ANOXIA AND HUMAN PULMONARY VASCULAR RESISTANCE [1,2]

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Although it has been recognized for some time that anoxia may result in an elevation of the pressure in the pulmonary artery, the mechanism of this response has not been satisfactorily explained.

Von Euler and Liljestrand (1) in 1946 demonstrated in anesthetized cats that breathing 10% to 11% oxygen in nitrogen caused a rise in pulmonary artery pressure which was not affected by vagotomy or excision of the stellate ganglia, and which they therefore attributed to a direct effect of anoxia on the pulmonary vessels. Although left atrial pressure was sometimes recorded directly (2), no measurements of cardiac output were made, so that the pressor effects of changes in vascular resistance could not be separated conclusively from those due to variations in blood flow.

Motley and his associates (3) in 1947 demonstrated the pulmonary hypertensive effect of anoxia in five unanesthetized human subjects, using the technique of cardiac catheterization. A slight fall in cardiac output occurred simultaneously with the rise in pulmonary arterial pressure and an inverse relationship between the two was suggested. Nevertheless, the two possible mechanisms of (a) stasis in the smaller pulmonary vessels associated with a decreased output of the left ventricle, or (b) pulmonary arteriolar constriction, could not be segregated except by inference.

Recent reviews (4–6) of the pulmonary circulation in general, have accepted the role of anoxia in the pathogenesis of pulmonary hypertension, and have implied that the mechanism involved is pulmonary vasoconstriction. However, vasoconstriction with an increase in the pressure gradient and resistance to blood flow across the human pulmonary vascular bed has heretofore not been conclusively demonstrated to result from anoxia.

The study of pressure in any closed fluid system requires not only a quantitative knowledge of the flow through the system, but an understanding of the resistance to that flow. In analyzing the resistance to the flow of blood from the pulmonary artery through the lungs to the left ventricle, the factor of left atrial or pulmonary venous pressure must be segregated from pulmonary vascular resistance. Without knowledge of the pulmonary venous or "capillary" pressure, it cannot be determined whether changes in pulmonary arterial pressure, themselves, are due primarily to changes in cardiac output or to variations in pulmonary arteriolar resistance.

In 1948 Hellems and co-workers (7) described a method for determining pulmonary "capillary" pressure in man and have since given adequate proof that this pressure varies with the pulmonary venous pressure (8). When the pulmonary artery pressure, the pulmonary "capillary" pressure, and the cardiac output are determined simultaneously, the pulmonary arteriolar resistance may be calculated (9).

It should be emphasized, as is mentioned by Dexter and his co-workers (10), that the term "arteriolar" resistance is used in the physiological sense, since no vessels having the anatomical characteristics of systemic arterioles are found in the lung, and Miller (11) avoids the word in his book. However, it may be used in the physiological sense to designate small vessels between the large branches of the pulmonary artery and the true pulmonary capillaries.

With the foregoing in mind, it was decided to examine the effect of anoxia upon the pulmonary arteriolar resistance in man.

MATERIAL

A study of the effects of anoxia in the normal pulmonary circulation was the primary purpose of this investigation, although a comparison of results in patients with pulmonary hypertension of various types was thought advisable. A total of 32 patients was studied. Twenty-one were considered to have normal cardiovascular-pulmonary systems; four had left ventricular failure of mild to moderate degree; four, pulmonary hypertension associated with obstructive emphysema; one, cor pulmonale and a large diaphragmatic hernia; one, minimal diffuse pulmonary fibrosis, cause undetermined; one, recently compensated hypertensive cardiovascular disease.

METHOD

The majority of the subjects were studied in the post-absorptive state, sedated by 1½ to 3 grains of seconal. Cardiac catheterization was performed according to the method of Cournand and Ranges (12). A double lumen catheter 125 cm. in length was usually employed so that pulmonary "capillary" pressure and pulmonary arterial pressure could be measured simultaneously. Pulmonary "capillary" pressure was determined by the method of Hellems, Haynes and Dexter (8) from the tip of the catheter, which was advanced into a branch of the pulmonary artery as far as possible so as to occlude the branch and transmit pressure distal to the point of occlusion. Pulmonary arterial pressure was recorded from the second lumen which terminated in a side aperture 10 cm. proximal to the catheter tip. The Hathaway blood pressure recording apparatus and Hathaway variable impedance gauges were employed. These latter were connected to the catheter and the indwelling arterial needle by means of two three-way stopcocks, one of which was turned into a drip bottle containing 5% glucose and 20 mg. of heparin per liter whenever pressure recordings or blood samples were not being taken. The second three-way stopcock was opened to atmospheric pressure to establish a base line at the end of each pressure recording, and was used in exhausting air bubbles from the system when connecting the pressure gauges initially. In most instances, electrocardiograms, ballistocardiograms, brachial arterial, pulmonary arterial, and pulmonary "capillary" pressures were recorded simultaneously by means of a five channel optical oscillograph.

Multiple cardiac output determinations were made in 13 of the subjects by the direct Fick method. Two minute samples of expired air were collected in Douglas bags, analyzed for oxygen and CO_2 in the Haldane apparatus, and measured in a Tissot spirometer. Duplicate samples were required to check within 0.03%.

As will be noted in Table I, the resting ventilation and oxygen consumption values occasionally appeared to be lower than expected. This was attributed to the degree of sedation accomplished by the pre-medication described, and was reflected in the control arterial oxygen saturations, which averaged 93.1%, also slightly below accepted normal values.

Pulmonary artery and brachial artery blood samples of 10–12 cc. each were obtained simultaneously over a period of 45 to 60 seconds during the collection of expired air, and were analyzed for CO_2 and oxygen in the Van Slyke manometric apparatus. Duplicate analyses were required to check within 0.2 volume per cent.

Control pressure tracings and cardiac output determinations were obtained usually after the catheter and indwelling arterial needle had been in place for 15 to 30 minutes or more. The rubber mouthpiece and attached flutter valve for air collection and gas breathing was inserted before control pressures were recorded. By means of a three-way respiratory stopcock attached to the valve and mouthpiece, the subjects were then caused to inspire from an anesthesia bag kept partially filled at all times by adjustment of a direct connection to a pressure tank containing 13% oxygen in nitrogen. Expiration was to the outside, and could be diverted to the Douglas bags for sampling by means of a second three-way respiratory stopcock.

The effect of the low oxygen breathing on the pulmonary artery pressure was observed on a cathode ray oscilloscope incorporated in the Hathaway pressure recording apparatus, and permanent records were made at frequent intervals. When a maximum sustained effect on the pulmonary artery pressure had been observed, usually within five to 10 minutes, blood and gas samples for a second cardiac output determination were collected. Pressure recordings were made immediately before and after the blood sampling.

