JCI The Journal of Clinical Investigation

STUDIES OF PULMONARY HYPERTENSION I. PULMONARY CIRCULATORY DYNAMICS IN PATIENTS WITH PULMONARY EMPHYSEMA AT REST

Paul N. G. Yu, … , S. John Vernarelli, Carol Gouverneur

J Clin Invest. 1953;32(2):130-137. https://doi.org/10.1172/JCI102721.

Research Article

STUDIES OF PULMONARY HYPERTENSION I. PULMONARY CIRCULATORY DYNAMICS IN PATIENTS WITH PULMONARY EMPHYSEMA AT REST[1]

By PAUL N. G. YU, FRANK W. LOVEJOY, JR., HOWARD A. JOOS, ROBERT E. NYE, JR., AND WILLIAM S. McCANN

WITH THE TECHNICAL ASSISTANCE OF S. JOHN VERNARELLI AND CAROL GOUVERNEUR

(From the Chest Laboratory of the Department of Medicine of the University of Rochester School of Medicine and Dentistry and the Medical Clinics of Strong Memorial and Rochester Municipal Hospitals, Rochester, N. Y.)

(Submitted for publication October 13, 1952; accepted November 19, 1952)

Studies of the pulmonary circulation in patients with pulmonary emphysema have been reported from several laboratories (1–11). These reports include observations at rest, during exercise, after intravenous digoxin, and during and after breathing low and high oxygen concentrations in the inspired air. Pulmonary hypertension is frequently observed at rest in these patients during cardiac catheterization. In most instances pulmonary artery pressure increases even after mild exercise, whereas the pulmonary artery pressure of normal subjects remains unchanged. Induced anoxia (breathing 10 per cent or 13 per cent oxygen in nitrogen) causes a definite rise in the pulmonary artery pressure, while breathing 100 per cent oxygen reduces the pressure slightly. Furthermore, there is a significant negative correlation between the magnitude of pulmonary hypertension and the oxygen saturation of the arterial blood.

The literature regarding "pulmonary capillary" pressure (12, 13) and pulmonary arteriolar resistance in patients with pulmonary emphysema is meager (8, 10, 11). The effects of hypercapnia upon the pulmonary circulation are not yet well defined (3, 4).

It is the purpose of this paper, (*a*) to report the "pulmonary capillary" pressure and pulmonary arteriolar resistance of 18 patients with pulmonary emphysema at rest and (*b*) to correlate various determinants including the partial pressure of CO_2 in the arterial blood (P_{aCO_2}) with pressure and resistance in the pulmonary circuit. In a subsequent manuscript (14) the hemodynamic effects of induced hypercapnia (breathing either 3.6 per cent or 6 per cent CO_2 in the inspired air) will be described in normal subjects and in patients with chronic pulmonary disease.

[1] This study was supported in part by a research grant-in-aid from the National Heart Institute of the National Institutes of Health, Public Health Service, and Hochstetter Fund.

MATERIAL AND METHOD

Eighteen patients were studied of whom 16 were men and 2 women, ranging in age from 38 to 76 years. All showed clinical, radiological and laboratory evidence of pulmonary emphysema. Two of the patients (D. C. and C. N.) had pulmonary fibrosis and one (C. N.) also had hypertensive cardiovascular disease. In three patients (C. N., J. M., and J. G.), the electrocardiogram showed evidence of right ventricular hypertrophy. Three patients (J. K., J. G., and M. M.) were digitalized for congestive heart failure prior to cardiac catheterization. In all cases the ratio between the residual volume and total capacity of the lung (RV/TC) was 48 per cent or more.

Lung volume and its subdivisions were determined by the helium dilution method described by Meneely and Kaltreider (15). The blood oxygen content and capacity were determined according to the method of Van Slyke and Neill (16). The technique for measuring partial pressure of CO_2 and O_2 in arterial blood (P_{aCO_2} and P_{aO_2}) was adapted from the method of Riley, Proemmel and Franke (17).

Cardiac catheterization was carried out in each patient 2 or 3 hours after a light breakfast, according to the method of Cournand and Ranges (18). A single or double lumen catheter was employed. The catheter was first advanced as far as possible into the distal radicle of one of the pulmonary arteries in order to occlude its lumen. The "pulmonary capillary" pressure was recorded by the method of Hellems, Haynes and Dexter (12, 13), satisfying the criteria of Fowler and his associates (19). With the double lumen catheter, the "pulmonary capillary" pressure and the pulmonary artery pressure were recorded simultaneously. When a single lumen catheter was used, the "pulmonary capillary" pressure was measured first and pressure was recorded continuously as the catheter was slowly withdrawn until its tip was just distal to the bifurcation of the pulmonary artery.

