CEREBRAL HEMODYNAMICS DURING CEREBRAL ISCHEMIA INDUCED BY ACUTE HYPOTENSION [1]

By FRANK A. FINNERTY, Jr., LLOYD WITKIN, and JOSEPH F. FAZEKAS with the technical assistance of MARIE LANGBART and WILLIAM K. YOUNG

(From the Department of Medicine, Georgetown University School of Medicine and the Georgetown and George Washington Medical Divisions, District of Columbia General Hospital, Washington, D. C.)

(Submitted for publication February 1, 1954; accepted May 20, 1954)

The extreme dependence of the brain upon its circulation for substrates essential for the maintenance of its metabolic activity is well recognized. A cessation of the cerebral circulation for only a few minutes, as occurs in cardiac arrest, results in irreversible brain damage. The brain, for the most part, is an aerobic organ and its large oxygen demands probably account for its unusual susceptibility to circulatory disturbances.

The oxygen consumed by the normal adult brain (3.5 cc. per 100 Gm. per min.) is extracted from approximately 800 cc. of blood passing through it each minute. The minimum blood flow requirements of the brain, *i.e.*, the rate at which signs of cerebral ischemia become manifest, have not been accurately determined. Previous efforts to estimate the critical rate have been made both in animals (1) and in man (2) but the procedures utilized for the determination of cerebral blood flow were not sufficiently quantitative to warrant definite conclusions.

In order to study this problem, cerebral hemodynamic and metabolic changes were determined before and during acute reductions in arterial pressure induced by drug administration and/or postural adjustments.

MATERIALS AND METHOD

Forty-four patients were studied. The subjects in whom hypotension was drug-induced were separated into the following four groups so that the influence of age and hypertension on the susceptibility of the brain to cerebral ischemia could be determined: Group 1, seven normotensive subjects under 50 years of age; Group 2, ten normotensive subjects over 60 years of age; Group 3, eight patients with essential hypertension; and Group 4, seven patients with malignant hypertension. In seven subjects, the mean arterial pressure was reduced significantly below normal but not to the extent of inducing signs of cerebral ischemia. Five patients with spontaneous postural hypotension were also studied.

Control studies were obtained after the subject had been tilted (head up) 30 to 40 degrees for a period of at least 30 minutes. The subjects in the drug-induced hypotension group were then given a 1 per cent solution of hexamethonium [2] intravenously at a rate of 1 mg. of the ion per minute and carefully observed for signs of cerebral ischemia. In the subjects with spontaneous postural hypotension, control studies were done in the horizontal position, and the subjects were then tilted 30 degrees head up, and the experimental flow was done when they developed signs of cerebral ischemia.

The manifestations of cerebral circulatory insufficiency were rather stereotyped and easily recognized. Sighing, yawning, staring, and confusion, *i.e.*, the inability to follow simple commands, were the first indications of cerebral ischemia. When any of these signs appeared, the hexamethonium injection was promptly discontinued, and the second, or experimental flow was begun. A fairly steady state was maintained during the first few minutes making postural adjustments unnecessary. If during the experimental flow, the patient became either unresponsive or too alert, postural adjustments were rapidly made to restore the desired clinical state. The degree of tilt required was usually not more than 10 to 20 degrees. In this way, the clinical state of the subject could be changed in a matter of seconds from one of alertness to confusion, and for the remainder of the flow, the subject was maintained in the latter state.

Scheinberg and Stead's modification (3) of Kety and Schmidt's procedure (4) for the determination of cerebral blood flow (CBF) was utilized in this study. The gas mixtures utilized were those described by Kety and Schmidt (4). Blood oxygen and CO_2 content were determined by the manometric technique of Van Slyke and Neill (5). Blood pH was determined using a Beckman pH meter and an anaerobic glass electrode at room temperature and corrected for 37 degrees centigrade. The cerebral oxygen consumption ($CMRO_2$), cerebral vas-

[1] This investigation was supported by a grant from the United Cerebral Palsy Foundation and a grant (PHS B-178) from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service.

