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CEREBRAL HEMODYNAMICS DURING CONTROLLED HYPOTENSION INDUCED BY THE CONTINUOUS INFUSION OF GANGLIONIC BLOCKING AGENTS (HEXAMETHONIUM, PENDIOMIDE AND ARFONAD)

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Research Article

CEREBRAL HEMODYNAMICS DURING CONTROLLED HYPOTENSION INDUCED BY THE CONTINUOUS INFUSION OF GANGLIONIC BLOCKING AGENTS (HEXAMETHONIUM, PENDIOMIDE AND ARFONAD) [1]

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Although the acute cerebral hemodynamic response to blood pressure elevation has been studied in normal man (1), there is very little information regarding the effect upon cerebral hemodynamics of reduction in blood pressure to hypotensive ranges. A moderate reduction in the systemic blood pressure appears to have very little effect on the cerebral circulation (2). However, when the blood pressure is markedly reduced one would anticipate that compensatory vasodilation of the cerebral vessels may be exceeded. Accordingly, the primary purpose of the current study was an estimation of the effect on the cerebral circulation of reduction in blood pressure produced by ganglionic blocking agents. An attempt was made to determine the critical level of reduction in arterial blood pressure beyond which further depression might produce cerebral ischemia and cerebral hypoxia. An estimation of this type is especially indicated because of the current use of controlled hypotension for some surgical procedures. The observations on the cerebral circulation in the current study were made on unanesthetized subjects in whom the blood pressure was reduced by continuous infusion of hexamethonium,[2] Pendiomide,[3] or Arfonad,[4] all of which are ganglionic blocking agents.

[1] This work was supported in part by grants from the Medical Research and Development Board, Office of the Surgeon General, Department of the Army under contract number DA-49-007-MD-314, and the Houston Heart Association.

[2] Supplied through the courtesy of Burroughs Wellcome & Co. as Hexameton, and Warner-Chilcott as Methium.

[3] Pentamethyl-diethyl-3-aza-pentane-1, 5 diammonium dibromide, supplied through the courtesy of Ciba Pharmaceutical Products as Pendiomide.

[4] D-3 4(1′, 3″-dibenzyl-2′ keto-immdizalido)-1,2,-trimethylene thiophanium d-camphor sulfonate, supplied through the courtesy of Hoffman-LaRoche as Arfonad.

METHODS

Observations on cerebral hemodynamics were made on 19 normal individuals using the nitrous oxide technique (3, 4) for estimating cerebral blood flow. The patients were divided into three groups. There were eight patients in group A who received hexamethonium, five patients in group B who received Pendiomide and six patients in group C who received Arfonad. The subjects were unanesthetized in order that obvious disturbances in cerebration could be detected should they occur when the blood pressure was reduced. All but one of the patients (No. 9) had normal arterial blood pressure at the time the studies were performed. The exception was a patient with labile hypertension whose blood pressure increased under stress, but was normal most of the time. Several additional patients showed a slight increase in systolic pressure at the time of the study, probably a result of the apprehension associated with the carrying out of the procedure. After suitable control observations (supine position) the blood pressure was reduced by administering one of the ganglionic blocking agents (hexamethonium,[2] Pendiomide[3] or Arfonad[4]). The cerebral blood flow studies were repeated after the desired reduction in arterial blood pressure had been obtained and the blood pressure had remained stable for 30 to 60 minutes. In patients who were particularly sensitive to any of the agents, an effort was made not to reduce the mean arterial blood pressure below 50 mm. Hg because of possible deleterious effects on the patient. The blood pressure was determined by simultaneous direct intra-arterial manometry and by auscultation and a mercury sphygmomanometer. The drugs were administered by continuous intravenous infusion using a concentration of hexamethonium and Pendiomide of 0.5 to 2 mg. per cc. of solution and of Arfonad of 4 mg. per cc. of solution in 5 per cent glucose in distilled water. The hexamethonium was given at the rate of 2 to 8 mg. per minute depending on the degree of reduction in arterial blood pressure that was attained. One patient who was relatively unresponsive to hexamethonium was given the drug at a rate of 8 mg. per minute for a total of 750 mg. Pendiomide was given at the rate of 3 to 6 mg. per minute. Usually a "floor" in the blood pressure was reached with both hexamethonium and Pendiomide and it was difficult to lower the pressure much farther. However, if the infusion was entirely discontinued the blood pressure usually rose 10 mm. Hg or

TABLE I

Cerebral hemodynamic response to blood pressure reduction with hexamethonium, Pendiomide or Arfonad *

