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Variations of Blood Constituents, As observed In 101 Patients**

Joseph H. Hafkenschiel, ... , Charles W. Crumpton, Carl K. Friedland

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# CEREBRAL OXYGEN CONSUMPTION IN ESSENTIAL HYPERTENSION<sup>1</sup>

CONSTANCY WITH AGE, SEVERITY OF THE DISEASE, SEX, AND VARIATIONS OF BLOOD CONSTITUENTS, AS OBSERVED IN 101 PATIENTS

By JOSEPH H. HAFKENSCHIEL, CHARLES W. CRUMPTON,<sup>2</sup> AND CARL K. FRIEDLAND WITH THE TECHNICAL ASSISTANCE OF HENRIETTA BRANDT, JANET MERRILL, AND NELLY K. LINCOLN

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

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It has been shown that patients with essential hypertension have the same cerebral oxygen demands as normotensive subjects (1-3). Thirty-four observations in 14 normotensive subjects formed the basis of Kety and Schmidt's report (1). Recently, measurements in six patients with essential hypertension have been reported (2), as part of a study of the effects of aging, arteriosclerosis and hypertension upon the cerebral circulation.

Our initial report included studies upon 13 hypertensive patients (3). Observations have now been made in 88 additional hypertensive patients distributed in several age groups (4-9). The results in these 101 patients have been analyzed to determine whether cerebral oxygen metabolism varies with age, sex, degree of vascular damage elsewhere in the body (10, 11), and with varying arterial and venous blood gas tension.

## METHODS

Patients reported in this study were selected according to the following clinical criteria: (a) A diastolic blood pressure persistently elevated above 100 mm. Hg; (b) damage in one or more vascular beds as evidenced by retinopathy, graded according to Wagener and Keith (11), electrocardiographic and/or fluoroscopic changes of left ventricular hypertrophy and impaired renal function as measured by urea clearance, and intravenous phenolsulphonphthalein excretion; and (c) hemoglobin values not less than 12 grams per 100 ml. and hematocrit levels not less than 38 per cent. At the time of these studies, no patient had evidence of mental or neurological

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<sup>2</sup> Present address: Wisconsin General Hospital, Madison, Wisconsin.

disturbances, congestive heart failure, or a blood urea nitrogen persistently above 20 mg. per cent.

Cerebral oxygen consumption (CMRO<sub>2</sub>) and cerebral blood flow (CBF) were measured by the nitrous oxide method (1), the validity of which we have tested by paired experiments (4).

## RESULTS

Table I contains the mean values for the 101 hypertensive patients analyzed for this report. Also tabulated are the standard errors of the cerebral functions measured and arterial and jugular venous blood constituents of the hypertensive group. Data previously reported (1, 12) for normotensive subjects are included for comparison. Cerebral oxygen consumption and CBF in both groups are almost identical. The significant differences ( $p < 0.01$ ) are in mean arterial pressure, cerebral vascular resistance and cerebral respiratory quotient, as noted previously (3).

Variations of CMRO<sub>2</sub> with age, Smithwick and Keith-Wagener groups, sex, and blood constituents in these patients are shown in Tables II, III, IV and V. There were no significant deviations in the mean values of any of the sub groups from normotensive values. Cerebral oxygen consumption varies directly with cerebral blood flow ( $r = 0.45 \pm 0.08$ ,  $p < 0.01$ ) and inversely with cerebral vascular resistance ( $r = -0.65 \pm 0.07$ ,  $p < 0.01$ ) (Figure 1). These observations suggest that the CMRO<sub>2</sub> does not vary significantly from normal in these selected patients with essential hypertension. More observations are needed in hypertensive patients over the age of fifty who have diastolic as well as systolic hypertension in order to compare their cerebral oxygen uptake with that of aged subjects with no central nervous system disease, who are reported by Fazekas, Alman, and

