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VENOUS ADMIXTURE TO THE PULMONARY CIRCULATION IN HUMAN SUBJECTS BREATHING 100 PER CENT OXYGEN *

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At any given time, the alveolar-arterial oxygen partial pressure difference (AaD) may be due to one or more of the three following mechanisms (1–5): *1*) failure of pulmonary capillary blood to come to complete equilibrium with alveolar gas; *2*) uneven ventilation perfusion ratios; and *3*) admixture of venous blood by direct shunting.

The first mechanism causes the diffusion component of the AaD, relating to diffusion across the alveolar-capillary membrane as well as chemical reaction rates of oxygen with hemoglobin (6, 7). The second mechanism accounts for the "distribution" component, and the third is spoken of as the "true," "pure," or "anatomical" shunt, or the "direct" venous admixture component.

When the inspired oxygen tension is low, as at high altitude or during breathing of hypoxic mixtures, particularly if either condition is combined with exercise, the diffusion component increases, whereas those due to direct venous admixture and to uneven ventilation-perfusion ratios diminish. These changes are used to determine the pulmonary diffusing capacity for oxygen (1–3, 8). On the other hand, breathing 100% oxygen increases the AaD due to direct venous-arterial shunting, and virtually eliminates all other components (9).

The role of diffusion impairment in the causation of arterial hypoxemia has been recently reevaluated (10), and a number of newer approaches have permitted a more precise definition of the distribution of ventilation-perfusion ratios and of its importance in gas exchange (11–15). There have been relatively few reports, however, on the incidence and magnitude of increased "direct" venous admixture in pulmonary disease (10, 16–19). The paucity of such reports has probably been due to the lack of practical techniques for the accurate measurement of blood oxygen tension at high levels.

This paper has two purposes. The first is to report on the size and composition of the AaD, measured during air and during oxygen breathing in 6 normal subjects, 15 patients with pulmonary emphysema, 14 with diffuse alveolar-capillary disease, and 12 markedly obese patients. The second is to present conclusions, derived from these results, on the role of "true" shunt in the pathogenesis of arterial hypoxemia in these patients.

METHODS

Patients. Three groups of patients and one of normal controls were examined. Group I consisted of 15 patients with clinical, X-ray, and laboratory findings of obstructive pulmonary emphysema. Group II comprised 14 patients with pulmonary diseases that appeared to involve primarily the alveolar-capillary area. All showed X-ray evidence of diffuse pulmonary infiltration or fibrosis and mild to severe impairment of lung function, including restriction of the vital capacity without spirographic evidence of airway obstructive disease, and lowering of resting arterial blood P_{O_2} with a normal or low P_{CO_2}. The etiologic diagnoses, confirmed by lung or lymph node biopsy in four patients and by bacteriologic examination in two were: sarcoidosis (seven patients), tuberculosis (two), disseminated lupus erythematosus (one), pulmonary alveolar proteinosis (one), Hand-Schuller-Christian disease (one), and undetermined causes (two). Group III was composed of 12 obese patients who otherwise demonstrated no evidence of cardiopulmonary disease. Their mean body weight was 112 kg; mean height, 170 cm; and mean body surface area, 2.22 m^2. The normal controls were healthy male and female laboratory personnel and student nurses, ranging in age from 18 to 34 years.

Procedure and calculations. The subjects, resting and recumbent, with a noseclip applied, breathed through a tightly fitting rubber mouthpiece attached to a two-way plastic valve having a dead space of 40 ml. Arterial blood and expired gas were sampled simultaneously during a

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period of room air breathing, and again after the subjects had breathed nearly pure oxygen, delivered on demand, usually for 20 to 30 minutes, but always for at least 10 minutes. The air and oxygen studies were performed within 1 hour.

Expired ventilation was recorded on a Tissot spirometer. Inspired and expired gases were analyzed for oxygen and carbon dioxide by the Scholander apparatus (20), and expired gas nitrogen was measured by the nitrogen meter. Arterial blood carbon dioxide tension (Pa_{CO_2}) was determined by the bubble equilibration technique of Riley, Campbell, and Shepard (21), or by the electrode of Severinghaus and Bradley (22). Arterial blood oxygen tension (Pa_{CO_2}) was measured *in vivo*, or *in vitro* at 37.5°C by a needle electrode (23); when applicable, it was also measured by the Riley method (21).