Patient	Auscultatory blood pressure: Control Syst.	Control Diast.	Drug Syst.	Drug Diast.	Mean blood pressure: C	D	DT	Cerebral blood flow: C	D	DT	Cerebrovascular resistance: C	D	DT	Cerebral O_2 uptake: C	D	DT	Dose mg./min.	Total dose† milligrams
Group A. Response to hexamethonium																		
1	147	85	80	50	101	53	63	54	34	36	1.9	1.6	1.8	3.6	2.9	2.5	4	275
2	120	80	68	50	96	54	61	56	40	40	1.7	1.4	1.5	2.8	3.1	2.3	4	300
3	100	60	70	46	76	56	57	52	47	50	1.5	1.2	1.1	2.5	2.7	2.4	2	90
4	142	85	100	78	100	80	—	69	58	—	1.5	1.4	—	3.0	2.6	—	8	750
5	128	90	73	55	104	60	—	75	36	—	1.4	1.7	—	4.1	3.3	—	2	60
6	140	80	96	56	98	66	—	50	38	—	2.0	1.7	—	2.6	2.4	—	4	245
7	140	100	100	60	111	66	—	51	36	—	2.2	1.8	—	2.9	2.7	—	3	275
8	145	90	90	54	108	61	—	52	44	—	2.1	1.4	—	4.1	3.7	—	3	80
Mean	133	84	85	56	99	62	60	57	42	42	1.8	1.5	1.5	3.2	2.9	2.4		
P Value						<0.01			<0.01			<0.05			<0.3			
Mean per cent‡ of control			64	68		63	67		73	78		87	85		93	82		
Group B. Response to Pendiomide																		
9	178	100	70	48	122	54	63	46	42	46	2.7	1.3	1.4	2.8	3.2	3.4	3	100
10	116	70	80	50	94	54	58	51	45	60	1.8	1.2	1.0	2.3	2.4	3.0	5	700
11	130	66	98	56	90	65	72	57	60	62	1.6	1.1	1.2	2.5	2.9	3.3	6	500
12	120	70	90	66	84	72	81	50	38	40	1.7	1.9	2.0	3.3	3.1	3.2	6	350
13	136	90	84	54	111	60	—	49	51	—	2.3	1.2	—	2.9	3.2	—	5	500
Mean	136	79	84	55	100	61	69	51	47	52	2.0	1.3	1.4	2.8	3.0	3.2		
P Value						<0.01			<0.4			<0.05			<0.4			
Mean per cent‡ of control			64	72		63	73		93	102		70	75		108	120		
Group C. Response to Arfonad																		
14	116	70	60	40	92	48	46	51	34	30	1.8	1.4	1.5	3.5	2.4	2.5	5	300
15	120	78	70	46	94	44	42	41	25	27	2.3	1.8	1.6	2.9	2.6	2.0	9	800
16	140	92	78	50	110	58	47	48	35	48	2.3	1.7	1.0	2.5	2.7	2.4	9	650
17	112	80	92	60	96	75	—	58	38	—	1.7	2.0	—	2.8	2.9	—	21	1,500
18	130	86	92	64	106	66	—	73	56	—	1.5	1.2	—	4.1	4.1	—	6	500
19	132	90	70	52	96	52	—	40	25	—	2.4	2.1	—	2.6	2.0	—	4	225
Mean	125	83	77	52	99	57	45	52	36	35	2.0	1.7	1.4	3.1	2.8	2.3		
P Value						<0.01			<0.05			<0.2			<0.50			
Mean per cent‡ of control			62	63		58	46		68	75		86	65		91	79		
Mean Value, Groups A, B, and C	131	82	82	54	99	60	59	54	41	44§	1.9	1.5	1.4	3.0	2.9	2.7		
Mean per cent of control,‡ Groups A, B, C (19 patients)			63	67		61	63		77	87		82	75		96	96		
P Value (19 patients, Groups A, B, and C)						<0.01			<0.01	§		<0.01			<0.3			

* Mean blood pressure (mm. Hg) = direct arterial manometry; Cerebral blood flow = cc./100 Gm. brain/minute; Cerebral vascular resistance = mean blood pressure/cerebral blood flow; Cerebral O_2 Uptake = cc./100 Gm. brain/minute; C, D, and DT = See Table II for key to abbreviations.

† Includes all patients who received ganglionic blocking agents (hexamethonium, Pendiomide, or Arfonad).

‡ Mean value for per cent of control observations of individual studies.

