HEMODYNAMIC EFFECTS OF 1-HYDRAZINOPHTHALAZINE IN PATIENTS WITH ARTERIAL HYPERTENSION [1]

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Although the literature concerning 1-hydrazinophthalazine (Hydralazine) contains many reports of its effects on arterial blood pressure, its relation to various vasomotor reflexes and autonomic blocking agents (1–4), as well as detailed studies of its pharmacological action in animals (5–7), information concerning hemodynamic effects in subjects having essential arterial hypertension is incomplete. The present report concerns various hemodynamic observations in 17 hypertensive patients to whom Hydralazine was administered intravenously.

MATERIAL AND METHODS

This study was done on 17 postabsorptive subjects chosen from the general medical wards. The clinical diagnosis in each case was essential hypertension, although one patient (No. 15) had, in addition, old chronic pyelonephritis involving the lower half of the left kidney. None of these patients was in cardiac decompensation clinically or as measured by the central venous pressure at the time of study. Special effort was made to secure basal conditions by maintaining as much comfort as possible and by explaining the procedure to the patient prior to the day of catheterization and again prior to each step of the procedure. One member of the team tried to establish rapport with each patient during the study by engaging him or her in light conversation about a non-medical subject, preferably one of the subject's choosing.

Cardiac output was determined in the supine position by means of the Fick principle. This was accomplished by placing a cardiac catheter in the pulmonary artery and an indwelling needle in a peripheral artery, usually the femoral. Expired air was collected for three minutes in a Tissot spirometer and analyzed by the Scholander apparatus for O_2 and CO_2 to 0.02 volumes per 100 cc. accuracy. Blood was collected in oiled heparinized syringes during the second minute of the output determination and analyzed for O_2 and CO_2 content by the Van Slyke-Neill method (8). Duplicate analyses of oxygen content were required to check within 0.2 volumes per 100 cc. Direct recordings of blood pressure were made through short flexible plastic tubes connected to Statham strain gauges and through a direct writing Sanborn Poly-Viso. Mean arterial blood pressures were obtained by planimetric integration of the arterial pulse tracing during the first and third minute of the cardiac output determination. Cardiac work and arterial resistances were calculated by the usual formulae (9, 10).

After control determinations, Hydralazine in the dosage indicated in Table I was given through the cardiac catheter into the pulmonary artery. The blood pressure was then observed by continuous inspection of the arterial pressure tracing until it had decreased and stabilized at its new level for at least 10 minutes. An average of 43 minutes elapsed following drug administration before the second cardiac output was determined. During this time some of the subjects had cerebral, some coronary, and some renal hemodynamic studies.

RESULTS

The results are shown in Table I. They are divided into two groups because of the marked yet unpredictable difference in response. Twelve patients, called Group One, experienced mild nasal obstruction, cutaneous facial flushing, and palpitation but no particular discomfort. Five subjects, called Group Two, experienced an adverse reaction characterized by a marked fall in blood pressure, pallor, apprehension, diaphoresis, nausea, and frequently emesis. When this occurred, 100 per cent O_2 was given by mask to produce relief of the patient's discomfort and a rise in blood pressure. In these cases the determination of the second cardiac output was delayed until the blood pressure was stable and symptoms were absent. One patient (No. 16) had a blood pressure fall from a mean of 173 to 24 mm. Hg accompanied by

