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THE EFFECTS OF GANGLIONIC AND ADRENERGIC BLOCKADE ON THE CIRCULATION OF THE YOUNG CHIMPANZEE

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The animals used in this study were handled in accordance with the "Principles of Laboratory Animal Care" established by the National Society for Medical Research.

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FOREWORD

This is the final report of a study conducted by the Department of Medicine, Ohio State University under Air Force Contract AF 29(600)-4385. The work was performed in support of Project 6892, Task 689201 from 1 October 1963 to 30 April 1965. Major Jerry Fineg of the 6571st Aeromedical Research Laboratory, Holloman AFB, New Mexico was project monitor.

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This technical report has been reviewed and is approved for publication.

CLYDE H. KRATOCHVIL, Lt Colonel, USAF, MC
Commander

ABSTRACT

In the present studies the role of the autonomic nervous system in circulatory control in young chimpanzees was evaluated through the use of selected autonomic blocking agents. Ganglionic blockade resulted in decreases in cardiac output, heart rate and arterial pressure. Beta adrenergic blockade resulted in similar decreases in cardiac output and heart rate, while arterial pressure was unchanged. Alpha adrenergic blockade caused a decrease in arterial pressure and peripheral resistance. Heart rate rose and cardiac output showed no consistent change following alpha adrenergic blockade.

These changes following autonomic or adrenergic blockade indicate that a significant amount of sympathetic-adrenergic stimulation of the circulation is present in the young resting chimpanzee. When compared to data obtained in resting humans, qualitatively similar changes are found for cardiac output and arterial pressure. The degree of adrenergic stimulation is greater in the chimpanzee. The response of heart rates to ganglionic blockade indicates that the parasympathetic system plays the dominant role in heart rate control in man, while the sympathetic system prevails in the chimpanzee. These findings suggest that similar data for other species would be most valuable in the area of comparative physiology, and should be considered in studies where various species are used as biological analogs of the human.

During ganglionic and alpha adrenergic blockade the chimpanzee showed a markedly increased tolerance to the circulatory effects of 90 degree head-up tilt when compared to the human. Arterial pressures adequate for cerebral perfusion were maintained for periods of head-up tilt lasting as long as 30 minutes. These data suggest that in the chimpanzee an effective autoregulatory mechanism for control of arterial resistance exists, independent of the autonomic or adrenergic systems.

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I. INTRODUCTION

Previous studies have demonstrated that young chimpanzees have significantly increased heart rates, cardiac outputs and systemic arterial pressures when compared to humans of the same age and weight. In addition, they demonstrate a greater circulatory tolerance to the effects of the vertical posture and gravity (1). These findings suggested the hypothesis that the chimpanzee is a species with relatively high sympathetic-adrenergic activity. The present studies were designed to yield data relative to this hypothesis. They consist of observations on the circulatory effects of pharmacologic blockade of specific autonomic or adrenergic components.

II. SUMMARY

The role of the autonomic nervous system in circulatory control in young resting chimpanzees was evaluated through the use of selected autonomic blocking agents.

1. Ganglionic blockade with trimethaphan induced decreases in heart rate of 22 percent, in cardiac output of 35 percent and in mean arterial pressure of 33 percent.

2. Beta adrenergic blockade with nethalide decreased heart rate 22 percent and cardiac output 25 percent, while mean arterial pressure was unchanged.

3. Alpha adrenergic blockade with phentolamine or phenoxybenzamine decreased mean arterial pressure 26 percent, while heart rate rose 16 percent to 23 percent. Cardiac output showed no consistent change.

4. Atropine caused an increase in heart rate, without significant change in cardiac output or arterial pressure.

5. During ninety degree head-up tilt during ganglionic or alpha adrenergic blockade the animals were able to maintain arterial pressures adequate for cerebral perfusion for periods as long as 30 minutes.

These data indicate that a significant amount of sympathetic-adrenergic stimulation of the circulation is present in the young resting chimpanzee. Comparison with data obtained in resting humans following

autonomic blocking agents shows qualitatively similar circulatory changes. However, the amount of adrenergic activity is somewhat greater in the chimpanzee. These findings are of interest in the area of comparative physiology. They suggest the need for similar data in other species that may be used as biological analogs of the human.

The ability of the chimpanzee to maintain cerebral perfusion during head-up tilt following ganglionic or alpha adrenergic blockade indicates an effective autoregulatory mechanism exists for peripheral arterial resistance, independent of the autonomic or adrenergic systems. Comparison of these studies with data for humans suggests that this control mechanism is not as effective or apparent in man during head-up tilt.

III. METHODS

Hemodynamic observations were made in young chimpanzees (Pan species) from the primate colony at the 6571st Aeromedical Research Laboratory at Holloman Air Force Base. The estimated ages of the animals were from 36 to 72 months and their weights ranged from 12.5 to 27 kg. Studies were performed following an 8 hour fast and with no premedication. The animals were seated in a specially designed restraint chair and secured at the neck, wrists, hips and ankles. Animals were positioned in a horizontal plane with the hips and knees flexed to 90 degrees. A thin polyethylene catheter (i.d. = 0.23 in. x 0.d. = 0.38 in., or i.d. = 0.034 in. x o.d. = 0.050 in.) was passed through an 18 or 15 g. thin-wall needle which had been positioned in an antecubital vein. The catheter was advanced with pressure monitoring into the inferior vena cava, the right atrium; and, in most animals, into the right ventricle and pulmonary arteries. Pressure measurements were obtained in all these chambers and the catheter was withdrawn to the right atrium where it remained for the rest of the study. A number 18 or 20 g. thin-wall Cournand needle was then introduced into a brachial artery. Pressure measurements were made using a Statham P23Db transducer placed midway between the anterior and posterior surfaces of the chest at the level of the fifth intercostal space. The mean pressures were obtained by electronic integration. Pressures were recorded only after catheters were adequately flushed and shown to be patent by withdrawal of blood.

