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THE CAUSE OF ARTERIAL HYPOXEMIA AT REST IN PATIENTS WITH "ALVEOLAR–CAPILLARY BLOCK SYNDROME" *

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Hypoxemia in patients with "alveolar-capillary block syndrome" is believed to be due to a barrier to the diffusion of oxygen caused by thickened alveolar and capillary membranes (1, 2). Theoretical considerations indicate that thickened membranes should not result in a Po_2 difference between alveolar gas and pulmonary capillary blood when patients with impaired diffusion breathe 100 per cent O_2. Inhalation of O_2, therefore, should always correct hypoxemia in patients in whom a barrier to diffusion is the only defect. The reasoning is as follows: inhalation of O_2 at sea level raises alveolar Po_2 to about 670 mm Hg, and the large initial Po_2 difference between alveolar gas and blood entering the pulmonary capillaries (600 to 630 mm Hg) causes a rapid diffusion of O_2 across even thickened alveolar-capillary membranes and prompt saturation of the hemoglobin (3, 4). After hemoglobin is saturated with O_2, the O_2 behaves like an inert gas and enters the blood only in physical solution and almost instantaneously, so that blood leaving the pulmonary capillaries is in equilibrium with the Po_2 in the alveolar gas.

Our original plan was to test this theory by measuring directly the arterial Po_2 of patients with "pure" alveolar-capillary block syndrome while they were breathing pure O_2. If the theory is correct (and if pulmonary artery-to-vein shunts are not increased in these patients) the arterial Po_2 should equal that of healthy subjects breathing pure O_2 (620 to 650 mm Hg). On analysis of our data we realized that the arterial hypoxemia in patients with alveolar-capillary block syndrome was due to uneven ventilation-blood flow relationships and increased vein-to-artery shunts rather than to a barrier to diffusion of O_2. This led us to conclude that pulmonary disease rarely alters alveolar-capillary membranes uniformly throughout the lung and, therefore, uneven ventilation-blood flow relationships must occur. Nonuniform distribution of gas and blood, we believe, represents an important cause of arterial hypoxemia in patients with "impaired diffusion."

SUBJECTS AND METHODS

We studied 11 patients with diseases in which the primary defect was alveolar-capillary block (Table I). The diagnosis was made on clinical grounds, X-ray and pulmonary function tests in all, by lung biopsy in four (E.S., J.R., O.B., P.S.), by lymph node biopsy in two (J.W., B.F.), and at autopsy in one (J.B.). The results of pulmonary function studies are shown in Table II. All the patients had slight to marked reduction in vital capacity and total lung capacity, normal or low arterial blood Pco_2, normal 7-minute nitrogen washout (5), normal or elevated alveolar ventilation, decreased diffusing capacity as determined by the single-breath CO test (6), and maximal flow rates considerably in excess of those characteristic of obstructive pulmonary disease such as asthma or emphysema. Pulmonary compliance was measured in four; in all of these it was below normal.

Each patient was then studied by the technique described by Finley (7) for the determination of uneven ventilation-blood flow distribution in the lungs. Briefly, the technique consists of *a*) continuous measurement of arterial Po_2 during nitrogen washout by a Clark O_2 electrode inserted in a flow-through cuvet, and *b*) simultaneous measurement of P_{N_2} and Pco_2 in inspired and expired gas at the mouthpiece. From these measurements the (A-a) Po_2 difference due to "absolute" shunt can be calculated (4), and curves can be drawn which describe the ventilation-blood flow relationship through well and poorly ventilated regions of the lungs. We calculated the mixed capillary O_2 saturation during breathing of air, assuming that the distribution of ventilation and blood flow through the lungs was the same as that calculated during O_2 breathing, and that the cardiac output remained the same. This calculation is similar to that made by Briscoe (8) for patients with emphysema.