The subjects were then allowed to breathe room air, the changes in pulmonary arterial pressure again being observed at frequent intervals on the cathode-ray oscilloscope. After it was apparent that the effects of the 13% oxygen breathing had dissipated, usually in 10 to 15 minutes, blood and gas samples for a third cardiac output determination were collected, pressure recordings again being made immediately before and immediately after the samplings.

In addition to the 13 subjects in whom repeated cardiac output determinations were made, pressure changes were recorded before, during, and after breathing 13% oxygen in 15 others. Five subjects breathed 5% CO_2 in air and nine breathed 100% oxygen instead of, or in some instances in addition to, the 13% oxygen in nitrogen, and pressure changes were recorded in a similar fashion.

Mean pulmonary arterial, brachial arterial, and pulmonary "capillary" pressures were determined from the photographic recordings by planimetric integration over two to four respiratory cycles. Pressures recorded through the catheter were corrected for the measured level of the gauges, using 10 cm. above the fluoroscope table as the arbitrary zero point (10). In the cases where the cardiac outputs were determined, the mean pressures immediately before and after collection of blood and gas samples were averaged for use in calculations of resistance.

Pulmonary arteriolar resistance was calculated by the

formula:

$$R = \frac{PA - PC}{CO} \times 1332$$

Where   R = arteriolar resistance in dynes sec. cm.$^{-5}$
PA = mean pulmonary artery pressure in mm. Hg
PC = mean pulmonary "capillary" pressure in mm. Hg
CO = cardiac output in cc. per second
1332 = conversion factor from mm. Hg to dynes per cm.^{2}

Total peripheral resistance was calculated according to the formula:

$$TPR = \frac{BA}{CO} \times 1332$$

When TPR = total peripheral resistance in dynes sec. cm.$^{-5}$
BA = mean brachial artery pressure in mm. Hg
CO = cardiac output in cc. per second

RESULTS

(1) Mean pulmonary artery pressure

Of 27 subjects who breathed 13% oxygen (see Tables I and II), 20 were normal, four had left ventricular failure due to various causes (Nos. 11, 23, 24, and 25), two had pulmonary emphysema and cor pulmonale (Nos. 27 and 28), and one had early pulmonary fibrosis, cause undetermined. The last patient breathed 13% oxygen during each of two catheterization studies (Nos. 10 and 26).

On 26 occasions, the mean pulmonary artery pressure was satisfactorily calculated before and during 13% oxygen breathing, and was found to rise 0.3 to 14.1 mm. Hg in all but one instance, where it fell 3.3 mm. Hg in a case of cor pulmonale. The average elevation was 24.6% of the control pulmonary artery pressure. In 23 of these subjects the mean pulmonary artery pressure was calculated after recovery from the anoxia, and returned in the direction of the control level or below it in every instance.

The standard error of the mean of the differences (sm) between the mean pulmonary arterial pressures before and during 13% oxygen breathing was determined from standard statistical formulae.[4]

The observed difference of the means divided by sm gave a t value of 6.24. This shows a very significant difference between the two pulmonary arterial pressures, since a t value of 2.79 or above is significant at the 1% level. Thus, the observed

[4] Fisher, R. A., Statistical Methods for Research Workers. Oliver & Boyd, Edinburgh, 1950, 11th ed., Section 13.

differences would occur less often than once in a hundred times by chance alone.

Similar calculations using the differences in pulmonary arterial pressure during and after 13% oxygen breathing showed a t value of 6.75, also indicating a high degree of statistical significance. It is noteworthy that the pulmonary artery pressure before and after recovery from 13% oxygen breathing were not significantly different on statistical analysis.

Because of a possible relationship between hyperventilation and elevation of pulmonary artery pressure, the effect of breathing 5% CO_2 in air—which caused an average increase in ventilation of 280% in a previous series of observations in our laboratory (13)—was recorded in five normal subjects (Table III). As can be seen, there was no consistent change in the pulmonary artery pressures, a slight rise resulting in two instances, and a slight fall in the other three. This finding is in contrast to the 13 cases in Table I where 13% oxygen breathing resulted in less than a doubling of control ventilation minute volume in 11 cases, and slightly more than two times the control value in the other two instances. As has been pointed out, however, marked changes in pulmonary artery pressure occurred in this group. These findings seem to eliminate the mild hyperventilation of 13% oxygen breathing as a contributing factor in the observed elevations of pulmonary artery pressure.

(2) Mean pulmonary "capillary" pressure

Satisfactory recordings for determination of pulmonary "capillary" pressure were obtained in 16 subjects before, during, and after the induced anoxia. Twelve of these were normal individuals, three had left ventricular failure and one early pulmonary fibrosis of undetermined cause. (See Tables I and II.)

In 13 of the subjects, no consistent or significant change in the mean pulmonary "capillary" pressure was noted during the entire period of observation. Variations of less than 3 mm. Hg without relation to the inspired gas were observed, and the limits of accepted normal range (10) were not exceeded.

In the three patients with left ventricular failure, changes of greater magnitude were observed,