Cardiac output was determined by the indicator diluation technique utilizing Indocyanine green with injections into the right atrium and sampling from the brachial artery. Arterial blood was drawn through a cuvette densitometer by means of a constant withdrawal syringe (Gilford Co.). Cardiac outputs were calculated by the Hamilton technique. A standard lead II of the electrocardiogram was recorded throughout. The output of the electrocardiogram channel was fed into a tachometer which permitted heart rate to be monitored continuously. Stroke volume was calculated by dividing heart rate into cardiac output. Peripheral resistance was calculated by dividing cardiac output into the mean arterial blood pressure.

Observations were made only when the animals were calm, since psychomotor arousal has been shown to result in a hyperdynamic circulatory state (1). The aroused psychomotor state could be detected by the presence of tachycardia and variations in arterial pressure, as well as the more obvious signs of body movement and vocalization. During many of the observations the animals appeared to be sleeping in the quiet, dimly lit room. Another factor which has been shown to influence the reliability of hemodynamic measurements is the loss of blood resulting from repeated cardiac output measurements (1). Each cardiac output determination results in a loss of 10 to 15 ml. of blood. Our data have shown that this exerts no appreciable effect upon the circulation in animals weighing 12 to 20 kg., until the blood loss exceeds 100 ml. Therefore all observations reported are those made before this amount of blood had been withdrawn.

The drugs studied included trimethaphan camphorsulfonate, nethalide (pronetholol)[1], phenoxybenzamine [2], and phentolamine. Trimethaphan, a potent ganglionic blocking agent, was given by a continuous intravenous infusion at rates of 2 to 3 mg. per minute (2, 3). Nethalide, a beta-adrenergic blocking agent, was given in doses of 5 mg./kg. as a single intravenous injection (4). Phenoxybenzamine, an alpha adrenergic blocking agent, was given as a single dose of 1 mg./kg. intravenously (5). Phentolamine, another alpha adrenergic blocking agent was given as a continuous intravenous infusion at a rate of 1 mg. per minute. In addition, several animals were given atropine in order to evaluate the role of the parasympathetic system. One or more control observations of cardiac output, heart rate, and right atrial and brachial artery pressures were made. Drug administration was begun and time permitted for the animals to reach a steady state. The hemodynamic observations were then repeated. The completeness of blockade was assessed by the response to the administration of norepinephrine in those animals undergoing

[1] Kindly supplied by Alex Sahagian-Edwards, M.D. of Ayerst Laboratories

[2] Kindly supplied as Dibenzyline by H.C. Carlson, Jr., M.D. and G. June Oswald of Smith Kline and French Laboratories.

alpha blockade, and to isoproterenol in those animals undergoing beta blockade.

IV. RESULTS

1. Ganglionic Blockade

The effects of ganglionic blockade are summarized in Table I and Figure 1. Trimethaphan infusion induced decreases in heart rate of 22 percent in cardiac output of 35 percent and in mean arterial pressure of 33 percent; while peripheral resistance and right atrial pressure showed no consistent change.

2. Beta Adrenergic Blockade

The effects of the administration of nethalide are summarized in Table II and Figure 2. Following nethalide, heart rate decreased 22 percent and cardiac output 25 percent; whereas mean arterial pressure was not significantly affected, and peripheral resistance tended to increase somewhat. Right atrial pressure rose slightly. Nethalide, in the doses used, blocked the heart rate and cardiac output response to 2 to 4 ug/min. of isoproterenol, or 5 to 24 ug/min. of epinephrine.

3. Alpha Adrenergic Blockade

The cardiovascular responses to phenoxybenzamine are summarized in Table III. With the blockade induced by this agent there was a variable response in cardiac output. Heart rate rose an average of 16 percent. Mean arterial pressure fell an average of 26 percent, while peripheral resistance fell 19 percent. Right atrial pressure was not significantly changed. Phenoxybenzamine abolished the pressor response to norepinephrine in doses of 12 to 20 ug/min.

In Table IV are shown the cardiovascular responses to the alpha adrenergic blocking agent, phentolamine. The cardiac output showed a variable response, so that the mean cardiac output was unchanged. Heart rate increased 23 percent. Mean arterial pressure and peripheral arterial resistance were decreased 26 percent each.

The tachycardia seen in response to the two alpha adrenergic blocking agents was reduced or eliminated by beta-adrenergic blockade in three animals. It was present in two of three animals after atropinization in doses of 1 mgm. i.v.