TABLE I

*Cerebral blood flow, oxygen uptake and blood constituents in 101 patients with essential hypertension: mean values and standard error compared with those of Kety and Schmidt for normotensive males of the third decade*

	Hypertension (101)*	Normals (34)*
<b>Cerebral</b>		
Blood flow, ml. per 100 Gm./min.	57 ± 1.3	54 ± 2.2
Oxygen uptake, ml. per 100 Gm./min.	3.5 ± 0.07	3.3 ± 0.07
Oxygen diff., ml. per 100 ml.	6.2 ± 0.11	6.3 ± 0.21
Resp. quotient	0.90 ± 0.01†	0.99 ± 0.02
Vascular resistance (pressure/flow)	2.8 ± 0.08‡	1.6 ± 0.07
<b>Arterial</b>		
Oxygen content, ml. per 100 ml.	17.2 ± 0.19	18.0
CO <sub>2</sub> content, ml. per 100 ml.	50.4 ± 0.56	49.0
pH	7.41 ± 0.005	7.40
pCO <sub>2</sub> , mm. Hg	42 ± 0.5	40
Mean blood pressure, mm. Hg	153 ± 2.1‡	86 ± 1.2
<b>Internal jugular</b>		
Oxygen content, ml. per 100 ml.	11.0 ± 0.2	11.0
CO <sub>2</sub> content, ml. per 100 ml.	56.1 ± 0.55	55.0
pH	7.35 ± 0.005	7.34
pCO <sub>2</sub>	51 ± 0.6	51
Oxygen saturation, per cent	62 ± 0.6	63
pO <sub>2</sub>	35 ± 0.4	36
Hematocrit	43.3 ± 0.3	44.5 ± 6.0‡
Hemoglobin	14.2 ± 0.14	15.0 ± 2.0‡

\* Figures in parentheses denote number of observations.

† Denotes significant difference from normal ( $p < 0.01$ ).

‡ Denotes mean values and standard deviations given by Wintrobe.

Bessman to show a decrease (13). Likewise, more observations are needed in hypertensive patients in the second and third decades, to compare with the young subjects having a normal blood pressure (1). Slightly higher values of CBF are evident in hypertensive patients between the ages of 16 and 30 (Table II), but the difference between the mean values for these and normotensive subjects (1) is not significant. Although there is a trend (Table II) for cerebral blood flow to be lower in the older patients in the hypertensive groups, likewise more patients must be studied in order to establish statistically significant differ-

TABLE II

*Variation of cerebral oxygen uptake and cerebral blood flow in hypertensive patients of various age decades*

Age group	Number of patients	Oxygen uptake		Blood flow	
		ml. per 100 Grams/minute			
		Mean	S.D.*	Mean	S.D.
16-20	2	3.1 ± 0.2		66 ± 6	
21-30	11	3.8 ± 0.7		62 ± 13	
31-40	32	3.7 ± 0.7		59 ± 12	
41-50	47	3.4 ± 0.7		55 ± 13	
51-60	8	3.3 ± 0.6		56 ± 11	
61-70	2	3.2 ± 0.4		50 ± 9	

\* S.D.: Standard Deviation.

TABLE III

*Variation of cerebral oxygen uptake and cerebral blood flow in hypertensive patients grouped as to severity of the disease*

Disease severity grade	Grouped according to the criteria of					
	Smithwick			Keith and Wagener		
	No.	CBF*	CMRO <sub>2</sub> †	No.	CBF	CMRO <sub>2</sub>
1	20	58 ± 13‡	3.6 ± 0.8	7	57 ± 11	3.5 ± 0.7
2	30	59 ± 14	3.5 ± 0.6	39	59 ± 14	3.8 ± 0.7
3	16	58 ± 15	3.5 ± 0.8	34	54 ± 14	3.4 ± 0.8
4	35	55 ± 10	3.4 ± 0.7	18	58 ± 10	3.5 ± 0.7

\* CBF denotes blood flow in ml. per 100 Grams of brain per minute.

