THE HEMODYNAMIC EFFECTS OF HYPOTENSIVE DRUGS IN MAN. III. HEXAMETHONIUM [1, 2, 3]

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While searching for derivatives of d-tubocurarine, Barlow and Ing (1) and Paton and Zaimis (2) independently synthesized a series of polymethylene bistrimethylammonium salts. The latter investigators demonstrated that the pharmacological properties of this series were related to the length of the polymethylene chain; the deca-compound produced neuromuscular block while the penta and hexa-compounds prevented the transmission of impulses across the synapses in all autonomic ganglia. They also carried out preliminary trials in man (3) but Arnold and Rosenheim were the first to use these agents in hypertension (4). Finally, Restall and Smirk demonstrated that it was possible to reduce blood pressure and obtain clinical improvement in hypertensive patients for long periods by the use of repeated parenteral doses of hexamethonium (5).

Studies in this laboratory have confirmed the observations of Restall and Smirk and in addition have shown the potentiating effect of l-hydrazinophthalazine (Apresoline) when alternated with doses of hexamethonium in patients with hypertension (6, 7). Our studies also suggested that hexamethonium may be useful in the treatment of acute peripheral vascular disorders associated with neurogenic vasospasm as well as in the evaluation of the sympathetic vasoconstrictor component in cases of peripheral vascular disease (8). Since from these previous studies it appeared that hexamethonium was a potent agent both for reducing blood pressure and increasing foot and digital blood flow a more complete analysis of its hemodynamic effects seemed indicated.

METHODS

The subjects were 25 hypertensive patients admitted to the wards of Georgetown University Hospital and the Veterans Administration Hospital and four normotensive young males (medical students). Hexamethonium was administered intravenously at a rate of 1 to 2 mg. per minute for the first 15 mg. and then at a rate of 5 mg. per minute, in all instances until a significant hypotensive effect had been obtained or until 50 to 100 mg. had been administered. All dosages refer to the amount of hexamethonium ion administered.

The methods used in this investigation were essentially similar to those described in a previous communication (9), with the following exceptions: the determination of arteriovenous oxygen difference were carried out using the spectrophotometric method of Hickam and Frayser (10). The oxygen content of the expired air was determined using a Pauling type oxygen analyzer.[5] The total peripheral resistance was calculated according to the method of Green, Lewis, Nickerson, and Heller (11). In the muscle blood flow experiments it was necessary to estimate the mean arterial pressure from the values for systolic and diastolic pressure as determined by the auscultatory method. The formula used was as follows: mean arterial pressure = .436 (pulse pressure) + diastolic pressure (12). Calf blood flow was measured as previously described except that a strain gage,[6] with a car-

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[2] Sponsored (in part) by the VA and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

[3] Hexamethonium dibromide (Bistrium) was supplied by H. Sidney Newcomer, M.D., E. R. Squibb and Sons, New York, New York.

[4] Research Fellow—Washington, D. C., Heart Association.

[5] Model C, Arnold O. Beckman, Inc., South Pasadena, California.

[6] Model P-23-B, Statham Laboratories, Beverly Hills, California.

rier-wave type amplifier and direct writing oscillograph,[7] replaced the Brodie's bellows apparatus. Glomerular filtration rate was determined by the clearance of sodium thiosulfate (13).

RESULTS

I. Cardiac function

Cardiac output, mean arterial pressure and total peripheral resistance

The changes in cardiac output and total peripheral resistance seemed to vary with the state of cardiac compensation. In the hypertensive patient with a compensated heart the usual response to hypotensive doses of hexamethonium was a slight decrease in cardiac output. Thus, in 11 post-treatment analyses carried out in six patients without heart failure the cardiac output decreased by 6 to 38 per cent (mean 22.0 per cent, S.D. 9.3) (Table I, Cases 1 through 6). The decrease in mean arterial pressure was of similar magnitude varying from 10 to 37 per cent (mean 23.5 per cent, S.D. 7.0). In only one instance did the arterial pressure fall to normotensive levels. The total peripheral resistance did not change significantly varying between + 19 and − 22 per cent (mean − 1.3 per cent).

In contrast, in four additional patients with congestive heart failure and one with malignant hypertension there was a significant increase in cardiac output in three and a slight increase in two patients following hexamethonium. The range for nine post-treatment determination was + 3 to 100 per cent and the mean 38 per cent, S.D. 35.4 (Table I, Cases 7 through 11). In these instances the total peripheral resistance fell significantly the range being 27 to 70 per cent and the mean 47 per cent, S.D. 14.1.

Other aspects of cardiac function

The heart rate usually increased moderately after hexamethonium. There were insignificant changes in rate in three patients, slowing in one and rises in six cases; the average increase was 14 beats per minute (Table I).

