EFFECTS OF OXYGEN AND ACETYLCHOLINE ON PULMONARY CIRCULATION IN VENTRICULAR SEPTAL DEFECT

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and

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One of the determining factors in the success or failure of surgical closure of V.S.D. is pulmonary hypertension associated with or without pulmonary vascular disease. As yet there is no means of quantitating pulmonary vascular disease, and one can only assess the degree of severity indirectly by estimating the pulmonary vascular resistance, using Poiseuille's equation where resistance is equal to pressure divided by flow.

Pulmonary vascular resistance can be attributed to organic vascular disease or functional vaso-constriction. Frequently, it is a combination of both. In this respect, it is essential to know how much of the increased resistance is contributed by functional vaso-constriction and how much by structural vascular changes—the former being completely reversible and the latter probably irreversible.

In this paper, the use of oxygen and acetylcholine in evaluating the vaso-reactivity of the pulmonary vascular bed in a group of patients with V.S.D. of various sizes is reported. The response to the vaso-dilating agents is measured by means of the fall in pulmonary systolic pressure; the greater the fall, the more effective is the agent. Since the response is so rapid and transient, it is not possible to estimate changes in pulmonary vascular resistance or in pulmonary blood flow if present.

METHOD

Tests with oxygen and acetylcholine were carried out in 47 patients with isolated V.S.D. There were 21 males and 26 females with an age range from infancy to 17 years (Fig. 1). The size of the defect was divided into 3 groups according to the pulmonary to systemic peak pressure ratio (Pp/Ps)—less than 0·5, between 0·5 and 0·9, and more than 0·9. As shown in Fig. 2, the maximum pulmonary flow was between 0·5 and 0·9; the pulmonary to systemic flow ratio (Qp/Qs) fell precipitously as the peak pressure ratio (Pp/Ps) rose beyond 0·9.

Similarly, the calculated pulmonary vascular resistance (Rp) expressed in units per M^2 also increased proportionately (Fig. 3). Since it was not possible to measure any changes in Qp/Qs or pulmonary vascular resistance while testing, it was assumed that the transient fall in pulmonary systolic pressure could reflect the degree of vaso-dilatation in the pulmonary arteries and arterioles.

In this group of 47 patients, the diagnosis of each had been confirmed by a right heart study including estimation of Qp/Qs, Pp/Ps and pulmonary vascular resistance before testing with oxygen and acetylcholine. After completing each diagnostic procedure, the patient was given 100% oxygen by inhalation for 5 minutes. Pulmonary pressure was recorded before and after oxygen was given. The pulmonary artery pressure fell even in a patient with a small V.S.D. as shown in Fig. 4.

Oxygen inhalation was stopped for 10 minutes, after which 2 mg. of freshly prepared acetylcholine was injected into the pulmonary artery. The pulmonary artery pressure was recorded immediately before and after acetylcholine injection. If no effect was observed after the initial dose, acetylcholine was increased to 5 mg. In a positive response as shown in Fig. 5, the fall in pulmonary artery pressure was almost immediate with the maximum effect occurring within 15 to 20 seconds. The pressure returned to its pre-injection level after about 1 minute.

Since acetylcholine was rapidly inactivated in the circulation, its direct infusion into the pulmonary artery in sufficient concentration produced immediate vaso-dilatation without affecting the systemic pressure. Side-effects in the given concentration were few e.g. irritative coughing, sinus tachycardia and S-T changes in electrocardiography (Fig. 6); but these were of no lasting consequence.

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AGE DISTRIBUTION OF PATIENTS WITH V.S.D

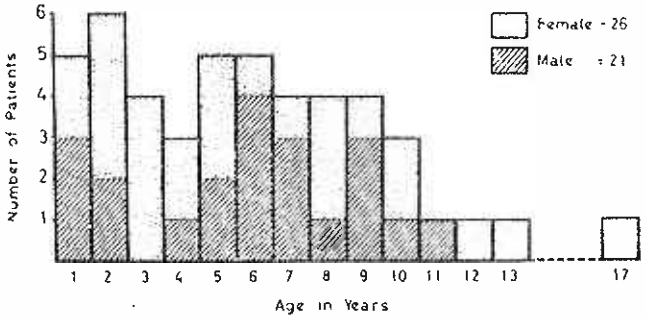

Fig. 1. This chart shows the age distribution of 47 patients with V.S.D.; there were 21 males and 26 females.

RELATIONSHIP BETWEEN Qp/Qs and Pp/Ps in V.S.D.