TABLE I
Physiologic effects of breathing 13% O₂

Subject Age, race, sex	Period*	Mean pressures mm. Hg			Art. O₂ cont. vol. %	Art. O₂ sat. %	M.V. O₂ cont. vol. %	A-V O₂ diff. vol. %	Min. vol. ventilation cc.	O₂ cons. cc./min.	C.O. L/min.	B.S. m²	Pulm. R. dynes sec. cm⁻⁵	% Rise pulm. R.
		P.A.	P.C.	B.A.										
1. N. J. 22 C.M. Normal	1	14.0	10.1	98.4	14.00	90.8	9.85	4.15	4,283	243	5.52	1.68	56.5	10.8
	2	16.4	11.5	107.1	12.99	84.3	9.03	3.96	7,381	248	6.26		62.6	
	3	15.0	12.6	120.2	14.89	96.6	9.97	4.92	4,756	253	5.14		37.3	
2. N. M. 43 C.F. Normal	1	15.8	8.4	62.8	15.02	91.0	11.12	3.90	2,518	160	4.09		144.6	12.8
	2	17.8	8.7	62.3	12.84	77.8	10.18	2.66	3,495	119	4.46	1.60	163.1	
	3	14.0	8.4	72.4	14.97	90.7	11.63	3.34	2,250	143	4.27		104.8	
3. A. H. 56 C.F. Normal	1	19.1	6.6		14.45	94.1	10.51	3.94	5,972	271	6.89		145.0	89.1
	2	24.8	7.3		12.08	78.7	7.79	4.29	9,830	219	5.10	1.44	274.2	
	3	18.9	6.5		14.22	92.6	9.12	5.10	5,527	226	4.43		223.7	
4. M. B. 60 C.M. Normal	1	18.0	6.7	107.5	18.57	96.1	13.21	5.36	4,270	227	4.24		212.9	68.1
	2	24.5	6.5	105.3	16.15	83.6	11.13	5.02	6,456	201	4.02	1.83	357.9	
	3	18.5	6.1	106.3	18.36	95.0	12.85	5.51	2,743	188	3.41		290.6	
5. P. S. 43 W.M. Normal	1	10.4	4.2	97.7	13.98	99.3	10.65	3.33	4,541	198	5.94		83.4	25.1
	2	14.5	4.8	110.6	12.03	85.4	9.16	2.87	9,015	213	7.43	1.60	104.3	
	3	11.2	4.5	110.2	13.21	93.8	10.05	3.16	4,133	208	6.58		81.4	
6. J. R. 36 C.M. Normal	1	15.3	4.6		13.10	89.7	9.48	3.62	4,522	203	5.59		152.9	46.6
	2	21.6	4.6		11.12	76.1	7.43	3.69	13,152	224	6.06	1.88	224.2	
	3	15.8	7.0		13.02	89.1	9.06	3.96	5,092	210	5.31		132.4	
7. W. B. 37 W.M. Normal	1	14.1	7.5	113.8	14.65	89.7	10.45	4.20	6,320	337	8.02		65.8	68.3
	2	16.8	7.8	105.6	11.79	72.1	7.09	4.70	9,805	306	6.50	1.78	110.6	
	3	13.2	7.6	117.8	14.33	87.7	9.46	4.87	6,211	297	6.10		73.4	
8. C. M. 49 W.M. Normal	1	17.2	7.3		15.48	90.3	10.85	4.63	5,185	238	5.13		154.2	11.9
	2	20.9	7.3		13.06	76.2	9.29	3.77	8,526	237	6.30	1.74	172.5	
	3	13.9	6.4		15.15	88.4	11.25	3.90	4,566	209	5.36		111.8	
9. J. S. 39 C.M. Normal	1	18.7	7.4		14.87		10.55	4.32	7,055	207	4.78		188.9	50.4
	2	19.0	6.7		13.50		8.77	4.73	7,894	164	3.46	1.85	284.1	
	3	17.2·	7.4		14.36		9.02	5.34	5,760	173	3.24		241.7	
10. L. J. 20 C.M. Early pul. fib.	1	26.6	14.4	143.9	16.69	92.7	11.89	4.80	6,056	349	7.27		134.1	101.5
	2	38.3	10.2	126.7	14.09	78.3	10.07	4.02	9,168	334	8.31	2.42	270.2	
	3	33.1	11.0	141.7	16.47	91.5	12.52	3.95	7,720	374	9.45		186.9	
11. R. E. 59 C.M. Congestive failure	1	43.6		91.5	15.22	93.5	5.39	9.83	4,076	381	1.94			
	2	49.8		103.3	13.10	80.5	3.87	9.23	5,536	317	1.72	1.59		
	3	41.5		78.7	14.39	88.4	5.19	9.20	3,142	354	1.93			
12. C. P. 30 C.M. Normal	1				17.80	95.1	13.42	4.38	2,942	236	4.70			
	2				15.38	82.2	11.82	3.56	6,747	225	6.64	1.86		
	3				17.78	95.0	13.57	4.21	4,991	249	6.24			
13. S. S. 58 W.M. Normal	1				16.26	94.9	12.49	3.77	3,489	167	4.14			
	2				14.48	84.6	11.70	2.78	8,853	186	6.68	1.96		
	3				15.74	91.9			2,851	165				

P. A. = pulmonary artery pressure
P. C. = pulmonary capillary pressure
B. A. = brachial artery pressure

M. V. = mixed venous
C. O. = cardiac output
B. S. = body surface
R. = pulmonary arteriolar resistance

* Period 1 = control observations
2 = observations during 13% O₂ breathing
3 = observations after recovery

TABLE II

Effect of breathing 13% O₂ in N₂ on brachial artery, pulmonary artery, and pulmonary capillary pressures

Subject Age, race, sex	Diagnosis	Mean press.	Control	13% O₂	Recovery	% Change P.A.
14. C. C. 46 C.M.	Normal	P. A. P. C. B. A.	16.6 9.9 119.4	19.5 9.8 115.6	16.8 12.7 116.8	+ 17.5
15. M. C. 73 W.M.	Normal	P. A. P. C. B. A.	12.2 11.5 108.0	13.2 10.7 105.2	11.9 10.3 106.7	+ 8.2 .
16. B. A. 21 C.F.	Normal	P. A. P. C. B. A.	14.0 12.9 103.5	17.2 9.6 89.7	15.2 10.4 94.8	+ 22.9
17. W. M. 49 C.M.	Normal	P. A. B. A.	17.5 79.9	20.2 77.9	18.2 72.0	+ 15.4
18. J. M. 22 C.M.	Normal	P. A. B. A.	15.9 75.5	24.3 80.5	22.3 97.9	+ 42.1
19. O. B. 37 C.M.	Normal	P. A. B. A.	16.6 98.0	30.1 95.0	17.9 89.4	+ 81.3
20. H. J. 43 W.M.	Normal	P. A. B. A.	16.8 97.5	35.9 107.9	18.5 105.6	+113.7
21. L. W. 19 W.M.	Normal	P. A.	17.1	22.2	17.1	+ 29.3
22. U. R. 44 C.M.	Normal	P. A. B. A.	11.1 95.3	13.9 100.1		+ 25.2
23. S. J. ? 40 C.M.	Hypertensive C. V. disease cong. fail.	P. A. P. C. B. A.	26.3 13.6 140.4	35.3 19.6 144.0	25.0 13.8 148.3	+ 34.2
24. I. W. 29 C.F.	Post partum myocarditis cong. fail.	P. A. P. C. B. A.	30.9 24.2 94.5	39.4 19.1 93.9	27.7 18.2 93.0	+ 27.5
25. W. B. 54 C.M.	Calcif. pericarditis cong. fail.	P. A. P. C. B. A.	29.6 ' 11.9 93.0	37.6 14.7 91.4	27.6 18.9 92.3	+ 27.0
26. L. J. 19 C.M.	Early pulmonary fibrosis	P. A. B. A.	21.1 101.6	29.1 75.2	23.8 79.8	+ 37.9
27. J. L. 54 W.M.	Emphysema; cor pulmonale	P. A.	35.3	32.0		− 9.3
28. C. C. 40 W.M.	Emphysema; cor pulmonale	P. A. B. A.	89.4 87.0	93.2 96.7		+ 4.2

and the upper limit of normal pulmonary "capillary" pressure was exceeded in each case. One patient showed a progressive rise, another a progressive fall, during the period of observation, and the third showed a transient rise of pulmonary "capillary" pressure during the induced anoxia, with a subsequent fall toward the control value.

No statistical significance could be shown between the differences in pulmonary "capillary" pressure breathing air and 13% oxygen, the t value being 0.22, as compared to the t value of 2.13 required to indicate significance at the 5% level.