Calculation of venous admixture was based on the equation:

$$\dot{Q}_{va}/\dot{Q}_t = (C_{\dot{c}} - C_a)/(C_{\dot{c}} - C_{\bar{v}}), \qquad [1]$$

where $\dot{Q}_{va}/\dot{Q}_t$ is the venous admixture ratio of the total pulmonary blood flow, and $C_{\dot{c}}$, C_a, and $C_{\bar{v}}$ are the oxygen content in pulmonary end-capillary, systemic arterial, and mixed venous blood, respectively. (For simpler nomenclature, the subscript O_2 has been omitted, where possible without ambiguity, from this equation and those to follow.)

Substituting oxygen saturation (S) for oxygen content, Equation 1 becomes:

$$\dot{Q}_{va}/\dot{Q}_t = (S_{\dot{c}} - S_a)/(S_{\dot{c}} - S_{\bar{v}}). \qquad [2]$$

In order to include in the estimate of venous admixture the contribution due to poor diffusion, the following modification of Equation 2 is necessary:

$$\dot{Q}_{va}/\dot{Q}_t = (S_A - S_a)/(S_A - S_{\bar{v}}), \qquad [3]$$

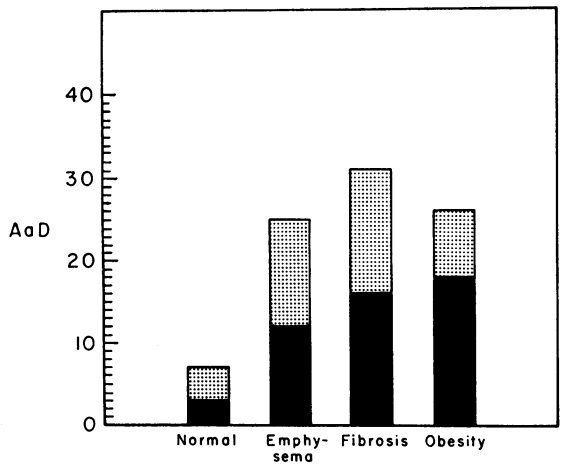

FIG. 1. MEAN ALVEOLAR-ARTERIAL OXYGEN TENSION DIFFERENCE (AaD) IN NORMAL SUBJECTS AND IN PATIENTS WITH EMPHYSEMA, DIFFUSE PULMONARY FIBROSIS, OR OBESITY. Height of bars represents total AaD during air breathing, and blackened segment, portion due to venous admixture after oxygen was breathed.

where S_A is the saturation of blood if it were in complete equilibrium with alveolar oxygen. We used this equation, previously discussed elsewhere (24), to calculate venous admixture during air breathing. The value of $S_A - S_{\bar{v}}$ was assumed to be 25%.

During 100% oxygen breathing, pulmonary end-capillary oxygen tension is that of alveolar gas, and if pulmonary capillary and peripheral arterial blood are both fully saturated, the difference in their oxygen content is due solely to the oxygen in physical solution. Thus Equation 1 becomes:

$$\dot{Q}_{va}/\dot{Q}_t = [(P_A - P_a)0.0031]/[C_a + (P_A - P_a)0.0031] - C_{\bar{v}}, \qquad [4]$$

where P_A is the "effective" alveolar oxygen tension (2), other symbols are as defined above, and 0.0031 is the solubility coefficient for oxygen in whole blood, expressed as volumes per 100 ml per millimeters Hg of oxygen tension. The denominator was assumed to be 5 volumes per 100 ml.

P_{AO_2} was calculated from the equation:

$$P_{AO_2} = P_{IO_2} - (Pa_{CO_2}/P_{ECO_2})(P_{IO_2} - P_{EO_2}), \qquad [5]$$

where P_{IO_2} is inspired oxygen tension, P_{EO_2} is expired oxygen tension, and P_{ECO_2} is expired CO_2 tension.

