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Henry A. Shenkin, … , Doris Golden, Peter Batson

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Research Article

THE EFFECTS OF AGING, ARTERIOSCLEROSIS, AND HYPERTENSION UPON THE CEREBRAL CIRCULATION [1]

By HENRY A. SHENKIN, PAUL NOVAK,[2] BERNARD GOLUBOFF, ALVIN M. SOFFE, AND LEONARD BORTIN WITH THE TECHNICAL ASSISTANCE OF DORIS GOLDEN AND MRS. PETER BATSON

(From the Departments of Neurosurgery, Research, and Medicine of the Albert Einstein Medical Center, Southern Division, Philadelphia, Penna.)

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Various investigators have applied the nitrous oxide method (1) to the study of the effects of aging, vascular sclerosis, and hypertension upon the cerebral blood flow and metabolism. Freyhan, Woodford, and Kety (2) measured the cerebral blood flow in cases manifesting psychoses secondary to advanced cerebral arteriosclerosis. Significant reductions of cerebral blood flow and oxygen utilization were noted. Scheinberg (3) reported reduction of both cerebral blood flow and oxygen consumption in patients with histories of previous cerebrovascular accidents. Greater reductions in these measurements were noted in patients who exhibited mental aberrations secondary to cerebrovascular disease. Fazekas, Alman, and Bessman (4) found a reduction of the cerebral blood flow and oxygen consumption in individuals above 50 years of age with no clinical evidence of cerebrovascular disease. Kety, Hafkenschiel, Jeffers, Leopold, and Shenkin (5) demonstrated the presence of a normal cerebral blood flow and oxygen consumption and an elevated cerebrovascular resistance in a series of cases of essential hypertension. The present investigation is an attempt to clarify and extend knowledge concerning the interrelated effects of aging, hypertension, and arteriosclerosis upon the cerebral hemodynamics and metabolism.

METHODS

The cerebral blood flow (CBF) was measured by the nitrous oxide technique (1). Patients were in the postabsorptive state and the recumbent position. The jugular venous pressure (JVP) was measured with a spinal fluid manometer using the level at which the vessel was entered as the "O" reference point. This is generally at the right atrial level in the supine position. The mean arterial blood pressure (MABP) was measured in a femoral artery with a damped mercury manometer. The oxygen and carbon dioxide contents of the blood were determined by the method of Van Slyke and Neill (6). The blood pH was determined anaerobically at room temperature with a glass electrode and corrected to body temperature using the formula of Rosenthal (7). The pCO_2 was determined from standard nomograms (6).

MATERIAL

The subjects have been divided into five groups: *1)* Normotensive individuals under 40 years of age with no clinical evidence of arteriosclerosis. *2)* Normotensive individuals above 50 years of age with systemic or cerebral vascular disease. Systemic arteriosclerosis was diagnosed by the presence of vascular calcifications, signs and symptoms of coronary artery disease, or peripheral vascular impairment. No attempt was made to further quantitate the severity of the arteriosclerosis. A mean arterial blood pressure of 115 mm. Hg has been arbitrarily used to separate the hypertensive from the normotensive. Cerebrovascular disease was considered present where a history of a past cerebrovascular accident was obtained. *3)* Hypertensive arteriosclerotic individuals above 40 years of age without a history of a cerebrovascular accident or mental deterioration. *4)* Hypertensive arteriosclerotic individuals above 40 years of age with a history of cerebrovascular accidents or mental deterioration. *5)* Hypertensive individuals with no evidence of vascular disease. Retinopathy was not more severe than grade II.

RESULTS

Tables Ia and Ib summarize clinical data and the values obtained for the various cerebral circulatory functions and blood constituents of Group 1. The mean values are comparable to normals established by others (1).

Tables IIa and IIb present the clinical, cerebral circulatory, and blood constituent data for Group 2. The mean CBF of 46 cc. per 100 gm. per min. is not significantly below the value noted for Group 1 ($p > .2$). The CVR of 2.1 mm. Hg per cc. per 100 gm. per min. is similarly higher, but not sig-

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[2] National Heart Institute Postdoctorate Research Fellow, 1952–53.

