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Research Article

THE EFFECTS OF BODY POSITION, GANGLIONIC BLOCKADE AND NOREPINEPHRINE ON THE PULMONARY CAPILLARY BED *†

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Roughton and Forster (1) have demonstrated that the volume of blood in the pulmonary capillaries (V_c) and the true diffusing capacity of the pulmonary membrane (D_M), which, presumably, is related to the thickness and area of the pulmonary capillary wall, may be calculated from measurements of the pulmonary diffusing capacity for carbon monoxide (D_{LCO}) at several different capillary oxygen tensions. Their method makes possible the study in the intact human of a capillary bed which is of great physiological and clinical importance. We have previously studied (2) the behavior of this bed in mild exercise and during change in position. In the present study, we have infused a ganglionic blocking agent and norepinephrine during change of body position and have correlated the changes which occurred in V_c and D_M with available information on the cardiovascular effects of these procedures to explore the manner in which the pulmonary capillary bed is regulated.

MATERIALS AND METHODS

Subjects for these studies were young adult male volunteers in good health. Physical characteristics of these subjects are given in Table I. In each subject, the tension of carbon monoxide in equilibrium with capillary blood was determined by a rebreathing method (3). The subject then lay on a comfortably padded tilt table and an intravenous infusion of 5 per cent dextrose in water was begun and allowed to run slowly. The experimental procedure shown in Table II was then carried out.

The infusion solution was then changed to either trimethapan camphor-sulfonate (Arfonad), a ganglionic blocking agent (5), 1 mg per ml, or norepinephrine (Levophed), 4 μg per ml. The rate of infusion of trimethapan was regulated so that the systolic blood pressure after one minute in the 45° head-up position was approximately 90 mm Hg; the rate of infusion of norepinephrine was regulated to maintain a systolic blood pressure of 140 mm Hg in the recumbent position. The experimental procedure given above was then repeated. In all studies in which trimethapan was used, the infusion was discontinued and a final equilibrium Pco was measured. Initial and final measurements of equilibrium Pco were used in computing D_{LCO} (2). In four of these subjects another control determination and study during the infusion of norepinephrine were carried out. In two subjects in whom norepinephrine was infused first, the infusion fluid was changed to trimethapan and a third set of measurements made under these conditions.

The P_{O_2} of each of the rebreathing bags was measured by a paramagnetic oxygen analyzer.[1] The reciprocal of the reaction rate of CO with hemoglobin at this P_{O_2} ($1/\theta$) was taken from the published graphs of Roughton, Forster and Cander (6) assuming λ of 2.5, and the V_c and D_M in each position were obtained graphically from the plot of $1/\theta$ against $1/D_{LCO}$.

TABLE I

Physical characteristics of subjects

Subject	Age	Ht	Wt	Vital capacity
	yrs	*cm*	*kg*	*L*
A. L.	24	180	73	6.1
E. H.	23	183	86	4.0
C. L.	31	180	73	2.9
D. J.	22	180	76	5.2
M. N.	23	175	77	4.6
N. Z.	35	171	80	4.4
J. L.	23	172	76	3.7
K. T.	22	178	64	4.6

* The material was presented in part at the fall meeting of the American Physiological Society, London, Ontario, Sept. 5, 1958 and at the Midwestern Section of the American Federation for Clinical Research, Chicago, Ill., Oct. 30, 1958.

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[1] Model E2, Beckman Instruments, Inc., Fullerton, Calif.

TABLE II

Plan of experiment

Time		Position	Gas breathed	Measurements*
min	*sec*			
0	0	Recumbent	Oxygen	
2	0	45° Head-up	Oxygen	
3	0	Recumbent	Oxygen	
4	0	Recumbent	0.3% CO, 10% He, 89.7% O_2†	D_{LCO}, blood pressure, pulse
4	30	Recumbent	Oxygen	
6	30	45° Head-up	Oxygen	
7	30	45° Head-up	0.3% CO, 10% He, 89.7% O_2†	D_{LCO}, blood pressure, pulse
8	0	Recumbent	Room air	
11	0	45° Head-up	Room air	
12	0	Recumbent	Room air	
13	0	Recumbent	0.3% CO, 10% He, 21% O_2, 68.7% N_2†	D_{LCO}, blood pressure, pulse
13	30	Recumbent	Room air	
15	30	45° Head-up	Room air	
16	30	45° Head-up	0.3% CO, 10% He, 21% O_2, 68.7% N_2†	D_{LCO}, blood pressure, pulse
17	0	Recumbent	Room air	

* D_{LCO} was measured by a rebreathing method (4).
† Obtained from The Matheson Company, East Rutherford, N. J.

