HÆMODYNAMIC ALTERATIONS INDUCED BY ISOPRENALINE IN PATIENTS WITH OBSTRUCTION TO RIGHT VENTRICULAR OUTFLOW

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Received April 26, 1965

It is now well established that there are two fundamentally distinct types of obstruction to left ventricular outflow, the first resulting from a discrete, fixed narrowing at a valvular, supra- or subvalvular level, and the second being produced by muscular hypertrophy in the left ventricular outflow tract. A number of designations, including obstructive cardiomyopathy (Goodwin *et al.*, 1960) and idiopathic hypertrophic subaortic stenosis (IHSS) (Braunwald *et al.*, 1960) have been applied to the latter condition. In patients with the discrete forms of obstruction to left ventricular outflow, the area of the stenotic outflow orifice remains constant during haemodynamic interventions which alter the systolic volume or the contractile state of the ventricle (Braunwald and Ebert, 1962), while with IHSS variations in the severity of obstruction may be induced by a variety of physiological and pharmacological stimuli. The dimensions of the obstructing orifice are not fixed in IHSS and the size of the left ventricular outflow tract varies, depending upon the contractile state of myocardium, the venous return, the systemic arterial pressure, and the systolic distending pressure (Whalen *et al.*, 1963; Krasnow *et al.*, 1963; Goodwin *et al.*, 1964; Wigle, 1964).

Although obstruction to right ventricular outflow is most commonly of the fixed type, in this chamber the obstruction may also result entirely from subvalvular muscular hypertrophy. The latter type of obstruction was first recognized in patients in whom the muscular hypertrophy developed as a result of severe valvular obstruction, and became unmasked by effective surgical treatment of the primary lesion (Kirklin *et al.*, 1953; Brock, 1955). More recently, muscular obstruction to right ventricular outflow has also been found to occur in the absence of treated valvular pulmonary stenosis, accompanying IHSS in some instances, or occurring in patients with idiopathic right and left ventricular hypertrophy unaccompanied by obstruction to left ventricular outflow (Braunwald *et al.*, 1964; Taylor, Bernstein, and Jose, 1964).

The infusion of isoprenaline (isoproterenol), a drug that exerts a powerful stimulating action on the contractile state of the myocardium, either intensifies or provokes obstruction to left ventricular outflow in patients with IHSS, and measurement of the haemodynamic response to this drug provides a useful test for detecting dynamic obstruction to left ventricular outflow (Braunwald and Ebert, 1962; Whalen *et al.*, 1963; Krasnow *et al.*, 1963). This observation suggested that study of the response of the right ventricular outflow tract to isoprenaline might allow differentiation of the fixed from the dynamic forms of right ventricular outflow obstruction, and provided the basis for the present investigation.

SUBJECTS AND METHODS

The 23 patients studied were divided into 3 groups. Group I consisted of 11 patients considered to have idiopathic hypertrophic subpulmonary stenosis. This group contained patient R.B., the only patient in the

series who exhibited no haemodynamic evidence of obstruction to right ventricular outflow in the basal state, but who developed a subvalvular systolic pressure gradient during isoprenaline infusion. Of the 11 patients in group I, 6 also had findings considered typical of IHSS with obstruction to left ventricular outflow in the basal state, the diagnosis in each patient having been established by a combination of clinical, haemodynamic, and angiographic techniques, as detailed elsewhere (Braunwald *et al.*, 1964). Of the other 5 patients, 2 (M.K. and R.B.) had evidence of left ventricular hypertrophy, exhibited no pressure gradients in the left ventricular outflow tract in the basal state, but developed left ventricular obstruction during the administration of isoprenaline. The 3 remaining patients in group I had no evidence of left ventricular obstruction either in the basal state or after isoprenaline. Two of these patients (K.Y. and W.S.) had evidence of left and right ventricular hypertrophy on electrocardiographic and angiocardiographic study, and were members of families affected by IHSS. Patient R.F. had idiopathic left ventricular hypertrophy, demonstrated by left ventricular angiocardiography, without obstruction to left ventricular outflow.