TABLE Ia

*Group 1: Clinical and cerebral circulatory data**

Subject	Age	Sex	Diagnosis	MABP	JVP	CBF	CVR	$CMRO_2$	R.Q
G. C.	40	M	Duodenal ulcer	99	186	47	1.8	2.8	1.00
S. W.	40	F	Psychoneurosis	84	90	77	1.0	4.2	0.93
F. B.	36	F	Trigeminal neuralgia	79	101	47	1.5	3.4	0.88
S. G.	25	F	Headache, functional	81	98	35	2.1	2.5	0.97
M. H.	18	F	Headache, functional	91	84	22	3.9	1.6	0.99
D. M.	31	M	Resp. infection	79	98	54	1.3	2.9	1.29
S. R.	36	F	Functional G.I.	100	73	38	2.5	2.0	0.78
A. H.	29	F	Functional G.I.	111	61	52	2.0	4.8	1.06
S. K.	26	M	Psychoneurosis	95	152	74	1.1	4.9	1.01
E. G.	26	F	Migraine	100	108	54	1.7	2.7	0.92
S. D.	23	F	Neurodermatitis	91	101	78	1.1	5.1	0.92
D. O.	27	F	Post op., mastoidect.	83	80	57	1.3	3.8	0.98
Mean	30			91	103	53	1.8	3.4	0.98
S.E.				±3	±10	±5	±0.5	±0.6	±0.01

* MABP: Mean arterial blood pressure, mm. Hg.
JVP: Jugular venous pressure, mm. H_2O.
CBF: Cerebral blood flow, cc. per 100 gm. per min.
CVR: Cerebrovascular resistance, mm. Hg per cc. per 100 gm. per min.
$CMRO_2$: Cerebral oxygen consumption, cc. per 100 gm. per min.
R.Q.: Cerebral respiratory quotient.
S.E.: Standard error.

nificantly so, than that for Group 1 ($p > .5$). The other cerebral circulatory measurements do not differ significantly from those presented for Group 1. The mean values for the various blood constituents listed fall within the normal range.

Table III lists the cerebral circulatory data for the individuals in Group 3, the hypertensive arteriosclerotic patients without previous vascular accidents or mental deterioration. The mean CBF of 39 cc. per 100 gm. per min. is 26 per cent below the normal of 53 cc. per 100 gm. per min. The mean CVR of 3.4 mm. Hg per cc. per 100 gm. per min. per cc. is 89 per cent higher than the value noted for Group 1. The mean $CMRO_2$ of 2.4 cc. per 100 gm. per min. is 27 per cent below the value recorded for Group 1. These values also differ significantly from the corresponding values of Group 2.

Table IVa presents the cerebral circulatory data for Group 4, patients similar to those of Group 3

TABLE Ib

*Group 1: Blood constituents**

Subject	AO_2	ACO_2	ApH	$ApCO_2$	VO_2	VCO_2	VpH	$VpCO_2$	$(A-V)O_2$	$(A-V)CO_2$
G. C.	16.8	47.3	7.33	46	10.8	53.3	7.30	51	6.0	6.0
S. W.	14.9	54.4	7.33	51	9.4	59.4	7.30	55	5.4	5.0
F. B.	14.6	40.1	7.31	39	7.3	46.6	7.28	47	7.3	6.4
S. G.	19.4	40.8	7.36	38	12.4	47.7	7.33	40	7.1	6.8
M. H.	17.9	39.6	7.42	32	10.6	46.9	7.39	36	7.3	7.3
D. M.	18.8	46.8	7.29	47	12.3	55.3	7.28	57	6.6	8.5
S. R.	16.5	51.4	7.34	48	11.3	55.4	7.29	57	5.2	4.1
A. H.	15.4	46.6	7.39	40	6.3	56.3	7.39	48	9.1	9.7
S. K.	20.2	50.9	7.39	45	13.5	57.6	7.33	51	6.6	6.7
E. G.	15.0	50.9	7.33	48	10.0	55.5	7.29	54	5.0	4.6
S. D.	11.9	48.5	7.38	42	5.3	54.5	7.32	49	6.6	6.0
D. O.	12.1	48.2	7.41	37	5.4	54.7	7.35	46	6.7	6.5
Mean	16.1	47.1	7.36	43	9.6	53.6	7.32	49	6.6	6.5
S.E.	±0.8	±1.4	±.02	±2	±0.8	±1.2	±.01	±2	±0.3	±0.5

* A: Arterial.
V: Venous (jugular).
O_2: Oxygen content, vol. per cent.
CO_2: Carbon dioxide content, vol. per cent.
S.E.: Standard error.

