THE EFFECTS OF ALTERED ARTERIAL TENSIONS OF CARBON DIOXIDE AND OXYGEN ON CEREBRAL BLOOD FLOW AND CEREBRAL OXYGEN CONSUMPTION OF NORMAL YOUNG MEN [1]

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A method for measuring quantitatively the volume of cerebral blood flow in man by inhalation of nitrous oxide (1) found its first application in a study of the cerebral circulatory effects of low CO_2 tension achieved by hyperventilation; of high CO_2 tension, and of high and low O_2 tensions obtained by inhalation of appropriate gas mixtures (2). Only the first part of this study, the effects of active and passive hyperventilation, has been published in detail (3). The purpose of the present paper is to present the remainder of these findings and to derive from them, together with those of the hyperventilation experiments, evidence bearing on the intrinsic control of the human cerebral circulation as revealed by quantitative measurements.

METHODS

The nitrous oxide technique is described in a preceding report (4). The subjects were young male volunteers in apparently good health. A set of control observations were made after the fasting subject had rested supine for more than an hour. After the control period, the experimental gas mixture (free of nitrous oxide) was administered for 15 to 30 minutes in order to approximate a steady state, and for the removal of N_2O absorbed by the brain during the control cerebral blood flow determination. At the end of this time a change was quickly made to a gas mixture similar to the preceding one but containing 15% N_2O and a second or "experimental" series of observations was made. The composition of the gas mixtures used was as follows: (*1*) for hyperventilation, room air followed by 21% O_2, 64% N_2, 15% N_2O; (*2*) for increased CO_2, 5 or 7% CO_2, 21% O_2, 74 or 72% N_2 followed by 5 or 7% CO_2, 21% O_2, 59 or 57% N_2, 15% N_2O; (*3*) for high O_2, 100% O_2 followed by 85% O_2, 15% N_2O; (*4*) for low O_2, 10% O_2, 90% N_2 followed by 10% O_2, 75% N_2, 15% N_2O.

Blood O_2 and CO_2 analyses were made by the manometric technique of Van Slyke and Neill (5). Blood pH measurements were made anaerobically at 37° C. using a glass electrode. CO_2 tension was calculated by means of the nomograms of Peters and Van Slyke (5). Mean arterial blood pressure was obtained directly from the femoral artery by means of a damped mercury manometer; systolic and diastolic pressures were also measured by the usual auscultatory method. In the middle of both the control and experimental periods ballistocardiograms were recorded. These were used for calculation of a value for cardiac output from the formula of Starr and associates (6), using the correction factor of 1.18 found by Cournand, Ranges and Riley (7).

Cerebral oxygen consumption (CMR_{O_2}) and cerebrovascular resistance (CVR) were calculated from the cerebral blood flow as described previously (4).

RESULTS

The essential data obtained are presented in Tables I, II and III. Mean values obtained with active or passive hyperventilation and previously reported (3) are included for the sake of completeness, with a correction in the cerebral blood flow and oxygen consumption values for the more accurate determination of the brain: blood partition coefficient of N_2O (1.0 instead of the previously used value of 1.3). The arterial and internal jugular N_2O concentration curves from which the cerebral blood flow is calculated are omitted for the sake of brevity but typical curves are shown in Figure 1.

Effects of CO_2 inhalation (5–7%)

There were six studies with 5% CO_2 and two with 7% CO_2; these were grouped together for calculation of mean values. Arterial blood CO_2 content, CO_2 tension, and hydrogen ion concentration all rose as expecfed. Cerebral blood flow underwent a striking and consistent increase averaging 75% (from a mean control value of 53 to a mean value of 93 cc./100 g./min.). Cerebral oxygen consumption was not significantly changed with the result that the increased volume flow was

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associated with an equivalent decrease in the arteriovenous oxygen difference. Along with the increased cerebral blood flow there was a marked reduction in the mean cerebrovascular resistance from 1.6 to 1.1 resistance units. With respect to the general circulatory effects of CO_2, there was a significant rise in arterial blood pressure though cardiac output was not significantly altered. This speaks for a net peripheral vasoconstriction, an effect quite opposite to that exerted on the cerebral circulation.