† CMRO<sub>2</sub> denotes oxygen uptake in ml. per 100 Grams of brain per minute.

‡ Figures represent mean values with the standard deviation of the individual differences.

TABLE IV

*Variation of cerebral oxygen consumption in men and women with hypertension\**

	Number	Oxygen uptake ml. per 100 Grams/min.
Men	50	3.4 ± 0.7
Women	51	3.6 ± 0.7

\* Figures represent mean values with the standard deviation of the individual differences.

TABLE V

Variation in cerebral oxygen consumption in patients with essential hypertension grouped according to the degree of difference in blood constituents and cerebral respiratory quotient

Mean values and standard deviations of blood constituents in 101 patients		Cerebral oxygen consumption ml. per 100 Grams/min.	
		Beyond $\pm 1$ S.D.*	Within $\pm 1$ S.D.
Arterial			
Oxygen content	17.2 $\pm$ 1.9	3.5 $\pm$ 0.7 (32)†	3.5 $\pm$ 0.7 (66)
Carbon dioxide	42 $\pm$ 5	3.5 $\pm$ 0.7 (22)	3.5 $\pm$ 0.7 (79)
Hydrogen ion	7.41 $\pm$ 0.05	3.5 $\pm$ 0.7 (17)	3.5 $\pm$ 0.7 (74)
Jugular			
Oxygen tension	35 $\pm$ 4	3.5 $\pm$ 0.7 (13)	4.1 $\pm$ 0.7 (21)
Cerebral			
Respiratory quotient	.90 $\pm$ 0.12	3.2 $\pm$ 0.6 (22)	3.5 $\pm$ 0.7 (79)

\* S.D.: Standard Deviation.

† Figures in parentheses denote number of observations.

ences. Our mean values (CBF 50 and CMRO<sub>2</sub> 3.2) for hypertensive patients aged 60 to 70 are about the same as those reported in normotensive patients of the same age group (2).

The mean values for cerebral arteriovenous oxygen difference, jugular venous blood carbon dioxide tension, oxygen tension and hydrogen ion concentration (Table I) suggest that cerebral ischemia is not a basic disturbance in this group of hypertensive patients having a mean age of 41  $\pm$  9 years, as was reported by Raab after he studied an older group (14). The data of Table I do not support the findings of Waldron and Goldstein (15) that a disturbance in acid-base balance exists in hypertension. We believe the younger mean age of our patients and absence of pulmonary disease may explain the discrepancy. The reduced cerebral respiratory quotient remains unexplained.

Linear distributions are not apparent when the individual observations of mean arterial pressure, arterial oxygen content, arterial carbon dioxide tension, arterial hydrogen ion concentration, jugular venous oxygen tension and cerebral respiratory quotient are plotted graphically against cerebral oxygen consumption. There, also, is not significant variation in the mean values of cerebral oxygen consumption when the patients are grouped according to the degree that the blood oxygen, pH, and CO<sub>2</sub> content vary (Table V).

#### COMMENT

The measurements of cerebral oxygen metabolism of this and the previous report (3) indicate

that the oxygen requirement of the hypertensive's brain is within the range of that of normal subjects and is essentially constant in selected patients of different ages and survival groups who have a normal central nervous system. Despite a mean increase of 75 per cent in cerebral vascular resistance, the blood supply to the brain is automatically adjusted to its oxygen requirements, probably through an intrinsic mechanism which adjusts the cerebrovascular resistance to alterations of perfusion pressure and thus maintains the cerebral blood flow within the normal range (5).

