JCI The Journal of Clinical Investigation

PULMONARY VASOCONSTRICTION IN RESPONSE TO PRECAPILLARY HYPOXEMIA

Edward H. Bergofsky, … , Ricardo Ferretti, Alfred P. Fishman

J Clin Invest. 1963;42(8):1201-1215. https://doi.org/10.1172/JCI104806.

Research Article

Journal of Clinical Investigation
Vol. 42, No. 8, 1963

PULMONARY VASOCONSTRICTION IN RESPONSE TO PRECAPILLARY HYPOXEMIA *

By EDWARD H. BERGOFSKY,† BERL G. BASS, RICARDO FERRETTI,‡ AND ALFRED P. FISHMAN

(From the Department of Medicine, Columbia University, College of Physicians & Surgeons, and the Cardiorespiratory Laboratory of the Presbyterian Hospital, New York, N. Y.)

(Submitted for publication January 17, 1963; accepted March 28, 1963)

The pulmonary arterial pressor response to acute hypoxia is generally attributed to pulmonary vasoconstriction (1). Moreover, the demonstration that the pulmonary pressor response can occur without the intervention of either the autonomic nervous system (2–4) or known neurohumoral mediators (5, 6) has led to the popular view that the pulmonary vasoconstriction is a consequence of local effects of acute hypoxia on the vascular wall (7).

There is much less unanimity concerning the particular vascular segment (or segments) affected by hypoxia. On the premise that the pulmonary capillaries cannot constrict, the bulk of the evidence has been interpreted as indicating that acute hypoxia elicits postcapillary vasoconstriction (7, 8). These experiments, however, which have involved either the breathing of hypoxic inspired mixtures either by both lungs (9) or by one lung (10), have rarely excluded the possibility that the precapillary vessels may also be involved in the pressor response (11). Furthermore, while experiments on isolated lungs and artificial preparations (12) have shown that acute hypoxia is capable of changing the caliber of the precapillary vessels, they have not settled the nature of this response: vasoconstriction or vasodilatation (12, 13), active or passive (14, 15).

The present study was concerned with the effects of precapillary hypoxemia on the pulmonary circulation. The experiments were performed on intact dogs and were of two types. The first involved the use of either 2,4-dinitrophenol (16) or of carbon monoxide to reduce markedly the oxygenation of mixed venous blood without affecting the oxygenation of pulmonary venous blood; we found that both of these agents elicited an increase in pulmonary arterial pressure. Since this pressor response might arise reflexly from a decrease in the oxygen tension in some chemosensitive area rather than from a local action of mixed venous blood on precapillary vessels, a second type of experiment was performed in which the oxygen tension of carotid arterial blood could be selectively varied; in this way, the possibility was investigated that a decrease in the oxygen tension of chemosensitive areas of the brain and carotid arteries was involved in the pressor response.

METHODS

The intact dog. The principles underlying the use of 2,4-dinitrophenol (DNP) and of carbon monoxide to reduce selectively the oxygen tension of mixed venous blood are illustrated with reference to the standard oxyhemoglobin dissociation curve in Figure 1. DNP decreases the mixed venous P_{O_2} by increasing the oxygen consumption without proportionate increase in the cardiac output (16, 17); on the other hand, carbon monoxide accomplishes the same end by decreasing the oxygen capacity of the blood.

These experiments were performed on fourteen fasted dogs, anesthetized with pentobarbital, 30 mg per kg body weight. The dogs were ventilated by means of a Bird mechanical respirator connected to an endotracheal tube. An open circuit was arranged so that the respirator could deliver different mixtures of inspired gas and so that expired gas could be collected in a 120-L gasometer. The respirator was set to effect an estimated normal alveolar ventilation (18) with provision for increasing alveolar ventilation upon demand. By this use of the

* Presented in part at the 46th annual meeting of the American Physiological Society, April, 1962. Supported in part by research grants H-2299 and HE-05741 from the National Institutes of Health, with additional support from the American Heart Association and the New York Heart Association.

† Work done during tenure of a Senior Research Fellowship of the New York Heart Association.

‡ Fellow of the Gildemeister Foundation, Santiago, Chile.

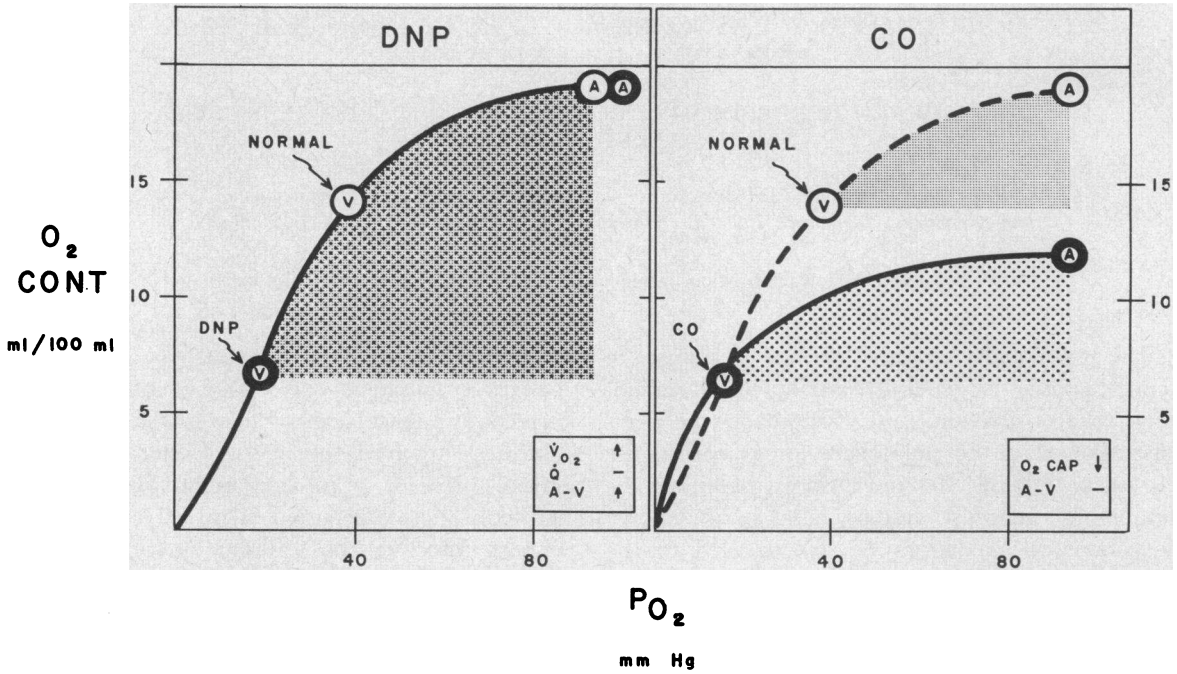

FIG. 1. THE MECHANISMS BY WHICH DINITROPHENOL (DNP) AND CARBON MONOXIDE (CO) LOWER THE OXYGEN TENSION OF MIXED VENOUS BLOOD. Left panel: the oxygenation of normal arterial and mixed venous blood (lightly circled A and V) is indicated on the standard oxyhemoglobin dissociation curve. DNP widens the arteriovenous difference in oxygen content (A-V) by increasing oxygen uptake ($\dot{V}_{O_2}$) without altering cardiac output ($\dot{Q}$). After DNP, the arterial oxygen tension (heavily circled A) is unchanged, whereas the mixed venous oxygen tension (heavily circled V) is decreased. Right panel: the oxyhemoglobin dissociation curve that results from the combination of CO with a fraction of the available hemoglobin has been superimposed on the standard curve taken from the left panel. The heavily circled A and V represent arterial and mixed venous blood gas composition after CO. Although the A-V difference for oxygen remains the same during CO breathing as during ambient air breathing, the mixed venous oxygen tension is considerably decreased.

respirator, the swing in intratracheal pressure during each breath was of the same order of magnitude (0 to + 5 cm water) throughout the different experiments.