(3) Cardiac output

In 13 individuals, determinations of cardiac output were made by the direct Fick method before, during, and after the period of 13% oxygen breath-

TABLE III

Effect of breathing 5% CO_2 in air on pulmonary arterial pressure

Subject Age, race, sex	Diagnosis	Mean press.	Control	5% CO_2	Recovery
18. J. M. 22 C.M.	Normal	P. A.	24.6	26.9	19.6
		B. A.	112.3	121.4	101.6
20. H. J. 43 W.M.	Normal	P. A.	17.8	17.3	16.8
		B. A.	95.0	103.1	97.5
21. L. W. 19 W.M.	Normal	P. A.	20.1	18.0	17.8
22. U. R. 44 C.M.	Normal	P. A.	11.9	15.9	11.1
		B. A.	95.8	88.0	97.5
29. H. K. 25 C.M.	Normal	P. A.	21.8	21.2	19.8

ing, as described. Eleven of these subjects were normal, one had left ventricular failure, and one early pulmonary fibrosis by roentgenogram. (See Table I.)

In seven of these subjects who were normal, there was a slight to moderate increase in cardiac output during the period of anoxia, followed by a return in the direction of the control value in the six where the recovery output was determined satisfactorily.

In four of the subjects, a continuous fall in cardiac output was noted during the entire period of observation. This was considered to be due to an elevation of the observed initial value resulting from anxiety, and the finding of a relatively low arteriovenous oxygen difference with a high oxygen consumption at the time of the control determination of cardiac output in three of these individuals (Nos. 3, 7, and 9) confirmed this impression (14). A similar elevation of cardiac output was found during recovery from anoxia in the case of early pulmonary fibrosis (No. 10).

The case with left ventricular failure showed an insignificant diminution of cardiac output during the anoxic period (No. 11).

Statistical analysis of this group as a whole, however, showed the cardiac output during induced anoxia to be not significantly different from that observed during the control or recovery periods.

(4) Pulmonary arteriolar resistance

The pulmonary artery and pulmonary "capillary" pressures and the cardiac output were satis-

factorily determined before, during, and after 13% oxygen breathing in 10 individuals, and the respective pulmonary arteriolar resistances were calculated. Nine of these subjects were normal and had normal control values. The patient with early pulmonary fibrosis of undetermined cause had a slightly elevated control mean pulmonary arterial pressure (Table I).

Each subject showed an increase in pulmonary arteriolar resistance during 13% oxygen breathing, with a fall during recovery in the direction of or below the control value. The anoxic increase in resistance varied from 10.8% to 101.5% of the air-breathing level, with an average rise of 48.5%.

Figures 1, 2, and 3 demonstrate the changes in pulmonary arteriolar resistance that were characteristically observed. Figure 1 is taken from the control record of P.S. (case No. 5), at which time the mean pulmonary artery pressure was 10.4 mm. Hg, the mean pulmonary "capillary" pressure was 4.2 mm. Hg, and the cardiac output was 5.94 L/min. The pulmonary arteriolar resistance was 83.4 dynes sec. cm.$^{-5}$.

Figure 2 is taken from the record of the same subject after five minutes of 13% oxygen breathing. At this time the mean pulmonary artery pressure had risen to 14.5 mm. Hg, and the mean pulmonary "capillary" pressure was 4.8 mm. Hg. The cardiac output had risen to 7.43 L/min. and the pulmonary arteriolar resistance to 104.3 dynes sec. cm.$^{-5}$.

Figure 3 represents the same subject 10 minutes after 13% oxygen breathing was discontinued. The mean pulmonary artery pressure had fallen to 11.2 mm. Hg, the pulmonary "capillary" pressure was 4.5 mm. Hg, and the cardiac output was 6.58 L/min. At this time the pulmonary arteriolar resistance had returned to 81.4 dynes sec. cm.$^{-5}$.

The T wave deformity seen in the electrocardiogram (ECG) of the three figures represents an artifact produced by proximity of the left arm electrode to one of the Hathaway variable impedance pressure gauges.

Especially noteworthy was the fact that pulmonary arteriolar resistance increased during anoxia in the four individuals mentioned above in whom the cardiac output fell continuously throughout the observation period. Also the one subject (No. 10) whose cardiac output rose continuously during
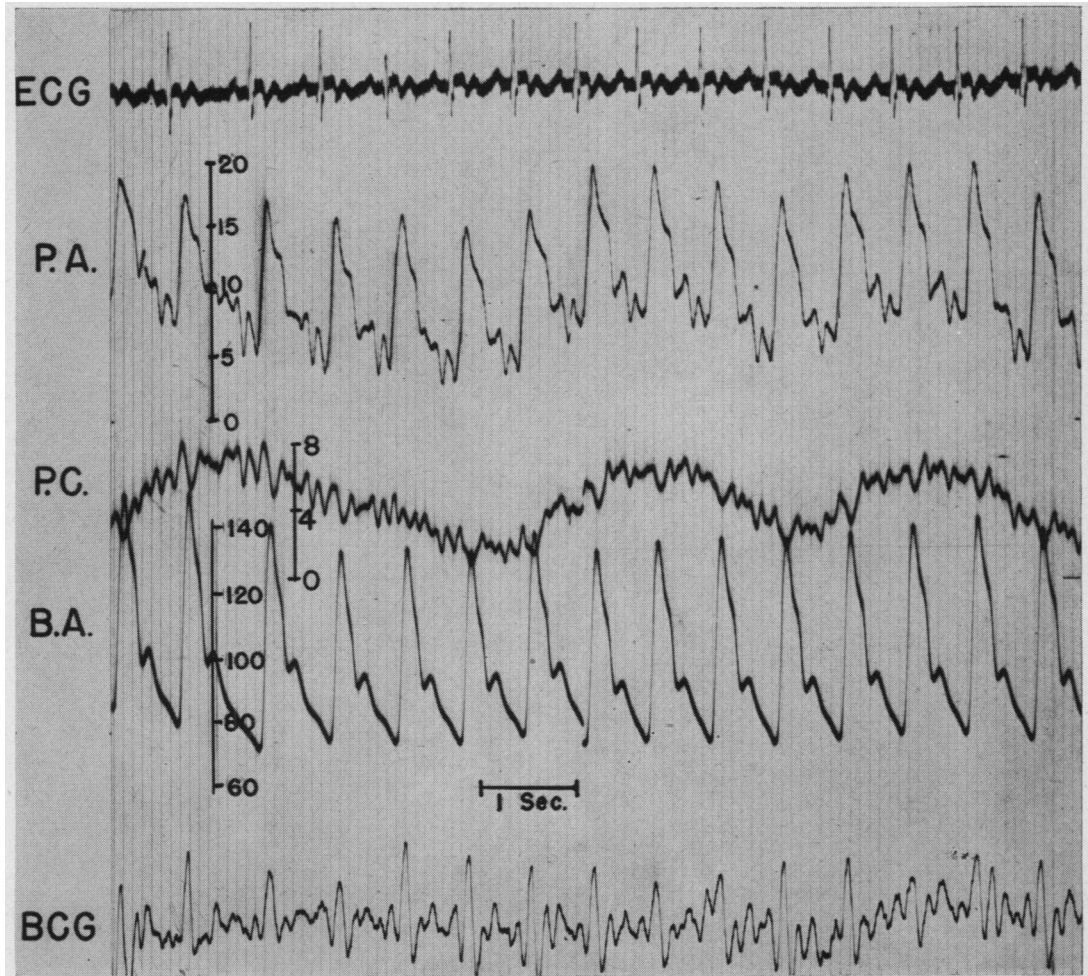
FIG. 1. EXCERPT FROM THE CONTROL PRESSURE TRACING OF P. S. (CASE 5)