This mechanism of regulating cerebral blood

TABLE VI

Cerebral oxygen uptake in essential hypertension—mean values after various experimental procedures

Procedure	No. of observations	Oxygen uptake	
		Initial	Experimental
Intravenous placebo	6	3.8	3.4
Procaine stellate block	5	3.5	3.0
Differential spinal block	17	3.3	3.2
20° head up tilt	18	3.5	3.8*
Sympathectomy	9	3.5	3.5
Sympathectomy and adrenalectomy	11	3.9	3.9
Depressor drugs			
Dihydroergocornine	12	3.5	3.6
Protoveratrine	15	3.5	3.5
Hydrazinophthalazine	8	3.6	3.2
Hexamethonium†	6	3.6	4.0
Altered arterial gas tension			
5% CO <sub>2</sub>	8	3.8	3.6

\* Denotes statistically significant increase ( $p < 0.01$ ).

† Data of Crumpton and Murphy, 1952 (18).

flow to meet the oxygen demands does not function perfectly inasmuch as we have observed increased cerebral arteriovenous oxygen differences when cerebral oxygen consumption has not changed or has increased during induced hypotension (5-7). Such observations suggest that the increased cerebral vascular resistance, although reversible, is not capable of complete relaxation under all conditions and that CBF is not precisely adjusted to keep unchanged the cerebral oxygen

consumption (Table VI), the arteriovenous oxygen difference, and jugular oxygen tension. The evidence to date suggests that reductions in the latter to 25 mm. Hg or lower may activate chemoreceptors and initiate reflexes to restore cerebral gaseous homeostasis (6).

The few observations in young patients with coarctation of the aorta suggest that cerebral oxygen consumption varies directly with cerebral blood flow. These patients show an increased

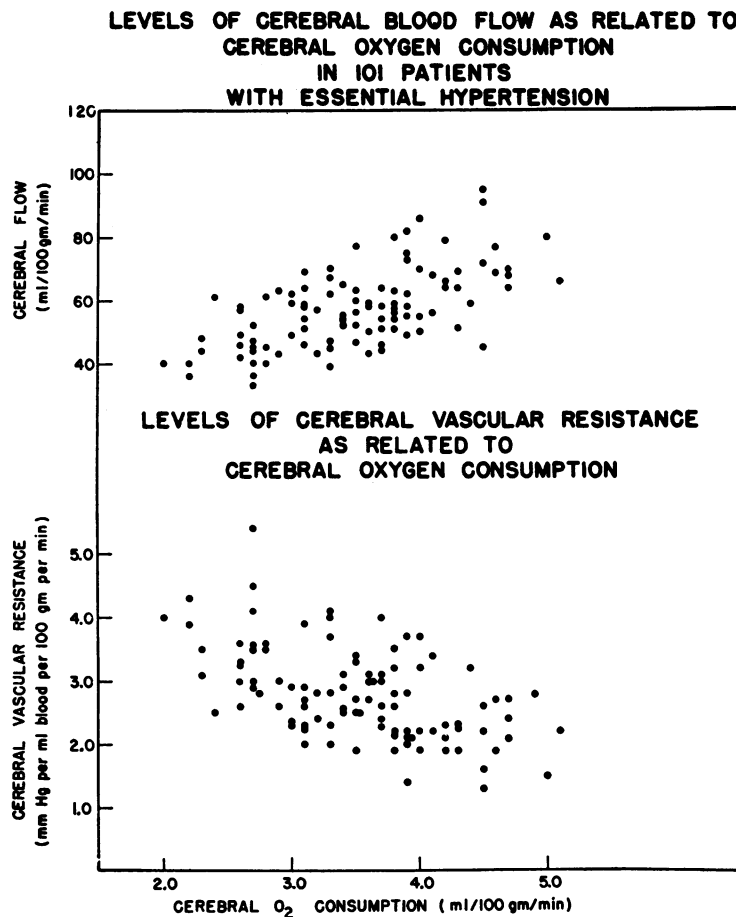


FIG. 1. THE INDIVIDUAL OBSERVATIONS IN 101 HYPERTENSIVE PATIENTS OF CEREBRAL OXYGEN CONSUMPTIONS HAVE BEEN PLOTTED AGAINST CEREBRAL BLOOD FLOW

