JCI The Journal of Clinical Investigation

The Blood Flow and Oxygen Consumption of the Brain in Patients with Essential Hypertension before and after Adrenalectomy

Joseph H. Hafkenschiel, … , Carl K. Friedland, Harold A. Zintel

J Clin Invest. 1954;33(1):57-62. https://doi.org/10.1172/JCI102870.

Research Article

THE BLOOD FLOW AND OXYGEN CONSUMPTION OF THE BRAIN IN PATIENTS WITH ESSENTIAL HYPERTENSION BEFORE AND AFTER ADRENALECTOMY [1]

By JOSEPH H. HAFKENSCHIEL, CARL K. FRIEDLAND, AND HAROLD A. ZINTEL
WITH THE TECHNICAL ASSISTANCE OF NELLY K. LINCOLN, HENRIETTA BRANDT, AND JANET MERRILL

(From the Hypertension Section, Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, the Department of Pharmacology and the Harrison Department of Research Surgery of the School of Medicine, University of Pennsylvania, Philadelphia, Pa.)

(Submitted for publication September 22, 1952; accepted September 23, 1953)

It has been shown that cerebral oxygen consumption and blood flow are normal and cerebral vascular resistance is increased in patients with essential hypertension (1). Clinicians have questioned the advisability of lowering arterial pressures in hypertensive patients because of the possible untoward effects consequent to decreased cerebral blood flow (2, 3). We have studied the effect of hypotension, induced by various means, on the oxygen consumption and blood flow of the brain.

During the hypotension obtained one hour after the injection of dihydroergocornine (4), protoveratrine (5), hexamethonium (6), and l-hydrazinophthalazine (7), cerebral blood flow and oxygen uptake were unchanged. Cerebral oxygen uptake was unchanged and cerebral vascular resistance was decreased during the hypotension induced by differential spinal sympathetic block (8). After thoracolumbar sympathectomy, cerebral blood flow and oxygen uptake remained constant and the cerebral vascular resistance was reduced toward normal values three weeks to six months after operation (9). Thus, in most of these instances, cerebral blood flow was not reduced and cerebral oxygen consumption remained unchanged when the arterial pressure was lowered either by the drugs tested or by surgical sympathectomy. These hemodynamic observations suggested that the cerebral circulation remains adequate when the blood pressure is lowered. The increased cerebral vascular resistance in hypertension apparently can be reduced by certain measures without reducing cerebral oxygen consumption and cerebral blood flow.

The present investigation was initiated to explore the effect of another hypotensive procedure, subtotal adrenalectomy (approximately 90 per cent), on arterial and jugular venous blood constituents, cerebral oxygen uptake, cerebral blood flow and cerebral vascular resistance in patients with severe hypertension. The tests were made at approximately the same postoperative intervals as in the postsympathectomy study (9).

METHODS

1. Choice of subjects: This report is based upon the data obtained from seven patients. In all patients cerebral blood flow studies were made before and again 1 to 15 months after subtotal adrenalectomy. Four patients (I. B., A. F., J. D., E. D.) had subdiaphragmatic sympathectomy at the time of the subtotal adrenalectomy (95 to 98 per cent) and were studied three to eight months postoperatively. Two patients (S. W. and T. C.) had subtotal adrenalectomy (91 to 93 per cent) alone. However, the blood pressure response of one (T. C.) was unsatisfactory and he later submitted to subdiaphragmatic sympathectomy. One patient (S. C.) had a thoracolumbar sympathectomy (Smithwick) and unilateral adrenalectomy nine months before 90 per cent resection of the remaining adrenal was accomplished.

Studies were repeated in three patients (I .B., A. F., and S. W.) approximately one year after operation. The patients were evaluated preoperatively and grouped in the life expectancy classification of Smithwick (10), patients in group IV having the poorest prognosis.