Pressures on the right side of the circulation were measured in seven patients and decreased in all instances. In the group with compensated hearts the pulmonary arterial pressure decreased in patient W. C. from 26/14 to 14/8 mm. Hg. In patient B. J. the right ventricular pressure decreased from 38/12 to 22/4 mm. Hg (Figure 1). In subject C. A., the mean right auricular pressure decreased from − 0.5 to − 2.5 mm. Hg. In the decompensated patients the pulmonary arterial pressure decreased in patient T. P. from 45/22 to 20/12 mm. Hg and in subject R. S. from 70/40 to 40/15 mm. Hg. The right ventricular pressures fell in subject J. C. from 115/25 to 85/18 mm. Hg and in subject A. C. from 130/20 to 80/8 mm. Hg. The decline in right heart pressures paralleled the fall in systemic arterial pressure.

II. Blood Flow Through Various Regions

Blood flow through the muscles (calf blood flow)

In a previous communication it was pointed out that a ten-fold increase in foot (primarily skin) blood flow occurred after hexamethonium (14). In the calf segment (primarily muscle) an increased blood flow as determined by the plethysmographic method also was observed but to a much smaller degree than that observed in the foot (Table II).

Ten hypertensive patients were studied. Two patients in the malignant phase had previous therapy with hexamethonium while the remaining eight were patients with essential hypertension who had received no previous treatment with hexamethonium. In the latter eight cases all exhibited an increase of muscle blood flow varying from 11 to 61 per cent (mean 39.4 per cent) of the control values. The crude peripheral resistance decreased by 26 to 56 per cent (mean 40.4 per cent). The increase of blood flow began simultaneously with the decrease of blood pressure and some increase persisted for at least an hour.

The two patients who had malignant hypertension and who had been under continuous dosages of hexamethonium immediately prior to testing showed a decrease of blood flow in one instance and no change in the other. It could not be determined from this limited data whether these atypical responses were associated with the development of tolerance to the vasodilating properties of the drug or represented a response peculiar to patients in the malignant phase of hypertension.

[7] Model 140-C, Sanborn Company, Cambridge, Massachusetts.

TABLE I

Effects of hexamethonium on mean arterial pressure, cardiac rate, cardiac output and total peripheral resistance

Patient and Diagnosis	Sex	Age	Surface area	Control					Hexamethonium I.V.	Time after drug	After hexamethonium				
				Arterial pressure	Mean arterial pressure	Cardiac rate	Cardiac output	Total peripheral resistance			Arterial pressure	Mean arterial pressure	Cardiac rate	Cardiac output	Total peripheral resistance
			sq. cm.	*mm. Hg*	*mm. Hg*	*per min.*	*L. per min.*	*units**	*mg.*	*minutes*	*mm. Hg*	*mm. Hg*	*per min.*	*L. per min.*	*units**
M. C. Essential hypertension	M	63	1.75	220/115	148	80	6.4	.023	10	7	140/95	111	84	5.5	.020
				220/115	148	80	6.3	.024		18	140/95	110	80	5.2	.021
A. F. Essential hypertension	M	31	1.96	250/140	175	81	5.4	.033	15	10	210/110	140	94	3.9	.036
				250/140	175	79	5.0	.035		23	215/120	158	90	4.6	.034
J. J. Essential hypertension	M	59	1.78	215/120	152	83	6.3	.024	25	8	130/100	112	75	5.8	.019
				215/120	152	71	6.1	.025							
C. A. Essential hypertension	M	58	1.98	220/120	152	93	7.1	.021	37	6	145/100	114	103	4.5	.025
				225/120	154	90	7.4	.021		19	125/90	106	98	5.2	.020
B. J. Essential hypertension	M	26	1.73	185/115	152	85	6.6	.023	30	9	148/100	116	100	4.5	.026
				180/120	156	82	6.7	.023		18	145/95	113	106	5.3	.022
W. C. Essential hypertension	M	34	1.78	240/130	164	90	6.6	.025	50	14	180/110	136	103	5.0	.027
				240/130	164	90	6.3	.026		24	178/110	134	103	5.7	.024

* $\frac{\text{Mean femoral arterial pressure in mm. Hg}}{\text{Cardiac output in ml. per minute}}$.