Pulmonary diffusing capacity was determined for carbon monoxide by the steady-state, physiologic dead-space method (25) in two patients, and for oxygen (3) in four.

To assess the magnitude of the *AaD* resulting from atelectasis, we measured it in 15 patients immediately after four deep breaths at the end of the nitrogen washout period. This was prompted by the observations that forcible inflation of the lungs reverses the alveolar closure occurring in anesthetized dogs (26), and that deeper inspiration raised arterial oxygen tension in hypoxemic obese subjects (27).

RESULTS

As originally formulated, the concept of venous admixture includes the distribution and direct shunting components of the AaD (1–3), but in this presentation, the term is used to describe the combined effects of all the mechanisms responsible for the AaD, measured at rest during air or oxygen breathing. This usage is justifiable, since under these circumstances, the contribution of diffusion barriers to the AaD is either negligible (10, 28), or, in extreme impairment of diffusion, inseparable from the distribution component (24).

In six normal subjects (Table I) breathing air, the AaD ranged from 3 to 11 and averaged 7 mm Hg. This corresponded to an estimated venous admixture of 3.3 ± 1.8% of the cardiac output. During oxygen breathing, the mean AaD was 26 with a range from 7 to 40 mm Hg. This was equivalent to a shunt of 1.6 ± 0.7%, which would

TABLE I

*Alveolar gas and arterial blood P_{O_2} and P_{CO_2}, and pulmonary venous admixture during air and 100% O_2 breathing in six normal subjects**

		Air					Oxygen						
Subject	DBP	P_{aCO_2}	P_{AO_2}	P_{aO_2}	AaD	$\dot{Q}_{va}/\dot{Q}_t$ ×100	F_{IO_2}	Time	P_{aCO_2}	P_{AO_2}	P_{aO_2}	AaD	$\dot{Q}_{va}/\dot{Q}_{vt}$ ×100
	mm Hg	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	%		*min*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	%
L.N.	717	43	97	94	3	1.5	0.99	10	36	659	636	23	1.4
C.B.	711	41	99	88	11	5.5	0.99	10	35	650	618	32	2.0
J.J.	716	40	101	94	7	3.5	0.99	10	42	654	631	23	1.4
A.K.	711	38	102	92	10	5.0	0.99	10	38	660	620	40	2.5
S.H.	722	40	102	98	4	2.0	0.99	11	36	662	655	7	.4
S.B.	715	42	98	93	5	2.5	0.99	15	41	650	617	33	2.0

* DBP = dry barometric pressure, calculated as ambient barometric pressure − P_{H_2O} at 37° C (47). Pa_{CO_2} = arterial blood carbon dioxide tension; $P_{A_{O_2}}$ = calculated "effective" alveolar gas oxygen tension; Pa_{O_2} = arterial blood oxygen tension; AaD = alveolar-arterial oxygen tension difference; $\dot{Q}_{va}/\dot{Q}_t \times 100$ = venous admixture, percentage of total pulmonary blood flow; $F_{I_{O_2}}$ = dry inspired oxygen concentration; and time = duration of oxygen breathing.

account for an AaD of about 3 mm Hg during air breathing.

All patients demonstrated some degree of increase in the AaD and the venous admixture (Tables II–V). In the air studies, the mean values and standard deviations of the AaD were 25 ± 10, 31 ± 8, and 26 ± 10 mm Hg, respectively, in the three groups. During oxygen breathing, these values were 120 ± 52, 134 ± 62, and 147 ± 58 mm Hg, corresponding to shunts of 7.4 ± 4, 8.3 ± 4, and 9.1 ± 5%.

The values for the component of the air breathing AaD resulting from these estimates of shunt measured on oxygen were calculated by use of the charts of Riley, Cournand, and Donald (3); Figure 1 gives the means for each group of patients and for the control subjects, together with the mean total AaD.

