EFFECT OF PRISCOL ON THE PULMONARY CIRCULATION IN COR PULMONALE

BY

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Pulmonary hypertension in chronic pulmonary disease is due mainly to the impairment of the pulmonary vascular bed. It is still doubtful, however, whether neuro-humoral factors also participate in the genesis of this hypertension. Because of the difficulties of the methods that have to be used in the study of this problem, little is known about the autonomous regulation of the lesser circulation in man. Lately there have been some attempts to extend our knowledge in this field by pharmacological investigations of the lesser circulation.

Most of the authors have dealt with pulmonary hypertension in congenital or acquired heart disease. Several substances have been employed as e.g. TEAB (Davies *et al.*, 1954; Scott *et al.*, 1955), hexamethonium (Gilmore *et al.*, 1952; Judson *et al.*, 1954; Wade *et al.*, 1956), theophyllin-ethylendiamin (Storstein *et al.*, 1958), regitin (Storstein *et al.*, 1957), serpasil (Halmágyi *et al.*, 1957), acetylcholin (Harris, 1957; Söderholm and Werkö, 1959; Wood, 1957), procain (Gottsegen *et al.*, 1959) and priscoll (Braun *et al.*, 1957; Dresdale *et al.*, 1951; Dresdale *et al.*, 1954; Rudolph *et al.*, 1958).

The genesis of hypertension in congenital and acquired heart disease, however, differs from that of hypertension in cor pulmonale. Little attention has been paid to pulmonary hypertension in cor pulmonale so that the number of studies concerned with the pharmacology of this problem is small. The only substances to be used in sufficiently large groups of subjects with cor pulmonale have been TEAB (Fowler *et al.*, 1950) and hexamethonium (Malamos *et al.*, 1957; Sancetta, 1955). However, results are difficult to assess since the doses of these substances used lowered systemic blood pressure. An attempt was therefore made to affect pulmonary hypertension in cor pulmonale pharmacologically by employing a substance that would lower pulmonary arterial blood pressure without substantially affecting systemic blood pressure. Since it was found (Widimský *et al.*, 1959) that priscoll fulfils these requirements, the effect of this drug upon patients with cor pulmonale has been investigated in greater detail.

Methods. Fifteen patients with pulmonary disease, 11 of these with pulmonary hypertension at rest, within an age range of 21–68 years were investigated by catheterization of the pulmonary circulation. One day before catheterization the following premedication was applied: phenobarbital 0.06 g. natr. bromati 0.6 g., chinidini sulphur 0.2 g., and on the day of catheterization phenobarbital 0.03 g., natrii bromati 0.3 g., and chinidini sulphur 0.1 g. were administered. Catheterization was performed in the usual manner, always in the morning. The catheter was introduced into the pulmonary artery and a Cournand needle was introduced into the femoral artery. Pulmonary arterial pressure, systemic blood pressure (Riva-Rocci, right arm), and pulse rate were measured. Pressures in the lesser circulation were measured with an electromanometer of Elema type and recorded with an Elema-42 mingograph, and the mean pressure was determined by electrical integration. Mean systemic blood pressure was estimated by adding one-third of the pressure amplitude to the diastolic pressure. Pulmonary arterial blood pressure, pulse rate, and systemic blood pressure were measured at 5-minute intervals for a total period of 20–30 minutes.

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At the end of this period of 20–30 minutes, oxygen consumption was measured. The expired air was collected for 3–5 minutes in Douglas bags and analysed with a Zeiss interferometer. During breathing into these bags pressures were again measured and simultaneously blood samples were drawn from the pulmonary and femoral arteries. Arterial oxygen saturation was estimated with a Brinkman hæmoreflectometer (Kipp-Delft). Blood hæmoglobin was done photometrically. Cardiac output was determined by the direct Fick method. In 9 patients pulmonary capillary venous pressure also was recorded.

After this initial period a dose of 10–30 mg. of priscol dissolved in 10 ml. of saline was injected into the pulmonary artery through a catheter. Pulmonary arterial pressure, systemic blood pressure, and pulse rate were recorded immediately after injection and 1, 3, 5, 10, 15, and 20 minutes thereafter. Oxygen consumption was measured in the 8–12-minute period in 6 patients. Since, in accordance with reports (Rudolph *et al.*, 1958) priscol application was without effect on oxygen consumption in these 6 subjects, oxygen consumption in the remaining 9 patients was measured only prior to priscol injection. Blood samples were taken 5, 10, and 15 minutes following injection. In 9 patients the measurement of pulmonary capillary venous pressure was repeated in the tenth minute.