2. Adrenal cortical substitution therapy: Five of the seven patients tested were receiving cortisone at the time of their initial postadrenalectomy cerebral blood flow study. These patients were maintained with oral cortisone (6 to 25 mg. per day) alone or cortisone and buccal desoxycorticosterone.[2] T. C. (along with S. C.) required no cortisone at the time of the initial postadrenalectomy study, but he required cortisone and desoxycorti-

[1] This investigation is being supported, in part, by research grants from the National Heart Institute, U. S. Public Health Service (H-361), the Squibb Institute for Medical Research, Sandoz Pharmaceuticals, Eli Lilly and Company and Ciba Pharmaceutical Products, Inc.

[2] Generous supplies of adrenal cortical extract, desoxycorticosterone acetate and cortisone were made available for our studies by the Upjohn, Ciba, Schering and Merck Companies.

costerone at the time of the postsympathectomy study, presumably because of interference with adrenal cortical remnants during the sympathectomy operations. I. B. did not require cortisone at the time of the second postadrenalectomy study. All patients were ambulatory and outpatients at the time of the postadrenalectomy tests.

3. Technique of study: Cerebral blood flow was determined in the supine position by the nitrous oxide method and cerebral oxygen consumption, mean arterial pressure and arterial and jugular venous blood constituents were determined as previously described (1, 7).

RESULTS

Table I contains the results obtained in each test. The means of eleven [8] observations in the seven patients after adrenalectomy are compared with the mean preoperative values in Table II. Mean preoperative values in this group of patients were not significantly different from those observed in a larger group of hypertensive patients (11). After adrenalectomy, mean values for cerebral oxygen consumption, jugular venous oxygen content, jugular venous oxygen saturation and tension, arterial and jugular venous carbon dioxide tension and cerebral respiratory quotient were not appreciably altered. The averages showed a slight increase in cerebral blood flow and a reduction in cerebral arteriovenous oxygen difference. The reductions in mean arterial pressure, cerebral vascular resistance, arterial and jugular hydrogen ion concentration, arterial and jugular venous carbon dioxide content and arterial oxygen content were also significant ($p < 0.05$).

[8] The postsympathectomy-unilateral adrenalectomy results in patient S. C. shown in Table I are not included. Both postadrenalectomy results in patient T. C. are included.

DISCUSSION

Wilkins' hemodynamic studies during procedures designed to lower the blood pressure of hypertensive patients have revealed that total and regional blood flows remained adequate in spite of sizeable lowerings of the pressure (12). The observations of Wilkins and his co-workers, the present study, and previously reported studies of cerebral blood flow and oxygen consumption in hypertensive patients (4–9) are reassuring in the face of the argument that hypertension is merely an adjustment to organic vascular disease and that to disturb this adjustment will cause cerebral or other regional circulatory embarrassment.

The data obtained by this investigation indicated, in the hypertensive patients studied, that the mean cerebral oxygen consumption, blood flow and arteriovenous oxygen difference and jugular venous oxygen tension were within the normal range and

TABLE I

Effects of subtotal adrenalectomy combined with sympathectomy on cerebral circulation and oxygen metabolism

Patient	Sex	Age	Smith-wick group	Carbon dioxide								Blood pH. 37°C.			
				Content *Volumes %*				Tension				Arterial		Venous	
				Arterial		Venous		Arterial		Venous					
				B*	A†	B	A	B	A	B	A	B	A	B	A
I. B.	F	44	IV	50.5	40.5 42.2	58.4	47.2 48.9	39	31 37	53	40 44	7.45	7.44 7.37	7.35	7.38 7.32
A. F.	F	50	IV	56.2	42.6 51.0	62.0	48.9 56.3	47	40 40	54	52 55	7.40	7.35 7.35	7.35	7.26 7.29
J. D.	M	42	II	47.8	41.5	56.4	49.9	40	37	50	46	7.41	7.40	7.36	7.36
E. D.	M	43	II	48.1	47.3	53.5	52.2	39	42	48	52	7.43	7.38	7.36	7.31
S. W.	M	47	IV	50.4	49.0 32.5	57.5	54.8 38.6	41	38 38	50	46 45	7.41	7.42 7.26	7.37	7.38 7.20
T. C.	M	42	IV	59.1	45.3 44.7	66.9	51.8 52.8	47	36 46	58	47 58	7.45	7.44 7.31	7.40	7.37 7.26
S. C.	F	33	IV	45.1	46.8 37.5	52.4	55.3 43.2	30	38 38	42	52 47	7.50	7.41 7.30	7.40	7.33 7.26

* B denotes study made before surgical procedure.
† A denotes study made after surgical procedure.