Effects of high oxygen concentrations

Inhalation of the high oxygen mixtures (85–100%) produced a slight but significant increase in arterial oxygen content with no change in the CO_2 content and tension or the pH of arterial blood. This speaks against any appreciable effects of these oxygen tensions on pulmonary ventilation at least during the first 30 minutes of inhalation. There was a significant decrease of 13% in mean cerebral blood flow (from 52 to 45 cc./100g./min.) with no change in cerebral oxygen consumption. Cerebrovascular resistance exhibited a moderate increase (from 1.7 to 2.2 resistance units) indicating vasoconstriction in the brain as the probable mechanism for the reduction in cerebral blood flow. There was a significant increase in systolic and diastolic blood pressure on auscultatory measurement and in mean arterial pressure measured di-

TABLE I

Effects of altered arterial CO_2 and O_2 tensions on blood constituents

Gas		Subject	Blood CO_2 content				Blood CO_2 tension				Blood O_2 content				Blood pH			
			Arterial		Int. jugular		Arterial		Int. jugular		Arterial		Int. jugular		Arterial		Int. jugular	
			C†	E‡	C	E	C	E	C	E	C	E	C	E	C	E	C	E
			vol. %				*mm. Hg*				*vol. %*							
21% O_2	5% CO_2	S. H.	46.7	49.9	54.0	54.3	42	50	55	58	16.0	16.1	9.5	11.4	7.38	7.33	7.30	7.28
		T. L.	49.4	51.7	55.7	57.2	42	47	53	54	15.7	15.0	9.6	10.7	7.38	7.36	7.33	7.33
		R. Ro.	47.3	50.7	55.1	55.0	41	48	53	56	16.5	16.6	9.6	11.4	7.38	7.34	7.32	7.30
		W. S.	51.5	53.2	57.1	57.4	48	54	60	60	16.5	16.8	10.7	12.7	7.35	7.31	7.29	7.28
		D. M.	48.3	50.4	54.6	55.1	41	46	50	51	18.6	18.5	12.6	14.0	7.40	7.36	7.35	7.33
		R. S.	48.5	52.0	53.8	54.8	42	53	54	58	14.8	15.5	9.8	12.3	7.37	7.30	7.30	7.27
	7% CO_2	J. B.	51.7	55.6	57.7	58.6	45	60	58	66	18.2	18.4	11.9	16.0	7.38	7.28	7.31	7.26
		W. H.	52.5	56.9	58.8	59.5	45	58	52	59	18.3	18.7	12.1	16.0	7.40	7.32	7.35	7.31
		Mean	49.5	52.5*	55.9	56.5*	43	52*	54	58*	16.8	16.9	10.7	13.0*	7.38	7.33*	7.32	7.30
85–100% O_2		J. E.	48.2	47.9	55.3	55.7	39	37	48	48	17.8	19.1	10.8	11.1	7.42	7.45	7.38	7.38
		T. L.	50.1	50.8	58.0	59.1	41	40	51	56	15.5	16.7	7.6	8.3	7.41	7.42	7.36	7.34
		S. H.	51.0	49.3	55.8	55.1	43	41	51	50	16.5	17.6	16.6	12.2	7.39	7.40	7.33	7.34
		R. Re.	51.1	50.9	56.7	57.4	42	42	52	53	16.1	17.5	10.8	10.9	7.40	7.40	7.34	7.34
		J. B.	49.3	49.5	55.6	56.7	43	43	53	54	16.2	17.8	10.5	11.2	7.38	7.39	7.32	7.32
		M. H.	51.4	51.6	57.5	58.7	42	42	52	53	17.2	19.0	11.2	11.5	7.41	7.41	7.36	7.35
		Mean	50.2	50.0	56.5	57.1	42	41	51	52	16.6	18.0*	10.4	10.9*	7.40	7.41	7.35	7.35
10% O_2		R. S.	47.7	48.2	52.4	50.9	41	38	49	43	16.1	9.7	11.1	6.4	7.38	7.41	7.33	7.39
		S. H.	50.6	50.9	55.5	53.9	41	37	48	43	17.0	11.0	11.8	7.0	7.42	7.46	7.37	7.41
		K. T.	45.4	44.9	53.0	48.9	35	31	46	33	17.8	11.6	10.8	7.8	7.45	7.50	7.38	7.68
		W. H.	50.7	49.7	57.1	54.6	42	36	51	44	18.7	13.1	12.4	7.6	7.41	7.48	7.36	7.41
		D. M.	46.8	45.9	54.5	51.5	40	34	51	42	19.4	13.2	12.5	8.0	7.40	7.47	7.34	7.41
		M. H.	49.1	49.0	56.2	53.4	42	37	51	45	17.7	11.2	10.7	6.5	7.39	7.43	7.34	7.40
		J. E.	47.0	46.6	54.5	51.5	39	36	51	43	19.0	12.3	10.8	7.5	7.40	7.45	7.34	7.38
		Mean	48.2	47.9	54.7	52.1*	40	36*	50	41	18.0	11.7*	11.4	7.3*	7.41	7.46*	7.35	7.41*
Hyperventilation active and passive Mean			50.1	41.7*	55.9	52.5*	45	26*	52	38*	17.9	18.6*	11.3	7.8*	7.38	7.54*	7.35	7.48*