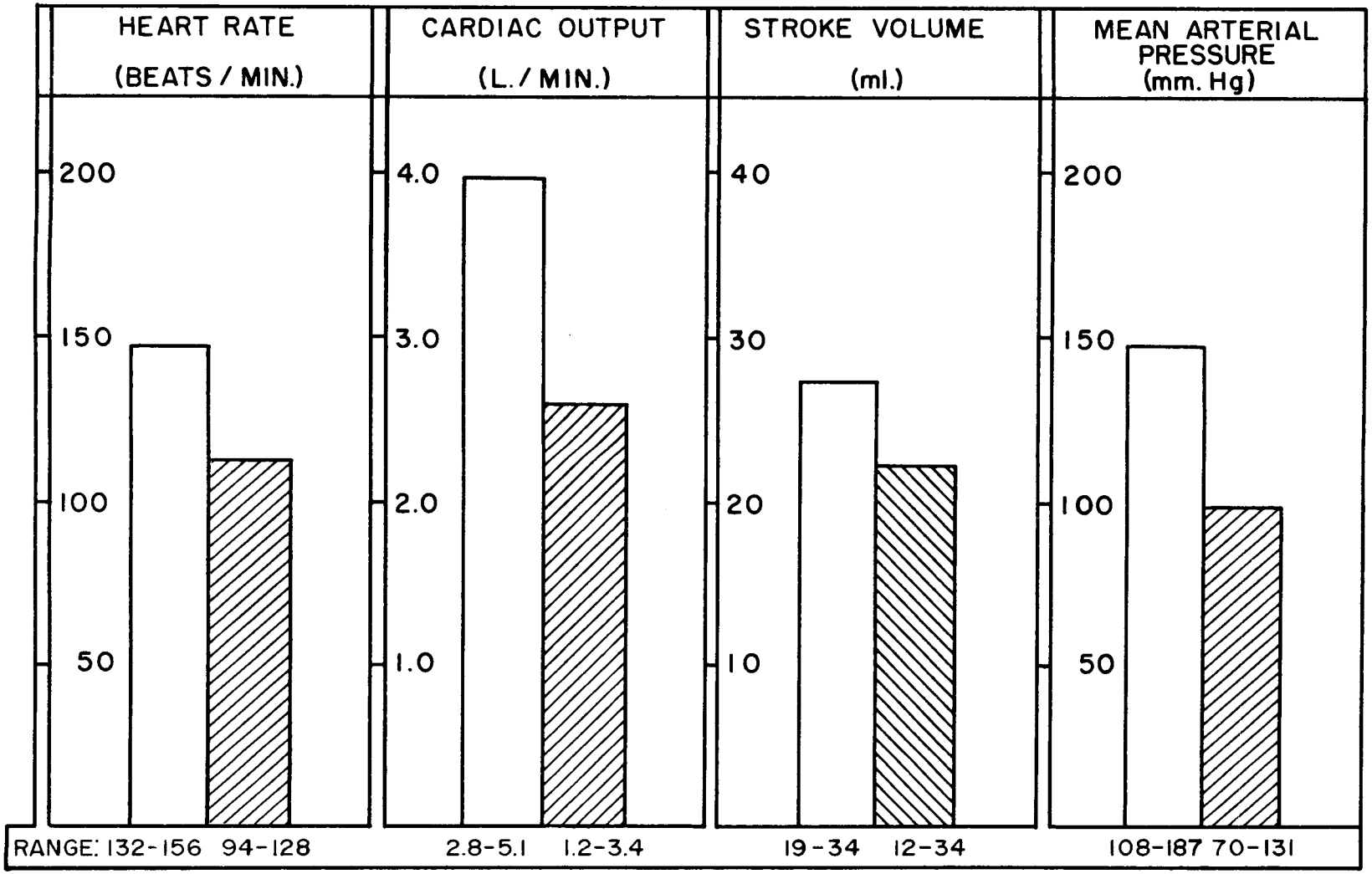

Fig. 1.

HEMODYNAMIC EFFECTS OF GANGLIONIC BLOCKADE WITH TRIMETHAPHAN IN 6 CHIMPANZEES
(AVERAGE DATA)

OPEN BARS = Control observations
HATCHED BARS = Observations during ganglionic blockade

Table I. HEMODYNAMIC EFFECTS OF GANGLIONIC BLOCKADE

WITH TRIMETHAPHAN IN SIX CHIMPANZEES

Chimp #	H.R. (beats/min.)		C.O. (L/min.)		S.V. (ml.)		BAP (mm Hg)		P.R.		R.A.P. (mm Hg)	
	C	T	C	T	C	T	C	T	C	T	C	T
128	156	139	3.62	2.54	23	18	178/118 (153)	132/87 (102)	42	41	-0.8	-1.2
85	147	130	4.14	3.11	28	24	170/122 (147)	93/53 (70)	35	23	0.0	0.0
129	132	104	3.49	2.00	26	20	127/88 (108)	95/60 (77)	31	38	0.0	-0.3
110	149	114	4.55	3.13	31	27	229/151 (187)	156/105 (131)	41	42	0.0	1.2
109	150	102	5.14	3.44	35	34	156/101 (129)	137/96 (118)	25	34	0.3	0.0
105	147	98	2.69	1.16	18	12	188/125 (152)	110/69 (88)	57	76	0.6	0.0
Mean	147	114	3.94	2.56	27	22	174/117 (146)	120/78 (98)	38	42	0.02	-0.03
S.D.	8.2	16.6	0.61	0.85	6.5	7.6	34/22 (27)	25/21 (24)	11.1	17.9	0.47	0.76
S.E.D.	5.83		0.133		0.76		9.71*		4.35		1.19	
t	5.54		9.07		5.71		4.98*		0.65		0.554	
p	< .005		< .001		< .005		< .005*		N.S.		N.S.	

