Phentolamine and Cardiovascular Performance

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Ahlquist (1948) proposed two distinct adrenergic receptor sites, the alpha- and beta-adrenergic receptors. Stimulation of the alpha-adrenergic receptors produces arteriolar constriction unaccompanied by any primary cardiac action, presumably due to the absence of alpha receptors in the heart. Selective blockade of the alpha receptors produces arteriolar dilatation, and this also is unaccompanied by any primary cardiac effect. This blockade can be accomplished by using the drug phentolamine.

Despite intensive studies on the adrenergic blocking activity of phentolamine there have been few reports analysing its haemodynamic effects and its mode of action. Taylor and his co-workers (1965a b, c) have investigated the haemodynamic effects in man of the acute intravenous injection of 5 mg. phentolamine and of intravenous infusion of the drug at a rate of 2 mg. per minute for 10 minutes. Both methods of administration produced an increase in the heart rate and cardiac output and a decrease in the systemic arterial pressure. They concluded that the hypotensive effect limited the clinical applicability of the drug.

We now report an investigation of the action of phentolamine in the dog, in which a marked increase in the force of myocardial contraction was shown. Based on this finding, the study was extended to investigate more fully the haemodynamic actions of this drug in man.

METHODS

Animals. Four normal mongrel dogs weighing 11.3 kg. to 22.7 kg. (25–50 lb.) were studied. They were lightly pre-anaesthetized with acetyl-promazine (1 mg./11.3 kg.) and succinyl-choline (1 mg./2.7 kg.). Pentothal was given intravenously until endotracheal intubation was established. They were maintained on a nitrous oxide and oxygen gas mixture, with intermittent

administration of methoxyflurane. Respiration was kept constant by a Bird respirator through a cuffed endotracheal tube.

After making an intercostal incision and spreading the ribs, the pericardium was opened and a strain gauge arch was attached on the right ventricle. Arterial blood pressure was measured through a Cournand needle in the femoral artery by means of a Satham pressure transducer. Continuous recordings of myocardial contractile force and blood pressure were made simultaneously with a multichannel oscillograph before and after the rapid intravenous injection of 5 mg. of phentolamine.

Human Subjects. Our observations were made in 5 patients (Group 1) with relatively normal left ventricles, who had never been in left ventricular failure, and 13 patients (Group 2) with abnormal left ventricles, who had previously been in left ventricular failure, and who underwent right and left heart catheterizations primarily as an aid to their clinical management. The diagnoses of the patients are listed in Table II.

Patients 4 and 16 were in atrial fibrillation; the rest were in sinus rhythm. Patients 3, 4, 6, 8, 9, 13, 14, 15, 16, and 17 were taking digoxin; the rest were not receiving any therapy.

Catheterization of the left ventricle was performed either by the Seldinger technique or by retrograde arterial catheterization through a brachial arteriotomy. A Cournand needle was placed into the opposite brachial artery. In order to ensure high fidelity tracings, the needle was directly connected to a Satham pressure transducer—P23Db. The first derivative of the brachial artery pressure could then be computed by an R-C differentiating circuit. A No. 7 Goodale-Lubin catheter was placed in the pulmonary artery. Cardiac output was determined by the Fick technique.

Left ventricular, pulmonary arterial, and systemic arterial pressures and cardiac output were measured in the resting state. The brachial artery dp/dt, and the left ventricular dp/dt, were also obtained. The latter was recorded through a catheter manometer system and measurements were made only when the pressure curves showed an undistorted wave form. Since the catheter values faithfully reproduce directional changes (Murphy

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et al., 1964), relative values of left ventricular dp/dt are reported in this study; no attempt was made to quantitate these values in absolute terms. Two of the patients in Group 1, and 7 of the patients in Group 2, then pedalled a bicycle ergometer for 6 to 7 minutes in the supine position. Pressures and cardiac output were measured 5 minutes after the onset of exercise.

At least 20 minutes after exercise, when the pressure in the pulmonary artery as well as the pressures and first derivatives in the left ventricle and brachial artery had returned to the control values, phentolamine was given by constant intravenous drip (0.3 mg. per minute). Pressure recordings and cardiac output data were repeated 10 and 20 minutes after the start of infusion. In the patients not exercised, phentolamine was infused after the resting control values had been recorded.

In 10 patients in the resting state, the left ventricular end-diastolic volume was calculated cine-angiographically, using a method based on the uniplanar modification of the methods of Dodge *et al.* (1960), and Klein, Herman, and Gorlin (1967). Ventriculograms were taken in the 30° right anterior oblique projection with a fixed distance from x-ray tube to table top. Cine films of a grid were made at the approximate level of the cardiac apex. The projected distance of this grid image was adjusted until actual and projected measurements were matched, so that left ventricular silhouettes free from the error of distortion and magnification were then obtained. The end-diastolic area (A) of the image was obtained by planimetry. The long axis (L) was measured directly.

The width was calculated from the equation $W = \frac{4A}{L\pi}$.