§ Increase in cerebral blood flow due to head down tilt was not statistically significant, $P < 0.2$.

more within a few minutes. When the infusion was then started again the pressure could be depressed nearly to the previous levels, indicating that the rate of infusion exerted some effect (although small) on the degree of reduction in blood pressure after ganglionic blockade was fairly well established. Since the hypotensive response to Arfonad was more marked and the duration of action relatively short as compared to hexamethonium and Pendiomide, the rate of infusion was more closely related to the hypotensive response. Somewhat larger doses of this drug were used than in the cases of hexamethonium and Pendiomide. The rate of infusion of Arfonad varied from 4 to 21 mg. per minute. After maximum blood pressure reduction was attained with these agents the concentration of nitrous oxide in the jugular venous blood failed to approximate the concentration of nitrous oxide in the arterial blood within the usual 10 minutes. Therefore, it was necessary to continue the inhalation of nitrous oxide and sampling procedures for 20 minutes in order to obtain dependable determinations.

Following the observations in the horizontally supine position the infusion of the blocking agent was continued in some of the patients in each group and they were placed in a 30 degree head down tilted supine position. The manometer was adjusted to the level of the carotid artery, and was connected in such a way that it automatically corrected for the difference in elevation between the femoral artery and the carotid artery. After the arterial blood pressure had stabilized in this position, determinations of cerebral blood flow were again made. Seven of the patients who were not tilted were given a

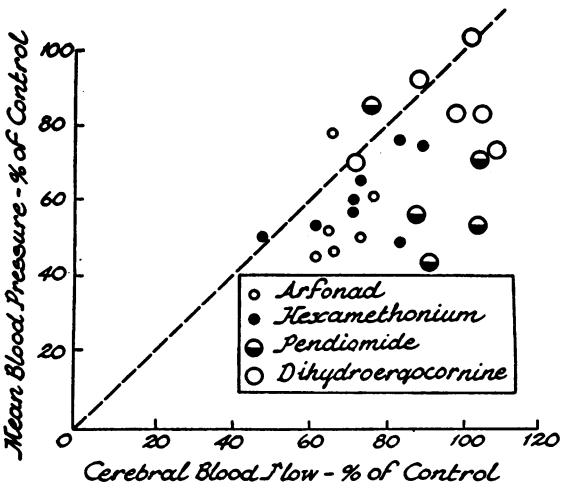

FIG. 1. CEREBRAL BLOOD FLOW FOLLOWING THE BLOCKING AGENTS (HEXAMETHONIUM, PENDIOMIDE, ARFONAD, AND DIHYDROERGOCORNINE) EXPRESSED IN PER CENT OF CONTROL AND PLOTTED AGAINST MEAN BLOOD PRESSURE EXPRESSED IN THE SAME MANNER

Cerebral blood flow is not depressed to the same degree as the mean blood pressure is and the pattern of response appears quite erratic. (Data on Dihydroergocornine taken from Hafkenschiel, Crumpton, and Moyer (2).)

vasopressor agent (nor-epinephrine or Aramine[5]) by continuous intravenous infusion in order to raise the blood pressure back to control levels or above. The rate of infusion of the blocking agent was not altered. Determinations of cerebral blood flow were then repeated. This offered additional information regarding the effect of reduction in blood pressure on cerebral hemodynamics as compared to any effect that the blocking agent might exert directly on the cerebral vessels.

RESULTS

There was a consistent reduction in mean blood pressure (P less than 0.01) in all patients. The rate of infusion was quite variable, and the total amount of drug employed if compared to the dog (5, 6) would have produced complete vagal ganglionic blockade with all three of the blocking agents. After the initial reduction in blood pressure was obtained, a "floor" was reached beyond which the pressure could not be lowered much farther regardless of the rate of infusion. If the initial rate of infusion was quite rapid the pressure was re-

[5] 'Aramine'; levo 1-(m-hydroxyphenyl)-2-amino-1- propanol.

