Cerebral Circulation During General Anesthesia and Hyperventilation in Man

Thiopental Induction to Nitrous Oxide and d-Tubocurarine

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Studies of cerebral circulation and gaseous metabolism were performed in six healthy young volunteers during anesthesia induced with thiopental and maintained with nitrous oxide and *d*-tubocurarine. The blood thiopental level was very low when measurements were made, and intravenous *d*-tubocurarine has been shown not to affect cerebral flow or metabolism. Therefore 70 per cent nitrous oxide was probably the agent chiefly responsible for the changes observed. When Pa_{CO_2} was normal, cerebral blood flow remained normal, but cerebral oxygen uptake decreased 23 per cent. About one third of this decrease was caused by a small decline in body temperature, with the remainder most likely owing to nitrous oxide. When mean arterial P_{CO_2} was decreased to 18.3 mm. of mercury, cerebral blood flow was halved, and mean jugular venous P_{O_2} declined to 19.8 mm. of mercury, a level generally assumed to be associated with suboptimal cerebral oxygenation. However, cerebral metabolic rate for oxygen did not decrease further at this low Pa_{CO_2}.

THE effects of some intravenous and inhalation anesthetics on human cerebral blood flow and metabolism have recently been reported.[1, 2, 3] However, there are as yet no measurements in man of cerebral circulation when thiopental, nitrous oxide, and *d*-tubocurarine have been administered. The extreme hyperventilation which is sometimes utilized with this anesthetic technique results in a greatly decreased arterial carbon dioxide tension (Pa_{CO_2}). This, in turn, could diminish cerebral blood flow to levels which might result in cerebral ischemia.

We have performed studies during this type of anesthesia with two purposes in mind —first, to ascertain the effects on cerebral blood flow and oxygen utilization of this combination of drugs; second, to study the cerebral effects of low Pa_{CO_2}. Some of the measurements were made at the low Pa_{CO_2} which can be produced by vigorous hyperventilation during anesthesia, while additional measurements were made in the presence of a normal Pa_{CO_2}.

Methods

Studies were performed during anesthesia without operation on six normal male volunteers ranging in age from 21 to 25 years. All had refrained from smoking and had taken no drugs for at least 36 hours. Thirty minutes after the intramuscular injection of secobarbital (1.5 mg./kg.) and atropine (0.5 mg.), anesthesia was induced with a single dose of thiopental (5 mg./kg.). Following an initial intravenous dose of 54 mg. of *d*-tubocurarine, a tracheal tube was inserted. No additional thiopental was given. Supplemental *d*-tubocurarine was administered as necessary to maintain apnea, the mean total dose being 105 mg., with a range of 90 to 120 mg.

Various inspired gas mixtures were pro-

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TABLE 1. Experimental Conditions (Six Subjects)

	Normocarbia		Hypocarbia	
	Mean	S. E.	Mean	S. E.
Time after start of induction (min.)	71.8	7.8	76.3	15.8
$\dot{V}_E$ (liters/min.)	15.17	0.93	14.57	0.80
V_T (ml.)	1,368	113	1,319	138
f (breaths/minute)	11.4	1.06	11.5	0.94
Arterial blood pressure (mm. Hg)				
Systolic	123.5	5.0	125.0	6.6
Diastolic	75.3	5.5	73.0	4.9
$P_{I_{O_2}}$ (mm. Hg)	226.2	19.3	224.4	19.0
$P_{I_{CO_2}}$ (mm. Hg)	27.2	2.64	0	—
Jugular venous thiopental concentration (mg./liter)	3.2	1.3	2.6	0.37
Nitrous oxide concentration* (vol.%)				
Arterial	28.8	0.68	28.3	0.50
Jugular venous	28.1	0.51	27.2	0.64
Rectal temperature (°C.)	36.5	0.40	36.5	0.32

* Measured in only 4 of the 6 subjects.