The left ventricular end-diastolic volume was then obtained from the equation $LVEDV = 4/3\pi \left(\frac{W}{2}\right)^2 \cdot \frac{L}{2}$.

The end-systolic volume was calculated by subtracting the stroke volume obtained by the Fick technique from the left ventricular end-diastolic volume. No attempt was made to calculate the end-systolic volume angiographically, since the reliability of this measurement is in doubt (Davilla and Sanmarco, 1966). After completion of the 20-minute cardiac output determination, but while the phentolamine infusion was still running, left ventricular angiograms were performed in 10 subjects.

Left ventricular function was assessed according to the following parameters:

- (1) $LVSW = \frac{LV_s}{100} - LV_d \times 1.36 \times 1.050 \times SI$
- (2) $LVSP = LVSW/SEP$

- (3) $MSER = SI/SEP$
- (4) $TTI_b = LV_s \times SEP$
- (5) $TTI_m = LV_s \times SEP \times HR$
- (6) $LVW = CI \times 1.36 \times 1.050 \times BA_m/100$
- (7) $PR = \frac{BA_m \times 1332}{CO}$

where LVSW = left ventricular stroke work (g.m./beat/m.² BSA); SI = stroke index (ml./beat/m.² BSA); LV_s = mean left ventricular systolic pressure (mm. Hg); LV_d = left ventricular end-diastolic pressure (mm. Hg); LVSP = mean left ventricular stroke power (g.m./beat/m.² BSA/systolic sec.); SEP = mean systolic ejection period (seconds); MSER = mean systolic ejection rate (ml./beat/m.² BSA/systolic sec.); TTI_b = tension time index per beat (mm. Hg sec./beat); TTI_m = tension time index per minute (mm. Hg seconds/min.); HR = heart rate (beats/min.); LVW = left ventricular work (kg. m./min/m.² BSA); BA_m = mean brachial artery pressure (mm. Hg); PR = systemic peripheral resistance (dynes/sec./cm.⁻⁵); CO = cardiac output (ml./sec.); 1.36 = conversion factor from mm. Hg to cm. H₂O; 1.050 = whole blood specific gravity; BSA = body surface area in square meters.

RESULTS

Animal Studies. The effects of phentolamine on heart rate, arterial pressure, and right ventricular contractile force are shown in Table I. The amplitudes of the contractile force recordings were measured in millimeters.

The intravenous administration of phentolamine increased the ventricular contractile force in all 4 dogs (Fig.). There was an average increase of 102 per cent. The response to the drug was transient, lasting about 5 minutes. There was a variable response of the pulse rate and blood pressure.

Human Subjects. Complete data on all 18 patients are presented in Tables II and III. In addition, average values and the percentage change from the control value after exercise and phentolamine infusion are listed in Table IV.

Exercise. Only 2 patients in Group 1 were exercised. Therefore, no valid comparison can be

TABLE I
CARDIOVASCULAR EFFECTS OF PHENTOLAMINE IN THE DOG

Dog	Control			Peak effect of phentolamine			Change		
	Cardiac force (mm.)	Femoral artery (mm. Hg)	Heart rate (beats/min.)	Cardiac force (mm.)	Femoral artery (mm. Hg)	Heart rate (beats/min.)	Cardiac force (%)	Femoral artery (mm. Hg)	Heart rate (beats/min.)
1	2	115/80	120	6	110/70	160	200	-5/-10	+40
2	18	175/125	140	24	175/120	160	33½	0/-5	+20
3	4	120/90	180	7	75/50	180	75	-45/-40	0
4	5	140/90	200	8	145/93	200	100	5/-3	0