Group II consisted of 6 patients who exhibited subvalvular obstruction to right ventricular outflow from 7 to 32 months after successful surgical relief of valvular pulmonary stenosis, and who were, therefore, considered to have secondary hypertrophic subpulmonary stenosis. Group III consisted of 6 patients with discrete obstruction to right ventricular outflow. Haemodynamic studies and angiocardiography revealed that 3 of these patients had valvular pulmonary stenosis, while the other 3 had discrete congenital subvalvular stenosis with intact ventricular septa.

After a stable basal haemodynamic state had been achieved, the right ventricular outflow pressure gradient was determined by withdrawing the catheter from the pulmonary artery into the right ventricle; the cardiac output was then measured by the indicator-dilution method. Following these observations the catheter tip was advanced again into the pulmonary artery and isoprenaline was infused at a dose ranging from 0.5 to 3.0 $\mu\text{g./min.}$ When a stable haemodynamic state had been achieved during the infusion, pressures in the pulmonary artery and right ventricle, and the cardiac output, were remeasured. The effective orifice areas in the right ventricular outflow tract were calculated using the Gorlin formula (Gorlin and Gorlin, 1951). In 9 of the patients in group I the effects of isoprenaline on the orifice area of the left ventricle were also studied by recording left ventricular and systemic arterial pressures together with the cardiac output before and during the administration of the drug.

RESULTS

In each of the 11 patients with idiopathic hypertrophic subpulmonary stenosis (group I) it was observed that the right intraventricular peak systolic pressure gradient increased following isoprenaline, rising from an average level of 8 to 24 mm. Hg. In patient R.B., in whom no pressure gradient was present in the basal state, a gradient of 21 mm. Hg was induced with the drug. The cardiac output increased by more than 1.0 l./min. in 9 of these patients and showed little change in 2 (Table I). Since, in each patient in whom the cardiac output rose, the rise was proportionally less than the square root of the increase in the pressure gradient across the right ventricular outflow tract, the calculated effective orifice index decreased from an average of 2.34 cm.^2 to 1.59 cm.^2 (Fig. 1-3). The obstruction to left ventricular outflow was intensified in 6 of the 9 patients in this group in whom the effects of isoprenaline on the left ventricular dynamics were studied. Isoprenaline did not induce a pressure gradient in the remaining 3 patients who had no obstruction in the resting state.

In the patients with secondary hypertrophic subpulmonary stenosis, the administration of isoprenaline resulted in an increase in the pulmonary outflow tract pressure gradient in all, from an average of 21 to 48 mm. Hg, and in a rise in cardiac output in 5 of the 6 patients (Table II). As in the patients in group I, despite the increase in flow across the obstruction, the effective right ventricular outflow orifice area was reduced in each patient (Fig. 4), falling from an average of 1.40 to 1.09 cm.^2

The effects of isoprenaline in the patients with discrete valvular or subvalvular obstruction to right ventricular outflow (group III) differed from those observed in the first two groups of patients (Table III). Although the pressure gradient across the outflow tract increased in each patient, rising from an average of 40 to 57 mm. Hg, the flow across the obstruction was raised sufficiently to account for the increase in the gradient, and the calculated pulmonary outflow area did not change, the average value remaining constant at 0.64 cm.^2 (Fig. 5).