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TABLE I

Hemodynamic functions before

Patient Age, Sex		Ht.	Wt.	SA	Pulse rate	Syst. MABP	Pulm. MABP	Min. vol. resp.	O_2 cons.	O_2 cons.	Art. O_2 Vol. %	M. ven. O_2 Vol. %	$\Delta A\text{-}V$ O_2 Vol. %
		Cm.	*Kg.*	*M²*		*mm. Hg*	*mm. Hg*	*L./ min.*	*cc./ min.*	*cc./L. Vent.*			
											Group One—Patients who had moderate		
1 46M	C†	181	84.0	2.05	80	161	14	4.33	276	64	17.2	13.1	4.1
	D‡				94	110	14	8.09	339	42	17.6	14.5	3.1
2 48F	C	158	66.5	1.67	78	126	8	4.58	252	55	14.1	10.3	3.8
	D				94	105	9	6.27	280	45	14.7	11.6	3.1
3 35M	C	182	78.6	2.00	70	157	19§	6.96	363	42	19.9	15.6	4.3
	D				92	135	21	8.12	374	46	20.5	17.3	3.2
4 49F	C	152	59.5	1.56	100	199	14	4.74	208	44	16.1	12.8	3.3
	D				100	187	—	5.70	215	38	15.1	11.4	3.7
5 44F	C	158	45.0	1.42	100	160	9	4.99	220	44	15.5	12.3	3.2
	D				112	118	10	6.60	235	36	15.2	11.9	3.3
6 33F	C	161	99.0	2.02	87	159	13	7.36	332	45	18.3	14.7	3.6
	D				126	115	10	9.55	352	37	18.9	16.3	2.6
7 57M	C	179	96.0	2.14	72	151	16	5.91	292	49	19.1	14.8	4.3
	D				73	119	13	8.75	331	38	20.0	17.0	3.0
8 49F	C	153	58.0	1.56	78	153	11	3.66	245	67	19.3	14.6	4.7
	D				95	108	9	4.75	242	51	19.8	16.3	3.5
9 31M	C	176	75.5	1.88	94	119	6	9.38	269	29	20.3	15.9	4.4
	D				126	117	9	7.27	351	48	20.1	17.0	3.1
10 60M	C	173	97.5	2.12	81	137	9	5.23	210	40	19.2	14.5	4.7
	D				93	126	10	3.92	114	36	19.3	15.7	3.6
11 51F	C	150	53.0	1.45	78	157	10	3.93	201	51	17.9	13.6	4.3
	D				115	126	6	4.22	186	44	18.1	13.6	4.5
12 47M	C	173	79.3	1.94	78	136	14	5.70	280	49	18.2	13.5	4.7
	D				98	128	11	7.60	303	40	18.7	15.3	3.4
C Ave.					83	151	11	5.56	262	48	17.9	13.8	4.1
D Ave.					102	125	10	6.74	277	42	18.2	14.8	3.3
% Change					+23%	−17%	−9%	+21%	+6%	−13%	+2%	+7%	−20%
P Value					<0.01	<0.01	<0.3	<0.05	<0.3	<0.1	<0.1	<0.01	<0.01
											Group Two—Patients who had marked		
13 49F	C	160	63.0	1.75	120	163	11	7.71	281	37	13.4	9.7	3.7
	D				98	72	6	8.17	278	34	13.1	8.7	4.4
14 57F	C	155	61.5	1.60	78	163	8	2.99	147	49	19.3	14.2	5.1
	D				72	87	7	4.99	188	38	18.2	14.0	4.2
15 40M	C	170	86.0	1.97	91	175	25	11.56	355	31	17.8	11.9	5.9
	D				93	72	13	13.74	415	30	16.9	11.4	5.5
16 50M	C	171	79.0	1.92	112	173	20	9.65	339	35	18.0	14.2	3.8
	D				125	121	10	8.95	289	32	16.5	12.9	3.6
17 32F	C	166	57.0	1.63	100	168	4	5.94	226	38	19.3	14.1	5.2
	D				102	105	7	7.56	196	26	19.0	14.3	4.7
C Ave.					100	168	14	7.57	270	38	17.6	12.8	4.8
D Ave.					98	91	9	8.68	273	32	16.7	12.3	4.5
% Change					−2%	−46%	−36%	+15%	+1%	−16%	−5%	−4%	−6%
P Value					<0.8	<0.01	<0.2	<0.1	<0.9	<0.1	<0.02	<0.2	<0.4

* SA M^2—Surface area in square meters.
Syst. MABP—Systemic mean arterial blood pressure in mm. Hg.
Pulm. MABP—Pulmonic mean arterial blood pressure in mm. Hg.
Min. vol. resp. L./min.—Minute volume of air.
O_2 cons. cc./min.—Oxygen consumption, cc. per minute.
O_2 cons. cc./L. Vent.—Oxygen consumption, cc. per litre ventilation.
Art. O_2 Vol. %—Arterial oxygen content in cc. per 100 cc. blood.
M. Ven. O_2 Vol. %—Mixed venous oxygen content in cc. per 100 cc. blood.
$\Delta A\text{-}V$ O_2 Vol. %—Arterial-mixed venous oxygen difference in cc. per 100 cc. blood.
Art. CO_2 Vol. %—Arterial CO_2 content in cc. per 100 cc. of blood.
M. V. CO_2 Vol. %—Mixed venous CO_2 content in cc. per 100 cc. of blood.
$\Delta A\text{-}V$ CO_2 Vol. %—Arterial-mixed venous CO_2 difference in cc. per 100 cc. blood.
CO_2 prod. cc./min.—CO_2 expired in cc. per min.
C.I.—Cardiac index in litres per square meter surface area per minute.

