, perfusion, diffusing capacity, and lung volume in each of the two ventilated and perfused groups of alveoli.

This combination of results is a unique one in that it is the only one which exactly fits all the other measurements as well as the arterial blood composition measured while breathing all four gases (4). An arteriovenous saturation difference of 25% is assumed. It has been shown that deviations from this assumed value have an insignificant effect on the results (4). Other assumptions made are described and discussed in previous papers and are believed not to influence the conclusions here. Total diffusing capacity of the lung is thus determined by a new method; it is now the sum of the diffusing capacity in the fast and slow spaces.

The use of graphic analogs

In order to consider the working of a nonhomogeneous lung, i.e. one in which different alveoli function in different degrees, it is necessary to separate what the causes are from what the effects are of oxygen transfer in a single alveolus. The five physiological causes or determinants in a single alveolus are: (*a*) mixed venous oxygen saturation, (*b*) inspired oxygen tension, (*c*) alveolar ventilation, (*d*) alveolar perfusion, and (*e*) alveolar diffusing capacity.

TABLE I
Methods of Diagnoses and Chest X-ray Findings

Patient	Date of onset (and death)	Diagnosis	Method of diagnosis	Dyspnea grade*	Roentgenographic interpretations
AND	Feb. '67	Alveolar cell carcinoma	Sputum smears	IV	Extensive homogeneous infiltrates in the left midzone and in both lower lung fields. Atelectasis of the right lower lobe (RLL).
WAL	Fall '66 (Fall '67)	Interstitial pulmonary fibrosis (etiology unknown)	Roentgenological evidence	IV	Cardiac enlargement. Fibrotic changes with numerous small patchy infiltrates throughout both lung fields.
BEL	Nov. '65	Sarcoidosis	Kveim test	II	Diffuse infiltrates in both lungs with enlargement of the hilar and paratracheal lymph nodes.
BEN	1963	Sarcoidosis with pulmonary fibrosis	Liver biopsy	II	In both lungs diffuse interstitial fibrotic changes with numerous small infiltrates without evidence of enlargement of hilar lymph nodes.
PLI	Jan. '66	Desquamative interstitial pneumonia	Open lung biopsy	I–II	Bilateral extensive homogeneous infiltrates. Left-sided pleural effusion.
MIL	Aug. '67	Eosinophilic granuloma	Open lung biopsy	None	Diffuse interstitial fibrotic changes and patchy infiltrates in both lungs.
MYE	Feb. '67	Mild acute glomerulonephritis (with moderate pulm. interest. edema)	Clinical and laboratory findings: hypertension (175/115), ascites, creatinine 1.7 mg/100 ml, proteinuria	I–II	Homogeneous densities in both lower lung fields. Interstitial pulmonary edema. Interlobar fluid in the lower partions of the oblique fissures.
FIS	Jan. '67 (April '67)	Acute glomerulonephritis (with pulm. interst. edema)	Confirmed by autopsy	II–III	Cardiac enlargement. Pleural effusion in the left costophrenic angle. Interstitial pulmonary edema.
WAR	1960	Sarcoidosis with pulmonary fibrosis	Scalene node biopsy	III–IV	Diffuse fibrosis throughout both lung fields with patchy infiltrates. Kyphoscoliosis.
DOR	1960	Systemic sclerosis with pulmonary fibrosis	Skin biopsy	None	Fibrotic changes throughout both lung fields without obvious parenchymal infiltrates.

* According to the classification of Mitchell and Filley 1964 (8).

The effects include alveolar oxygen tension, the end capillary blood oxygen tension and saturation, and the end capillary–alveolar oxygen tension difference or gradient. The use of the coordinates of the oxygen dissociation curve, as in Fig. 1, has the advantage that these five physiological determinants can be translated into four graphic analogs. These are represented by numbered lines in Fig. 1 which deals quantitatively with oxygen transfer in an alveolus with a low ventilation: perfusion ratio and a low diffusing capacity or Bohr integral. (*1*) Mixed venous saturation is represented by the height of the base line at 68% saturation. The intersection of this line with the oxygen dissociation curve at the semicircle on the left gives the venous oxygen tension (35 mm Hg). (*2*) "Inspired" oxygen tension is represented by a vertical line at 142 mm Hg on the x axis. All oxygen tensions and blood saturations in the alveolus must lie within the area circumscribed by venous saturation below, by "inspired" oxygen tension on the right, and by the oxygen dissociation curve above and on the left. (*3*) Alveolar ventilation ($\dot{V}_A$) and perfusion ($\dot{Q}$) combine to give a ventilation: perfusion ratio, ($\dot{V}_A/\dot{Q}$). This is represented by an isopleth, or line of constant ventilation: perfusion ratio, running through all combinations of end capillary blood saturation and alveolar oxygen tension compatible with a given ratio. Such lines originate at the inspired point (diamond) and have a slope proportional to the ratio which is 0.32 in Fig. 1. The point at which this line intersects the oxygen dissociation curve gives the end capillary saturation, 87%, an dthe alveolar and end capillary blood oxygen tension, 55 mm Hg, in an alveolus with this ventilation: perfusion ratio and with no barrier to diffusion. The oxygen dissociation curve itself is an isopleth of perfect diffusion or infinite Bohr integral. (*4*) The diffusing capacity (D_L) of the alveolus is represented by a Bohr integral isopleth. Such lines originate at the venous point with a slope approximately proportional to the Bohr integral which is 0.36 mm Hg^{-1} in this case. The Bohr integral is proportional to the diffusing capacity: perfusion ratio as explained in the legend of the figure.

The point where the two isopleths intersect at the black triangle gives, on the x axis, the alveolar oxygen tension (79 mm Hg), and on the y axis, the end capillary oxygen saturation (82%) which result when the ventilation: perfusion ratio is 0.32 and the Bohr integral is 0.36 mm Hg^{-1}. The open triangle lying on the oxygen dissociation curve represents the resulting end capillary blood oxygen tension (47 mm Hg). The horizontal distance between the two triangles represents the end capillary–alveolar oxygen tension gradient, 32 mm Hg in this alveolus.

Thus when numerical values are assigned to the five physiological determinants or the four analogs, it is quickly possible to obtain alveolar oxygen tension and end capillary saturation graphically; this is otherwise possible only after a tedious trial and error calculation or by using a computer. The graphic tools needed, i.e. families of ventilation: perfusion ratio isopleths and of Bohr integral isopleths, are available from the National Documentation Institute (Washington, D. C.) (3).

