CEREBRAL CIRCULATION AND METABOLISM DURING THIOPENTAL ANESTHESIA AND HYPERVENTILATION IN MAN *

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Cerebral effects of hyperventilation in normal man, e.g., dizziness, faintness, and impairment of mental function, may be in part related to reduced cerebral oxygen tension (P_{O_2}) resulting from hypocapneic cerebral vasoconstriction (1). The prevalent use of controlled respiration during the administration of general anesthetics in the operating room raises questions concerning the extent of hyperventilation which can occur under these conditions and its effect on cerebral P_{O_2}. It is generally recognized that most unconscious patients whose respirations are controlled will unwittingly be hyperventilated by the anesthetist (2, 3), and certain anesthetic techniques actually rely upon hyperventilation to achieve their effectiveness (4). Thus the existence of hypocarbia in a substantial fraction of anesthetized patients is extremely likely. However, it has not been shown whether the intrinsic reactivity of cerebral blood vessels to P_{CO_2} is lost or preserved during general anesthesia. The present study had as its aims: measurement of the effects of thiopental anesthesia on cerebral blood flow (CBF) at normal and reduced arterial P_{CO_2} and, if hyperventilation did cause cerebral vasoconstriction during anesthesia, determination of the extent to which this could reduce internal jugular venous oxygenation.

METHODS

Eleven physically normal male volunteers and two female hospital patients were studied. With the exception of one of the patients who was 41 years old, the ages of the subjects ranged from 21 to 27 years. Minor opera-

tions were performed after completion of the study in the two patients just mentioned. All subjects were studied in the early morning (7 a.m.) and had fasted since the previous midnight. Atropine sulfate, 0.4 mg, was given intravenously to each before the induction of anesthesia.

Anesthesia was induced with thiopental sodium (2.5 per cent) in doses approximating 200 mg, and was thereafter continued by means of intravenous infusions of 0.5 per cent thiopental. Immediately after the induction of anesthesia, 60 mg succinyldicholine was injected intravenously to permit tracheal intubation with a cuffed Magill's tube of appropriate size. Ventilation was controlled by a Bird respirator supplied either with compressed air or with a mixture of 15 per cent N_2O and 21 per cent O_2 in N_2. Respiratory paralysis was assured by injecting d-tubocurarine intermittently as required. Heparin, 100 mg, was given intravenously before blood sampling began; 100 mg protamine was given intravenously at the end of sampling. Total doses of thiopental and d-tubocurarine ranged from 10 to 55 and from 0.7 to 1.3 mg per kg, respectively.

Each study comprised two phases. In one phase, ventilation was adjusted to maintain arterial P_{CO_2} at a level approximating and not less than 40 mm Hg; in the other, P_{CO_2} levels below 20 mm Hg were sought. The order of the phases was varied so that in 7 of the 13 normocarbia preceded hypocarbia, whereas the opposite sequence occurred in the remaining subjects. In all instances, 30 or more minutes elapsed between measurements to permit elimination of nitrous oxide.

Measurements were begun after respiratory minute volume had been held constant for a period sufficient to permit P_{CO_2} to stabilize at the desired level for 10 minutes or longer. Expired gas was sampled through an 18-gauge needle inserted into the endotracheal tube, and was analyzed for CO_2 using a Liston-Becker analyzer (5). Total respiratory volume was estimated with a Wright anemometer. Respiratory rate was counted from the P_{CO_2} record. Blood pressures in the femoral arterial and jugular bulb were transduced by Statham strain gauges and were recorded together with the electrocardiogram (lead II) and the fronto-occipital electroencephalogram on a Grass polygraph. Rectal temperature was measured with a calibrated thermistor thermometer. Values reported are averages of readings taken immediately be-

fore, during, and immediately after measurements of cerebral blood flow (CBF).