TABLE IIa

*Group 2: Clinical and cerebral circulatory data**

Subject	Age	Sex	Diagnosis	MABP	JVP	CBF	$CMRO_2$	CVR	R.Q.
M. D.	59	F	Functional G.I.	100	65	48	3.3	2.0	0.89
S. A.	64	M	Duodenal ulcer	99	75	29	1.5	3.2	1.12
H. S.	75	M	Chronic cholecystitis	100	38	38	3.0	2.6	1.01
J. P.	70	M	Acute gastritis	77	59	98	6.4	0.8	0.51
E. G.	56	F	Old CVA	98	98	54	3.9	1.7	0.92
B. D.	68	M	Headache, functional	95	156	45	2.8	1.8	0.81
W. H.	55	M	Old CVA	100	107	41	2.8	2.2	0.96
E. L.	66	M	Bronchiogenic Ca	91	90	80	3.1	1.1	0.68
E. G.	55	M	Pituitary tumor	86	77	33	1.0	2.4	0.83
M. S.	62	M	ASCVD	100	108	36	2.2	2.6	0.97
W. F.	73	M	Pancreatic Ca	107	90	48	3.2	2.1	0.80
M. So.	65	M	Rheumatoid arthritis	102	—	40	2.4	2.4	1.00
H. K.	65	M	Multiple myeloma	93	82	54	2.9	1.6	0.97
F. F.	75	M	ASCVD	88	82	51	2.7	1.6	0.91
B. B.	75	F	Old CVA	90	80	32	2.0	2.6	1.19
S. K.	58	F	Headache, functional	72	54	51	3.5	1.3	0.96
J. L.	76	M	Viral pneumonitis	115	60	42	3.3	2.7	0.99
A. F.	80	M	ASCVD	98	39	41	2.3	2.3	1.12
C. Z.	86	F	ASCVD	105	90	37	1.0	2.7	0.84
J. S.	45	M	ASCVD	105	116	41	2.2	2.3	1.07
A. Di.	61	M	G.I. malignancy	96	74	45	2.7	2.0	0.83
I. K.	69	M	ASCVD	87	88	40	2.1	2.1	0.71
T. B.	69	F	ASCVD	88	108	30	1.7	2.7	0.95
Mean	68			95	83	46	2.7	2.1	0.88
S.E.				±2	±6	±3	±0.2	±0.1	±0.05

* See footnote Table Ia.

TABLE IIb

*Group 2: Blood constituents**

Subject	AO_2	ACO_2	ApH	$ApCO_2$	VO_2	VCO_2	VpH	$VpCO_2$	$(A-V)O_2$	$(A-V)CO$
M. D.	18.5	48.1	7.31	47	11.6	54.3	7.27	55	6.9	6.2
S. A.	18.4	44.8	7.34	43	13.4	50.4	7.30	53	5.0	5.6
H. S.	17.0	60.7	7.35	56	9.1	68.6	7.30	70	7.8	7.9
J. P.	15.1	50.0	—	—	8.6	53.3	—	—	6.5	3.3
E. G.	19.8	46.3	7.36	43	12.6	52.3	7.30	47	7.2	6.6
B. D.	18.1	43.6	—	—	12.0	48.5	—	—	6.1	4.9
W. H.	16.4	49.0	7.37	42	9.7	55.4	7.31	51	6.8	6.5
E. L.	9.9	48.6	7.45	34	6.0	51.3	7.36	41	3.9	2.6
E. G.	19.5	42.5	—	—	16.6	44.8	—	—	2.9	2.4
M. S.	19.2	48.6	7.31	49	13.5	54.5	7.29	57	5.7	5.9
W. F.	19.7	52.0	7.33	51	12.9	57.3	7.27	60	6.8	5.4
M. S.	16.4	51.3	—	—	10.3	57.3	—	—	6.0	6.0
H. K.	13.8	32.3	—	—	8.5	37.5	—	—	5.3	5.1
F. F.	12.1	42.0	—	—	6.9	47.5	—	—	5.2	4.8
B. B.	15.0	44.9	—	—	8.7	52.4	—	—	6.3	7.5
S. K.	16.7	47.4	7.33	45	9.9	53.9	7.31	53	6.8	6.5
J. L.	16.5	44.5	7.39	38	8.8	52.1	7.33	46	7.7	7.6
A. F.	14.5	49.0	7.35	44	8.8	55.4	7.32	53	5.7	6.4
C. Z.	16.1	50.2	7.37	44	13.3	52.5	7.34	50	2.8	2.3
J. S.	18.9	47.5	7.35	43	13.6	53.1	7.31	53	5.2	5.6
A. D.	17.8	47.7	7.36	43	11.7	52.8	7.29	55	5.1	6.1
I. K.	18.7	51.1	7.37	47	13.3	54.8	7.35	49	5.3	3.7
T. B.	17.6	50.3	7.36	45	11.8	55.8	7.32	52	5.8	5.5
Mean	16.8	47.5	7.36	45	10.9	52.9	7.31	53	5.8	5.4
S.E.	±0.5	±1.1	±.01	±1	±0.5	±1.2	±.02	±2	±0.3	±0.3