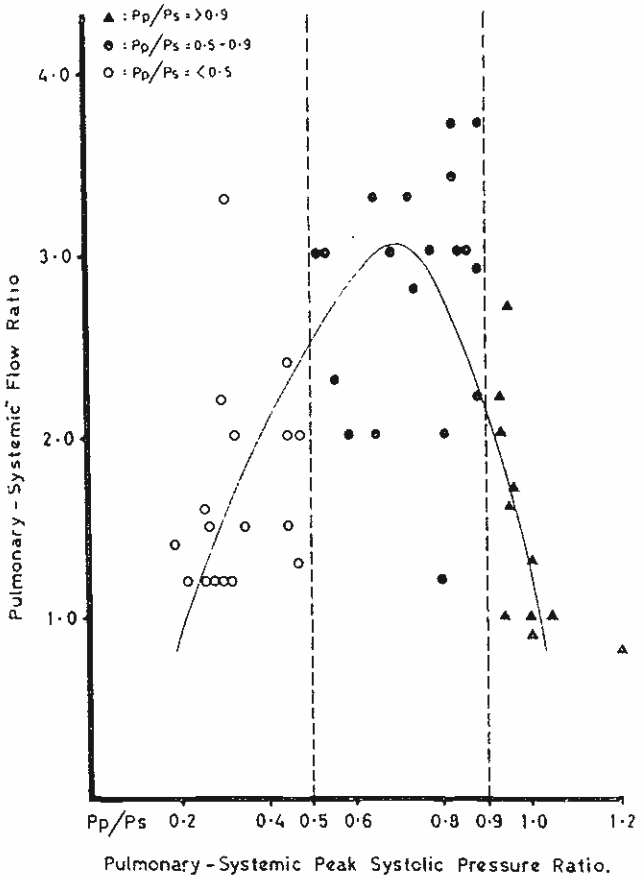

Fig. 2. This graph shows the relationship between the pulmonary to systemic flow ratio (Qp/Qs) and the pulmonary to systemic peak pressure ratio (Pp/Ps) of 47 cases of V.S.D. The maximum pulmonary blood flow seems to lie between 0·5 and 0·9 in (Pp/Ps).

RELATIONSHIP BETWEEN Pp/Ps AND PULMONARY VASCULAR RESISTANCE IN V.S.D.

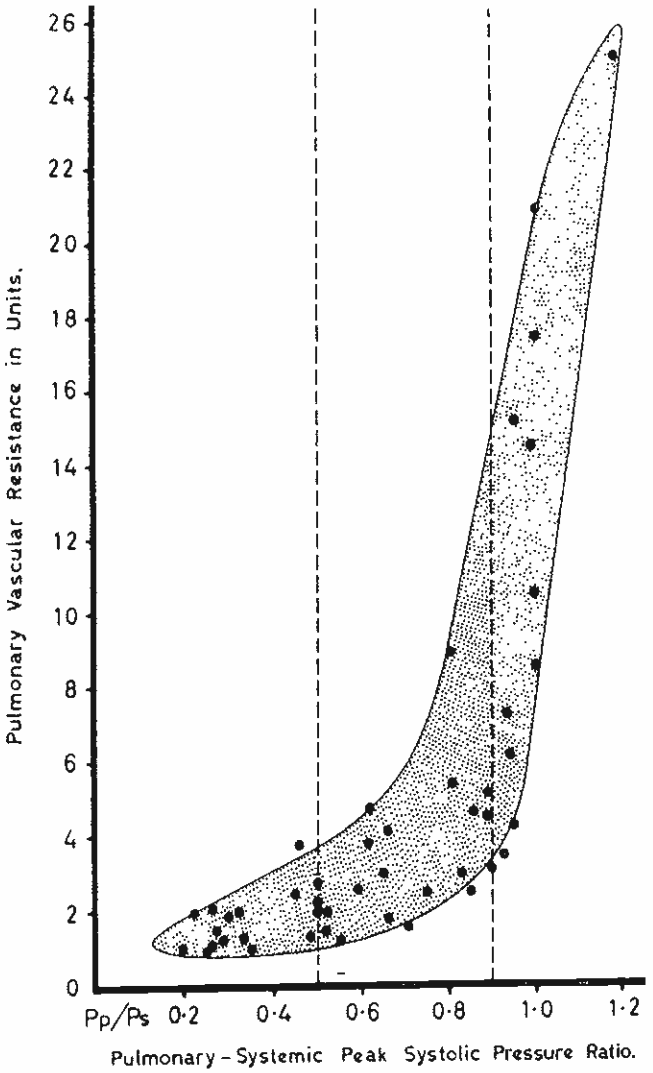

Fig. 3. This graph shows the rapid increase in pulmonary vascular resistance measured in Units/M² as Pp/Ps rise beyond 0·9.

