INFLUENCE OF ACETYLCHOLINE ON THE PULMONARY ARTERIAL PRESSURE

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Received July 22, 1956

It is still a matter for debate whether active variation in the calibre of the vessels of the pulmonary circulation can be caused by physiological or pharmacological stimuli. In most observations, the agents used to test the pulmonary circulation are known to have an effect also on the systemic circulation and often on the cardiac output. Under these circumstances the pulmonary arterial pressure is liable to be influenced by factors other than local alterations in the calibre of the vessels of the lesser circulation.

In an attempt to circumvent these difficulties, it was decided to study the effects of acetylcholine on the pressures in the pulmonary circulation in a group of patients. Ellis and Weiss (1932) demonstrated the destruction of acetylcholine in the blood stream in man by the lack of cumulative action during its prolonged intravenous infusion. They and also Carmichael and Fraser (1933) observed flushing of the head and upper part of the body when acetylcholine was injected in sufficient dosage into a vein, while intra-arterial injection caused a regional dilatation of arteries and arterioles but no general effects. Since acetylcholine is destroyed so rapidly in the blood stream, it might be possible to inject it into the pulmonary artery in such a dose that it was inactivated before reaching the systemic circulation (Tiffenau and Beauvallet, 1944). In this way it was hoped that any vaso-motor effect of the drug would be confined to the pulmonary circulation.

In animals, the action of acetylcholine is most evident in the systemic circulation, where it causes widespread arterial vasodilatation irrespective of whether these vessels are supplied by the sympathetic or parasympathetic systems (Hunt and Taveau, 1906; Dale, 1914; Hunt, 1917*a* and 1917*b*). Reports of the activity of the drug in the pulmonary circulation, however, have been conflicting (Hunt, 1917*a*; Daly, 1932 and 1933; von Euler, 1932; Franklin, 1932; Gaddum and Holtz, 1933; Johnson *et al.*, 1937; Hamilton *et al.*, 1939; Petrovskaia, 1939; Foggie, 1940; Friedberg *et al.*, 1943; von Euler and Liljestrand, 1946; Dirken and Heemstra, 1948).

METHODS

Forty-seven patients were investigated. They had all been referred for diagnostic cardiac catheterization and had various disorders, which are given in Table I. Six of the children were anaesthetized with rectal pentothal: the remaining patients were conscious and received no premedication. All were in as near a basal state as possible. Three of the anaesthetized children had been given atropine.

A Cournand catheter was placed so that its tip lay in the main pulmonary artery. Between the hilt of the catheter and the head of the manometer was interposed a two-way tap with a short side-arm, through which a small volume of a solution of acetylcholine could be introduced into the lumen of the catheter. A recording of the pressure in the pulmonary artery was begun and, after an appropriate interval, the solution of acetylcholine was suddenly washed through the catheter into the pulmonary artery by means of a syringe filled with saline attached to the side-arm. With rapid manipulation of tap and syringe, the injection time was usually about two seconds. The recording of pressure was continued until the effects of the injection had disappeared or until it was apparent that there was no alteration in the pulmonary arterial pressure. In three cases the tip of the catheter lay in the right ventricle and then the right ventricular systolic pressure

* Work done during tenure of the Wiltshire Memorial Research Scholarship (1953-55) and submitted as part of a Ph.D. thesis at the University of London.