TABLE I—*Continued*

Patient and Diagnosis	Sex	Age	Surface area	Control					Hexamethonium I.V.	Time after drug	After hexamethonium				
				Arterial pressure	Mean arterial pressure	Cardiac rate	Cardiac output	Total peripheral resistance			Arterial pressure	Mean arterial pressure	Cardiac rate	Cardiac output	Total peripheral resistance
			sq. cm.	*mm. Hg*	*mm. Hg*	*per min.*	*L. per min.*	*units**	*mg.*	*minutes*	*mm. Hg*	*mm. Hg*	*per min.*	*L. per min.*	*units**
T. P. Essential hypertension with heart failure. (Digitalized)	M	68	1.86	265/140	194	82	4.8	.040	7	8	200/115	150	90	5.0	.030
				275/145	202	84	4.5	.045		13	235/120	156	90	4.8	.031
J. C. Essential hypertension with heart failure	M	53	1.70	200/110	145	91	4.6	.030	8	8	120/90	105	91	6.1	.017
				200/110	145	90	4.3	.034							
A. C. Essential hypertension with heart failure	F	49	2.01	260/150	188	90	5.8	.033	18	7	152/84	114	92	7.9	.014
				220/150	182	85	6.4	.028		13	140/80	106	75	6.4	.017
R. S. Essential hypertension with heart failure	M	52	1.80	190/105	130	104	2.6	.050	24	12	100/64	80	85	4.5	.018
				188/106	130	100	1.9	.068		22	114/76	90	88	3.8	.024
T. N. Malignant hypertension†	M	32	1.81	215/125	150	107	3.5	.044	30	7	155/105	118	135	6.0	.020
				220/125	155	105	3.5	.044		16	150/100	118	122	4.3	.028

† Papilledema.

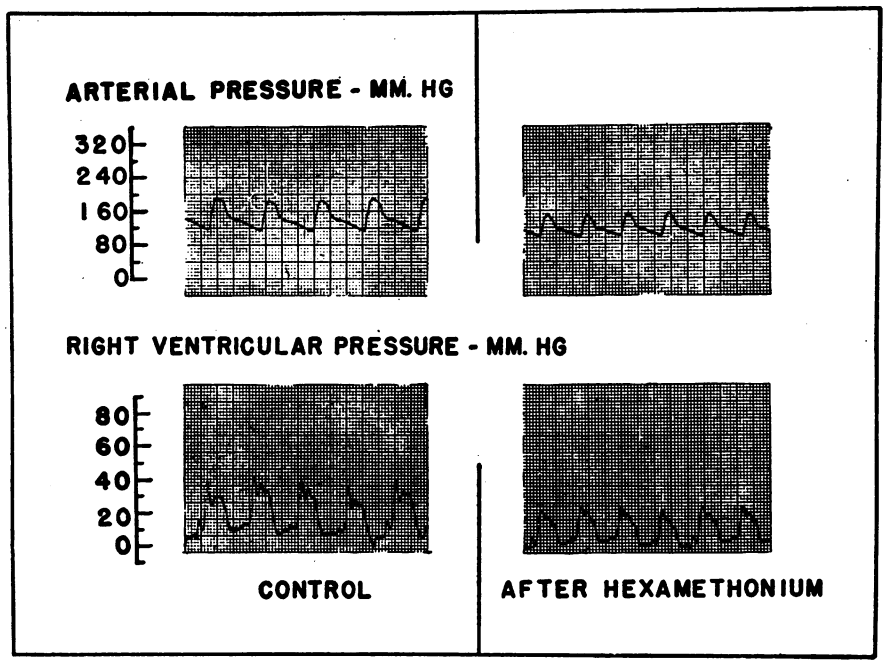

FIG. 1. CUTTINGS TAKEN FROM THE RECORDINGS OF SYSTEMIC ARTERIAL (ABOVE) AND RIGHT VENTRICULAR PRESSURES (BELOW) IN PATIENT B. J. BEFORE AND 19 MINUTES AFTER THE INTRAVENOUS ADMINISTRATION OF 30 MG. OF HEXAMETHONIUM

The reduction of arterial pressure was accompanied by a considerable decrease of right ventricular pressure. See text and Table I for further details.

Blood flow through the hepatic-portal circuit

Determinations of estimated hepatic-portal blood flow were carried out in five hypertensive and two normal subjects. In all of the hypertensive patients the mean arterial pressure decreased following hexamethonium, the range being 20 to 40 per cent and the mean 28 per cent (Table III). In four cases estimated hepatic blood flow decreased by 8 to 54 per cent (mean 25 per cent) while in the remaining case it was unchanged. The hepatic-portal vascular resistance fell in all except one of the hypertensive patients.

One of the normal subjects exhibited insignificant changes in estimated hepatic portal flow and peripheral vascular resistance while in the remaining subject hepatic blood flow decreased 19 per cent and peripheral resistance also was reduced slightly. Thus in four or five hypertensive and one of two normotensive subjects the estimated hepatic portal blood flow decreased moderately and in the remaining two cases did not change significantly.