TABLE I—*Continued*

Patient	Sex	Age	Smithwick group	Oxygen								Cerebral									
				Content *Volumes %*				Tension *mm. Hg*		Saturation *% oxy. Hb.*		Blood flow‡		Oxygen uptake‡		Vascular resistance§		Respiratory quotient		Mean art. press. *mm. Hg*	
				Arterial		Venous		Venous		Venous											
				B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
I. B.	F	44	IV	17.1	14.9 15.5	9.1	8.2 7.9	30	27 30	55	51 52	50	44 44	4.0	2.9 3.3	3.7	2.7 2.6	0.99	1.00 0.88	186	119 116
A. F.	F	50	IV	15.2	13.6 14.8	8.7	7.3 9.0	32	29 35	58	47 61	52	64 64	3.4	4.0 3.7	3.4	1.5 1.8	0.89	1.00 0.91	175	98 116
J. D.	M	42	II	19.5	18.9	10.7	10.7	30	26	55	47	38	37	3.3	3.0	4.6	3.9	0.98	1.02	174	143
E. D.	M	43	II	18.5	18.0	12.2	12.9	39	39	69	68	72	86	4.5	4.4	2.2	1.4	0.86	0.96	158	116
S. W.	M	47	IV	17.2	13.8 17.3	9.8	7.8 10.4	30	32 37	55	58 61	51	56 49	3.8	3.4 3.4	2.8	2.3 2.4	0.96	0.97 0.88	144	126 116
T. C.	M	42	IV	19.5	19.7 19.4	11.5	12.5 11.3	30	36 36	57	65 61	49	63 72	3.9	4.5 5.8	3.7	2.2 1.5	0.98	0.90 1.00	181	138 107
S. C.	F	33	IV	14.8	17.1 14.4	7.6	8.5 8.6	24	29 29	44	51 47	55	39 74	4.0	3.4 4.3	3.2	4.3 1.4	1.01	0.99 0.98	175	168 100

‡ cc./100 Gm./min.
§ Cerebral vascular resistance is mean arterial pressure divided by cerebral blood flow expressed as mm. Hg/cc. blood/100 Grams brain/minute.

TABLE I—*Continued*

Patient	Sex	Age	Smithwick	Time after operation *Months*	Type of surgical procedure
I. B.	F	44	IV	3 12	98% adrenalectomy and bilateral subdiaphragmatic sympathectomy and splanchnicectomy.
A. F.	F	50	IV	3 12	98% adrenalectomy and bilateral subdiaphragmatic sympathectomy and splanchnicectomy.
J. D.	M	42	II	8	98% adrenalectomy and bilateral subdiaphragmatic sympathectomy and splanchnicectomy.
E. D.	M	43	II	3	95% adrenalectomy and bilateral subdiaphragmatic sympathectomy and splanchnicectomy.
S. W.	M	47	IV	1 15	93% adrenalectomy.
T. C.	M	42	IV	3 6	91% adrenalectomy. Bilateral subdiaphragmatic sympathectomy and splanchnicectomy.
S. C.	F	33	IV	3 14	Smithwick sympathectomy and total right adrenalectomy. 90% left adrenalectomy, *i.e.*, 95% total adrenalectomy.

were not reduced by the 30 per cent decrease in mean arterial pressure after adrenalectomy.

When the mean reductions in cerebral vascular resistance and mean arterial pressure after sympathectomy (9) were compared with the reductions observed in the patients who had sympathectomy plus adrenalectomy (eight observations in six patients), it is apparent that the reductions observed after adrenalectomy combined with sympathectomy were significantly greater ($p < 0.01$) than after sympathectomy alone (Table III).