[2] Supplied through the courtesy of E. R. Squibb and Sons, New York, N. Y.

cular resistance (CVR), and cerebral oxygen delivery (CDO_2) were calculated as follows:

$$CMRO_2 \text{ (cc. } O_2\text{/min./100 Gm. of brain)} = \frac{CBF \times (A-V)O_2}{100};$$

$$CVR \text{ (mm. Hg/cc. blood/min./100 Gm. of brain} = \frac{MAP}{CBF};$$

$$CDO_2 \text{ (cc. } O_2\text{/min./100 Gm. of brain)} = \frac{CBF \times \text{arterial } O_2}{100}.$$

TABLE IA

Cerebral hemodynamics in acute hypotension associated with cerebral ischemia *

Young Normotensive Subjects

Age	CBF		CVR		$CMRO_2$		AVO_2		MAP	
	C	E	C	E	C	E	C	E	C	E
46	36.8	23.9	2.4	1.8	2.5	2.7	6.72	11.46	88	44
42	43.6	31.9	2.2	0.8	2.6	2.7	5.90	8.55	94	26
35	40.6	30.2	2.1	1.2	2.6	2.5	6.47	8.27	84	36
39	57.4	38.1	1.3	0.9	2.7	3.4	4.64	9.06	75	35
30	58.2	36.2	1.3	1.1	3.4	3.0	5.83	8.21	78	39
32	38.3	29.1	2.3	1.3	2.7	2.6	7.17	8.83	88	38
35	44.0	29.9	1.9	1.0	3.1	3.3	6.94	11.08	83	29
Mean Values										
37	45.6	31.3†	1.9	1.2†	2.8	2.9	6.24	9.35†	84	35†

* In this and other tables, CBF signifies cerebral blood flow in cc./min./100 Gm. of brain; CVR, cerebral vascular resistance in mm. Hg/cc. blood/min./100 Gm. of brain; $CMRO_2$, cerebral oxygen consumption in cc./min./100 Gm. of brain; AVO_2, arterio-venous oxygen difference in volumes per cent; MAP, mean arterial blood pressure in mm. of Hg.

† Significant difference, $p < .01$.

TABLE IB

Cerebral hemodynamics in acute hypotension associated with cerebral ischemia *

Elderly Normotensive Subjects

Age	CBF		CVR		$CMRO_2$		AVO_2		MAP	
	C	E	C	E	C	E	C	E	C	E
59	41.5	34.8	1.4	0.7	1.8	2.0	4.43	5.62	60	23
85	31.3	26.4	2.6	2.0	1.7	2.1	5.44	7.99	82	54
60	41.6	19.6	2.2	1.5	3.1	2.8	7.36	14.01	93	29
88	40.6	30.8	2.2	0.8	2.3	2.4	5.73	7.84	88	24
75	44.6	23.4	1.9	1.2	3.4	3.1	7.71	13.12	85	27
93	47.7	28.6	1.4	0.6	2.3	2.3	4.75	7.94	68	17
77	64.2	35.6	0.9	0.8	3.6	3.2	5.55	8.91	55	28
72	47.7	31.8	1.8	0.9	2.5	2.8	5.20	8.67	88	28
67	66.2	31.8	1.1	0.9	2.9	3.0	4.40	9.30	70	28
69	57.4	27.4	1.7	1.1	3.3	2.9	5.80	10.67	96	30
Mean Values										
75	48.3	29.0†	1.7	1.1†	2.7	2.7	5.64	9.41†	79	29†

* See Table IA for explanation of abbreviations.

† Significant difference, $p < .01$.

TABLE IC

Cerebral hemodynamics in acute hypotension associated with cerebral ischemia *

Subjects with Essential Hypertension

Age	CBF		CVR		$CMRO_2$		AVO_2		MAP	
	C	E	C	E	C	E	C	E	C	E
56	58.4	28.5	2.2	2.2	2.2	2.6	3.76	8.98	130	64
59	43.9	27.4	2.4	1.1	2.4	2.5	5.45	9.27	105	31
72	48.8	33.9	2.7	2.0	3.4	3.1	7.08	9.10	134	68
65	45.6	30.3	2.2	1.5	3.4	3.2	7.48	10.39	102	45
53	49.1	32.1	2.1	0.7	2.9	2.7	5.97	8.41	103	23
68	43.3	35.4	3.0	1.8	2.8	3.1	6.50	8.68	128	65
65	49.9	17.5	2.1	2.2	2.5	2.1	4.96	11.96	103	38
60	44.4	28.0	2.3	1.5	3.0	2.5	6.78	9.01	102	43
Mean Values										
62	47.9	29.1†	2.4	1.6†	2.8	2.7	6.00	9.48†	113	47†

* See Table IA for explanation of abbreviations.