In the first four studies CBF was determined over a 10-minute period, by the continuous sampling modification of the nitrous oxide method (6). The "syringe integration" sampling procedure was first suggested by Schienberg and Stead (7). As the result of the pronounced reduction in CBF which was encountered in these subjects, it was thought desirable to determine CBF in the remaining subjects over a 25-minute period, with intermittent sampling (8). The first two samples for N_2O were collected between 0 and 1, and between 1 and 1.5 minutes, as described by Kety and Schmidt (8), with additional samples at 3.5, 6, 15, and 25 minutes. Cerebral vascular resistance (CVR), cerebral oxygen consumption (CMR_{O_2}), and cerebral carbon dioxide production (CMR_{CO_2}) were calculated as previously described (8).

In the first four studies, thiopental concentrations (9), pH, and metabolic gas values were determined on the 10-minute integrated blood samples drawn during the determination of CBF. In the remainder, these measurements were made on three 7-ml samples of arterial and venous blood drawn at a uniform rate during three 30-second periods: one immediately before, one in the middle, and one immediately after the 25-minute N_2O measurement period. The samples were combined before analysis. Blood pH was determined anaerobically in a MacInnes-Belcher glass electrode connected to an EIL electrometer. The output of the electrometer was recorded on a Texas Instrument Company Rectiriter; resolution was 0.001 pH units. The glass electrode was enclosed in an electrically shielded air chamber, the temperature of which averaged 36.7° C and the extremes differed from this by no more than 0.04° C. Blood pH was corrected to the measured rectal temperature with the coefficient 0.0147 per degree C (10), and was also corrected for glycolysis and for effects of whole blood on the glass electrode (11).

Determinations of whole blood metabolic gas composition and N_2O content were performed manometrically in duplicate as described elsewhere (6). Percentage oxygen saturation of hemoglobin was estimated from the manometrically measured values after corrections for physically dissolved oxygen and, in addition, for hemoconcentration in the determination of the oxygen capacity (12, 13). Cerebral venous blood P_{O_2} was estimated from values for percentage hemoglobin saturation, pH, and body temperature, with the nomogram of Severinghaus (14). Plasma CO_2 content was estimated from the whole blood values with the nomogram of Van Slyke and Sendroy. The P_{CO_2} was calculated from plasma CO_2 content, and blood pH by means of the Henderson-Hasselbalch equation, using the solubility factor and pK' of CO_2 in plasma suggested by Severinghaus, Stupfel and Bradley (11, 15).

RESULTS

The principal data obtained in the 13 studies performed are shown in Tables I, II, and III. It

will be noted that values for brain circulation and metabolism for Subjects 8 and 9 are not reported. In these studies, a leak occurred in the breathing system used for administering the nitrous oxide mixture.

Thiopental anesthesia. The values for cerebral hemodynamics and metabolism in Table I, observed during anesthesia without hypocapnia, were all grossly and significantly different from corresponding values found in normal conscious young adults: CVR, 1.6 mm Hg per ml per 100 g per minute; CBF, 53 ml per 100 g per minute; and CMR_{O_2}, 3.3 cc per 100 g per minute (1, 16). Anesthesia at an average P_{CO_2} of 43.8 mm Hg and a normal arterial oxygen saturation was associated with an elevated CVR (2.9 mm Hg per ml per 100 g per minute) and with very low values for CBF (27.6 ml per 100 g per minute) and CMR_{O_2} (1.5 cc per 100 g per minute). Under these circumstances, values for internal jugular venous P_{O_2} and P_{CO_2}, and for the difference in arterial-cerebral venous O_2 content were close to normal. The absence of any difference in arterial and internal jugular venous thiopental levels indicates that brain and blood were in approximate equilibrium.

Thiopental anesthesia with hyperventilation. Overventilation to an average arterial P_{CO_2} of 17.5 mm Hg produced no further changes in CMR_{O_2}, but did cause an additional reduction in CBF to 16.4 ml per 100 g per minute, and a reduction in internal jugular venous oxygen saturation and P_{O_2} to 41.6 per cent and 20.6 mm Hg, respectively, despite an increase in arterial oxygen saturation from 94.8 to 98.8 per cent. There was no change in the "depth" of anesthesia estimated electroencephalographically, although there was a large increase in the concentration of thiopental in the blood during respiratory alkalosis.