TABLE I

and after 1-hydrazinophthalazine *

Art. CO_2 Vol. %	M.V. CO_2 Vol. %	AA-V CO_2 Vol. %	CO_2 prod.	C.I.	Tot. syst. resist.	Tot. pulm. resist.	LV work	RV work	Drug dose	Time from drug to CO	C.V.P.	R.Q.
			cc./min.	*L./m²*	*dynes/cm.⁻⁵/sec.*		*Kg. meters/mm.*		*mg./Kg.*	*min.*	*mm. Hg*	
hypotension after hydrazinophthalazine												
46.9	48.9	2.0	165	3.3	1,918	167	14.7	1.3			RA = +3.3	0.60
41.7	43.7	2.0	231	5.3	805	102	16.3	2.1	0.55	56	RA = +0.7	0.68
50.9	54.0	3.1	158	4.0	1,518	97	11.3	0.7			—	0.63
48.0	49.9	1.9	204	5.4	930	79	12.8	1.1	0.25	46	ED = −1.3	0.73
49.8	52.2	2.4	243	4.2	1,485	—	18.0	2.2			ED = +1.5	0.67
44.5	46.3	1.8	287	5.9	923	—	21.5	3.4	0.34	30	ED = 0	0.77
51.9	54.8	2.9	147	4.0	2,523	—	17.1	1.2			RA = 0	0.71
45.4	47.3	1.9	129	3.7	2,571	—	14.8	—	0.32	45	RA = 0	0.60
49.3	51.5	2.2	166	4.8	1,874	105	14.8	0.8			—	0.76
43.4	45.8	2.4	184	5.0	1,341	108	11.2	0.9	0.25	55	ED = 0	0.78
45.3	47.5	2.2	236	4.6	1,379	108	19.9	1.6			RA = −1.9	0.71
39.3	40.7	1.4	259	6.7	678	61	21.2	1.9	0.33	31	RA = −1.8	0.73
43.3	47.7	4.4	228	3.2	1,783	192	13.9	1.5			—	0.78
39.2	41.3	2.1	270	5.2	862	94	17.9	2.0	0.25	29	ED = 0	0.82
49.5	52.2	2.7	165	3.3	2,353	164	10.9	0.8			—	0.67
45.1	48.6	3.5	183	4.4	1,253	105	10.2	0.9	0.25	26	ED = +1.4	0.76
43.0	45.7	2.7	313	3.3	1,554	83	9.9	0.5			—	1.16
39.1	40.7	1.6	221	6.0	823	60	17.9	1.3	0.25	53	RA = −2.2	0.63
39.8	43.9	4.1	164	2.1	2,454	165	8.3	0.6			—	0.78
38.2	40.3	2.1	103	1.9	2,562	197	6.7	0.5	0.20	32	RA = 0	0.73
50.0	53.5	3.5	145	3.2	2,685	160	10.0	0.6			ED = +0.9	0.72
45.9	49.1	3.2	129	2.9	2,427	123	7.1	0.4	0.20	30	ED = +0.9	0.70
45.3	48.1	2.8	200	3.1	1,826	189	11.0	1.1			ED = +3.9	0.71
39.7	41.5	1.8	207	4.6	1,147	96	15.5	1.3	0.25	30	ED = +3.0	0.68
47.1	50.0	2.9	194	3.6	1,963	143	13.3	1.1				0.74
42.5	44.6	2.1	201	4.8	1,360	103	14.4	1.4	0.29	39		0.72
−10%	−10%	−24%	+4%	+33%	−31%	−28%	+8%	+27%				−3%
<0.01	<0.01	<0.01	<0.7	<0.01	<0.01	<0.02	<0.3	<0.05				< 0.7
hypotension after 1-hydrazinophthalazine												
46.4	50.0	3.6	211	4.4	1,713	116	16.9	1.1				0.75
42.9	45.1	2.2	195	3.6	805	81	5.5	0.6	0.35	51	ED = −1	0.70
46.4	49.5	3.1	88	1.8	4,551	246	6.4	0.4			ED = −1	0.60
42.2	44.6	2.4	125	2.8	1,553	129	5.3	0.4	0.25	45	ED = −1.5	0.67
43.5	49.1	5.6	340	3.1	2,326	332	14.3	2.0			ED = 0	0.96
38.5	43.3	4.8	326	3.8	762	132	7.4	1.3	0.30	42	—	0.78
45.1	47.5	2.4	262	4.6	1,551	179	21.0	2.4			ED = +2.4	0.77
45.1	47.7	2.6	242	4.2	1,243	98	13.7	1.1	0.25	102	RA = −0.3	0.84
44.7	48.4	3.7	166	2.7	3,077	81	9.9	0.3			ED = −2	0.73
39.7	42.8	3.1	179	2.6	2,021	131	6.0	0.4	0.25	32	ED = −2	0.92
45.2	48.9	3.7	213	3.3	2,644	191	13.7	1.2				0.76
41.7	44.7	3.0	213	3.4	1,277	114	7.6	0.8	0.28	54		0.78
−8%	−9%	−19%	0	+3%	−52%	−40%	−45%	−33%				+3%
<0.02	<0.02	<0.05	0	<0.9	<0.05	<0.2	<0.02	<0.2				—