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TABLE I

Clinical data

Patient	Sex	Age	Ht	Wt	BSA	Clin. diag.*	X-ray diagnosis	Pathol. diagnosis
			cm	*kg*	*m²*			
J.W.	♂	44	158	65.0	1.66	PS	Bilat. fibronod. densities	Noncaseating granuloma (lymph node)
F.F.	♀	44	162	52.6	1.55	H-R syn.	Diffuse bilat. infiltrates	
E.S.	♀	53	168	77.0	1.82	PIF	Diffuse nod. infiltrates	Patchy interstit. fibrosis, atelectasis†
J.R.	♂	43	165	75.0	1.82	H-R syn.	Bilat. pulm. fibrosis	Interstit. fibrosis†
R.R.	♂	61	169	74.6	1.86	PIF	Diffuse nod. changes	
B.F.	♀	23	167	50.8	1.55	PS	Diffuse patchy infiltrates	Noncaseating granuloma (lymph node)
H.S.	♀	35	164	58.2	1.63	PIF	Retic. densities throughout	
O.B.	♀	46	161	58.0	1.61	PIF	Diffuse nod. densities	Interstit. fibrosis, inflammation†
P.S.	♂	76	168	65.5	1.75	PIF	Diffuse infiltrates	Interstit. fibrosis†
A.W.	♂	70	168	79.2	1.89	H-R syn.	Extensive bilat. infiltrates	
J.B.	♀	21	165	56.9	1.62	CVD	Bilat. patchy infiltrates	Extensive interstit. fibrosis‡

* PS = pulmonary sarcoidosis; H-R syn. = Hamman-Rich syndrome; PIF = pulmonary interstitial fibrosis; CVD = collagen vascular disease.
† Based on lung biopsy.
‡ Based on postmortem examination.

The saturation drop due to shunts during inhalation of O_2 was then subtracted to give the calculated arterial saturation. This final value represents the arterial saturation resulting only from unevenness of ventilation and perfusion and vein-to-artery shunts in the lung. In Patients A.W. and J.B. this calculation was carried out only during the initial study and not late in the course of their illness (the calculation of unevenness of pulmonary blood flow in the presence of large pulmonary artery-to-vein shunts may be inaccurate).

TABLE II

Pulmonary function data *

Patient	VC	TLC	SBo_2	7-min N_2 washout	PDS/VT	VA	$Paco_2$	DCO	MEFR	MIFR	CL
	% predict.		*Δ% N_2*	*% N_2*	*ml/ml*	*L/min*	*mm Hg*	*% predict.*	*L/min*	*L/min*	*L/cm H_2O*
J.W.	74	73	4.0	1.0	0.34	6.8	32	58	136	333	
F.F.	54	44	11.0	2.0	0.53	3.1	42	54	214	147	0.02
E.S.	78	83	5.0	1.2	0.33	4.3	35	34	120	125	
J.R.	70	80	2.5	2.2	0.42	5.7	40	23	375	250	0.06
R.R.	99	75	3.5	1.4	0.50	4.3	30	49	330	273	
B.F.	43	44	5.5	1.0	0.35	5.8	34	52	330	250	
H.S.	71	68	2.5	0.9	0.41	4.4	32	58	107	136	0.07
O.B.	50	57	5.5	1.7	0.41	3.7	36	53	188	150	
P.S.	56	57	7.0	1.2			39	32	115	107	0.07
A.W.	35	51	6.0	0.5	0.59	5.3	28	5	250	230	
J.B.	93	93	1.7	0.9	0.25	4.6	34	74	300	250	

* VC = vital capacity; TLC = total lung capacity; SBo_2 = rise in N_2 concentration between 750 and 1,250 ml expired after a single breath of pure O_2; PDS = physiological dead space; VT = tidal volume; VA = alveolar ventilation; $Paco_2$ = arterial CO_2 tension; DCO = breath-holding diffusing capacity for CO at rest; MEFR and MIFR = maximal expiratory and inspiratory flow rates; CL = lung compliance.

TABLE III

*Maximal arterial blood O_2 tension (mm Hg) during inhalation of O_2**

Patient	P_B	P_{ACO_2}	P_{AO_2}	P_{aO_2}	(A-a)P_{O_2}
J.W.	744	32	661	563	98
F.F.	745	25	669	627	42
E.S.	747	30	666	644	22
J.R.	746	39	656	639	17
R.R.	750	34	665	660	5
B.F.	743	35	657	610	47
H.S.	745	26	668	585	83
O.B.	747	33	663	581	82
P.S.	742	29	662	598	64
A.W.	743	31	661	630	31
	743	23	669	262	407
J.B.	747	34	662	624	38
	745	60	634	40	594

* P_B = barometric pressure; P_{ACO_2} = alveolar CO_2 tension; P_{AO_2} = alveolar O_2 tension; P_{aO_2} = arterial O_2 tension; (A-a) P_{O_2} = alveolar-to-arterial O_2 tension difference. Second values for A.W. and J.B. represent studies late in the disease. P_{H_2O} was assumed to be 47 mm Hg in all cases; P_{AO_2} is calculated from measured P_B, P_{AN_2} (4 mm in all cases), P_{ACO_2} and assumed P_{H_2O}.