For blood samples and pressures, a no. 7 cardiac catheter was introduced, under fluoroscopic control, from the jugular vein into the right pulmonary artery; a no. 6 cardiac catheter was passed retrogradely from the femoral artery into the left ventricle; and an indwelling arterial needle was inserted into the remaining femoral artery. Blood pressures were recorded by Statham P23D pressure transducers connected to an oscilloscopic recorder.[1] The cardiac output was measured, in the conventional way, by the Fick principle. In order to achieve a steady state of respiration and circulation, each control period on ambient air was continued for at least 10 minutes, and each test period involving an inspired mixture other than ambient air was continued for at least 20 minutes. Expired gas was collected in the gasometer during the last two minutes of each period; arterial and venous blood samples were drawn, at comparable rates, during the middle minute of the gas collection.

Immediately after two control periods of assisted respiration on ambient air (periods 1 and 2), eight of the fourteen dogs received an intravenous infusion of DNP (6 mg per kg) at a rate of 18 mg per minute. Blood pressures were recorded either continuously or every few minutes until the close of the experiment. Samples for the determination of the cardiac output were drawn at 10 and 45 minutes after the end of the injection (periods 3 and 4). In five of the eight animals treated with DNP, 99% oxygen was substituted for ambient air immediately after period 4 and administered through the mechanical respirator for an additional 20 minutes (period 5). The final period consisted of 25 minutes of ambient air breathing through the respirator (period 6).

In the remaining six dogs, the two control periods of assisted respiration on ambient air were followed by two consecutive periods in which 0.2% carbon monoxide in air was substituted for the ambient air. After 30 and 50 minutes, samples were collected for the determination of the cardiac output. Blood pressures were measured either continuously or intermittently as above.

Perfused-carotid-artery dog. As shown in Figure 2, a bypass was included in the circulation in such a way that the common carotid arteries could be perfused either

[1] Electronics for Medicine, Inc., White Plains, N. Y.

by arterial blood from the femoral arteries or by venous blood from the inferior vena cava.

This part of the study involved eleven dogs. After anesthesia with pentobarbital, the trachea was intubated for assisted respiration. Thereafter, as may be seen in Figure 2, the following steps were taken: *1*) a no. 7 cardiac catheter was placed in the right pulmonary artery, *2*) an indwelling arterial needle was placed in one femoral artery, *3*) the inferior vena cava and the aorta were cannulated with wide-bore plastic tubing by way of a femoral vein and the remaining femoral artery, respectively, *4*) both common carotid arteries were ligated as low in the neck (as far from the carotid sinuses) as possible, *5*) the left ventricle was catheterized retrogradely (no. 6 cardiac catheter) by way of one common carotid below the ligature, *6*) both common carotid arteries were cannulated above the ligatures with side-bore plastic tubing, and *7*) an indwelling arterial needle was placed immediately below the bulb of the remaining external jugular vein; in order to maintain free blood flow, no ligatures were applied to either jugular vein. Before the first period, the extracorporeal system was filled with heparinized blood from a donor dog. Perfusion was accomplished by a Sigmamotor finger pump. The rate of perfusion (of the order of 20 ml per kg per minute) was adjusted to maintain the carotid arterial blood pressure within a few millimeters Hg of the aortic blood pressure.

Before each perfusion experiment, the responsivity of each animal's pulmonary circulation to acute hypoxia was tested. This involved successive periods of breathing: *1*) ambient air, *2*) 12% oxygen in nitrogen, and *3*) ambient air. Each inspired gas mixture was supplied by the respirator; each period lasted for 15 to 20 minutes. Seven of the eleven dogs manifested an increase in pulmonary arterial mean pressure of at least 3 mm Hg during this preliminary trial; only the data from these responsive dogs are included in this report.

For each dog, a perfusion experiment consisted of five 20-minute periods: *1*) control, i.e., perfusion of the carotid arteries with arterial blood during ambient air breathing, *2*) perfusion of the carotid arteries with venous blood during ambient air breathing, *3*) a second control, *4*) perfusion of the carotid arteries with arterial blood during breathing of an inspired mixture of 12% oxygen in nitrogen, and *5*) a final control. Blood pressures in the pulmonary artery and left ventricle were measured every few minutes. Blood and gas samples for the measurement of cardiac output were collected (as above) during the last two minutes of the periods. In addition, blood was drawn from below the jugular bulb before the close of each period.

In four of the seven dogs, the experiment was extended to include observations during which blood flow through the vertebral arteries was arrested while the carotid arteries were perfused with blood drawn from either the femoral arterial or venous cannula. The occlusion of the vertebral arteries was accomplished without thoracotomy. Through an incision low in the neck, the ipsilateral vertebral, or subclavian arteries, or both, were located in the mediastinum by digital palpation. A long clamp was then passed along the course of the palpating finger to the artery. The procedure was then repeated on the other side. That blood flow through both vertebral arteries had been interrupted was shown in two ways: *1*) by briefly clamping the carotid arteries as well as the intrathoracic arteries; when the intrathoracic clamps were properly placed on the vertebral or subclavian arteries, the blood pressure in the cephalad part of the carotid artery fell from systemic arterial to jugular venous levels, and *2*) by verifying the position of the intrathoracic clamps at autopsy.

Analytic techniques and calculations. The O_2 and CO_2 contents of expired air were measured by the micro-Scholander technique (19). The O_2 and CO_2 contents and the O_2 capacity of blood were analyzed by the method of Van Slyke and Neill (20). In the carbon monoxide experiments, two special precautions were taken to obtain reliable measurements of the oxygen saturation: *1*) the equilibration of blood with room air for the determination of the O_2 capacity by the method

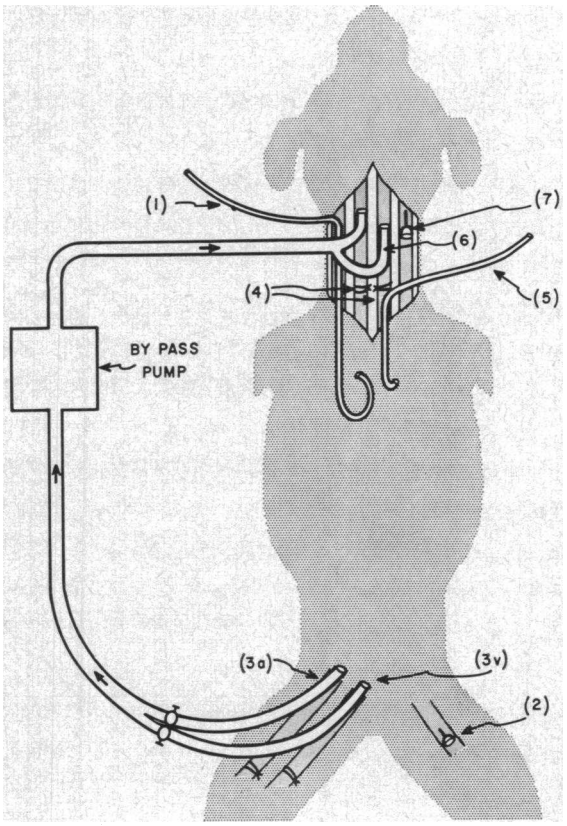

FIG. 2. PERFUSED-CAROTID-ARTERY DOG. The circulatory bypass is connected in such a way that the common carotid arteries can be perfused either by arterial blood from the abdominal aorta (3a) or by venous blood from the inferior vena cava (3v). Other numbers are described in Methods section.