Blood flow through the kidneys

Two of the seven cases studied exhibited no significant change in renal blood flow (D. G. and H. B., Table IV). However, changes in arterial pressure also were insignificant in these two subjects despite relatively high doses of hexamethonium. In the remaining five cases there was a reduction of renal plasma flow which paralleled the fall in arterial pressure (Table IV and Figure 2). However, in four of these cases all of whom were hypertensives, the renal plasma flow returned to or above the control levels after periods varying from 15 to 50 minutes following the time of drug administration. In all four instances the plasma flow rose despite a continued significant reduction of arterial pressure. In the remaining case, a normal subject, the plasma flow remained reduced up to 50 minutes after hexamethonium. Thus, the usual pattern of response to hypotensive doses of hexamethonium was an early decrease in renal plasma flow followed by a return to control values despite continued reduction of arterial pressure.

TABLE II

Effects of hexamethonium on blood flow in the calf

Patient and Diagnosis	Sex	Age	Control			Hexamethonium intravenously	After hexamethonium					
			Arterial pressure	Blood flow per 100 ml. leg volume	Peripheral resistance		Time after drugs	Arterial pressure	Blood flow per 100 ml. leg volume	Mean change	Peripheral resistance	Mean change
			mm. Hg	*ml. per min.*	*units**	*mg.*	*minutes*	*mm. Hg*	*ml. per min.*	*per cent*	*units**	*per cent*
W. F.	M	50	178/130	5.4	28	30	3	125/95	8.3		13	
Essential			168/125	5.6	26		6	130/92	8.3		13	
hypertension			180/128	5.4	28		10	135/100	8.0		14	
			180/128	4.8	32		20	135/98	8.3		14	
			175/125	5.6	26		35	125/90	8.9		12	
							45	125/90	8.2		13	
							60	125/90	8.2		13	
										+55		−54
J. J.	M	46	165/110	5.0	27	50	4	140/100	6.5		18	
Essential			160/105	4.8	27		8	135/100	7.6		15	
hypertension			160/105	4.1	32		15	135/100	7.1		16	
			180/110	4.7	30		25	140/105	7.7		16	
							35	145/110	7.8		16	
							40	140/110	8.3		14	
										+61		−45
B. R.	M	31	165/115	8.0	17	100	5	155/115	11.9		11	
Essential			170/120	10.1	14		8	165/115	11.7		12	
hypertension			165/120	8.5	17		15	155/110	12:0		11	
			165/115	7.7	18		25	155/110	12.0		11	
										+40		−31
T. N.	M	34	220/140	8.9	20	100	3	185/145	6.5		25	
Essential			220/145	8.2	22		5	178/135	5.8		27	
hypertension.			230/145	6.4	29		6	180/135	5.4		27	
(Formerly							9	175/130	5.1		29	
malignant)							16	165/130	4.8		30	
Hexamethonium							20	170/135	4.1		37	
treated.							28	175/135	4.1		37	
							40	170/135	3.9		38	
							45	170/130	3.8		43	
							55	170/130	3.8		39	
										−40		+42
E. T.	M	36	145/110	3.5	36	14	5	120/90	8.6		12	
Essential			155/110	4.2	31		10	120/90	8.6		12	
hypertension			155/110	2.5	52		20	125/90	5.8		18	
							38	130/90	6.1		18	
							58	130/90	5.3		20	
							63	135/95	5.5		20	
							75	140/95	5.4		21	
										+47		−56

* $\frac{\text{"Mean" arterial pressure (12) in mm. Hg}}{\text{Blood flow in ml. per 100 ml. leg volume per min.}}$