* See footnote Table Ib.

TABLE III

*Group 3: Clinical and cerebral circulatory data**

Subject	Age	Sex	Diagnosis	MABP	JVP	CBF	CVR	$CMRO_2$	R.Q.
M. S.	68	M	HASCVD	120	60	33	3.5	2.4	0.98
S. F.	64	F	HASCVD	132	54	33	3.9	2.6	1.05
J. L.	62	M	HASCVD	156	78	41	3.7	2.7	0.77
A. W.	62	F	HASCVD	125	145	44	2.6	3.7	0.92
E. S.	66	F	HASCVD	138	123	39	3.3	1.6	1.05
I. B.	41	F	Pheochromocytoma	160	108	42	3.6	1.6	1.16
Mean	61			139†	95	39†	3.4†	2.4	0.99
S.E.				±7	±15	±2	±0.2	±0.3	±0.06

* See footnote Table Ia.
† Differs significantly from value for Group 1, $p < .05$.

but with the history of a past cerebrovascular accident or mental deterioration. The values do not differ significantly from those noted for Group 3. Table IV summarizes the blood constituent data for Groups 3 and 4. No significant variations from normal are observed.

Table Va presents the clinical and cerebral circulatory data for Group 5, cases of essential hypertension uncomplicated by clinically demonstrable arteriosclerosis. All quantities measured, with the exceptions of MABP and CVR, are within normal limits. The high mean JVP, although not significantly different from that noted for the other groups, cannot be explained at present. Variations of the JVP will be discussed in another paper (8). The MABP of 136 mm. Hg is comparable to values noted for Groups 3 and 4. The CVR of 2.7 mm. Hg per cc. per 100 gm. per min. is significantly lower than that noted for Groups 3 or 4. Table Vb presents the data for the blood constituents of Group 5. No significant variations from the normal are observed.

DISCUSSION

The presence of a CBF and $CMRO_2$, not significantly different from normal in a group whose mean age is 68, suggests that aging per se has little effect upon these quantities. The failure to obtain results in complete agreement with Fazekas, Alman, and Bessman (4) seems based upon the consideration of the factor of hypertension in the present analysis. In the absence of hypertension, the degree of arteriosclerosis is apparently insufficient to affect significantly the measured cerebral circulatory functions. The wide spread of values in the normotensive arteriosclerotic group and the apparent trend toward a lowered CBF and $CMRO_2$, which could prove significant in a study of a larger group, suggests that hypertension is only one of many contributory factors. However, hypertension emerged from the present series as the one readily definable factor in predicting the occurrence of a reduced CBF and $CMRO_2$ in arteriosclerotic individuals. Thus, in the hypertensive arteriosclerotic groups the CBF and

TABLE IVa

*Group 4: Clinical and cerebral circulatory data**

Subject	Age	Sex	Diagnosis	MABP	JVP	CBF	CVR	$CMRO_2$	R.Q.
E. S.	45	M	Old CVA	141	210	51	2.5	2.6	1.27
S. S.	45	F	Mental deterior.	140	65	23	6.3	2.5	0.86
C. K.	50	F	Old CVA	143	35	29	4.9	2.6	0.99
S. G.	51	M	Old CVA	117	55	34	3.3	2.1	1.11
S. L.	53	M	Old CVA	123	59	41	3.0	2.8	0.88
D. K.	60	F	Mental deterior.	120	100	33	3.4	2.6	0.88
J. S.	57	M	Old CVA	134	120	48	2.7	2.7	1.08
Mean	51			131	92	37†	3.7†	2.6†	1.01
S.E.				±4	±32	±4	±0.5	±0.1	±0.07

* See footnote Table Ia.
† Differs significantly from value for Group 1, $p < .05$.