RESULTS

Table I shows the clinical data of the individual patients. Table II presents the results. All values in the latter table refer to the 10th minute following injection, when in most of the patients pulmonary arterial pressure changes were greatest. In 12 patients the mean pulmonary arterial pressure decreased and in the remaining three practically no change was observed: no increase in pulmonary arterial pressure was observed. In 9 of the 15 patients the fall in pressure exceeded 10 per cent of the initial level, and in 5 priscol caused a return to normal of the pulmonary arterial pressure. Pulmonary capillary venous pressure, as far as it was measured, showed in the majority of cases a small rise, so that there was a distinct decrease in pressure gradient across the lesser circulation. Respiratory changes in pulmonary blood pressure were unaffected by priscol. Mean systemic blood pressure remained practically unchanged (11 cases): it increased in three cases and decreased only in one.

TABLE I
CLINICAL DATA OF INDIVIDUAL PATIENTS

Case No.	Age and sex	Diagnosis	Priscol: dose in mg.
1	40 F	Chronic disseminated pulm. tuberculosis, emphysema	10
2	57 M	Chronic fibrocaceous pulm. tuberculosis	10
3	63 M	Chronic fibrocaceous pulm. tuberculosis	10
4	59 M	Emphysema, chronic bronchitis	20
5	54 M	Emphysema, chronic bronchitis	20
6	57 M	Chronic fibrocaceous pulm. tuberculosis	10
7	52 F	Chronic fibrocaceous pulm. tuberculosis	20
8	55 M	Chronic fibrocaceous pulm. tub., multiple pulm. cysts	20
9	21 F	Pulmonary fibrosis	30
10	68 M	Chronic fibrocaceous pulm. tub., right thoracoplasty C. 4–7	20
11	39 M	Thrombo-embolic pulm. disease, pulm. fibrosis	20
12	68 M	Chronic pulm. fibrocaceous tuberculosis	30
13	60 M	Chronic fibrocaceous pulm. tub., bullous emphysema	30
14	59 M	Silicosis	20
15	56 M	Silicosis	20

Cardiac output increased in 10 patients, remained substantially unchanged in 4, and decreased only in 1 patient. A decrease in total pulmonary resistance by more than 10 per cent was observed in 13 patients, and in 2 it was practically unchanged. Pulmonary arteriolar resistance decreased in all patients by more than 30 per cent of the initial value.

TABLE II
HEMODYNAMIC CHANGES AFTER PRISCOL IN 15 PATIENTS

	Mean PAP mm. Hg		PC mm. Hg		Cardiac output ml. a minute			Total pulmonary resistance			Pulmonary arteriolar resistance			Gradient (PAP-PC)		Arterial O ₂ percentage saturation		Mean systemic blood pressure in mm. Hg		Total peripheral resistance in dyn/sec/cm ⁻⁵		Pulse rate a minute	
	B	A	B	A	B	A	C	B	A	C	B	A	C	B	A	B	A	B	A	B	A	B	A
1.	68.1	48.3	11.0	—	4650	5770	+24	1170	670	-43	982	—	—	57.1	—	64	54	85.0	83.3	1460	1155	94	94
2.	41.2	38.0	5.2	—	8030	8400	+5	410	361	-12	358	—	—	36.0	—	79	77	93.3	93.3	930	886	110	120
3.	28.6	21.0	4.5	—	6250	5850	-6	355	286	-20	308	—	—	24.1	—	89	89	110.0	115.0	1405	1570	62	62
4.	26.4	22.2	2.5	3.9	4000	4480	+12	525	396	-25	326	215	-32	23.9	18.3	90	93	103.3	103.3	2060	1885	84	100
5.	20.0	15.5	3.8	6.9	6930	7300	+5	230	169	-30	187	94	-50	16.2	8.6	81	85	93.3	90.0	1075	985	76	80
6.	26.0	24.0	3.5	3.9	4210	6760	+61	493	284	-42	426	238	-44	22.5	20.1	85	80	106.6	106.6	2020	1250	96	108
7.	21.5	20.8	4.0	—	7630	7800	+2	225	212	-6	267	—	—	17.5	—	85	83	93.3	93.3	975	955	88	88
8.	22.9	17.5	1.7	10.4	4580	5760	+26	400	242	-40	370	98	-73	21.2	7.1	88	84	93.3	93.3	1625	1295	94	107
9.	24.6	18.3	9.2	3.3	3850	6800	+77	510	215	-58	320	176	-45	15.4	15.0	88	89	75.0	84.0	1555	985	104	104
10.	19.5	18.5	—	—	4220	4750	+13	369	311	-16	—	—	—	—	—	93	93	91.6	106.6	1740	1790	90	100
11.	18.3	14.8	5.8	11.7	5810	4700	-19	251	252	0	171	53	-69	12.4	3.1	90	87	103.3	116.6	1420	1980	94	107
12.	13.8	13.1	2.8	7.8	7000	11550	+65	157	91	-42	125	37	-70	11.0	5.3	92	83	96.6	96.6	1100	666	83	94
13.	40.5	9.0	—	—	3650	4960	+36	885	145	-84	—	—	—	—	—	81	74	90.0	83.3	1965	1340	72	107
14.	28.0	16.5	7.2	7.3	3150	4410	+29	710	299	-58	527	167	-68	20.8	9.2	81	83	106.6	103.3	2700	1870	100	107
15.	16.6	15.9	7.2	9.1	2950	5320	+81	448	238	-47	254	90	-65	9.4	6.8	91	91	80.0	80.0	2160	1200	78	106
Av.	27.7	20.9	4.8	7.1	5127	6307	+23	475	278	-41	317	142	-55	16.9	10.4	84.9	83	94.8	96.6	1612	1321	88	99