Abbreviations: C = control, T = trimethaphan, H.R. = heart rate, C.O. = cardiac output, S.V. = stroke volume, BAP = brachial artery pressure (mean), P.R. = peripheral arterial resistance, R.A.P. = mean right atrial pressure, S.D. = standard deviation, S.E.D. = standard error of the difference, t = student's t test using SED, p = probability.
* = values for mean pressures.

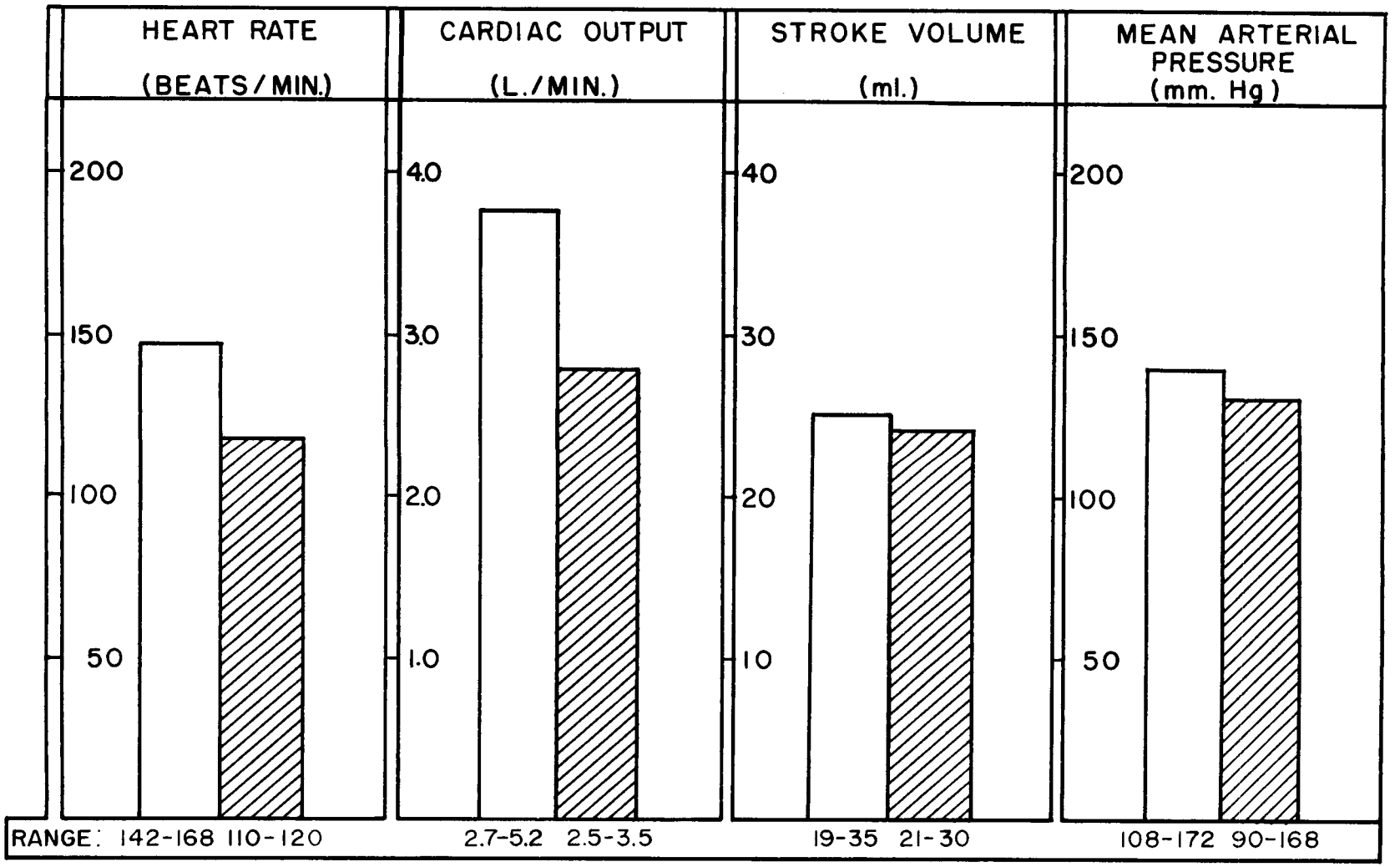

Fig. 2.

HEMODYNAMIC EFFECTS OF β ADRENERGIC BLOCKADE WITH NETHALIDE IN 5 CHIMPANZEES
(AVERAGE DATA)

OPEN BARS = Control observations
HATCHED BARS = Observations during beta adrenergic blockade