TABLE I
DETAILS OF EACH PATIENT AND THE EFFECTS OF ACETYLCHOLINE

Case No.	Sex and age (years)	Diagnosis	Before acetylcholine				Effects of acetylcholine				
			Pulmonary arterial pressure (mm. Hg)	PA mean pressure (mm. Hg)	Wedge pressure (mm. Hg)	Pulmonary "arteriolar" resistance (dynes. sec. cm. ⁻⁵)	Pulmonary arterial pressure	Wedge pressure	Systemic blood pressure	Cough	Heart rate
1	F 33	MS	57/28	44	30	180	0	+ 5	—	0	0
2	F 46	MS	115/50	77	41	820	-20/12.5	+2.5	—	0	0
3	F 43	PDA	140/10	59	5	270	-42.5/7.5	—	—	0	0
4	F 40	MS. MI	64/35	50	33	290	-12.5/10	+10	0	0	0
5	F 25	MS. AI	66/41	53	37	150	-12.5/7.5	—	—	0	0
6	F 33	MS	116/56	82	46	770	-20/10	—	0	0	0
7	F 8	Normal	34/18	24	13	—	0	—	—	0	0
8	M41	ASD	170/68	125	—	—	0	—	—	0	0
9	F 60	Pl. Emphysema	68/25	44	—	—	-20/15	—	0	0	0
10	M 3	VSD†	85/52	70	14	—	-22.5/27.5	—	-10/10	0	0
11	M15	Normal	28/14	19	16	100	0	—	-20/10	+	+
12	M17	VSD	40/21	29	18	—	0	—	—	0	0
13	M25	MS	28/11	17	16	10	0	0	—	0	0
14	M39	MS	44/24	33	30	—	0	0	—	0	0
15	M56	MI. A fibr.	55/25	46	31	350	-12.5/0	—	—	0	0
16	F 38	MS	88/33	57	36	350	-15/10	—	0	+	+
17	M42	ASD	155/58	95	—	—	0	—	—	0	0
18	M39	Pulmo. Hypert.	105/47	67	—	—	-12.5/5	—	—	0	0
19†	F 45	MS. TI, A Fibr.	124/57	89	—	—	0	—	—	0	0
20	F 3	PDA. ASD	60/40	51	9	—	0	—	—	0	0
21	M 4	Cong. MS†	50/22	35	28	—	0	—	—	0	0
22	M50	Emphysema	39/22	30	13	330	0	0	0	0	0
23	F 40	Eisenmenger	140/55	93	4	—	0	—	—	+	+
24	F 30	MS	39/18	28	24	—	0	—	—	0	0
25	F 40	MS	100/73	84	32	480	-10/10	—	—	0	0
26	F 9	ASD	120/70	94	13	1550	0	—	—	0	0
27	F 11	ASD	29/17	22	12	130	0	—	—	0	0
28	F 16	MS	63/25	39	22	280	+5/10	—	—	+	+
29	F 29	MS	91/42	60	—	—	-25/5	—	—	+	+
30	M 8	Eisenmenger	93/58	74	7	—	+10/10	—	—	+	+
31	M29	Pulm. fibrosis	57/36	47	—	—	-12.5/5	—	-20/10	+	+
32	M11	Normal	35/19	26	13	150	0	—	—	0	0
33	F 30	MS	28/13	18	15	60	0	—	—	+	+
34	F 23	Pulm. hypert.	85/50	63	—	—	-20/15	—	—	0	0
35	M 7	VSD	26/13	20	13	—	0	—	—	+	+
36	F 48	MS	52/25	38	28	120	-20/10	—	0	0	0
37	F 24	MS	48/26	38	29	110	0	+10	—	0	0
38	F 40	MS	160/65	100	44	1210	0	0	—	0	0
39	F 40	MS. AI	38/20	27	20	80	0	0	—	0	0
40	F 30	MS	108/39	77	—	—	-50/*	—	—	0	0
41	F 21	MS	38/20	29	20	140	0	—	—	+	+
42	M39	Atrial fibr.	32/21	27	—	—	0	—	—	0	0
43	F 40	MS. AF	51/42	47	33	290	0	—	—	0	0
44	F 53	ASD	56/21	44	14	160	0	—	—	0	0
45	M30	Pulm. hypert.	113/57	80	11	1780	0	—	—	0	0
46	F 34	MS	83/31	50	28	260	-12.5/*	—	—	0	0
47	M49	MS	73/38	50	34	280	-15/*	—	—	0	0

* Right ventricular pressure.

† Patient given atropine

was taken as indicating the pulmonary arterial systolic pressure. In some patients a double-lumen catheter was used. Acetylcholine was then injected through the side-opening of the catheter and thus arrived in the right ventricle while the pressure in the main pulmonary artery was recorded from the terminal opening.

In nine patients the pulmonary artery wedge pressure was measured via the terminal opening of a double-lumen catheter while acetylcholine was injected into the pulmonary artery via the side opening. In each of these cases, the recording of a true wedge pressure was verified by the shape of the tracing and by the withdrawal of highly oxygenated blood. In nine patients a recording of pressure in a systemic artery was made during the injection of acetylcholine into the right ventricle or pulmonary artery.

