

# STUDIES OF PULMONARY HYPERTENSION I. PULMONARY CIRCULATORY DYNAMICS IN PATIENTS WITH PULMONARY EMPHYSEMA AT REST<sup>1</sup>

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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<sub>2</sub> in the arterial blood (P<sub>aCO<sub>2</sub></sub>) 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<sub>2</sub> in the inspired air) will be described in normal subjects and in patients with chronic pulmonary disease.

## 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<sub>2</sub> and O<sub>2</sub> in arterial blood (P<sub>aCO<sub>2</sub></sub> and P<sub>aO<sub>2</sub></sub>) 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 Hellem, 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.

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

Case	Age	Sex	Vital capacity		Residual volume		RV/TC × 100	Arterial blood		O <sub>2</sub> cons. cc./min./M <sup>2</sup> BSA	Cardiac output L./min.	Cardiac index L./min./M <sup>2</sup> BSA	Pulmonary artery pressure			"Pulmonary capillary" pressure mm. Hg	PAM-PCm gradient mm. Hg	Total pulmonary resistance dynes-sec.-cm. <sup>-2</sup>	Pulmonary arteriolar resistance	Right auricular pressure mm. Hg
			Obs.	Pred.	Obs.	Pred.		S	D				M							
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	168	4.2	3.2	15	9	13	8	5	237	95	5
D. C.	72	M	1660	43	2010	110	56	85	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	156*	7.4	4.0	25	9	15	9	6	162	65	2
L. P.	66	M	2180	66	2020	135	48	80	42	152	8.6	4.9	25	12	16	10	6	149	57	6
T. J.	45	M	2170	59	3900	351	64	94	40	136	6.5	3.9	25	10	16	7	9	197	99	3
R. M.	67	M	2600	72	3960	243	60	92	34	138	4.7	2.6	28	12	17	9	8	284	132	2
H. C.	63	M	1680	45	1820	110	52	93	42	152	4.5	2.5	28	14	20	7	13	358	232	8
H. W.	52	M	1820	50	3090	186	63	84	35	162	7.0	4.3	29	10	21	3	18	240	206	2
B. R.	51	M	1690	47	2280	136	58	83	43	160	5.8	3.4	38	15	22	10	12	303	166	6
J. T.	62	M	1914	27	1530	336	85	81	57	131	3.5	2.3	37	16	24	6	18	554	408	6
J. C.	55	M	1340	39	1510	98	53	90	55	108	3.4	2.3	34	11	26	-1	27	610	638	0
J. M.	52	M	1370	35	5400	335	80	93	45	164	3.8	3.8	31	20	27	7	20	410	292	5
J. K.	76	M	990	32	3680	261	79	89	60	166	3.8	2.7	46	19	27	12	15	558	314	7
J. C.	65	M	970	28	3890	265	81	91	48	196	10.7	6.6	46	21	28	9	19	412	280	6
F. Z.	48	M	2000	53	2890	258	59	90	45	125	4.5	2.9	38	21	30	9	21	532	370	4
J. G.	61	M	920	28	3430	235	79	82	71	145	4.0	3.2	37	20	31	9	22	780	440	7
M. M.	63	F	890	37	3000	277	77	74	67	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.<sup>2</sup> 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):

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

$$PAR = \frac{PAm - "PCm"}{\dot{Q}_b} \times 1332$$

where TPR and PAR = resistance in dynes-sec.-cm.<sup>-2</sup>

" 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.<sup>2</sup>

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

<sup>2</sup> 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 $p_{O_2}$ ( $P_{aO_2}$ )	+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.

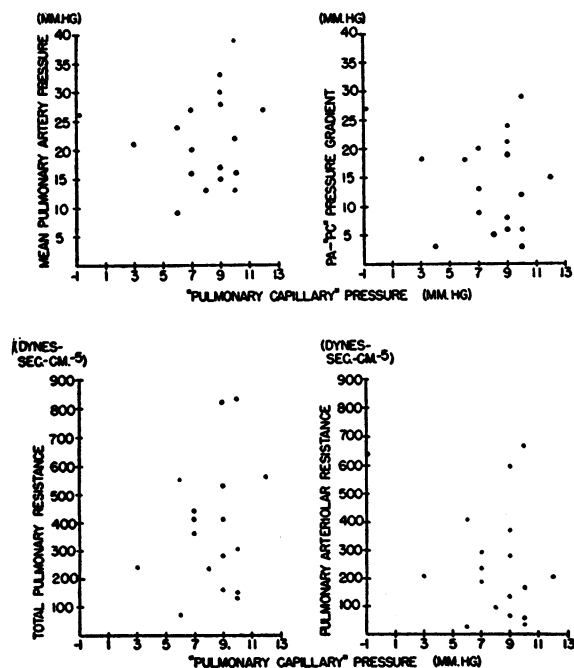


FIG. 1. "PULMONARY CAPILLARY" PRESSURE IN PULMONARY EMPHYSEMA IS PLOTTED AGAINST PULMONARY ARTERY PRESSURE, THE PA—"PC" GRADIENT, TOTAL PULMONARY RESISTANCE AND PULMONARY ARTERIOLAR RESISTANCE