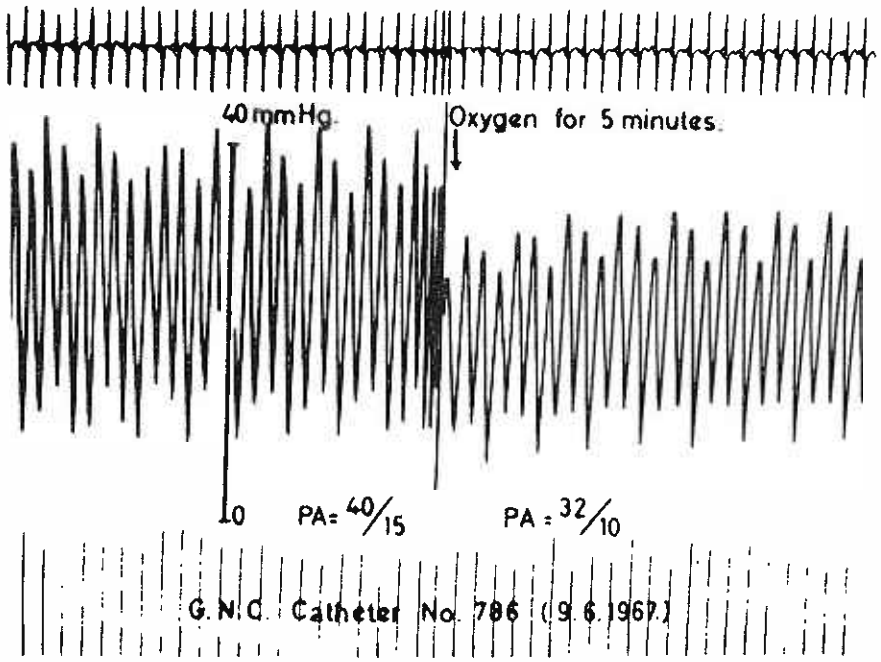

Fig. 4. This is the recording of the pulmonary arterial pressure (P.A.) of a small V.S.D.; the pressure fell from 40/15 mm. Hg. to 32/10 mm. Hg. after 5 minutes of oxygen.

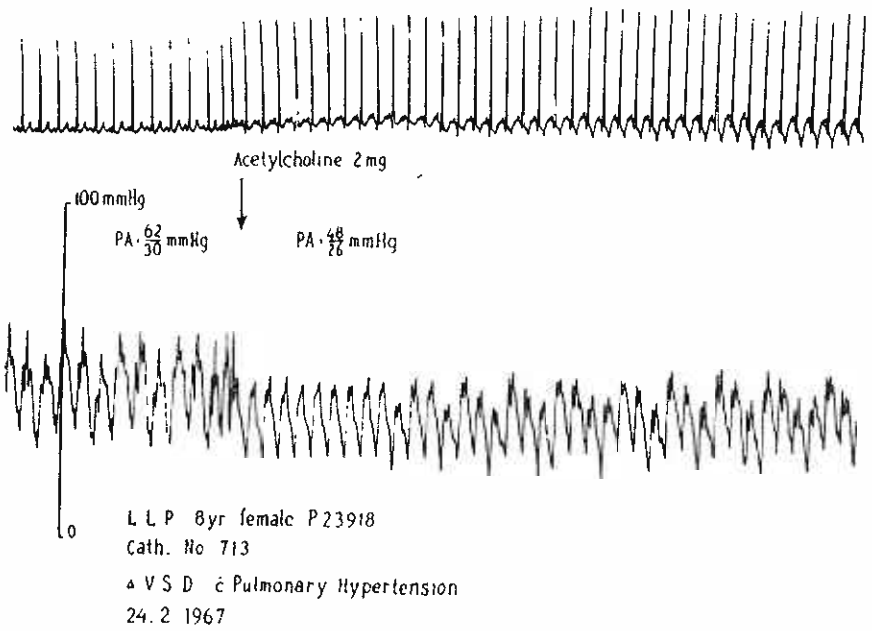

Fig. 5. This is the recording of the pulmonary arterial pressure (P.A.) of V.S.D. with pulmonary hypertension and a large L-R shunt; the pressure fell from 62/30 to 48/26 mm. Hg. after giving 2 mg. of acetylcholine. Note the changes in S-T segment in E.C.G. after acetylcholine.

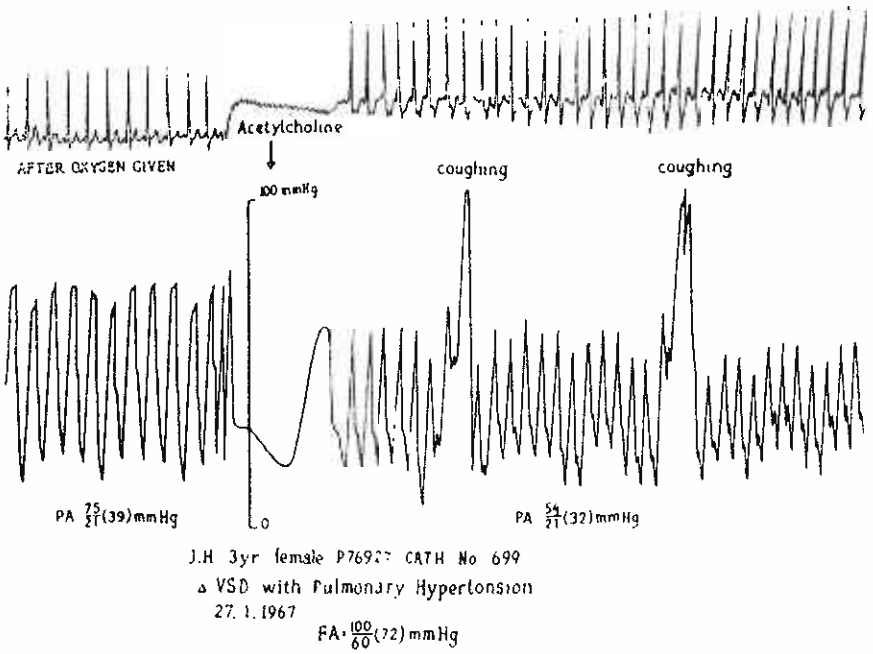

Fig. 6. This recording shows the effects of acetylcholine e.g. sinus tachycardia, S-T changes in E.C.G. with inversion of T wave and coughing of the patient besides the reduction of pulmonary arterial pressure from 75/21 to 54/21 mm. Hg.