† Significant difference, $p < .01$.

TABLE ID

Cerebral hemodynamics in acute hypotension associated with cerebral ischemia *

Subjects with Malignant Hypertension

Age	CBF		CVR		$CMRO_2$		AVO_2		MAP	
	C	E	C	E	C	E	C	E	C	E
33	46.0	27.9	3.8	3.4	2.6	2.8	5.66	10.03	173	95
39	59.6	39.0	2.8	2.4	3.5	3.3	5.85	8.51	166	95
41	62.6	39.7	2.8	2.7	3.4	2.9	5.44	7.38	173	106
47	75.9	41.0	2.7	2.8	4.3	3.5	5.72	8.52	203	114
42	58.8	26.2	3.2	2.6	3.6	2.9	6.11	11.21	188	69
42	62.4	38.5	2.9	2.0	3.1	3.0	4.92	7.72	183	78
36	56.9	33.7	2.9	1.9	3.7	3.1	6.56	9.48	166	64
Mean Values										
40	60.3	35.1†	3.0	2.5	3.5	3.1	5.75	8.98†	179	89†

* See Table IA for explanation of abbreviations.

† Significant difference, $p < .01$.

The mean arterial blood pressure (MAP) was obtained directly from the femoral artery by means of a damped anaeroid manometer (6) and also by the usual auscultatory method. Since the subjects were tilted, it was necessary to correct for the hydrostatic pressure differences between the femoral and carotid arteries. This pressure differential was equal to the vertical height between the two arteries which varied somewhat in individual studies. The mean arterial pressures, presented in the tables are the calculated mean carotid pressures. This correction, as well as the fact that the subjects were resting in a tilted position for approximately thirty minutes, probably accounts for the normotensive values in some of the subjects with essential hypertension (Table IC).

TABLE IE

Cerebral hemodynamics in acute hypotension associated with cerebral ischemia *

Subjects with Postural Hypotension

Age	CBF		CVR		$CMRO_2$		AVO_2		MAP	
	C	E	C	E	C	E	C	E	C	E
52	59.1	31.3	2.4	1.8	3.2	2.9	5.42	9.22	143	56
47	52.1	36.5	1.7	1.8	3.0	2.5	5.76	6.75	90	64
79	47.7	32.0	1.3	1.1	2.3	2.9	4.74	8.99	63	36
69	44.9	28.6	3.2	1.9	1.9	2.6	4.23	9.09	144	55
78	75.2	47.3	1.0	0.8	3.4	3.4	4.55	7.21	74	39
Mean Values										
65	55.8	35.1†	1.9	1.5	2.8	2.9	4.94	8.25‡	103	50†

* See Table IA for explanation of abbreviations.
† Significant difference, $p < .05$.
‡ Significant difference, $p < .01$.

Electrocardiograms were taken before, during, and after the experimental procedure in 21 subjects, and the internal jugular venous pressures were recorded before and during the study in 14 subjects. The internal jugular venous pressures were measured by means of a spinal fluid manometer; the zero point was considered to be the needle level.

RESULTS

An analysis of the results obtained in the 37 subjects in whom the mean arterial pressure was reduced to levels at which signs of cerebral ischemia became manifest discloses the following: The mean arterial pressure fell from a mean value of 109 mm. Hg to 48 mm. Hg ($p < .01$). The rate of cerebral blood flow decreased significantly from a mean of 51 to 31.5 cc./100 Gm./min. ($p < .01$). The mean cerebral vascular resistance also fell significantly from 2.2 to 1.5 ($p < .01$). The mean cerebral arteriovenous oxygen difference increased significantly from 5.80 volumes per cent to 9.20 volumes per cent ($p < .01$). Despite definite signs of cerebral ischemia, the cerebral oxygen utilization did not change appreciably from control values during the experimental flow. The CO_2 content of the arterial and cerebral venous blood did not change significantly with a reduction of the mean arterial pressure. Similarly there were no significant changes in the blood pH in eleven of the subjects studied.