TABLE IVb

*Groups 3 and 4: Blood constituents**

Subject	AO_2	ACO_2	ApH	$ApCO_2$	VO_2	VCO_2	VpH	$VpCO_2$	$(A-V)O_2$	$(A-V)CO_2$
M. S.	21.2	40.5	7.37	38	13.9	47.6	7.32	48	7.3	7.1
S. F.	16.8	45.6	—	—	8.8	53.8	—	—	8.0	8.4
E. S.	19.2	44.9	7.30	47	14.1	51.3	7.25	55	5.0	6.5
S. S.	22.5	54.1	7.39	47	10.1	64.7	7.37	59	12.3	10.6
C. K.	19.1	37.8	7.51	22	10.2	46.6	7.41	38	8.9	8.8
S. G.	10.8	39.9	—	—	4.7	46.6	—	—	6.0	6.7
S. L.	19.0	48.1	7.38	42	12.3	54.1	7.33	52	6.8	6.0
D. K.	17.4	43.8	7.50	27	9.6	50.7	7.44	39	7.8	6.9
J. L.	19.6	49.8	7.43	40	13.0	54.9	7.39	45	6.7	5.1
A. W.	19.2	49.1	7.41	41	10.9	56.9	7.37	47	8.4	7.7
J. S.	21.2	48.2	7.38	43	15.6	54.2	7.28	57	5.6	6.0
E. S.	15.5	51.6	—	—	11.4	56.0	—	—	4.4	4.1
I. B.	13.7	59.8	7.34	56	9.9	64.0	7.31	62	3.8	4.2
Mean	18.1	47.2	7.40	40	11.1	53.9	7.35	50	7.0	6.8
S.E.	±0.9	±1.7	±0.02	±3	±0.8	±4.5	±0.02	±3	±0.6	±0.5

* See footnote Table Ib.

$CMRO_2$ were significantly reduced. Furthermore, the CVR in these cases was 31 per cent greater than that noted for uncomplicated hypertensives although the elevations of MABP noted in both groups were similar. The presence of a more severe degree of arteriosclerosis, particularly of the arteriolar variety, would seem to explain the impaired cerebral circulation and metabolism where hypertension and arteriosclerosis coexist.

The present data failed to demonstrate any significant differences between the hypertensive arteriosclerotic group with and that without a history of cerebrovascular accidents or mental deterioration. A comparison of these data with those of Freyhan, Woodford, and Kety (2) for patients with psychoses secondary to hypertensive arteriosclerotic vascular disease also fails to show a clear difference:

	MABP *mm. Hg*	CBF *cc./100 gm./min.*	$CMRO_2$ *cc./100 gm./min.*	CVR *mm. Hg/cc./100 gm./min.*
Freyhan:	136	42	2.8	3.3
Present series:	139	39	2.4	3.4

It would therefore appear that their implication that a reduced CBF and $CMRO_2$ is the basis for the origin of the mental symptoms in their patients is not valid. Their conclusion was based upon the comparison of results with values for young normal individuals rather than a control group composed of individuals with comparable hypertension and arteriosclerosis but without psychoses.

The validity of these, and other data derived by the application of the nitrous oxide method to the study of pathological states, is subject to the objection that increased contamination with extra-

TABLE Va

*Group 5: Clinical and cerebral circulatory data**

Subject	Age	Sex	Diagnosis	MABP	JVP	CBF	CVR	$CMRO_2$	R.Q.
B. B.	38	F	Ess. hyp.	133	120	50	2.5	3.1	0.98
G. B.	38	F	Ess. hyp.	154	137	60	2.4	3.7	1.09
C. H.	46	F	Ess. hyp.	160	160	47	3.2	3.3	0.77
S. P.	39	F	Ess. hyp.	116	120	55	1.9	2.8	0.79
D. B.	45	F	Ess. hyp.	132	107	67	1.9	3.7	0.81
R. S.	56	M	Ess. hyp.	121	165	31	3.5	1.9	1.15
Mean	44			136†	135	52	2.6†	3.1	0.93
S.E.				±7	±10	±5	±0.3	±0.3	±0.07

* See footnote Table Ia.