No attempt will be made to appraise correlations among changes in physiological variables, since the nature of the experimental design does not lend itself to this type of analysis.

DISCUSSION

The possibility that the results obtained were influenced by the muscle relaxants used will first be examined. Actions of succinyldicholine on the myoneural junction are terminated within a few minutes by hydrolysis of the molecule, and it is un-

TABLE I

Circulation, metabolism, and electroencephalogram *

Subj.	Cerebral blood flow (ml/100g/min)		Cerebral vascular resistance (mm Hg/ml/100g/min)		Cerebral metabolic rate of O_2 consumption (cc O_2/100g/min)		Cerebral metabolic rate of CO_2 production (cc CO_2/100g/min)		Cerebral respiratory quotient		Arterial blood pressure (mm Hg)		Venous blood pressure (mm Hg)		EEG level†	
	T	T+H	T	T+H	T	T+H	T	T+H	T	T+H	T	T+H	T	T+H	T	T+H
1	49.6	26.3	2.1	3.2	3.4	3.3	3.5	3.4	1.03	1.03	118	91	+14	+7	2	2
2	28.8	14.9	2.0	4.3	0.8	0.9	0.6	1.1	0.75	1.22	56	60	-2	-4	4	5-6
3	27.0	13.3	2.5	7.7	0.2	0.6	0.3	0.7	1.50	1.17	69	84	+1	-18	4-5	5
4	30.9	15.5	2.0	5.9	1.6	1.1	1.4	1.2	0.88	1.09	62	92	+1	0	3	3-4
5	24.2	16.7	2.5	4.8	2.0	2.5	1.8	2.5	0.90	1.00	82	85	+12	+5	3	3
6	18.9	13.9	4.0	6.8	1.7	2.2	1.5	2.1	0.88	0.95	81	94	+5	+4	4-5	3
7	19.5	9.8	4.8	9.6	1.2	1.2	1.3	1.2	1.08	1.00	91	88	-2	-6	3	3-4
8											94		+7	+1	3	3
9											90		+2	0	3	3
10	22.6	30.4	2.8	2.3	1.3	1.2	1.3	1.1	1.00	0.92	72	78	+8	+7	4-5	5-6
11	27.6	13.3	3.0	6.1	1.4	1.8	1.4	2.0	1.00	1.11	85	81	+1	0	4-5	4
12	26.3	13.2	2.7	6.2	1.8	1.9	1.7	2.0	0.94	1.05	90	93	+18	+11	4	4-5
13	28.0	13.2	3.1	6.4	1.6	1.5	1.5	1.6	0.94	1.07	83	80	-4	-5	4	3
$\bar{X}$	27.6	16.4	2.9	5.8	1.5	1.7	1.5	1.7	0.99	1.06	83	86	+5	0	4	4
$\bar{d}$		-11.2		+2.9		+0.1		+0.2		+0.07		+3		-5		0
SE_d		± 2.37		±0.48		±0.10		±0.11		±0.060		± 3.6		± 1.4		±0.2
p		< 0.001		<0.001		>0.3		<0.1, <0.05		>0.3		> 0.4		< 0.01		1.00

* Abbreviations used: T indicates thiopental anesthesia; T + H indicates thiopental anesthesia with hyperventilation; $\bar{X}$ = mean values; $\bar{d}$ = mean of differences between condition T and condition T + H; SE_d = standard error of difference; p = probability that changes are not significantly different from zero.