TABLE I

*Respiratory and circulatory effects of 2,4-dinitrophenol**

Dog	Wt	Time $\bar{p}$ DNP	$F_{I_{O_2}}$	R_E	$\dot{V}_E$	$\dot{V}_{O_2}$	Sa_{O_2}	$P\bar{v}_{O_2}$	Pa_{CO_2}	$P\bar{v}_{CO_2}$	pH_a	$\dot{Q}$	Pulmonary arterial pressure			Left ventricular pressure		Pulmonary vascular resistance
													s	d	m	s	d	
no.	*kg*	*min*			*L/min*	*ml/min*	*%*	*mm Hg*	*mm Hg*	*mm Hg*		*L/min*	*mm Hg*			*mm Hg*		*mm Hg/ ml/sec*
1	9	−20	.21	.91	5.0	49	99	42	30	33	7.40	1.20	18	12	14	122	7	0.350
		−10	.21	.85	5.3	56	98	42	31	33	7.44	1.34	17	12	14	120	7	0.314
		+10	.21	.76	5.9	113	98	33	44	46	7.26	1.64	28	19	23	120	7	0.585
		+45	.21	.89	6.4	105	98	28	34	38	7.38	1.35	26	15	20	126	7	0.590
2	16	−20	.21	.80	6.0	110	95	40	30	31	7.44	2.83	25	10	16	142	7	0.192
		−10	.21	1.00	6.6	97	95	41	28	30	7.45	2.63	25	10	15	144	7	0.183
		+10	.21	.80	7.8	247	96	25	29	34	7.42	2.37	37	17	25	144	7	0.456
		+45	.21	.81	8.5	262	93	23	31	34	7.43	2.10	33	15	23	149	7	0.450
3	14	−20	.21	.77	4.1	91	97	45	28	31	7.46	2.80	22	14	16	124	7	0.194
		−10	.21	.70	4.8	84	97	44	29	32	7.42	2.22	20	13	15	120	7	0.216
		+10	.21	.77	5.6	157	95	35	36	38	7.40	2.86	30	17	22	122	7	0.312
		+45	.21	.96	9.1	154	95	26	31	34	7.43	2.01	26	16	21	134	8	0.389
4	10	−20	.21	.86	5.7	95	96	45	27	29	7.46	2.98	26	10	16	155	7	0.181
		−10	.21	.89	5.6	98	95	45	30	29	7.44	2.98	25	10	15	155	7	0.165
		+10	.21	.90	7.4	231	98	33	32	34	7.42	3.80	34	19	24	150	7	0.269
		+45	.21	.82	7.3	234	94	28			7.39	3.83	31	16	21	150	7	0.300
		+65	.99	.91	7.4	250	100	37				2.91	28	16	18	152	7	0.222
		+90	.21	.88	8.1	262	94	26	26	33	7.46	2.85	32	17	22	146	7	0.312
5	12	−20	.21	.84	4.4	92	98	42	27	29	7.47	2.28	18	10	14	116	6	0.210
		−10	.21	.96	4.8	106	96	40	28	30	7.44	2.74	19	10	14	118	6	0.175
		+10	.21	.70	5.2	225	92	28	36	40	7.37	3.10	34	23	27	122	6	0.406
		+45	.21	.81	5.8	226	92	25	37	39	7.37	2.62	28	19	22	126	7	0.343
		+65	.99	.92	5.8	225	100	35	33	43	7.34	2.81	21	15	18	126	7	0.235
		+90	.21	.82	5.9	219	94	24	34	37	7.35	2.90	27	19	23	120	6	0.352
6	9	−20	.21	.82	4.2	59	94	46	33	34	7.41	1.79	25	15	17	144	7	0.335
		−10	.21	.84	4.2	58	95	47	31	34	7.42	1.82	27	16	18	140	7	0.362
		+10	.21	.76	5.4	110	94	31	41	51	7.29	1.73	40	21	26	142	8	0.594
		+45	.21	.78	4.5	116	96	25	34	38	7.38	2.01	35	19	23	140	8	0.519
		+65	.99	.81	4.9	121	100	37	33	38	7.38	2.00	30	16	19	146	7	0.359
		+90	.21	.79	4.9	139	97	24	32	40	7.37	2.00	35	20	23	148	7	0.481

* Symbols: Time $\bar{p}$ DNP = time with respect to infusion of 2,4-dinitrophenol (− = before start of infusion, + = after end of infusion), $F_{I_{O_2}}$ = fraction of oxygen in inspired gas, R_E = respiratory exchange ratio of expired gas, $\dot{V}_E$ = minute ventilation (BTPS), $\dot{V}_{O_2}$ = oxygen uptake (STPD), Sa_{O_2} = oxyhemoglobin saturation of arterial blood, $P\bar{v}_{O_2}$ = oxygen tension of mixed venous blood, Pa_{CO_2} = carbon dioxide tension of arterial blood, $P\bar{v}_{CO_2}$ = carbon dioxide tension of mixed venous blood, $\dot{Q}$ = cardiac output, and s, d, and m = systolic, diastolic, and mean blood pressures, respectively.

TABLE I—(*Continued*)

Dog no.	Wt kg	Time p DNP min	$F_{I_{O_2}}$	R_E	$\dot{V}_E$ L/min	$\dot{V}_{O_2}$ ml/min	Sa_{O_2} %	$P\bar{v}_{O_2}$ mm Hg	Pa_{CO_2} mm Hg	$P\bar{v}_{CO_2}$ mm Hg	pH_a	$\dot{Q}$ L/min	Pulmonary arterial pressure s	Pulmonary arterial pressure d	Pulmonary arterial pressure m	Left ventricular pressure s mm Hg	Left ventricular pressure d	Pulmonary vascular resistance mm Hg/ml/sec
7	16	−20	.21	.80	3.7	80	97	48	25	29	7.43	4.21	22	13	17	132	5	0.171
		−10	.21	.88	4.4	94	96	43	26	31	7.41	4.68	21	14	18	130	5	0.162
		+10	.21	.77	5.4	173	98	37	32	36	7.36	3.61	32	22	26	134	6	0.332
		+45	.21	.75	5.6	163	95	34	31	34	7.39	4.08	28	18	22	132	5	0.266
		+65	.99	1.00	5.9	186	100	43	26	31	7.42	3.81	25	14	19	130	5	0.220
		+90	.21	.84	5.8	172	93	31	27	31	7.41	3.95	29	19	23	131	5	0.275
8	9	−20	.21	.70	5.1	67	98	49	25	27	7.46	2.23	26	14	18	126	9	0.242
		−10	.21										25	14	18	125	9	
		+10	.21	.72	5.9	131	99	39	36	43	7.31	2.34	33	19	24	125	9	0.382
		+45	.21	.90	6.9	128	98	35	29	32	7.36	2.38	32	18	23	127	9	0.353
		+65	.99	.76	5.8	151	100	42	30	35	7.39	2.45	29	16	20	125		
		+90	.21	1.00	6.7	116	99	30	27	33	7.41	1.80	33	19	24	127		
Mean		−20	.21	.81	4.8	80	97	45	28	30	7.44	2.54	23	12	16	133	7	0.234
		−10	.21	.87	5.1	85	96	43	29	31	7.43	2.63	22	12	15	132	7	0.225
		+10	.21	.77	6.1	173	96	33	36	39	7.35	2.68	34	20	25	132	7	0.417
		+45	.21	.83	6.8	174	95	28	32	36	7.40	2.55	30	17	22	136	7	0.401
		+65	.99	.88	6.0	187	100	39	30	37	7.38	2.80	27	15	19	136	6	0.259
		+90	.21	.87	6.3	182	95	27	29	35	7.40	2.70	31	19	23	134	6	0.355

of Van Slyke and Neill was restricted to 15 minutes (21) and 2) the oxygen saturation of each sample was determined separately, in duplicate, by the spectrophotometric method of Nahas (22). Each of these methods has, in our hands, a reproducibility of ± 3%. In none of the data included in this report were the differences between the two types of measurement greater than 4%. The data in the tables and figures were obtained by the method of Van Slyke and Neill. The blood pH was measured at 37° C with a glass electrode and a Radiometer pH-meter. The carbon monoxide content of blood was determined by the palladium chloride method of Allen and Root (23).

The oxygen tension of blood was derived from the blood pH and oxygen saturation by use of a standard oxyhemoglobin dissociation curve (24). In the carbon monoxide experiments, the dissociation curve was modified to take into account the presence of carbon monoxide (25). The CO_2 tension of blood was calculated from the blood pH and the CO_2 content of serum from the line charts of Van Slyke and Sendroy (26). The pulmonary vascular resistance was calculated as the ratio of mean pulmonary arterial pressure minus mean left ventricular diastolic pressure to the cardiac output. For the experimental periods involving DNP and carbon monoxide, the method of least squares was used to calculate the constants of the best linear equations relating pulmonary vascular resistance to mixed venous O_2 tension; the significance of the constants was assessed by the Fisher *t* test.