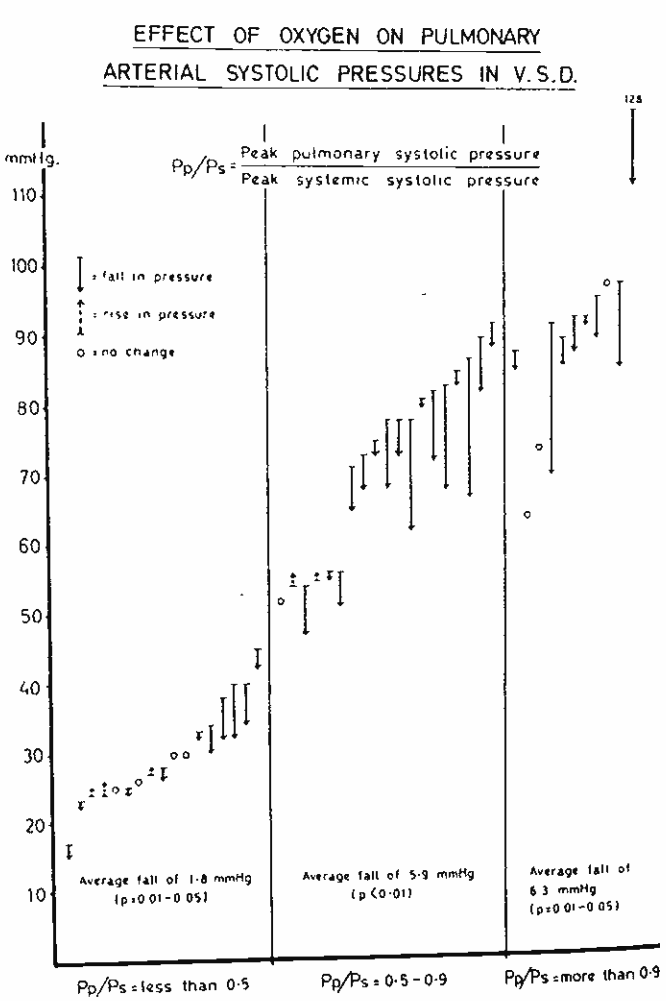

Fig. 7. This chart summarises the effect of oxygen on the pulmonary arterial pressure in the three groups of patients with V.S.D., showing a significant fall in pressure in all groups.

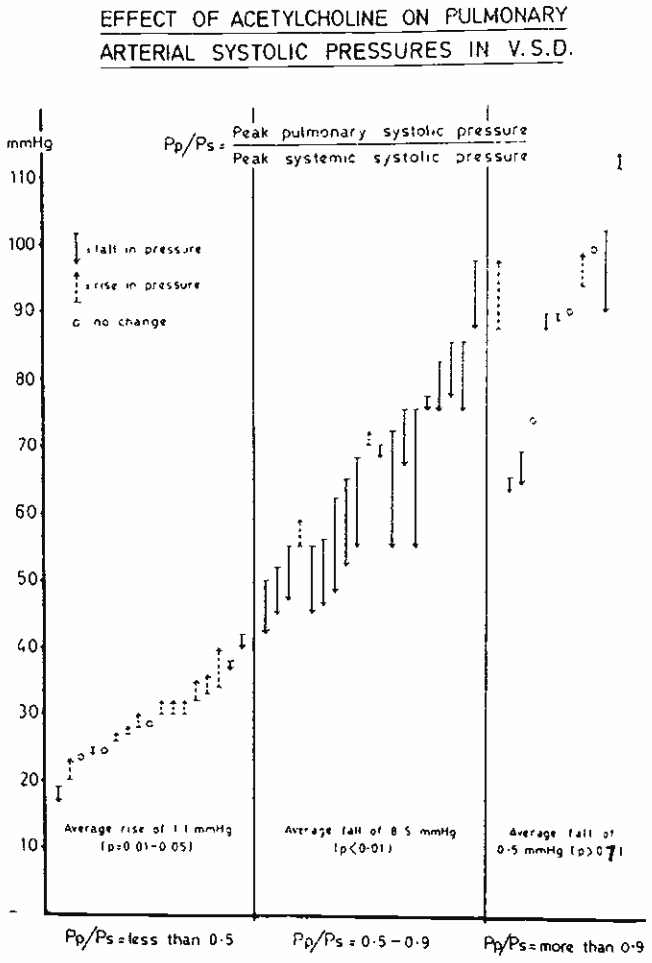

Fig. 8. This chart summarises the effect of acetylcholine on the pulmonary arterial pressure in all patients with V.S.D., showing a highly significant fall only in group (ii) where Pp/Ps = 0·5-0·9; note the rise in group (i) where Pp/Ps in less than 0·5.

RESULTS

The haemodynamic results of 47 cases of V.S.D. are presented in Table I. These cases were divided into 3 groups according to Pp/Ps: (i) Pp less than 0·5; (ii) Pp/Ps between 0·5 and 0·9; (iii) Pp/Ps more than 0·9. Their results were separately analysed. The differences between the pulmonary artery pressures before and after testing with oxygen and acetylcholine and also the differences in response to these two agents were analysed by paired t-test.