* Indicates statistically significant changes.
† C = Control period, room air tensions of O_2 and CO_2.
‡ E = Experimental period, special gas mixture.

TABLE II

Effects of altered arterial CO_2 and O_2 tensions on cerebral circulation and metabolism

Inspired gas		Subject	Cerebral									
			Blood flow		O_2 consumption		Vascular resistance		RQ		A-VO_2	
			C†	E‡	C	E	C	E	C	E	C	E
			cc./100 g./min.		*cc./100 g./min.*		*mm. Hg / cc./100 g./min.*				*vol. %*	
21% O_2	5% CO_2	S. H.	48	65	3.1	3.1	1.7	1.4	1.12	.94	6.5	4.7
		T. L.	50	67	3.1	2.9	1.6	1.3	1.03	1.28	6.1	4.3
		R. Ro.	46	75	3.2	3.9	1.8	1.2	1.13	.83	6.9	5.2
		W. S.	63	90	3.7	3.7	1.3	0.9	.97	1.02	5.8	4.1
		D. M.	56	80	3.4	3.6	1.4	1.2	1.05	1.05	6.0	4.5
		R. S.	63	141	3.2	3.9	1.3	0.7	1.06	1.00	5.0	2.8
	7% CO_2	J. B.	53	135	3.3	3.2	1.7	0.8	.95	1.25	6.3	2.4
		W. H.	45	90	2.8	2.4	1.9	1.0	1.01	1.00	6.2	2.7
		Mean	53	93*	3.2	3.3	1.6	1.1*	1.04	1.05	6.1	3.8*
85–100% O_2		J. E.	40	34	2.8	2.7	2.2	2.7	1.01	.98	7.0	8.0
		T. L.	50	52	4.0	4.4	1.8	1.9	1.00	.99	7.9	8.4
		S. H.	60	49	2.9	2.6	1.4	1.8	.98	1.07	4.9	5.4
		R. Re.	61	55	3.2	3.7	1.5	2.1	.96	.98	5.3	6.7
		J. B.	57	41	3.2	2.7	1.5	2.3	1.10	1.09	5.7	6.6
		M. H.	43	39	2.6	2.9	2.0	2.5	1.02	.95	6.0	7.5
		Mean	52	45*	3.1	3.2	1.7	2.2*	1.01	1.01	6.1	7.1*
10% O_2		R. S.	71	93	3.6	3.1	1.2	0.9	.94	.82	5.0	3.3
		S. H.	60	81	3.1	3.2	1.2	0.8	.96	.75	5.2	4.0
		K. T.	44	82	3.1	3.1	2.0	1.0	1.08	1.05	7.0	3.8
		W. H.	47	58	3.0	3.2	1.9	1.2	1.01	.90	6.3	5.5
		D. M.	57	67	3.9	3.5	1.5	1.2	1.11	1.08	6.9	5.2
		M. H.	52	75	3.6	3.5	1.8	1.0	1.01	.94	7.0	4.7
		J. E.	44	54	3.6	2.6	2.1	1.6	.92	1.02	8.2	4.8
		Mean	54	73*	3.4	3.2	1.7	1.1*	1.00	.94	6.6	4.5*
Hyperventilation active and passive Mean			52	34*	3.5	3.7	1.7	2.9*	0.88	1.00	6.6	10.8*

