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Research Article

THE EFFECTS OF 1-HYDRAZINOPHTHALAZINE UPON CORONARY HEMODYNAMICS AND MYOCARDIAL OXYGEN METABOLISM IN ESSENTIAL HYPERTENSION [1]

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Since it has been shown that the most deleterious effects of hypertension occur in cerebral, renal and coronary vascular beds, it seems wise to evaluate these circulatory regions in relation to the effect of anti-hypertensive drugs. Reports of the hemodynamic effects of Hydralazine [4] on the renal (1–3) and cerebral (4, 5) circulations are already available, but comparable information is lacking in relation to the coronary circulation. Observations concerning coronary flow after the administration of Hydralazine are particularly desirable since it is known to precipitate angina pectoris in some patients (6). The current report concerns an investigation of the cardiovascular hemodynamic effects of Hydralazine in subjects with arterial hypertension.

MATERIAL AND METHOD

Eleven hypertensive subjects from general medical wards were studied. Five of these subjects served as controls with determination of the various cardiac functions before and after administration of 1 cc. of saline solution.

Six served as experimental subjects with the same determinations made before and after Hydralazine. The determination of hemodynamic functions in this study was by the usual methods and has been reported previously from this laboratory (7). The determination of coronary blood flow was by the nitrous oxide saturation method (8). In each patient, cardiac output was determined by the Fick principle. The catheter was then withdrawn from the pulmonary artery and placed in the coronary sinus for coronary blood flow determination. Approximately one-half hour after administration of either Hydralazine or saline through the cardiac catheter coronary blood flow determination was repeated. The catheter was then placed in the pulmonary artery and cardiac output was again determined. Thus each patient served as his own control, and the five patients who received the saline placebo served as controls for the method and procedure.

RESULTS

The results are seen in Table I. Significant changes occurred in the placebo (saline) group in only two of the determinations made. One was a slight fall in the body respiratory quotient and the other a slight fall in the mixed venous oxygen content. The reason for these two changes is not apparent, but it is of interest that their significance depends upon the consistency rather than the magnitude of change.

After administration of Hydralazine, hemodynamic changes occurred similar to those already reported by others (1, 3) and by this laboratory (7). These changes included an increase in heart rate, a fall in systemic blood pressure and peripheral arterial resistance, a decreased arterial and mixed venous carbon dioxide content, and a smaller arteriovenous carbon dioxide difference. The change in cardiac index in this series was variable, as has already been reported (7), but the mean average tended to increase following Hydralazine administration. Total body carbon dioxide production and oxygen consumption were unchanged and the respiratory quotient was constant. The hemodynamic data concerning these five patients were reported previously exclusive of the coronary metabolic data (7). Hydralazine

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[4] Hydralazine was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

produced an increase in coronary blood flow in five out of six subjects, the over-all increase being 34 per cent. Simultaneously, with the decrease in perfusion pressure, there was a fall in coronary vascular resistance (− 35 per cent). The increased coronary blood flow was accompanied by a decrease in the arterial-coronary sinus oxygen difference, such that left ventricular oxygen utilization was unchanged.

DISCUSSION

This study reveals that Hydralazine decreases coronary vascular resistance to such a degree that an increase in flow occurs in spite of the reduced perfusion pressure. Simultaneously, the arteriovenous oxygen difference across the myocardium narrows so that the left ventricular oxygen consumption per 100 g. remains unchanged. It was noted previously that the blood carbon dioxide levels were altered by the administration of Hydralazine (7), and these observations show that the changes are extended to the coronary circulation where a significant fall in coronary sinus carbon dioxide level occurs. These were correlated previously with an increase in minute volume of respiration and a decrease in oxygen consumption per liter of ventilation. Similar changes occurred in this series but were not significant, probably because this group is smaller than the previous series.

The reason for the precipitation of angina by Hydralazine is not apparent from this study. In four out of five subjects the coronary blood flow per kg. meter of left ventricular work rose. Although no clear relationship is noted here between left ventricular work and oxygen consumption it is interesting that in all but one subject the number of cc. of available oxygen per kg. meter of left ventricular work [(Art. O_2 × CBF) ÷ L.V. Work] increased after Hydralazine. In confirmation of these ratios the coronary sinus blood oxygen content rose in each instance and therefore the myocardial oxygen tension must have been higher after Hydralazine than it was before. Four out of five patients eliminated more CO_2 from the heart per kg. meter of left ventricular work after Hydralazine but it cannot be stated definitely whether this was due to the falling level of CO_2 in the blood and heart. In view of these findings it may be speculated that angina is precipitated only in those patients who have a fixed coronary vascular resistance, which cannot compensate for the decrease in perfusion pressure and therefore have a reduction in coronary flow. We did not observe such a response in this series. The possibility also exists that Hydralazine specifically alters myocardial oxidative metabolism so that available oxygen is not utilized and angina is precipitated by a metabolic block.