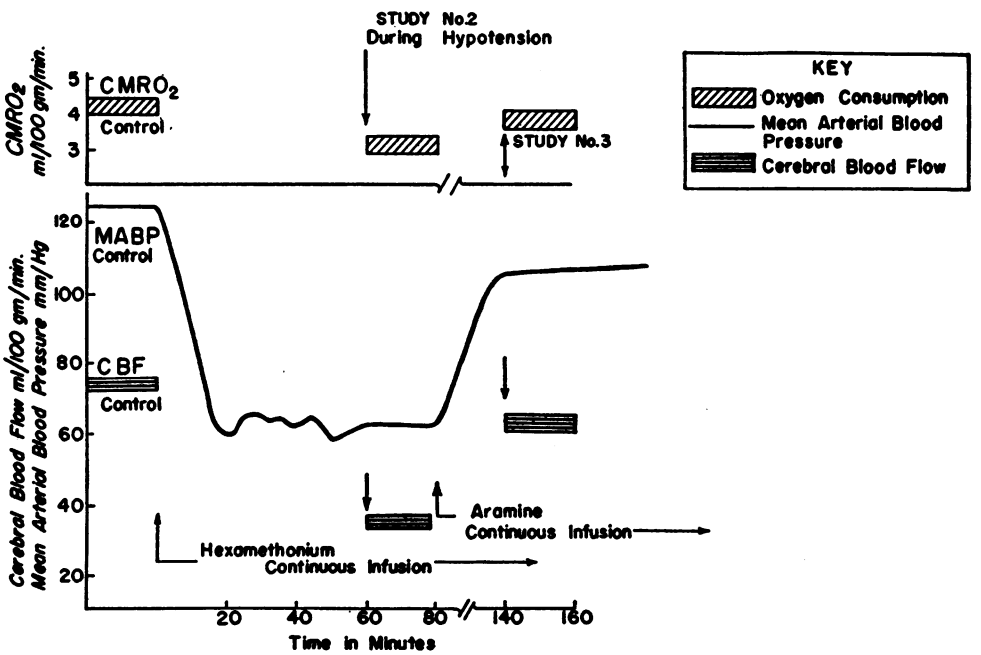

FIG. 2. THE EFFECT ON BLOOD PRESSURE (MABP) PLOTTED, ALONG WITH CEREBRAL OXYGEN CONSUMPTION ($CMRO_2$) AND CEREBRAL BLOOD-FLOW (CBF)

All are depressed following the establishment of ganglionic blockade with hexamethonium. However, when the blood pressure is elevated with an infusion of Aramine, cerebral blood flow and $CMRO_2$ increase towards the control value.