The inspiration of four deep breaths at the end of the nitrogen washout period (Table VI) decreased the venous admixture in six obese patients (from 12.4 ± 5.8 to 9 ± 2.3%, $p < 0.05$). There was a mean slight fall in five patients with emphysema ($p > 0.1$) and no fall ($p > 0.8$) in four patients with diffuse pulmonary fibrosis. The changes in alveolar gas and arterial blood Po_2 and Pco_2 are shown in Table VI.

During oxygen breathing, Pa_{CO_2} remained within normal limits in all six normal subjects. Oxygen breathing, however, induced or aggra-

TABLE II

*Alveolar gas and arterial blood P_{O_2} and P_{CO_2}, and pulmonary venous admixture during air and 100% O_2 breathing in 15 patients with obstructive pulmonary emphysema (group I)**

		Air					Oxygen						
Patient	DBP	P_{aCO_2}	P_{AO_2}	P_{aO_2}	AaD	$\dot{Q}_{va}/\dot{Q}_t$ ×100	F_{IO_2}	Time	P_{aCO_2}	P_{AO_2}	P_{aO_2}	AaD	$\dot{Q}_{va}/\dot{Q}_t$ ×100
	mm Hg	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	%		*min*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	%
W.S.	724	35	108	73	35	19	0.97	15	36	660	549	111	6.9
A.H.	709	38	101	82	19	14	0.95	15	40	641	587	54	3.3
R.O.	707	38	101	68	33	27	0.95	15	41	638	517	121	7.5
W.J.	709	38	101	74	27	19	0.95	15	42	639	487	152	9.4
N.A.	720	49	93	55	38	38	0.99	25	60	636	448	188	11.7
T.P.	720	40	102	66	36	26	0.99	30	47	643	582	61	3.8
A.C.	718	39	102	65	37	27	0.99	15	43	647	506	141	8.7
R.S.	721	43	98	77	21	12	0.95	15	44	649	575	74	4.6
D.R.	710	40	100	82	18	10	0.99	15	40	642	603	39	2.4
P.H.	705	69	78	46	32	50	0.99	20	75	610	383	227	14.1
J.S.	713	45	94	76	18	12	0.99	25	51	648	537	111	6.9
J.B.	713	50	91	84	7	4	0.99	15	51	644	566	78	4.8
R.N.	715	40	101	85	16	8	0.99	12	41	668	583	85	5.3
J.P.	716	58	79	56	23	28	0.99	27	62	623	512	111	6.9
B.P.	714	62	74	61	13	17	0.99	20	64	625	383	242	15.0

* Symbols as in Table I.

TABLE III

*Alveolar gas and arterial blood P_{O_2} and P_{CO_2}, and pulmonary venous admixture during air and 100% O_2 breathing in 14 patients with diffuse pulmonary fibrosis or infiltration (group II)**

		Air						Oxygen						
Patient	DBP	P_{ACO_2}	P_{AO_2}	P_{aO_2}	AaD	$\dot{Q}_{va}/\dot{Q}_t$ ×100	D_L	F_{IO_2}	Time	P_{ACO_2}	P_{AO_2}	P_{aO_2}	AaD	$\dot{Q}_{va}/\dot{Q}_t$ ×100
	mm Hg	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	%	*ml/mm Hg/min*		*min*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	%
G.H.	712	36	105	73	32	18		0.97	10	36	648	610	38	2.4
K.B.	709	38	101	65	36	26	7.7†	0.95	15	35	646	500	146	9.1
C.K.	707	41	103	57	46	38	2.9‡	0.99	20	50	650	436	214	13.3
Q.G.	711	43	96	65	31	25		0.99	15	43	640	407	233	14.4
L.S.	711	40	100	64	36	27		0.99	20	41	647	527	120	7.4
H.C.	716	40	101	75	26	15		0.99	20	51	637	572	65	4.0
V.S.	718	42	98	75	23	14		0.99	20	43	666	561	105	6.5
S.J.	716	40	102	84	18	9	15.3†	0.99	16	38	649	560	89	5.5
W.M.	715	35	107	66	41	27		0.99	22	30	664	588	76	4.7
V.A.S.	709	41	98	54	44	41	5.7‡	0.99	15	61	638	442	196	12.2
V.H.	712	39	101	75	26	15		0.99	26	46	626	446	180	11.2
C.S.	712	39	101	75	26	15		0.99	20	39	645	473	172	10.6
R.G.	716	45	98	76	22	13	27.6†	0.99	16	45	654	586	68	4.2
G.J.	715	40	106	78	28	15	8.6†	0.99	22	41	668	489	179	11.1