RESULTS

The results obtained are shown in Table III. These data are summarized in Table IV. Arrows indicate significant differences when the data are subjected to variance analysis (7). In the trimethapan group, studies on D. J. and J. L. are included although norepinephrine was infused before trimethapan was given. The changes following trimethapan in these subjects are of approximately the same magnitude and direction as in those in whom trimethapan infusion immediately followed the control. The direction of changes from the recumbent position during the various procedures employed is indicated in Table V.

DISCUSSION

Limitations of the methods. We have discussed elsewhere the accuracy of the rebreathing method of measuring D_{LCO} used in these studies (4) and of the computation of V_c and D_M (2).

With regard to the rebreathing method, we concluded that the values obtained by its use are less subject to errors due to uneven ratios of diffusing capacity to alveolar volume or to alveolar ventilation than other methods using carbon monoxide. Further, any changes in the volume of the lung during the procedures used in these studies are taken account of, since a measurement of the combined volume of lung and rebreathing bag is obtained simultaneously with a measurement of D_{LCO}.

With regard to the computation of V_c and D_M, we felt that the values obtained were approximate rather than exact and that the chief usefulness of such computations lay in detecting changes in these parameters. The fact that the values of V_c and D_M that satisfy a given value of D_{LCO} lie on a rectangular hyperbola must be borne in mind in assessing the significance of such changes. Because of this relation, it is possible that a change in D_{LCO} within the limits of experimental error might cause a striking change in the computed values of V_c or D_M. Standard statistical methods, such as those used in this study, should distinguish such random changes from significant alterations. In addition, we may compare data on the effects of tilting in the present study with data we have previously reported (2) on changes in V_c and D_M in the sitting and recumbent positions using a different method of measuring D_{LCO} (Table VI). The absolute values for D_{LCO} and V_c differ, especially the latter, but the direction of change is the same. D_M increased in the sitting position in the single breath studies, but did not change in the rebreathing data. However, the

TABLE III

*Measurements of diffusing capacity, capillary volume and membrane diffusing capacity**

Subject	Position	Drug	D_{LCO} P_{O_2} 100	D_{LCO} P_{O_2} 600	V_c	D_M	Blood pressure	Pulse
			ml/mm Hg × min		*ml*	*ml/mm Hg × min*	*mm Hg*	
A. L.	R	N	39.6	26.5	211	52	113/67	57
	T	N	36.5	20.4	125	60	100/73	71
	R	A	38.8	23.2	153	60	101/64	67
	T	A	38.6	19.8	107	84	102/74	79
	R	N	35.8	22.6	175	50	105/61	66
	T	N	37.5	19.1	107	83	103/74	85
	R	L	44.5	23.1	137	99	140/81	56
	T	L	43.8	23.5	151	72	141/82	66
E. H.	R	N	37.4	24.6	176	52	120/80	58
	T	N	34.7	21.2	145	54	118/92	59
	R	L	42.4	25.4	182	64	143/86	59
	T	L	38.2	23.4	167	55	141/87	53
C. L.	R	N	32.0	19.9	143	47	130/100	
	T	N	24.0	15.0	120	33		
	R	A	30.3	15.3	83	62	137/92	
	T	A	22.0	12.0	69	41	80/57	
D. J.	R	N	39.1	21.7	143	64	120/170	70
	T	N	37.1	19.8	119	69	112/68	76
	R	L	48.5	27.0	159	84	128/85	57
	T	L	36.4	21.7	154	55	140/91	68
	R	A	35.5	18.4	105	67	100/71	71
	T	A	30.9	15.3	87	62	86/74	102
M. N.	R	N	31.8	18.4	109	59	118/78	77
	T	N	28.1	16.8	112	45	119/88	88
	R	A	29.2	17.5	119	45	115/82	101
	T	A	26.3	15.2	95	45	101/90	122
	R	N	29.0	17.8	125	44	124/78	81
	T	N	28.7	16.4	107	47	124/88	98
	R	L	32.8	18.9	135	48	151/99	76
	T	L	29.5	17.5	132	42	142/91	79
N. Z.	R	N	24.1	15.2	114	35	106/80	60
	T	N	22.6	12.6	79	35	106/82	62
	R	A	21.4	14.1	114	29	100/80	62
	T	A	18.7	11.1	77	28	90/80	82
	R	N	21.2	14.7	139	27	111/74	66
	T	N	19.8	12.2	85	30	107/75	64
	R	L	24.0	15.9	128	32	144/93	49
	T	L	26.0	16.2	119	38	136/85	54
J. L.	R	N	23.6	14.5	95	37	110/65	75
	T	N	21.0	13.9	104	30	108/83	84
	R	L	23.0	14.8	108	33	140/100	48
	T	L	23.0	15.6	130	31	140/93	59
	R	A	20.3	13.2	100	28	102/72	84
	T	A	19.6	11.2	71	35	70/58	120
K. T.	R	N	34.8	20.1	130	59	108/64	65
	T	N	34.3	18.4	111	62	102/77	71
	R	A	36.0	19.6	122	57	98/68	63
	T	A	30.8	15.3	90	55	78/66	87
	R	N	34.8	21.1	144	55	107/65	63
	T	N	33.0	17.9	113	58	102/75	70
	R	L	39.2	22.8	150	65	146/89	51
	T	L	34.0	21.8	158	51	142/83	50