Explanations: PAP=pulmonary arterial pressure, PC=pulmonary capillary venous pressure, TPR=total pulmonary resistance, PAR=pulmonary arteriolar resistance, and PR total peripheral resistance, all in dynes/sec./cm.⁻⁵. Gradient=pressure gradient between the PAP and PC in mm. Hg, B=before priscol, A=after priscol (in the tenth minute). C=percentage change of initial value. Av=average.

Total peripheral resistance in the systemic circulation decreased in 8 patients, remained substantially unchanged in 5, and increased in 2 patients. Table II shows also the changes of the average values and Fig. 1 presents percentage average changes.

FIG. 1.—Average changes in several haemodynamic factors after prisol, expressed as the percentage change of the initial values, increases above the line and decreases below it. Abbreviations as in notes to Table II, and PR=peripheral systemic resistance, and BP=blood pressure.

The decreases in pulmonary arterial pressure and in total pulmonary and pulmonary arteriolar resistance were related to the corresponding initial values (Fig. 2, 3, 4). The higher the initial levels, the greater the decrease that could be expected. Right heart work was substantially unchanged: 6 times it decreased, 5 times it was unchanged, and 4 times it increased.

Arterial blood oxygen saturation was changed by more than 2 per cent of saturation in 7 patients, in 5 of whom it increased, but in 8 patients the changes were less than 2 per cent. Pulse rate in 10 patients was increased by more than 6 strokes a minute and in 5 patients no change was observed. Drops in pulmonary arterial blood pressure, and in total pulmonary and pulmonary vascular resistances were also found at an elevated or unchanged total peripheral resistance (Table II): however, in cases where the latter had decreased, the former falls were greater but not statistically significant.

DISCUSSION

Prisol injection into the lesser circulation caused the following changes in most patients with pulmonary disease: a decrease in pulmonary arterial blood pressure, a decrease in pulmonary vascular resistance, and a rise in cardiac output. A decrease in pulmonary vascular resistance at a simultaneously increased blood flow has, according to numerous authors, to be assessed with care. Experimental work on healthy dogs showed that the pulmonary bed is dilated by an increased blood flow so that there is a decrease in the calculated pulmonary resistance (Borst *et al.*, 1956; Edwards, 1951; and Williams, 1954).

DECREASE OF THE MEAN PAP
AFTER PRISCOL

FIG. 2.—Decrease of the mean pulmonary arterial pressure after prisol.

DECREASE OF TPR
AFTER PRISCOL

FIG. 3.—Decrease of the total pulmonary resistance (TPR) after prisol.

FIG. 4.—Decrease of the pulmonary arteriolar resistance (PAR) after priscol.

Edwards (1951) compares the lung with a highly elastic bag, the resistance of which changes inversely with blood flow. Williams (1954) also found an increased resistance at low intravascular pressures, which he interpreted as a narrowing or closing of the vessels in some part of the pulmonary vascular bed. In a complex distensible low pressure system, such as the pulmonary vascular bed in healthy dogs, vascular lumen is minimal and some vessels are probably closed (Borst *et al.*, 1956; Williams, 1954). In the period of great blood flow more capillaries are open and it is possible that their opening is stimulated by a raised pulmonary arterial blood pressure (Borst *et al.*, 1956): changes in intravascular pressure due to changes in blood flow thus make the interpretation of resistance values difficult. These relations have been established in the lungs of healthy dogs, but it is highly doubtful whether they apply in a pulmonary vascular bed that is anatomically considerably limited, as in cor pulmonale. Moreover, the factors mentioned above act immediately, whereas the maximal effect on pulmonary arterial blood pressure was established in the tenth minute.