The mean pulmonary artery pressure (P.A.) is 10.4 mm. Hg, the mean pulmonary "capillary" pressure (P.C.) is 4.2 mm. Hg, and the cardiac output 5.94 L/min. The pulmonary arteriolar resistance is therefore 83.4 dynes sec. cm.$^{-5}$.

the period of observation, showed a fall in pulmonary arteriolar resistance after discontinuance of the 13% oxygen breathing, as did the other nine subjects. Thus the lack of direct correlation between cardiac output and pulmonary arteriolar resistance was effectively demonstrated in these five cases.

The t value calculated from sm and the observed mean of the differences between the pulmonary arteriolar resistances before and during the induced anoxia, was 3.99. This shows a very significant difference between the two resistances, since a t value of 3.25 or above is significant at the 1% level. Thus, the observed differences would

occur less often than once in a hundred times by chance alone.

Similar calculations using the differences in pulmonary arteriolar resistance during and after 13% oxygen breathing showed a t value of 7.44, also indicating a high degree of statistical significance. It is noteworthy that the pulmonary arteriolar resistances before and after 13% oxygen breathing were not significantly different on statistical analysis.[5]

[5] To determine the variability in measurements of mean pulmonary artery pressures and mean pulmonary "capillary" pressures, and in the cardiac output, the following studies were made. In 21 subjects of the present group duplicate resting measurements of pulmonary artery pres-
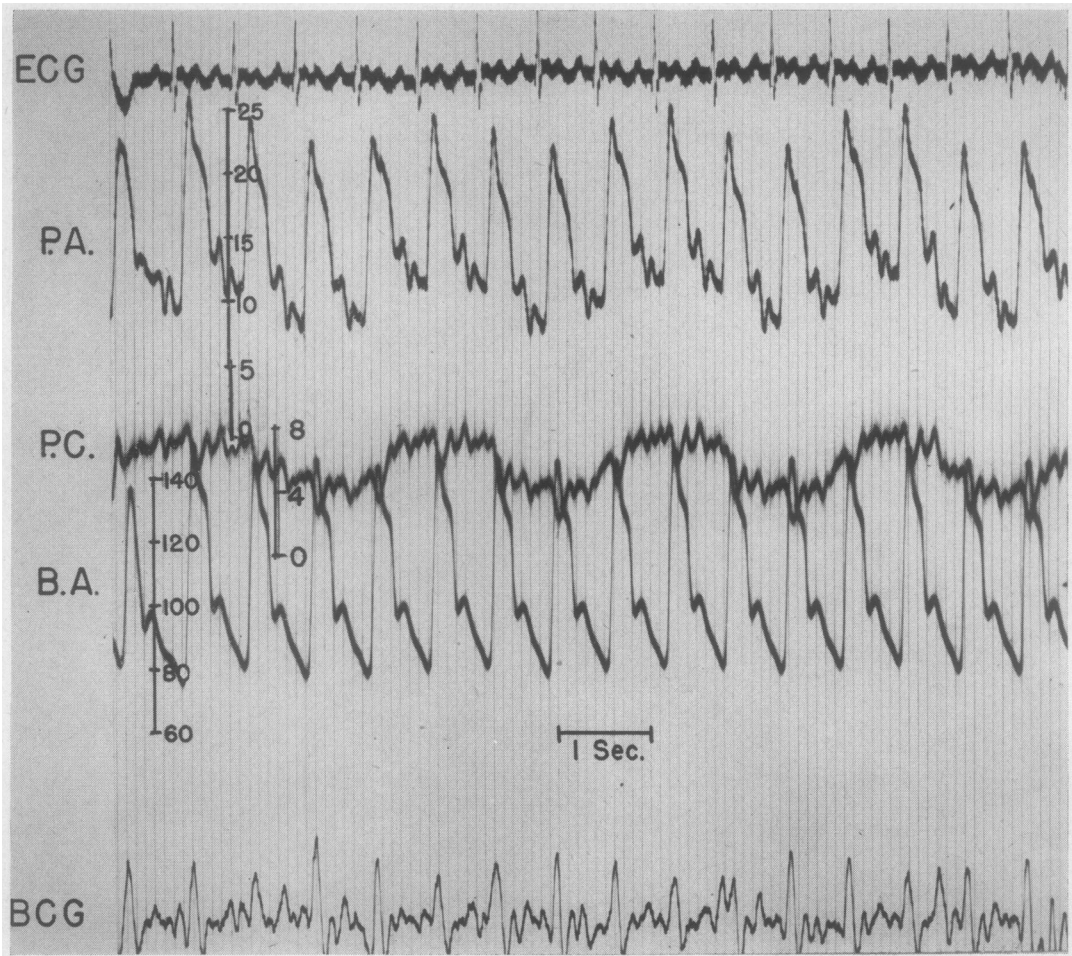
FIG. 2. EXCERPT FROM THE PRESSURE TRACING OF THE SAME INDIVIDUAL AS FIGURE 1, TAKEN AFTER FIVE MINUTES OF 13% OXYGEN BREATHING

The mean pulmonary artery pressure (P.A.) is now 14.5 mm. Hg, the mean pulmonary "capillary" pressure (P.C.) 4.8 mm. Hg, and the cardiac output 7.43 L/min. The pulmonary arteriolar resistance is 104.3 dynes sec. cm.$^{-5}$.

(5) Related findings

The brachial artery pressure was measured directly before and during 13% oxygen breathing in 20 subjects, and after the anoxia in 18 of these. No

sure were made before and after breathing 13% oxygen. In 10 controls duplicate determinations of resting pulmonary artery pressure were made before and after duplicate Fick cardiac outputs. The mean difference between the 31 pairs of measurements in the resting state was 1.7 mm. Hg, giving a standard error of the mean of 1.7 ± 0.58 mm. Hg.