* The following abbreviations are used: R, recumbent; T, tilted 45°; N, glucose infusion; A, trimethapan (Arfonad) infusion; L, norepinephrine (Levophed) infusion; D_{LCO}, diffusing capacity of lungs; p_{O_2}, approximate alveolar oxygen tension; V_c, capillary blood volume; D_M, membrane diffusing capacity.

TABLE IV

Summary of results *

Condition	D_{LCO} P_{O_2} 100 R	D_{LCO} P_{O_2} 100 T	D_{LCO} P_{O_2} 600 R	D_{LCO} P_{O_2} 600 T	V_c R	V_c T	D_M R	D_M T
Control	32.1 →	29.1	19.5 →	16.7	135 →	110	51	48
Trimethapan	30.2 →	26.7	17.3 →	14.3	114 →	85	50	51
Control	31.5	30.2	19.6 →	17.2	143 →	111	47	53
Norepinephrine	36.3 →	33.0	21.1	19.9	143	144	61 →	49

* Abbreviations are the same as in Table III. Arrows indicate significant differences.

TABLE V

Relation of V_c and D_M to hemodynamic changes *

Position	Procedure	PAP	CO	PCP	PVR	TMP	V_c	D_M	Reference no.
Tilted	None	↓	↓	↓	↑	↓	↓	0	(8)
Recumbent	Trimethapan	↓	↓	[↓]	[0]	↓	↓	0	(9, 10)
Tilted	Trimethapan	[↓↓]	[↓↓]			↓↓	↓↓	0	(11)
Recumbent	Exercise	↑	↑	0	0	↑	↑	↑	(2, 12)
Recumbent	Norepinephrine	↑	0	↑	?	↑	0	↑	(13, 14)
Tilted	Norepinephrine		[0]			[↑]	0	0	Text

* Abbreviations: PAP = pulmonary artery pressure; CO = cardiac output; PCP = pulmonary "capillary" (or wedge) pressure; PVR = pulmonary vascular resistance; TMP = transmural pressure in capillary (deduced, see text); blank = no data; ? = conflicting results. Arrows indicate direction of change from recumbent position, no drug administered. For other comment see text.

conclusion drawn from the two sets of data is the same. In each case there is an increase in surface area and/or decrease in diffusion path per unit of capillary volume. This comparison strengthens our confidence in the *qualitative* validity of the changes found in these studies.

Interpretation of results. Physiological study of the capillary circulation of the lung has been made directly by biomicroscopy and indirectly by the techniques used in this study. The available data on the behavior of the pulmonary capillaries using the indirect technique are summarized in Table V.

The pulmonary capillary bed may either passively conform to events elsewhere in the cardiovascular system or possess active vasomotion. That is, the observed changes in this bed may be either secondary or primary.