* D_L = diffusing capacity of the lung for oxygen (†) or for carbon monoxide (‡); ot her symbols as in Table I.

vated carbon dioxide retention in six of the emphysematous patients, in two obese patients, and, unexpectedly, in four patients with pulmonary fibrosis.

DISCUSSION

Interpretation of the results is based on comparison of the calculated venous admixture on air and on oxygen breathing. When pure oxygen is breathed and alveolar nitrogen washout completed, the diffusion and distribution components become negligible and the AaD can then result only from *1*) direct venous admixture, either through normally existing channels or through direct pulmonary arteriovenous shunts or portal-mediastinal-pulmonary venous communications, and *2*) perfusion of alveoli that cannot receive any of the inspired oxygen because they are atelectatic, or completely occluded by exudate or thickened walls.

Accuracy of the methods. The procedures and calculations used in this investigation necessitated a number of assumptions and simplifications. The effects of these assumptions on the accuracy of the results, and the reliability of the methods in general, are discussed below.

TABLE IV

*Alveolar gas and arterial blood P_{O_2} and P_{CO_2}, and pulmonary venous admixture during air and 100% O_2 breathing in 12 obese patients (group III)**

		Air					Oxygen						
Patient	DBP	P_{ACO_2}	P_{AO_2}	P_{aO_2}	AaD	$\dot{Q}_{va}/\dot{Q}_t$ ×100	F_{IO_2}	Time	P_{ACO_2}	P_{AO_2}	P_{aO_2}	AaD	$\dot{Q}_{va}/\dot{Q}_t$ ×100
	mm Hg	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	%		*min*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	%
A.A.	713	35	106	60	46	35	0.97	10	35	668	435	233	14.4
C.H.	712	34	107	79	28	14	0.97	10	34	668	587	81	5.0
S.B.	715	38	103	86	17	8	0.97	10	38	656	494	162	10.0
A.C.	718						0.95	10	59	632	441	191	11.8
J.F.	718	39	102	84	18	10	0.95	10	46	644	472	172	10.7
G.M.	718	42	98	73	25	17	0.95	10	39	636	505	131	8.1
A.B.	722	40	102	87	15	8	0.99	14	41	663	601	62	3.8
A.H.	711	34	107	71	36	22	0.99	12	41	654	548	106	6.6
E.D.	716	34	107	87	20	9	0.99	15	40	654	583	78	4.8
S.M.B.	719	46	94	78	16	10	0.99	20	48	661	517	144	8.9
J.D.	719	51	89	56	33	35	0.99	21	68	626	392	234	14.5
M.T.	709	35	117	89	28	11	0.99	10	43	659	483	129	8.0

* Symbols as in Table I.

TABLE V

*Mean values and standard deviations of measurements during air and oxygen breathing**

Diagnosis	Air				Oxygen			
	$P_{A_{O_2}}$	Pa_{O_2}	AaD	$\frac{\dot{Q}_{va}}{\dot{Q}_t} \times 100$	$P_{A_{O_2}}$	Pa_{O_2}	AaD	$\frac{\dot{Q}_{va}}{\dot{Q}_t} \times 100$
Normal	100 ± 2	93 ± 3	7 ± 3	3.3 ± 1.8	656 ± 5	630 ± 15	26 ± 12	1.6 ± 0.7
Emphysema	95 ± 10	70 ± 11	25 ± 10	20.7 ± 12	641 ± 12	521 ± 70	120 ± 52	7.4 + 4
Fibrosis	101 ± 3	70 ± 8	31 ± 8	21.3 ± 10	648 ± 12	514 ± 67	134 ± 62	8.3 ± 4
Obesity	103 ± 7	77 ± 11	26 ± 10	16.3 ± 10	652 ± 14	505 ± 66	147 ± 58	9.1 ± 5

* Symbols as in Table I.