TABLE IIA
COMPLETE OBSERVED HAEMODYNAMIC DATA ON 18 PATIENTS

Patient No. and condition	Experm. state	Rt. atrium mean (mm. Hg)	Rt. ventr. (mm. Hg)	Pulm. art. (mm. Hg)	Mean	Lt. ventr. (mm. Hg)	Per cent lt. ventr. dp/dt (mm. Hg/sec.)	Brach. art.		Brach. art. dp/dt (mm. Hg/sec.)	Rate (beats/min.)	Syst. ejection time	
								(mm. Hg)	Mean			Sec./beat	Rate correct
1 Normal functional murmur	Rest	0	20/2	20/8	11	140/9		140/80	95	680	65	0.28	0.38
2 Mitral stenosis	Exercise			34/10	16	160/9	+64	160/90	115	950	88	0.32	0.46
	Phentol.					135/4	+64	140/90	110	820	88	0.30	0.44
	Phentol.	0	75/0	70/28	45	130/3	+91	140/90	110	850	88	0.28	0.42
3 Mitral stenosis	Rest			60/30	40	150/5	+18	130/80	95	543	60	0.30	0.40
	Phentol.			60/30	40	145/3	+14	160/90	115	755	65	0.29	0.39
	Phentol.	2	45/5	45/18	30	90/8		150/80	100	725	65	0.29	0.39
4 Mitral stenosis	Rest			50/25	35	100/10	+68	100/60	75	750	58	0.28	0.38
	Phentol.			50/10	22	95/10	+76	110/65	80	685	58	0.30	0.40
	Phentol.	4	50/4	50/10	22	95/10	+76	100/65	77	650	62	0.30	0.40
5 Idiopathic hypertrophic subaortic stenosis	Rest			55/30	38	125/5	+27	140/90	110	490	100	0.24	0.40
	Phentol.			20/9	12	130/0	+64	130/80	95	630	100	0.24	0.40
	Phentol.	1	20/2	35/15	20	145/12	+50	125/85	100	630	110	0.22	0.40
6 Primary myocardial disease	Rest			20/9	12	135/0	+62	120/80	92	700	72	0.30	0.42
	Exercise			22/9	13	135/0	+44	110/60	80	880	88	0.30	0.44
	Phentol.							135/75	95	880	79	0.28	0.41
7 Primary myocardial disease	Rest							110/70	85	880	75	0.28	0.40
	Exercise	0	32/0	32/11	18	105/8		110/80	90	440	84	0.24	0.37
	Phentol.			100/50	60	175/30	+91	175/100	125	630	100	0.24	0.40
8 Primary myocardial disease	Rest			35/12	20	130/5	+39	145/100	115	475	88	0.24	0.38
	Exercise	1	45/2	30/12	18	120/0	+28	120/80	95	475	88	0.24	0.38
	Phentol.			45/20	30	95/25		100/0	88	370	94	0.20	0.35
9 Primary myocardial disease	Rest			75/40	60	115/28	+86	120/100	108	616	125	0.18	0.38
	Exercise					110/25	+93	115/90	100	310	107	0.20	0.37
	Phentol.			50/35	42	110/25	+93	140/95	110	780	115	0.20	0.38
10 Primary myocardial disease	Rest			18/7	11	170/10		170/85	115	785	84	0.28	0.41
	Exercise	0	20/2	45/17	25	180/20	+37	180/90	120	1120	100	0.30	0.46
	Phentol.			20/8	12	150/0	+16	155/85	110	1090	88	0.30	0.44
11 Primary myocardial disease	Rest			22/8	12	150/0	+25	170/100	125	1120	100	0.23	0.39
	Exercise	1	36/2	35/10	18	170/4		170/85	115	1100	68	0.28	0.38
	Phentol.			70/30	50	200/15	+87	210/110	145	1740	100	0.30	0.46
12 Hypertension	Rest			29/8	13	170/0	+18	170/95	120	1100	79	0.30	0.43
	Exercise			32/10	16	200/0	+129	200/100	135	1320	88	0.28	0.42
	Phentol.	0	65/0	65/32	45	90/26		100/70	80	425	107	0.24	0.41
13 Aortic insufficiency	Rest			80/35	50	95/26	+27	110/80	90	480	115	0.22	0.40
	Exercise			60/30	40	100/27	+32	105/65	80	425	107	0.24	0.41
	Phentol.												
14 Primary myocardial disease	Rest			40/15	22	110/23		110/80	90	450	84	0.20	0.34
	Exercise	0	40/0	90/40	60	150/30	+94	150/100	115		115	0.23	0.41
	Phentol.					140/16	+30	140/80	100	645	94	0.24	0.39
15 Primary myocardial disease	Rest			26/11	16	115/2	+20	115/75	90	310	94	0.24	0.39
	Exercise	0	32/0	32/12	20	185/8		190/115	140	955	88	0.24	0.38
	Phentol.			70/35	45	220/20	+55	220/90	130	1400	115	0.26	0.44
16 Aortic insufficiency	Rest			26/9	15	180/5	+33	185/90	120	1090	94	0.24	0.39
	Exercise			24/7	14	175/0	+55	190/95	125	1065	107	0.23	0.40
	Phentol.	3	55/3	55/25	35	110/22		110/50	70	1040	75	0.30	0.42
17 Aortic stenosis	Rest			75/40	52	130/30	+118	140/65	90	1400	107	0.30	0.47
	Exercise			65/30	40	120/20	+51	130/65	85	1120	84	0.30	0.43
	Phentol.			60/35	45	120/16	+66	130/55	80	1260	88	0.30	0.44
18 Carcinoid, myocardial and tricuspid incomp., pulm. stenosis	Rest			23/9	14			150/95	113	660	87	0.23	0.37
	Exercise	0	22/0	16/7	10			160/90	113	800	107	0.22	0.39
	Phentol.			16/7	10			160/95	116	820	115	0.20	0.38
19 Primary myocardial disease	Rest			85/42	56	155/30		165/110	128	730	115	0.22	0.40
	Exercise	10	85/10	75/40	52	163/17	+14	170/105	127	850	120	0.22	0.41
	Phentol.			75/40	52	150/17	+9	170/100	124	910	115	0.22	0.40
20 Aortic stenosis	Rest			30/10	17	135/8		138/53	81	930	60	0.28	0.38
	Exercise	0	30/0	27/8	14	130/8	+11	150/52	85	1080	46	0.26	0.33
	Phentol.			24/8	13	130/7	+11	142/62	88	1120	46	0.26	0.33
21 Aortic stenosis	Rest			28/13	18	175/5		150/85	106	480	63	0.38	0.48
	Exercise	1	29/2	22/10	14	180/5	+24	160/75	103	630	65	0.34	0.44
	Phentol.			22/10	14	175/5	+33	160/85	110	610	68	0.34	0.44
22 Carcinoid, myocardial and tricuspid incomp., pulm. stenosis	Rest			20/10	14	135/3		155/90	112	850	83	0.30	0.43
	Exercise	8	30/8	20/6	11	150/2	+23	165/85	112	1000	88	0.28	0.42
	Phentol.			18/6	10	158/2	+23	165/85	112	1020	88	0.28	0.42