The notion of a passive or secondary change in the pulmonary capillary bed needs some clarification. For a vessel which contains muscular and fibrous elements in its wall (as arterioles and venules), the criteria for such a change have been succinctly stated by Burton (15): The size of a vessel is governed by the pressure difference be-

TABLE VI

Effects of position; comparison of methods *

Method	Subjects	D_{LCO} P_{O_2} 100 R	D_{LCO} P_{O_2} 100 T	D_{LCO} P_{O_2} 600 R	D_{LCO} P_{O_2} 600 T	V_c R	V_c T	D_M R	D_M T
Single breath	4	31.6	26.9	15.0	11.5	86	59	77	99
Rebreathing	7	32.1	29.1	19.5	16.7	135	110	51	48

* Abbreviations are the same as in Table III. "Single breath" results were previously published (2) and were done in sitting rather than tilted position.

tween its lumen and the surrounding tissue (transmural pressure) and by the tension in its wall. If the size changes in the same direction as the transmural pressure, this change may be (but *not* must be) passive; if size and transmural pressure change in opposite directions, active vasomotion is involved. Capillaries, however, are simple endothelial tubes and on biophysical grounds should open fully if the transmural pressure exceeds a certain value (critical opening pressure); no gradations in patency between closed and fully open should occur (16). The remarkable constancy of pulmonary capillary diameter seen by biomicroscopy (17) confirms this prediction. To call a change in the pulmonary capillaries passive we must assume that the critical closing pressures of the pulmonary capillaries cover a range of values from low to high and that these critical closing pressures do not alter during the change in question. Then, during a rise in transmural pressure the critical opening pressure of certain capillaries previously closed should be exceeded and these capillaries will open, increasing V_c (or vice versa during a fall of transmural pressure). If these assumptions are not proved, active vasomotion cannot be excluded. On the other hand, if transmural pressure and V_c change in opposite directions, the change cannot be explained on a passive or secondary basis and active vasomotion is involved.

We are not aware of measurements of pulmonary capillary transmural pressure. However, the mean capillary transmural pressure must bear some relation to the pressure in the pulmonary artery and the pulmonary veins.

In Table V we have summarized the data available on the changes in the pulmonary circulation during the procedures we employed and our deductions from this data as to changes in the capillary transmural pressure. Transmural pressure must, of course, exceed pulmonary venous pressure and, barring venous constriction, these two pressures must change together. Pulmonary "capillary" (or wedge) pressure is an acceptable measure of pulmonary venous pressure in man (18), and in Table V we have used it as an index of changes in transmural pressure. Pulmonary artery pressure is a less reliable guide to changes in transmural pressure because, although it must always exceed transmural pressure, the two need not change together, since the resistance of the pulmonary arterioles is interposed.

In addition to mean pulmonary artery pressure and pulmonary arteriolar resistance, the transmural pressure in the capillaries may be affected by changes in the vertical distance from the capillaries to the root of the pulmonary artery during changes in position. We believe this last factor is of less importance than the other two since its effects tend to cancel out. The anterior portions of the lungs are supplied against gravity in the recumbent position while the superior portions are similarly affected in the erect position. The well known decrease of oxygen uptake in the upper lobes when the subject is upright (19) has as its corollary an increase in oxygen uptake in the lower lobes.

Certain comments on Table V should be made here. We have not found measurements of pulmonary "capillary" pressure during trimethapan administration and have used the data of Fowler and associates (10) for a related drug, tetra-ethyl ammonium. Fowler (11) does not specify the ganglionic blocking agent used in his studies. The data on pulmonary vascular resistance during norepinephrine administration are conflicting (13, 14), but the conclusion that capillary transmural pressure rises seems warranted, regardless of change in pulmonary vascular resistance. The data on the effects of norepinephrine infusion during head-up tilt are scanty. DeFazio, Regan and Binak [2] have found that cardiac output did not change when a patient was tilted during norepinephrine infusion. The secretion of norepinephrine is a normal response to assuming the upright position (20) and deficiency of such secretion has been reported in orthostatic hypotension (21). Presumably, norepinephrine infusion prevents venous pooling and thus maintains cardiac output, pulmonary artery pressure and transmural pressure at or above control values. The data which have been specificially mentioned above are indicated by brackets in Table V.

It will be seen that during tilting, trimethapan infusion and exercise, transmural pressure and V_c change in the same direction. These changes

[2] Personal communication.

might be passive or secondary to the variation in transmural pressure brought about by events elsewhere in the cardiovascular system. However, during norepinephrine infusion in the recumbent position in which hemodynamic data suggest that capillary transmural pressure increases, V_c does not change. This is evidence in favor of active vasomotion in the pulmonary capillary bed.