Table II. HEMODYNAMIC EFFECTS OF BETA ADRENERGIC BLOCKADE WITH NETHALIDE IN FIVE CHIMPANZEES

Chimp #	H.R. (beats/min.)		C.O. (L/min.)		S.V. (ml.)		BAP (mm Hg)		P.R.		R.A.P. (mm Hg)	
	C	N	C	N	C	N	C	N	C	N	C	N
128	168	120	4.17	2.76	25	23	170/115 (145)	153/100 (132)	35	48	0.7	0.7
110	144	110	3.27	2.75	23	25	202/140 (172)	200/130 (168)	53	61	0.9	1.1
109	148	116	5.16	3.46	35	30	154/96 (122)	142/100 (122)	24	35	0.0	2.0
149	135	120	3.30	2.48	24	21	167/110 (137)	164/118 (138)	41	56	0.8	1.0
129	144	112	2.70	2.51	19	22	130/84 (108)	114/74 (90)	40	31	0.0	1.0
Mean	148	116	3.72	2.79	25	24	164/109 (136)	155/104 (130)	39	46	0.46	1.16
S.D.	10.7	4.6	0.96	0.58	5.9	3.6	26/21 (24)	31/21 (28)	10.5	13.0	0.42	0.48
S.E.D.	5.24		0.278		1.52		3.734*		4.31		0.069	
t	6.15		3.28		0.66		1.87 *		1.76		9.96	
p	< .005		< .05		N.S.		N.S. *		N.S.		< .001	

Abbreviations: C = control, N = nethalide, other abbreviations same as in Table I.

Table III. HEMODYNAMIC EFFECTS OF ALPHA ADRENERGIC BLOCKADE WITH PHENOXYBENZAMINE IN NINE CHIMPANZEES

Chimp #	H.R. (beats/min.)		C.O. (L/min.)		S.V. (ml.)		BAP (mm Hg)				P.R.		R.A.P. (mm Hg)	
	C	P	C	P	C	P	C		P		C	P	C	P
128	154	216	3.99	4.27	26	20	182/122	(148)	148/82	(96)	37	22	1.5	1.3
110	138	172	3.48	3.44	25	20	166/108	(140)	180/66	(88)	41	26	-0.5	-1.5
129	163	159	2.83	2.10	17	13	184/132	(150)	158/94	(108)	53	51	0.0	-1.5
105	139	170	3.43	2.73	25	16	208/132	(158)	174/106	(128)	46	47	0.0	-1.0
107	135	168	3.87	4.67	29	28	142/87	(112)	140/84	(104)	29	22	-0.7	-0.4
105	140	163	3.62	1.96	26	12	189/124	(151)	118/62	(76)	42	39	1.2	-0.2
129	147	162	2.41	2.38	16	15	142/102	(122)	116/57	(69)	51	29	1.0	-0.8
148	180	174	4.07	3.79	23	22	201/144	(180)	191/140	(166)	44	44	-0.8	-0.5
128	170	201	4.05	5.42	24	27	166/105	(131)	144/96	(123)	37	23	0.8	1.7
Mean	152	176	3.52	3.42	23	19	176/118	(144)	152/88	(106)	42	34	0.1	-0.3
S.D.	15	19	0.57	1.23	4.26	5.77	24/18	(20)	26/25	(29)	7.4	13.4	0.9	1.0
S.E.D.	6.96		0.294		1.69		7.848*				2.64		0.301	
t	3.49		0.57		2.50		4.72 *				3.25		1.22	
p	< .025		N.S.		< .050		< .005*				< .025		N.S.	

Abbreviations: C = control, P = phenoxybenzamine, other abbreviations same as in Table I.

Table IV. HEMODYNAMIC EFFECTS OF ALPHA ADRENERGIC BLOCKADE WITH PHENTOLAMINE IN SEVEN CHIMPANZEES

Chimp #	H.R. (beats/min.)		C.O. (L/min.)		S.V. (ml.)		BAP (mm Hg)		P.R.		B.A.P. (mm Hg)	
	C	Pt	C	Pt	C	Pt	C	Pt	C	Pt	C	Pt
171	170	196	3.28	2.56	20	13	204/133 (150)	144/54 (67)	46	26	0.9	-0.7
149	132	192	4.11	4.67	31	24	179/111 (148)	164/100 (130)	36	28	0.5	0.8
129	134	119	3.57	2.93	26	25	165/111 (133)	147/94 (107)	37	37	-0.3	-1.6
154	136	184	4.33	4.80	32	26	156/100 (116)	151/78 (92)	27	19	0.5	-3.0
128	151	196	4.07	4.68	27	24	185/121 (151)	178/100 (120)	37	26	0.1	0.0
107	134	185	4.43	5.13	33	28	166/116 (136)	156/90 (113)	31	22	-0.3	-0.7
110	154	166	4.48	4.47	29	27	182/118 (146)	174/92 (114)	33	26	-1.0	-0.4
Mean	144	177	4.04	4.18	28	24	177/101 (140)	159/87 (106)	35	26	0.17	-0.75
S.D.	14	28	0.45	1.00	4.8	5.0	16/19 (13)	13/16 (7)	5.9	5.3	0.7	1.2
S.E.D.	10.08		0.232		0.923		8.387*		2.25		0.532	
t	3.22		0.059		4.80		4.04 *		4.01		1.53	
p	< .025		N.S.		< .005		< .010*		< .010		N.S.	

Abbreviations: C = control, Pt = phentolamine, other abbreviations same as Table I.

4. Parasympathetic Blockade

Three animals received atropine intravenously in a single dose of 1 mgm. This agent caused an increase in heart rate of 27 to 50 beats per minute. There was no change in cardiac output or arterial pressure.

5. Response to Head-up Tilt During Autonomic and Adrenergic Blockade

In Figure 3 the response of three chimpanzees to 90 degree head-up tilt during ganglionic blockade is illustrated. These animals were able to maintain their arterial pressure despite large decreases in cardiac output. No tendency toward severe hypotension or fainting was seen even after periods of tilt lasting as long as 30 minutes.