made with the control state. In Group 2 comparison is possible, since 7 of the 13 patients were exercised. During the stress of exercise, the oxygen consumption increased by 187 per cent and

the arteriovenous oxygen difference widened by 74 per cent. The cardiac index rose 64 per cent; this was associated with a 24 per cent fall in the peripheral resistance. The rise in the cardiac index

TABLE IIB
COMPLETE DERIVED HAEMODYNAMIC DATA ON 18 PATIENTS

Patient No. and condition	Experm. state	AV O ₂ diff. (vol. %)	O ₂ con. sumpt. (ml./min./m. ²)	Cardiac index (l./min./m. ²)	Stroke index (ml./beat m. ²)	LVSWI (g.m./beat m. ²)	LVSP (g.m./beat m. ² /syst. sec.)	MSER (ml./beat m. ² /syst. sec.)	TTIb (mm. Hg/sec./beat)	TTIm (mm. Hg/sec./min.)	Lt. ventr. work (kg.m./min./m. ²)	Periph. resist. (dyne sec.-cm. ⁻⁵)
1 Normal functional murmur	Rest	3.6	94	2.6	40	75	269	143	39	2545	3.5	1490
	Exercise	4.8	265	5.52	63	136	424	192	51	4500	9.1	853
	Phentol.	2.5	95	3.77	42	82	273	140	42	3700	5.9	1190
2 Mitral stenosis	Phentol.	2.9	107	3.70	42	76	272	150	37	3200	5.8	1201
	Rest	4.2	167	4.0	67	122	407	223	39	2340	5.4	1100
	Phentol.	5.6	148	2.66	41	85	293	142	44	2830	4.4	2010
3 Mitral stenosis	Phentol.	5.5	172	3.13	48	98	338	165	42	2730	4.5	1570
	Rest	4.5	131	2.91	50	59	210	179	25	1465	3.1	1120
	Phentol.	5.4	148	2.73	47	61	203	157	30	1740	3.1	1280
4 Mitral stenosis	Phentol.	3.6	139	3.89	62	75	250	207	29	1770	4.3	870
	Rest	5.7	145	2.48	25	43	178	104	30	3000	3.9	1730
	Phentol.	4.7	102	2.15	22	39	163	92	31	3120	2.9	1690
5 Mitral stenosis	Phentol.	5.3	101	1.91	18	31	141	82	30	3020	2.7	2900
	Rest	3.4	148	4.36	60	112	373	200	39	2810	5.7	886
6 Idiopathic hypertrophic subaortic stenosis	Exercise	5.8	287	4.94	56	107	357	187	44	3820	5.7	680
	Phentol.	2.5	177	7.1	90	174	620	322	38	3000	9.7	565
	Phentol.	4.4	147	3.35	44	85	302	157	38	2840	4.1	1070
7 Primary myocardial disease	Rest	5.0	133	2.64	31	43	179	129	25	2120	3.4	1540
	Exercise	10.1	329	3.25	33	68	284	137	42	4200	5.5	1700
	Phentol.	3.7	137	3.70	43	77	320	179	31	2750	6.1	1365
	Phentol.	3.4	121	3.58	41	70	292	171	29	2540	4.9	1170
8 Primary myocardial disease	Rest	8.4	130	1.54	16	16	80	80	19	1785	1.9	2260
	Exercise	12.5	234	1.87	16	20	111	89	21	2590	2.9	2280
	Phentol.	6.9	134	1.93	18	22	110	90	22	2350	2.8	2020
	Phentol.	6.5	147	2.26	20	25	125	100	22	2530	3.5	1930
9 Primary myocardial disease	Rest	4.4	110	2.50	29	66	236	104	48	4000	4.1	2010
	Exercise	8.0	246	3.08	31	71	237	103	54	5400	5.3	1780
	Phentol.	5.7	152	2.67	31	67	223	103	45	3980	4.2	1810
	Phentol.	4.8	136	2.82	28	60	260	122	35	3450	5.0	1930
10 Primary myocardial disease	Rest	4.3	96	2.22	33	78	278	118	48	3230	3.7	2040
	Exercise	6.9	406	5.5	59	156	520	263	60	6000	11.4	970
	Phentol.	4.3	128	2.97	38	92	307	127	51	4030	5.1	1585
	Phentol.	5.6	193	3.44	39	111	396	139	56	4940	6.6	1550
11 Primary myocardial disease	Rest	7.0	165	2.36	22	20	83	92	22	2310	2.7	1625
	Phentol.	5.1	202	3.96	35	34	155	159	21	2300	5.1	1210
	Phentol.	4.3	153	3.59	34	35	146	142	24	2570	4.1	1065
12 Hypertension	Rest	6.1	117	1.91	22	27	135	110	22	1850	2.5	1870
	Exercise	9.9	484	4.9	43	74	320	187	35	3970	8.1	930
	Phentol.	5.4	124	2.29	24	43	179	100	34	3160	3.3	1730
	Phentol.	4.5	114	2.54	29	74	308	121	44	3900	5.1	2420
	Exercise	9.1	425	4.58	41	117	450	158	57	6560	8.5	1220
	Phentol.	4.5	138	3.08	33	83	346	138	43	4060	5.3	1720
	Phentol.	4.9	159	3.26	30	75	326	130	40	4300	5.8	1680
13 Aortic insufficiency	Rest	5.3	158	2.98	40	50	167	133	33	2480	3.0	990
	Exercise	9.5	346	3.63	34	49	163	113	39	4160	4.7	1050
	Phentol.	5.1	172	3.37	40	57	190	133	36	3020	4.1	1070
	Phentol.	3.8	183	4.80	54	80	267	180	36	3170	5.5	700
14 Primary myocardial disease	Rest	4.2	124	2.95	34	34	148	148	36	3170	4.8	2060
	Phentol.	4.8	142	2.96	28	28	127	127	36	3170	4.8	2040
	Phentol.	4.9	165	3.38	29	29	145	145	36	3170	5.6	1840
15 Primary myocardial disease	Rest	7.0	190	2.73	24	43	196	109	34	3920	5.0	1810
	Phentol.	4.5	232	5.15	45	85	386	204	33	4202	9.1	930
	Phentol.	4.5	232	5.15	45	85	386	204	33	3800	9.1	930
16 Aortic insufficiency	Rest	6.7	153	2.28	38	69	247	136	38	2270	2.6	1280
	Phentol.	5.7	226	3.98	88	155	596	338	34	1560	5.0	803
	Rest	5.9	145	2.46	39	95	250	103	66	1555	3.7	1815
	Phen ol.	3.4	154	4.54	70	175	515	206	61	4180	6.7	965
17 Aortic stenosis	Phentol.	4.3	178	4.16	61	148	435	180	60	4050	6.5	1125
	Rest	4.6	138	3.0	36	68	227	120	40	3360	4.8	1770
18 Carcinoid, myocardial and tricuspid incomp. pulm. stenosis	Phentol.	4.8	145	3.24	37	83	297	132	42	3700	5.2	1640
	Phentol.	4.8	145	3.24	37	83	297	132	44	3890	5.2	1640