The symbols used are defined as follows: $\dot{V}_E$ is expired minute ventilation; V_T is tidal volume; f represents respiratory rate. $P_{I_{O_2}}$ is the partial pressure of oxygen in inspired gas. Similarly, $P_{I_{CO_2}}$ is the partial pressure of carbon dioxide in the inspired mixture.

vided by mixing the previously analyzed contents of gas cylinders in the Nargraf head of a specially adapted McKesson anesthesia machine, the output of which supplied a Bird Respirator. Mechanical hyperventilation with 70 per cent nitrous oxide and 30 per cent oxygen was provided by the Bird Respirator in a non-rebreathing system. The peak inspiratory pressure at the endotracheal tube, measured with a Statham transducer, was kept between 15 and 20 cm. of water, and pressure at the end of expiration was allowed to fall to zero before another inspiration began.

Measurements were made in all subjects during the hypocarbia produced by hyperventilation. Additional measurements were made in the same subjects with sufficient carbon dioxide added to the 70 per cent N_2O–30 per cent O_2 mixture to produce a normocarbic state, while the same degree of hyperventilation was maintained. The first series of measurements were made during hypocarbia in three subjects, and during normocarbia in the other three. All measurements were made and samples drawn only after end-tidal P_{CO_2} had been stable for at least ten minutes.

Gases from within the tracheal tube were sampled continuously and passed through an infrared analyzer for the determination of inspired and end-tidal CO_2 concentrations. The oxygen concentration of inspired gas was measured continuously by a polarographic electrode. Expired minute ventilation (V_E) was measured with a calibrated dry gas meter. Body temperature was determined with a calibrated thermistor probe in the rectum, and maintained as close to 37.0° C. as was possible with an electric blanket.

Needles placed in a femoral artery and the superior bulb of a jugular vein permitted the measurement of arterial and jugular venous pressures, using Statham transducers. Arterial and jugular venous blood samples were drawn anaerobically from these two sites. Blood loss due to sampling did not exceed 500 ml., and was replaced with 0.9 per cent saline as samples were drawn.

Cerebral blood flow was measured by a modification of the Kr^{85} method of Lassen and Munck,[4] sampling intermittently for 14 to 17 minutes. The method yields a normal value of 44.4 ml./100 g./minute (S.D. = 5.4) in this laboratory, and a norm of 44.3 ml./100 g./minute (S.D. = 6.4) as reported by Lassen and Lane.[5] In this laboratory mean cerebral vascular resistance measured by this technique in conscious normal man is 1.88 mm. of mercury/ml./100 g./minute (S.D. = 0.39). Similarly,

TABLE 2. Blood Gas Measurements (Six Subjects)

	Normocarbia		Hypocarbia		Significance of Difference
	Mean	S. E.	Mean	S. E.	
Arterial					
P_{O_2} (mm. Hg)	139.6	6.62	145.3	9.24	>0.5
P_{CO_2} (mm. Hg)	41.3	2.38	18.3	1.54	<0.001
*p*H	7.392	0.0168	7.601	0.0166	<0.001
Venous					
P_{O_2} (mm. Hg)	41.4	3.66	19.8	1.66	<0.001
P_{CO_2} (mm. Hg)	50.0	1.98	32.3	1.65	<0.001
*p*H	7.344	0.013	7.494	0.0159	<0.001

in this laboratory the normal value for cerebral oxygen consumption (CMR_{O_2}) in awake man is 3.09 ml./100 g./minute (S.D. = 0.47). Blood *p*H, P_{CO_2} and P_{O_2} were measured with appropriate electrodes, making corrections for temperature, electrode drift, and the metabolic changes which occur in blood with the passage of time.[6] Blood thiopental concentration was measured by the method of Brodie *et al.*[7] Blood oxygen and carbon dioxide contents, as well as N_2O concentrations were determined manometrically in a Van Slyke apparatus.