The response of eight animals to 90 degree head-up tilt during alpha adrenergic blockade with phentolamine or phenoxybenzamine is summarized in Table V. There was a fall in cardiac output of 32 percent and a decrease in mean arterial pressure of 17 percent. Peripheral resistance rose significantly despite the presence of alpha adrenergic blockade. There was little or no change in heart rate. No tendency toward fainting was seen after tilting for periods as long as 20 to 30 minutes during alpha adrenergic blockade.

V. DISCUSSION

Trimethaphan inhibits nerve transmission through autonomic ganglia. Thus, in animals receiving this drug, physiologic activation of the sympathetic and parasympathetic neuro-effector mechanisms cannot occur. Indeed, the heart and systemic resistance vessels are freed from sympatho-adrenergic and vagal control (2, 6). In the chimpanzee trimethaphan administration resulted in significant decrease in cardiac output, heart rate and arterial pressure, reflecting the high degree of autonomic activity present under the conditions of this study. However, these observations on the effects of trimethaphan do not delineate the specific autonomic components responsible for the observed circulatory effects. Further, uncertainty exists regarding the ability of ganglionic blocking agents to inhibit the compensatory release of catecholamines from the adrenal medulla. Such a release could occur as a response to severe hypotension (7). In view of these considerations our observations were extended to include the study of agents which block more specifically the adrenergic cardioactive or vasoactive influences.

Table V. HEMODYNAMIC EFFECTS OF HEAD-UP TILT DURING ALPHA ADRENERGIC BLOCKADE IN NINE CHIMPANZEES

Chimp #	Drug	H.R. (beats/min.) 0°	H.R. (beats/min.) 90°	C.O. (L/min.) 0°	C.O. (L/min.) 90°	S.V. (ml.) 0°	S.V. (ml.) 90°	BAP (mm Hg) 0°	BAP (mm Hg) 90°	P.R. 0°	P.R. 90°
128	P	207	202	4.26	2.75	21	14	156/88 (104)	160/84 (100)	25	36
129	P	186	165	2.34	1.54	13	9	164/94 (110)	154/88 (100)	47	65
105	P	169	171	2.56	1.71	15	10	165/92 (110)	150/66 (84)	43	47
107	P	168	174	4.67	2.75	28	16	140/84 (104)	114/70 (86)	22	31
105	P	163	166	1.96	1.43	12	9	118/62 (76)	76/40 (48)	39	34
129	P	162	168	2.38	1.69	15	10	98/48 (64)	122/58 (70)	27	42
128	Pt	190	204	4.48	2.88	24	15	186/107 (138)	164/90 (98)	31	34
107	Pt	185	184	5.13	3.32	28	19	157/89 (113)	152/74 (92)	22	28
110	Pt	154	183	4.04	3.63	26	20	170/96 (118)	172/71 (98)	29	27
Mean		176	180	3.54	2.41	20	14	150/84 (104)	140/79 (86)	32	38
S.D.		17	15	1.21	0.83	6	4	27/18 (22)	31/18 (13)	9	11
M.D.		4		1.13		6		18*		6	
S.E.D.		4.516		0.1940		0.9646		4.558*		2.5165	
t		0.810		5.793		6.911		3.922*		2.605	
p		N.S.		< 0.001		< 0.001		< 0.005*		< 0.050	

Abbreviations: P = phenoxybenzamine, Pt = phentolamine, 0° = observations in horizontal position, 90° = observations in vertical position, M.D. = difference between the means. Other abbreviations as in Table I.
* = values for mean arterial pressure only.