RESULTS

The highest arterial blood P_{O_2} for each of these patients during the inhalation of O_2 is shown in Table III. Compared with the arterial P_{O_2} of normal subjects during pure O_2 breathing (8), the (A-a) P_{O_2} difference is within normal limits in Patients F.F., E.S., J.R., R.R., B.F., A.W., and J.B when studied initially (the second values for AW. and J.B. represent studies late in the course of their disease). This proves that the theoretical considerations are indeed correct; i.e., when the P_{O_2} is increased to high levels in the alveolar gas, there is no (A-a) P_{O_2} difference except that due to normal venous admixture (pulmonary artery-to-vein shunts, bronchial and thebesian venous drainage into the postpulmonary capillary circulation).

The data show, in addition, that some patients with alveolar-capillary block have more than the normal flow through anatomic shunts (J.W., H.S., O.B., P.S.). In the two subjects who later succumbed to their disease (A.W. and J.B.), there was a marked increase in the flow through shunts. We do not know whether this is due to actual development of pulmonary artery-to-vein shunts or to continued blood flow to regions with no ventilation (obstructed airways).

Of even greater interest is that when 10 of the 11 patients were breathing air their measured arterial O_2 saturations agreed well with those calculated on the basis of uneven ventilation to blood flow ratios (Table IV); this indicates that their anoxemia can be explained entirely on the basis of uneven distribution without invoking the factor of impaired diffusion. Late in the disease process, venous admixture became the dominant factor in causing arterial hypoxemia. The single-breath O_2 test (9) was abnormal in 8 of the 11 patients, which suggests uneven distribution of ventilation in time as well as in regions of the lung. This asynchrony of emptying reflects an uneven distribution of alveolar compliances and resistances, undoubtedly related to uneven dis-

TABLE IV

*Fractional ventilation and perfusion of well and poorly ventilated regions **

	Well ventilated region				Poorly Ventilated Region							
Patient	$\%\dot{V}_A$	$\%\dot{Q}_c$	$\dot{V}_A/\dot{Q}_c$	Sc_{O_2}	$\%\dot{V}_A$	$\%\dot{Q}_c$	$\dot{V}_A/\dot{Q}_c$	Sc_{O_2}	Calc. Sc_{O_2} (mixed)	$Sc_{O_2}-Sa_{O_2}$	Calc. Sa_{O_2}	Observed Sa_{O_2}
Normal	0.60	0.60	1.00	97.5	0.40	0.40	1.00	97.5	97.5	0.5	97.0	97.0
J.W.	0.54	0.15	3.00	99.0	0.46	0.85	0.50	95.0	96.0	2.5	93.5	94.0
F.F.	0.91	0.53	1.45	98.0	0.09	0.47	0.20	86.0	93.5	0.5	93.0	95.0
E.S.	0.87	0.60	1.20	98.0	0.13	0.40	0.25	88.0	92.0	1.5	90.5	91.0
J.R.	0.73	0.70	0.85	97.5	0.27	0.30	0.75	96.5	97.0	0.5	96.5	97.0
R.R.	0.73	0.68	0.90	97.5	0.27	0.32	0.70	96.0	97.0	0.0	97.0	97.0
B.F.	0.92	0.87	0.90	97.5	0.08	0.13	0.55	95.0	96.5	1.5	95.0	93.5
H.S.	0.73	0.25	2.45	98.5	0.27	0.75	0.30	91.0	93.5	1.5	92.0	94.0
O.B.	0.62	0.32	1.70	98.0	0.38	0.68	0.50	95.0	96.5	1.5	95.0	95.0
P.S.	0.91	0.76	1.00	97.5	0.09	0.24	0.30	91.0	95.5	1.5	94.0	91.0
A.W.	0.85	0.28	3.00	99.0	0.20	0.72	0.27	89.0	92.5	0.5	92.0	93.0
J.B.	0.65	0.35	1.00	97.5	0.65	0.35	1.00	97.5	97.5	0.5	97.0	99.0

* $\dot{V}_A$ = alveolar ventilation to region; $\dot{Q}c$ = pulmonary capillary blood flow to region; Sc_{O_2} = saturation of the end-capillary blood leaving region; Sc_{O_2} (mixed) = saturation of the mixed end-capillary blood; $Sc_{O_2}-Sa_{O_2}$ = difference in saturation between mixed end-capillary blood and arterial blood due to anatomical shunts.

tribution of thickening of alveolar-capillary membranes.