RESULTS

Dinitrophenol

The effects of DNP on pulmonary gas exchange, on the gaseous composition of the blood, and on the pulmonary circulation are listed for each animal in Table I. For each dog in this table, the data for the two control periods (− 20 and − 10 minutes, respectively) are followed by the data for the subsequent two or more test periods.

Pulmonary gas exchange. Before the infusion of DNP, the minute ventilation and gas exchange of the eight dogs was fairly steady: successive values for minute ventilation and oxygen uptake did not differ by more than 15%, and the respiratory exchange ratios ranged from 0.70 to 1.00, with an average difference of 0.06 between the two control periods.

After the infusion of DNP, the respiratory exchange ratios changed slightly and inconsistently from the control. In contrast to the lack of consistent change in the respiratory exchange ratios, the minute ventilation increased after the DNP,

and by 10 minutes after the end of the infusion (+ 10 minutes in Table I), the average increase was 23%. The magnitude of the increase was not uniform: in five of the eight dogs, it ranged from 25 to 33%; in the other three dogs, from 12 to 16%. Nor was the subsequent behavior of the ventilation entirely regular: in five of the eight dogs, the ventilation continued to increase over the next 35 minutes (+ 45 minutes); in the other three dogs, the ventilation either remained unchanged (dogs 4 and 7) or decreased (dog 6). The oxygen uptake of each animal doubled within the 10 minutes after the end of the infusion and remained at this level for the next 35 to 80 minutes of the study (+ 45, + 65, and + 90 minutes, respectively).

Blood gases. During the control periods, the arterial oxygen saturations ranged from 94 to 99%, with an average value of 96%. Except in dog 5, where the saturation decreased to 92%, these values were unaffected by the infusion of DNP. On the other hand, the oxygen tension of mixed venous blood decreased regularly after DNP: before the infusion of DNP, the oxygen tension of the mixed venous blood averaged 44 to 45 mm Hg; by 10 minutes after the end of the infusion, the average value was 33 mm Hg; and by 45 minutes, it had decreased further to 28 mm Hg.

Before the infusion of DNP, the CO_2 tension of arterial and mixed venous blood averaged 29 and 31 mm Hg, respectively. Within 10 minutes after the end of the infusion, the arterial CO_2 tensions had increased (by 2 to 13 mm Hg) in all but one animal (dog 2); the average increase was 7 mm Hg. During this same time, the mixed venous blood CO_2 tension increased in all animals (by 4 to 17 mm Hg), with an average increase of 8 mm Hg. Subsequently (+ 45 minutes), the arterial and mixed venous CO_2 tensions returned towards control values, averaging 4 and 6 mm Hg more than control, respectively. Both the arterial and venous pH decreased during the infusion of DNP. Ten minutes after the infusion, the arterial pH averaged 0.08 less than control (range of 0.03 to 0.16); 35 minutes later (+ 45 minutes), the arterial pH averaged only 0.04 U less than control (range of 0.02 to 0.10). The changes in mixed venous pH, not shown in Table I, were also small and followed the same pattern of change.

The behavior of the blood gases during the final two experimental periods (dogs 4 to 8) will be considered below with respect to the breathing of 99% oxygen.

Pulmonary circulation. In each dog, the two control values (− 20 and − 10 minutes) for cardiac output, pulmonary arterial pressure, and left ventricular pressure all agreed within 15%. After the infusion of DNP, the cardiac output changed slightly and inconsistently, in no case varying by more than 27% of control. In contrast, the pulmonary arterial pressures increased in each instance, with an average increase of 9 mm Hg at the first test period (+ 10 minutes) and of 6 mm Hg at the second test period (+ 45 minutes). Throughout these two test periods, the left ventricular diastolic pressure remained unchanged. The pulmonary vascular resistances increased on the average by 0.19 mm Hg per ml per second at the first test period and by 0.17 mm Hg per ml per second at the second period (+ 45 minutes). A statistically significant relationship ($p = < 0.01$) was found to exist between the increases in pulmonary vascular resistance ($\bar{R}_p$) and the decreases in the mixed venous O_2 tension ($P\bar{v}_{O_2}$); it is expressed by the equation: $\Delta\bar{R}_p = -0.003 + 0.0097 \times \Delta P\bar{v}_{O_2}$.

Effect of breathing 99% oxygen after DNP. The effect of breathing oxygen on the hemodynamic changes produced in the pulmonary circulation by infusion of DNP was examined in the last five dogs of Table I. As may be seen, the substitution of 99% oxygen for ambient air about an hour after the end of the infusion of DNP (+ 65 minutes) effected full saturation of the arterial blood and (not shown in this table) increased the dissolved oxygen in the arterial plasma to an average value of 1.9 ml per 100 ml of blood. The pH and the CO_2 tension of arterial blood remained unchanged. The oxygen tension of mixed venous blood increased from an average value of 26 to 39 mm Hg.

The metabolic and hemodynamic effects associated with the increase in oxygenation are summarized in the last two columns of Figure 3. Neither the oxygen uptake nor the cardiac output changed appreciably. However, the pulmo-

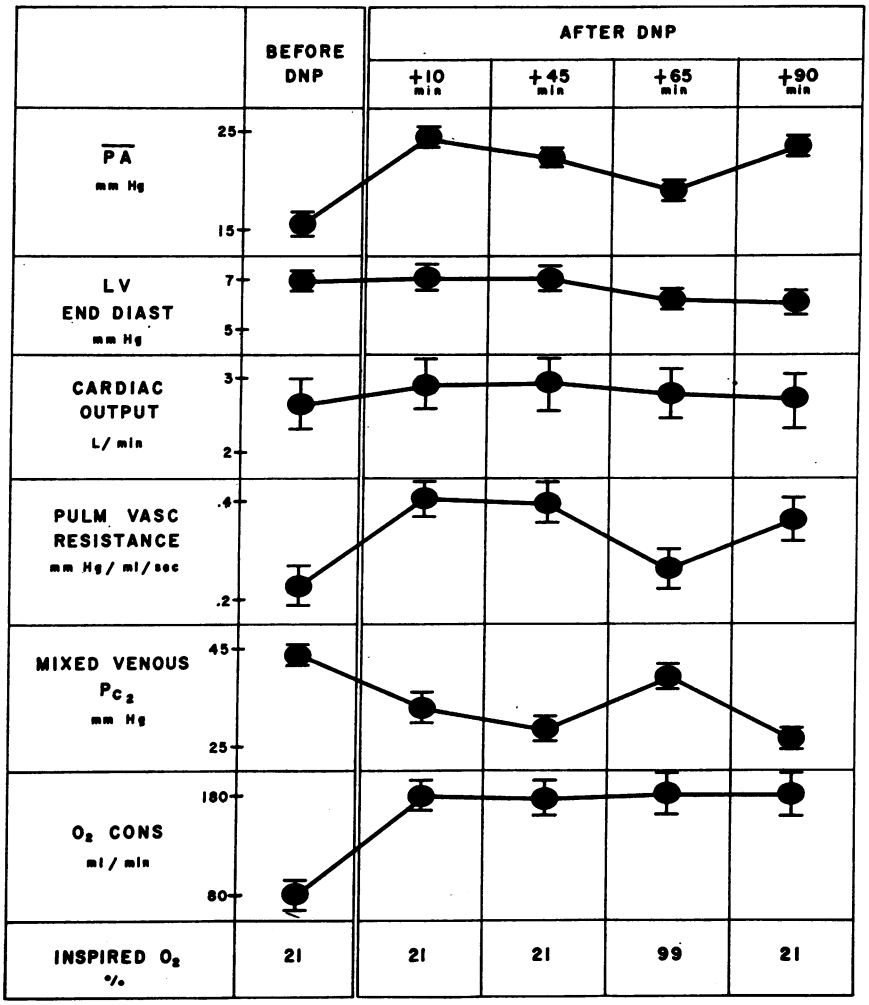

FIG. 3. EFFECT OF DINITROPHENOL (DNP) ON THE PULMONARY CIRCULATION. Before DNP = average of values taken 10 and 20 minutes before infusion of DNP; after DNP = time elapsed after the end of the infusion of DNP; $\overline{PA}$ = mean pulmonary arterial pressure; LV end diast = end-diastolic pressure in the left ventricle; pulm vasc resistance = calculated pulmonary vascular resistance; O_2 cons = oxygen uptake. Each solid circle represents the mean of the values in the last five dogs of Table I. Each crossbar represents 1 SE of the mean value.

nary arterial pressure and the pulmonary vascular resistance decreased to near-control values.