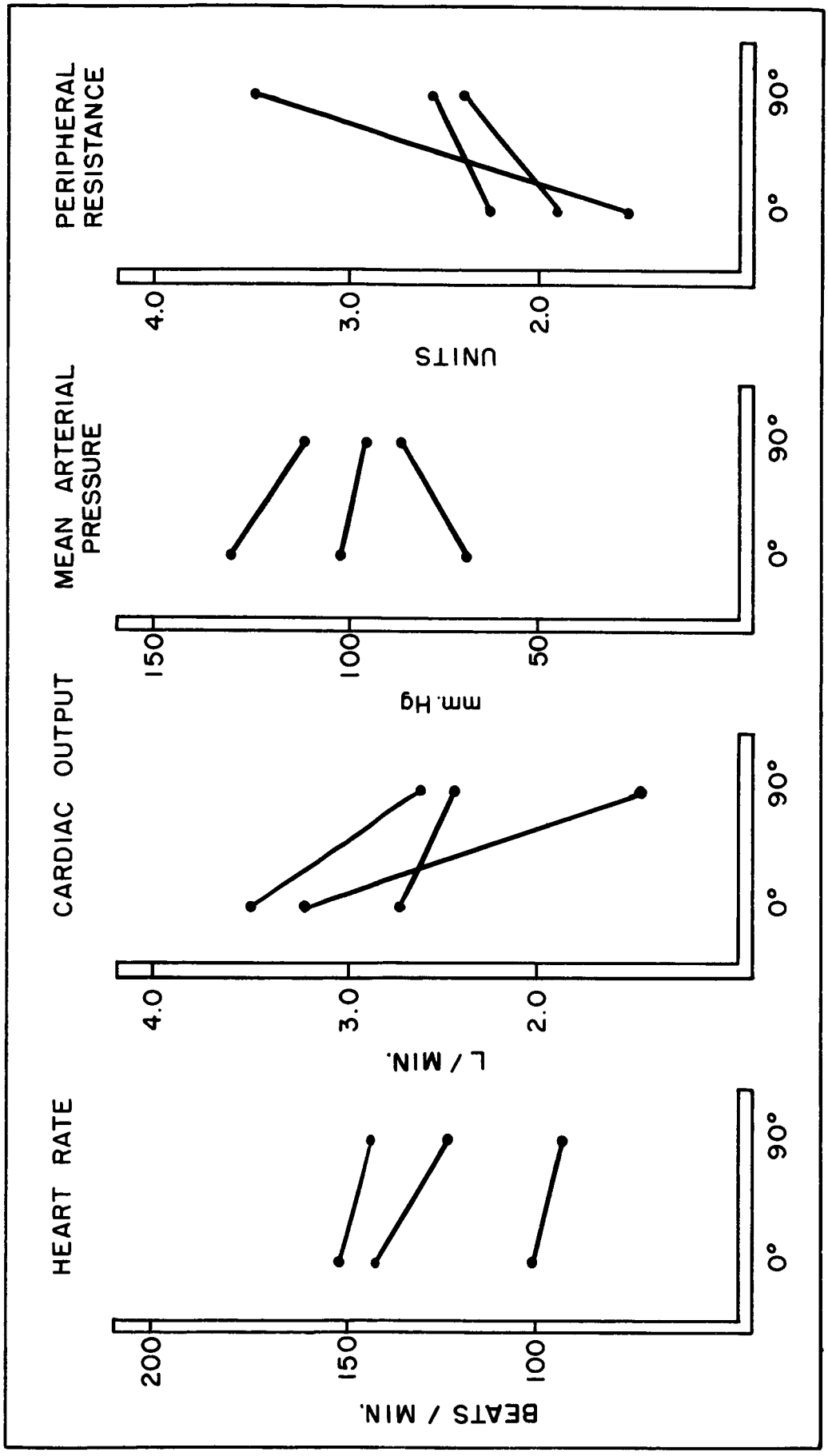

Fig. 3.

HEMODYNAMIC EFFECTS OF HEAD-UP TILT WITH GANGLIONIC BLOCKADE

Two "receptor sites", designated alpha and beta, for the action of catecholamines have been postulated. Stimulation of the beta receptors by catecholamines results in cardiac acceleration and increased force of contraction accompanied by arterial dilatation. Stimulation of the alpha type receptors causes peripheral vasoconstriction without direct action on the heart (8). The drug nethalide blocks beta receptors without blocking the alpha receptors. When this agent was given to the chimpanzee a fall in cardiac output and heart rate quite similar to that induced by ganglionic blockade resulted. However, blood pressure did not change significantly and peripheral resistance tended to rise. These data confirm the presence of a high level of beta adrenergic stimulation of the heart in the chimpanzee, when studied under the conditions of this experiment.

The alpha receptors may be blocked by the agents phentolamine phenoxybenzamine without an affect upon beta receptors (5). In our studies, such blockade resulted in no consistent change in cardiac output, while the blood pressure fell quite markedly. The elevated heart rate which occurred in these animals may be a reflex cardioaccelerator response to the fall in peripheral resistance or could be due to the action of catecholamines which are released from the adrenergic nerve endings (9, 10). The latter possibility was investigated by giving nethalide or propranolol to three animals during alpha adrenergic blockade. The induction of beta blockade in combination with alpha blockade resulted in a decrease in the heart rate response. This suggests that the tachycardia may have been induced by compensatory catecholamine release or sympathetic beta receptor stimulation of the heart. The cardioaccelerator response to alpha adrenergic blockade persisted in two out of three animals who had received atropine, indicating this is probably not a parasympatholytic-mediated tachycardia.

The action of these blocking agents (ganglionic, alpha adrenergic and beta adrenergic) would indicate that a significant amount of sympathetic-adrenergic stimulation of the circulation is present in this species at rest. Although atropine caused a relative tachycardia, the response to ganglionic blockade was a decrease in heart rate, confirming the predominance of sympathetic activity. The data were not obtained in obviously aroused animals, and great care was taken to maintain them in a quiescent state. Indeed, the subjects often appeared to be sleeping at the time of observations. While these data cannot be interpreted as reflecting the "natural" or truly "basal" state of the animals, the evidence for adrenergic activity is unequivocal.

Data are lacking regarding the level of adrenergic, circulatory stimulation present in most other species except man. Certain contrasts and similarities between man and chimpanzee are noteworthy in this regard. In normal man ganglionic blockade causes an increase in heart rate with little decrease in cardiac output (11, 12). Blood pressure falls in both species. These observations suggest that the parasympathetic system is dominant in heart rate control in resting man while the sympathetic system prevails in the chimpanzee. The difference in effect of ganglionic blockade on cardiac output may be related to varying degrees of venous pooling in the two species as well as to differing levels of sympathetic activity. Recent data show a qualitatively similar response to beta adrenergic blockade in man when compared to the data for the chimpanzee reported here (13). In both species heart rate slows, cardiac output falls and arterial pressure is unchanged. The degree of change in heart rate and cardiac output is greater in the chimpanzee. The effects of alpha adrenergic blockade are also qualitatively similar in the two species, with a larger relative decrease in arterial pressure in the chimpanzee. Thus, it would appear that sympathetic-adrenergic activity plays an active role in control of the resting circulation in both man and chimpanzee; the level of such activity being clearly greater in the lower order primate.