SUMMARY AND CONCLUSIONS

1. Coronary blood flow and myocardial oxygen metabolism have been studied in eleven hypertensive subjects.

2. Compared with the five placebo studies, there were in the six Hydralazine studies statistically significant changes in that coronary blood flow increased by 34 per cent, coronary vascular resistance decreased by 35 per cent, and the arterial-coronary sinus oxygen difference decreased by 27 per cent due to an 81 per cent increase in the coronary sinus oxygen content.

3. The cardiac metabolic rate for oxygen remained unchanged.

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TABLE I

Patient	Age	Sex	Ht. in *cm.*	Wt. in *kg.*	SA[1] in M^2	Card. rate	Syst.[2] BP mean *mm. Hg*	PA[3] BP mean *mm. Hg*	Min.[4] vol. resp. *L.*	O_2[5] cons. *cc./ min.*	O_2[6] cons./ L. vent.	Art.[7] O_2 *Vol. %*	Mixed[8] venous O_2 *Vol. %*	ΔArt.[9] m. ven. O_2 *Vol. %*	CS[10] O_2 *Vol. %*	ΔArt.[11] CSO_2 *Vol. %*	Art.[12] CO_2 *Vol. %*
									Part I—Control series								
T. O.	35	M	168	87	2.0	83	125	15	7.2	314	44	21.2	16.8	4.4	7.4	13.1	41.4
						82	142	17	6.7	284	42	21.2	16.9	4.3	7.6	13.6	41.5
C. S.	31	M	168	70	1.8	81	129	7	5.0	228	46	18.7	14.3	4.4	7.3	11.4	42.9
						81	132	6	4.7	218	46	18.3	13.4	4.9	7.2	11.1	42.3
H. J.	45	M	170	59	1.7	89	162	17	6.2	236	38	18.4	13.2	5.2	6.9	11.5	48.5
						84	166	19	6.0	247	41	18.6	12.3	6.3	6.3	12.3	46.4
H. P.	46	M	171	75	1.9	65	154	16	5.9	290	49	17.0	12.1	4.9	6.7	10.3	50.0
						69	158	13	6.0	293	49	16.4	11.3	5.1	6.9	9.4	49.5
G. D.	57	M	165	80	1.9	83	128	14	7.7	253	33	20.1	15.0	5.1	5.8	14.3	47.6
						79	139	14	9.8	277	28	19.4	14.8	4.6	5.8	13.6	42.8
1st ave.	43					80	140	14	6.4	264	42	18.9	14.3	4.8	6.8	12.1	46.1
SD†						±9	±19	±4	±1.1	±37	±6	±1.4	±1.8	±0.4	±0.6	±1.6	±3.7
2nd ave.						79	147	14	6.6	264	41	18.8	13.7	5.1	6.8	12.0	44.5
SD†						±6	±14	±5	±1.9	±31	±8	±1.7	±2.2	±0.8	±0.7	±1.8	±3.4
Change						−1	+7	0	+0.2	0	−1	−0.1	−0.6	+0.3	0	−0.1	−1.6
% Change						−1%	+5%	0	+3%	0%	−2%	−1%	−5%	+7%	0	−1%	−3%
P value													<0.05				
									Part II—Hydralazine series								
H. J.	31	M	176	76	1.9	92	119	6	9.4	269	29	20.3	15.9	4.4	6.1	14.2	43.0
						128	117	9	7.3	351	48	21.3	16.5	4.8	11.2	8.9	39.1
R. J.	47	M	173	79	1.9	78	136	14	5.7	280	49	18.2	13.5	4.7	5.4	12.8	45.3
						98	128	11	7.6	303	40	18.7	15.3	3.4	11.9	6.8	39.7
A. R.	63	F	166	73	1.8	85	128	12	6.6	228	35	15.5	11.0	4.5	4.7	10.8	36.8
						87	75	12	10.6	207	20	15.3	11.2	4.1	5.8	9.5	33.1
J. P.	32	F	166	57	1.6	100	168	4	5.9	226	38	19.3	14.1	5.2	3.6	15.7	44.7
						102	105	7	7.6	196	26	19.0	14.3	4.7	7.8	11.2	39.7
J. V.	62	M	160	91	1.9	63	120	—	—	—	—	21.7	—	—	5.5	16.2	38.5
						75	109	—	—	—	—	22.0	—	—	9.5	12.5	36.2
Y. B.	51	F	150	53	1.5	78	157	10	3.9	201	51	17.9	13.6	4.3	3.6	14.3	50.0
						115	126	6	4.2	186	44	18.1	13.6	4.5	5.8	12.3	45.9
Cont. ave.	48					83	138	9	6.3	241	40	18.8	13.6	4.6	4.8	14.0	43.1
S.D.†						±13	±20	±4	±2.0	±33	±9	±2.1	±1.7	±0.4	±1.0	±2.0	±4.8
Drug ave.						101	110	9	7.5	249	36	19.1	14.2	4.3	8.7	10.2	39.0
S.D.†						±19	±19	±3	±2.3	±74	±12	±2.4	±2.0	±0.6	±2.6	±3.8	±4.3
Change						+18	−28	0	+1.2	+8	−4	+0.3	+0.6	−0.3	+3.9	−3.8	−4.1
% Change						+22%	−20%	0	+19%	+3%	−10%	+2%	+1%	−7%	+81%	−27%	−10%
P value						<0.05	<0.05	—	<0.3	<0.8	<0.5	<0.3	<.2	<0.4	<0.01	<0.01	<0.01