LVSWI, left ventricular stroke work index; LVSP, left ventricular stroke power; MSER, mean systolic ejection rate; TTIb, tension time index per beat; TTIm, tension time index per minute.

was due to the 33 per cent increase in the heart rate and the 28 per cent increase in the stroke index. The left ventricular stroke work, left ventricular

stroke power, and mean systolic ejection rate increased mainly because of the increase in the stroke index. The left ventricular dp/dt rose 81 per cent

FIG.—The effects of 5 mg. phentolamine on right ventricular contractile force in a normal dog.

TABLE III
VENTRICULAR VOLUMES

Patient No.	Experimental state	End-diastolic vol. (ml.)	End-diastolic vol. (ml./m. ²)	End-systolic vol. (ml.)	End-systolic vol. (ml./m. ²)	Stroke vol. (ml.)	Stroke vol. (ml./m. ²)	Ejection fraction
2	Rest	168	97	53	30	115	67	0.69
	Phentolamine	161	94	78	46	83	48	0.52
3	Rest	166	90	74	40	92	50	0.55
	Phentolamine	146	79	32	17	114	62	0.78
6	Rest	121	66	64	35	57	31	0.47
	Phentolamine	102	55	28	14	74	41	0.72
7	Rest	322	159	289	143	33	16	0.10
	Phentolamine	218	107	178	87	40	20	0.18
8	Rest	152	82	98	51	54	29	0.36
	Phentolamine	107	58	55	30	52	28	0.49
9	Rest	132	65	66	32	66	33	0.50
	Phentolamine	97	48	18	9	79	39	0.81
10	Rest	276	166	239	144	37	22	0.13
	Phentolamine	127	76	71	42	56	34	0.44
11	Rest	303	151	259	129	44	22	0.15
	Phentolamine	242	120					
12	Rest	161	89	108	70	53	29	0.33
	Phentolamine	150	82	95	52	55	30	0.37
13	Rest	380	199	304	159	76	40	0.20
	Phentolamine	290	152	187	98	103	54	0.35

presumably because of an increase in left ventricular contractility. The left ventricular end-diastolic pressure rose 79 per cent with exercise.