Fig. 2 illustrates the use of these analogs in a lung composed of two groups of alveoli. The fast group with a high ventilation is identified by the subscript 1 in algebraic symbols and by a square in the figures. The slow group with a

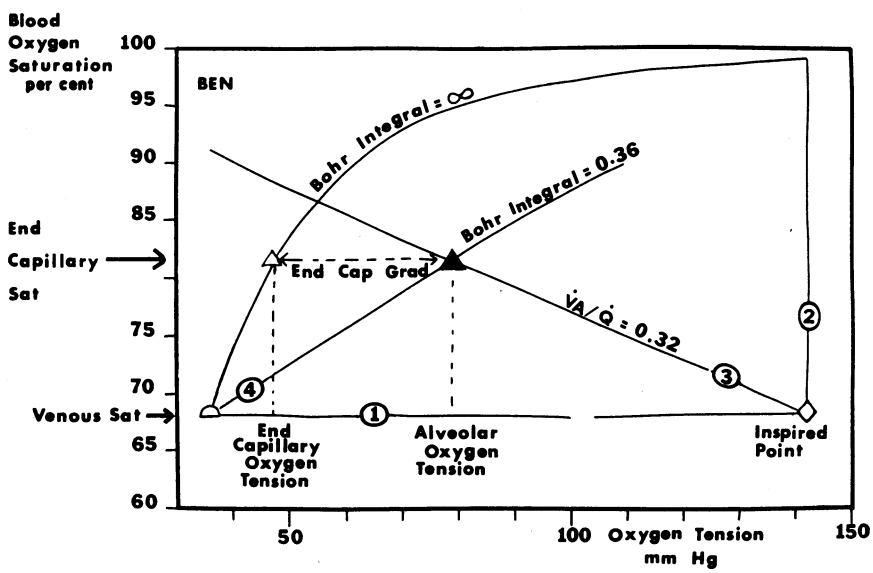


FIGURE 1 Diagram showing the four analogs which determine oxygen transfer in a single alveolus. These are (1) mixed venous saturation, 68%, (2) "inspired" oxygen tension, 142 mm Hg, (3) Ventilation:perfusion ratio, $\dot{V}_A/\dot{Q}$ = 0.32, and (4) Bohr integral, B = 0.36 mm Hg^{-1}. The last two isopleths originate at the inspired and mixed venous points respectively. The oxygen dissociation curve is the isopleth for an infinite Bohr integral. "Inspired" oxygen tension, $P'_{I_{O_2}}$, is the inspired tension, $P_{I_{O_2}}$, modified by a small correction for alveolar carbon dioxide tension: $P'_{I_{O_2}} = P_{I_{O_2}} - P_{A_{CO_2}} \cdot F_{I_{O_2}}$. The Bohr integral is related to the diffusing capacity (D_L), blood flow ($\dot{Q}$), and oxygen capacity (Cap) by the relationship $B = (100 \cdot D_L) : (\dot{Q} \cdot Cap)$, and has a normal value of 1.5 mm Hg^{-1}. The data in this figure are those for the slow space of patient BEN.

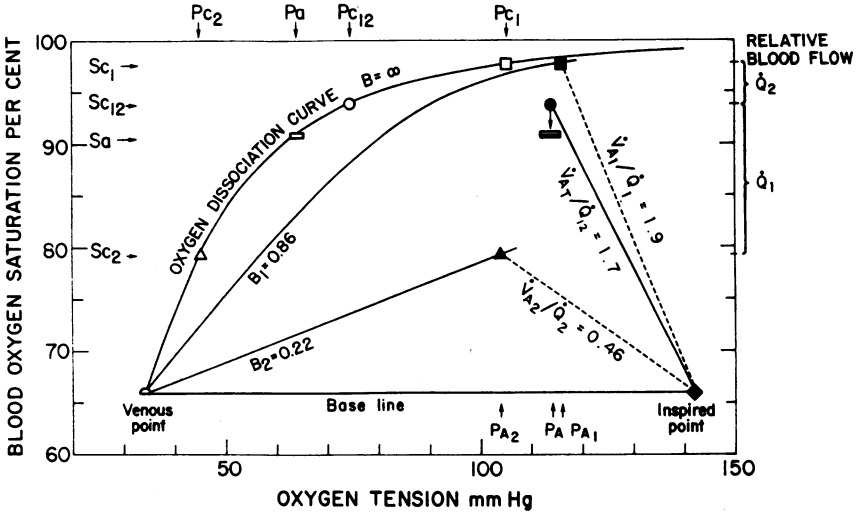


FIGURE 2 Oxygen transfer in a lung composed of two groups of alveoli with different entilation: perfusion ratios and Bohr integrals. The fast space, slow space, and mixed end capillary blood are identified by a square, triangle, and circle respectively, and by the subscripts 1, 2, and 12 in algebraic symbols. Oxygen saturation and tension in end capillary and arterial blood are indicated by the symbols Sc, Pc, Sa, and Pa. Mixed alveolar oxygen tension is indicated by the symbol P_A. The mixing equations for blood are $Sc_{12} = (\dot{Q}_1 \cdot Sc_1 + \dot{Q}_2 \cdot Sc_2)/\dot{Q}_{12}$ and $Sa = (\dot{Q}_{12} \cdot Sc_{12} + \dot{Q}s \cdot S\bar{v})/\dot{Q}_T$. The mixing equation for alveolar gas is $P_A = (\dot{V}_{A1} \cdot P_{A1} + \dot{V}_{A2} \cdot P_{A2})/\dot{V}_{AT}$. $\dot{Q}$ is blood flow, $\dot{V}_A$ is alveolar ventilation, S is oxygen saturation, and P_A is alveolar oxygen tension. The subscripts c, a, and $\bar{v}$ refer to end capillary, arterial, and mixed venous blood. The numerical subscripts 1, 2, and 12 refer to the fast space, the slow space, and the mixture of blood or gas emerging from both spaces. The subscript T designates total cardiac output or alveolar ventilation.

low ventilation: perfusion ratio is identified by the subscript 2 and by a triangle in the figures. It can be seen that for relatively high values of the Bohr integral, $B_1 = 0.86$ mm Hg^{-1}, the Bohr integral isopleth is a curved line which merges into the oxygen dissociation curve. For low values, $B_2 = 0.22$ mm Hg^{-1}, the isopleth is nearly a straight line.

The situation is different from that in a single alveolus in that new entities arise as the result of admixture of the output of the various alveoli which have to match the measurements made on the patient. The alveolar oxygen tensions in the two groups of alveoli (P_{A1} and P_{A2}) are mixed in proportion to their ventilations ($\dot{V}_{A1}$ and $\dot{V}_{A2}$) to give mixed alveolar oxygen tension (P_A). The end capillary blood oxygen saturations (Sc_1 and Sc_2) are mixed in proportion to their blood flows ($\dot{Q}_1$ and $\dot{Q}_2$) to give the mixed end capillary blood oxygen saturation (Sc_{12}). Finally mixed end capillary blood is mixed with venous blood, when a shunt is present, to give the observed arterial oxygen saturation (Sa).

As a result of this mixing the vertical distances between triangle and circle and between square and circle are respectively proportional to the perfusions ($\dot{Q}_1$ and $\dot{Q}_2$) of the fast and slow spaces as indicated on the right margin. Corresponding horizontal distances are proportional to the respective ventilations ($\dot{V}_{A1}$ and $\dot{V}_{A2}$) of the fast and slow spaces. Horizontal distances between the points on the right and the dissociation curve on the left give various alveolar and capillary and alveolar arterial gradients as outlined in the caption of the figure. Thus figures of this type convey a great deal of information about oxygen transfer in a nonhomogeneous diseased lung.