TABLE II—*Continued*

Patient and Diagnosis	Sex	Age	Control			Hexamethonium intravenously	After hexamethonium					
			Arterial pressure	Blood flow per 100 ml. leg volume	Peripheral resistance		Time after drugs	Arterial pressure	Blood flow per 100 ml. leg volume	Mean change	Peripheral resistance	Mean change
			mm. Hg	*ml. per min.*	*units**	*mg.*	*minutes*	*mm. Hg*	*ml. per min.*	*per cent*	*units**	*per cent*
I. E.	M	50	220/140	4.5	39	100	5	220/140	7.0		25	
Malignant			220/140	5.1	34		20	210/140	5.4		32	
hypertension.							35	210/145	4.2		41	
Hexamethonium							50	210/145	4.6		38	
treated										+ 1		− 1
G. H.	M	29	170/110	8.7	16	50	5	140/90	11.6		10	
Chronic			170/110	10.2	13		20	140/90	13.0		9	
glomerulo-			170/110	10.6	13		35	130/85	11.6		9	
nephritis							55	130/85	13.0		8	
							70	145/95	11.5		10	
										+22		−34
B. M.	M	55	175/110	2.0	69	28	3	130/90	2.2		49	
Essential			165/110	1.7	79		4	115/88	2.1		47	
hypertension			175/110	1.8	77		7	120/90	1.8		57	
							9	115/85	1.8		54	
							18	115/85	2.0		49	
							26	130/95	2.3		48	
							37	142/102	2.1		57	
							39	132/95	2.0		55	
										+11		−31
W. A.	M	42	175/125	4.1	36	50	2	148/105	6.7		19	
Essential			172/130	4.3	35		6	145/105	6.7		18	
hypertension			175/125	4.2	35		8	140/105	7.0		17	
			175/125	4.8	31		16	145/105	7.3		17	
			175/125	4.1	36		29	138/110	7.1		17	
							40	125/100	6.0		20	
							50	130/100	5.7		20	
							62	135/105	5.9		20	
										+52		−46
R. C.	M	32	196/130	4.0	40	50	2	164/128	4.6		31	
Essential			196/130	3.7	43		3	160/128	4.9		29	
hypertension			192/130	3.8	41		5	164/125	4.8		30	
			196/130	3.5	45		7	160/130	5.0		35	
							12	170/130	4.6		32	
							24	162/132	4.6		32	
							34	168/134	4.6		32	
							54	166/134	4.9		30	
										+27		−26

TABLE III

Effects of hexamethonium on estimated hepatic blood flow

Patient and Diagnosis	Sex	Age	Surface area	Control			Hexamethonium I.V.	After hexamethonium			
				Mean arterial pressure	E.H.B.F.	Estimated hepatic vascular resistance		Time after drug	Mean arterial pressure	E.H.B.F.	Estimated hepatic vascular resistance
			sq. m.	*mm. Hg*	*ml. per min.*	*units**		*min.*	*mm. Hg*	*ml. per min.*	*units**
C. P.	M	48	1.85	216	592	.365	2	2	118	425	.278
Malignant				184	529	.348		8	108	323	.334
hypertension								14	128	474	.270
								22	124	489	.254
E. G.	M	38	1.90	118	2008	.057	50	11	87	933	.093
Essential				118	1875	.063		24	92	894	.103
hypertension								37	94	932	.101
S. J.	M	52	1.75	165	872	.189	5	7	110	770	.143
Essential				155	924	.168		12	110	776	.142
hypertension								17	110	742	.148
H. C.	M	40	1.97	150	874	.172	10	5	125	793	.158
Essential				160	696	.230		10	130	817	.159
hypertension				140	585	.239					
							18	16	125	524	.236
								24	100	833	.120
E. T.	M	36	1.80	140	1113	.126	15	1	110	1097	.100
Essential				141	1030	.137		5	98	1007	.092
hypertension				144	1089	.132		10	95	883	.108
R. B.	M	29	1.72	70	1792	.039	50	6	63	2155	.029
Normal				70	1496	.047		18	63	1933	.033
				63	1974	.032		29	65	1428	.046
								40	65	1244	.052
P. S.	M	24	2.14	82	1524	.054	100	4	60	1510	.040
Normal				79	1520	.052		12	52	1396	.037
				79	1524	.052		23	58	981	.059
								34	60	1388	.043
								50	66	1416	.047

* $\frac{\text{Mean femoral arterial pressure in mm. Hg}}{\text{Blood flow in ml. per minute}}$.