TABLE I
EFFECTS OF ISOPRENALINE IN IDIOPATHIC HYPERTROPHIC SUBPULMONARY STENOSIS

Patient and age (yr.)	Condition	HR (beats/min.)	Syst. press. (mm. Hg)		Peak RV-infund. grad. (mm. Hg)	CO (l./min.)	Eff. RV outflow orif. (cm. ²)	Peak LV-BA grad. (mm. Hg)	Eff. LV outflow orif. (cm. ²)
			RV	Infund.					
R.E.	Control	68	41	15	26	6.70	1.96	33	1.89
32	Iso. 1.4 µg.	72	67	15	52	7.65	1.46	49	1.26
J.E.	Control	90	36	30	6	5.03	2.48	12	1.30
36	Iso. 2.0 µg.	150	53	25	28	7.28	1.91	55	0.79
I.H.	Control	78	42	39	3	4.08	>3.00	3	>3.00
19	Iso. 1.0 µg.	102	57	41	16	9.78	2.66	63	1.66
M.K.	Control	84	38	32	6	6.78	2.24	0	>3.00
51	Iso. 1.2 µg.	96	48	36	12	9.74	1.69	53	0.92
S.H.	Control	72	37	32	5	4.76	2.31	13	1.17
24	Iso. 1.5 µg.	102	65	51	14	3.87	0.91	79	0.38
R.B.	Control	84	32	32	0	5.17	>3.00	0	>3.00
29	Iso. 2.0 µg.	120	48	27	21	8.18	1.90	41	1.59
K.Y.	Control	90	26	23	3	3.92	>3.00	0	>3.00
10	Iso. 2.0 µg.	110	43	29	14	5.72	1.97	0	>3.00
R.F.	Control	84	30	18	12	5.72	1.86	0	>3.00
48	Iso. 1.0 µg.	84	52	26	26	6.14	1.04	0	>3.00
W.S.	Control	84	36	30	6	9.85	>3.00	0	>3.00
16	Iso. 1.5 µg.	108	69	36	33	11.10	2.02	0	>3.00
R.P.	Control	66	28	23	5	4.96	1.98	50*	0.69*
14	Iso. 2.0 µg.	96	41	24	17	8.61	1.27	—	—
V.S.	Control	78	35	18	17	3.42	0.94	135*	0.47*
61	Iso. 2.0 µg.	96	70	39	31	5.12	0.63	—	—
Average values	Control	80	35	27	8	5.49	2.34	7	2.48
	Iso.	103	56	32	24	7.56	1.59	38	1.73

HR=heart rate, Syst. press.=systolic pressure, RV=right ventricle, Infund.=right ventricular infundibulum, CO=cardiac output, Eff. RV outflow orif.=effective right ventricular outflow orifice, LV=left ventricle, BA=brachial artery, Eff. LV outflow orif.=effective left ventricular outflow orifice, Iso.=isoprenaline and dose, µg./min. *These values are not used in calculating average values.

TABLE II
EFFECTS OF ISOPRENALINE IN SECONDARY HYPERTROPHIC SUBPULMONARY STENOSIS

Patient and age (yr.)	Condition	HR (beats/min.)	Syst. press. (mm. Hg)		Peak RV-infund. grad. (mm. Hg)	CO (l./min.)	Eff. RV outflow orif. (cm. ²)	Pre-operative findings		
			RV	Infund.				Syst. press. (mm. Hg)		Peak RV-PA grad. (mm. Hg)
								RV	PA	
S.K.	Control	76	23	17	6	4.86	1.96	156	14	142
15	Iso. 1.0 µg.	115	38	17	21	7.41	1.40			
S.S.	Control	78	45	18	27	3.90	0.83	118*		
40	Iso. 2.8 µg.	120	145	25	120	6.11	0.55			
L.P.	Control	75	45	25	20	4.12	0.96	192	12	180
21	Iso. 2.5 µg.	95	60	25	35	5.77	0.82			
G.H.	Control	84	27	17	10	6.20	2.49	75	10	65
10	Iso. 1.0 µg.	108	54	20	35	9.70	1.97			
V.D.	Control	75	42	20	22	4.04	1.18	152	12	140
42	Iso. 3.0 µg.	95	55	20	35	5.24	1.04			
T.M.	Control	85	70	30	40	5.47	0.99	145	16	129
52	Iso. 2.0 µg.	110	84	40	44	5.12	0.76			
Average values	Control	79	42	21	21	4.76	1.40	145	13	132
	Iso.	107	73	25	48	6.56	1.09			

PA=pulmonary artery. Other abbreviations as in Table I. * This value not used in calculating the averages.