† Method of interpretation from D. K. Kiersey, R. G. Bickford, and A. Faulconer, Jr., Electroencephalographic patterns produced by thiopentone sodium during surgical operations: Description and classification. Brit. J. Anaesth. 1951, 23, 141, as modified by Brechner, V. L. in The Electroencephalogram During Anesthesia, published by Edin Division of Epsco, Inc, Worcester 8, Mass., 1958.

likely that any important pharmacological actions would persist beyond this period. The effects of d-tubocurarine are of longer duration, but they do not include any action on the central nervous system sufficient to impair consciousness (17). In the absence of demonstrable central nervous system depression, it appears unlikely that d-tubocurarine would alter cerebral metabolic rate. Earlier studies from this laboratory (18) have shown that thiopental alone depresses cerebral metabolic rate; after doses roughly half those used in the present study, cerebral oxygen consumption averaged 2.1 ml per 100 g per minute, a 36 per cent reduction from normal values. The reduction found in the present study (55 per cent) is that which would be expected if the dose-response curve followed the exponential (logarithm of the dose: effect) relation so frequently encountered in biological systems. Although these arguments do not prove that d-tubocurarine fails to alter CMR_{O_2}, they do appear to minimize the importance of such an action, if it exists. Despite its apparent failure to depress central nervous system function to any large degree, there is evidence that vascular smooth

TABLE II

Arterial and internal jugular venous blood parameters *

Subj.	O₂ content T	O₂ content T+H	O₂ capacity T	O₂ capacity T+H	Hb saturation T	Hb saturation T+H	CO₂ content T	CO₂ content T+H	pH T	pH T+H	Pco₂ T	Pco₂ T+H	Thiopental T	Thiopental T+H
	ml/100 ml		ml/100 ml		%		ml/100 ml		units		mm Hg		mg/L	
1	17.1	17.8	19.3	19.0	91.8	96.7	47.9	31.3	7.35	7.52	43.9	19.7	7	11
2	14.0	15.8	16.0	16.5	91.4	98.7	50.7	33.7	7.29	7.63	50.4	16.1	37	54
3	12.7	14.0	14.7	14.8	90.6	97.8	48.3	36.6	7.26	7.53	51.4	21.3	24	30
4	19.1	21.0	21.1	21.9	89.6	95.0	46.0	33.8	7.32	7.57	45.4	19.7	23	30
5	17.3	19.0	17.0	18.3	99.4	100+	47.9	34.5	7.40	7.65	38.2	16.1	22	31
6	18.9	21.1	19.8	20.4	94.5	100+	45.9	35.5	7.37	7.64	40.3	17.6	25	34
7	19.8	20.9	20.1	20.5	97.0	100+	45.9	29.8	7.37	7.66	40.6	14.2	32	40
8	18.4	19.3	19.2	18.5	94.8	100+	47.0	37.2	7.35	7.62	43.1	18.7	21	33
9	18.1	19.5	19.5	19.4	91.8	98.5	49.4	32.0	7.30	7.59	50.8	17.7	28	43
10	19.1	18.5	19.1	18.2	98.4	100+	48.6	36.5	7.41	7.68	38.7	16.4	36	45
11	18.8	18.9	19.0	18.8	97.4	98.9	51.3	35.7	7.38	7.69	43.7	15.5	25	35
12	16.9	17.0	17.0	17.0	97.6	98.2	49.8	36.6	7.38	7.67	40.6	16.0	28	43
13	18.0	17.9	18.1	17.3	97.8	100+	51.2	37.9	7.39	7.64	41.8	18.0	22	32
X̄	17.6	18.5	18.5	18.5	94.8	98.8	48.5	34.7	7.35	7.62	43.8	17.5	25	35
d̄	+1.0		+0.1		+4.0		−13.8		+0.27		−26.3		+10	
SE_d̄	±0.24		±0.17		±0.69		±0.71		±0.011		±1.11		±1.04	
p	<0.01		>0.5		>0.001		<0.001		<0.001		<0.001		<0.001	