TABLE I—*Summary data of measurements of pulmonary function and circulation in 18 patients with pulmonary emphysema*

Case	Age	Sex	Vital capacity Obs.	Vital capacity Pred.	Residual volume Obs.	Residual volume Pred.	RV/TC×100	Arterial blood Sat.	Arterial blood P_{aCO_2}	Arterial blood P_{aO_2}	O_2 cons. *cc./min./M²BSA*	Cardiac output *L./min.*	Cardiac index *L./min./M²BSA*	Pulmonary artery pressure *mm. Hg* S	Pulmonary artery pressure *mm. Hg* D	Pulmonary artery pressure *mm. Hg* M	"Pulmonary capillary" pressure *mm. Hg*	PAm–PCm gradient *mm. Hg*	Total pulmonary resistance *dynes-sec.-cm.⁻⁵*	Pulmonary arteriolar resistance *dynes-sec.-cm.⁻⁵*	Right auricular mean pressure *mm. Hg*
			cc.	%	*cc.*	%	%	%	*mm. Hg*													
E. S.	38	F	2370	75	2220	247	48	93	—	72	169	9.6	6.1	17	7	9	6	3	70	25	2
L. F.	54	M	2020	61	2540	171	56	98	36	71	168	4.2	3.2	15	9	13	8	5	237	95	5
D. C.	72	M	1660	43	2010	110	56	85	42	64	126	7.6	3.6	23	9	13	10	3	131	32	9
E. J.	49	M	2410	61	1950	160	45	92	49	73	156*	7.4	4.0	25	9	15	9	6	162	65	2
L. P.	66	M	2180	66	2020	135	48	80	42	45	152	8.6	4.9	25	12	16	10	6	149	57	6
T. J.	45	M	2170	59	3900	351	64	94	40	59	136	6.5	3.9	25	10	16	7	9	197	99	3
R. M.	67	M	2600	72	3960	243	60	92	34	63	138	4.7	2.6	28	12	17	9	8	284	132	2
H. C.	63	M	1680	45	1820	110	52	93	42	65	152	4.5	2.5	28	14	20	7	13	358	232	8
H. W.	52	M	1820	50	3090	186	63	84	35	52	162	7.0	4.3	29	10	21	3	18	240	206	2
B. R.	51	M	1690	47	2280	136	58	83	43	50	160	5.8	3.4	38	15	22	10	12	303	166	6
J. T.	62	M	914	27	1530	336	85	81	57	65	131	3.5	2.3	37	16	24	6	18	554	408	6
C. N.	55	M	1340	39	1510	98	53	90	55	63	108	3.4	2.3	34	11	26	−1	27	610	638	0
J. M.	52	M	1370	35	5400	335	80	93	45	60	164	5.5	3.8	31	20	27	7	20	410	292	5
J. K.	76	M	990	32	3680	261	79	89	60	62	166	3.8	2.7	46	19	27	12	15	558	314	7
J. C.	65	M	920	28	3890	265	81	91	48	70	196	10.7	6.6	46	21	28	9	19	412	280	6
F. Z.	48	M	2000	53	2890	258	59	90	45	60	125	4.5	2.9	38	21	30	9	21	532	370	4
J. G.	61	M	920	28	3430	235	79	82	71	48	145	4.0	3.2	37	20	31	9	22	780	440	7
M. M.	63	F	890	37	3000	277	77	74	67	46	155	4.7	3.3	75	28	49	10	39	834	666	7

* Oxygen consumption obtained at rest the following day.

A No. 19 needle was inserted into either the brachial or femoral artery. The cardiac output was determined according to the direct Fick principle. Oxygen consumption was measured by a method similar to that described previously (20). Mixed venous and arterial blood samples were obtained simultaneously as the oxygen consumption was determined. Pressures were recorded in both the pulmonary and systemic arteries after measuring the cardiac output. Finally, the catheter was withdrawn to the right ventricle, right auricle, and superior vena cava. Blood samples and pressure records were obtained from each site.