TABLE IV

Effects of hexamethonium on renal clearances

Patient and Diagnosis	Sex	Age	Surface area	Control					Hexamethonium I.V.	After hexamethonium					
				Arterial pressure	Renal plasma flow	Glomerular filtration rate	Filtration fraction	Urine volume		Time after drug	Arterial pressure	Renal plasma flow	Glomerular filtration rate	Filtration fraction	Urine volume
			sq. m.	*mm. Hg*	*ml. per min.*	*ml. per min.*	*per cent*	*ml. per min.*	*mg.*	*minutes*	*mm. Hg*	*ml. per min.*	*ml. per min.*	*per cent*	*ml. per min.*
A. Z. Essential hypertension	M	52	1.78	248/142 248/140	248 258	69 69	28 27	7.9 7.5	40	5 15 30 50	218/130 204/130 198/126 200/122	246 229 242 272	72 56 59 65	29 24 24 24	6.2 3.9 4.2 4.2
C. S. Essential hypertension	M	38	1.86	172/110 166/110	411 393	88 93	21 24	2.6 3.1	30	5 15 30	85/58 78/58 89/65	289 287 455	73 69 62	25 24 14	2.5 4.0 4.6
A. S. Malignant hypertension	M	60	2.26	188/118 186/114 190/118	366 327 418	106 94 117	29 29 28	6.8 5.1 5.8	10	10 30 50	148/ 92 156/104 168/110	149 373 341	43 72 79	29 19 23	1.3 1.5 1.5
D. G. Malignant hypertension and uremia	M	28	1.65	208/112 214/118	215 214			1.4 1.5	50	10 30	212/126 200/120	234 222			1.5 1.4
M. Y. Essential hypertension	F	48	1.89	230/134 225/135	448 368	88 84	20 23	7.9 7.5	25	5 15 30 50	180/110 176/114 168/110 174/110	296 381 343 321	54 70 64 70	18 18 19 22	3.6 3.7 3.0 2.7
H. B. Normal	M	36	1.78	108/76 104/72	520 319	103 86	20 27	6.5 6.4	80	5 15 30 50	100/70 102/74 100/74 104/76	379 581 414 360	85 86 91 74	23 15 22 21	7.5 7.7 7.6 5.0
R. B. Normal	M	29	1.70	100/70 100/68	812 672	203 179	13 14	5.0 4.4	60	5 15 30 50	96/66 100/72 95/70 98/70	705 286 322 322	203 93 111 106	14 17 17 16	5.3 0.6 2.2 2.1

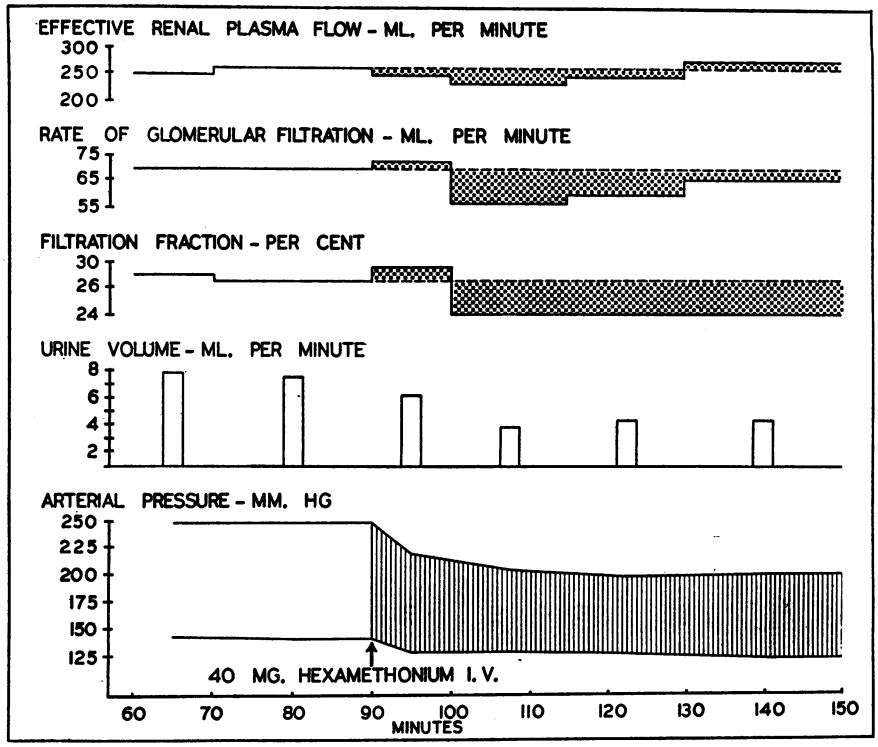

FIG. 2. CHART OF EFFECTIVE RENAL PLASMA FLOW, GLOMERULAR FILTRATION RATE, FILTRATION FRACTION, URINE VOLUME AND ARTERIAL PRESSURE BEFORE AND AFTER THE INTRAVENOUS ADMINISTRATION OF 40 MG. OF HEXAMETHONIUM ION IN PATIENT A. Z.

In the early period there was a decrease in renal plasma flow, glomerular filtration rate and urine volume. However, 45 minutes after hexamethonium renal plasma flow had returned to and glomerular filtration rate approached control values despite continued significant reduction in filtration fraction, urine volume and arterial pressure.