Similar calculations were made for the pulmonary "capillary" pressures, using duplicate resting measurements in the 13 of the present group with normal pressures, and in eight control subjects with normal pres-

constant variations were noted in the calculated mean pressures, although minor changes of a few mm. Hg in either direction were the rule. The total peripheral vascular resistances before, dur-

sures. The mean difference of duplicate measurements was 1.3 mm. Hg. The standard deviation of the differences was 1.18 mm. Hg. The standard deviation of the mean of the difference was 0.29 mm. Hg, giving a standard error of the mean of the differences equal to 1.3 ± 0.57 mm. Hg.

In nine resting control subjects duplicate determinations of the Fick cardiac output were made. The mean difference in the duplicates was 9.7%. The standard deviation of the differences was 8.14%. The standard deviation of the mean of the difference was 2.9%. The standard error of the mean was 9.7 ± 5.8%.
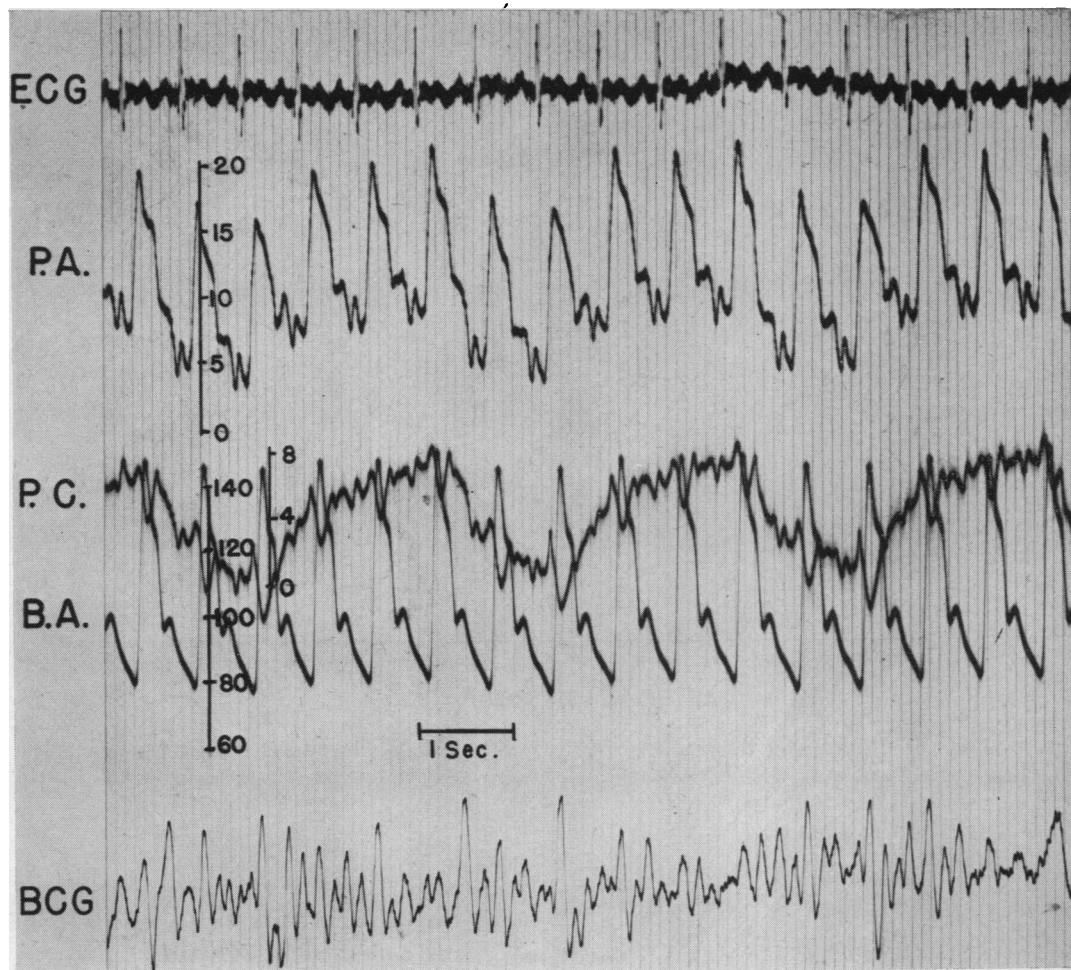
FIG. 3. PRESSURE RECORDING FROM THE SAME INDIVIDUAL AS FIGURES 1 AND 2, TAKEN 10 MINUTES AFTER AIR BREATHING WAS SUBSTITUTED FOR 13% OXYGEN

The mean pulmonary artery pressure (P.A.) has fallen to 11.2 mm. Hg, the mean pulmonary "capillary" pressure (P.C.) is 4.5 mm. Hg, and the cardiac output 6.58 L/min. The pulmonary arteriolar resistance is 81.4 dynes sec. cm.$^{-5}$. Note the change in the ballistocardiogram (BCG) from that in Figure 1.

ing, and after 13% oxygen breathing were calculated in seven of the 13 subjects who had multiple cardiac output determinations. Variations up to 20% of control values were observed in both directions again without constant relation either to the changes in cardiac output or pulmonary arteriolar resistance or to mean brachial artery pressure.

The ballistocardiograms were characterized by relatively normal complexes during control observations on the majority of normal subjects (Figure 1). However, during and after 13% oxygen breathing the complexes invariably became ab-

normal in such a way that quantitative calculations therefrom were considered to be impossible. An example of the observed change is shown in Figures 2 and 3. It cannot be stated at this time whether these ballistic alterations associated with anoxia were due to a direct effect on the myocardium. A study of this problem and of the relation between cardiac outputs determined from the ballistocardiogram and by the direct Fick method will be considered in a subsequent communication.