The greater reduction in arterial carbon dioxide content and arterial pH after adrenalectomy (Tables II and III) are unexplained. The changes in arterial carbon dioxide content, tension and pH in individual patients did not correlate well with the increased cerebral blood flow, reduced cerebral vascular resistance or reduced mean arterial pressure. All but one patient (J. D.) have shown an increase in arterial hydrogen ion concentration when measurements were made three to fifteen months after adrenalectomy. This patient had the least reduction (18 per cent) in mean arterial pressure of this group.

The whole blood buffer base, (BB +) b, is the quantity that gives a true measure of acid or alkali deficit or excess in the extracellular fluid. When the mean values of Table II were entered on

TABLE II

*Mean changes in cerebral hemodynamics and oxygen metabolism and blood constituents of patients with essential hypertension after adrenalectomy**

	B†	A†	s.d.†	t†	p†
Mean arterial pressure	170	118	23.6	7.3	<0.01
Cerebral blood flow	52	59	10.2	2.2	0.05
Cerebral vascular resistance	3.4	2.2	0.6	6.0	<0.01
Cerebral oxygen uptake	3.8	3.9			
Cerebral arteriovenous oxygen difference	7.5	6.7	0.5	5.3	<0.01
Jugular venous oxygen content	9.9	9.7			
Jugular oxygen saturation	56	56			
Jugular pH	7.37	7.32	0.06	2.8	<0.05
Jugular oxygen tension	31	32			
Femoral arterial oxygen content	17.4	16.4	1.1	3.0	<0.05
Arterial carbon dioxide content	51.0	43.1	5.3	5.0	<0.01
Arterial carbon dioxide tension	40	38			
Jugular venous carbon dioxide content	58.1	49.5	5.5	5.2	<0.01
Jugular venous carbon dioxide tension	51	48			
Arterial pH	7.44	7.37	0.06	3.7	<0.01
Cerebral respiratory quotient	0.95	0.95			

* The averages include all eleven post adrenalectomy observations (1 month to 15 months) in seven patients regardless of time after operation.

† B denotes values preoperatively; A values postoperatively; s.d. denotes standard deviation of individual differences; t the ratio of difference between means and estimated standard deviation; and p, probability. Units are same as in Table I.

the nomogram of Singer and Hastings (13), the (BB +) b before adrenalectomy was within the normal range, 50 mEq. per L. and after adrenalectomy was below normal, being 42 mEq. per L. This suggested a metabolic acidosis with the base deficit probably caused by loss of sodium.

As is well known adrenal cortical insufficiency is associated with a loss of sodium, chloride, and bicarbonate and retention of potassium (14). It has been stated that the loss of sodium exceeds that of chloride and in addition urinary ammonia excretion is decreased (15). These factors would combine to produce a metabolic acidosis. While no measurements of excretion were made in our patients, mild adrenal cortical insufficiency cannot be excluded.

TABLE III

*Mean changes and standard deviation of individual differences in cerebral hemodynamics and oxygen metabolism of patients with essential hypertension after sympathectomy combined with adrenalectomy compared with the changes observed after sympathectomy**

Operative procedure and number of observations	Mean arterial pressure	Cerebral vascular resistance pressure/flow	Cerebral blood flow	Cerebral arterio-venous oxygen differences	Jugular oxygen content	Arterial carbon dioxide content
	mm. Hg		*cc./100 Gm./min.*	*vols. %*	*vols. %*	*vols. %*
Adrenalectomy combined with sympathectomy (8 observations in 6 patients)	−61 ± 17†	−1.4 ± 0.6	8 ± 11	−0.8 ± 0.6	−0.5 ± 0.9	−7.7 ± 4.5
Sympathectomy (9 observations in 9 patients—Data of Shenkin)	−20 ± 23	−0.5 ± 0.5	2 ± 11	−0.3 ± 1.0	−1.4 ± 1.0	−0.2 ± 4.0
Statistical significance of difference means	$p < 0.01$	$p < 0.01$	$p > 0.1$	$p > 0.1$	$p > 0.05$	$p < 0.01$

* After sympathoadrenal surgery greater reductions (significant difference of difference means) were observed in mean arterial pressure, cerebral vascular resistance and arterial carbon dioxide content.