(i) *Pp/Ps less than 0·5* (Table II)

There were 17 cases in this group. With inhalation of oxygen, there was, on an average, a fall in pulmonary systolic pressure of 1·8 mm. Hg. which was found by paired t-test to be statistically significant ($0·01 < p < 0·05$). With acetylcholine, there was an average rise of 1·1 mm. Hg. which was also statistically significant ($0·01 < p < 0·05$). The difference in divergent responses to these agents was highly significant (p = less than 0·01). (See Table III).

(ii) *Pp/Ps between 0·5 and 0·9* (Table IV)

There were 19 cases in this group. Oxygen produced, on an average, a fall of 5·9 mm. Hg. and acetylcholine a fall of 8·5 mm. Hg. both of which were highly significant (p = less than 0·01). However, the difference between the degree of response to these agents was not significant (p = more than 0·1) (See Table V).

(iii) *Pp/Ps more than 0·9* (Table VI)

There were 11 cases in this group with pulmonary vascular disease. Oxygen produced an average fall of 6·3 mm. Hg. which was significant ($0·01 < p < 0·05$). With acetylcholine, there was an average fall of only 0·5 mm. Hg. which was not significant (p = more than 0·7). The difference between the two responses was significant ($0·01 < p < 0·05$) (See Table VII).

The analysis of the above data is summarised in Figs. 7 and 8.

RESULT OF SURGERY

Twenty of the patients had complete surgical closure of their ventricular septal defects. The pulmonary artery pressure fell in 19 patients following surgery (Fig. 9). It is interesting to note that in one patient (Cath. No. 828) whose pulmonary systolic pressure responded to oxygen with a fall of 22 mm. Hg. but to acetylcholine with a fall of only 5 mm. Hg., the pulmonary vascular resistance rose from 7·2 to 23 units one year after surgery. In another patient (Cath. No. 683) who responded to oxygen with a drop of 10 mm. Hg. and to acetylcholine 2 mm. Hg., the pulmonary vascular resistance rose from 8·4 to 32 units on re-catheterisation study performed 18 months later without surgery.

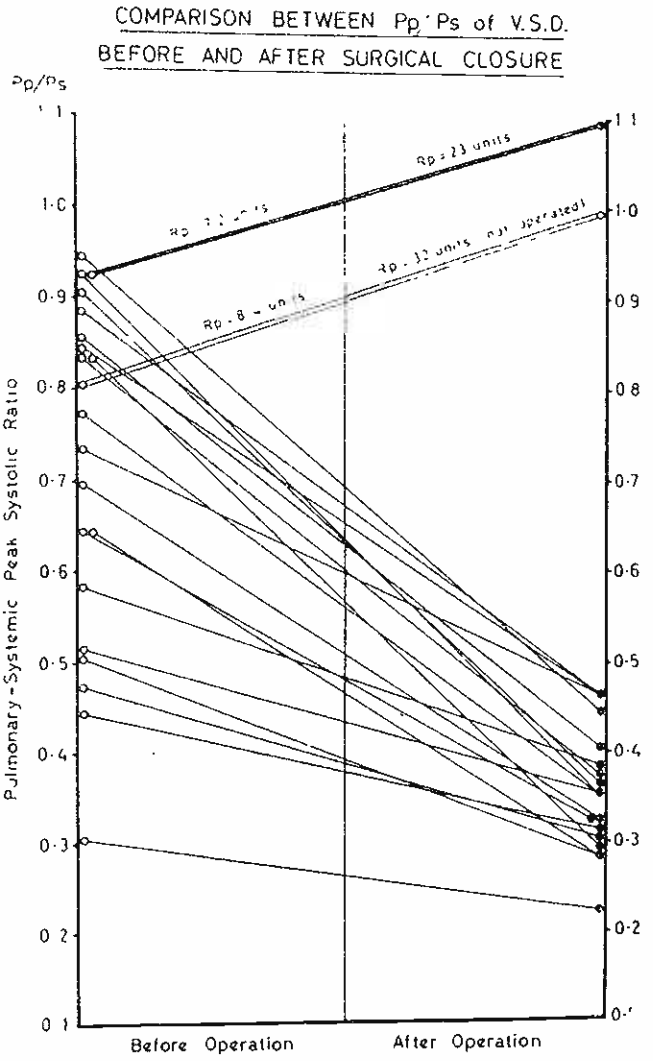

Fig. 9. This chart shows the fall in pulmonary arterial pressure in 19 patients after surgery; in one patient, the pressure rose, increasing the pulmonary vascular resistance to 7·2 to 23 Units.

DISCUSSION

The significance of the observation in testing the pulmonary artery pressure using oxygen and acetylcholine lies in the demonstration of a labile component contributing towards the pulmonary vascular resistance in V.S.D. If this labile factor causing vaso-constriction is predominant, it is more likely that the pulmonary hypertension will fall after surgical closure of the defect, hence a more favourable surgical prospect. This is illustrated in the results of complete correction of 19 patients presented.

TABLE I

EFFECTS OF OXYGEN AND ACETYLCHOLINE ON PULMONARY ARTERY PRESSURE IN V.S.D.