DISCUSSION

The administration of the powerful cardiotonic agent, isoprenaline, resulted in intensification of the subvalvular obstruction to right ventricular outflow in patients with idiopathic hypertrophic subpulmonary stenosis and in patients with hypertrophic subpulmonary stenosis secondary to severe obstruction of the pulmonary valve. In addition, it provoked the development of subpulmonary obstruction in a single patient with subaortic obstruction, who had no obstruction to right ventricular outflow in the basal state. In contrast, it did not attenuate the outflow orifice in patients with congenital valvular pulmonary stenosis or discrete subvalvular stenosis. These observations indicate that muscular obstruction to right ventricular outflow, whether primary in nature, or secondary to valvular stenosis, is dynamic and may vary in severity.

Other investigators have observed that the administration of isoprenaline results in an augmentation of the peak systolic pressure gradient in patients with valvular aortic or pulmonary stenosis (Moss and Quivers, 1963; Moss and Duffie, 1963). Moreover, in some patients who were studied after pulmonary valvulotomy, marked rises in the outflow pressure gradient occurred (Moss and Quivers, 1963). Although the changes in cardiac output induced by the drug were not measured, and determinations of the effects of isoprenaline on the outflow orifice were, therefore, not possible, it now appears likely that the large increases in the pressure gradient that were produced in the latter group

FIG. 1.—Values for the effective right ventricular outflow orifice area during the control period and during the administration of isoprenaline in patients with idiopathic hypertrophic subpulmonary stenosis. The horizontal bars represent the mean values.

FIG. 2.—Effects of isoprenaline (isoproterenol) in a patient with idiopathic hypertrophic subpulmonary stenosis. Grad.=peak systolic pressure gradient. C.O.=cardiac output. P.O.=effective right ventricular outflow orifice area. PA=pulmonary artery. RV Infund.=right ventricular infundibulum. RV=right ventricle.

FIG. 3.—Effects of isoprenaline (isoproterenol) in a patient with idiopathic hypertrophic subpulmonary and subaortic stenosis. A.O.=effective left ventricular outflow orifice area. LV=left ventricle, BA=brachial artery. Other abbreviations as in Fig. 2.

resulted from constriction of the hypertrophied infundibulum in response to the positive inotropic action of the drug. Goodwin *et al.* (1964) observed that isoprenaline sometimes resulted in increases in pressure gradients across the right ventricular outflow tract in patients with idiopathic hypertrophic subpulmonary stenosis, but the changes were relatively small and determinations of the orifice area were not made.

Little information has, heretofore, been available concerning the fundamental nature of the obstruction to right ventricular outflow in patients with idiopathic hypertrophic subaortic stenosis, though the possibility has been considered that obstruction in the right ventricle is entirely secondary

TABLE III
EFFECTS OF ISOPRENALINE IN DISCRETE OBSTRUCTION TO PULMONARY OUTFLOW

Patient and age (yr.)	Diagnosis	Condition	HR (beats/min.)	Syst. press. (mm. Hg)		Peak RV-PA grad. (mm. Hg)	CO (l./min.)	Eff. RV outflow orif. (cm. ²)
				RV	PA			
P.L. 11	PS	Control	90	93	28	65	5.42	0.61
		Iso. 1.2 μ g.	126	127	28	99	7.10	0.56
A.G. 19	PS	Control	78	45	22	23	3.80	0.92
		Iso. 2.0 μ g.	96	78	21	57	5.40	0.84
J.Y. 17	PS	Control	100	94	12	82	7.14	0.54
		Iso. 1.5 μ g.	114	109	12	97	10.30	0.64
J.M. 9	Sub. PS	Control	96	45	15	30	2.72	0.63
		Iso. 0.8 μ g.	104	55	20	35	4.87	0.76
P.E. 10	Sub. PS	Control	78	45	18	27	1.96	0.46
		Iso. 0.5 μ g.	114	63	25	38	2.27	0.38
D.S. 6	Sub. PS	Control	90	28	18	10	2.16	0.69
		Iso. 0.5 μ g.	114	36	18	18	3.08	0.65
Average values		Control	89	58	18	40	3.87	0.64
		Iso.	111	78	21	57	5.50	0.64