* Indicates statistically significant changes.
† C = Control period, room air tensions of O_2 and CO_2.
‡ E = Experimental period, special gas mixture.

rectly, but there were no observable changes in cardiac rate, stroke volume, or minute output. Here also there must have been vasoconstriction accompanying the inhalation of these concentrations of oxygen, but in this case the cerebral vessels participated.

Effects of 10% oxygen

The relative anoxia produced by inhalation of 10% oxygen was reflected in a pronounced fall in arterial oxygen content from a control value of 18.0 to 11.7 vol. %. Although there were no measurements of pulmonary ventilation an increase in this function must certainly have occurred to account for the observed significant decreases in pCO_2 and hydrogen ion concentration found in arterial blood. Cerebral blood flow was regularly increased, the average rising from 54 to 73 cc./100g./min., an increase of 35%, which occurred in the face of a significant reduction in femoral mean arterial pressure. There was a decrease in cerebrovascular resistance from 1.7 to 1.1, showing that anoxia of this degree was just as effective as 5–7% CO_2 in dilating cerebral vessels even though cerebral blood flow was considerably more augmented in the latter case because of the contributing effects on the systemic circulation. There was no consistent or significant change in

TABLE III

Effects of altered CO_2 and O_2 tensions on circulatory functions

Inspired gas		Subject	Stroke volume *ml.*				Cardiac output *liters/min.*				Pulse rate				Auscultatory blood pressure *mm. Hg*				Mean arterial blood pressure direct *mm. Hg*	
			CI†	CII	CIII	E‡	CI	CII	CIII	E	CI	CII	CIII	E	CI	CII	CIII	E	CIII	E
21% O_2	5% CO_2	S. H.	76	74	72		4.1	3.9	3.4		54	53	47		98/68	96/62	100/68	112/80	82	94
		T. L.	64	67	67	63	4.0	3.9	3.7	3.9	62	58	55	62	106/70	112/75	106/68	115/76	78	84
		R. Ro.	63	66	60	63	2.8	4.0	3.6	3.5	45	60	60	55		98/65	98/70	108/68	84	89
		W. S.	76	73	73	74	6.0	6.1	5.8	6.3	79	83	78	85	100/60	100/58	108/62	110/62	80	83
		D. M.	80	92	92	79	5.2	5.4	5.9	5.8	65	59	64	74		105/70	110/70	120/82	81	96
		R. S.	73	76	72	81	4.5	4.9	4.3	5.7	62	65	60	71	105/68	110/68	118/72	125/78	80	93
	7% CO_2	J. B.		70	77	66		4.3	4.3	4.5		62	61	65		104/70	105/72	128/85	88	110
		W. H.	77	81	75	80	5.2	5.9	5.6	5.7	68	73	74	72	100/66		110/72	110/80	86	93
		Mean	73	75	74	72	4.5	4.8	4.7	5.1	62	64	62	69	102/66	104/67	107/69	116*/76*	82	93*
85–100% O_2		J. E.	89	86	88	83	5.6	4.9	5.7	5.4	63	57	65	65		95/63	100/78	105/78	89	93
		T. L.		67	59	65		4.0	3.4	3.8		60	57	59		112/82	108/70	115/85	88	100
		S. H.		75	71	68		5.0	4.0	3.8		66	57	56		105/70	100/70	115/80	83	86
		R. Re.		86	90	85		3.9	4.1	4.0		45	45	47		115/70	120/70	135/98	89	114
		J. B.		76	80			3.9	4.2			51	52			105/75	105/70	115/85	84	96
		M. H.		65	68	66		3.9	4.3	3.5		60	64	53		105/75	112/72	120/80	88	96
		Mean		76	76	73		4.3	4.3	4.1		57	57	56		106/73	108/72	118*/84*	87	98*
10% O_2		R. S.		74	76	72		4.7	4.5	6.6		64	59	92		106/76	105/75	112/70	87	86
		S. H.		79	78	78		4.9	4.4	5.5		62	56	71		102/75	102/70	90/62	75	64
		K. T.		83	79	75		3.7	3.5	5.9		45	44	78		108/76	108/72	108/65	87	79
		W. H.		77	76	77		5.4	5.2	5.2		70	69	68		105/85	108/76	102/62	88	71
		D. M.		76	87	86		5.6	5.9	5.8		74	68	68		104/70	104/70	94/68	83	79
		M. H.			60	54			3.2	4.9		48	54	90		100/63	122/82	122/82	93	76
		J. E.		83	83	78		4.8	5.6	6.6		58	68	84		115/85	114/88	108/65	91	86
		Mean		79	77	74*		4.9	4.6	5.8*		60	60	79*		106/76	109/76	105/68*	86	78*
Hyperventilation active and passive Mean				72	69	60*		5.0	4.7	4.5		70	68	75		109/77		112/86	90	98*