† Denotes the mean change with the direction denoted by plus or minus and the mean changes are followed by the standard deviation of the individual differences.

Our data on this metabolic acidosis after adrenalectomy showing an increased blood flow to the brain are at variance with the experimentally induced acidosis reported by Schieve and Wilson (16). These investigators observed a reduction in cerebral blood flow and an increase in cerebral arteriovenous oxygen difference and cerebral vascular resistance. The metabolic acidosis of diabetes which Kety, Polis, Nadler, and Schmidt studied (17) also showed a reduced cerebral blood flow and increased cerebral vascular resistance. However, cerebral arteriovenous oxygen difference did not change with the restoration to normal of both the arterial hydrogen ion concentration and arterial carbon dioxide tension. The mean cerebral oxygen uptake of the diabetic patients was increased toward normal as the acidosis was corrected. Thus, the results observed in diabetic acidosis are probably not pertinent as mean cerebral oxygen consumption was unchanged in the acute experiments of Schieve and Wilson as well as in the postadrenalectomy studies.

The data presented afford no direct evidence bearing upon the mechanism by which the cerebral vascular resistance was reduced following sympathoadrenal surgery. On the other hand the hypothesis (9) that an intrinsic mechanism reciprocally adjusts the cerebral vascular resistance to alterations of perfusion pressure does not appear to be invalidated by these studies. We have shown that cerebral blood flow is increased not only with excess hydrogen ions but is also increased when 5 per cent carbon dioxide is inhaled (18) so that chemical factors as well as nervous must be considered.

The observations of Clark, Crosley, and Barker on renal blood flow, renal vascular resistance and glomerular filtration rate in patients studied before and after subtotal adrenalectomy are of interest (19). The change in glomerular filtration rate after adrenalectomy was found to be small and variable. In five of six patients effective renal blood flow increased at a time when mean arterial blood pressure was decreased by adrenalectomy, thus indicating a reduction in overall renal vascular resistance.

SUMMARY

Studies are reported of cerebral blood flow and oxygen consumption and arterial and internal jugular blood gases in seven patients with severe essential hypertension before and after a reduction in blood pressure achieved by 90 per cent adrenalectomy alone or combined with sympathectomy.

Mean values of oxygen consumption, jugular venous oxygen content, and jugular venous oxygen tension remained essentially unchanged and cerebral blood flow increased slightly after adrenalectomy.

The high cerebral vascular resistance of essential hypertension has been lowered toward the normal range. The mechanism of the reduction has not been established. A compensated metabolic acidosis was observed after subtotal adrenalectomy. The mean reduction in cerebral vascular resistance as well as the mean decrease in mean arterial pressure appeared to be greater after combined sympathectomy-adrenalectomy than the reductions observed after sympathectomy alone.

Data from this and other studies of the effect of reduction of blood pressure by surgical procedures and depressor drugs suggest that the increased cerebral vascular tone of certain selected hypertensive patients is reversible, and that cerebral oxygen uptake and jugular venous oxygen tension remain constant in the supine position when the perfusion pressure is lowered by these procedures.

ACKNOWLEDGMENT

The authors wish to acknowledge the aid of Drs. C. W. Crumpton, W. C. Klingensmith, and D. P. McCallie in some of the tests and the assistance of Drs. Charles C. Wolferth, Carl F. Schmidt, and William A. Jeffers in the preparation of this manuscript.