† Differs significantly from value for Group 1, $p < .05$.

TABLE Vb

*Group 5: Blood constituents**

Subject	AO_2	ACO_2	ApH	$ApCO_2$	VO_2	VCO_2	VpH	$VpCO_2$	$(A-V)O_2$	$(A-V)CO_2$
B. B.	15.2	48.6	7.44	37	9.1	54.6	7.35	47	6.1	6.0
G. B.	16.6	45.7	7.41	37	10.4	52.4	7.33	49	6.2	6.7
C. H.	16.5	54.9	7.38	47	9.5	60.3	7.35	52	7.1	5.4
S. P.	14.7	48.5	7.39	41	9.6	52.6	7.31	51	5.1	4.0
D. B.	16.2	52.2	7.41	42	10.7	56.6	7.33	51	5.5	4.4
R. S.	16.0	44.8	7.40	37	10.0	51.7	7.36	43	6.0	6.9
Mean	15.9	49.1	7.41	40	9.9	54.7	7.34	49	6.0	5.6
S.E.	±0.3	±1.6	±0.01	±2	±0.3	±1.3	±0.01	±1	±0.3	±0.5

* See footnote Table Ib.

cerebral blood may occur in the sampling from the internal jugular bulb. No direct studies of this point other than for normals (9) are available. However, the appearance of the curves plotted from blood nitrous oxide contents did not suggest appreciable contamination. Also of great importance is the fact that the nitrous oxide method measures blood flow per 100 gm. of perfused brain. In the presence of significant areas of infarcted brain, the *total* cerebral blood flow would be reduced to a greater extent than might be assumed on the basis of data indicating flow per 100 gm. of perfused brain.

A good correlation between a reduced CBF and a reduced $CMRO_2$ has been noted in the present study (correlation coefficient 0.75). The possibility that the decreased CBF is secondary to the decreased $CMRO_2$ may be mentioned but is unlikely. Alternative, but not mutually exclusive, explanations of this phenomenon are: *1*) A decreased availability of oxygen because of a decreased CBF causes the reduced $CMRO_2$; *2*) In arteriosclerotic vascular disease there is a diminished capillary interface or a diminished capillary permeability for gaseous exchange; *3*) There is a decreased need for oxygen by the brain occurring independently but concurrently with the drop in CBF. Studies designed to test the ability of arteriosclerotics to maintain a constant $CMRO_2$ in the face of induced reductions in CBF, and *in vitro* studies of brains of hypertensive arteriosclerotic animals offer avenues for further investigation of this relationship.

The occurrence of levels of cerebral oxygen consumption below those usually found in diabetic coma (10) or pentothal narcosis (11) has been observed in conscious, alert individuals. Such observations emphasize the difficulties encountered in attempting to correlate levels of consciousness or mental activity with cerebral oxygen consumption. Although it is probably true that the cerebral oxygen consumption of an unconscious individual is lower than that particular individual's cerebral oxygen consumption in the conscious state, there appears to be no generally applicable absolute value for cerebral oxygen consumption which is characteristic of the presence of consciousness or unconsciousness.

CONCLUSIONS

1. Cerebral circulatory studies have been carried out on 54 individuals for the purpose of determining the effects of aging, arteriosclerosis, and hypertension upon the cerebral blood flow and metabolism.

2. Aging, arteriosclerosis unaccompanied by hypertension, and hypertension unaccompanied by arteriosclerosis were not found to reduce significantly the cerebral blood flow and metabolism.

3. The occurrence of hypertension and arteriosclerosis together was found to be accompanied by significant reductions of cerebral blood flow and oxygen consumption. This is ascribed to a greater severity of the arteriosclerosis, particularly of the arteriolar variety, in these cases.

4. No greater decreases of the cerebral blood flow and oxygen consumption were found in patients with clinical cerebrovascular disease when compared to values for similar patients without such manifestations.

5. Hypertension emerged from the present study as the one readily definable factor in predicting the occurrence of a reduced cerebral blood

flow and oxygen consumption in arteriosclerotic individuals.

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