TABLE II

Effect of blood pressure reduction on cerebral blood oxygen and carbon dioxide *

Patient	Arterial O_2 *volume per cent*			Venous O_2 *volume per cent*			Cerebral arterial-venous O_2 difference *volume per cent*			Arterial CO_2 *volume per cent*			Venous CO_2 *volume per cent*			Arterial P CO_2		
	C	D	DT	C	D	DT	C	D	DT	C	D	DT	C	D	DT	C	D	DT
Group A. Response to hexamethonium																		
1	17.7	16.3	16.3	11.0	7.9	9.4	6.7	8.4	6.9	44.5	43.0	44.0	52.5	53.4	52.5	40	43	44
2	14.1	13.9	14.1	9.1	6.1	8.3	5.0	7.8	5.8	45.1	43.4	45.5	49.3	51.5	53.0	46	38	40
3	13.4	12.9	13.1	8.6	7.2	8.3	4.8	5.7	4.8	43.3	43.0	43.5	47.6	48.6	49.4	34	35	32
4	14.1	13.7	—	9.8	9.2	—	4.3	4.5	—	43.6	45.5	—	47.5	50.3	—	33	35	—
5	17.0	16.5	—	11.6	7.4	—	5.4	9.1	—	42.0	41.5	—	48.0	49.7	—	45	38	—
6	15.9	14.7	—	10.7	8.5	—	5.2	6.2	—	45.3	46.1	—	51.2	53.0	—	49	41	—
7	17.4	16.6	—	11.7	9.2	—	5.7	7.4	—	37.2	40.0	—	43.4	46.1	—	41	44	—
8	17.6	15.5	—	9.7	7.1	—	7.9	8.4	—	36.6	38.6	—	44.6	45.5	—	40	45	—
Mean	15.9	15.0	14.5	10.3	7.8	8.7	5.6	7.2	5.8	42.2	42.6	44.3	48.0	49.8	51.6	41	40	39
P Value		<0.3			<0.01			<0.05			<0.5			<0.3			<0.5	
Mean per cent of control†		95	97		76	91		129	106		101	100		104	104		98	97
Group B. Response to Pendiomide																		
9	15.9	14.3	15.0	9.7	6.6	7.7	6.2	7.7	7.3	47.9	48.4	48.4	53.0	53.9	55.3	43	42	39
10	18.3	17.9	17.1	13.8	12.6	12.1	4.5	5.3	5.0	41.1	42.3	42.0	45.6	47.1	46.8	43	45	45
11	14.4	14.2	13.6	10.1	9.4	8.2	4.3	4.8	5.4	44.6	46.1	45.5	49.4	50.2	50.0	33	33	33
12	18.2	18.2	17.7	11.7	10.1	9.6	6.5	8.1	8.1	38.1	38.4	37.1	44.3	45.0	45.5	38	39	39
13	15.1	13.4	—	9.1	7.2	—	6.0	6.2	—	41.2	42.5	—	46.9	49.1	—	42	44	—
Mean	16.4	15.6	15.9	10.9	9.2	9.4	5.5	6.4	6.5	42.6	43.5	43.3	47.8	49.1	49.4	40	41	39
P Value		<0.5			<0.3			<0.3			—			<0.5			—	
Mean per cent of control†		95	95		84	83		116	120		102	101		103	103		102	100
Group C. Response to Arfonad																		
14	13.8	12.1	12.6	7.0	5.1	4.4	6.8	7.0	8.2	46.9	49.3	44.5	52.6	55.1	52.0	38	41	36
15	16.2	15.7	15.7	9.2	5.6	8.4	7.0	10.2	7.3	43.6	43.1	45.4	49.5	52.9	53.9	35	35	36
16	14.1	15.9	14.5	8.9	8.2	9.4	5.2	7.7	5.1	45.2	40.0	46.4	50.0	47.6	52.5	33	28	34
17	16.4	18.6	—	11.6	10.9	—	4.8	7.7	—	42.3	43.6	—	46.6	51.3	—	41	49	—
18	15.9	16.4	—	10.3	9.1	—	5.6	7.3	—	46.4	51.6	—	52.7	58.1	—	42	48	—
19	20.0	18.3	—	13.6	10.3	—	6.4	8.0	—	41.3	43.8	—	47.0	51.2	—	43	47	—
Mean	16.1	16.2	14.3	10.1	8.2	7.4	6.0	8.0	6.9	44.3	45.2	45.4	49.7	52.7	52.8	39	41	35
P Value		>0.5			<0.20			<0.01			>0.5			<0.2			<0.5	
Mean per cent of control†		101	97		81	87		135	108		102	101		106	104		106	100
Mean Value, Groups A, B, and C	16.1	15.5	15.0	10.4	8.3	8.6	5.7	7.2	6.4	43.0	43.7	44.2	48.5	50.5	51.1	40	41	38
Mean per cent of control,† Groups A, B, and C		97	96		80	86		127	112		102	101		104	104		102	99
P Value (19 patients), Groups A, B, and C		<0.4			<0.01			<0.01			—			<0.10			—	

* C = Control; D = After blood pressure reduction with ganglionic blocking agent; DT = Thirty degree head down tilt during continuous infusion of blocking agent; P CO_2 = Partial pressure of carbon dioxide.

† Mean value for per cent of control observations of individual studies.

duced farther and could be maintained at a lower level than if the drug was given more slowly during the initial infusion. This type of response was particularly marked with Arfonad. Although the blood volume is not greatly altered with these hypotensive agents (7), the taking of as little as 15 to 20 cc. samples of blood would frequently cause a sharp reduction in blood pressure which persisted for 5 to 20 minutes. The explanation of this response to the taking of such small amounts of blood is not obvious to the authors.

When the mean blood pressure, determined by direct arterial mercury manometry, is compared to the auscultatory pressure there is usually a parallel reduction. However, at lower levels of pressure, the mean blood pressure which was determined manometrically occasionally approached the auscultatory diastolic pressure. This should be considered when only auscultatory observations on blood pressure are taken during surgical procedures employing controlled hypotension.

The blood pressure frequently did not increase significantly when the patient was placed in a 30 degree head down tilted position. In the three patients receiving Arfonad there was no increase after head down tilt perhaps a reflection of the greater degree of vasodilatation in these patients. The ganglionic blocking agents were administered

at the same rate in the tilted position as they were in the horizontal position, thus maintaining equivalent degrees of ganglionic blockade.

In the horizontally supine position, the cerebral blood flow was depressed (Groups A, B, & C) following the reduction in blood pressure in 17 out of 19 subjects, (P less than 0.01) but the change was usually not marked. Percentagewise the reduction in cerebral blood flow was not as marked as the reduction in mean blood pressure (Figure 1). Presumably, when the blood pressure is only slightly reduced initial vasodilatation is adequate (2). However, at lower levels of blood pressure, compensatory vasodilatation is insufficient to maintain the cerebral blood flow.