Case	Age (Years)	Sex	Cath. No.	Pp Ps	Qp Qs	Rp (Units M^2)	P.A. Pressure (mm. Hg.)				Operation
							Oxygen		Acetylcholine		
							Before	After	Before	After	
1. C.L.Y.	7	M	585	0·52	3·0	1·4	52 26	52 26	52/20	45/15	
2. C.S.H.	6	M	615	0·85	3·0	2·4	81 48	80 48	82/50	75·45	-
3. M. S. b. O.	6	M	659	0·96	1·7	14·3	128/86	112 67	110/85	112/80	-
4. A.L.K.	4	F	676	0·83	3·7	2·9	75/37	73 32	75/37	66/37	
5. L.M.W.	7	M	680	1·00	0·9	21·0	93/60	92/64	93·64	98/60	-
6. S.	6	M	683	0·80	1·2	8·4	78/48	68,44	77/45	75/47	-
7. U.A.	9	F	694	0·69	3·0	3·8	83/42	68/26	72/32	57/21	-
8. J.H.	3	F	699	0·83	3·4	2·4	82 28	72 19	75/21	54/21	
9. M.H.D.	4	M	701	0·65	2·0	4·7	73/26	68 24	68/24	55/18	-
10. L.Y.P.	10	M	703	0·74	2·8	4·2	71/40	65/31	65/35	52/23	
11. L.L.P.	8	F	713	0·78	3·0	2·8	78/42	62/30	62/30	48/26	-
12. L.S.C.	7	F	716	0·95	2·7	4·2	90/55	86/48	90/49	90/49	--
13. W.L.K.	9	M	722	1·00	1·0	17·5	96/61	90/57	89/57	88/55	—
14. T.B.C.	6	M	723	0·59	2·0	2·5	56/27	55/25	55/23	45/18	--
15. T.L.W	8	F	725	0·86	3·0	4·7	90/50	82/44	86/42	76/36	-
16. R.S.	3/12	F	732	0·45	1·5	2·6	34/14	30/15	30/15	32/14	--
17. S.L.C.	7	M	740	0·45	2·0	2·0	45/14	42/12	42/16	40/16	-
18. P.J.S.	9½	M	741	0·33	2·0	1·2	30/11	30/11	30/11	32/12	—
19. T.M.L.	3	F	743	0·25	2·2	0·8	24/8	26/10	26/10	26/12	--
20. A.H.P.	2	F	747	0·27	1·5	1·4	24/11	25/12	25/12	25/10	—
21. C.K.W.	9/12	F	749	0·93	2·2	3·4	64/21	64/21	65/24	63/25	--
22. D.F.G.	9/12	M	757	0·73	3·3	1·8	54/28	47/19	50/25	42/20	—
23. A. b. A.	5	M	758	0·95	1·6	6·1	74/60	74/66	74/60	74/60	—
24. A.B.	11	M	763	0·26	1·6	1·0	26/10	26/10	26/10	25/12	—
25. H.K.M.	3	F	770	0·65	3·3	1·7	55/16	56/25	56/25	46/15	-
26. C.B.C.	9	M	771	0·94	1·0	15·1	98/53	98/53	98/53	98/79	—
27. N.P.Y.	5	F	772	0·26	1·2	2·0	25/15	25/15	28/13	28/13	-
28. P.M.	5	F	775	0·90	3·7	3·0	85/36	83/31	85/34	77/26	-
29. L.C.H.	10	F	780	0·48	2·0	1·2	38/15	32/12	38/15	37/14	-
30. M.P.	5	F	785	0·30	1·2	1·8	30/14	30/15	28/12	30/14	--
31. G.N.C.	1½	M	786	0·45	2·4	2·4	40/15	32/10	32/13	35/15	—
32. A.	8	F	794	1·00	1·3	8·1	93/47	88/40	89/42	87/38	--
33. B.	2	F	798	0·56	2·3	1·1	*56/0-6	*51/0-5	*55/0-6	*47/0-5	—
34. T.M.C.	6	F	799	0·32	1·2	1·9	40/11	34/9	34/13	40/16	—
35. Z. bte. S.	2	F	802	0·28	1·2	1·1	17/7	15/6	18/7	16/10	—
36. L.C.K.	2	M	803	0·19	1·4	0·9	23/12	22/11	20/11	23/12	—
37. L.T.C.	1	M	805	0·35	1·5	0·9	27/10	28/12	30/11	32/9	—
38. F.K.C.	5	M	806	0·51	3·0	2·9	54/30	56/30	55/25	59/25	-
39. K.P.C.	4	F	810	0·89	2·8	5·1	92/44	89/44	97/48	87/36	-
40. S.L.K.	13	F	811	0·31	3·3	2·1	25/13	24/13	26/13	27/14	--
41. K.K.H.	9½	M	814	1·20	0·8	25·0	98/57	86/55	101/57	89/51	—
42. A.B.	10	F	815	1·00	1·0	10·5	88/55	85/51	87/52	97/52	—
43. L.C.H.	12	F	821	0·22	1·2	1·8	28/13	26/11	27/11	28/12	—
44. T.S.P.	2½	M	824	0·47	1·3	2·6	33/10	32/9	33/11	36/15	—
45. T.B.K.	3	F	825	0·81	2·0	5·4	87/43	67/30	70/36	68/33	—
46. P.M.	17	F	828	0·93	2·0	7·2	92/52	70/30	69/38	64/38	-
47. R. bte. S.	2	F	835	0·89	2·2	4·5	78/42	74/39	70/35	72/38	—

*R.V. pressure.