During the final period of ambient air breathing, the values for blood gas composition and for pulmonary hemodynamics returned to approximately the same levels as before the previous period of oxygen breathing.

Carbon monoxide

The effects of breathing a mixture of 0.2% carbon monoxide in air on pulmonary gas exchange, blood gaseous composition, and the pulmonary circulation appear in Table II. The data for each animal were obtained during two control periods (− 20 and − 10 minutes) and during two test periods (30 and 50 minutes) after the breathing of carbon monoxide was begun. For convenience, the two animals (dogs 13 and 14) in which the breathing of carbon monoxide was not associated with a change in mixed venous oxygen tension are separated in Table II from the four animals in which the mixed venous

TABLE II

*Respiratory and circulatory effects of breathing 0.2% carbon monoxide in air**

Dog	Wt	Time $\bar{P}_{CO}$	R_E	$\dot{V}_E$	$\dot{V}_{O_2}$	Ca_{CO}	Sa_{O_2}	$P\bar{v}_{O_2}$	Pa_{CO_2}	$P\bar{v}_{CO_2}$	pH_a	$\dot{Q}$	Pulmonary arterial pressure s	Pulmonary arterial pressure d	Pulmonary arterial pressure m	Left ventricular pressure s	Left ventricular pressure d	Pulmonary vascular resistance
no.	*kg*	*min*		*L/min*	*ml/min*	*ml/100 ml*	*%*	*mm Hg*	*mm Hg*	*mm Hg*		*L/min*	*mm Hg*			*mm Hg*		*mm Hg/ml/sec*
Unchanged cardiac output																		
9	8.0	−20	.94	4.6	62	0.10	95	47	35	38	7.37	1.63	22	9	13	128	7	0.220
		−10	.94	5.1	65		97	48	35	38		1.55	21	9	13	132	7	0.231
		+30	.75	4.6	51	4.00	96	25	37	39	7.32	1.47	29	12	16	132	7	0.367
		+50	.72	3.8	53	6.67	95	20	38	40	7.32	1.56	30	13	17	119	7	0.385
10	11.4	−20	1.00	4.8	75		93	48	37	37	7.35	2.58	24	12	16	127	6	0.233
		−10	.94	4.3	73		95	49	36	40	7.35	2.87	23	12	16	118	6	0.208
		+30	.73	4.8	98		95	32	37	41	7.31	2.85	29	14	19	118	6	0.270
		+50	.70	4.9	99		98	27	37	42	7.30	2.57	31	15	19	108	5	0.325
11	11.0	−20	.90	5.8	90	0.11	96	35	22	26	7.48	2.18	25	12	15	146	6	0.245
		−10	.79	5.7	92		95	34	22	27	7.47	2.20	23	12	14	141	6	0.218
		+30	.69	5.7	93	7.49	91	22	22	26	7.40	2.70	31	14	19	140	6	0.289
		+50	.80	5.7	84	9.39	95	18	20	24	7.37	2.50	31	14	20	131	6	0.336
12	8.5	−20	.70	4.0	56	0.45	96	43	37	39	7.37	1.72	23	12	15	121	7	0.279
		−10	.71	4.0	58		96	43	36	38	7.37	1.70	22	12	15	120	7	0.281
		+30	.68	4.0	59	7.14	97	28	34	38	7.37	1.91	27	14	17	118	7	0.315
		+50	.70	4.2	54	9.20	97	23	35	38	7.36	2.16	29	15	19	105	7	0.333
Mean		−20	.89	4.8	71	0.22	95	43	33	35	7.39	2.03	24	11	15	131	6	0.244
		−10	.84	4.8	72		96	44	32	36	7.40	2.08	22	11	15	128	6	0.235
		+30	.71	4.8	75	6.21	95	27	32	36	7.34	2.23	29	14	18	127	7	0.310
		+50	.73	4.6	72	8.42	96	22	32	36	7.34	2.20	30	14	19	116	6	0.345
Increased cardiac output																		
13	10.1	−20	.82	4.5	88	0.04	99	40	36	38	7.38	1.90	21	9	12	100	6	0.186
		−10	.80	4.6	92		93	40	36	37	7.38	2.06	21	9	12	95	6	0.174
		+30	.76	4.8	82	5.86	99	41	36	39	7.34	3.03	24	12	15	95	6	0.176
		+50	.86	4.7	78	8.19	95	44	31	33	7.34	3.61	24	13	15	88	6	0.147
14	8.0	−20	.91	4.4	69	0.11	99	42	34	40	7.32	1.57	23	11	13	140	7	0.225
		−10	.85	3.8	70		94	40			7.29	1.49	23	11	13	140	7	0.240
		+30	.96	6.7	82	7.06	95	38	20	22	7.43	3.15	28	14	18	131	6	0.225
		+50	.79	4.5	82	9.96	98	39			7.30	3.42	28	15	18	126	6	0.208

* Time $\bar{P}_{CO}$ = time after the start of breathing of 0.2% carbon monoxide in air; Ca_{CO} = concentration of carbon monoxide in arterial blood; other symbols as in Table I.

oxygen tension did decrease during the experiment.

Pulmonary gas exchange. In none of the six animals did the values for minute ventilation and oxygen uptake obtained during the two successive control periods differ by more than 10%. The respiratory exchange ratios during these control periods ranged from 0.70 to 1.00, with no greater difference than 0.11 between successive control values in any single dog. In contrast to the experiments with DNP, the breathing of carbon monoxide did not appreciably affect either the minute ventilation or the oxygen uptake.

Blood gases. The carbon monoxide content of arterial blood was measured in five of the six