Pressures were recorded by means of a Statham strain gauge connected to an amplifier in a multi-channel direct-writing oscillograph.[2] The electrocardiogram and pneumogram were recorded simultaneously. The pressure records were calibrated with a mercury manometer. Systolic and diastolic pressures were measured for at least three respiratory cycles and the average values calculated. Mean pressures were measured by planimetric integration of the pressure tracings during at least two respiratory cycles. The arbitrary zero point of all pressures was 6.5 cm. below the angle of Louis with the patient in a recumbent position.

Total pulmonary resistance and pulmonary arteriolar resistance were calculated as follows (21):

$$TPR = \frac{PAm}{\dot{Q}_b} \times 1332$$

$$PAR = \frac{PAm - \text{“PCm”}}{\dot{Q}_b} \times 1332$$

where TPR and PAR = resistance in dynes-sec.-cm.$^{-5}$

" PAm = mean pulmonary artery pressure in mm. Hg.

" "PC" = mean "pulmonary capillary" pressure in mm. Hg.

" $\dot{Q}_b$ = cardiac output in cc./second.

" 1332 = conversion factor from mm. Hg to dynes/cm.^{2}

OBSERVATIONS

The pertinent data are summarized in Table I. Some of the data have been subjected to statistical analysis. Correlations between the various determinants and the pulmonary pressures and resistances are shown in Table II and plotted in Figures 1 and 2.

1. *Pulmonary artery and "capillary" pressures and gradient*

The mean pulmonary artery pressure exceeded 15 mm. Hg in 14 of the 18 patients. The highest

[2] Sanborn Poly-Viso Cardiette

TABLE II

Coefficients of correlation between various determinants in 18 patients with pulmonary emphysema

	Mean pulmonary artery pressure	Mean "pulmonary capillary" pressure	Total pulmonary resistance	Pulmonary arteriolar resistance
Arterial blood p_{CO_2} (P_{aCO_2})	+0.693**	+0.284	+0.742**	+0.651**
$\frac{RV}{TC} \times 100$	+0.624**	+0.081	+0.544*	+0.420
Arterial blood O_2 saturation	−0.490*	−0.002	−0.318	−0.312
Cardiac index	−0.396	+0.208	−0.518*	−0.452
Arterial blood p_{O_2} (P_{aO_2})	−0.426	+0.093	−0.085	−0.272
Right auricular pressure	+0.292	+0.643**	+0.279	−0.114

** Highly significant.
* Significant.

pressure was 49 mm. Hg. The RV/TC of this patient was 77 per cent, the arterial blood oxygen saturation 74 per cent, and the P_{aCO_2} 67 mm. Hg. In general, the degree of pulmonary hypertension varied directly with the severity of hypercapnia, emphysema and anoxia, and inversely with the vital capacity. The mean pulmonary artery pressure did not correlate significantly with either cardiac index or "pulmonary capillary" pressure.

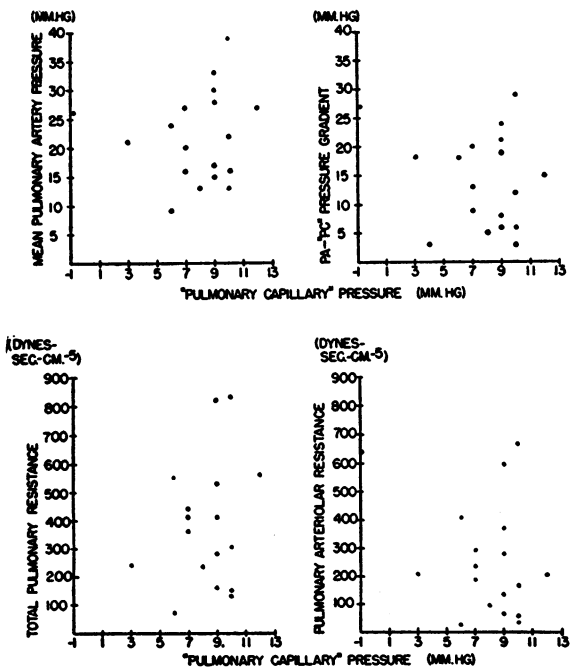

FIG. 1. "PULMONARY CAPILLARY" PRESSURE IN PULMONARY EMPHYSEMA IS PLOTTED AGAINST PULMONARY ARTERY PRESSURE, THE PA—"PC" GRADIENT, TOTAL PULMONARY RESISTANCE AND PULMONARY ARTERIOLAR RESISTANCE

No significant relationship exists between "pulmonary capillary" pressure and any of these factors.