The dose of acetylcholine varied from 0.25 to 8.0 mg. In those patients in whom an effect was observed, the average effective dose given was 2.3 mg. When the effect on the systemic arterial pressure was being observed, the dose of acetylcholine was the maximum that had been used in studying the pressures in the pulmonary circulation in the same patient. There were no recordings of pressure simultaneously in the pulmonary artery or pulmonary wedge position and systemic artery.

Pressures were measured by means of a capacitance manometer, using a direct writing recording apparatus (Bareham). Zero was taken at the level of the table on which the patient lay. In the control observations taken before injection of the drug, the average levels of systolic and diastolic pressures in the pulmonary artery were read during two or more respiratory cycles and the mean pressure was measured by means of planimetry over a similar period of time. The rapid alterations in pressure following the injection of acetylcholine did not allow of so accurate a measurement. In most instances, also, reduced paper speed at this time did not permit measurement of mean pressures. Observations of pressures following the injection of the drug are therefore limited to systolic and diastolic levels and these are given to the nearest 2.5 mm. Hg. Variations in pressure were ignored if they could not be repeated, using the same dose of acetylcholine, after an interval of five minutes.

The evanescent effect of the drug on the pulmonary arterial pressure would have made any simultaneous measurement of pulmonary blood flow impracticable. By using continuous infusions of acetylcholine, it might have been possible to have reached a steady state during which estimations of pulmonary blood flow would have been most valuable. However, the apparatus for carrying this out with sufficient accuracy was not available. In the assessment of resting pulmonary arteriolar resistance made before the injection of acetylcholine, the oxygen uptake was measured from the slope of a spirometric tracing.

RESULTS

A brief reference to these results has been made previously (Harris, 1955a). Details of each patient are given in Table I.

Pulmonary Arterial Pressures. In twenty-seven patients there was no alteration in the pressure in the pulmonary artery after the injection of acetylcholine. In two there was a slight rise in pressure, but in both this was accompanied by coughing and tachycardia. In eighteen patients, acetylcholine caused a transient fall of varying degree. Fig. 1 shows recordings from a patient in whom the fall was particularly apparent and gives an indication of the reproducibility of the effect. Only in Case 36 was the pressure in the pulmonary artery reduced to within the normal range. The fall in pressure would usually start three or four seconds after the injection and reach its greatest

FIG. 1.—Recordings of pulmonary arterial pressure in Case 10. The time of injection of acetylcholine coincides with the sudden wide movements of the recording pen just prior to the fall in pressure. On each occasion, the dose of acetylcholine was 0.25 mg. injected into the pulmonary artery. One major horizontal division represents approximately 7 sec. The scale of pressures is in mm. Hg.

FIG. 2.—The effects of injection of 2 mg. acetylcholine in Case 4. (A) Pulmonary arterial pressure. (B) Wedge pressure. (C) Brachial arterial pressure. The arrows indicate the start of the injection. One major horizontal division represents approximately 7 sec. The start of tracing (B) is at a fast rate to show the wedge curve; at this point, each major horizontal division represents 0.2 sec. The scale of pressure is in mm. Hg.

degree after ten to twenty seconds. The subsequent rise was not so abrupt and might even be prolonged for several minutes (Fig. 2).

Pulmonary Artery Wedge Pressure. In five patients there was no change in the wedge pressure after injection of acetylcholine into the pulmonary artery: in four there was a slight but distinct transient rise (Fig. 2). In the five cases where the wedge pressure was unchanged, the pulmonary arterial pressure was also unaffected by acetylcholine. Of the four cases where the wedge pressure was found to rise, two showed a fall and two showed no change in pulmonary arterial pressure when acetylcholine was injected into the right ventricle. All except one of these nine had mitral stenosis.

Systemic Arterial Pressure. There was no change in the systemic arterial pressure in six, and a transient fall in three patients following the injection of acetylcholine into the right ventricle or pulmonary artery. These nine patients tended to be taken more frequently from those in whom acetylcholine had caused a fall in pressure in the pulmonary artery, since information was being especially sought on how much the fall in pulmonary arterial pressure could be caused by vasodilatation in the systemic circulation. Thus, in seven of them there had been a fall in pulmonary arterial pressure following injection of the drug. Of these seven, only two showed a fall in systemic arterial pressure due to acetylcholine. Of the remaining two in whom the pulmonary arterial pressure had not responded to acetylcholine, the systemic arterial pressure fell in one and was unchanged in the other.