Results

The experimental conditions are shown in table 1. There were no significant differences between hypocarbic and normocarbic values for any of the parameters reported in table 1 except $P_{I_{CO_2}}$.* This variable was altered intentionally in order to achieve normocarbia in the presence of hyperventilation. As can be seen from table 1, minute ventilations of about 15 liters were employed, with inspired oxygen tensions near 225 mm. of mercury. Arterial blood pressure remained normal in the presence of this degree of mechanical ventilation, and it was not affected by lowering of Pa_{CO_2}.

At the time measurements were made the blood thiopental concentration had decreased to levels not usually associated with sleep.[8] Both the mean arterial and jugular venous nitrous oxide concentrations were approaching the equilibrium level which might be expected with the inhalation of 70 per cent N_2O (32.9 vol. %).

The arterial and jugular venous blood gas measurements are shown in table 2. Arterial oxygenation is seen to be adequate during both phases of the study. The arterial P_{CO_2} and *p*H values are both normal in the normocarbic phase, and represent respiratory alkalosis during the hypocarbic phase. Jugular venous blood gas values are all normal during normocarbia, but abnormal during hypocarbia. The changes in jugular venous blood are those which would be expected with decreased cerebral blood flow during hypocarbia.

* Paired *t*-tests were used throughout to compare mean values.

TABLE 3. Cerebral Circulatory and Metabolic Measurements (Six Subjects)

	Normocarbia		Hypocarbia		Significance of Difference
	Mean	S. E.	Mean	S. E.	
Perfusion pressure* (mm. Hg)	82.8	4.99	83.8	4.80	>0.5
Cerebral blood flow (ml./100g./min.)	40.5	3.70	20.5	1.7	<0.001
Cerebral vascular resistance (mm. Hg/ml./100 g./min.)	2.17	0.20	4.20	0.31	<0.001
Cerebral metabolic rates					
CMR_{O_2} (ml./100 g./min.)	2.39	0.19	2.50	0.20	>0.5
CMR_{CO_2} (ml./100 g./min.)	2.11	0.19	2.44	0.16	>0.2

* Perfusion pressure = mean arterial blood pressure less mean jugular venous pressure.

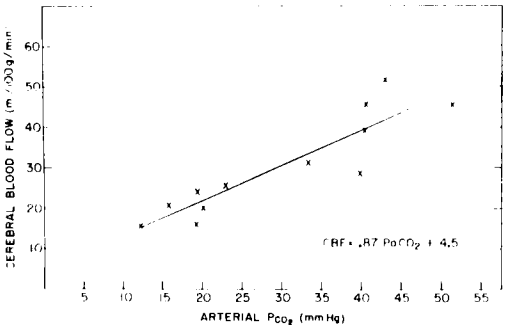

FIG. 1. Cerebral blood flow as a function of arterial P_{CO_2} during anesthesia with thiopental, nitrous oxide, and *d*-tubocurarine (six subjects).

Measurements pertaining to cerebral circulation and metabolism are listed in table 3. Cerebral perfusion pressure was within the normal range and remained unchanged by hypocarbia. Cerebral blood flow was normal at normal Pa_{CO_2}, but was approximately halved during hypocarbia. Cerebral vascular resistance, within the normal range during normocarbia, nearly doubled during hypocarbia. During normocarbia, the cerebral metabolic rate for oxygen (CMR_{O_2}) was 23 per cent lower than the normal value of 3.09 ml./100 g./minute. It was not changed by hypocarbia. CMR_{CO_2} followed the same pattern.

The relation of cerebral blood flow to arterial P_{CO_2} is demonstrated in figure 1, and a linear regression relating the two variables is illustrated.

The relation of jugular venous P_{O_2} to cerebral blood flow is demonstrated in figure 2, along with its calculated linear regression.

Discussion

The factors which may affect cerebral blood flow and metabolism during anesthesia include the cerebral perfusion pressure, blood oxygen tension, body temperature, drugs, and blood carbon dioxide tension. Each of these factors will be considered.