This table shows the haemodynamic data of 47 patients with V.S.D. and also the effects of oxygen and acetylcholine on the pulmonary arterial pressure (P.A.) before and after administration.

TABLE II

Pp/Ps - 0·5		Effect of Oxygen on P.A. Systolic Pressure (mm. Hg.)			Effect of Acetylcholine on P.A. Systolic Pressure (mm. Hg.)		
Case (Initials)	Cath. No.	Pressure Before Oxygen P_o'	Pressure After Oxygen P_o''	Difference $P_o'-P_o''$ (D_o)	Pressure Before Acetylcholine P_a'	Pressure After Acetylcholine P_a''	Difference $P_a'-P_a''$ (D_a)
G.N.C.	786	40	32	8	32	35	3
T.M.C.	799	40	34	6	34	40	-6
L.C.K.	803	23	22	1	20	23	-3
Z. bte. S.	802	17	15	2	18	16	2
L.T.C.	805	27	28	-1	30	32	-2
L.C.H.	780	38	32	6	38	37	1
M.P.	785	30	30	0	28	30	-2
N.P.Y.	772	25	25	0	28	28	0
A.B.	763	26	26	0	26	25	1
A.H.P.	747	24	25	-1	25	25	0
T.M.L.	743	24	26	-2	26	26	0
P.J.S.	741	30	30	0	30	32	-2
S.L.C.	740	45	42	3	42	40	2
R.S.	732	34	30	4	30	32	-2
S.L.K.	811	25	24	1	26	27	-1
L.C.H.	821	28	26	2	27	28	-1
T.S.P.	824	33	32	1	33	36	-3

This table shows the pulmonary systolic pressures before and after administration of oxygen and acetylcholine in 17 patients with V.S.D. in which Pp/Ps is less than 0·5.

TABLE III

	n, Number of Pairs of Observation	Mean of Difference Between Pairs of Observation	S.D. of Difference Between Pairs of Observation	t (Paired t-test)	p
Between P_o' and P_o''	17	1·8 mm. Hg.	2·8 mm. Hg.	2·60	Between 0·01 and 0·05
Between P_a' and P_a''	17	-1·1 mm. Hg.	2·1 mm. Hg.	2·21	Between 0·01 and 0·05
Between D_a and D_o	17	-2·9 mm. Hg.	3·9 mm. Hg.	3·03	<0·01

This table shows the statistical analysis of the data in Table II by paired t-test.

TABLE IV

Pp/Ps = 0.5 to 0.9		Effect of Oxygen on P.A. Systolic Pressure (mm. Hg.)			Effect of Acetylcholine on P.A. Systolic Pressure (mm. Hg.)		
Case (Initials)	Cath. No.	Pressure Before Oxygen P_o'	Pressure After Oxygen P_o	Difference $P_o' - P_o''$ (= D_o)	Pressure Before Acetylcholine P_a'	Pressure After Acetylcholine P_a''	Difference $P_a' - P_a''$ (= D_a)
A.L.K.	676	75	73	2	75	66	9
U. bte. A.	694	83	68	15	72	57	15
J.H.	699	82	72	10	75	54	21
M. H. b. D.	701	73	68	5	68	55	13
L.Y.P.	703	71	65	6	65	52	13
L.L.P.	713	78	62	16	62	48	14
T.B.C.	723	56	55	1	55	45	10
T.L.W.	725	90	82	8	86	76	10
D.F.G.	757	54	47	7	50	42	8
P.M.	775	85	83	2	85	77	8
S.	683	78	68	10	77	75	2
B.	798	56	51	5	55	47	8
F.K.C.	806	54	56	−2	55	59	−4
H.K.M.	770	55	56	-1	56	46	10
C.L.Y.	585	52	52	0	52	45	7
C.S.H.	615	81	80	1	82	75	7
K.P.C.	810	92	89	3	97	87	10
R. bte. S.	835	78	74	4	70	72	−2
T.B.K.	825	87	67	20	70	68	2

This table shows the pulmonary systolic pressures of 19 patients before and after administration of oxygen and acetylcholine in the group of V.S.D. in which Pp/Ps is between 0·5 and 0·9.

TABLE V

	n, Number of Pairs of Observation	Mean of Difference Between Pairs of Observation	S.D. of Difference Between Pairs of Observation	t (Paired t-test)	p
Between P_o' and P_o''	19	5·9 mm. Hg.	6·1 mm. Hg.	4·24	$<0·01$
Between P_a' and P_a''	19	8·5 mm. Hg.	5·9 mm. Hg.	6·22	$<0·01$
Between D_a and D_o	19	2·6 mm. Hg.	7·4 mm. Hg.	1·53	$>0·10$

This table shows the statistical analysis of the data in Table IV by paired t-test.