In none of these 18 patients did the "pulmonary capillary" pressure exceed 12 mm. Hg, the upper limit in normal subjects (22). A representative tracing of patient M. M. is shown in Figure 3.

The pulmonary artery-"pulmonary capillary" pressure gradient was greater than 10 mm. Hg (the upper limit of normal) in 11 of the 18 patients. The correlation between the gradient and the pulmonary artery pressure was highly significant (R = + 0.930). Similarly, the gradient

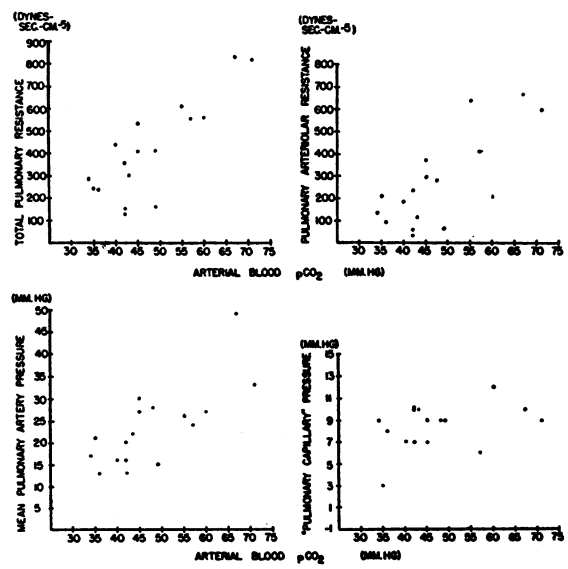

FIG. 2. THE P_{aCO_2} IN PULMONARY EMPHYSEMA IS RELATED TO THE PRESSURE AND RESISTANCE IN THE PULMONARY CIRCUIT

Note the significant correlation between the P_{aCO_2} and each of the following: pulmonary artery pressure, total pulmonary resistance and pulmonary arteriolar resistance. There is no correlation between the P_{aCO_2} and "pulmonary capillary" pressure. See text for discussion.

correlated significantly with the P_{aCO_2} ($R = +0.557$). No significant correlation was found between the gradient and "pulmonary capillary" pressure, arterial blood oxygen saturation, P_{aO_2} or cardiac index.

2. Pulmonary resistance

The total pulmonary resistance exceeded the upper limit of normal (250 dynes-sec.-cm.$^{-5}$) in 14 patients. Pulmonary arteriolar resistance was greater than 150 dynes-sec.-cm.$^{-5}$ (the upper limit of normal) in 13 patients. Pulmonary resistance was increased in all patients whose mean pulmonary artery pressure was 20 mm. Hg or more. Correlations of the pulmonary resistance with various determinants are presented in Table II. Neither the total pulmonary resistance nor the pulmonary arteriolar resistance correlated significantly with "pulmonary capillary" pressure ($R = 0.020$ and -0.353, respectively).

3. Cardiac output and index

Cardiac output and index varied considerably among patients. The cardiac index of six patients was less than 2.8 liters/minute/M_2 and exceeded 5.0 liters/minute/M_2 in two patients. These indices approximate the lower and upper limits of normal subjects respectively (21). There was a significant negative correlation between cardiac index and total pulmonary resistance. Cardiac index did not correlate significantly with the mean pulmonary artery pressure, mean "capillary" pressure, or pulmonary arteriolar resistance.

4. Anoxia and hypercapnia

The arterial blood oxygen saturation of all but two patients was less than 94 per cent. The lowest value was 74 per cent. P_{aO_2} of all patients was considerably reduced. A significant negative correlation was demonstrated between the arterial blood oxygen saturation and mean pulmonary artery