Tables I, A through E, present the results of the individual groups. Table II presents data on seven subjects in whom the mean arterial pressure was not lowered sufficiently to induce signs of cerebral ischemia.

Though considerable variation is seen in the level of arterial pressure at which signs of cerebral ischemia became manifest, ranging from mean values of 89 mm. Hg in the malignant hypertensive group to 29 mm. Hg in the normotensive group over 60 years of age, the value for the cerebral blood flow is not appreciably different in the individual groups studied (Tables I, A through E). The mean value for cerebral blood flow in the group of subjects in whom cerebral ischemia was not induced (Table II) is significantly higher than in any of the other groups.

TABLE II

Cerebral hemodynamics in acute hypotension without cerebral ischemia *

Age	Diagnosis	CBF		CVR		$CMRO_2$		AVO_2		MAP	
		C	E	C	E	C	E	C	E	C	E
67	Pneumonia	66.8	38.3	1.2	1.1	3.0	3.3	4.46	8.59	82	44
36	Diabetes	65.7	45.8	1.1	1.2	3.8	3.9	5.78	8.55	72	54
23	Dermatitis	77.2	57.2	1.1	1.2	2.7	2.9	3.47	5.01	87	69
18	Rheumatic fever	57.0	49.5	1.4	1.3	3.4	3.6	6.04	7.24	78	66
66	Hypertension	54.9	32.5	3.1	1.6	2.7	3.2	4.92	9.81	168	53
48	Hypertension	50.6	38.8	2.5	1.8	2.9	3.1	5.79	7.96	128	70
43	Uremia	61.4	44.9	2.2	2.2	1.8	1.9	2.87	4.17	133	98
Mean Values											
43		61.9	43.9†	1.8	1.5	2.9	3.1	4.76	7.33‡	107	65‡

* See Table IA for explanation of abbreviations.
† Significant difference, $p < .01$.
‡ Significant difference, $p < .05$.

The mean cerebral vascular resistance fell significantly in both the young and elderly normotensive subjects (Table IA and IB) and subjects with essential hypertension (Table IC). The cerebral metabolic rate did not change significantly from the control values in any of the individual groups. In all groups presented, the cerebral arteriovenous oxygen difference was significantly increased.

In the 14 subjects studied, the internal jugular venous pressure decreased from 83 to 47 mm. of water with an average decrease of 36. Since this represents a difference of approximately 3 mm. Hg, it would only change the cerebral vascular resistance by 0.1 units.

Of interest was the complete lack of clinical and electrocardiographic evidence of coronary insufficiency in these acute studies, particularly in the elderly subjects, many of whom had abnormal electrocardiograms. The control electrocardiograms in 15 subjects were abnormal—two subjects showed evidence of old posterior myocardial infarction, the rest showed non-specific myocardial changes. When symptoms of cerebral ischemia developed, the average heart rate was 64 per minute, a reduction of 35 per cent.

DISCUSSION

Cerebral blood flow and arterial pressure

It is evident from these studies that despite the subject's age, original level of arterial pressure, per cent reduction of arterial pressure, or original rate of cerebral blood flow, signs of cerebral ischemia developed when the mean cerebral blood flow was reduced to 31.5 cc. per min. per 100 Gm. of brain. The mean values of the experimental cerebral blood flows for the individual groups varied between 29 and 35 cc. per 100 Gm. of brain per min. The fact that in the group without cerebral ischemia (Table II) the subjects were alert despite a mean cerebral blood flow of 43.9 indicates that the critical rate of cerebral blood flow is below this value. Apparently significant reductions in cerebral blood flow from normal are possible without inducing manifestations of cerebral ischemia.

The degree of fall in arterial pressure required to produce cerebral ischemia, as might be anticipated, was related to the cerebral vascular resistance. When the cerebral vascular resistance could be significantly reduced (all groups except the postural hypotensive group and the malignant hypertensive group), the arterial pressure could be lowered markedly before signs of cerebral ischemia became manifest. When the vascular resistance could not be significantly reduced, the level of arterial pressure at which cerebral ischemia developed was higher. Only in situations where the vascular resistance remains fixed, can there be a direct relationship between per cent reduction in cerebral blood flow and mean arterial pressure. Since the mean arterial pressure at which signs of cerebral ischemia developed varied considerably (89 to 29 mm. Hg), it is evident that a critical level of arterial pressure as such does not exist.