As the blood pressure was reduced, the oxygen was extracted more completely from the blood flowing through the brain. As a result, the jugular blood oxygen content was reduced (Table II) (P less than 0.01). This compensation (increased oxygen extraction) was not always adequate, and there was a general tendency for cerebral oxygen consumption ($CMRO_2$) to decrease. However, there were only four patients in whom the cerebral oxygen uptake per minute was reduced more than 0.5 cc. In all of these patients, the blood pressure was reduced to 60 mm. Hg or below. The reduction in $CMRO_2$ for 19 patients was not statistically significant (P less than 0.3).

There was no effect on the blood carbon dioxide except that the carbon dioxide content of jugular blood increased slightly (P less than 0.10). Partial pressure of carbon dioxide in arterial blood was not altered (Table II). The blood (arterial and venous) pH's were not altered significantly. For example, the mean arterial pH's for hexamethonium and Pendiomide during the control periods were 7.47 and 7.47, respectively, and were 7.50 and 7.46 after the drugs. The pH's were not altered by the head down tilt. The average venous pH's for hexamethonium and Pendiomide were 7.40 and 7.41, respectively, before the drug and 7.41 and 7.41 after it. After the tilt the pH's were 7.42 and 7.41, respectively. As with hexamethonium and Pendiomide, the arterial and venous blood pH's were not altered significantly by the administration of Arfonad.

Generally, the subjective manifestations for the

TABLE III

Side reactions to hexamethonium, Pendiomide and Arfonad and the effect on the respiratory rate, pulse rate, and hematocrit

Patient	Respiratory rate			Pulse rate			Hematocrit			Side effects during maximum hypotension
	C*	D*	DT*	C	D	DT	C	D	DT	
				Group A.		*Response to hexamethonium*				
1	15	17	16	72	90	92	43	43	43	Restless
2	22	20	24	101	89	92	45	41	40	Marked apprehension—improved on tilt
3	11	13	14	114	96	98	40	37	35	Felt chilly
4	18	18	—	88	90	—	38	36	—	Stuffy nose
5	23	19	—	112	130	—	50	47	—	Restless
6	18	16	—	80	78	—	30	31	—	None
7	14	17	—	80	76	—	49	48	—	Irregular respirations
8	24	22	—	88	68	—	41	40	—	None
				Group B.		*Response to Pendiomide*				
9	19	19	17	111	115	115	34	36	35	Irregular respirations, lethargy
10	28	25	27	89	93	89	37	37	38	Restless, cerebral symptoms, lethargy—improved on tilt
11	17	18	19	76	96	88	40	40	40	None
12	20	18	19	84	82	80	38	38	37	None
13	21	19	—	117	106	—	45	40	—	None
				Group C.		*Response to Arfonad*				
14	21	20	19	84	91	92	43	44	42	Dizzy, disoriented, nausea
15	20	21	21	81	90	85	45	42	43	Restless, vomited
16	22	21	20	84	87	81	41	41	41	None
17	18	16	18	59	66	67	50	50	50	None
18	21	21	—	84	85	—	45	44	—	Restless
19	22	20	—	84	84	—	50	49	—	Dizzy, restless, nausea, confused

* C = Control observations.
D = After blood pressure reduction with blocking agent.
DT = Observation with thirty degree head down tilt while receiving blocking agent.

patients in this study more or less paralleled the observations on cerebral blood flow and cerebral oxygen consumption ($CMRO_2$). Signs of cerebral hypoxia (restlessness, dizziness, syncope, disorientation) were not significant except in some of the patients in whom the mean arterial blood pressure approached 55 mm. Hg or fell below this level. The mean arterial blood pressure was reduced to 48 and 52 mm. Hg, respectively in the two patients (numbers 14 and 19) who became disoriented. However, in another patient (number 15) the mean blood pressure was reduced to 44 mm. Hg without producing disorientation, but this patient became nauseated and vomited. It appears that when the mean pressure was reduced below 55 to 60 mm. Hg the ability of the cerebral circulation to adjust adequately for the prevention of hypoxia was unpredictable. The response to Arfonad (Tables I and II) was essentially the same as to hexamethonium and Pendiomide except that the degree of reduction in blood pressure with Arfonad was slightly greater than with the latter agents. Consequently signs of hypoxia were more frequently encountered when the blood pressure was reduced with Arfonad. Symptoms of hypoxia which were associated with the reduction in blood pressure improved when the head was tilted down despite the fact that the observations did not indicate a significant increase either in cerebral blood flow or in cerebral oxygen uptake.