Since primates and other species have been proposed as suitable biological analogues for the circulation of the human, data relative to "basal" levels of adrenergic activity are needed before appropriate conclusions can be drawn from such studies. Such studies would also be of value in the area of comparative physiology. Slow or fast heart rates seem to be typical of certain phylogenetic groups (14). The adrenergic receptor system could be the determinant of these characteristics. Studies similar to the present one would yield data illuminating this hypothesis.

During ganglionic and alpha adrenergic blockade the chimpanzee was able to maintain pressures adequate for cerebral perfusion for periods of ninety degree tilt lasting as long as 20 to 30 minutes, despite a marked decrease in cardiac output. The animals were studied during periods of apparent muscular inactivity so that exertion did not seem to contribute to the preservation of arterial pressure. Such manuvers with human subjects during ganglionic or alpha receptor blockade would result in a rapid fall in arterial pressure and syncope (15, 16). These data suggest an autoregulatory mechanism for control of arterial resistance in this species independent of the autonomic or adrenergic systems. Future studies of this non-adrenergic mechanism in this species might lend further insight into systems of circulatory control.

REFERENCES

1. Weissler, A. M., Schoenfeld, C. D., Carter, V. L., Cohen, S., Stilson, A. E., Jr., and Warren, J. V. The effects of psychomotor arousal, hemorrhage, and the upright posture on the circulation of the young chimpanzee. Technical Report No. ARL-TDR-63-28, Holloman AFB, NMexico, 1963.

2. Randall, L. O., Peterson, W. G., and Lehmann, G. "The ganglionic blocking action of thiophanium derivatives." J. Pharmacol. Exp. Ther. 97:48, 1949.

3. McCubbin, J. W. and Page, I. H. "Nature of the hypotensive action of thiophanium derivative (RO2-2222) in dogs." J. Pharmacol. Exp. Ther. 105:437, 1952.

4. Black, J. W., and Stephenson, J. S. "Pharmacology of a new adrenergic beta-receptor blocking compound (nethalide)." Lancet 2:311, 1962.

5. Moran, N. C. and Perkins, M. E. "An evaluation of adrenergic blockade of the mammalian heart." J. Pharmacol. Exp. Ther. 133:192, 1961.

6. Frye, R. L. and Braunwald, E. "Studies on Starling's law of the heart. I. The circulatory response to acute hypervolemia and its modification by ganglionic blockade." J. Clin. Invest. 39:1043, 1960.

7. Hickler, R. B., Wells, R. E., Jr., Tyler, H. R., and Hamlin, J. T. "Plasma catecholamine and electroencephalographic responses to acute postural change." Amer. J. Med. 26:410, 1959.

8. Ahlquist, R. P. "A study of the adrenotropic receptors." Am. J. Physiol. 153:586, 1948.

9. Millar, R. A., Keener, E. B., and Benfey, B. G. "Plasma adrenaline and noradrenaline after phenoxybenzamine administration, and during haemorrhagic hypotension, in normal and adrenalectomized dogs." Brit. J. Pharmacol. 14:9, 1959.

10. Benfey, B. G., Ledoux, G., and Segal, M. "The action of anti-sympathomimetic drugs on the urinary excretion of adrenaline and noreadrenaline." Brit. J. Pharmacol. 14:380, 1959.

11. Assali, N.S., Douglass, R.A., Jr., and Suyemoto, R. "Observations on the hemodynamic properties of a thiophanium derivative, RO 2-2222, (Arfonad), in human subjects." Circulation 8:62, 1953.

12. Freis, E.D., Rose, J.C., Higgins, T.F., Kelley, R.T., Schnaper, H.W., and Johnson, R.L. "The hemodynamic effects of hexamethonium in man." (abstract) J. Clin. Invest. 31:629, 1952.

13. Harris, W.S., Schoenfeld, C.D., Brooks, R.H. and Weissler, A.M. Effects of beta adrenergic blockade on the hemodynamic responses to epinephrine in man. Submitted for publication.

14. Spector, W.S., Handbook of Biological Data, W.B. Saunders Company, Philadelphia, 1956, p. 279.

15. O'Donnel, T.V. "Studies in postural hypotension following ganglionic blocking drugs." Clin. Sci. 18:237, 1959.

16. Freis, E.D., Stanton, J.R., Finnerty, F.A., Jr., Schnaper, H.W., Johnson, R.L., Rath, C.E. and Wilkins, R.W. "The collapse produced by venous congestion of the extremities or by venesection following certain hypotensive agents." J. Clin. Invest. 30:435, 1951.

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In the present studies the role of the autonomic nervous system in circulatory control in young chimpanzees was evaluated through the use of selected autonomic blocking agents. Ganglionic blockade resulted in decreases in cardiac output, heart rate and arterial pressure. Beta adrenergic blockade resulted in similar decreases in cardiac output and heart rate, while arterial pressure was unchanged. Alpha adrenergic blockade caused a decrease in arterial pressure and peripheral resistance. Heart rate rose and cardiac output showed no consistent change following alpha adrenergic blockade.

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