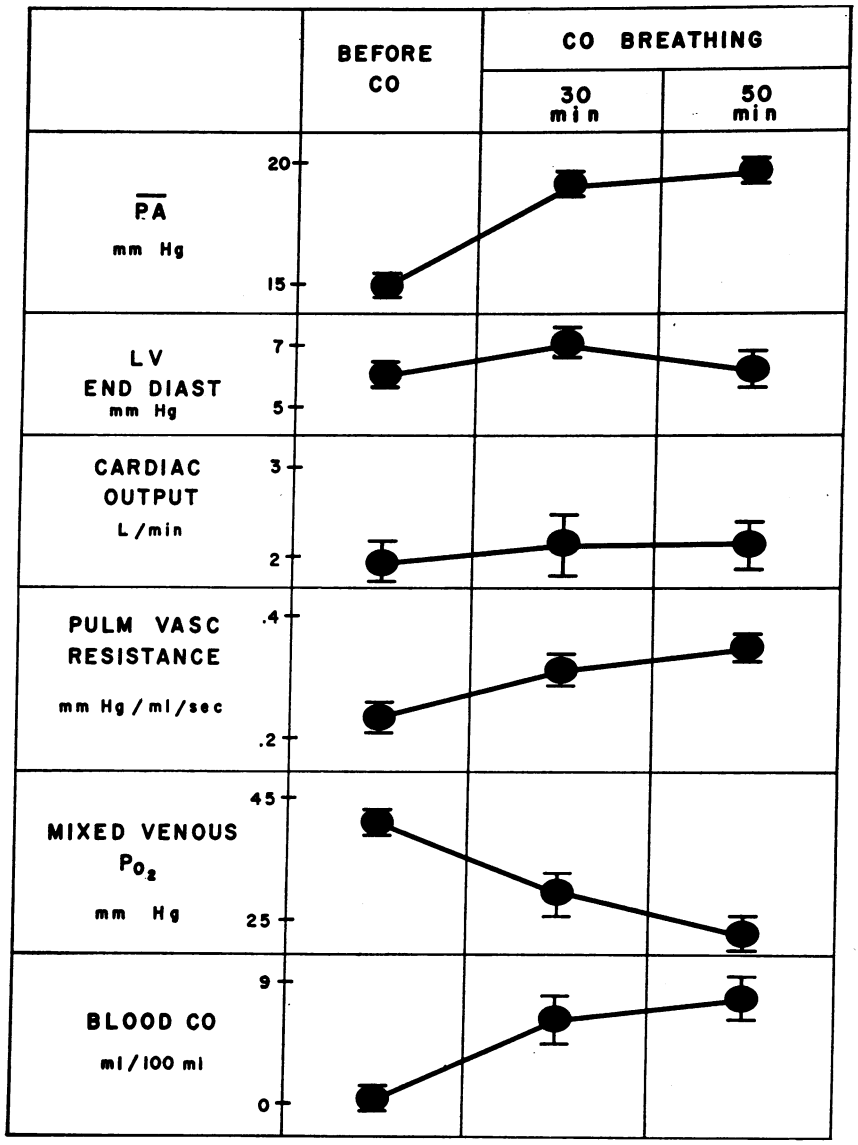

FIG. 4. EFFECT OF BREATHING 0.2% CARBON MONOXIDE (CO) ON PULMONARY CIRCULATION. Before CO = averages of values taken 10 and 20 minutes before CO breathing began; blood CO = the concentration of carbon monoxide in the arterial blood. Only the four dogs in which the cardiac output did not change are illustrated in this figure. Other symbols as in Figure 3.

dogs. In each of these dogs, the content of carbon monoxide was negligible during the control period and increased progressively as the carbon monoxide mixture was breathed. After 30 minutes of breathing carbon monoxide, the average content was 6.5 ml per 100 ml and after 50 minutes, 9.0 ml per 100 ml. The arterial oxygen saturations ranged from 93 to 99% during the control periods and did not change during the breathing of carbon monoxide. In the six animals, the mixed venous oxygen tensions during the control periods ranged from 40 to 49 mm Hg; moreover, in any single dog, the values obtained during the two control periods did not differ by more than 2 mm Hg. In the first four dogs of Table II, in which the cardiac output was unaffected by breathing carbon monoxide, the mixed venous oxygen tensions fell progressively during the test periods: the average mixed venous oxygen tension was 27 mm Hg after 30 minutes of breathing carbon monoxide and 22 mm Hg after 50 minutes of breathing carbon monoxide. On the other hand, in the two animals in which the cardiac output did increase during the carbon monoxide breathing, the mixed venous oxygen tensions differed by only a few mm Hg from the control values. As may also be seen in Table II, the changes in blood CO_2 tensions and pH were less during carbon monoxide breathing than after the infusion of DNP. Only in dog 14 did the arterial CO_2 tension and pH undergo appreciable changes; in this animal, the changes in the blood occurred after 30 minutes of breathing carbon monoxide, in association with an unexplained increase in minute ventilation.

Pulmonary circulation. As indicated previously, Table II was subdivided according to the effect of carbon monoxide breathing on the cardiac output. In the first three dogs of this table, during the breathing of 0.2% carbon monoxide, the change in the cardiac output from the control period did not exceed 10%; in the fourth (dog 11), the increase in cardiac output was approximately 25% of the control value.

As Figure 4 indicates, the mean pulmonary arterial pressures in these first four dogs ranged from 13 to 16 mm Hg during the control periods. In each dog, the pulmonary arterial pressures increased during carbon monoxide breathing: the increments in systolic pressure exceeded the increments in diastolic pressure, and the increase in mean pressures ranged from 2 to 5 mm Hg after 30 minutes of carbon monoxide and from 3 to 6 mm Hg after 50 minutes of carbon monoxide. During these periods, the left ventricular systolic pressure fell, on the average, by 13 mm Hg, but the left ventricular diastolic pressures did not change by more than 1 mm Hg. The calculated pulmonary vascular resistance increased on the average by 0.07 mm Hg per ml per second after 30 minutes of carbon monoxide breathing and by 0.105 mm Hg per ml per second after 50 minutes of carbon monoxide breathing.

The lower part of Table II deals with the pulmonary hemodynamic effects of carbon monoxide in the two dogs in which the cardiac output increased sufficiently during the test periods to prevent a decrease in the mixed venous oxygen tension. As in the first four dogs, the cardiac outputs during the two control periods varied by less than 10%. After 30 minutes of carbon monoxide breathing, however, they had increased by 50 and 111% and after 50 minutes, by 77 and 130%. The pulmonary arterial pressures increased in both animals, by 3 and 5 mm Hg, respectively, without change in the left ventricular diastolic pressures. The calculated pulmonary vascular resistance decreased slightly in both dogs. As in the DNP experiments, a statistically significant relationship ($p = < 0.01$) was found to exist between the increases in pulmonary vascular resistance ($\bar{R}_p$) and the decrements in the oxygen tension of the mixed venous blood ($P\bar{v}_{O_2}$). It is expressed by the equation: $\Delta\bar{R}_p = 0.00002 + 0.0048 \times \Delta P\bar{v}_{O_2}$. On the other hand, as the two regression equations indicate, DNP produced larger increases in pulmonary vascular resistance for equivalent decreases in mixed venous oxygen tension.

Hypoxemia of the brain and carotid chemoreceptors

The pulmonary circulatory effects of perfusing both common carotid arteries with venous blood (see schema of Figure 2) are shown in the first three columns of Figure 5. As the figure indicates, the oxygen tension of arterial and mixed venous blood was measured during all three pe-

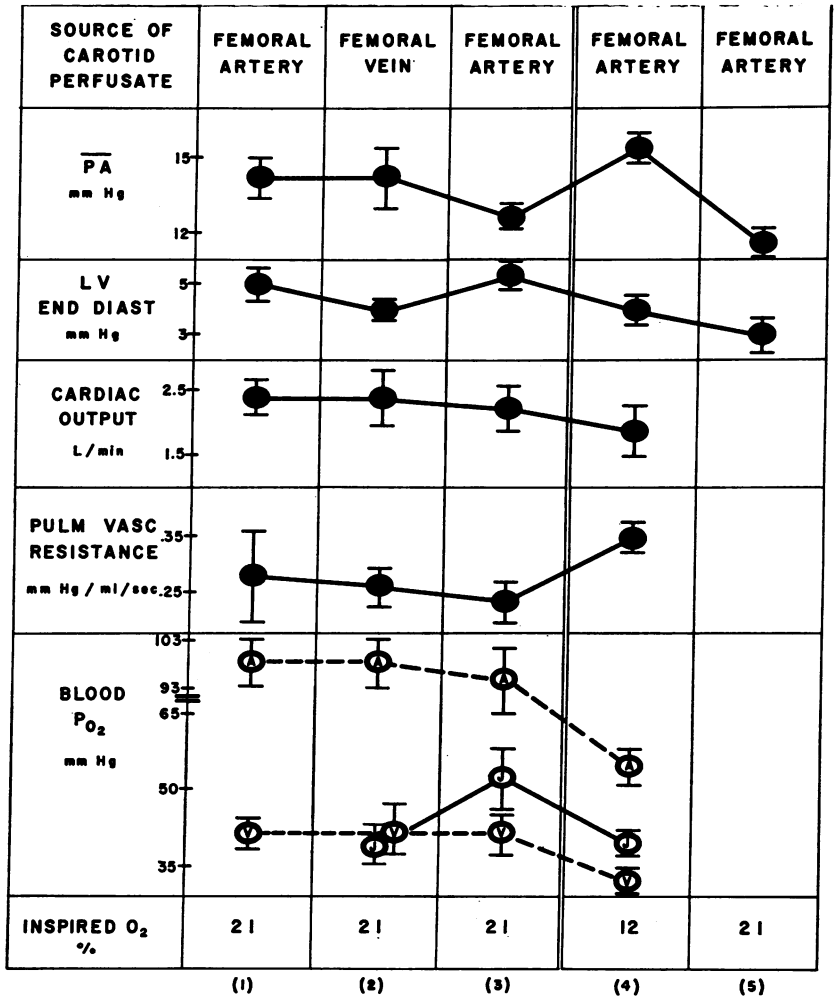

FIG. 5. CIRCULATORY EFFECTS OF SUBSTITUTING VENOUS FOR ARTERIAL BLOOD AS THE CAROTID ARTERIAL PERFUSING MEDIUM IN 7 DOGS. Each circle represents a mean value, and each crossbar, 1 SE of the mean. The open circles A, V, and J represent arterial, mixed venous, and jugular blood, respectively. Other symbols as in Figure 3.