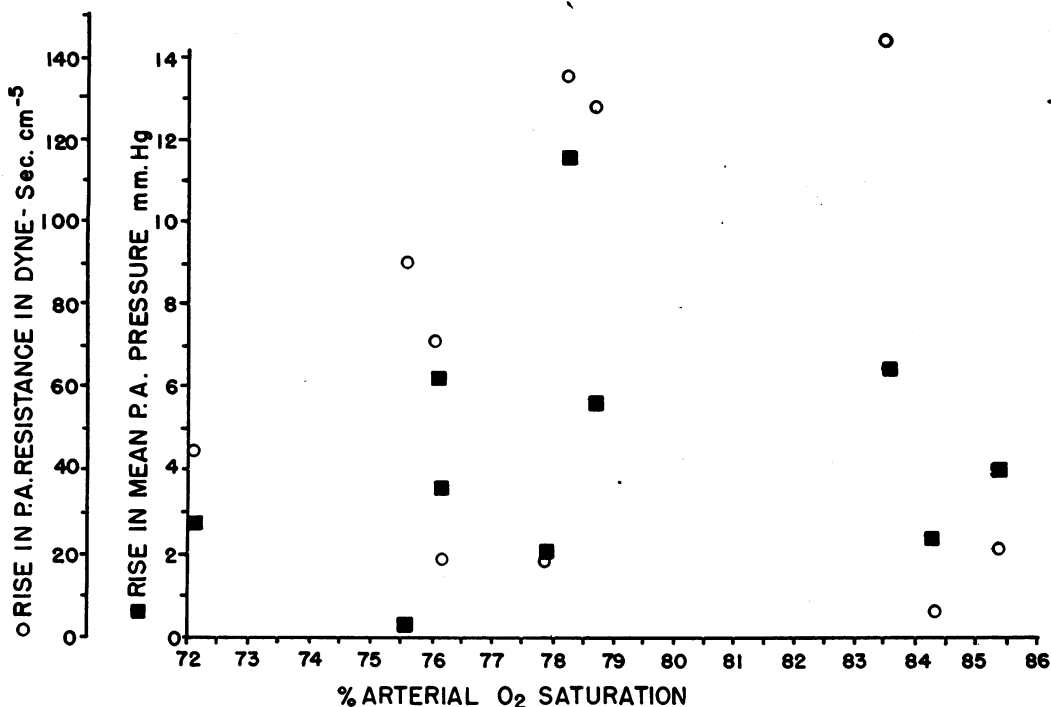In 12 subjects, the arterial oxygen saturation was reduced an average of 13.1% during 13%

FIG. 4. LACK OF CORRELATION BETWEEN ARTERIAL O_2 SATURATION AND THE OBSERVED ELEVATIONS OF PULMONARY ARTERY PRESSURE OR PULMONARY ARTERIOLAR RESISTANCE

oxygen breathing to levels between 72.1% and 85.4% (av. 79.9% sat.), the mean control saturation being 93.1% (Table I). In the individual cases there was no direct correlation between the specific value to which the arterial oxygen saturation was depressed and the observed elevation of pulmonary artery pressure or pulmonary arteriolar resistance (Figure 4).

The oxygen consumption during 13% oxygen breathing was increased 5 to 21 cc./min. in five of the 13 subjects in whom multiple cardiac output determinations were made and fell 1 to 64 cc./ min. in the others, including the patient with left ventricular failure and the four subjects mentioned above whose initial oxygen consumption was considered to be elevated because of anxiety.

During anoxia the arterio-venous oxygen difference fell slightly below the control and recovery values in nine of the subjects in whom this determination was made, and rose slightly in four others, three of whom had the low initial A–V oxygen differences presumably associated with anxiety.

DISCUSSION

Hellems, Haynes and Dexter (8) have presented convincing evidence that the method described by them and employed in the present study for obtaining pulmonary "capillary" pressure in man is valid, and that such pressure is nearly identical and varies directly with pulmonary venous pressure. Pressures obtained through catheters occluding small branches of the pulmonary artery and of the pulmonary vein have been measured by them in dogs (7) and in human subjects having atrial septal defects (8), with the finding of close agreement between the two pressures in each group. Blood obtained from a catheter recording pulmonary "capillary" pressure has been repeatedly found by them (8) and also in our laboratory to be fully saturated with oxygen, indicating the absence of contamination by pulmonary artery blood. Repeated observations by fluoroscopy and by study of continuous pressure tracings during slow withdrawal of the catheter occluding a branch of the pulmonary artery, have shown a slight but definite snap of the tip of the catheter as it suddenly ceases

to obstruct the vessel, and becomes subject to arterial pulsations, which in turn are abruptly recorded on the tracings.

The pressure gradients measured in the present study indicated resistance to the flow of blood from the main pulmonary artery to the capillary bed adjacent to the catheter tip, occluding a small branch of the pulmonary artery. It is assumed that this locally recorded pulmonary "capillary" pressure is representative of the entire lung, and thus can be used in conjunction with the cardiac output to calculate the total pulmonary vascular resistance.

It is apparent from the data presented (particularly of oxygen consumption) that a steady state was not achieved throughout the period of observation in all cases, especially in Nos. 3, 7, 9, and 10, as noted. It is also apparent that the effects of anoxia had not always entirely subsided when the recovery measurements were made. However, the fact that the pulmonary vascular resistances during the anoxic periods always changed in the same direction, and were significantly different statistically from the resistances beforehand and afterward, indicates that the changes observed were independent of variations in oxygen consumption (utilization).

The results indicate that anoxia caused a prompt increase in the pulmonary vascular resistance, which was in turn rapidly dissipated when the anoxia was relieved. This increase in resistance to blood flow must have occurred as a result of vasoconstriction.

Although vasoconstriction in the systemic circulation is largely mediated through the autonomic nervous system, it has been generally believed that the lesser circulation is not subject to autonomic influences. In 1939, Hamilton, Woodbury and Vogt (15) studied the effect of various drugs upon the pulmonary arterial and venous pressures in unanesthetized dogs, and concluded that there was no evidence of autonomic control of the pulmonary circulation. Von Euler and Liljestrand (1), in studying anesthetized cats breathing 10% to 11% oxygen in nitrogen, found that the resulting rise in pulmonary artery pressure was not affected by vagotomy or excision of the stellate ganglia. Since no associated changes in directly measured left atrial pressure were observed (2), the anoxic rise in pulmonary artery pressure was considered to be mediated through a local effect of the degree of oxygenation of the venous blood in the arterioles of the lungs. Dirken and Heemstra (16), however, found that resection of part of the sympathetic trunk increased· pulmonary blood flow in rabbits, while vagotomy had no effect. These same observers (17) have reported intense pulmonary constriction in experimental anoxia of the lung exposed to nitrogen while the opposite lung was exposed to oxygen. Previously published data from this laboratory (18) showed that in four of six cases with pulmonary hypertension, intravenous injection of the autonomic blocking agent, tetraethylammonium chloride, caused a significant fall in pulmonary arteriolar resistance. In four patients with normal pulmonary artery pressure, intravenous TEAC did not lower pulmonary arteriolar resistance, suggesting that in some cases of pulmonary hypertension, at least one component of the increased resistance is mediated through the autonomic nervous system.

At the present time, therefore, it has not been determined whether the pulmonary arteriolar vasoconstriction demonstrated to result from oxygen want is mediated through the autonomic nervous system, or depends on a direct local effect upon the pulmonary vessels.

Since the work of Motley and his associates (3) demonstrating the pulmonary hypertensive effect of anoxia in five unanesthetized human subjects, it has been suggested by investigators in the same laboratory (19), McMichael (20) and others, that long-standing pulmonary disease may lead to persistent pulmonary hypertension by the same mechanism which produced it in Motley's acute experiments. The possibility appeared that if one component of chronic pulmonary hypertension is anoxic vasoconstriction, breathing 100% oxygen should reverse this effect, at least in part. Also, it was noted that Von Euler and Liljestrand (1) demonstrated a fall in pulmonary artery pressure of anesthetized cats during 100% oxygen breathing, which they felt might be due to a relief of the excessive desaturation of venous blood inherent in their experimental conditions.