Cerebral Perfusion Pressure. In normal conscious man, cerebral vascular tone adapts to the perfusion pressure in such a way as to maintain cerebral blood flow at a normal value over a wide range of perfusion pressures.[9, 10] We have reported a similar cerebral vascular response during halothane anesthesia in man.[2] It seems reasonable to expect the same phenomenon during other types of anesthesia as well. However, in this study no effect was exerted by this factor, as cerebral perfusion pressure remained normal in all subjects during both the normocarbic and hypocarbic phases.

Blood Oxygen Tension. When arterial oxygenation is inadequate, cerebral vascular dilatation occurs, flow increases, and CMR_{O_2} may decrease. However, these phenomena do not appear to occur until arterial P_{O_2} has decreased below 60 mm. of mercury.[11] When 80 per cent oxygen is inhaled and arterial P_{O_2} rises, cerebral blood flow in man is unchanged, provided that Pa_{CO_2} remains normal.[11, 12] It thus seems reasonable to state that the arterial P_{O_2} of about 140 mm. of mercury in this study did not affect cerebral blood flow or metabolism.

Body Temperature. As body temperature declines, the metabolic demands of the brain decrease, and the cerebral vasculature tends to constrict. The lesser cerebral blood flow is probably still adequate to supply the more slowly metabolizing cerebral tissue. Considerable decreases in cerebral blood flow and oxygen consumption have been reported in anesthetized, hypothermic man.[13, 14] Cohen *et al.*,[3] studying lightly anesthetized man, have estimated that CMR_{O_2} decreases about 15 per cent per degree centigrade as temperature

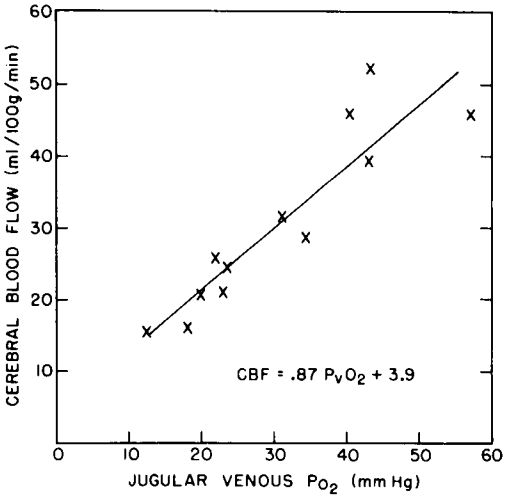

FIG. 2. Cerebral blood flow as a function of jugular venous P_{O_2} during anesthesia with thiopental, nitrous oxide, and *d*-tubocurarine (six subjects).

declines. In the present study, the maintenance of mean rectal temperature at 36.5° C. allows us to estimate a change in CMR_{O_2} of about 8 per cent due to decreased temperature. Little or no effect on cerebral blood flow would be exerted by this temperature change.

Drug Effects. Figure 3 illustrates the cerebral blood flow of man measured in the conscious state and during two kinds of anesthesia. Halothane, a cerebral vasodilator, is seen to be associated with increased cerebral blood flow.[2] In the present study, brain blood flow at normal P_{CO_2} appears to be little different from that of awake man. Though high blood levels of thiopental (*e.g.*, 25–35 mg./liter) result in cerebral vascular constriction and decreased CMR_{O_2},[1, 15] the low blood concentration present in this study (table 1) could not exert an appreciable effect on the cerebral vasculature or oxygen uptake.[16] Intravenous *d*-tubocurarine in slightly smaller doses (40–75 mg. total) has been shown not to affect cerebral hemodynamics or metabolism.[2, 3] Seventy per cent nitrous oxide now appears to exert no appreciable effect on the cerebral vasculature.

Cerebral oxygen consumption was decreased by 23 per cent in this study, of which 8 per cent may be attributed to temperature change. The remaining 15 per cent decrease, which must have been a drug-induced change, is very likely caused by 70 per cent nitrous oxide. This decrease in CMR_{O_2} may be compared to:

(1) A 9 per cent decrease reported during light halothane anesthesia, all of which may have been induced by temperature change.[2]

(2) A 55 per cent decrease following large doses of thiopental,[1] 21 per cent being attributable to decline in temperature.