1) The measurement of Pa_{o_2} by the needle electrode is subject to error due to a small flow artifact, temperature sensitivity, and drift in current output (23). We attempted to minimize these errors by performing frequent calibrations of the electrode in gas-equilibrated water samples, and by making all *in vitro* measurements at 37.5° C.

2) The temperature of the pulmonary capillary and of systemic arterial blood was assumed to be 37.5° C. An underestimation of this temperature would result in an underestimation of Pa_{O_2}, Pa_{CO_2}, and $P_{A_{H_2O}}$. All of these errors would combine to lead to an overestimation of the AaD by as much as 8.5 mm Hg per degree Centigrade in a subject breathing room air (29), and 38 mm Hg per degree Centigrade in a subject breathing oxygen. Preliminary work by Farhi, Edwards, and Velasquez (30) confirms that pulmonary capillary temperature in normal resting man is approximately 37.5° C.

3) For the calculation of venous admixture (Equations 3 and 4, above), all possible sources of venous admixture were considered collectively

TABLE VI

*Effect of four deep breaths at the end of nitrogen washout on the alveolar-arterial oxygen tension difference and pulmonary venous admixture during oxygen breathing**

Diagnosis	Patient	Tidal breathing						After four deep breaths				
		Time	Pa_{CO_2}	$P_{A_{O_2}}$	Pa_{O_2}	AaD	$\frac{\dot{Q}_{va}}{\dot{Q}_t} \times 100$	Pa_{CO_2}	$P_{A_{O_2}}$	Pa_{O_2}	AaD	$\frac{\dot{Q}_{va}}{\dot{Q}_t} \times 100$
		min	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	%	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	%
I. Emphysema												
	N.A.	25	60	636	448	188	11.7	55	641	484	157	9.7
	J.S.	25	51	648	537	111	6.9	47	652	573	79	4.9
	P.H.	20	75	610	383	227	14.1	74	611	401	210	13
	R.N.	12	41	668	583	85	5.3	41	668	583	85	5.3
	J.C.	20	45	658	474	184	11.4	43	660	503	157	9.7
	Mean		54	644	485	159	9.9	52	646	509	137	8.5
	SD		14	22	78	59	3.6	13	22	73	55	3.4
	p											> 0.1
II. Fibrosis												
	C.S.	20	39	645	473	172	10.6	32	652	486	166	10.3
	M.L.H.	20	56	632	517	115	7.1	49	639	517	122	7.6
	R.G.	16	45	654	586	68	4.2	45	654	563	91	5.6
	G.J.	22	41	668	489	179	11.1	36	673	492	181	11.2
	Mean		45	650	516	134	8.3	41	655	515	140	8.7
	SD		8	15	50	52	3.2	8	13	35	41	2.5
	p											> 0.8
III. Obesity												
	S.M.B.	20	48	661	517	144	8.9	45	664	535	129	7.9
	A.C.	10	59	632	441	191	11.8	53	638	471	167	10.4
	J.D.	21	68	626	392	234	14.5	65	629	469	160	9.9
	F.M.	20	71	624	261	363	22.5	58	647	454	193	12
	A.S.	18	45	630	540	90	5.6	42	633	542	91	5.6
	M.T.	10	43	659	483	176	10.9	42	660	531	129	8
	Mean		56	639	439	200	12.4	51	645	500	145	9
	SD		12	17	102	93	5.8	9	14	40	36	2.3
	p											< 0.05

* Symbols as in Table I.

as one shunt-flow of blood having the same oxygen content as the mixed venous blood entering the pulmonary capillaries. This condition holds in the case of direct pulmonary arteriovenous communications and of blood perfusing alveoli that permit no oxygen transfer, but is only a rough approximation for other sources of venous admixture.

4) The use of an assumed value for the difference in oxygen content or saturation between blood in equilibrium with alveolar gas and mixed venous blood introduces a source of inaccuracy, but venous admixture is relatively insensitive to changes in this variable (12, 31).