B. Internal jugular venous parameters

Subj.	O₂ content T	O₂ content T+H	Hb saturation T	Hb saturation T+H	Po₂ T	Po₂ T+H	CO₂ content T	CO₂ content T+H	pH T	pH T+H	Pco₂ T	Pco₂ T+H	Thipoental T	Thipoental T+H
	ml/100 ml		%		mm Hg		ml/100 ml		units		mm Hg		mg/L	
1	10.2	5.1	54.9	27.6	33.2	17.5	55.0	44.3	7.29	7.40	55.7	35.2	8	13
2	11.4	9.9	74.8	62.8	45.7	27.9	52.9	40.9	7.27	7.53	54.4	23.7	30	51
3	11.9	9.8	84.8	69.8	61.2	33.5	49.4	41.8	7.24	7.47	54.3	27.8	22	27
4	13.8	13.8	64.9	62.6	37.1	28.9	50.6	41.3	7.28	7.50	53.3	27.5	21	26
5	9.1	4.3	52.9	23.5	28.8	12.6	55.5	49.4	7.33	7.51	50.1	30.7	21	31
6	9.9	5.5	49.5	27.0	29.0	15.0	53.8	50.3	7.32	7.51	51.9	32.4	23	32
7	13.4	9.2	66.2	44.4	37.3	21.1	52.8	42.0	7.32	7.53	51.0	26.1	31	39
8	13.2	5.6	68.2	29.7	39.2	16.0	52.4	50.8	7.31	7.50	51.6	32.6	21	33
9	12.7	6.3	64.6	32.0	33.5	18.7	54.4	45.3	7.24	7.47	61.9	31.1	28	40
10	13.5	14.5	70.2	79.1	37.1	34.8	54.4	40.1	7.36	7.62	47.5	20.0	34	45
11	13.6	5.2	71.1	27.7	38.0	14.8	56.3	50.4	7.34	7.53	51.7	30.5	24	29
12	10.0	2.8	58.2	16.5	29.3	9.3	56.3	51.5	7.34	7.52	50.4	30.4	33	42
13	12.3	6.6	67.4	37.6	35.2	18.3	56.6	49.7	7.35	7.51	50.7	30.8	22	31
X	11.9	7.6	65.2	41.6	37.3	20.6	53.9	46.0	7.31	7.51	52.7	29.1	24	34
d	− 4.3		−23.6		−16.6		− 7.9		− 0.20		+ 23.5		+ 9	
SE_d	±0.81		± 4.26		± 1.81		± 1.00		± 0.011		± 1.21		± 1.2	
p	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	

* Abbreviations as in Table I.

TABLE III

Respiration *

Subj.	$\dot{V}_E$ T	$\dot{V}_E$ T+H	V_T T	V_T T+H	f T	f T+H
	L/min, ATPD		*L*		*breaths/min*	
1	7.80	16.20	0.622	1.209	12.6	13.4
2	2.15	13.23	0.537	0.917	4.0	14.5
3	3.21	9.52	0.558	0.912	5.8	10.4
4	4.99	17.39	0.763	1.121	6.5	15.5
5	6.47	17.43	0.729	1.363	8.9	12.8
6	7.23	19.10	0.852	1.209	8.5	15.8
7	6.41	24.49	0.835	1.316	7.7	18.6
8	5.32	12.78	0.795	1.170	6.7	11.2
9	7.67	15.31	1.565	1.597	4.9	9.6
10	4.05	12.30	0.620	1.140	6.5	10.8
11	5.14	16.76	0.751	1.262	6.8	13.3
12	2.78	12.20	0.651	1.058	4.3	11.6
13	3.69	16.43	0.661	1.559	5.6	10.5
$\bar{X}$	5.15	15.63	0.765	1.218	6.8	12.9
$\bar{d}$		+10.48		+0.453		+ 6.1
SE_d		± 0.86		±0.0552		± 0.79
p		< 0.001		<0.001		< 0.001

* Abbreviations same as in Table I.

muscle is affected by curare. Direct actions on blood vessels, however, appear only at high concentrations of curare (as after intra-arterial injection) and are opposite in direction (19, 20) to the changes observed in the present study. An influence of curare on responses to hyperventilation is believed unlikely, since the results were independent of the order in which the studies were carried out; yet when hyperventilation preceded normal ventilation, the dose of curare given prior to the period of study was roughly one-half that administered when the reverse order of procedure was employed.