riods; the corresponding oxygen tension of jugular venous blood was measured only during the test period and the succeeding control period. Not shown are the values for arterial and mixed venous pH, which did not change by more than 0.04 during the three experimental periods. As may be seen in Figure 5, perfusion of the carotid vessels with venous rather than arterial blood lowered the average jugular venous oxygen tension by 11 mm Hg without changing the oxygen tension of either systemic arterial or mixed venous blood. Despite this decrease in jugular venous oxygen tension during venous perfusion, there was no appreciable change in pulmonary arterial pressure, cardiac output, or calculated pulmonary vascular resistance.

The last two columns of Figure 5 show that the failure of pulmonary vascular resistance to increase during the venous perfusion was not attributable to a loss of reactivity on the part of the pulmonary vessels. This reactivity was tested in the conventional way by administering a hypoxic inspired gas mixture (12% oxygen in nitrogen) while the carotid vessels were perfused with systemic arterial blood. It may be seen that during these experiments, the jugular venous

TABLE III

*Circulatory effects of perfusing the carotid arteries with venous blood before and after occluding the vertebral arteries**

	Vertebrals open		Vertebrals closed	
Source of carotid perfusing medium	Femoral artery	Femoral vein	Femoral artery	Femoral vein
Mean pulmonary arterial pressure, *mm Hg*	14 (.86)	14 (.70)	12 (1.12)	11 (1.25)
Left ventricular diastolic pressure, *mm Hg*	4 (.90)	4 (.04)	3 (.02)	4 (.86)
Jugular venous O_2 tension, *mm Hg*	56 (1.58)	40 (6.60)	46 (12.9)	25 (2.1)

* Mean values of four dogs are given, with the standard errors of the means in parentheses.

oxygen tension decreased to values similar to those observed during the venous perfusion of the carotid vessels. In contrast to the venous perfusion experiments, however, the oxygen tension of arterial and mixed venous blood also decreased appreciably (average arterial values decreased from 94 to 54 mm Hg and mixed venous values from 41 to 32 mm Hg). Accompanying the systemic hypoxia was an average increase in pulmonary arterial pressure of 3 mm Hg and an average increase in pulmonary vascular resistance of 0.116 mm Hg per ml per second.

In order to exclude the possibility that the vertebral arteries were delivering oxygenated blood to critical areas of the brain during the venous perfusion of the carotid arteries, the experiments shown in the first three columns of Figure 5 were repeated in four dogs during occlusion of the vertebral arteries. The results are summarized in Table III. As anticipated, closure of the vertebral arteries resulted in lower oxygen tensions in jugular venous blood during both arterial and venous perfusion of the carotid arteries than when the vertebral arteries were open. Despite this inordinate reduction in the oxygen tension of jugular venous blood, however, there was no appreciable change in either pulmonary arterial or left ventricular end-diastolic pressures.

DISCUSSION

The present study has demonstrated that, in the intact anesthetized dog, a decrease in the oxygen tension of mixed venous blood elicits an increase in pulmonary arterial pressure. Since this pressor response occurred during controlled ventilation and in the absence of any change in either tracheal pressure, cardiac output, or left ventricular pressure, it is attributed to pulmonary vasoconstriction. Moreover, since the decrease in oxygen tension was confined to the precapillary segments, without either alveolar or postcapillary hypoxia, it seems reasonable to conclude that the decrease in the oxygen tension of the mixed venous blood elicited precapillary vasoconstriction by a direct effect of the low oxygen tension on the precapillary vascular wall.

Assessment of alternate explanations

At least four alternate explanations received serious consideration: *1*) that DNP and carbon monoxide induced pulmonary vasoconstriction by their direct pharmacologic effects rather than by their indirect effects on mixed venous oxygen tension, *2*) that changes in the pH and carbon dioxide tension of the blood, rather than in the oxygen tension, were responsible for the pulmonary vasoconstriction, *3*) that a decrease in the oxygen tension at some extrapulmonary, rather than intrapulmonary, site brought about the pulmonary vasoconstriction, and *4*) that instead of directly affecting the precapillary vessels, precapillary hypoxemia elicited postcapillary vasoconstriction reflexly.

Pharmacologic effects of DNP and carbon monoxide. Several lines of evidence indicate that these agents elicited pulmonary vasoconstriction by way of their effects on the oxygen tension of mixed venous blood rather than by their direct pharmacologic actions: *1*) except for their effectiveness in reducing the oxygen tension of mixed venous blood, the actions of the two agents are pharmacologically distinct; *2*) the pulmonary vasoconstriction elicited by DNP was reversed by the breathing of an enriched oxygen mixture which relieved mixed venous hypoxemia; and *3*) at equivalent concentrations of carbon monoxide in systemic arterial blood, the pulmonary vasoconstriction occurred only in those animals in which the oxygen tension of mixed venous blood decreased. The failure to adduce evidence for a direct pulmonary vasoconstrictor effect of carbon monoxide in the present studies is consistent with observations in the isolated lung which indicate that carbon monoxide elicits vasodilatation rather than vasoconstriction (27).

Such a vasodilating effect of carbon monoxide is also consistent with the present observation that for equivalent decrements in the oxygen tension of mixed venous blood, DNP exerted a greater pressor effect than did carbon monoxide.

Changes in blood pH and carbon dioxide tension. Neither acidosis nor an increase in blood carbon dioxide tension appear to be involved in the pulmonary vasoconstriction elicited by DNP or carbon monoxide. This conclusion is based on the fact that under similar experimental conditions in the dog, increments in pulmonary vascular resistance comparable to those observed in the present study could only be elicited by much larger changes in the arterial and venous carbon dioxide tension and pH (28).

Extrapulmonary hypoxemia. There are two likely mechanisms by which DNP or carbon monoxide could act from without the lungs to elicit pulmonary vasoconstriction: *1*) by reducing the oxygen tension in extrapulmonary chemoreceptors, particularly in the brain or in the carotid arteries, to initiate a pulmonary vasoconstrictor reflex and *2*) by stimulating the release of catechol amines. The first possibility was excluded experimentally by showing that preferential reduction in the oxygen tension of blood leaving the brain did not elicit pulmonary vasoconstriction. The second possibility is unlikely since *1*) the pressor response to tolerable levels of hypoxemia does not involve the catechol amines and *2*) the usual changes in left heart pressures elicited by the catechol amines did not occur in the present study (29).

Intrapulmonary reflexes. Alveolar-vascular (30) and vascular-vascular axone (4) reflexes have been invoked by some investigators to account for the pulmonary vasoconstriction of acute hypoxia. It has been pointed out elsewhere that there is little evidence for the operation of such reflexes in the pressor response to acute hypoxia, since the pressor response may be elicited in the isolated lung after treatment with several pharmacologic denervators (3). Consequently, although undiscovered reflex pathways may conceivably exist within the lung, there is no experimental basis to implicate them in the pressor response to precapillary hypoxemia.