It is, however, significant that decreases in pulmonary arterial blood pressure and in pulmonary vascular resistance after priscol could be found also in patients whose cardiac outputs were practically unaffected or even decreased (patients 2, 3, 5, 7 and 11).

In the observations of the above-mentioned authors there was always a rise in pulmonary arterial blood pressure at increased blood flows. In an anatomically impaired pulmonary vascular bed in man also, there were always rises of pulmonary arterial blood pressure at increased blood flows, e.g. during muscular work (Söderholm, 1957): this, however, was usually larger than in healthy subjects. In our observations priscol caused a fall in pulmonary arterial blood pressure regardless of increased blood flow. Some authors (Cournand, 1950 and 1957, and Judson *et al.*, 1954) object that the fall in pulmonary arterial blood pressure that follows some drugs in men might be caused by a shift of blood from the lesser circulation to the systemic circulation at a simultaneous fall of systemic peripheral resistance. Against this mechanism the following arguments may be put forward: (1) the decreases in pulmonary vascular resistance and in total pulmonary resistance and pulmonary arterial blood pressure could be found also in 7 patients where there was no substantial change in peripheral

resistance or where the latter had even increased (patients 2, 3, 4, 5, 7, 10, 11); and (2) the fall in pulmonary arterial blood pressure combined with an increase in pulmonary capillary venous pressure cannot be explained by a decrease in the pulmonary blood volume (Harris, 1957).

Nor can bronchial constriction account for the pressure changes in the lesser circulation. This is borne out by the fact that priscol is without effect on ventilation and oxygen consumption (Rudolph *et al.*, 1958) and that, according to our observations, respiratory variations in intravascular pressure in the pulmonary circulation remained unchanged.

In contrast to reported data (Braun *et al.*, 1957; Dresdale *et al.*, 1954; Söderholm and Werkö, 1959; Storstein *et al.*, 1958) a fall in arterial oxygen saturation was not met with as frequently as has been reported after the use of hypotensive drugs. Only in 5 patients was there a significant fall in arterial oxygen saturation and this might be due to a shift in ventilation-perfusion ratio, in the sense of increased blood flow through the poorly ventilated areas (Dresdale, 1951 and 1954; Söderholm and Werkö, 1959).

The hæmodynamic reaction observed in the lesser circulation may be explained, we believe, purely by a dilatation of the pulmonary vascular bed due to priscol either by a blockade of sympathetic hyperactivity and/or by a local effect on the pulmonary bed. The extent of this hæmodynamic reaction depends on the initial level. The greater the initial pressure values in the pulmonary artery, the greater was the decrease that could be expected. This is in agreement with the findings of other authors on the pharmacology of pulmonary hypertension in mitral stenosis (Braun *et al.*, 1957; Gottsegen *et al.*, 1959). These findings are, according to Harris (1957), accounted for by the fact that only the hypertrophied muscles of the pulmonary vessels that are found in pulmonary hypertension of various origins are capable of significant relaxation and contraction. Patel (1958), however, advances a different explanation. The finding of a higher increase in pulmonary vascular resistance due to nor-adrenalin infusion in healthy subjects than in patients with impaired pulmonary vascular resistance is explained by a decreased contractive ability of the abnormal pulmonary bed. Patel's data, however, may also be interpreted in just the opposite way, i.e. by assuming that contracted vessels are less affected by nor-adrenalin.

Priscol application thus demonstrates the functional factor of hypertension in cor pulmonale. The therapeutic effect of priscol in cor pulmonale is doubtful since the changes in the pulmonary arterial pressure observed are merely of a maximum duration of 10–15 minutes. The possible significance of priscol in differentiating between anatomical and functional components in cor pulmonale cannot be excluded. Here it has to be borne in mind that in 5 patients (5, 8, 9, 13, and 14) there was even a temporary return to normal of pulmonary arterial blood pressure. These observations show that the functional factor may be decisive in the genesis of pulmonary hypertension as has already been suggested by some post-mortem findings (Dresdale *et al.*, 1951). The data presented show again that pharmacotherapy of pulmonary hypertension in cor pulmonale may become justified though a suitable substance has still to be found.

SUMMARY

The injection of priscol (10–30 mg.) into the pulmonary artery was investigated in 15 subjects with pulmonary disease, 11 of whom had chronic cor pulmonale. Significant decreases of pulmonary arterial pressure, pulmonary vascular resistance, and total pulmonary resistance occurred in most of them. Systemic arterial pressure remained unchanged. The response to priscol was related to the initial level of pulmonary arterial pressure and total pulmonary and pulmonary vascular resistance. Arterial oxygen saturation and systemic peripheral resistance did not show any consistent changes. It is possible that the decrease of pulmonary arterial pressure was due to vasodilatation in the periphery of the pulmonary arterial tree.

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