* Indicates statistically significant changes.
† CI, CII, CIII = Control periods at approximately 30 minute intervals.
‡ E = Experimental period.

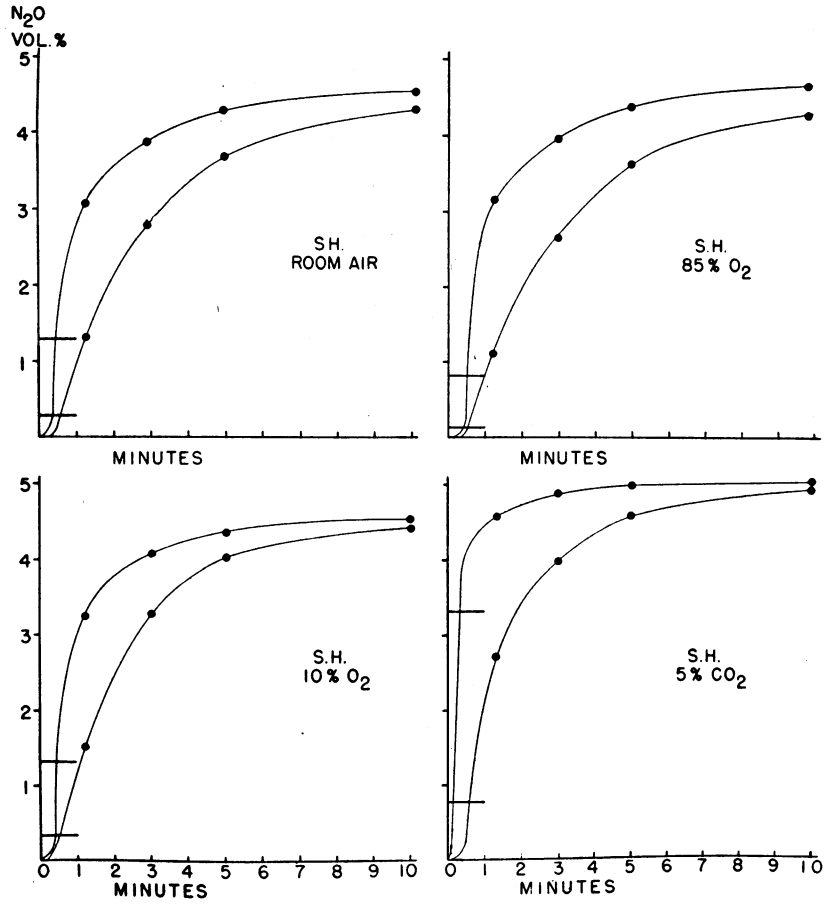

FIG. 1. SAMPLE N_2O CURVES OBTAINED ON ONE SUBJECT AT DIFFERENT TIMES REPRESENTING ONE OF THE ROOM AIR CONTROL PERIODS, 85% O_2, 10% O_2 AND 5% CO_2

cerebral oxygen consumption. The general circulatory effects of anoxia in this group were a significant increase in cardiac output resulting from an acceleration in ventricular rate, yet a fall in mean arterial blood pressure, suggesting a considerable degree of peripheral vasodilatation.