RESULTS

Table II gives anthropometric data and the results of routine lung function tests. These patients have no significant airway obstruction since the formed expiratory volume (FEV) in 1 sec averages 81% of vital capacity (VC). There are only slightly reduced values in three patients (FIS, PLI, and BEN). However, vital capacity is reduced in all cases to between 50 and 82% of its normal value, predicted from age and height (13), presumably because the pulmonary lesions reduce compliance and so limit vital capacity. Total lung capacity (TLC) is likewise reduced and the residual volume (RV) is somewhat increased on the average.

Table III gives data for each patient while breathing each of four inspired gases. These patients were all hyperventilating to varying degrees as manifested by high values for minute ventilation. The respiratory rate is also raised in most cases. Arterial oxygen saturation while breathing air (21% inspired oxygen) varies widely in different cases, the lowest being 68% in AND and highest being 97% in WAR. Arterial carbon dioxide

TABLE II

Age, Height, Weight, and Lung Volumes

Patient	Age, sex	Height	Weight	FEV	VC	FEV/VC	VC % of predicted	TLC	RV/TLC
	yr	*in.*	*lb.*	*liters*	*liters*	%		*liters*	%
Group I									
AND	61, m	69.5	120	1.65	1.89	87	51	3.71	50
WAL	64, f	61.5	145	1.05	1.19	89	50	1.89	40
Group II									
BEL	27, m	68	137	2.40*	3.15*	76*	74		
BEN	28, f	66	119	1.18	2.04	57	64	3.71	45
PLI	36, m	67	98	1.40	2.16	65	54	3.81	43
MIL	24, m	71.5	155	3.20	3.30	96	73	6.3	48
Group III									
YE	38, m	69.8	167	2.11	2.39	87	58	6.06	61
FIS	58, m	74	218	2.14	3.38	63	82	6.14	45
WAR	51, f	64.8	119	1.19	1.28	93	47	2.25	43
DOR	51, f	59.5	113	1.47	1.57	93	63	3.65	57
Mean‡		66	139	1.71	2.13	81	61	4.17	48

* These measurements were obtained after the other data and after considerable improvement on steroid therapy.

‡ Mean values of all patients except BEL.

tension tends to be low, the average value being 35 mm Hg.

Table IV gives the total alveolar ventilation while breathing air which is determined by substracting the product of respiratory rate and combined anatomical and instrumental dead space from the minute ventilation. Anatomical dead space in milliliters is taken to be equal to body weight in pounds (14). The table also shows the distribution of the ventilation, i.e., the ventilation of the fast and slow spaces. The latter receive between 2 and 30% of the total alveolar ventilation.

Cardiac output, $\dot{Q}_T$, or more precisely hemoglobin flow (footnote Table V), $\dot{Q}'_T$, was estimated from the oxygen consumption and from the assumption that the arteriovenous saturation difference is 25%. The exact value of the cardiac output makes very little difference to our consideration of the distribution of blood flow. Table V shows the distribution of the cardiac output between the two differently ventilated lung spaces and the shunt. The latter is derived from the measured arterial oxygen tension during 100% oxygen breathing. The patients have been divided into three groups on the basis of the distribution of perfusion and of ventilation: perfusion ratios. In group I are two patients in whom there was a significant shunt. In group II are four patients in whom there is no significant shunt but significant inequalities in ventilation: perfusion ratios within the lung. Group III includes four patients with no significant shunt and no significant inhomogeneity in ventilation: perfusion ratios, i.e. the values for the fast and slow spaces are about the same, as is the fractional perfusion in Table VI when compared to the fractional ventilation in Table III.

Distribution of perfusion between the fast and slow space varies widely; between 7 and 43% of the cardiac output perfuses the slow space. There is no consistant difference in this respect between our groups of patients. The overall ventilation: perfusion ratio, i.e. that between total alveolar ventilation and total alveolar perfusion ($\dot{V}_{AT}/\dot{Q}_{12}$), averaged 1.65 and was above the normal value of about unity in most patients, especially those in group II. This is a reflection of the fact that these patients were, on the whole, hyperventilating. The ratio in the fast space $\dot{V}_{A1}:\dot{Q}_1$ slightly exceeded the overall value (except in MYE and FIS).

The ventilation: perfusion ratio of the least ventilated lung spaces varies greatly around the mean value (0.77) in different patients. In three (BEL, BEN, and MIL), it is less than 0.4; and in four (AND, MYE, FIS, and WAR), it is more than 1.0.

Table VI presents the distribution of lung volume and of diffusing capacity. The total volume of the differently ventilated lung spaces as measured is the functional residual capacity (L_T). It varies from 1.1 to 4.2 liters. The least ventilated alveoli (slow space) occupy a volume of 1.2 liters on the average ranging from 22 to 91% of the functional residual capacity. The fast space occupies 1.3 liters on the average. Although the mean volumes of the fast and slow spaces are nearly equal, there are considerable differences between the

TABLE III
Ventilation and Arterial Blood

Patient	Inspired oxygen concentration F_{IO_2}	Minute ventilation $\dot{V}_E$	Respiratory rate f	Arterial oxygen saturation* S_a	Arterial carbon dioxide tension $P_{a_{CO_2}}$
	%	*liters/min*	*min*$^{-1}$	%	*mm Hg*
1	*2*	*3*	*4*	*5*	*6*
AND	100	17.7	27	78.5	31
	41	13.5	25	73.8	30
	29	16.2	24	71.2	29
	21	18.5	25	68.2	27
WAL	100	11.5	23	(369)	32
	29	12.2	22	90.7	36
	24	14.8	23	88.5	33
	21	14.2	24	86.0	31
BEL	100	12.4	24	(625)	33
	29	12.6	20	96.0	35
	24	11.8	20	94.1	37
	21	12.7	17	89.8	35
BEN	100	10.9	22	(663)	35
	24	11.7	23	95.0	35
	21	12.0	21	93.0	33
	18	13.0	24	87.0	32
PLI	100	9.3	25	(675)	37
	21	8.7	25	92.4	40
	18	10.0	29	88.9	39
	14	12.4	33	80.7	36
MIL	100	14.0	24	(680)	31
	21	12.9	21	96.6	41
	18	14.9	21	95.5	35
	14	13.5	20	89.8	32
MYE	100	8.5	21	(650)	42
	24	10.5	21	96.0	37
	21	10.0	24	94.0	36
	18	10.7	24	90.7	35
FIS	100	14.7	17	(688)	30
	21	14.7	17	95.0	29
	18	14.7	16	92.7	28
	14	16.4	17	82.0	26
WAR	100	8.3	20	(634)	42
	21	7.9	18	97.0	42
	18	8.3	19	93.4	44
	14	9.7	22	81.2	39
DOR	100	9.3	25	(666)	35
	21	8.6	24	96.9	38
	18	9.1	24	95.2	39
	14	9.9	26	84.3	37
Mean	21	12.0	21	90.9	35

* Figures in parentheses give arterial oxygen tension while breathing 100% oxygen.

patients. In some of them the fast space has a greater volume than the slow space and vice versa.