PS=valvular pulmonary stenosis. Sub. PS=subpulmonary stenosis. Other abbreviations as in Tables I and II.

in nature (Oakley, 1964). However, obstructive disease of the right ventricular outflow tract seems clearly to exist not only in association with obstruction to left ventricular outflow, but by itself as well, in the absence of a pressure gradient within the left ventricle. Thus, in a group of 64 patients with IHSS who were reported from this clinic (Braunwald *et al.*, 1964), 10 exhibited right ventricular obstruction in the basal state; in 7 of these 10 patients the obstruction within the left ventricle was more severe than that observed in the right; in 1 the gradients were equal; in 1 the gradient was larger in the right ventricle; and in 1 there was no gradient at all within the left ventricle. Taylor *et al.*

FIG. 4.—Effects of isoprenaline (isoproterenol) in a patient with secondary hypertrophic subpulmonary stenosis. Abbreviations as in Fig. 2.

FIG. 5.—Values for the effective right ventricular outflow orifice area during the control period and during isoprenaline infusion in patients with discrete obstruction to pulmonary outflow.

that decrease the end-systolic volume of the right ventricle, such as nitroglycerin, or the Valsalva manoeuvre, might also reduce the pulmonary outflow orifice in patients with muscular obstruction to right ventricular outflow, as they do in patients with muscular obstruction to left ventricular outflow (Braunwald *et al.*, 1964).

SUMMARY

The dynamic nature of the obstruction to ventricular ejection was determined in 23 patients with different forms of obstruction to right ventricular outflow, 20 of whom had haemodynamic evidence of subvalvular pulmonary stenosis. Cardiac output and right ventricular outflow pressure gradients were recorded, and the effective areas of the outflow tract were calculated before and during infusion of isoprenaline, an agent that stimulates the contractile state of the myocardium. Intensification of the obstruction to right ventricular outflow was observed in 17 of the patients studied. In the 11 patients with idiopathic hypertrophic subpulmonary stenosis, isoprenaline reduced the outflow orifice by an average of 0.75 cm.² In the 6 patients with secondary hypertrophic subpulmonary stenosis who were studied following successful surgical relief of valvular pulmonary stenosis, isoprenaline reduced the outflow orifice by an average of 0.31 cm.² No attenuation of the outflow orifice was noted in the 3 patients with valvular pulmonary stenosis nor in the 3 patients with discrete congenital subvalvular stenosis. These observations indicate that muscular obstruction to right ventricular outflow is dynamic, that it can vary in severity depending on the heart's catecholamine background, and that the fundamental nature of the obstructive process is similar in both ventricular outflow tracts. In conclusion, the response to isoprenaline infusion provides a useful test for assessing the nature of subvalvular obstruction to right ventricular outflow.

(1964) have also studied one patient having obstruction to right ventricular outflow only. The intensification of obstruction to right ventricular ejection induced by isoprenaline in patients with idiopathic hypertrophic subpulmonary stenosis reported herein suggests that the fundamental nature of the obstructive process is similar in both ventricles, though quantitatively the changes on the right side of the heart produced by the drug are usually not as marked as those on the left. The responses to the drug in this group, as well as in the patients with obstruction to right ventricular outflow following surgical relief of valvular pulmonary stenosis, contrasted with the response of patients with discrete subpulmonary obstruction, and the administration of isoprenaline would, therefore, appear to be a useful diagnostic test for characterizing the nature of subpulmonary obstruction. Furthermore, the response to isoprenaline makes it likely that other interventions that stimulate the contractile state of the myocardium, such as the digitalis glycosides, muscular exercise, as well as interventions

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