Phentolamine. Among the subjects in Group 1, phentolamine produced minimal varying directional responses in the cardiac index and stroke index. The percentage change from the control value was negligible. The left ventricular dp/dt rose 48 and 58 per cent at 10 and 20 minutes, respectively, due presumably to an increase in left ventricular contractility. There was only a minimal change in the brachial artery systolic pressure and pulse rate. Patient 5, with idiopathic hypertrophic subaortic stenosis, was of interest in that he first showed a significant increase followed by a decrease in the cardiac index. The late fall in output was associated with a larger systolic gradient, as measured between the left ventricle and brachial artery.

Among the subjects in Group 2, there were similar directional changes in the haemodynamic para-

meters at the 10- and 20-minute test period. In contrast to exercise, phentolamine administration after 20 minutes produced only a 23 per cent increase in oxygen consumption, but the arteriovenous oxygen difference narrowed by 14 per cent. (When the AV difference was less than 5 vol. % it increased with phentolamine, and when it was more than 5 vol. % it decreased.) A marked increase in the cardiac index occurred, which was associated with a 24 per cent reduction in the peripheral resistance. In patients 6, 7, and 13, the cardiac index rose more with phentolamine than with exercise. The rise in the cardiac index was not only due to the 12 per cent rate increase, but also to the 35 per cent rise in the stroke index. An increase in the mean systolic ejection rate, left ventricular stroke power, and left ventricular stroke work occurred, as would be expected with an increase in the stroke index. The tension time index per minute rose less than with exercise, because of the smaller increase in the systemic systolic pressure. The left ventricular dp/dt rose 43 per cent, due presumably to an increase in

TABLE IVA

AVERAGE CHANGES OF HAEMODYNAMIC PARAMETERS BEFORE AND AFTER PHENTOLAMINE IN PATIENTS 1-5 WITH RELATIVELY NORMAL LEFT VENTRICLES

	Rest	10 min. Phentolamine	% Change	20 min. Phentolamine	% Change
Oxygen consumption (ml./min./m. ²)	137	134	-2	133	-3
Stroke index (ml./beat/m. ²)	48	48	0	43	-10
Systemic peripheral resistance (dyne-sec.-cm. ⁻⁵)	1265	1347	+7	1522	+20
Brachial artery systolic pressure (mm. Hg)	127	135	+6	125	-2
Pulmonary artery systolic pressure (mm. Hg)	42	43	+2	47	+12
Arteriovenous oxygen difference (vol. %)	4.3	4.1	-5	4.3	0
Cardiac index (l./min./m. ²)	3.27	3.68	+13	3.20	-2
Pulse rate (beats/min.)	71	78	+10	80	+13
Left ventricular stroke work (g. m./beat/m. ²)	82	88	+6	73	-11
Left ventricular stroke power (g. m./beat/m. ² /syst. sec.)	287	310	+8	261	-9
Mean systolic ejection rate (ml./beat/m. ² /syst. sec.)	170	171	0	152	-10
Left ventricular work (kg. m./min./m. ²)	4.3	5.2	+22	4.3	0
Tension time index per minute (mm. Hg/sec./min.)	2432	2878	+18	2712	+11
Tension time index per beat (mm. Hg/sec./beat)	34	37	+9	35	+3
Systolic ejection period (sec./beat)	0.28	0.28	0	0.27	-4
Systolic ejection period (rate corrected)	0.40	0.41	+2	0.40	0
Left ventricular end-diastolic pressure (mm. Hg)	6	5	-17	4	-33
Left ventricular dp/dt (mm. Hg/sec.)			+48		+58
Brachial artery dp/dt (mm. Hg/sec.)	633	754	+19	747	+18

TABLE IVB

AVERAGE CHANGES OF HAEMODYNAMIC PARAMETERS BEFORE AND AFTER EXERCISE AND BEFORE AND AFTER PHENTOLAMINE IN PATIENTS 6-18 WITH ABNORMAL LEFT VENTRICLES

	Rest	Exercise	% Change	Rest	20 min. Phentolamine	% Change
Oxygen consumption (ml./min./m. ²)	123	353	+187	138	169	+23
Stroke index (ml./beat/m. ²)	29	37	+28	31	42	+35
Systemic peripheral resistance (dyne-sec.-cm. ⁻⁵)	1876	1419	-24	1802	1364	-24
Brachial artery systolic pressure (mm. Hg)	137	171	+25	139	151	+9
Pulmonary artery systolic pressure (mm. Hg)	37	75	+100	39	35	-10
Arteriovenous oxygen difference (vol. %)	5.5	9.4	+74	5.6	4.8	-14
Cardiac index (l./min./m. ²)	2.33	3.83	+64	2.52	3.64	+44
Pulse rate (beats/min.)	82	109	+33	84	94	+12
Left ventricular stroke work (g. m./beat/m. ²)	50	79	+58	57	84	+47
Left ventricular stroke power (g. m./beat/m. ² /syst. sec.)	198	298	+51	205	321	+57
Mean systolic ejection rate (ml./beat/m. ² /syst. sec.)	114	150	+32	116	165	+42
Left ventricular work (kg. m./min./m. ²)	3.4	6.6	+94	3.7	5.6	+51
Tension time index per minute (mm. Hg/sec./min.)	2766	4697	+70	2950	3283	+11
Tension time index per beat (mm. Hg/sec./beat)	34	44	+29	37	37	0
Systolic ejection period (sec./beat)	0.25	0.26	+4	0.26	0.25	-4
Systolic ejection period (rate corrected)	0.38	0.43	+13	0.39	0.39	0
Left ventricular end-diastolic pressure (mm. Hg)	14	25	+79	14	8	-43
Left ventricular dp/dt (mm. Hg/sec.)			+81			+43
Brachial artery dp/dt (mm. Hg/sec.)	734	1151	+57	709	865	+22