DISCUSSION

These experimental findings lend the support of quantitative measurements in man to the already prevalent belief (8 to 11) that the cerebral blood vessels are strongly influenced by the carbon dioxide and oxygen tensions of the arterial blood. They also afford a previously unavailable insight into some important relationships here involved, for the reason that they permit quantitative comparisons in the normal, intact state. Previous observations in unanesthetized man were made by methods which did not justify quantitative deductions (9, 10, 12) and the only truly quantitative measurements in animals were made under conditions more or less remote from the normal (13).

It is of interest to compare these results on cerebral blood flow with studies on the coronary circulation, the most recent being those on the heart *in situ* of Eckenhoff, Hafkenschiel and Landmesser (14) who found a reduction of 11% with pure oxygen, a 64% increase with 10% oxygen, but little effect from inhalation of 5–7% carbon dioxide.

The data on cerebral oxygen consumption demonstrate that except for an increase associated only with active hyperventilation (3) there is no significant change in oxygen utilization by the brain in the ranges of gas tension studied. This lends substance to the assumption made by investigators

who used the cerebral arteriovenous oxygen difference as a measure of blood flow under similar circumstances (9), although it is difficult to see a justification for such an assumption *a priori*. Indeed, it is somewhat surprising that neither hyperventilation nor anoxia showed any depression of cerebral oxygen utilization, even though both were accompanied by definite mental changes. These were the only cases, however, which exhibited any decrease in internal jugular oxygen content and this was markedly reduced in both (7.3 and 7.8 vol. % for 10% O_2 and hyperventilation, respectively). The possibility presents itself that a reduced mean cortical pO_2, as reflected in the lowering of the pO_2 of internal jugular blood, might well be a factor in producing the mental effects. Thus derangements in consciousness may occur when the complex oxidation processes with which consciousness is associated are forced to operate at a lowered oxygen tension even though the gross oxygen consumption by the whole brain may be within normal limits. The conclusion is apparent that the higher psychic functions are associated with biochemical changes so subtle and complex as to render any attempt to describe them in terms of mere oxygen utilization no more adequate than to predict the fidelity of a radio by its power requirements. This is not to imply the con-