Cerebral vascular resistance

The initial values for the cerebral vascular resistance in the individual groups varied. The finding of an increased cerebral vascular resistance in the hypertensive subjects confirms the results of Kety and others (7–10). The highest mean value for the cerebral vascular resistance was noted in the malignant hypertension group. While the increased cerebral vascular resistance in the essential hypertension group was significantly reduced with hypotension, the cerebral vascular resistance in the malignant hypertension group remained relatively fixed. It may be that the inability to overcome this increased cerebral vascular tone accounted for the development of signs of cerebral ischemia at normal levels of arterial pressure.

It was particularly interesting that the elderly normotensive subjects showed a significant reduction in cerebral vascular resistance when their mean arterial pressures were reduced. This confirms previous observations demonstrating considerable alterations in the vascular tone of elderly subjects (11, 12). In the group studied, the cerebral vascular resistance was not as high as we expected it might be. In a preliminary study (13) on elderly hypertensive subjects with a markedly elevated cerebral vascular resistance, signs of cerebral ischemia have occurred at normotensive levels. An overall decrease in cerebral vascular resistance in normotensive and hypertensive subjects with cerebral arteriosclerosis should not be taken to mean that all cerebral vessels are capable of under-

going the same degree of relaxation. It is possible that with an acute drop in blood pressure, circulation through the more rigid cerebral vessels may be seriously impaired. This may explain why transient episodes of cerebral ischemia may sometimes be associated with a relatively slight decrease of the mean arterial pressure. The explanation for the decrease in cerebral vascular resistance attendant with the reduction in mean arterial pressure is not apparent from these studies since there was no change in either pH or CO_2 content.

Cerebral metabolic rate

Even though signs and symptoms of cerebral ischemia were present in most of the subjects studied, there was no significant change in cerebral oxygen utilization between the control and induced hypotension studies. There can be no question that in these acute experiments the manifestations of cerebral ischemia were most likely due to a decreased oxygen delivery to certain cerebral cells since there was neither hypoglycemia nor any obvious impairment of cerebral enzymatic activity. It is suggested from the neurological signs evoked that not all regions of the brain were equally affected by the cerebral ischemia. The variable sensitivity of the different areas of the brain to reduced oxygen tensions and to depressant drugs is well recognized. It may be that with a reduction of the rate of cerebral blood flow those areas with the highest metabolic requirements are first affected. The failure to observe significant changes in cerebral oxygen utilization in these studies may be due to the fact that the method employed is not sufficiently sensitive to reflect changes in the metabolic activity of a relatively small number of cerebral cells. In this regard it should be mentioned that during sleep (14) and with light Pentothal® anesthesia (15) one does not observe significant changes in cerebral oxygen utilization with this procedure.

Cardiovascular effects

The fact that small doses of hexamethonium were given (average dose was 8 mg. of the ion) and the frequent finding of bradycardia and increased perspiration in the drug-induced studies suggests that full blocking doses of the drug were not given, and the effects observed were not entirely drug-induced. The hypotensive effect of small doses of the ganglionic blocking agent enhanced by tilting apparently activated vasovagal reflexes which accounted for the bradycardia observed. With the onset of collapse, cardiac output and right ventricular pressures decreased sharply (16). These latter observations are consistent with the concept that the mechanism of cerebral ischemia was due to loss of peripheral vasoconstrictor tone which in our tilted subjects promoted failure of venous return and hence of cardiac output.

SUMMARY AND CONCLUSIONS

1. The effect of cerebral ischemia induced by the intravenous administration of hexamethonium and/or tilting on cerebral hemodynamics and metabolism was determined in young and elderly normotensive subjects and in subjects with essential and malignant hypertension. Seven subjects with postural hypotension were also studied.

2. In all subjects, signs and symptoms of cerebral ischemia developed when the cerebral blood flow was reduced to 31.5 cc. per 100 Gm. of brain per min. (mean value).