Although administration of thiopental and other respiratory depressant drugs in man during natural breathing has been found to cause decreased oxygen utilization, blood flow in the brain under these circumstances has been found to increase, to remain unchanged, or to decrease relatively less than oxygen consumption (18, 21–25). Since cerebral vasodilatation is an expected accompaniment of the arterial hypercapnia secondarily induced by the respiratory depression, the direct actions of a depressant drug upon cerebral vessels may be masked or even reversed by the powerful indirect influence of changes in arterial P_{CO_2} (26–28). The findings of the present study will be discussed first from the standpoint of thiopental effects which appear to be unrelated to changes in P_{CO_2}, and second with regard to effects of P_{CO_2} in the presence of thiopental. In each instance the findings will be referred to existing information concerning the brain metabolism and hemodynamics of resting, conscious subjects (26, 27).

Thiopental anesthesia. The rate of brain oxygen consumption in our anesthetized subjects, who were maintained close to normal arterial P_{CO_2}, represents a reduction of approximately 55 per cent from that observed in conscious, normocapneic subjects (16, 26, 27). This depression of metabolism is as low as any previously found during various types of unconsciousness resulting from drug administration (16, 26, 27). In the present study, the depth of anesthesia as determined from clinical signs, EEG level, and blood thiopental content, was profound. Since there is normally a close relation between depth of anesthesia and depression of brain metabolism (26, 27, 29), the finding of a low CMR_{O_2} had been anticipated. Presumably, a greater depth of anesthesia would have been associated with still further depression of CMR_{O_2}. Despite this degree of metabolic depression, the absence of change in RQ suggests that brain metabolism was not qualitatively altered.

Brain blood flow was also markedly reduced by thiopental administration to about 50 per cent of normal levels. This finding was not wholly expected, especially in view of previous suggestions that narcotic agents depress cerebral vascular tone (16) and the discrepant findings of previous studies of the effects of barbiturate anesthesia on CBF cited above. The reduction of CBF in this study could be ascribed only in small part to reduced arteriovenous perfusion pressure; its major cause was a large increase in CVR.

The observed high cerebral vascular resistance could have been due to any of a number of factors, ranging from an action of thiopental upon the smooth muscle of brain vessels to an effect somehow related to depression of brain oxygen metabolism. Thiopental has in fact been demonstrated to exert constrictor action upon the smooth muscle of isolated strips of rabbit aorta, and to enhance the vasoconstrictor activity of norepinephrine (30), but in concentrations greater than those used in the present study. Since the direct actions of drugs upon brain vessels do not appear to be qualitatively different from those upon other vascular smooth muscle, a constrictor effect of thiopental upon cerebral vessels remains as a possible

contributor to the high CVR observed in the anesthetized subjects.

For many years it has been assumed that the blood flow through the brain is adjusted to the local metabolic demands of brain tissue. Such intrinsic adjustments are usually related to local alterations of P_{CO_2} secondary to changes in the rate of carbon dioxide production or oxygen utilization (16, 26, 27, 31, 32). Evidence for an influence of CNS activity upon brain blood flow does exist in the form of enhanced rate of blood flow in the visual cortex during photic stimulation of the retina (33, 34) and the increased brain blood flow which accompanies administration of convulsant drugs (16, 26, 27, 31, 32). It has been pointed out elsewhere, however, that the association of increased brain blood flow and rate of CMR_{CO_2} may not be real, and that the basis for adjustment of blood flow to neuronal activity need not be either rise in central P_{CO_2} or fall in central P_{O_2} (35). Evidence offered for this opposite view is that elevation of central P_{CO_2}, unaccompanied by concurrent arterial hypercapnia, does not increase blood flow through the brain (35–37).