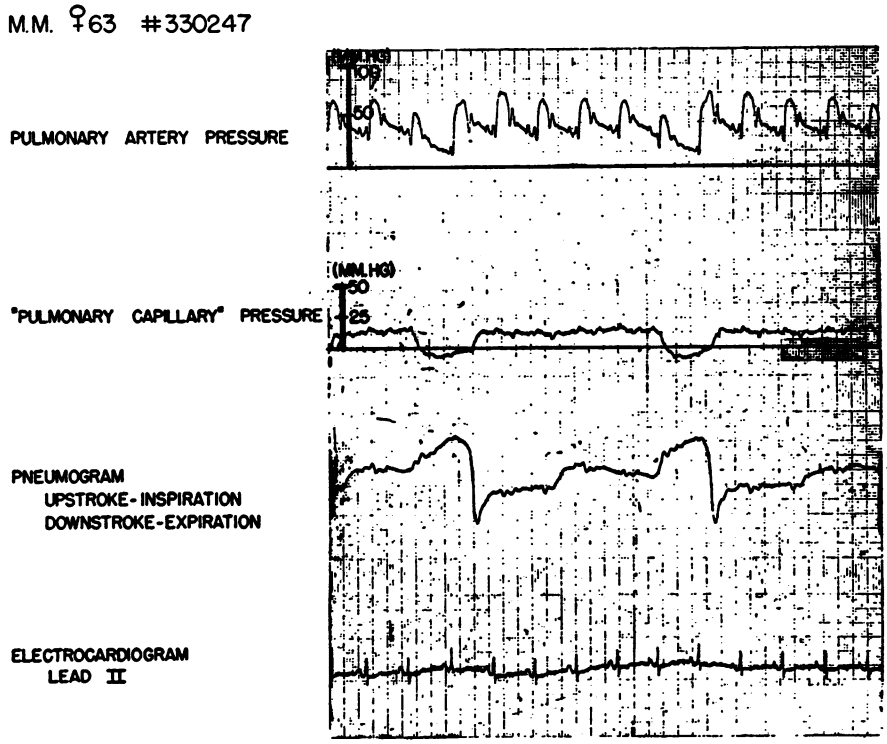

FIG. 3. TRACINGS OF PULMONARY ARTERY AND "PULMONARY CAPILLARY" PRESSURES IN PATIENT M. M.

Note the high pulmonary artery pressure with normal "pulmonary capillary" pressure and the difference in magnitude between pulmonary artery diastolic and "pulmonary capillary" pressures.

pressure. Arterial blood oxygen saturation did not correlate significantly with "pulmonary capillary" pressure, total pulmonary resistance, or pulmonary arteriolar resistance. Similarly, the P_{aO_2} did not correlate significantly with pressure and resistance in the pulmonary circuit.

The P_{aCO_2} exceeded 44 mm. Hg in 10 patients, and in all patients with a mean pulmonary artery pressure of more than 22 mm. Hg. A highly significant correlation was observed between the P_{aCO_2} and each of the following: mean pulmonary artery pressure, total pulmonary resistance, and pulmonary arteriolar resistance. The level of statistical significance was distinctly higher than that of the arterial blood oxygen saturation correlated with the same respective factors. On the other hand, there was no significant correlation between the P_{aCO_2} and either "pulmonary capillary" pressure or cardiac index.

5. Lung volume studies

The absolute amount of residual air exceeded normal in all but one patient, and the ratio between residual volume and total capacity (RV/TC) was more than 48 per cent in all cases. Conversely, the vital capacity was less than 76 per cent of the value predicted according to age and height in each instance. The RV/TC ratio correlated significantly with both mean pulmonary artery pressure and total pulmonary resistance. There was no correlation between the RV/TC ratio and either pulmonary arteriolar resistance or "pulmonary capillary" pressure.

DISCUSSION

The mechanism for the production of pulmonary hypertension in pulmonary emphysema is quite different from that in mitral stenosis and left ventricular failure. In the latter conditions, the increasing pressure is primarily registered in the left auricle and is transmitted to the pulmonary vein, "pulmonary capillary," and pulmonary artery. The pulmonary hypertension, therefore, is essentially "post-capillary" in nature. Factors such as anoxia and secondary changes of the pulmonary vascular tree may also play a role in elevating the pulmonary artery pressure (9, 23).

One important anatomic change in pulmonary emphysema is the destruction of small vessels in the lung with consequent restriction and narrowing of the vascular bed. This distorts the ratio between pulmonary blood flow and vascular capacity and is at least partly responsible for the production of chronic pulmonary hypertension. Our studies, and those of other investigators (8, 11) have shown that the pulmonary artery pressure of these patients may increase three- or fourfold when the "pulmonary capillary" pressure is still within the normal range. These observations suggest that the pulmonary hypertension produced in pulmonary emphysema is essentially "pre-capillary" in nature. Since the "pulmonary capillary" pressure is an index of left auricular pressure (24), our data support the concept that patients with pulmonary emphysema show no evidence of left ventricular failure (4, 8). The changes in the lungs and in the right side of the heart are usually progressive and eventually irreversible.