left ventricular contractility. The left ventricular end-diastolic pressure fell 43 per cent. The left ventricular end-diastolic volume decreased in all subjects in whom this measurement was made. An increase in the systolic ejection fraction was also observed in all patients in Group 2.

No patient complained of any symptoms due to the infusion of the drug. No arrhythmias were noted and no patient developed chest pain. However, all the patients in Group 2 developed a desire to urinate during the infusion of the drug. A copious diuresis occurred at approximately 20 minutes, just before the second left ventricular angiogram.

DISCUSSION

Taylor and his group (1965b, c) observed, after the administration of large doses of phentolamine,

an increase in the cardiac output and heart rate and a fall in the systemic vascular resistance. They postulated that the decrease in the peripheral resistance produced a reflex increase in the cardiac output. Evans, Smulyan, and Eich (1967) recently observed a similar increase in the cardiac output after phentolamine administration, and came to a similar conclusion. Measurements of the force of contraction using a strain gauge arch, or of the speed of contraction, employing the left ventricular dp/dt, were not, however, recorded by these workers. Therefore, they could not evaluate any possible primary cardiac effect of the drug.

In our animal studies, the increase in the force of contraction after phentolamine injection suggested that this agent could improve cardiac dynamics in the Group 2 patients. By using the left ventricular dp/dt, we hoped to demonstrate that phentolamine

had a positive inotropic effect in man. However, the left ventricular maximal dp/dt increases with an acute increase in the heart rate, left ventricular end-diastolic pressure, mean aortic pressure, and aortic diastolic pressure, as well as with increased left ventricular contractility (Gleason and Braunwald, 1962; Wallace, Skinner, and Mitchell, 1963). All these parameters must, therefore, be analysed before an increase in contractility can be invoked. The determination of directional changes of the left ventricular first derivative can be accomplished with great accuracy using a catheter manometer system (Murphy *et al.*, 1964). Thus, if the left ventricular dp/dt shows a large percentage increase when all the other haemodynamic parameters remain essentially unchanged, then an increase in contractility must have occurred. In our Group 1 patients, the administration of phentolamine produced little or no change in the heart rate, cardiac pressures, cardiac output, or left ventricular volume. The 58 per cent increase in the left ventricular first derivative must, therefore, indicate an increase in contractility. In our Group 2 patients, the cardiac output rose significantly, not only because the heart rate was increased, but also because the stroke volume was augmented. The increase in the ejection of blood from the heart appears to be the result of positive inotropism and reduction in after-load to be due to contraction. The latter appears through primary vasodilatation and ease of run-off of blood during systole. The low dose of phentolamine (0.3 mg./min.) that we employed in our study produced a rise in the systemic pressure due to the predominant inotropic effect. The higher doses used by other investigators probably produced predominant vasodilatation with a resultant fall in the systemic pressure, masking the inotropic effect of the drug. This is similar to the clinical experience with isoprenaline, which can initially produce a rise in systemic pressure due to the contractility effect. When the dose is increased, the systemic pressure falls, due to the dominant vasodilatation effect. This is not a new concept. Goodman and Gilman (1965) state that phentolamine given intravenously produces vasodilatation and cardiac stimulation. The blood pressure response varies with the relative contribution of the two effects. The dilatation is due primarily to a direct action on vascular smooth muscle, though with higher doses alpha-adrenergic blockade may also be involved. Our present work supports and extends their observations.

The conspicuous increase in the left ventricular dp/dt in the Group 2 patients was consistent with an increased inotropism greater than that which could be attributed to cardiac rate. This was associated with a decrease in both the end-systolic and end-

diastolic ventricular volumes and pressures. The reduced left ventricular end-diastolic pressure and the increased mean systolic ejection rate from a smaller end-diastolic volume can only result from an increased shortening velocity of the myocardial fibres (Sonnenblick *et al.*, 1965), and thus reflects a positive inotropic action. The increased velocity of contraction is associated with an augmentation of myocardial oxygen consumption (Sonnenblick *et al.*, 1965). The tension time index per beat (Sarnoff *et al.*, 1958), which is another haemodynamic determinant of oxygen consumption of the heart, barely changed in our patients. However, with an increase in the heart rate, the tension time index per minute increased significantly.

The diuresis observed in this group of patients is probably due to the improvement in cardiac dynamics. The drug may also have a primary renal effect, but this was not investigated.