The possible site of such vasomotion is of interest. In general, arterioles are joined to venules by thoroughfare or preferential channels which have thin muscular walls and are direct continuations of the feeding arteriole. True capillaries arise as lateral branches of these thoroughfare channels (22). Garcia-Ramos (17) has concluded that this arrangement of thoroughfare channels with lateral branches exists in the lungs. A ring of smooth muscle (precapillary sphincter) is known to exist at the junction of true capillaries with their thoroughfare channels in other organs and such sphincters are exquisitely sensitive to circulating vasoconstrictors like norepinephrine (22). If such sphincters existed in the lung, their constriction might prevent the increased transmural pressure from opening previously closed capillaries.

It should be reiterated at this point that because a change in capillary volume *could* be explained by a passive conformity of the capillary bed to a change in transmural pressure does not mean that this is the mechanism involved. The occurrence of capillary vasomotion is not excluded in certain of these situations. Thus, if the norepinephrine secreted during tilting (20) were to constrict the precapillary sphincters, capillary volume might decrease independently of changes in transmural pressure. However, capillary volume goes up on exercise when norepinephrine release also occurs (23) and trimethapan, which should block norepinephrine release, causes a more profound drop of capillary volume on tilting, not a less profound change as one might predict if one views capillary vasomotion as the mechanism governing the capillary bed. This, of course, assumes that trimethapan has no action of its own on the precapillary sphincters as shown in the rat mesentery (24).

Thus, from the limited evidence available, the changes in capillary volume which occur on tilting, during exercise and during trimethapan infusion can be more readily explained as passive responses of the capillary bed to events elsewhere in the cardiovascular system, which vary transmural pressure, than as active vasomotion of this bed. However, the fact that capillary volume does not increase during norepinephrine infusion suggests that under certain circumstances active vasomotion does occur in the pulmonary capillary bed. It is possible that both secondary and primary effects on the capillary bed occur in most situations, but more subtle experiments involving perfusion and quantitative biomicroscopy would be necessary to detect this interaction.

Interpretation of the changes in D_M in these studies is more complex than that of the changes in V_c. D_M presumably is a measure of the surface area of the capillaries in contact with the alveoli and of the distance that gas must travel from alveolus to capillary. Either or both of these parameters may change.

According to the Starling hypothesis, in a "solid" organ capillary transmural pressure, the osmotic pressure of the blood, and tissue pressure are in equilibrium. If transmural pressure rises, fluid passes from the capillary until tissue pressure increases to restore equilibrium. The process is reversed if transmural pressure falls. It is not known if significant tissue pressure can develop in this way between the alveolar and capillary walls in a "spongy" organ like the lung or if fluid passing from the capillary remains within this wall, thickening it. If this latter process does occur, a fall in transmural pressure would cause fluid to enter the capillary and decrease the distance for diffusion. This is a possible explanation of the finding that D_M did not change during tilting or trimethapan infusion, which decrease transmural pressure. During exercise both D_M and transmural pressure increase. V_c also increases, however, indicating that more capillaries are open with greater surface area. The increase in D_M during norepinephrine infusion remains unexplained.

Measurement of changes in lung tissue volume (25) concurrently with D_M might place interpretations of D_M on a sounder footing. Thus, if lung tissue volume were to fall on tilting, although D_M did not change, there might be some support for the speculation advanced above that this is due to

passage of fluid from the alveolar capillary space into the capillary.

SUMMARY

1. The pulmonary capillary blood volume (V_c) and the diffusing capacity of the pulmonary membrane (D_M) were calculated from measurements of diffusing capacity of the lungs for carbon monoxide ($D_{L_{CO}}$) in normal subjects in the recumbent and 45° head-up tilted positions, during a control period and during the infusion of trimethapan (Arfonad) and norepinephrine (Levophed).

2. V_c fell during head-up tilting. The infusion of trimethapan in the recumbent position also decreased V_c and accentuated its decrease during the head-up tilt. D_M did not change significantly during these procedures.

3. Norepinephrine did not change V_c in the recumbent position, but led to an increase in D_M. The decrease in V_c on tilting was abolished by norepinephrine.

4. V_c changed in the same direction as did the capillary transmural pressure deduced from available hemodynamic data during tilting, trimethapan infusion, and exercise. This could be due to passive conformity of the capillary bed to changes in transmural pressure. Active vasomotion, however, cannot be excluded. V_c did not change, although transmural pressure probably was increased during norepinephrine infusion in the recumbent position. This is best explained by active vasomotion in the pulmonary capillaries.

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