III. Other Aspects of Renal Function

Glomerular filtration rate was determined in six of the subjects listed in Table IV. In three hypertensive patients there was a reduction of glomerular filtration rate followed by a rise toward but not to the control values (A. Z., A. S., and M. Y., Table IV and Figure 2). In one hypertensive and one normal subject there was a continued fall in glomerular filtration rate throughout the experimental period. The final normal subject who had exhibited no significant change in arterial pressure or renal blood flow also showed no change in glomerular filtration rate. It was apparent, therefore, that the rate of glomerular filtration decreased paralleling the blood pressure fall and complete compensation usually did not occur during the experimental period. The filtration fraction decreased in all of the hypertensive patients. In the two normal subjects there was no significant change in the patient who showed no reduction of arterial pressure and a slight rise in filtration fraction in the other.

The volume of urine flow did not change in the two cases who exhibited insignificant reduction of arterial pressure (D. G. and H. B., Table IV). Four of the five remaining cases exhibited a reduction of urine volume which persisted throughout the experimental period. The final patient (C. S.) exhibited a slight rise in urine volume.

DISCUSSION

Previous hemodynamic studies in this laboratory demonstrated that hexamethonium produces a marked to complete abolition of such vasoconstrictor reflexes as the vasopressor "overshoot" following the Valsalva maneuver, the cold pres-

sor response and the reflex vasoconstrictions to "noxious" stimuli as determined by digital plethysmography (15). As would be expected following such inhibition of moderator reflexes by a ganglionic blocking agent the pressor responses to epinephrine and norepinephrine were augmented considerably, after as compared to before, hexamethonium (16). In a constant temperature cold room the increase in foot blood flow was as great following hexamethonium as after extradural or intrathecal anesthesia in normal subjects, suggesting nearly complete ganglionic blockade in man (14). In addition, probably by reason of the inhibition of vasoconstrictor reflexes, hexamethonium was found to induce marked hypotension in normal or hypertensive subjects following minor degrees of blood loss such as that occasioned by the brief application of venous tourniquets to the extremities or by small venesections of 250 to 500 cc. of blood (17). Thus, the previous studies demonstrated that hexamethonium in man interferes with transmission of sympathetic vasoconstrictor impulses more completely than any previously known agent. The present investigation has determined the effects of such widespread inhibition of sympathetic impulses on cardiovascular dynamics.

In the patients who did not exhibit congestive heart failure and whose cardiac outputs were in the normal range, the hypotensive response to hexamethonium was accompanied by a decreased cardiac output and little or no change in total peripheral resistance. These observations are in approximate agreement with those of Werkö, Frisk, Wade, and Eliasch (18), but are opposed to those of Gilmore, Kopelman, McMichael, and Milne (19) who found essentially no change in cardiac output after hexamethonium. Thus, the reduction of arterial pressure in the present series seemed to be secondary to a diminished cardiac output rather than to arteriolar vasodilation. The decreased cardiac output in turn appeared to be due to a failure of venous return since the pressures on the right side of the circulation were reduced uniformly.

The failure of venous return probably was produced by pooling of blood in the peripheral circulation. Such pooling could be due to (1) an increase in the total vascular capacity, and (2) the blockade of reflex vasoconstrictor responses (17).

By contrast in the patients with congestive heart failure or malignant hypertension the decreases in systemic and right heart pressures were accompanied by an increased cardiac output and decreased total peripheral resistance. These divergent observations in the patients with heart failure as compared to compensated subjects may be explained, however, in the light of the following considerations: first, in the case of the heart failure subjects the peripheral pooling of blood induced by hexamethonium would act like a venesection reducing the loading pressure of the congested right side of the heart thereby facilitating its recovery. Second, it is evident that patients with this type of heart failure are in a state of elevated vasoconstrictor tone since normal or elevated levels of systemic arterial pressure are maintained despite a cardiac output which usually is reduced. Hexamethonium by its blocking action on vasoconstrictor reflexes abolishes this increased tone thus permitting a decrease in total peripheral resistance and thereby also in the demand for cardiac work. These considerations and their implications in regard to the nature of congestive heart failure have been discussed more fully in another communication (20).

Muscle blood flows increased only moderately, while renal and hepatic-portal blood flows fell during the maximum action of the drug. Foot blood flow increased approximately ten fold (14) but since this vascular area is small in relation to the total vasculature the decrease in vascular resistance in the foot had little influence on the total peripheral resistance. These results suggest that there is an uneven distribution of sympathetic vasocontrictor nerves in different vascular areas. Only in a single region, the distal parts of the extremities, was a marked increase in flow observed. In the other and larger vascular areas (muscles, hepatic-portal and renal vascular beds) moderate increases or actual decreases in flow occurred while the total peripheral resistance usually was only slightly reduced. These data do not support the view that the sympathetic vasoconstrictor system is of great importance in regulating arteriolar tone in the resting, supine subject except for its role in temperature regulation of the skin particularly of the distal parts of the extremities. The results also emphasize the fallacies inherent in drawing conclusions as to the overall

vasodilating effects of agents which increase skin temperature, color or blood flow.