In view of these considerations, the effect on the pulmonary artery pressure of 10–20 minutes of 100% oxygen breathing was recorded in nine subjects (Table IV). Two of these were normal,

TABLE IV

Effect of 100% O₂ breathing on pulmonary arterial pressure

Subject Age, race, sex	Diagnosis	Mean press.	Control	100% O₂	Recovery	% Change P. A.
18. J. M. 22 C.M.	Normal	P. A. B. A.	22.3 97.9	22.4 101.1	24.6 112.3	+ 0.4
22. U. R. 44 C.M.	Normal	P. A. B. A.	11.1 97.5	12.8 92.5	11.1 95.3	+15.3
30. R. S. 68 W.M.	Hypt. C-V disease	P. A. B. A.	20.6 118.8	21.4 128.0		+ 3.9
26. L. J. 19 C.M.	Early pulmonary fibrosis	P. A. B. A.	25.4 100.6	25.4 101.6	21.1 101.6	0
27. J. L. 54 W.M.	Emphysema; cor pulmonale	P. A.	35.1	28.7	35.3	−18.3
28. C. C. 40 W.M.	Emphysema; cor pulmonale	P. A. B. A.	88.9 98.0	85.3 107.7	89.4 87.0	− 4.1
31. G. A. 59 W.M.	Diaphrag. hernia; cor pulmonale	P. A. P. C. B. A.	41.1 11.9 104.1	35.3 15.1 129.0	41.5 15.6 130.5	−14.1
32. D. H. 60 W.M.	Emphysema; cor pulmonale	P. A.	57.4	47.2	47.5	−17.8
33. J. S. 54 W.M.	Emphysema; cor pulmonale	P. A.	39.6	35.3		−10.9

one had compensated systemic hypertension, one early pulmonary fibrosis, and five had chronic pulmonary hypertension with cor pulmonale. A slight rise or no change in mean pulmonary artery pressure was found in the subjects with control values that were normal or nearly so, whereas a definite decline in pulmonary artery pressure was found in the five individuals with chronic pulmonary hypertension. In three of the five, the mean pulmonary artery pressure resumed its previous elevation soon after the subjects were returned to breathing ambient air.

Although no cardiac output determinations were made during these observations, and the number of cases was too small for statistical analysis, the results are consistent with the possibility that anoxic elevation of pulmonary arteriolar resistance may be a contributing and reversible factor in the production and maintenance of at least some types of chronic pulmonary hypertension.

In support of this view is the finding by Cournand (6) of a linear correlation between the degree of arterial oxygen unsaturation and the degree of pulmonary hypertension in a large group of patients with chronic pulmonary emphysema. Fac-

tors other than anoxia are usually simultaneously at work, however, as has been clearly pointed out by Ferrer and associates and others (19, 5). Distortion of the pulmonary flow-vascular capacity ratio results in pulmonary hypertension in most types of chronic lung disease when there is increased right ventricular output, hypervolemia, increased blood viscosity due to polycythemia, or progressive anatomic restriction of the pulmonary vascular bed.

Anoxia may also participate in the variety of pulmonary hypertension associated with mitral stenosis and with left ventricular failure. Here the retrograde transmission of rising left atrial pressure is mechanically responsible for a similar rise in pulmonary capillary and pulmonary artery pressure, but with maintenance of an essentially normal gradient in the early stages (9). However, it has been demonstrated by Dexter and his co-workers (10) that when the pulmonary "capillary" pressure in mitral stenosis exceeds a critical value of 20–25 mm. Hg an additional element of pulmonary arteriolar constriction supervenes, resulting in a further precipitous rise in pulmonary artery pressure. Since this critical range of pul-

monary "capillary" hydrostatic pressure approximates the osmotic pressure of plasma (21), it appears reasonable to assume that the delivery of oxygen from the alveolar air to the pulmonary capillary blood may be interfered with due to excessive congestion and beginning edema formation. The role in this embarrassment played by thickening of the capillary basement membrane in mitral stenosis (22) remains a matter of conjecture. However, the arteriolar constriction which provides the abrupt increment in pulmonary artery pressure observed in both mitral stenosis and in left ventricular failure (10, 23) may in turn be the result of anoxia.

Dexter and his associates (10) have pointed out that this increased resistance may be considered teleologically as a compensatory mechanism preventing to some extent sudden increases in flow through the capillaries to the incompetent left ventricle or to the narrow mitral valve and therefore protecting the pulmonary capillaries from a higher hydrostatic pressure and pulmonary edema. It appears likely that such a mechanism may be initiated by anoxia.

Although anoxia and its attendant increase in pulmonary arteriolar resistance may be regarded as a common denominator in many instances of pulmonary hypertension, it should be emphasized, as pointed out by Liljestrand (2), that the same mechanism may also provide valuable local regulation of blood flow normally, and in conditions where there is unequal oxygenation in various parts of the lung. The flow of blood will be directed away from parts of the lung which are badly aerated and distributed to parts where the purposes of the lesser circulation can be better fulfilled, without noticeable change in the pulmonary artery pressure.

It has been pointed out by Cournand (6) that such delicate adjustment is notably absent in chronic pulmonary disease, where, in addition to pulmonary hypertension, one of the principal causes of physiologic disorder is the disturbance in local alveolar ventilation-perfusion relationships.

SUMMARY

1. The effects of anoxia on the human pulmonary circulation were studied by means of cardiac catheterization.

2. On 26 occasions, 13% oxygen breathing caused an average rise in mean pulmonary artery pressure of 24.6% above the control levels.

3. No significant change in mean pulmonary "capillary" pressure was observed in 16 subjects who breathed 13% oxygen.

4. No statistically significant change in cardiac output could be attributed to anoxia in 13 subjects in whom multiple Fick determinations were made.

5. Simultaneous determinations of mean pulmonary artery and pulmonary "capillary" pressures and cardiac output were made before, during, and after 13% oxygen breathing in ten individuals. The pulmonary arteriolar resistances calculated therefrom showed an average increase of 48.5% during the low-oxygen breathing, a difference which is shown to be highly significant statistically.

6. Changes observed in the systemic blood pressure, total peripheral resistance, ballistocardiogram, arterial oxygen saturation, oxygen consumption, and arterio-venous oxygen difference are described.

7. Evidence for and against autonomic mediation of the observed anoxic pulmonary vasoconstriction is reviewed.

8. The increase in pulmonary vascular resistance observed to result from anoxia is discussed as to its probable contribution to the pulmonary hypertension of chronic lung disease, mitral stenosis, and left ventricular failure.

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