Precapillary vasoconstriction during acute hypoxia

Although previous attempts to identify the particular pulmonary vascular segment affected by acute hypoxia are conflicting in some respects, they have led to the general notion that the pulmonary *postcapillary* segments are involved (7). This view is based largely on the assumption that the breathing of hypoxic inspired mixtures effects far greater reductions in the oxygen tension of capillary and postcapillary segments than in the oxygen tension of mixed venous blood. However, the recent demonstrations that the diffusion of oxygen occurs rapidly through pulmonary precapillary vessels (31, 32) as well as through systemic arterioles (33) has seriously challenged this view. Indeed, the present study, as well as that of Boake, Daley, and McMillan (34), raises the possibility that even the pulmonary pressor response to breathing hypoxic gas mixtures may act by way of *precapillary,* rather than postcapillary, vasoconstriction.

The experiments involving the combined effects of DNP and oxygen breathing are of special interest with respect to establishing the length of the precapillary vessels that vasoconstricts when mixed venous oxygen tension is abnormally low. Thus, the failure of oxygen breathing to reverse completely the precapillary vasoconstricting effect of DNP may mean that not only the terminal precapillary segments, i.e., those that allow the rapid diffusion of oxygen through their walls, but also the more proximal precapillary segments may participate in the vasoconstriction. Unfortunately, the number of observations in the present study is too small for further analysis.

The demonstration that exaggerated precapillary hypoxemia elicits pulmonary vasoconstriction leaves unexplained the failure of large increments in pulmonary arterial pressure to occur during exercise when mixed venous oxygen tensions are quite low. This apparent discrepancy may arise, however, from the overwhelming of the active vasoconstricting influence of precapillary hypoxemia by the passive vasodilating effects of exercise.

SUMMARY

1) The present study investigated the relationship between pulmonary vascular resistance and

the oxygen tension of blood perfusing pulmonary precapillary vessels. For this purpose, dinitrophenol and carbon monoxide were used to reduce the oxygen tension of mixed venous blood without affecting the alveolar or pulmonary venous oxygen tensions.

2) A decrease in the oxygen tension of the mixed venous blood elicited an increase in pulmonary arterial pressure and in pulmonary vascular resistance.

3) Evidence was adduced to indicate that the pressor response originated in a direct effect of the mixed venous oxygen tension on the pulmonary precapillary vessels, rather than in either the pharmacologic effects of dinitrophenol or carbon monoxide, changes in the blood pH or carbon dioxide tension, or changes in the oxygen tension at some extrapulmonary chemosensitive site.

REFERENCES

1. Von Euler, U. S., and G. Liljestrand. Observations on the pulmonary arterial blood pressure in the cat. Acta physiol. scand. 1946, **12**, 301.
2. Logaros, G. Further studies of the pulmonary arterial blood pressure. Acta physiol. scand. 1947, **14**, 120.
3. Duke, H. N. Pulmonary vasomotor responses of isolated perfused cat lungs to anoxia and hypercapnia. Quart. J. exp. Physiol. 1951, **36**, 75.
4. Stroud, R. C., and H. Rahn. Effect of O_2 and CO_2 tensions upon the resistance of pulmonary blood vessels. Amer. J. Physiol. 1953, **172**, 211.
5. Von Euler, U. S., and F. Lishajko. Catechol amines in the vascular wall. Acta physiol. pharmacol. neerl. 1957, **6**, 295.
6. Nisell, O. The influence of blood gases on the pulmonary vessels of the cat. Acta physiol. scand. 1951, **23**, 85.
7. Fishman, A. P. Respiratory gases in the regulation of the pulmonary circulation. Physiol. Rev. 1961, **41**, 214.
8. Duke, H. N., and E. M. Killick. Pulmonary vasoconstriction to anoxia: its site of action. J. Physiol. (Lond.) 1952, **117**, 78P.
9. Motley, H. L., A. Cournand, L. Werko, A. Himmelstein, and D. Dresdale. The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. Amer. J. Physiol. 1947, **150**, 315.
10. Dirken, M. N. J., and H. Heemstra. Adaptation of the lung circulation to ventilation. Quart. J. exp. Physiol. 1948, **34**, 213.
11. Cournand, A. The mysterious influence of unilateral pulmonary hypoxia upon the circulation in man. Acta Cardiol. (Brux.) 1955, **10**, 429.
12. Nisell, O. Reactions of the pulmonary venules of the cat with special reference to the effect of the pulmonary elastance. Acta physiol. scand. 1951, **23**, 361.
13. Aviado, D. M., Jr., J. S. Ling, and C. F. Schmidt. Effect of anoxia on pulmonary circulation: reflex pulmonary vasoconstriction. Amer. J. Physiol. 1957, **189**, 253.
14. Duke, H. N. Site of action of anoxia on the pulmonary blood vessels of the cat. J. Physiol. 1954, **125**, 373.
15. Patel, D. J., and A. C. Burton. Active constriction of small pulmonary arteries in rabbit. Circulat. Res. 1957, **5**, 620.
16. Huckabee, W. Effect of phosphorylative uncoupling in tissues on cardiac output of intact animals. Fed. Proc. 1961, **20**, 131.
17. Stockton, A. B., and W. C. Cutting. Clinical circulatory effects of dinitrophenol. J. Amer. med. Ass. 1934, **103**, 912.
18. Guyton, A. C. Measurements of the respiratory volumes of laboratory animals. Amer. J. Physiol. 1947, **150**, 70.
19. Scholander, P. F. Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples. J. biol. Chem. 1947, **167**, 235.
20. Van Slyke, D. D., and J. M. Neill. The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. I. J. biol. Chem. 1924, **61**, 523.
21. Roughton, F. J. W. The kinetics of the reaction $CO + O_2Hb \leftrightarrows O_2 + COHb$ in human blood at body temperature. Amer. J. Physiol. 1945, **143**, 609.
22. Nahas, G. G. Spectrophotometric determination of hemoglobin and oxyhemoglobin in whole hemolyzed blood. Science 1951, **113**, 723.
23. Allen, T. H., and W. S. Root. An improved palladium chloride method for the determination of carbon monoxide in blood. J. biol. Chem. 1955, **216**, 319.
24. Dill, D. B., H. T. Edwards, and W. V. Consolazio. Blood as a physicochemical system. XI. Man at rest. J. biol. Chem. 1937, **118**, 635.
25. Roughton, F. J. W. Respiratory functions of blood *in* Handbook of Respiratory Physiology, W. M. Boothby, Ed. Randolph Field, Tex., U.S.A.F. School of Aviation Medicine, 1954.
26. Van Slyke, D. D., and J. Sendroy, Jr. Studies of gas and electrolyte equilibria in blood. XV. Line charts for graphic calculations by the Henderson-Hasselbalch equation, and for calculating plasma carbon dioxide content from whole blood content. J. biol. Chem. 1928, **79**, 781.

27. Duke, H. N., and E. M. Killick. Pulmonary vasomotor response of isolated perfused cat lungs to anoxia. J. Physiol. 1952, **117**, 303.
28. Bergofsky, E. H., D. E. Lehr, and A. P. Fishman. The effects of changes in hydrogen ion concentration on the pulmonary circulation. J. clin. Invest. 1962, **41**, 1492.
29. Goldring, R. M., G. M. Turino, G. Cohen, A. G. Jameson, B. G. Bass, and A. P. Fishman. The catecholamines in the pulmonary arterial pressor response to acute hypoxia. J. clin. Invest. 1962, **41**, 1211.
30. Rossier, P. H. and A. Bühlmann. Cor pulmonale et pathophysiologie alvéolaire. Cardiologia 1954, **25**, 132.
31. Staub, N. C. Gas exchange vessels in the cat lung. Fed. Proc. 1961, **20**, 107.
32. Jameson, A. G. Diffusion of gases from alveolus to precapillary arteries. Science 1963, **139**, 826.
33. Davies, P. W., and F. Brink, Jr. Microelectrodes for measuring local oxygen tension in animal tissues. Rev. sci. Instr. 1942, **13**, 524.
34. Boake, W. C., R. Daley, and I. K. R. McMillan. Observations on hypoxic pulmonary hypertension. Brit. Heart J. 1959, **21**, 31.