For each space the separate diffusing capacity for oxygen (D_{L_1} and D_{L_2}) has been determined, their sum being the total diffusing capacity of the lung (D_{L_T}) (column *8*). There are three patients (MIL, FIS, and DOR) in whom the total diffusing capacity is more than 10 ml/min·mm Hg, i.e., a nearly normal value. In the other patients, it is considerably lower, ranging from 3.7 to 6.8 ml/min·mm Hg. The mean percentage of the total diffusing capacity, which included in the slow space (D_{L_2}) column *7*), is 10% (column *9*). This is much less than the percentage of lung volume in that space (54%) (column *5*).

A comparison of D_{L_T} (column *8*) with the values for the diffusing capacity for oxygen as determined by the method of Riley and Cournand (15) shows (column *10*) that the total oxygen diffusing capacity determined by the new method gives somewhat higher values. Likewise, the new method gives somewhat higher values than does the steady-state carbon monoxide diffusing capacity, except in one subject (AND).

Table VII gives the values for the Bohr integrals, B_1 and B_2, in the two lung spaces. In the fast space, it

TABLE IV
Ventilation during Air Breathing

Patient	Alveolar ventilation: Total $\dot{V}_{A_T}$	Alveolar ventilation: Fast space $\dot{V}_{A_1}$	Alveolar ventilation: Slow space $\dot{V}_{A_2}$	Fractional ventilation: Fast space $\dot{V}_{A_1}/\dot{V}_{A_T}$	Fractional ventilation: Slow space $\dot{V}_{A_2}/\dot{V}_{A_T}$
	liters/min	*liters/min*	*liters/min*	%	%
1	*2*	*3*	*4*	*5*	*6*
AND	13.4	12.7	0.67	95	5
WAL	9.3	8.5	0.80	91	9
BEL	8.6	8.2	0.43	95	5
BEN	8.3	7.8	0.51	94	6
PLI	4.2	3.1	1.09	74	26
MIL	8.4	8.2	0.20	98	2
MYE	4.6	3.6	0.99	78	22
FIS	10.0	7.7	2.34	77	23
WAR	4.7	3.2	1.53	68	32
DOR	4.5	No significant uneven ventilation detected			
Mean	7.9*	7.0	0.95	86	14

This data is that applicable during air breathing. Minor variations in minute ventilation breathing other inspired gases result in minor variations in the entities given here, which were allowed for in subsequent interpretations and can be seen in Figs. 4 and 5 where variations in the slope of the overall ventilation: perfusion ratio isopleth are apparent in some cases.

* Excluding DOR.

TABLE V

Distribution of Perfusion and Ventilation: Perfusion Ratios

Patient	Oxygen consumption $\dot{V}_{O_2}$	Oxygen capacity of blood capacity	Cardiac output* $\dot{Q}_T'$	Fractional perfusion: Shunt $\dot{Q}_s/\dot{Q}_T$	Fractional perfusion: Fast space $\dot{Q}_1/\dot{Q}_T$	Fractional perfusion: Slow space $\dot{Q}_2/\dot{Q}_T$	Ventilation: perfusion ratio*: Overall value $\dot{V}_{A_T}/\dot{Q}_{12}'$	Ventilation: perfusion ratio*: Fast space $\dot{V}_{A_T}/\dot{Q}_1'$	Ventilation: perfusion ratio*: Slow space $\dot{V}_{A_2}/\dot{Q}_2'$
	ml/min	*ml/ml*	*liters/min*	%	%	%			
Group I									
AND	305	0.200	6.1	46	44	10	4.06	4.75	1.08
WAL	261	0.202	5.2	18	58	24	2.16	2.77	0.65
Group II									
BEL	370	0.206	7.4	3	73	24	1.31	1.66	0.24
BEN	282	0.156	5.6	0	68	32	1.47	2.02	0.29
PLI	194	0.145	3.9	0	57	43	1.08	1.39	0.66
MIL	317	0.184	6.3	0	93	7	1.32	1.39	0.36
Group III									
MYE	233	0.156	4.7	0	80	20	0.97	0.95	1.07
FIS	403	0.153	8.1	0	77	23	1.24	1.23	1.28
WAR	189	0.159	3.8	2	66	32	1.28	1.29	1.25
DOR	236	0.154	4.7	0			0.94	0.94	0.94
Mean	279	0.200	5.7‡	8‡	68‡	24‡	1.65	1.94	0.76

* Since ventilation: perfusion ratio isopleths and Bohr integral isopleths apply to a standard oxygen capacity of 0.2 ml of O_2/ml of blood, the figures for blood flow and $\dot{V}_A:\dot{Q}'$ ratios are given in terms of "hemoglobin flow," $\dot{Q}'$(4). Blood flow ($\dot{Q}$) may be derived from "hemoglobin flow" ($\dot{Q}'$) and oxygen capacity (Cap) by the relationship $\dot{Q} = \dot{Q}' \cdot 0.2 : \text{Cap}$.

‡ Without DOR.

ranges from 0.47 to 1.31 mm Hg^{-1} with a mean value of 0.86 mm Hg^{-1} (column 3). In the slow space, it is considerably lower, averaging 0.22 mm Hg^{-1} (column *4*). Also summarized in this table are the end capillary oxygen saturations of blood leaving the fast (column *5*) and slow space (column *6*) for each of the inspired gas mixtures. During air breathing, blood leaving the fast space is always fully saturated; but while breathing 14% oxygen, saturation may fall as low as 86% as in subject WAR. In the slow space, on the other hand, end capillary blood is markedly unsaturated while breathing air, except in WAR and DOR. Furthermore, the degree of unsaturation varies greatly between patients. The saturation of mixed end capillary blood (column *7*) is the mean of the two end capillary saturations weighted by the blood flow through each lung compartment. It has the same value as mixed oxygen arterial saturation (Table III, column *5*) unless there is a shunt which lowers arterial saturation.

Figs. 3, 4 and 5 summarize the findings in the three groups of patients. This method of presentation is used for the sake of brevity.[1] The mixed alveolar end capillary oxygen tension difference, shown by the horizontal distance between circles and the oxygen dissociation curve, averaged 37 mm Hg while breathing air. The alveolar arterial oxygen tension gradient averaged somewhat more, 42 mm Hg, due to the presence of a shunt in some cases.

In all patients except WAR the alveolar arterial gradient of oxygen tension increased when mixtures higher in oxygen were breathed. In the two patients in group I the increases are large and self-evident in Fig. 3; the gradient rose to 226 mm Hg in AND while breathing 41% oxygen, the expected behavior with a large shunt.

In the patients in group II there was a moderate increase in this gradient on enriched oxygen mixtures. For example, in BEL breathing 21, 24, and 29% oxygen, it was respectively 54, 58, and 84 mm Hg. In MIL on the other hand the increase was small. Breathing 14, 18, and 21% oxygen, the gradient was 12, 14, and 23 mm Hg. In group III the gradient behaved similarly during enrichment of the inspired gas with oxygen, except in those two cases, WAR and DOR, where the arterial point in the diagram rises till it lies on the oxygen dissociation curve. In these cases there is a small decrease in the alveolar arterial oxygen tension gradient as calculated here when the inspired gas is enriched with oxygen.