The findings of normal "pulmonary capillary" pressure in these patients were in agreement with the observations of Dexter and his associates (8) and Fowler, Westcott, and Scott (25). The latter investigators (25) observed a significant correlation between the "pulmonary capillary" pressure and the pulmonary artery diastolic pressure in 54 subjects, including 10 patients with chronic pulmonary disease, predominantly pulmonary emphysema. The data on our 18 patients with pulmonary emphysema did not yield a significant correlation between the "pulmonary capillary" pressure and the pulmonary artery diastolic pressure ($R = +0.416$). The discrepancy is explained in that pulmonary hypertension was absent or minimal in many of their patients. The pulmonary artery diastolic and "pulmonary capillary" pressures in those patients were both low, and a good correlation between the two would be expected.

Patients with mitral stenosis and left ventricular failure show a parallel elevation of both pressures, because the pulmonary artery diastolic pressure is directly related to the "pulmonary capillary" pressure. Our unpublished observations in patients with mitral stenosis show an excellent correlation between the "pulmonary capillary" pressure and the pulmonary artery diastolic pressure as long as the "pulmonary capillary" pressure remains under 30 mm. Hg. When the "pulmonary

capillary" pressure exceeds 30 mm. Hg, there may be a precipitous increase in the pulmonary artery diastolic pressure and the two pressures no longer correlate. These observations were confirmed by the recent data of Lukas and Dotter (26). This distinction between patients with pulmonary emphysema and those with mitral stenosis is important because the mechanism of pressure change in the pulmonary circuit is quite different in the two diseases.

In patients with pulmonary emphysema, the main physiologic disturbances in the ventilatory and circulatory systems are anoxia and hypercapnia. The effects of anoxia on the pulmonary circulation in man have been studied and discussed by many workers (4, 10, 11, 27, 28), and the importance of anoxia in the pathogenesis of pulmonary hypertension has been generally accepted (3, 4, 10). Our patients with chronic pulmonary disease showed a significant negative correlation between the degree of pulmonary hypertension and the oxygen saturation of the arterial blood. This correlation was especially significant when the oxygen saturation was less than 82 per cent (4). The resulting pulmonary hypertension is probably caused by pulmonary vasoconstriction with increased pulmonary arteriolar resistance (10). Fowler and his co-workers (10) have shown that breathing 13 per cent oxygen in nitrogen caused a consistent rise in mean pulmonary artery pressure and mean pulmonary arteriolar resistance above the control value but did not alter the "pulmonary capillary" pressure or cardiac output. Our observations (29) in several patients with pulmonary emphysema agree with those reported by Fowler and his associates. Other factors contributing to pulmonary hypertension may be polycythemia and hypervolemia resulting from anoxia (3, 4, 30). Polycythemia and hypervolemia may cause engorgement of the pulmonary vessels with further reduction of the distensibility of the pulmonary vascular bed. This may enhance pulmonary hypertension whenever the blood flow is increased.

Cournand and associates (3, 4) have stated, "The influence of CO_2 retention in the blood upon the pulmonary circulation is not as yet well defined." The blood CO_2 is frequently elevated in patients with moderate and marked pulmonary emphysema. Harvey and her associates (30) demonstrated a highly significant correlation between the P_{aCO_2} and mean pulmonary artery pressure in a recent study of 48 cases of chronic pulmonary disease. They found no correlation between P_{aCO_2} and cardiac index. The present studies also show a highly significant correlation between the P_{aCO_2} and the mean pulmonary artery pressure and pulmonary resistance. In contrast, no significant correlation was found between the P_{aCO_2} and either "pulmonary capillary" pressure or cardiac index. We are fully aware that correlation and causation are not the same. However, the findings suggest that hypercapnia as well as anoxia may be important in the genesis of pulmonary hypertension in patients with chronic pulmonary disease. This is supported by our studies of patients with chronic pulmonary disease, as they breathed 6 per cent CO_2. The mean pulmonary artery pressure rose during the period of CO_2 breathing. This was not due to anoxia, because there was a concomitant increase in the arterial blood oxygen saturation in some patients. The implications and significance of these changes during induced hypercapnia will be presented in a subsequent paper (14). The general cardiocirculatory effects of hypercapnia in patients with chronic pulmonary diseases have been discussed elsewhere (31–33).