The marked increase in the cardiac output in the Group 2 patients and the negligible change in the cardiac output in the Group 1 patients may at first appear to be paradoxical. This varying response has, however, been explained by Braunwald, Ross, and Sonnenblick (1967). They state that the contractile state of the myocardium is not the factor that limits the volume of blood ejected by the heart in the normal person, and that an improvement of myocardial contractility by a drug with a positive inotropic effect, like digitalis, would not be expected to increase the output in a normal subject. On the other hand, in the presence of congestive heart failure, the cardiac output is usually limited by the contractile state of the myocardium, and a positive inotropic influence would be expected to raise the cardiac output (Braunwald *et al.*, 1967). Similarly, the intravenous administration of a digitalis preparation to patients with mitral stenosis in sinus rhythm does not produce any essential clinical or haemodynamic improvement (Werkö *et al.*, 1958; Beiser *et al.*, 1968).

The positive inotropic action of phentolamine may be due to a direct or indirect mechanism. (1) Phentolamine may act like isoprenaline and directly stimulate the beta adrenergic sites in the heart; or (2) it may act like morphine and produce a sympatho-adrenal discharge which indirectly stimulates the beta-adrenergic receptors of the myocardium (Vassalle, 1961). Recently, Dairman and his associates (1968) have presented data that throw new light on phentolamine's mechanism of action. They administered phentolamine (5 mg./kg.) to rats. At the height of receptor blockade, the conversion of a tracer dose of tyrosine- ^{14}C to nor-epinephrine in heart, brain, and adrenals was increased threefold, with no alteration in specific

activity of tyrosine in blood and tissues. From these studies, they concluded that receptor blockade led to increased synthesis and release of norepinephrine in the 3 organs that were assayed. Our studies, with smaller doses of phentolamine, have indicated a positive inotropic effect, and in view of the findings of Dairman *et al.*, it could reasonably be assumed that the inotropic effect is a direct one, resulting from increased production of catecholamines in the myocardium.

Clinical Implications. Several implications concerning the clinical management of patients in congestive heart failure or shock may be drawn from these findings. The beneficial effects of phentolamine are apparent. The patient in congestive heart failure shows a favourable haemodynamic response after the parenteral administration of phentolamine; this response will occur even if the patient is taking cardiac glycosides. In those patients with pulmonary oedema, phentolamine administration should produce a rapid alleviation of this cardiovascular emergency. It seems plausible that an effective oral form of this drug should also be of benefit for the patient in congestive heart failure.

Bradley and Weil (1965) have investigated the usefulness of phentolamine in 13 patients in shock. The drug was infused intravenously at an average rate of 0.6 mg. per minute for an average duration of 22 minutes. The cardiac output increased from an average of 2.8 to 3.6 l./min./m.² and the arterial pressure decreased from a mean of 73 to 59 mm. Hg. Improvement in systemic blood flow was manifested by a reduction in mean circulation time, an increase in peripheral skin temperature, and an increase in urine flow. They concluded that in selected instances an adrenolytic drug might be used in conjunction with, or in preference to, a pressor amine to improve effective blood flow in circulatory shock.

However, the decline in the arterial pressure limited the drug's clinical applicability for patients in shock. If one administers 0.3 mg. per minute of phentolamine to such patients, one might expect an increase rather than a fall in the systemic pressure. This is worthy of further investigation because of its clinical and therapeutic importance.

Since phentolamine has a positive inotropic effect, it will produce or increase the left ventricular gradient in patients with idiopathic hypertrophic sub-aortic stenosis. It may be preferable to use this agent rather than isoprenaline, since phentolamine does not produce an alarming increase in heart rate nor an alarming arrhythmia.

SUMMARY

In 4 dogs, the rapid intravenous injection of 5 mg. of phentolamine produced a 102 per cent average increase in the force of contraction, as measured by the strain gauge arch attached to the right ventricle.

After this experimental finding, 5 patients (Group 1) with relatively normal left ventricles who had never been in left ventricular failure, and 13 patients (Group 2) with abnormal left ventricles who had previously been in left ventricular failure, were studied at right and left heart catheterization. Cardiac pressures, cardiac output, and left ventricle dp/dt were measured before, and 10 and 20 minutes after, the continuous intravenous administration of 0.3 mg. phentolamine per minute. The left ventricular end-diastolic volume was calculated angiographically before and after 25 minutes of continuous phentolamine administration.

Among the subjects in Group 1, phentolamine produced small varying directional responses in the cardiac index, with only minimal changes in the brachial artery systolic pressure and pulse rate. Among the subjects in Group 2, phentolamine produced a marked increase in the cardiac index with moderate increases in the brachial artery systolic pressure and pulse rate. The left ventricular dp/dt, which is a measure of contractility, increased in all patients. The left ventricular end-diastolic volume decreased in all subjects in whom this measurement was made.

It is concluded that phentolamine has a prominent inotropic effect. When administered to the patient in congestive heart failure, there is a striking haemodynamic improvement.

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