5) In the use of data obtained during oxygen breathing to interpret observations made during air breathing, error could arise from neglect of such possible effects of oxygen breathing as *a*) the tendency of some poorly ventilated alveoli to become atelectatic, *b*) pulmonary vasodilatation and redistribution of pulmonary blood flow, and *c*) change in the cardiac output. The magnitude of this error is difficult to predict, owing to the complex factors involved (32).

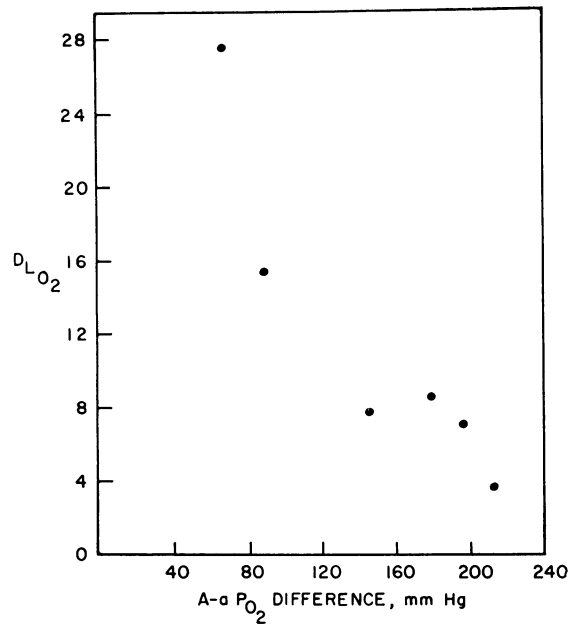

FIG. 2. PLOT OF PULMONARY DIFFUSING CAPACITY FOR OXYGEN ($D_{L_{O_2}}$) AGAINST ALVEOLAR-ARTERIAL OXYGEN PARTIAL PRESSURE DIFFERENCE, MEASURED DURING OXYGEN BREATHING, IN SIX PATIENTS WITH DIFFUSE DISEASES OF THE ALVEOLAR-CAPILLARY BED. Values shown for $D_{L_{O_2}}$ represent direct measurements in four patients (K.B., S.J., R.G., and G.J.), and calculations in two (C.K. and V.A.S.) of 1.23 × measured diffusing capacity for carbon monoxide (data from Table III).

The AaD and pulmonary venous admixture in normal man. The mean AaD in our normal subjects during oxygen breathing (26 ± 12 mm Hg) is somewhat higher than the values reported by Berggren (11.3 ± 1.5 mm Hg) (16) and by Wilson and associates (16 ± 11 mm Hg) (18), somewhat lower than the estimates of Morgan and Nahas (57 mm Hg) (33), and of Fasciolo and Chiodi (35.8 ± 19.6 mm Hg) (17), and in close agreement with Finley's (15) data.

Our estimate of a direct shunt of about 1.6% of the cardiac output would account for an AaD of approximately 3 mm Hg during air breathing. Since the effect of diffusion barriers could be neglected under the conditions of this study, the remainder of the AaD—namely, 4 mm Hg—must have been the result of nonuniform distribution of ventilation in relation to perfusion. A distribution component of this magnitude was calculated for upright subjects by West (34) and was quoted in a theoretical analysis by Farhi (35). Assuming even perfusion, and on the basis of helium-mixing studies, Briscoe (36) predicted a mean AaD of 9 mm Hg due to uneven ventilation-perfusion. The relatively large distribution fraction (80%) of the AaD described by Asmussen and Nielsen (37, 38) is due to the larger total AaD (17 ±.97 mm Hg) in their subjects.