DISCUSSION

It has recently been pointed out that patients with alveolar-capillary block may have considerable overventilation of some regions of the lung (10) and overperfusion of others (11). Our data suggest that this unequal distribution of ventilation and perfusion and venous admixture account for the hypoxemia of these patients at rest. Because of this, we believe that the usual concept that thickened alveolar-capillary membranes cause arterial hypoxemia at rest because of impairment of O_2 diffusion should be modified.

To illustrate this, we have calculated the effect on the O_2 diffusing capacity, D_{LO_2}, of increasing the thickness of the alveolar-capillary membranes. We used the equation (12)

$$\frac{1}{D_{LO_2}} = \frac{1}{D_M} + \frac{1}{\theta V_c}$$

where D_M is the diffusing capacity of the membrane, θ is the oxyhemoglobin reaction rate constant, and V_c is the pulmonary capillary blood volume. This equation allows us to calculate the effect of increasing the thickness of the alveolar-capillary membranes, assuming that the diffusing coefficient of the membranes remains unchanged when their thickness is increased. Normally the resistance to diffusion through the membranes is about equal to the resistance to diffusion offered by the red blood cell. If D_{LO_2} equals 20 ml per minute per mm Hg P_{O_2}, and if we assume that the membrane is 1 μ thick, then doubling the thickness would halve D_M, according to Fick's first law (12). This would result in decreasing D_{LO_2} to 13.3 ml per minute per mm Hg P_{O_2}. If θV_c is decreased correspondingly, D_{LO_2} would be reduced to 10 ml per minute per mm Hg P_{O_2}. The effect on D_{LO_2} of increasing membrane thickness, with θV_c constant, is shown graphically by the hyperbolic curve of Figure 1. These values are deduced from data of the kinetics of the reaction $Hb + O_2 \rightleftharpoons HbO_2$ for human erythrocytes at various levels of O_2 saturation when applied to a forward type of Bohr integration (13). The calculations indicate that there is a large safety factor for the diffusion of O_2 (14); D_M can be reduced to one-sixth to one-eighth of its normal

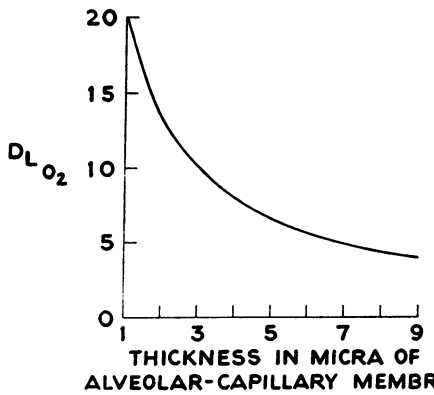

FIG. 1. GRAPH SHOWING RELATIONSHIP BETWEEN D_{LO_2} AND THICKNESS OF ALVEOLAR CAPILLARY MEMBRANES.

value before a measurable (1 mm Hg) (A-a) P_{O_2} difference due to impaired diffusion occurs, all else kept constant.

It is important to consider what increasing the thickness of the membrane to 6 to 8 μ does to the resting volume of alveoli. The normal range of alveolar diameter is 60 to 300 μ (15). The reduction in volume would be approximately 60 per cent for the smaller alveoli and 20 per cent for those in the middle range. If the alveolar-capillary membranes were not thickened uniformly, some of the smaller alveoli could be completely filled, and their capillaries might act as pulmonary artery-to-vein shunts (16).

Uneven thickening of alveolar-capillary membranes would have important effects on the distribution of ventilation. Compliance of fibrotic alveoli would be decreased because of stiffening of their walls and because of their reduced size (17). Both factors would reduce the ventilation to the affected alveoli.

If the perfusion of these affected alveoli was not reduced proportionately, hypoxemia of the arterial blood would occur because of uneven ventilation-perfusion relationships and venous admixture. The data presented here suggest that this is the case.

An analysis of the course of O_2 uptake in the pulmonary capillaries by the method of Staub, Bishop and Forster (13), which is based on single-breath Pco data and the reaction kinetics of O_2 and red blood cells, agrees with the present conclusion. They calculated that, under a wide variety of conditions in healthy subjects and in

patients with impaired diffusion, no significant desaturation (alveolar to end-capillary Po_2 difference), due to diffusion, results.

SUMMARY

1. Hypoxemia in 11 patients with a clinical diagnosis of alveolar-capillary block syndrome could be explained on the basis of uneven distribution of ventilation in relation to blood flow and pulmonary artery-to-vein shunting; the latter factor became more important late in the course of the illness.

2. Uneven changes in compliance of alveoli could account for the uneven ventilation.

3. The increase in pulmonary artery-to-vein shunting could result from the complete filling of some air spaces with the thickened alveolar capillary membranes.

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