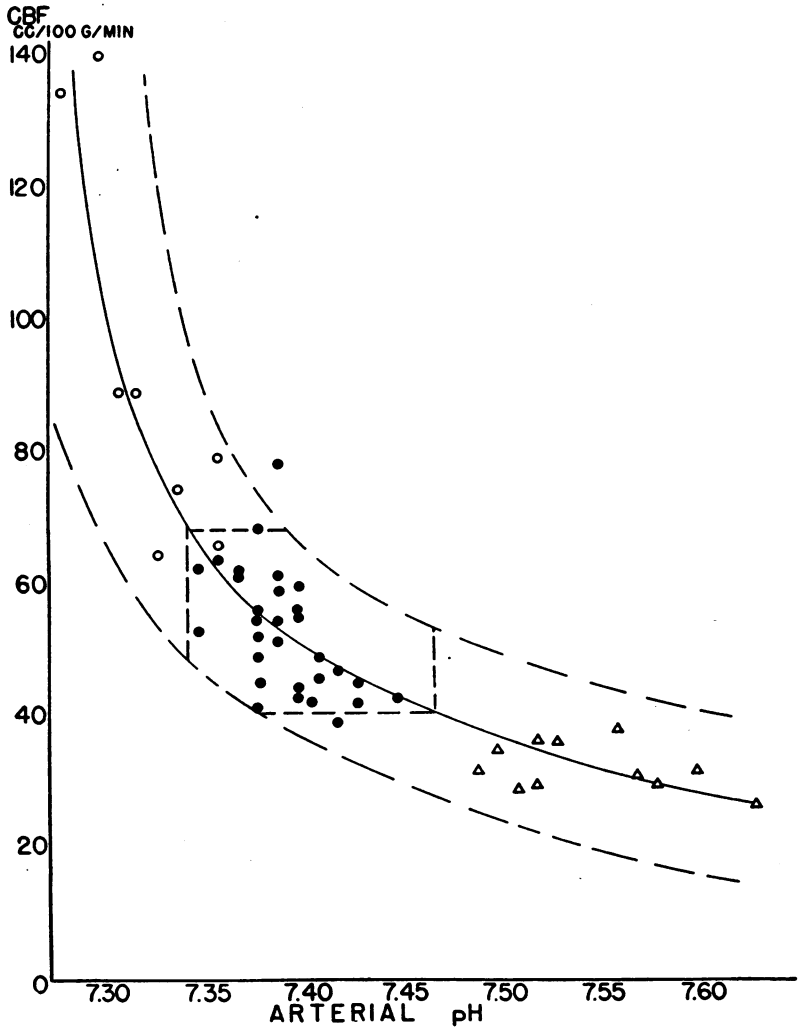

FIG. 2. THE RELATIONSHIP BETWEEN CEREBRAL BLOOD FLOW AND ARTERIAL pH
The latter was varied from the normal (dots) by hyperventilation (triangles) or by inhalation of 5–7% CO_2 (open circles). The broken curves bound 98% of the observations while the central polygon encloses 94% of the normal values.

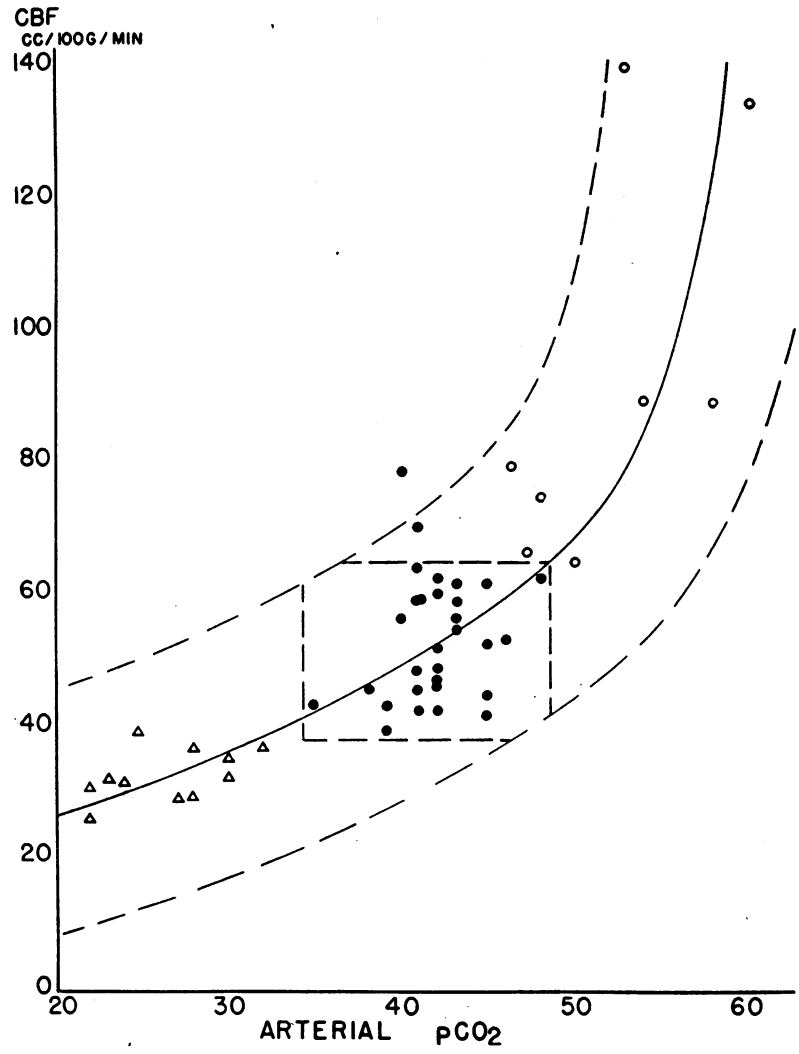

FIG. 3. THE RELATIONSHIP BETWEEN CEREBRAL BLOOD FLOW AND ARTERIAL CO_2 TENSION

Symbols and construction are similar to those in Figure 2.