TABLE VI

Pp/Ps > 0.9		Effect of Oxygen on P.A. Systolic Pressure (mm. Hg.)			Effect of Acetylcholine on P.A. Systolic Pressure (mm. Hg.)		
Case (Initials)	Cath. No.	Pressure Before Oxygen P_o'	Pressure After Oxygen P_o''	Difference $P_o' - P_o''$ (= D_o)	Pressure Before Acetylcholine P_a'	Pressure After Acetylcholine P_a''	Difference $P_a' - P_a''$ (= D_a)
L.S.C.	716	90	86	4	90	90	0
C.K.W.	749	64	64	0	65	63	2
A.	794	93	88	5	89	87	2
A. b. A.	758	74	74	0	74	74	0
M.S. b. O	659	128	112	16	110	112	—2
L.M.W.	680	93	92	1	93	98	—5
C.B.C.	771	98	98	0	98	98	0
W.L.K.	722	96	90	6	89	88	1
K.K.H.	814	98	86	12	101	89	12
P.M.	828	92	70	22	69	64	5
A.B.	815	88	85	3	87	97	—10

This table shows the pulmonary systolic pressures before and after administration of oxygen and acetylcoline in 11 patients with V.S.D. in which Pp/Ps is more than 0·9.

TABLE VII

	n, Number of Pairs of Observation	Mean of Difference Between Pairs of Observation	S.D. of Difference Between Pairs of Observation	t (Paired t-test)	p
Between P_o' and P_o''	11	6·3 mm. Hg.	7·3 mm. Hg.	2·84	Between 0·01 and 0·05
Between P_a' and P_a''	11	0·5 mm. Hg.	5·5 mm. Hg.	0·27	>0·7
Between D_a and D_o	11	—5·8 mm. Hg.	7·1 mm. Hg.	2·73	Between 0·01 and 0·05

This table shows the statistical analysis of the data in Table VI by paired t-test.

Hypoxia can produce vaso-constriction in the pulmonary vessels as shown in a study on comparative effects of breathing a mixture of gas with low oxygen concentration in one lung and a mixture with normal oxygen concentration in the other; vaso-constriction occurs in the hypoxic lung (Himmelstein *et al*, 1958)[4]. Patients especially infants and children undergoing cardiac catheterisation have to be sedated. Heavy sedation in some can cause hypoventilation with resultant hypoxia. The pulmonary pressure recorded under this condition may be higher than usual. Breathing oxygen of high concentration can produce a fall in pulmonary artery pressure. A reduction of 33% of pulmonary vascular resistance while breathing oxygen alone compared with breathing atmospheric air has been reported by Shepherd *et al* (1959).[6]

Comparison of breathing air and oxygen has been carried out in 31 patients with V.S.D. (Marshall *et al*, 1961).[5] With oxygen, the pulmonary blood flow increased by 32% on an average and the pulmonary vascular resistance decreased by 36%, but there was no consistent change in pulmonary wedged pressure. Apparently, these changes were independent of the presence of pulmonary hypertension.

In our study, a significant fall in pulmonary systolic pressure occurred in all three groups of patients with V.S.D., but the maximal fall occurred in group (ii) with a large L-R shunt and Pp/Ps = 0·5-0·9. In addition, acetylcholine was used in the same patients for comparison.

Harris (1957)[3] found that acetylcholine injected into the pulmonary artery of patients with pulmonary hypertension secondary to L-R shunt produced a transient fall in pulmonary pressure. He suggested that this fall was caused by a decrease in pulmonary vascular resistance as a result of vaso-dilatation. Crittenden *et al* (1959),[1] basing their observation on 15 patients with a significant reduction of pulmonary hypertension with acetylcholine, considered a positive response as an indication of good operative risk, and a negative response as evidence of irreversible pulmonary vascular disease. Shepherd *et al* (1959)[6] used continuous infusion of acetylcholine and found that there was a reduction of 31% of pulmonary vascular resistance with acetylcholine alone and 57% with acetylcholine and oxygen administered simultaneously. Severe pulmonary vascular disease did not respond to acetylcholine (Wood, 1958).[7]

From the data obtained in our study, acetylcholine appeared to be a more effective test of vaso-constrictive component than oxygen, selective within a range where surgical closure of V.S.D. would more likely lead to a return of normal pulmonary circulation. Oxygen had a wider range of action, producing a significant fall in pulmonary artery pressure in the small defects as well as in the group of patients who obviously had severe pulmonary vascular disease.

Acetylcholine can either dilate or constrict pulmonary vessels, but the threshold dose of acetylcholine for dilatation is smaller than that for vaso-constriction (Daly and Hebb, 1966).[2] In our study, there was a significant rise in pulmonary pressure in the small defects where Pp/Ps was less than 0·5. The concentration of acetylcholine used could have been higher in view of a smaller pulmonary circulatory blood volume compared to the large L-R shunt in group (ii) cases, thus producing vaso-constriction.

The comparison between the effects of oxygen and acetylcholine on the pulmonary artery pressure in patients with V.S.D. has been studied because of the unpredictable effects and possibly misleading interpretation in using oxygen alone. It is recommended that acetylcholine alone or combined with oxygen would be a better method of evaluating pulmonary hypertension.

SUMMARY

The effects of oxygen and acetylcholine on the pulmonary arterial pressure were tested in 47 patients with isolated ventricular septal defects and their results were compared. The patients were divided into three groups according to their pulmonary to systemic peak pressure ratios: (i) less than 0·5; (ii) between 0·5 and 0·9; (iii) more than 0·9. Acetylcholine produced a highly significant fall in pulmonary systolic pressure in group (ii) patients who had pulmonary hypertension secondary to a large left-to-right shunt. Oxygen produced a significant fall not only in group (ii) patients but also in group (i) patients who had small defects and group (iii) patients who had large defects complicated by pulmonary vascular disease.

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