[1] Body surface area in square meters.
[2] Systemic arterial blood pressure mean in mm. Hg.
[3] Pulmonary arterial blood pressure mean in mm. Hg.
[4] Minute volume of air exhaled in litres.
[5] cc. of O_2 consumed per minute.
[6] cc. of O_2 consumed per litre of exhaled air.
[7] Arterial O_2 content in vol. per 100 cc.
[8] Mixed venous (pulmonary arterial) O_2 content in vol. per 100 cc.
[9] Arterial-mixed venous O_2 difference in cc. per 100 cc.
[10] Coronary sinus O_2 content in vol. per 100 cc.
[11] Arterial-coronary sinus O_2 difference in vol. per 100 cc.
[12] Arterial CO_2 content in vol. per 100 cc.
[13] Mixed venous (pulm. arterial) CO_2 in vol. per 100 cc.
[14] Arterial-mixed venous CO_2 difference in vol. per 100 cc.
[15] Coronary sinus CO_2 content in vol. per 100 cc.

TABLE I

Mixed[13] venous CO_2 Vol. %	ΔArt.[14] venous CO_2 Vol. %	CS[15] CO_2 Vol. %¶	ΔArt.[16] C.S. CO_2 Vol. %	CO_2[17] prod./ min.	Cardiac[18] index	Total[19] periph. resist.	Total[20] pulm. resist.	L.V.[21] work	R.V.[22] work	Cor.[23] blood flow	CMR[24] O_2	C.V.R.[25]	Drug[26] dose in mg.	Drug in mg./ kg.	Time[27] from drug to study	Body[28] R.Q.
							Part I—Control series									
45.5	4.1	52.3	10.9	245	3.8	1330	155	12.8	1.5	67	8.8	1.9	Saline	—	—	0.78
45.8	4.3	52.2	10.7	217	2.6	2187	262	10.0	1.2	62	8.4	2.1		—	32	0.76
46.1	3.2	50.6	7.7	179	2.9	1989	114	9.1	0.5	72	8.1	1.8	Saline	—	—	0.79
44.9	2.6	50.0	7.7	163	2.5	2370	99	8.0	0.3	63	9.4	2.1		—	24	0.78
52.6	4.1	57.3	8.8	197	2.7	2853	293	10.0	1.0	81	9.3	2.1	Saline	—	—	0.84
51.5	5.1	56.6	10.2	195	2.3	3384	386	8.9	1.0	90	11.1	1.9		—	23	0.79
53.0	3.0	58.3	8.3	220	3.2	1990	219	12.0	1.3	65	6.7	2.2	Saline	—	—	0.76
53.1	3.6	56.9	7.4	216	3.1	2161	174	12.5	1.0	69	6.5	2.1		—	23	0.74
51.5	3.9	58.5	10.9	280	2.6	2042	222	8.7	1.0	49	6.9	2.6	Saline	—	—	1.11
47.8	5.0	57.9	15.1	274	3.1	1862	194	11.2	1.2	50	6.7	2.7		—	34	0.99
														Ave.	=27	
49.7	3.7	55.4	3.7	224	3.0	2041	201	10.5	1.1	67	8.0	2.1	—	—	—	0.86
±3.6	±0.5	±2.9	±0.4	±40	±0.5	±541	±60	±1.8	±0.4	±14	±1.1	±0.3	—	—	—	±0.14
48.6	4.1	54.7	4.1	213	2.7	2393	223	10.1	0.9	67	8.4	2.2	—	—	—	0.81
±3.6	±0.8	±3.4	±1.0	±41	±0.4	±583	±108	±1.8	±0.4	±15	±1.9	±0.3	—	—	—	±0.10
−1.1	+0.4	−0.7	+0.4	−11	−0.3	+352	+22	−0.4	−0.2	0	+0.4	+0.1	—	—	—	−0.05