* Tot. syst. resist.—Total systemic arterial resistance in dynes per cm.$^{-5}$/sec.
Tot. pulm. resist.—Total pulmonary arterial resistance in dynes per cm.$^{-5}$/sec.
LV work—Left ventricular work in Kg. meters per minute.
RV work—Right ventricular work in Kg. meters per minute.
Time from drug to CO—Time in minutes between the administration of the drug and the determination of the second cardiac output.
C.V.P.—Central venous pressure measured either as right ventricular end diastolic pressure (ED) or right atrial mean pressure (RA) in mm. Hg.
R.Q.—Respiratory quotient for total body.

† Control.
‡ After Hydralazine.
§ Right ventricular systolic mean.

nodal bradycardia. He was given O_2 by mask, then methoxamine 2 mg. intravenously, followed by 12 mg. intramuscularly, to maintain his pressure high enough for the second output. The data derived from this study would have been omitted from the report except that his response is similar to the rest of those in Group Two. The average dose of Hydralazine was the same in both groups.

The cardiac rate in Group One increased from a mean in the control period of 83 beats per minute to a mean of 102 beats per minute ($p < 0.01$) after the intravenous administration of Hydralazine. In Group Two, who had marked hypotension, no increase in pulse rate occurred, and in two cases (No. 15 and No. 16) there was nodal rhythm with bradycardia during the period of greatest hypotension.

Systemic arterial blood pressure consistently fell. The average fall of the mean pressure in Group One was 26 mm. Hg ($p < 0.01$), and in Group Two 77 mm. Hg ($p < 0.01$). In Group Two the average maximum fall in blood pressure was 108 mm. Hg and was usually transient. Effort was made to prevent such falls by decreasing the Hydralazine dose gradually during the series but they occurred unpredictably. The decrease in the pulmonary arterial pressure was not statistically significant in either group. Calculation of cardiac output indicated that there was an increase of 33 per cent ($p < 0.01$) in Group One and no change in Group Two. Stroke volume rose slightly but not significantly in both groups. Peripheral arterial resistance was reduced by 31 per cent ($p < 0.01$) in Group One and 52 per cent in Group Two ($p < 0.05$), whereas total pulmonary resistance fell by 28 per cent ($p < 0.02$) and 40 per cent ($p < 0.2$), respectively, in the two groups. With the concomitant fall in peripheral arterial blood pressure and the change in cardiac output, cardiac work against pressure fluctuated unpredictably. The left ventricular work fell in Group Two (-45 per cent, $p < 0.02$) and right ventricular work rose in Group One ($p < 0.05$).

In Group One O_2 consumption and arterial O_2 level were not significantly changed by Hydralazine. The increased cardiac output produced a decrease in arteriovenous O_2 difference ($p < 0.01$) because of the increase in the mean mixed venous O_2 content of 1.0 volume per 100 cc. By contrast, in Group Two there was a fall in arterial O_2 content ($p < 0.02$). Here the variability of mixed venous O_2 was such that no statistically significant change occurred in the arteriovenous O_2 difference. Oxygen consumption remained the same.

In 10 patients of Group One the minute volume of respiration increased after the administration of Hydralazine, the average increase for the entire group being 21 per cent ($p < 0.05$). As would be expected in these circumstances, the arterial CO_2, mixed venous CO_2 and arterio-mixed venous CO_2 difference all decreased ($p < 0.01$). In Group Two the arterial and venous blood CO_2 content changes were similar but less significant, probably because of the smaller number of patients. Constant CO_2 production and unchanged respiratory quotients of both groups attested to the attainment of a reasonably steady state by the time of the second hemodynamic determinations.