[1] A complete table of end capillary and alveolar oxygen tensions and of alveolar end capillary oxygen tension differences may be obtained by writing to W. A. Briscoe, Cornell University Medical College, New York 10021, asking for Table VIII of this publication.

TABLE VI

Distribution of Lung Volumes and Diffusing Capacity

Patient	Lung volumes: Functional residual capacity L_T	Lung volumes: Fast space L_1	Lung volumes: Slow space L_2	Lung volumes: Slow space fractional volume L_2/L_T	Diffusing capacity for oxygen: Fast space D_{L_1}	Diffusing capacity for oxygen: Slow space D_{L_2}	Diffusing capacity for oxygen: Total lung D_{LT}	Diffusing capacity for oxygen: Slow space fractional diffusing capacity D_{L_2}/D_{LT}	Diffusing capacity for oxygen: Riley's method D_L	Diffusing capacity for carbon monoxide: Predicted D_{LCO}	Diffusing capacity for carbon monoxide: Measured D_{LCO}	Fractional uptake of CO FU
	liters	*liters*	*liters*	%	*ml/min*	*mm*	*Hg*	%		*mm/min·mm*	*Hg*	%
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
Group I												
AND	2.4	1.6	0.7	32	3.6	0.1	3.7	3	3.5	14	8.0	27
WAL	1.1	0.1	1.0	91	3.6	0.5	4.1	12	3.7	12	3.3	16
Group II												
BEL	1.5	0.8	0.7	47	5.0	1.0	6.0	16	5.6		6.2	
BEN	2.5	1.3	1.2	47	4.6	1.3	5.9	22	5.3	22	5.2	23
PLI	2.4	0.8	1.6	68	5.8	0.9	6.7	13	6.2			
MIL	3.8	2.9	0.8	22	13.3	0.04	13.3	0.3	12.6	24	10.1	30
Group III												
MYE	4.2	2.6	1.5	36	6.5	0.3	6.8	4	6.1			
FIS	3.7	1.4	2.3	63	12.4	0.8	13.2	6	12.3			
WAR	1.4	0.2	1.2	83	5.6	0.9	6.5	14	6.2	16	4.9	26
DOR	2.6						10.1		9.3	15	7.8	34
Mean	2.6	1.3	1.2	54	6.7	0.6	7.6	10	7.1	17	6.6	24

In the fast space the alveolar end capillary oxygen tension gradient, while breathing the inspired mixture lowest in oxygen, varied from 35 mm Hg in BEL breathing 21% oxygen to as little as 8 mm Hg in PLI breathing 14% oxygen. This gradient became negligible while breathing enriched oxygen mixtures.

In the slow space the alveolar end capillary oxygen tension difference averages 54 mm Hg while breathing air. As can be seen by the horizontal distances between the triangles and the oxygen dissociation curve, this difference increases when the inspired gas is enriched with oxygen in all cases except WAR. This conflicts with the notion that when the diffusing capacity is low the gradient should be less when enriched oxygen mixtures are breathed. This concept, as has already been pointed out (1), is based on consideration of a homogeneous lung with a relatively high ventilation: perfusion ratio. The quantitative consideration of nonhomogeneous lungs containing a low diffusing capacity and a low ventilation: perfusion ratio shows that this direction of change is the opposite of that expected. This is an example of the rule that unhomogeneous lungs display basic qualitative as well as quantitative differences from homogeneous lungs.

DISCUSSION

The patients presented here are a variegated group. However, they are alike in that all were considered to have diffusion difficulty on the basis of their clinical picture and their roentgenographic abnormalities. Laboratory studies in alveolar capillary block characteristically show that vital capacity is reduced but bellows function is well preserved with only a slight reduction in forced expiratory volume. Arterial oxygen saturation is often normal at rest but falls on exercise. Arterial carbon dioxide tension tends to be low. The patients studied here on the whole conform with these typical findings. None of them had gross airway obstruction; the forced expiratory volume in 1 sec averaged 81% of the vital capacity. All but FIS had a reduction in vital capacity and total lung capacity. In most of these patients there was a significant reduction of the diffusing capacity for oxygen and carbon monoxide. In three patients, (MIL, FIS, and DOR), the reduction was only moderate. The diffusing capacity for oxygen was somewhat higher than that for carbon monoxide. There is a striking divergence in one patient (AND) in whom a low diffusing capacity for oxygen was coupled with a relatively high diffusing capacity for carbon

monoxide. At present, there is no explanation for the discrepancy.

These findings are consistent with those generally accepted in pulmonary sarcoidosis (16–18), systemic sclerosis (19–21), idiopathic interstitial pulmonary fibrosis (22–25), and other diseases with pulmonary fibrosis (26–29). A restrictive ventilatory defect has been the most frequently described early abnormality in these diseases. The diffusing capacity of the lung has been subnormal whatever the method used (18, 30, 31) and markedly lowered, not only in the advanced stages of these diseases but sometimes also in the earlier stages. As Wilson, Rodman, and Robin (32) pointed out, a significantly reduced diffusing capacity for carbon monoxide seems to be consistently present in systemic sclerosis when neither X-ray abnormalities within the lungs nor a reduction in vital capacity can be found. The relatively high diffusing capacity in MIL with eosoinophilic granuloma is in keeping with the findings of other authors in this disease (27, 33).

TABLE VII
Bohr Integrals and End Capillary Saturation

Patient	Inspired oxygen concentration F_{IO_2}	Bohr integral*		End capillary saturation		Mixed end capillary saturation Sc_{12}
		Fast space B_1	Slow space B_2	Fast space Sc_1	Slow space Sc_2	
	%	*mm Hg*$^{-1}$	*mm Hg*$^{-1}$	%	%	%
1	*2*	*3*	*4*	*5*	*6*	*7*
AND	41			99.8	74.8	95.1
	29			99.2	63.6	92.5
	21	0.67	0.10	97.6	54.1	89.5
WAL	29			99.3	88.6	96.2
	24			99.0	81.6	94.0
	21	0.59	0.21	97.8	75.9	91.5
BEL	29			99.3	89.3	96.8
	24			98.9	82.9	94.9
	21	0.47	0.29	95.3	76.3	90.6
BEN	24			99.0	86.4	95.0
	21	0.60	0.36	98.4	81.4	93.0
	18			93.6	72.9	87.0
PLI	21	1.31	0.27	97.9	84.9	92.4
	18			96.7	78.4	88.9
	14			91.3	66.4	80.7
MIL	21	1.13	0.04	98.1	76.6	96.6
	18			97.1	74.2	95.5
	14			91.5	67.5	89.8
MYE	24			98.6	85.5	96.0
	21	0.87	0.15	97.1	81.5	94.0
	18			94.3	76.3	90.7
FIS	21	1.00	0.19	97.9	85.4	95.0
	18			96.4	80.7	92.7
	14			86.4	67.4	82.0
WAR	21	1.12	0.38	98.0	96.5	97.5
	18			96.6	88.5	93.9
	14			86.2	72.6	81.7
DOR	21	1.07				96.6
	18					95.2
	14					84.3
Mean	21	0.86	0.22	97.6	79.2	93.7

* In each case, the Bohr integral figures are placed on the line giving findings while breathing air, though they also apply to studies breathing other oxygen mixtures.