SUMMARY

Hemodynamic studies are reported in 18 patients with pulmonary emphysema at rest.

1. The degree of pulmonary hypertension varied directly with the severity of emphysema, hypercapnia and anoxia.

2. "Pulmonary capillary" pressure was normal in all cases.

3. The pulmonary artery-"pulmonary capillary" pressure gradient exceeded normal in 11 patients and correlated significantly with pulmonary artery pressure and with the severity of hypercapnia.

4. Total pulmonary resistance and pulmonary arteriolar resistance exceeded normal in all instances of pulmonary hypertension but correlated well only with the degree of CO_2 retention.

5. Cardiac output and index were variable. Cardiac index correlated negatively with the total pulmonary resistance.

6. The oxygen saturation of arterial blood varied inversely with mean pulmonary artery pres-

sure but did not parallel the other determinants. The oxygen tension of arterial blood did not vary predictably with any of the determinants.

7. The carbon-dioxide tension of arterial blood correlated closely with mean pulmonary artery pressure, total pulmonary resistance and pulmonary arteriolar resistance, but not with the "pulmonary capillary" pressure.

8. The ratio of residual volume to total capacity (RV/TC) varied directly with mean pulmonary artery pressure and total pulmonary resistance.

Certain mechanism in the pathogenesis of pulmonary hypertension are discussed in detail. The role of anoxia is confirmed and attention is directed to the probable importance of carbon-dioxide retention in elevating pulmonary artery pressure and increasing pulmonary vascular resistance.

ACKNOWLEDGMENT

The authors wish to express their appreciation and thanks to Dr. S. Lee Crump, Assistant Professor of Radiation Biology and Scientist (Statistics), Atomic Energy Project, University of Rochester, for his help and criticism on the statistical aspects of this study, and to Mrs. Julia N. Gooding for preparing the manuscript.