Other Effects. Coughing and tachycardia occurred in many patients when higher doses of acetylcholine were given. These two symptoms occurred together. Often associated with the

desire to cough was an irritating or burning feeling in the throat or deep inside the chest. On two occasions, the respiratory variation in intravascular pressure in the chest was found to increase following the injection of acetylcholine and this was thought to indicate constriction of the bronchioles. Transient bradycardia such as was described by Carmichael and Fraser (1933) was observed only once. Tachycardia following acetylcholine was, however, common and might persist for several minutes. Abnormality of the electrocardiogram was observed only once when two ventricular premature beats followed the injection, which had been made into the right ventricle. No patient complained of flushing or burning of the skin and, since the investigation was carried out in a red light, it was not possible to observe any reddening of the skin. In no patient did the injection of acetylcholine give any cause for alarm.

In three patients in whom a fall in pulmonary arterial pressure had been caused by the injection of acetylcholine, a similar injection of saline carried out with the same ritual caused no alteration in pressure in the pulmonary artery. The effects of coughing, by itself, on the pulmonary arterial pressure were not comparable with those due to acetylcholine.

DISCUSSION

From the results quoted above, the pressures in the pulmonary circulation in the majority of cases did not respond to acetylcholine. About one in every three patients, however, showed a transient fall in pulmonary arterial pressure following the injection of the drug, an effect that does not seem to be related to the fall in pressure sometimes found in the systemic arteries. When the wedge pressure has been affected, it has risen. Probably, in these cases, the brief rise in wedge pressure has been made more apparent by the presence of mitral stenosis which was present in all and would delay the speed with which the left ventricle could restore the left atrial pressure.

A fall in pulmonary arterial pressure accompanied by a rise in wedge pressure cannot be accounted for by a reduction in pulmonary blood volume due to systemic vasodilatation. Neither would bronchoconstriction be expected to have this effect on the pressures in the pulmonary circulation. A reduction in cardiac output is unlikely to have given rise to so immediate a fall in pulmonary arterial pressure, but in the absence of measurement this must be accepted as possible. The fall in pulmonary arterial pressure has not been due to a bradycardia such as was observed in dogs by Johnson *et al.* (1937).

There would seem, therefore, to be strong indications that acetylcholine has caused a vasodilatation in the branches of the pulmonary artery. Why, however, should such vasodilatation occur in some patients and not in others? A clue to the answer may be given by the histogram in Fig. 3 where the patients are arranged according to the mean pulmonary arterial pressure that had been measured before giving the drug. When the pressure in the pulmonary artery was normal, a fall in pressure following the injection was never found. As the mean pressure in the pulmonary artery rose, there was a gradual increase in the proportion of patients showing a fall in pressure until, between mean pressures of 50–70 mm. Hg, almost every case showed a response. Thereafter, the proportion of patients showing a response fell off and all the patients within the higher ranges of pulmonary arterial pressure were once more unresponsive.

This peculiar distribution of the responsive group within the total series of patients has been tested by means of the χ^2 test, and would arise by chance less often than once in a hundred times. Further analyses, the details of which are given elsewhere (Harris, 1955b), showed that the type of disease or the age or sex of the patient had no specific influence on the action of acetylcholine. It seems, therefore, that the responsiveness of the pulmonary circulation to the action of acetylcholine is related in a distinctive way to the initial level of pressure in the pulmonary artery.

The wide differences in pulmonary arterial pressure that occur between the various patients are mainly due to differences in the resistance of flow offered by the smaller branches of the pulmonary artery, so that the effects of acetylcholine are most probably related primarily to the nature of the resistance occurring at this level. The development of pulmonary arterial hypertension is accompanied by distinctive changes in the structure of the small pulmonary arteries. Thus, the

are reduced by the opening or closing of alternative channels for the passage of blood through the lungs. This cushioning effect may gradually be lost in the presence of an increasing pulmonary hypertension since it is possible that the level of pressure in the pulmonary artery then comes to exceed by an increasing amount the critical opening and closing pressures of the small arterial branches. Further, although the same fractional change in resistance should produce an equal fractional change in pulmonary arterial pressure, yet the absolute change in pulmonary arterial pressure will naturally increase as the initial level of pressure becomes higher. Further, it might be argued that subintimal thickening, by encroaching upon the size of the lumen of a small pulmonary artery, would actually magnify any fractional alterations in the size of the lumen following activity of the media. All of these factors could play a part in increasing the effects of acetylcholine in pulmonary hypertension, though none can explain the final diminution of the effect of acetylcholine when the pulmonary arterial pressure becomes extremely high.