REFERENCES

1. 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.
2. McMichael, J., The management of hypertension. Brit. M. J., 1952, **1**, 933.
3. Dripps, R. D., Objective tests of circulatory adequacy *in* Advances in Medicine and Surgery from the Graduate School of Medicine of the University of Pennsylvania. Philadelphia, W. B. Saunders Company, 1952, p. 174.
4. Hafkenschiel, J. H., Crumpton, C. W., Moyer, J. H., and Jeffers, W. A., The effects of dihydroergocor-

nine on the cerebral circulation of patients with essential hypertension. J. Clin. Invest., 1950, **29**, 408.

5. Crumpton, C. W., Klingensmith, W. C., Keffer, N. J., and Hafkenschiel, J. H., Effects of protoveratrine on cerebral hemodynamics and oxygen metabolism in hypertensive subjects. Federation Proc., 1951, **10**, 32.
6. Crumpton, C. W., Murphy, Q. R., Whitmore, J. J., Capps, R. T., and Orth, O. S., Cerebral circulatory and metabolic changes following intramuscular hexamethonium bromide (C-6) in subjects with severe hypertensive retinopathy. Federation Proc., 1952, **11**, 335.
7. Hafkenschiel, J. H., and Friedland, C. K., The effects of l-hydrazinophthalazine on cerebral blood flow, vascular resistance, oxygen uptake and jugular oxygen tension in hypertensive subjects. J. Clin. Invest., 1953, **32**, 655.
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. Shenkin, H. A., Hafkenschiel, J. H., and Kety, S. S., Effects of sympathectomy on the cerebral circulation of hypertensive patients. Arch. Surg., 1950, **61**, 319.
10. Smithwick, R. H., The effect of sympathectomy upon the mortality and survival rates of patients with hypertensive cardiovascular disease *in* Hypertension. A symposium held at the University of Minnesota on September 18, 19, and 20, 1950, in honor of E. T. Bell, B. J. Clawson and G. E. Fahr, E. T. Bell, ed., Minneapolis, University of Minnesota Press, 1951, p. 429.
11. Hafkenschiel, J. H., Crumpton, C. W., and Friedland, C. K., Cerebral oxygen consumption in essential hypertension. Constancy with age, severity of the disease, sex, and variations of blood constituents, as observed in 101 patients. J. Clin. Invest., 1954, **33**, 63.
12. Wilkins, R. W., The hemodynamic effects of various types of therapy in hypertensive patients *in* Hypertension. A symposium held at the University of Minnesota on September 18, 19, and 20, 1950, in honor of E. T. Bell, B. J. Clawson and G. E. Fahr, E. T. Bell, ed., Minneapolis, University of Minnesota Press, 1951, p. 400.
13. Singer, R. B., and Hastings, A. B., An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. Medicine, 1948, **27**, 223.
14. Sorkin, S. Z., Addison's disease. Medicine, 1949, **28**, 371.
15. Loeb, R. F., The adrenal cortex. Combined staff clinics. Am. J. Med., 1949, **7**, 100.
16. Schieve, J. F., and Wilson, W. P., The changes in cerebral vascular resistance of man in experimental alkalosis and acidosis. J. Clin. Invest., 1953, **32**, 33.
17. Kety, S. S., Polis, B. D., Nadler, C. S., and Schmidt, C. F., The blood flow and oxygen consumption of the human brain in diabetic acidosis and coma. J. Clin. Invest., 1948, **27**, 500.
18. Hafkenschiel, J. H., and Friedland, C. K., Physiology of the cerebral circulation in essential hypertension: the effects of 5% carbon dioxide oxygen mixtures on cerebral hemodynamics and oxygen metabolism. Proceedings American Society for Pharmacology and Experimental Therapeutics, Madison, Wisconsin, September 10, 1952. Abstract, J. Pharmacol. & Exper. Therap., 1952, **106**, 391.
19. Clark, J. K., Crosley, A. P., Jr., and Barker, H. G., Effect of sub-total adrenalectomy on renal hemodynamics and electrolyte excretion in human hypertension. Proc. Am. Soc. Clinical Investigation, April 30, 1951. J. Clin. Invest., 1951, **30**, 633.