3. The degree of fall in mean arterial pressure which resulted in cerebral ischemia varied from 29 to 80 mm. Hg.

4. Subjects with a relatively fixed cerebral vascular resistance (malignant hypertension) developed cerebral ischemia at higher mean arterial pressures.

5. Although blood pressures were lowered to levels resulting in clinical signs and symptoms of cerebral ischemia, no change in the over-all cerebral oxygen consumption was noted.

6. The development of clinical signs of cerebral insufficiency without simultaneous clinical or laboratory evidence of coronary insufficiency suggests that the brain may be more sensitive to acute hypotension than is the heart.

REFERENCES

1. Fog, M., Cerebral circulation, the reaction of the pial arteries to a fall in blood pressure. Arch. Neurol. & Psychiat., 1937, **37**, 351.
2. Lennox, W. G., Gibbs, F. A., and Gibbs, E. L., Relationship of unconsciousness to cerebral blood flow and to anoxemia. Arch. Neurol. & Psychiat., 1935, **34**, 1001.

3. Scheinberg, P., and Stead, E. A., Jr., The cerebral blood flow in male subjects as measured by the nitrous oxide technique. Normal values for blood flow, oxygen utilization, glucose utilization, and peripheral resistance, with observations on the effect of tilting and anxiety. J. Clin. Invest., 1949, **28**, 1163.
4. Kety, S. S., and Schmidt, C. F., The nitrous oxide method for quantitative determination of cerebral blood flow in man: Theory, procedure and normal values. J. Clin. Invest., 1948, **27**, 476.
5. Peters, J. A., and Van Slyke, D. D., Quantitative Clinical Chemistry. Baltimore, Williams & Wilkins, 1931.
6. Alman, R. W., and Fazekas, J. F., Apparatus for continuous blood pressure observation. New England J. Med., 1953, **248**, 105.
7. Kety, S. S., Hafkenschiel, J. H., Jeffers, W. A., Leopold, I. H., and Shenkin, H. A., The blood flow, vascular resistance and oxygen consumption of the brain in essential hypertension. J. Clin. Invest., 1948, **27**, 511.
8. Kety, S. S., King, B. D., Horvath, S. M., Jeffers, W. A., and Hafkenschiel, J. H., The effects of an acute reduction in blood pressure by means of differential spinal sympathetic block on the cerebral circulation of hypertensive patients. J. Clin. Invest., 1950, **29**, 402.
9. Hafkenschiel, J. H., Crumpton, C. W., Moyer, J. H., and Jeffers, W. A., The effects of dihydroergocornine on the cerebral circulation of patients with essential hypertension. J. Clin. Invest., 1950, **29**, 408.
10. Harmel, M. H., Hafkenschiel, J. H., Austin, G. M., Crumpton, C. W., and Kety, S. S., The effect of bilateral stellate ganglion block on the cerebral circulation in normotensive and hypertensive patients. J. Clin. Invest., 1949, **28**, 415.
11. Bessman, A. N., Alman, R. W., and Fazekas, J. F., Effects of acute hypotension on cerebral hemodynamics and metabolism of elderly patients. Arch. Int. Med., 1952, **89**, 893.
12. Fazekas, J. F., Bessman, A. N., Cotsonas, N. J., Jr., and Alman, R. W., Cerebral hemodynamics in cerebral arteriosclerosis. J. Gerontol., 1953, **8**, 137.
13. Fazekas, J. F., and Kleh, J., Unpublished data.
14. Mangold, R., Sokoloff, L., Therman, P. O., Conner, E. H., Kleinerman, J. I., and Kety, S. S., Cerebral blood flow and oxygen consumption during natural sleep. Federation Proc., 1951, **10**, 89.
15. Kety, S. S., Woodford, R. B., Harmel, M. H., Freyhan, F. A., Appel, K. E., and Schmidt, C. F., Cerebral blood flow and metabolism in schizophrenia; the effects of barbiturate semi-narcosis, insulin coma and electroshock. Am. J. Psychiat., 1948, **104**, 765.
16. Finnerty, F. A., Jr., Rose, J. C., Partenope, E., and Freis, E. D., Jr., Unpublished data.