−2%	+11%	−1%	+11%	−5%	−10%	+17%	+11%	−4%	−18%	0%	+5%	+5%	—	—	—	−6%
																<0.01
							Part II—Hydralazine series									
45.7	2.7	45.2	2.2	313	3.3	1554	83	9.9	0.5	70	10.0	1.7	19	0.25	30	1.16
40.7	1.6	43.3	4.2	221	6.0	823	60	17.9	1.3	110	9.8	1.0	—	—	—	0.63
48.1	2.8	52.6	7.3	200	3.1	1826	189	11.0	1.1	76	9.7	1.8	20	0.25	30	0.71
41.5	1.8	45.0	5.3	207	4.6	1147	96	15.5	1.3	118	8.0	1.0	—	—	—	0.68
38.7	1.9	43.5	6.7	143	2.8	2015	187	8.8	0.8	79	8.6	1.6	18	0.25	30	0.62
35.8	2.7	43.8	10.7	159	2.8	1189	184	5.1	0.8	71	6.8	1.2	—	—	—	0.77
48.4	3.7	55.8	11.1	166	2.7	3077	81	9.9	0.3	119	18.7	1.4	14	0.25	32	0.73
42.8	3.1	48.3	8.6	179	2.6	2021	131	6.0	0.4	167	18.7	0.6	—	—	—	0.92
—	—	50.2	11.7	—	—	—	—	—	—	56	9.1	2.1	15	0.17	32	—
—	—	44.8	8.6	—	—	—	—	—	—	72	7.8	1.5	—	—	—	—
53.5	3.5	59.8	9.8	145	3.2	2685	160	10.0	0.6	98	14.1	1.6	11	0.20	30	0.72
49.1	3.2	54.7	8.8	129	2.9	2427	123	7.1	0.4	132	16.2	1.1	—	—	—	0.70
46.9	2.9	51.2	9.3	193	3.0	2231	160	9.9	0.7	83	11.7	1.7	—	—	—	0.79
±2.0	±0.7	±6.2	±1.5	±71	±0.3	±631	±46	±0.8	±0.3	±22	±4.0	±0.2	—	—	—	±0.21
42.0	2.5	46.6	10.2	179	3.8	1521	119	10.3	0.8	112	11.2	1.1	16	0.23	31	0.74
±4.3	±0.7	±4.3	±3.1	±37	±1.5	±672	±46	±5.9	±0.5	±37	±5.0	±0.3	—	—	—	±0.11
−4.9	−0.4	−4.6	+0.9	−14	+0.8	−710	−41	+0.4	+0.1	+28	−0.5	−0.6	—	—	—	−0.05
−10%	−14%	−8%	+9%	−7%	+27%	−32%	−26%	+4%	+14%	+34%	−5%	−35%	—	—	—	—
<0.01	<0.05	<0.02	<0.5	<0.6	<0.3	<0.01	<0.3	—	<0.4	<0.05	<0.5	<0.01	—	—	—	<0.8

[16] Arterial-coronary sinus CO_2 difference in vol. per 100 cc.
[17] CO_2 produced in cc. per minute.
[18] Cardiac index in litres per sq. meter body surface area per min.
[19] Total systemic arterial resistance in dynes per cm.$^{-5}$/sec.
[20] Total pulmonary arterial resistance in dynes per cm.$^{-5}$/sec.
[21] Left ventricular work in kg. meters per min.
[22] Right ventricular work in kg. meters per min.
[23] Coronary blood flow in cc. per 100 gm. myocardium per min.
[24] Cardiac O_2 utilization per 100 gm. per min.
[25] Coronary vascular resistance (MABP ÷ cor. blood flow).
[26] Hydralazine dose given through cardiac cath.
[27] Hydralazine dose in mgm. per kg. body weight.
[28] Body respiratory quotient.
† Standard deviation from the mean.

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