The hemodynamic effects of hexamethonium, however, are due to more than simple inhibition of sympathetic vasoconstrictor nerves since the drug interferes with transmission through all autonomic ganglia. Vasodilator nerves which synapse in the ganglia as well as vasoconstrictor impulses will be inhibited. For example, blockade of vasodilator impulses is seen in the cessation of salivary flow following the drug (21). Thus, the results observed after hexamethonium may be in reality the net effect of combined inhibition of autonomic vasoconstrictor and vasodilator impulses.

The pattern of change in renal function was qualitatively similar to that observed after certain other hypotensive agents including veratrum viride (9), the dihydrogenated alkaloids of ergot (22) and sodium nitrite given as a single, oral dose (23). The renal vasculature did not share in the decrease in vascular resistance associated with the fall in arterial pressure. This is indicated by the fact that the renal plasma flow decreased sharply at the onset of the hypotensive response regardless of the drug used. However, as the arterial pressure stabilized at a lower level or began to rise the resistance of the renal vessels decreased to permit a return to normal rates of plasma flow. This effect, which was first observed by Smith and his co-workers folowing spinal anaesthesia, has been interpreted by him as indicating an autonomy of the renal arterioles (24).

A recent study by Machinnon indicated that the closely related compound, pentamethonium produced a decrease in renal blood flow in both normotensive and hypertensive subjects (25). However, the design of his experiments was such that only the early hypotensive response to the drug was studied. Thus, insufficient time was allowed to permit observation of the later return of renal plasma flow to control levels. Mills, Moyer, and Handley found no change in renal clearances following hexamethonium in normal subjects but observed some diminution in hypertensive patients (26).

As a result of the percentally greater fall in glomerular filtration rate than in plasma flow there was a decrease in filtration fraction which in hypertensive subjects approached normal values. The urine during this period became quite concentrated suggesting that tubular function was not significantly impaired. This pattern of change has been observed with hypotensive agents of all types tested in this laboratory (23) and therefore probably is secondary to the sudden alteration of arterial pressure rather than to any specific action of individual drugs on the kidney.

From the point of view of effects on hemodynamics the response to hexamethonium does not appear to be entirely desirable. Thus, cardiac output may decrease, renal clearances especially glomerular filtration rate fall at least temporarily and homeostatic, vasomotor reflexes are seriously compromised. However, despite these apparently undesirable and abnormal acute actions, the clinical response to hexamethonium frequently has appeared to be beneficial (5, 7, 8). These correlative clinical and experimental studies emphasize the fact that the results of hemodynamic analysis need not always indicate the desirability of a given agent in clinical practice where other factors may determine the usefulness of the drug.

SUMMARY AND CONCLUSIONS

Hexamethonium administered to hypertensive and normal subjects produces the following hemodynamic effects:

1. In hypertensive patients who do not have cardiac decompensation the reduction of systemic arterial pressure is accompanied by a decrease in right heart pressures and cardiac output. The total peripheral resistance does not change significantly. It is suggested that these alterations are the result of a combination of "venous pooling" and failure of reflex vasoconstriction.

2. In patients with heart failure the fall in systemic arterial pressure appears to be accompanied by a reduction of right heart pressures, an increase in cardiac output and a significant decrease in total peripheral resistance. These alterations may be due to unloading of the congested right side of the heart as well as to inhibition of vasoconstrictor reflexes activated by the low output heart failure.

3. In contrast to the marked increase in blood flow in the foot observed previously, blood flow through the muscles increases only moderately. Since the arterial pressure falls after hexametho-

nium a significant decrease in peripheral resistance is assumed to occur in this area.

4. Despite a moderate reduction of hepatic vascular resistance estimated hepatic-portal blood flow usually decreases after hexamethonium.

5. Renal plasma flow decreases paralleling the initial fall in arterial pressure and then rises to approximate control levels despite a continued hypotensive response. This is consistent with previous observations indicating an autonomy of tone of the renal arterioles.

6. In most cases the changes in glomerular filtration rate follow a pattern similar to the alterations in renal plasma flow, but occasionally filtration may remain below control values. Oliguria with increased concentration of urine usually occurs. All of these renal effects begin to diminish after 30 to 60 minutes despite continued significant hypotension.

7. The studies to date suggest that sympathetic vasoconstrictor nerves blocked by hexamethonium exert the controlling influence on homeostatic adjustments to postural change as well as in maintaining the tone of the vessels of the distal part of the extremities. However, in resting supine subjects such nerves appear to exert a much less important influence on arteriolar tone in the hepatic-portal, renal and muscle areas.

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