In the present study the association of thiopental-induced depression of cerebral metabolism and the concomitant decrease in blood flow are not related to altered central P_{CO_2} since, in spite of the gross reduction of CO_2 production, the observed values for arterial and jugular venous P_{CO_2} are not reduced below normal.

Thiopental anesthesia and hyperventilation. The absence of a further change in CMR_{O_2} during hyperventilation is consistent with numerous observations that alteration in P_{CO_2} does not affect cerebral O_2 uptake (26, 27). This, together with the lack of change in EEG level, suggests that cerebral activity was similar in the two experimental phases. Since both methods are gross, it cannot be said that a particular region of the brain was unaffected, but only that the over-all effect was negligible. During hyperventilation CBF was decreased from an already reduced level to a value only 30 per cent of normal. This reduction of CBF in response to hyperventilation is of the same magnitude per millimeter Hg decrease in arterial P_{CO_2} as that found by Kety and Schmidt in normal young men (1), indicating that deep thiopental anesthesia does not interfere with cerebral vascular reactivity to hypocapnia. Whether this is also

true of other general anesthetic agents cannot be answered at present.

It is perhaps surprising that hyperventilation failed to increase anesthetic (EEG) "depth" in the subjects studied, particularly since concentrations of thiopental in blood were significantly elevated during hypocarbia. However, since thiopental is a weak acid with a pK nearly equal to normal arterial pH, an increase in pH of 0.3 U can be estimated to reduce the fraction of barbiturate in the acid (active) form by about one-third. Thus, the concentration of pharmacologically active drug presented to the nervous system was essentially the same during hyperventilation and normal ventilation.

The extremely low oxygen content of internal jugular venous blood drawn during hyperventilation raised the question of the adequacy of cerebral oxygenation. The reduction in CBF without further change in CMR_{O_2} during hyperventilation under anesthesia resulted in a nearly twofold increase in arterial-cerebral venous O_2 content difference, and consequently in marked reductions in internal jugular P_{O_2} and oxygen saturation, despite the increase in arterial saturation. Certainly a reduction in oxygenation of unanesthetized subjects results in a decline in brain oxygen consumption (38). It has been suggested that in unanesthetized subjects unconsciousness may develop when the cerebral venous P_{O_2} falls to levels below 15 to 20 mm Hg (35, 39, 40) and that even under normal conditions the cerebral cortex verges upon insufficiency (41). There are steep diffusion gradients from capillaries to cerebral neurons, and in regions between capillaries small reductions in capillary P_{O_2} might reduce the availability of oxygen below necessary levels. A great deal has been written on this subject, almost all of which is speculation. It is undoubtedly true that hyperventilation can cause cerebral vasoconstriction, can severely reduce cerebral P_{O_2} [as measured by an oxygen electrode inserted in the cerebral cortex (42), or by measurements of blood draining the brain (38)], and can reduce psychomotor function and impair consciousness (43). In anesthetized men, hyperventilation appears by clinical criteria to deepen the level of anesthesia (4). But it remains uncertain whether reduced P_{O_2} alone causes these changes in cerebral function. In the light of present knowledge, these changes might

equally well result from the removal of tonic facilitatory actions of CO_2, or from concurrent effects of lowered oxygen and carbon dioxide tensions.

SUMMARY AND CONCLUSIONS

1. Administration of large doses of thiopental to normal subjects caused significant and nearly proportional reductions in cerebral metabolic rate and cerebral blood flow; cerebral vascular resistance was increased.

2. Hyperventilation during anesthesia produced no further reduction in oxygen consumption, although it decreased blood flow to extremely low levels.

3. These results are interpreted to mean that the reactivity of cerebral blood vessels to carbon dioxide is preserved even at profound levels of thiopental anesthesia.

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