The method of intrepretation used here has been described and discussed at length (1, 2, 4). It is tedious to perform and involves the use of several assumptions. The assumption that the arteriovenous oxygen saturation difference is 25% is made. In a previous study of the validity of this assumption, it was found that the assumption of a different value for the arteriovenous difference led to the derivation of very similar sets of values for the distribution of perfusion in the lung. Another assumption made is that the distribution of ventilation and perfusion between the slow and fast space is unchanged when the inspired gas is slightly enriched with oxygen. However, this is not necessary for the derivation of the results. If it were known that perfusion of the slow space increased by a certain fraction of its initial value when an enriched oxygen mixture was administered, then the distribution of perfusion could be determined while breathing both gases. Having no such data on the magnitude of changes in distribution in our patients, we have assumed there were none. Finally, the major assumption made is that the lung can be treated as if it contained only too differently functioning groups of alveoli plus an arteriovenous shunt. Any increase in this number of groups of alveoli would add greatly to the complexity of the presentation without concomitant advantages. Subject to these limitations the data presented here give an unusually complete description of the processes of oxygen transfer in these patients.

Group I (*Fig. 3*). Two of the cases had significant arterial oxygen unsaturation while breathing air (68.2 and 86.0% in AND and WAL, respectively). Right-to-left shunting made a major contribution to this as indicated by the degree to which the bar (arterial) lies below the circle (mixed end capillary) in Fig. 3. In both patients the effect of the shunt was augmented by low end capillary saturation of blood oxygenated in the slow space. However, the short distance between square and circle, relative to triangle and circle in AND indicates that this unsaturated blood flow was small in amount, in fact 10% of the cardiac output. The unsaturation of this blood was not due to a low ventilation: perfusion ratio, 1.08, but to a very low Bohr integral, 0.10, in the slow space. In WAL, a lesser degree of unsaturation in the slow space was due to the combination of a moderately low ventilation: perfusion ratio, 0.65, with a low Bohr integral, 0.21 mm Hg^{-1} (normal value: 1.5 mm Hg^{-1}). These two patients had the lowest values

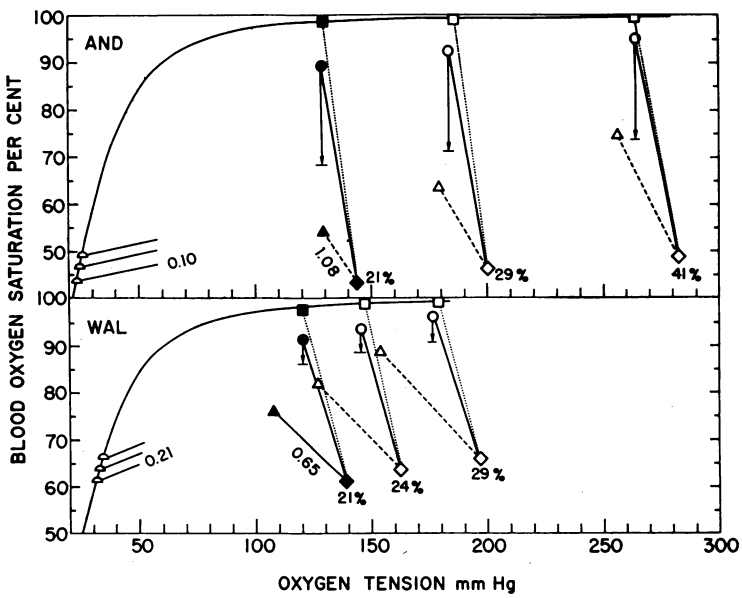


FIGURE 3 Results in two patients with significant arteriovenous shunting. Symbols are the same as in Fig. 2. The inspired oxygen concentration per cent is indicated under each inspired point (diamond), and the values of the Bohr integral (left) and ventilation:perfusion ratio (right) in the slow space are indicated under the appropriate isopleth. Squares, triangles, and circles respectively indicated blood oxygen saturation and alveolar oxygen tension in the fast space, the slow space, and in mixed blood and alveolar gas from these spaces. Horizontal bars indicate arterial oxygen saturations.

for the oxygen diffusing capacity (3.7 and 4.1 ml of O_2/min·mm Hg). These values lie in a critical range in which in an ideal homogeneous lung breathing air at rest arterial oxygen unsaturation may or may not occur depending on small changes in total diffusing capacity, in total alveolar ventilation, and in the oxygen consumption of the body. Indeed with the measured values of these entities, arterial oxygen saturations would have been 90 and 96% in AND and WAL were it not for the shunt and the uneven distribution of ventilation, perfusion, and diffusing capacity between alveoli.

Group II (*Fig. 4*). Unevenness of ventilation:perfusion ratios made a significant contribution to arterial oxygen unsaturation breathing air or mixtures containing less oxygen in three of the cases (BEL, BEN, and PLI). They were alike in having similar values for total diffusing capacity (5.9, 6.0, and 6.7 ml/min·mm Hg). In this group of four patients, values of total diffusing capacity, total alveolar ventilation, and oxygen consumption were such that if distribution had been ideal the oxygen saturation of blood in all alveoli and in the brachial artery would have been 94% in BEL and 97 or 98% in the other three patients, according to our calculations. Insofar as arterial oxygen saturation is reduced this reduction is due to the inhomogeneity both of the ventilation:perfusion ratios and of the Bohr integrals in these patients, not to an inadequate total diffusing capacity.

It is not easy in these patients to separate the effects of maldistribution of ventilation:perfusion ratios from those of maldistribution of Bohr integrals. However, it is possible with the aid of Fig. 4 to assess the disturbances within the slow space. The arterial unsaturation (89.8%) in BEL is caused by the unsaturation of blood oxygenated in the slow space (76.3%) due to a low Bohr integral and a low ventilation:perfusion ratio therein. The shunt of 3% of the cardiac output does not play a significant role. In BEN a higher end capillary saturation (81.4%) and hence a higher arterial saturation (93%) is attained because the Bohr integral and ventilation:perfusion ratio in the slow space are greater than they are in BEL as shown by the steepness of both isopleths in Fig. 4. In PLI nearly the same arterial oxygen saturation as in BEN is maintained, despite a lower Bohr integral, by virtue of a higher saturation of blood in the slow space (84.9%) due to a much higher ventilation:perfusion ratio which is only slightly reduced below normal. This is the case despite a higher fractional perfusion of the slow space as shown by the relative distance of square and triangle from the circle.