Cerebral oxygen consumption varies directly with cerebral blood flow ( $r = 0.45$ ) and inversely with cerebral vascular resistance ( $r = -0.65$ ). The highest cerebral oxygen uptake (5.1) was observed in a 31 year-old female with CBF 66. Three patients were observed with low  $CMRO_2$  (2.0 to 2.2) and all had low CBF (36 to 40). These findings confirm the observations of Shenkin *et al.* (2) that levels of cerebral oxygen consumption below those usually found in diabetic coma or pentothal narcosis do occur in conscious subjects without clinical evidence of cerebral impairment.

blood flow and a normal cerebral arteriovenous oxygen difference (16). After the aortic defect was corrected the flow was reduced toward normal and cerebral arteriovenous oxygen difference remained unchanged (17). Further observations in such patients are needed.

The individual observations in CBF and  $CMRO_2$  are plotted in the upper half of Figure 1. These data suggest that cerebral blood flow increases as oxygen consumption increases. Reduction of arterial pressure by differential spinal sympathetic block, has disclosed that, despite a reduction in cerebral blood flow, cerebral oxygen uptake remains unchanged as a result of an increased cerebral arteriovenous oxygen difference (6). More recent studies of the effect of 5 per cent carbon dioxide inhalation in hypertensive subjects disclose that the  $CMRO_2$  remains constant as the cerebral blood flow increases and the cerebral arteriovenous oxygen difference is reduced (8). Thus the evidence at hand indicates that the cerebral oxygen consumption in patients with essential hypertension is kept constant by a reciprocal relationship between CBF and the cerebral arteriovenous oxygen difference.

Experiments designed to study the effect of reductions in cerebral vascular resistance (Table VI) (4, 5, 7, 8, 9, 18) further suggest that cerebral oxygen consumption remains constant as a result of a reciprocal relationship between cerebral blood flow and cerebral arteriovenous oxygen difference keeping cerebral jugular oxygen tension above 25 mm. Hg. These observations demonstrate how misleading statistically significant coefficients of correlation might be (Figure 1) if causal relationships are assumed and if experiments are not designed to test the suggested hypothesis. The results of our studies add to the growing body of evidence that the cerebral oxygen metabolic rate is about 50 ml. of oxygen per minute, assuming a 1400 gram brain, in both the patients with essential hypertension and in normotensive subjects of various age groups (1, 2, 19).

#### SUMMARY

Measurements of cerebral blood flow, arteriovenous oxygen difference and cerebral oxygen consumption were made using the nitrous oxide method in 101 selected patients with essential

hypertension. Mean values for cerebral oxygen uptake have been calculated for patients grouped as to age, severity of the disease and sex. The data on cerebral oxygen consumption have been plotted graphically against cerebral blood flow, cerebral vascular resistance, cerebral respiratory quotient, mean arterial pressure, arterial oxygen content, carbon dioxide tension, hydrogen ion concentration and jugular venous oxygen tension.

The cerebral oxygen uptake in patients with essential hypertension is the same as that of normotensive subjects. There is likewise no significant variation in oxygen uptake or blood flow in hypertensive patients regardless of age, severity of the disease, sex, or the degree that arterial blood constituents differ.

Cerebral blood flow varies directly with cerebral oxygen consumption and inversely with cerebral vascular resistance, but there is no evidence at present of a causal relationship.

From the data obtained, we believe the following conclusions may be drawn:

The cerebral oxygen consumption in healthy hypertensive patients varies widely but is not significantly different from that of normotensive subjects and does not vary appreciably in hypertensive patients of different sexes, ages or prognosis groups.

The constancy of cerebral oxygen consumption in these studies suggests that the cerebral vessels in hypertension may possess an effective, but somewhat imperfect, intrinsic control in relation to the oxygen metabolic demands of the brain.

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