verse, that a change in cerebral oxygen utilization does not effect consciousness, for when the former is significantly diminished, mental function deteriorates (15 to 17).

These data offer evidence in man for a delicate control over the internal environment of the brain achieved through the intrinsic regulation of the tone of cerebral vessels. Such a homeostatic mechanism has previously been suggested (11, 18 to 20). An examination of the blood changes which occurred in these studies (Table I) shows that in each case where an abnormal change has been imposed on the arterial blood the change is considerably damped in the internal jugular blood which represents a closer approximation to the state of affairs in the brain itself. Thus in hyperventilation where arterial CO_2 content and tension and pH were changed by 8.4 vol. %, 19 mm., and 0.16 units, respectively, the corresponding changes in internal jugular blood were 3.4 vol. %, 14 mm., and 0.13 units. The inhalation of 5–7% CO_2 produced changes in arterial CO_2 content and tension and pH of 3.0 vol. %, 9 mm., and 0.05 units while internal jugular blood showed corresponding changes of only 0.6 vol. %, 4 mm., and 0.02 units. High oxygen inhalation produced a 1.4 vol. % increase in arterial oxygen content as contrasted with only a 0.5 vol. % increase in

cerebral venous blood. Anoxia produced a reduction in arterial oxygen content of 6.3 vol. %, but only a 4.1 vol. % decrease in the venous value. Aside from establishing the intrinsic nature of these responses our data throw no further light on the mechanism which mediates them, whether it be by direct action on the vessel walls or by an intrinsic reflex via the well-established cerebral vasodilator nerves (21). In the cases of CO_2 inhalation and hyperventilation it is impossible to decide whether the prime stimulus is CO_2 tension or the concomitant change in hydrogen ion concentration. Figures 2 and 3 show that very good correlations exist between cerebral blood flow and either arterial pCO_2 or arterial pH. There is evidence in our data on patients in diabetic acidosis (16) where an increase in hydrogen ion concentration is associated with a decrease in pCO_2 that beyond certain limits arterial pH may become the dominant factor in cerebrovascular tone as well as respiration.

In the application of this concept to the adjustment of cerebral blood flow to local metabolic needs, which previous work has shown to exist (20) it is a fortunate fact that increased pCO_2 and hydrogen ion concentration as well as a decrease in pO_2, all products of metabolism, appear individually capable of producing vasodilatation and therefore of maintaining the adjustment of flow to metabolism in the brain, although it is probable that this adjustment is achieved by a summation of these and many other vasodilator products of metabolism.

SUMMARY

1. The effects of the inhalation of 5–7% CO_2, 85–100% O_2, and 10% O_2, were studied on the composition of arterial and internal jugular blood; on blood flow, oxygen consumption, and vascular resistance of the brain; on cardiac output and blood pressure.

2. CO_2 inhaled in concentrations of 5–7% produces an increase in cerebral blood flow averaging 75%. O_2 inhaled in concentrations of 85–100% is associated with a reduction in cerebral blood flow of 13%, while 10% O_2 produced an increase of 35% in this function. These changes are statistically significant.

3. Calculation of cerebrovascular resistance indicates that in every case the change in blood flow is due to a change in the vascular resistance of the brain.

4. Cerebral oxygen consumption is not significantly altered by changes in the composition of inspired air over the ranges studied.

5. Mean arterial blood pressure rose significantly during the CO_2 and high O_2 inhalations and fell slightly with 10% O_2.

6. The only significant change in cardiac minute volume was an increase which occurred during 10% O_2 inhalation and resulted from an increase in rate rather than stroke volume.

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