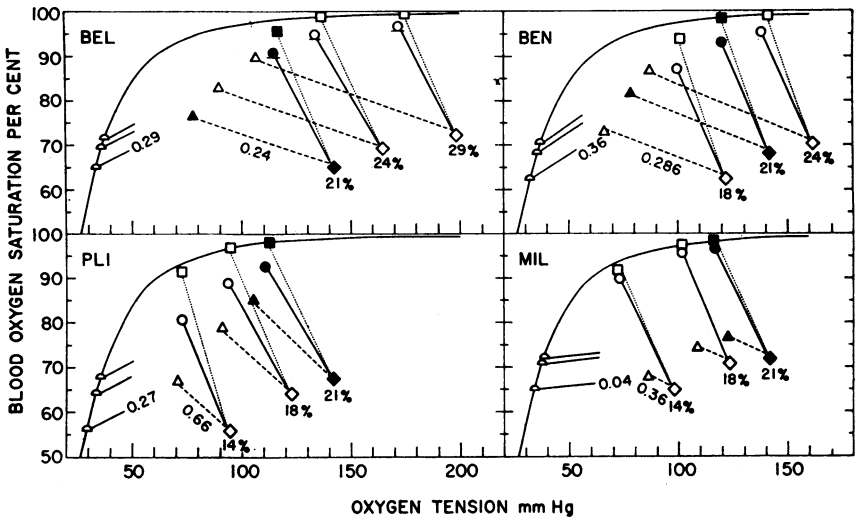


FIGURE 4 Results in four patients with inequalities both in ventilation: perfusion ratios and in Bohr integrals within the lung. Symbols are the same as in Fig. 3.

Thus in these three different patients a low ventilation: perfusion ratio, a low Bohr integral, and a large relative perfusion of the slow space contribute in varying degrees to the reduction of arterial oxygen saturation below its ideal value, about 97%, while breathing air. In MIL arterial blood was nearly fully saturated (96.6%) with oxygen. The blood oxygenated in the slow space was markedly unsaturated (76.6%) due to a very low Bohr integral and a low ventilation: perfusion ratio. It thus almost functioned as a shunt but its blood flow was small, only 7% of the cardiac output, as indicated by the relatively large distance between triangle and circle in Fig. 4. It therefore contributed little to mixed arterial blood. However, in this patient as in the other three patients in this group, maldistribution of ventilation: perfusion ratios, as well as maldistribution of Bohr integrals, were both present.

Group III (Fig. 5). There was virtually no unevenness of ventilation: perfusion ratios between the fast and slow spaces with both having ratios between 0.94

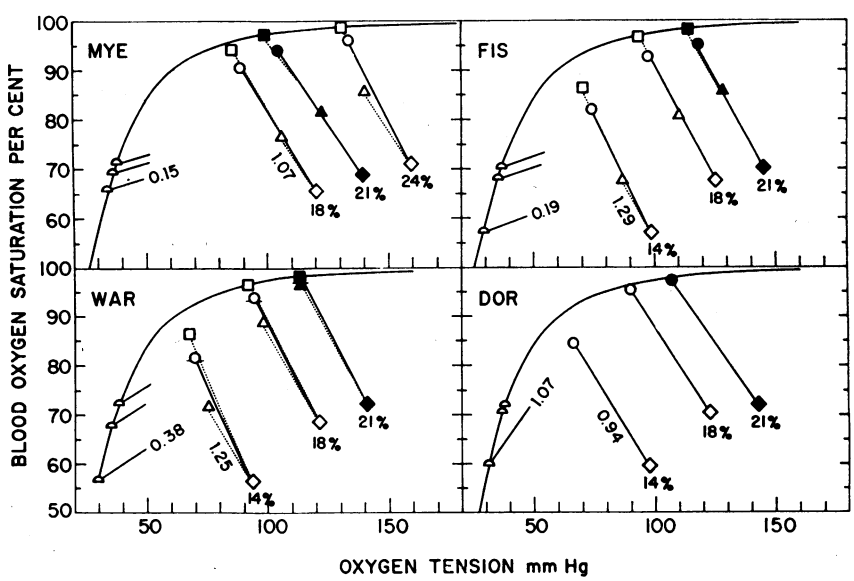
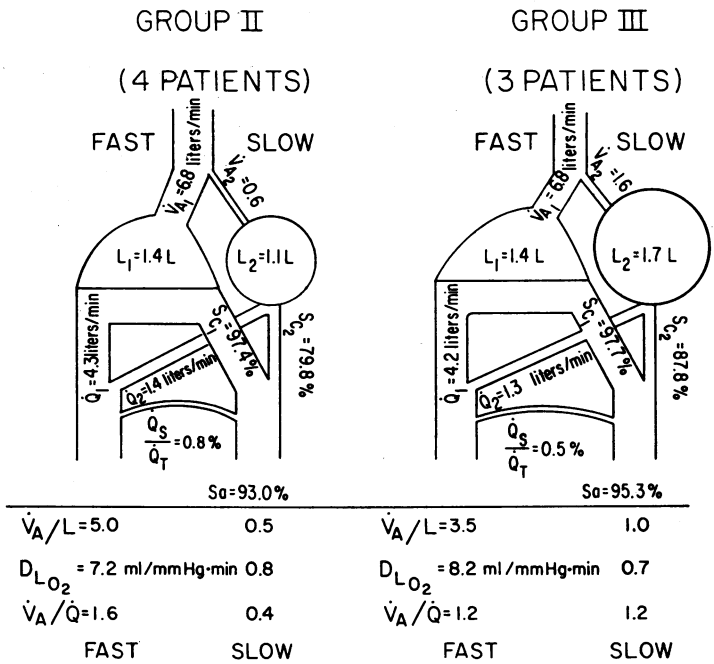


FIGURE 5 Results in four patients with no inequalities in ventilation: perfusion ratios within the lung. Three of them have inequalities in Bohr integral isopleths. Symbols are the same as in Figs. 3 and 4.



$\dot{V}_A/L$=5.0	0.5	$\dot{V}_A/L$=3.5	1.0
$D_{L_{O_2}}$ = 7.2 ml/mmHg·min	0.8	$D_{L_{O_2}}$ = 8.2 ml/mmHg·min	0.7
$\dot{V}_A/\dot{Q}$=1.6	0.4	$\dot{V}_A/\dot{Q}$=1.2	1.2
FAST	SLOW	FAST	SLOW

FIGURE 6 Diagram showing differences between mean values in groups II and III. The width of airways and blood vessels in proportional to the flow of air or blood through them. The area of the balloons is proportional to alveolar volume. The length of contact between air spaces and blood vessels is proportional to diffusing capacity. The subscripts 1 and 2 are used in symbols to designate fast and slow spaces respectively. $\dot{Q}s/\dot{Q}t$ is shunt flow expressed as a percentage of cardiac output. $\dot{V}_A$, L, and $\dot{Q}$ are respectively alveolar ventilation, lung volume, and blood flow. Sc and Sa are end capillary and arterial oxygen saturations. In the tabular portion of the figure $\dot{V}_A/L$ is alveolar ventilation per minute per unit lung volume, D_{LO_2} is diffusing capacity and $\dot{V}_A/\dot{Q}$ is ventilation:perfusion ratio.

and 1.29. This is illustrated in Fig. 5 by the nearly identical slopes of the ventilation:perfusion ratio isopleths for the fast space (squares), the slow space (triangles), and for the lung as a whole (circles). Moreover, in the fourth patient in this group (DOR), the data are compatible with a homogeneous lung in which not only the ventilation:perfusion ratio but also the Bohr integral and $D_L:\dot{Q}$ ratio are the same in all alveoli. This is a rare occurrence.