Venous admixture in emphysema. The presence of an increased AaD and venous admixture during oxygen breathing in emphysematous patients may be explained by several mechanisms. Two of these relate to the behavior of the least ventilated alveoli. When oxygen is breathed, these alveoli either become atelectatic and act as shunts, or remain open but nonventilated (39, 40). In the latter case, inspired oxygen could reach the alveoli by "diffusion respiration," but their washout of nitrogen might take longer than 1 hour (40). In this investigation, oxygen breathing was carried out for 15 to 30 minutes, which probably resulted in an incomplete nitrogen washout from such alveoli and thereby could account for a portion of the observed AaD. A third possible mechanism is that of augmented flow in the bronchial veins. The expansion of the broncho-

pulmonary venous collateral circulation in advanced emphysema has been demonstrated by Liebow (41). Finally, although it is possible that direct pulmonary arteriovenous communications exist in some patients with chronic emphysema, Fritts and co-workers (19), using intravenous injection of krypton^{85} dissolved in T-1824 dye, found no increase in pulmonary arteriovenous shunt-flow in eight emphysematous patients. These authors point out, however, that Kr^{85} and oxygen may not detect the same anatomic pathways.

Venous admixture against diffusion limitation in patients with diffuse pulmonary fibrosis or infiltration. The relationship between venous admixture during oxygen breathing and the pulmonary diffusing capacity for oxygen in six patients with diffuse alveolar-capillary disease is illustrated in Figure 2. It is apparent from this plot that as diffusing capacity worsens, so does venous admixture, suggesting that both effects are related to one mechanism that alters alveolar units in such a way that they cease to function as diffusing units and act instead as shunting units. This could result from obliteration of alveolar spaces, or marked thickening of the alveolar-capillary membrane (10, 24). In this respect, there is a striking resemblance between the relationship plotted in Figure 2 and that calculated by Finley, Swenson, and Comroe (10) for the change in diffusing capacity with increased thickness of the alveolar-capillary membrane.

In one patient (R.G.), and possibly in another (S.J.), the measured diffusing capacity for oxygen (27.6 and 15.3 ml per mm Hg per minute, respectively), was within normal limits, but the AaD was increased. This apparent discrepancy may be related to the error in estimating diffusing capacity by this method in resting subjects with little or no impairment of diffusion (42, 43). It is also possible that when relatively few alveolar units have become functionless, the increase in venous admixture would be apparent before any reduction in the overall diffusing capacity could be detected. The effect of unequal distribution of diffusion impairment on the AaD has been discussed by Piiper (44) and by Piiper, Haab, and Rahn (45).

The data reported here indicate that an increase in the shunt component of the AaD is a common finding in patients with diffuse alveolar-capillary disease. These patients have also been shown to have grossly uneven distribution of ventilation in relation to blood flow (10). Since these two mechanisms contribute more importantly to the altered gas exchange than the reduction in pulmonary diffusing capacity itself, one might question the applicability of the term "alveolar-capillary block" (46) in these cases. A pure form of diffusion limitation can be seen, however, during exercise at high altitude (47).

Increased venous admixture in obesity. The findings of an increased venous admixture that persisted to a large extent during oxygen breathing and decreased with deep inspiration are in keeping with the opinion, previously presented (27), that atelectasis is a major cause of hypoxemia in obesity. The data, however, do not rule out other mechanisms of venous admixture on oxygen.

Effect of deep breaths. The reduction in venous admixture on oxygen after the inspiration of four deep breaths was probably due to the opening of atelectatic alveoli. A similar effect has been noted by Finley and associates (48) in anesthetized dogs during positive-pressure breathing. The slight or absent fall in venous admixture observed respectively in the patients with obstructive emphysema or diffuse pulmonary fibrosis suggests that relatively little or no atelectasis was present.

SUMMARY

1) Pulmonary venous admixture was determined during air breathing and after breathing 100% oxygen in 6 normal subjects, in 15 patients with chronic obstructive pulmonary emphysema, 14 with diffuse pulmonary fibrosis or infiltration, and 12 with marked obesity. *2*) All groups of patients demonstrated a mean increase in venous admixture relative to the normal subjects. *3*) Deep breathing reduced the shunt on oxygen in obese patients, but not in patients with emphysema or pulmonary fibrosis. *4*) The shunt component remaining after nitrogen washout could be explained largely by the continued perfusion of alveoli that were atelectatic or otherwise nonventilated, or that permitted no oxygen diffusion.

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