The effect on cerebral hemodynamics of raising the blood pressure from hypotensive to normotensive levels with Aramine or nor-epinephrine is demonstrated in Table IV. The mean arterial blood pressure increases more than cerebrovascular resistance. As a result, cerebral blood flow increases. At the same time the $A–VO_2$ difference decreases and cerebral oxygen consumption increases slightly.

COMMENTS

It appears that normotensive patients are consistently able to prevent cerebral hypoxia by a combination of vasodilation and increased extraction of oxygen from the blood when the blood pressure is not reduced below a mean pressure of about 55 to 60 mm. Hg. A number of patients (but not all) will even be able to adjust to blood pressure levels below 55 to 60 mm. Hg but it is unpredictable whether or not the compensatory adjustments will be adequate to prevent hypoxia. It is obvious in Figure 1 that there is no direct relationship between cerebral blood flow and mean arterial blood pressure. Initially, vasodilatation is nearly complete as was seen with Dihydroergocornine (2) in Figure 1. However, as the blood pressure was reduced farther, cerebral blood flow was depressed. When the mean blood pressure fell below approximately 55 to 60 mm. Hg cerebral oxygen uptake was also depressed in some patients. Although maximum vasodilatation may have occurred in these patients, it would appear that the brain is able to extract oxygen more completely (when the cerebral arterial blood pressure is adequate)

TABLE IV

Observations on cerebral oxygen metabolism and cerebral hemodynamic response to blood pressure elevation with vasopressor agent following initial hypertension due to ganglionic blockade

Patient	Ganglionic blocking agent	Vasopressor agent	Mean blood pressure (*mm. Hg*)			Cerebral blood flow*			Cerebro-vascular resistance*			Cerebral oxygen consumption*			Arterial-venous oxygen*		
			C§	D§	V§	C	D	V	C	D	V	C	D	V	C	D	V
3	Hexamethonium	Norepinephrine	100	80	140	69	58	65	1.5	1.4	2.2	3.0	2.6	3.4	4.3	4.5	5.2
5	Hexamethonium	Aramine	104	61	105	75	36	65	1.4	1.7	1.6	4.1	3.3	4.0	5.4	9.1	6.1
6	Hexamethonium	Aramine	98	66	118	49	36	64	2.0	1.7	1.8	2.6	2.4	2.9	5.2	6.2	4.5
8	Hexamethonium	Aramine	108	61	120	52	44	56	2.1	1.4	2.1	4.1	3.7	3.8	7.9	8.4	6.7
13†	Pendiomide	Norepinephrine	111	66	110	49	51	53	2.3	1.2	2.1	2.9	3.2	3.0	6.0	6.2	5.7
17‡	Arfonad	Norepinephrine	96	75	105	58	38	51	1.7	2.0	2.1	2.8	2.9	3.2	4.8	7.7	6.3
19	Arfonad	Norepinephrine	96	52	120	40	25	36	2.4	2.1	3.3	2.6	2.0	2.4	6.4	8.0	6.6

* See Table IA for methods of measurement.

† When blood pressure increased from 110 to 145 the cerebral blood flow decreased to 38 and the arterial-venous oxygen increased to 3.4 volume per cent.

‡ When blood pressure increased from 105 to 155, the cerebral blood flow decreased to 49 and the arterial-venous oxygen increased to 6.1 to 6.3.

§ C—Control observations. D—Observations after blood pressure reduction with ganglionic blocking agent. V—Observations after blood pressure elevation with vasopressor agent.

from the blood flowing through it, as has been previously demonstrated under conditions of hyperventilation (8) and after the administration of Aminophylline (9). The failure of more complete extraction of oxygen in the current study may be due in part to inadequate perfusion of plasma and oxygen through the capillary walls at these reduced blood pressure levels.

The reduction in cerebral blood flow appears to be related to the degree of blood pressure reduction rather than to the blocking agent employed. Since Arfonad is the most potent of the ganglionic blocking agents used one can expect to approach or pass below this critical level more frequently with this agent than with hexamethonium or Pendiomide if maximum blood pressure reduction is employed. Henry, Gauer, Kety, and Kramer (10) concluded that under conditions of gravitational stress, unconsciousness was not lost until the mean arterial blood pressure approached 25 mm. Hg. This is probably related to their method for lowering the blood pressure (positive acceleration) and the conclusions are hardly applicable to the current study. Scheinberg and Stead (11) observed that when the mean cerebral arterial pressure was reduced from 84 to 55 mm. Hg by changing from the supine to the upright position, there was a significant reduction in cerebral blood flow. This is in essential agreement with the current observations.