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

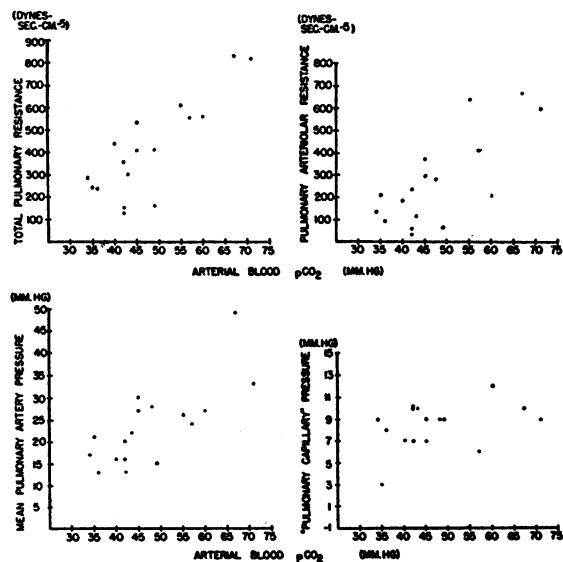


FIG. 2. THE  $P_{aCO_2}$  IN PULMONARY EMPHYSEMA IS RELATED TO THE PRESSURE AND RESISTANCE IN THE PULMONARY CIRCUIT

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  $P_{\text{aCO}_2}$  ( $R = +0.557$ ). No significant correlation was found between the gradient and "pulmonary capillary" pressure, arterial blood oxygen saturation,  $P_{\text{aO}_2}$ , or cardiac index.

## 2. Pulmonary resistance

The total pulmonary resistance exceeded the upper limit of normal (250 dynes-sec.-cm.<sup>-5</sup>) in 14 patients. Pulmonary arteriolar resistance was greater than 150 dynes-sec.-cm.<sup>-5</sup> (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.  $P_{\text{aO}_2}$  of all patients was considerably reduced. A significant negative correlation was demonstrated between the arterial blood oxygen saturation and mean pulmonary artery

M.M. ♀63 #330247

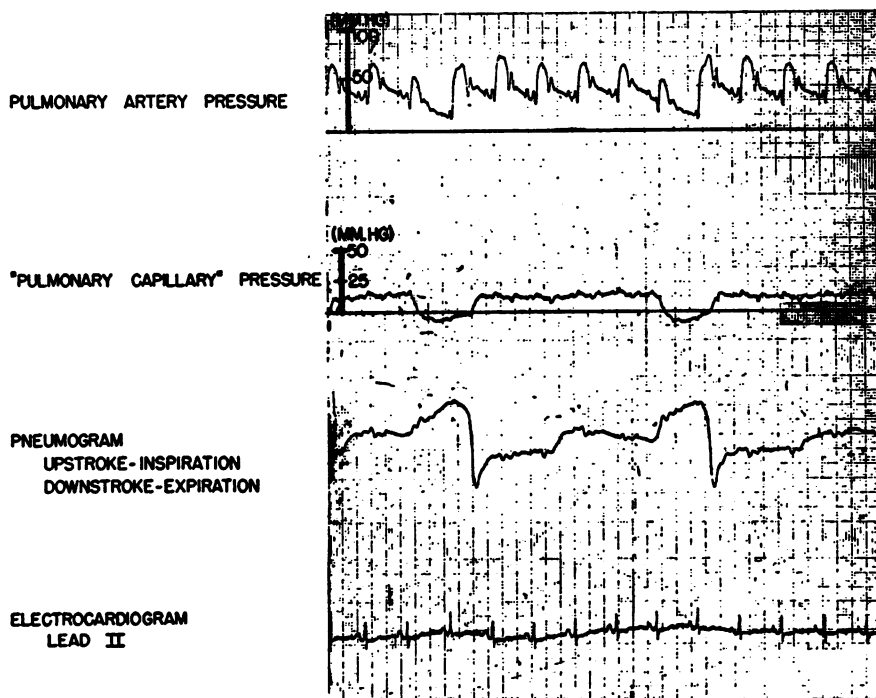


FIG. 3. TRACINGS OF PULMONARY ARTERY AND "PULMONARY CAPILLARY" PRESSURES IN PATIENT M. M.

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 four-fold 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<sub>2</sub> retention in the blood upon the pulmonary circulation is not as yet well defined." The blood CO<sub>2</sub> is frequently elevated in patients with moderate and marked pulmonary emphysema. Harvey and her associates (30) dem-

onstrated a highly significant correlation between the P<sub>aCO<sub>2</sub></sub> and mean pulmonary artery pressure in a recent study of 48 cases of chronic pulmonary disease. They found no correlation between P<sub>aCO<sub>2</sub></sub> and cardiac index. The present studies also show a highly significant correlation between the P<sub>aCO<sub>2</sub></sub> and the mean pulmonary artery pressure and pulmonary resistance. In contrast, no significant correlation was found between the P<sub>aCO<sub>2</sub></sub> 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<sub>2</sub>. The mean pulmonary artery pressure rose during the period of CO<sub>2</sub> 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<sub>2</sub> 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.

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