The exact way in which acetylcholine might cause pulmonary vasodilatation is not revealed by these observations. Its rapid action on the pulmonary arterial pressure suggests that vasodilatation in the pulmonary circuit is most probably due to a direct influence of the drug on the muscle fibres in the walls of the vessels. One of the three patients who had been given atropine had a substantial fall in pulmonary arterial pressure after acetylcholine, and it seems likely, therefore, that the doses of acetylcholine used were but little inhibited by a therapeutic concentration of atropine in the tissues.

SUMMARY

The rapid injection of acetylcholine into the pulmonary artery or right ventricle has caused a transient fall of the pulmonary arterial pressure in 18 of 47 patients with various abnormalities. There is strong evidence that this fall was due to vasodilatation in the periphery of the pulmonary arterial tree. The response to acetylcholine was related to the initial level of pulmonary arterial pressure in a distinctive manner. It was found most frequently in patients with a moderate rise of pulmonary arterial pressure and did not occur when this was normal or when it was greatly raised. These results may be related to the structural alterations that occur in the small pulmonary arteries in association with pulmonary hypertension.

I am most grateful to Dr. Terence East for advice and encouragement.

REFERENCES

- Bareham, F. R. To be published.
 Brown, J. W., Heath, D., and Whitaker, W. (1955). *Brit. Heart J.*, **17**, 273.
 Carmichael, E. A., and Fraser, F. R. (1933). *Heart*, **16**, 262.
 Civin, W. H., and Edwards, J. E. (1950). *Circulation (N.Y.)*, **2**, 545.
 Dale, H. H. (1914). *J. Pharmacol.*, **6**, 147.
 Daly, I. de B. (1933). *Physiol. Rev.*, **13**, 149.
 — and von Euler, U. S. (1932). *Proc. Roy. Soc. B.*, **110**, 92.
 Dirken, M. N. J., and Heemstra, H. (1948). *Quart. J. exper. Physiol.*, **34**, 227.
 Ellis, L. B., and Weiss, S. (1932). *J. Pharmacol.*, **44**, 235.
 von Euler, U. S. (1932). *J. Physiol.*, **74**, 271.
 — and Liljestrand, G. (1946). *Acta. physiol. Scand.*, **12**, 301.
 Foggie, P. (1940). *Quart. J. exp. Physiol.*, **26**, 225.
 Franklin, K. J. (1932). *J. Physiol.*, **75**, 471.
 Friedberg, L., Katz, L. N., and Steinitz, F. S. (1943). *J. Pharmacol. exper. Therap.*, **77**, 80.
 Gaddum, J. H., and Holtz, P. (1933). *J. Physiol.*, **77**, 139.
 Hamilton, W. F., Woodbury, R. A., and Vogt, E. (1939). *Amer. J. Physiol.*, **125**, 130.
 Harris, P. (1955a). *Brit. Heart J.*, **17**, 85.
 — (1955b). University of London Thesis.
 Hunt, R. (1917). *Amer. J. Physiol.*, **45**, 197 and 231.
 —, and Taveau, R. de M. (1906). *Brit. med. J.*, **2**, 1788.
 Johnson, V., Hamilton, W. F., Katz, L. N., and Weinstein, W. (1937). *Amer. J. Physiol.*, **120**, 624.
 Kaump, D. H., and Dry, T. J. (1938). *Arch. intern. Med.*, **61**, 1.
 Larrabee, W. F., Parker, R. L., and Edwards, J. E. (1949). *Proc. Mayo Clin.*, **24**, 316.
 Petrovskaja, B. (1939). *Quart. J. exper. Physiol.*, **29**, 277.
 Selzer, A., and Laqueur, G. L. (1951). *Arch. intern. Med.*, **87**, 218.
 Tiffenau, R., and Beauvallet, M. (1944). *Compts. rendu. Soc. Biol., Paris*, **138**, 747.