The total diffusing capacity of these last four patients varied considerably. It was 6.5 ml/min·mm Hg in WAR, who had pulmonary sarcoidosis in an advanced stage, and 10.1 ml/min·mm Hg in DOR, who had systemic sclerosis with roentgenological evidence of pulmonary fibrosis. The other patients, FIS and MYE, both had acute glomerulonephritis with the typical roentgenographic signs of pulmonary interestitial edema (34). Their total diffusing capacities were 13.2 and 6.5 ml/min·mm Hg. The oxygen saturation was more than 94% in all four of these patients while breathing air. It is well known that diffusion difficulty is compatible with a normal arterial oxygen saturation at rest breathing air. Only two of Finley's 10 cases of diffusion difficulty (35), only two of Wilson's 19 cases of scleroderma (32), six of Austrian's 12 cases (6), none of Svanborg's 37 cases with pulmonary sarcoidosis (18), and five out of 31 cases with alveolar-capillary block syndrome measured by Marks, Cugell, Cadigan, and Gaensler (30) had a saturation below 92% at rest. In most of these case the diffusing capacity was more or less reduced.

In three out of four patients in this third group, diffusing capacity was different in different lung spaces. In MYE the blood oxygenated at a normal ventilation:perfusion ratio in the slow space was only 82% saturated while breathing air because of the low diffusing capacity in that space. This reduced the mixed arterial oxygen saturation below what it would have been if the Bohr integral had been the same everywhere. For example, in MYE with a total diffusing capacity of 6.8 ml

of O_2/mm Hg·min and a total cardiac output of 4700 ml/min, the overall Bohr integral is $(6.8 \times 100)/(4700 \times 0.2) = 0.72$. With this Bohr integral and an overall ventilation: perfusion ratio, $\dot{V}_{AT}:\dot{Q}_T$, of 0.97 in a homogeneous lung, arterial oxygen saturation would have been 96.7%, 2.7% higher than the observed value.

Differences between groups II and III. The findings in the four patients in the second group and in three of the patients in the third group is given in Fig. 6.

There are several characteristics which both groups have in common. Total alveolar ventilation is slightly increased, i.e., greater than cardiac output. Total alveolar ventilation, cardiac output, distribution of blood flow between the fast and slow spaces, and the magnitude of the shunt are about the same in the two groups. However, the following differences are shown. The slow space alveolar ventilation in group II is relatively small, the ventilation per minute being about half the volume of the space, while in group III, the slow space ventilation per minute is larger and nearly equal to the volume of the slow space. This accompanies substantial differences with regard to ventilation: perfusion ratios. Thus, there is a considerable uneveness of ventilation: perfusion ratios in group II but not in group III. The distribution of diffusing capacity is also unequal but similar in both groups. In both, the diffusing capacities of the slow spaces are substantially less than expected in spaces occupying about half the lung volume. The combination of uneveness of ventilation: perfusion ratio and diffusing capacity–perfusion ratio causes a greater degree of unsaturation of end capillary blood oxygenated in the slow space in group II than in group III. This group appears to be the first in which disturbance of blood-gas exchange by $D_L:\dot{Q}$ maldistribution without $\dot{V}_A:\dot{Q}$ maldistribution has been documented in man.

In both patients with pulmonary edema (FIS and MYE), the reduction if any in arterial oxygen saturation at rest breathing air was small. However, as has been reported by Arndt, Baltzer, and Löhr (36), much greater disturbances in arterial oxygen tension and saturation are found in patients with chronic renal failure and pulmonary interstitial edema. In their patients, some of whom were young men and hence not likely to have ventilation: perfusion ratio disturbances due to obstructive airway disease, an inverse correlation was found between the severity of the edema, as judged by the roentgenological evidence, and the arterial oxygen tension. It was suggested that the thickening of the pulmonary membrane due to accumulation of fluid, found by electron microscopy by Meessen and Schultz (37), was the cause of the decrease in the arterial oxygen tension, the more so, since an increase in arterial oxygen tension was observed immediately after excess body fluid had been removed by hemodialysis. Meessen and Schultz showed that the thickness of the membrane may increase fourfold before fluid enters the alveoli during progression from the interstitial to the intra-alveolar phase of pulmonary edema. Staub, Hitoschi, and Pearce (38) recently found a threefold increase of the average membrane thickness in severe experimental edema. They do not expect this to contribute significantly to a change in the arterial blood oxygen saturation although it would cause some decrease in the measured diffusing capacity. In order to decrease arterial oxygen saturation while breathing air at rest by diffusion difficulty alone in a homogeneous lung, it is necessary that the diffusing capacity be greatly reduced. However, reduction of diffusing capacity in less ventilated parts of the lung is capable of interfering with oxygen transfer even though total diffusing capacity is high.

Significance of reduced diffusing capacity. There has been much discussion as to the real nature of defective function in patients with a low diffusing capacity. Thus, in patients with obstructive pulmonary disease, Hatzfeld, Wiener, and Briscoe (39) have recently emphasized that uneven ventilation–diffusing capacity ratios contribute largely to the reduced apparent diffusing capacity measured by conventional methods. In patients without obstructive disease, Sharp, Sweany, and van Lith (40) suggested that separation of $D_L:\dot{Q}$ and $\dot{V}_A:\dot{Q}$ disturbances may have little physiologic meaning in many types of diffuse lung disease since they probably could not occur separately in the absence of coexisting airway obstruction. This may apply to the patients in group II. However, it clearly does not apply to the patients in group III. In contrast to Sharp et al., Finley, Swenson, and Comroe (35) maintained that in patients with alveolar capillary block syndrome the mechanism which reduces arterial saturation is not an impediment to the process of diffusion, but instead, is solely one of unevenness of ventilation: perfusion relationships. They stated that "the usual concept, that thickened alveolar capillary membranes cause arterial hypoxemia at rest because of impairment of oxygen diffusion, should be modified." This in itself now needs modification. In the four patients in group II, unevenness of ventilation: perfusion ratios occurred but it was not the only cause of hypoxemia since its effects were added to those of the disturbances in the diffusing capacity. However, in the four patients in group III, there was virtually no unevenness of ventilation: perfusion ratios and the only disturbances affecting blood-gas transfer lay in some reduction of the total diffusing capacity and in its uneven distribution relative to blood flow. Thus, the present study shows that blood-gas disturbance in disease can in fact be caused purely by reduction of the diffusing capacity especially if this change is distributed unevenly within the lung. However, this has, in our cases as in

those of Finley et al., caused only a mild degree of arterial oxygen unsaturation. Moreover, it is of interest that two of these cases suffered from interestitial pulmonary edema which according to Schermuly, Nieth, and Biskamp (41) is a frequent complication of renal disease, as it was in these cases. These seem to be the first cases with pulmonary interstitial edema in whom a pure form of diffusion difficulty could be detected by means of a somewhat sophisticated yet highly applicable new method.

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