Cerebral vasoconstrictor tone is probably not affected directly by blockade of the sympathetic ganglia because procaine blockade of the superior cervical ganglia (12, 13) fails to increase cerebral blood flow. Since cerebral blood flow is most likely regulated by autonomous regulatory mechanisms at the local tissue level, the depression in cerebral blood flow which occurs during hypotension is merely a reflection of inadequate hydrostatic pressure. In the current study, when a vasoconstrictor agent was administered and the blood pressure raised from hypotensive levels to normotensive ones, the cerebral blood flow increased. The increase in cerebral blood flow which occurs under these conditions is in direct contrast to the cerebrovascular response to these same pressor agents (14) when administered to normotensive individuals with a subsequent increase in blood pressure to hypertensive levels since under the

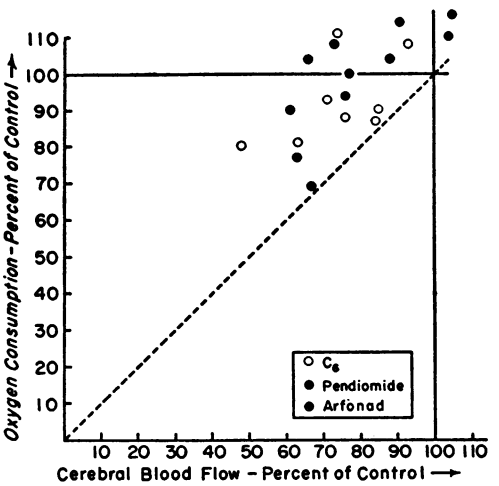

FIG. 3. CEREBRAL BLOOD FLOW EXPRESSED AS PER CENT OF CONTROL PLOTTED AGAINST OXYGEN CONSUMPTION EXPRESSED IN THE SAME MANNER

Cerebral blood flow is depressed in excess of cerebral oxygen consumption due to increased extraction of oxygen from the cerebral blood.

latter circumstances cerebral blood flow is reduced. If the reduction in cerebral blood flow which also occurs following the administration of ganglionic blocking agents were not a result of the hypotension, then raising the pressure with an adrenergic drug would not be expected to increase cerebral blood flow, but might actually reduce it (14). If such a pressure-flow relationship is accepted, then the value of vasopressor agents in the treatment of normal volemic hypotensive states seems well substantiated in so far as cerebral blood flow is concerned. These observations would tend to invalidate the suggestion (1) that the use of vasoconstrictor agents such as norepinephrine might depress cerebral blood flow when used for the treatment of severe hypotensive states.

The failure of head down tilt to increase cerebral blood flow was a completely unexpected observation, and one for which the authors have no explanation. Some of the patients who demonstrated mental disturbances during hypotension were improved when the head was tilted down. This observation is not necessarily incompatible with the observations of a continued reduction in average cerebral blood flow per unit volume of brain since the improvement in cerebral function may merely represent improved circulation to the

cortical areas rather than an increase in the total amount of blood flowing through the brain.

SUMMARY AND CONCLUSIONS

1. Observations have been made on the cerebral hemodynamic response of 19 patients during controlled hypotension employing a continuous infusion of one of three ganglionic blocking agents; *i.e.*, hexamethonium, Pendiomide or Arfonad. Arfonad appeared to be the most potent hypotensive agent and the one with the shortest duration of action. A "floor" in the blood pressure was reached with all three agents, beyond which it was difficult if not impossible to reduce the blood pressure. It was possible to attain a maximum reduction in blood pressure by initially administering the blocking agent at a rapid rate. This was most apparent with administration of Arfonad.

2. After the blood pressure was reduced, cerebral blood flow decreased in 17 out of 19 subjects. The degree of reduction in cerebral blood flow was related to the degree of reduction of blood pressure rather than to any particular blocking agent. As the cerebral blood flow decreased, the oxygen was extracted more completely from the blood flowing through the brain, thus maintaining cerebral oxygen consumption. When the blood pressure was reduced below 55 to 60 mm. Hg this compensation was sometimes inadequate which resulted in a reduction in $CMRO_2$ (< 0.5 cc. per minute) and occasional symptoms of cerebral hypoxia. When the blood pressure was then raised to normotensive levels with a vasopressor agent, cerebral blood flow increased towards normal, thus indicating that the reduction in cerebral blood flow during the administration of the ganglionic blocking agent was probably due to the hypotension.

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