REFERENCES

1. Cournand, A., Recent observations on the dynamics of the pulmonary circulation. Bull. N. Y. Acad. Med., 1947, **23**, 27.
2. Riley, R. L., Himmelstein, A., Motley, H. L., Weiner, H. M., and Cournand, A., Studies of the pulmonary circulation at rest and during exercise in normal individuals and in patients with chronic pulmonary disease. Am. J. Physiol., 1948, **152**, 372.
3. Cournand, A., Some aspects of pulmonary circulation in normal man and in chronic cardiopulmonary diseases. Circulation, 1950, **2**, 641.
4. Ferrer, M. I., New concepts of chronic cor pulmonale. N. Y. State J. Med., 1950, **50**, 1817.
5. Ferrer, M. I., Harvey, R. M., Cathcart, R. T., Webster, C. A., Richards, D. W., Jr., and Cournand, A., Some effects of digoxin upon the heart and circulation in man. Digoxin in chronic cor pulmonale. Circulation, 1950, **1**, 161.
6. McMichael, J., Heart failure of pulmonary origin. Edinburgh M. J., 1948, **55**, 65.
7. Hickam, J. B., and Cargill, W. H., Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. J. Clin. Invest., 1948, **27**, 10.
8. Dexter, L., Pulmonary circulatory dynamics in health and disease at rest. Bull. New England Med. Center, 1949, **11**, 240.
9. Borden, C. W., Wilson, R. H., Ebert, R. V., and Wells, H. S., Pulmonary hypertension in chronic pulmonary emphysema. Am. J. Med., 1950, **8**, 701.
10. Westcott, R. N., Fowler, N. O., Scott, R. C., Hauenstein, V. D., and McGuire, J., Anoxia and human pulmonary vascular resistance. J. Clin. Invest., 1951, **30**, 957.
11. Dexter, L., Whittenberger, J. L., Gorlin, R., Lewis, B. M., Haynes, F. W., and Spiegl, R. J., The effect of chronic pulmonary disease (Cor pulmonale and hypoxia) on the dynamics of the circulation in man. Trans. A. Am. Physicians, 1951, **64**, 226.
12. Hellems, H. K., Haynes, F. W., Dexter, L., and Kinney, T. D., Pulmonary capillary pressure in animals estimated by venous and arterial catheterization. Am. J. Physiol., 1948, **155**, 98.
13. Hellems, H. K., Haynes, F. W., and Dexter, L., Pulmonary 'capillary' pressure in man. J. Appl. Physiol., 1949, **2**, 24.
14. Lovejoy, F. W., Jr., Yu, P. N. G., Joos, H. A., Nye, R. E., Haroutunian, L. M., and McCann, W. S., Studies of pulmonary hypertension. II. The role of carbon dioxide retention in the pathogenesis of pulmonary hypertension. To be published.
15. Meneely, G. R., and Kaltreider, N. L., The volume of the lung determined by helium dilution. Description of the method and comparison with other procedures. J. Clin. Invest., 1949, **28**, 129.
16. Peters, J. P., and Van Slyke, D. D., Quantitative Clinical Chemistry, Vol. II, Baltimore, Williams and Wilkins, 1932.
17. Riley, R. L., Proemmel, D. D., and Franke, R. E., A direct method for determination of oxygen and carbon dioxide tensions in blood. J. Biol. Chem., 1945, **161**, 621.
18. Cournand, A., and Ranges, H. A., Catheterization of the right auricle in man. Proc. Soc. Exper. Biol. & Med., 1941, **46**, 462.
19. Fowler, N. O., Westcott, R. N., Scott, R. C., and McGuire, J., The effect of nor-epinephrine upon pulmonary arteriolar resistance in man. J. Clin. Invest., 1951, **30**, 517.
20. Bruce, R. A., Lovejoy, F. W., Jr., Pearson, R., Yu, P. N. G., Brothers, G. B., and Velasquez, T., Normal respiratory and circulatory pathways of adaptation in exercise. J. Clin. Invest., 1949, **28**, 1423.
21. Gorlin, R., Haynes, F. W., Goodale, W. T., Sawyer, C. G., Dow, J. W., and Dexter, L., Studies of the circulatory dynamics in mitral stenosis. II. Altered dynamics at rest. Am. Heart J., 1951, **41**, 30.
22. Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B. G., Goodale, W. T., and Hellems, H. K., Studies of the pulmonary circulation in man at rest. Normal variations and the interrelations between increased pulmonary blood flow, elevated pulmonary arterial pressure, and high pulmonary "capillary" pressure. J. Clin. Invest., 1950, **29**, 602.

23. Parker, F., Jr., and Weiss, S., The nature and significance of structural changes in the lungs in mitral stenosis. Am. J. Path., 1936, **12**, 573.
24. Dow, J. W., and Gorlin, R., Pulmonary 'capillary' pressure as an index of left atrial mean pressure in dogs. Federation Proc., 1950, **9**, 33.
25. Fowler, N. O., Jr., Westcott, R. N., and Scott, R. C., Pulmonary artery diastolic pressure: its relationship to pulmonary arteriolar resistance and pulmonary "capillary" pressure. J. Clin. Invest., 1952, **31**, 72.
26. Lukas, D. S., and Dotter, C. T., Modifications of the pulmonary circulation in mitral stenosis. Am. J. Med., 1952, **12**, 639.
27. Motley, H. L., Cournand, A., Werko, L., Himmelstein, A., and Dresdale, D., The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. Am. J. Physiol., 1947, **150**, 315.
28. Fishman, A. P., McClement, J., Himmelstein, A., and Cournand, A., Effects of acute anoxia on the circulation and respiration in patients with chronic pulmonary disease. J. Clin. Invest., 1952, **31**, 770.
29. Unpublished data.
30. Harvey, R. M., Ferrer, M. I., Richards, D. W., Jr., and Cournand, A., Influence of chronic pulmonary disease on the heart and circulation. Am. J. Med., 1951, **10**, 719.
31. McCann, W. S., The effects of emphysema of the lungs on the cerebral and coronary circulation. Post-Grad. M. J., 1951, **9**, 225.
32. McCann, W. S., Lovejoy, F. W., Jr., and Yu, P. N. G., The failing lung. New York State J. Med., 1952, **52**, 1983.
33. McCann, W. S., Lovejoy, F. W., Jr., and Yu, P. N. G., Cardio-circulatory aspects of the pneumoconiosis. Presented at the Seventh Saranac Symposium, September 22–26, 1952, Saranac Lake, N. Y.