DISCUSSION

A previous report of cardiac output after administration of Hydralazine was made by Wilkinson, Backman, and Hecht (11) in a total of six patients. They found a markedly greater increase in the cardiac output in four normotensive patients (average + 112 per cent) than in two hypertensive patients (average + 19 per cent). Further data are reported by Assali, Kaplan, Oighenstein, and Suyemoto (12) who by the ballistocardiographic method demonstrated an increase in cardiac output and a decrease in peripheral resistance after Hydralazine administration to pregnant normotensive, toxemic and hypertensive subjects. A similar pattern was found by the Fick principle in their three patients with toxemia. Moyer (13) by the pulse contour method, and Freis, Rose, Finnerty, and Partenope (14) by the Fick principle demonstrated an increase in cardiac output. Our observations in general confirm and extend these earlier reports.

The data from Group One suggest that the primary change after administration of Hydralazine to these patients with hypertension is a decrease in the vascular resistance both in the systemic cir-

culation (− 31 per cent) and in the lung (− 28 per cent). Accompanying this decrease in vascular resistance there is a fall in systemic arterial pressure (− 17 per cent) and a rise in cardiac output (+ 33 per cent). In spite of the increase in cardiac output, calculated left ventricular pressure work is not increased and the O_2 consumption remains essentially the same. It seems clear that the vasodilatation produced by this drug is quite general since it is found in cerebral (15, 16), hepatic (7, 14), renal (11, 17), and coronary vascular beds (18) as well as in the systemic and pulmonary vascular beds as a whole as shown in this study. However, the degree of vasodilatation is not the same in all areas (11, 18). Skin temperature was not found to increase generally by Wilkinson, Backman, and Hecht but did occur locally after direct intra-arterial administration (11). It was shown to rise in local areas after intravenous administration in pregnant patients by Assali, Kaplan, Oighenstein, and Suyemoto (12).

The changes produced in Group Two were complicated by the precipitation of marked hypotension and the resulting adjustments which occur secondary to such a hemodynamic condition. It seems probable that this marked hypotensive effect was due to failure of venous return because of peripheral and splanchnic pooling of blood. This cannot be stated with certainty, since the central venous pressure was measured at the beginning and end of the procedure, not during the most hypotensive phase. The slight fall in arterial O_2 content appears related to the marked hypotensive phase.

A mild degree of hyperventilation occurred in both groups as shown by the increase in minute volume of respiration, and further manifested by the fall in arterial and venous CO_2 contents. Although pH determinations were not done in this study, arterial pH as determined by Hafkenschiel and his associates (15) showed a slight rise after administration of Hydralazine. The reason for this hyperventilation is not known, but the fact that it was less in the Group Two patients, who were most apprehensive and uncomfortable, suggests that it was not psychogenic.

During the study and in retrospect since its completion an attempt has been made to determine what factor or factors accounted for the different response of Group One and Group Two. Statistical testing indicates that Group Two patients had, on the average, higher mean arterial blood pressure ($p < 0.02$), lower stroke index ($p < 0.05$), and lower O_2 consumption per liter ventilation ($p < 0.05$) than Group One patients. None of the other factors which we measured could be shown statistically to be related to the difference in response. It is interesting to speculate that the response to 1-hydrazinophthalazine may be related to cardiac reserve. The increase in cardiac output of normal patients (Wilkinson, Backman, and Hecht) was 112 per cent, our Group One hypertensive subjects had only a 33 per cent increase and the Group Two hypertensive subjects, with an even higher arterial blood pressure, showed no significant change. Other patients in Group One who did not experience adverse symptoms but who had severe hypertension, *e.g.*, No. 4, or a very low initial cardiac output, as No. 10, also had no increase in cardiac output after the drug was given. This suggests that there is a continuous spectrum of response from the patient who becomes flushed and warm, develops tachycardia, and increases his cardiac output and left ventricular work to the patient who develops marked hypotension, pallor, sweating, apprehension, bradycardia with nodal rhythm, and whose cardiac output and cardiac work fall.

CONCLUSIONS

1. Administration of 1-hydrazinophthalazine intravenously to 17 subjects with arterial hypertension produced a decrease in peripheral and pulmonary vascular resistance with a decrease in systemic arterial blood pressure accompanied generally by increased cardiac output. However, when severe hypotension occurred, cardiac output remained the same or fell.

2. Left ventricular work fell when marked hypotension occurred, but otherwise was unchanged.

3. Hyperventilation occurred after Hydralazine administration in 14 of 17 patients with a fall in arterial and mixed venous CO_2 and a decrease in arteriovenous CO_2 difference.

4. No significant change occurred in O_2 consumption, total CO_2 production, or respiratory quotient.

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