(3) A 36 per cent decrease following moderate doses of thiopental,[15] with temperature change playing an unknown role here.

The brain's rate of oxygen consumption is used in all the above comparisons rather than its rate of carbon dioxide production. Although CMR_{CO_2} should change in a manner parallel to CMR_{O_2}, the CMR_{CO_2} is a less reliable measure of cerebral metabolic rate, as a steady state for CO_2 is not as likely within the brain tissue as it is for the less soluble gas, oxygen.

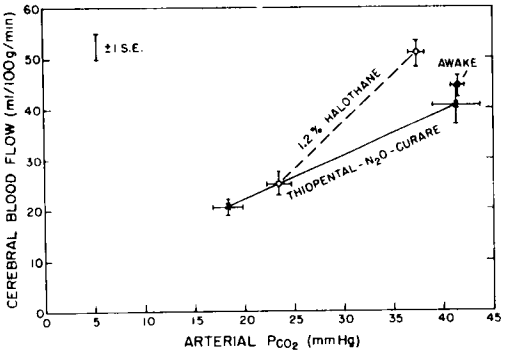

FIG. 3. Cerebral blood flow at normal and low levels of arterial P_{CO_2}. Each of the points represents a mean of six or more measurements made in this laboratory using the same techniques described in this work.

Blood Carbon Dioxide Tension. The factor exerting the greatest influence on cerebral vascular resistance in awake man is the blood carbon dioxide tension. During general anesthesia this remains true. The reactivity of the cerebral vessels to carbon dioxide has been demonstrated in man anesthetized with large doses of thiopental,[1] and it is illustrated during two other kinds of anesthesia in figure 3. This figure also shows that, when Pa_{CO_2} is very low, the cerebral blood flow is approaching a minimal level, close to the minimum value of about 18 ml./100 g./minute observed by Reivich in monkeys at Pa_{CO_2} levels down to 5 mm. of mercury during pentobarbital anesthesia.[17] It would seem that, with some if not all anesthetic agents, cerebral blood flow approaches a common low level when Pa_{CO_2} is decreased below 25 mm. of mercury. As carbon dioxide tension declines further, the additional decrease in cerebral flow is likely to be small.

The two lowest cerebral blood flows observed in this study were about one third of normal, 15.5 and 16.0 ml./100 g./minute (fig. 1). The question naturally arises—Is this adequate cerebral perfusion? Is the brain tissue hypoxic when its flow is so low? We did not find evidence indicating cerebral hypoxia in an earlier study of hyperventilation during halothane and oxygen anesthesia.[3] However, the degree of hyperventilation attained in the present study was greater. In fact we believe it to be a level of overbreathing which is not commonly achieved in the clinical use of this

technique. Thus, the changes which we have observed are likely to be greater than those which will occur during the general use of this anesthetic technique.

With the low cerebral blood flow produced by extreme hypocarbia, we did not find an additional decrease in CMR_{O_2}. However, the mean jugular venous P_{O_2} decreased to 19.8 mm. of mercury. In the three subjects in whom this measure was lowest it varied from 12.6 mm. of mercury to 19.8 mm. of mercury (fig. 2). Cerebral venous P_{O_2} values in this range have generally been considered to indicate suboptimal cerebral oxygenation, and are often associated with other evidence for the existence of mild to moderate cerebral hypoxia. These indications include changes in measures of carbohydrate metabolism and in the electroencephalogram.[9, 10] An investigation of these criteria in eleven subjects is reported separately.

Summary and Conclusions

Studies of cerebral circulation and gaseous metabolism were performed in healthy male volunteers during anesthesia induced with thiopental, and maintained with nitrous oxide and *d*-tubocurarine.

In the absence of change in Pa_{CO_2} cerebral blood flow remained normal, and cerebral oxygen utilization decreased by 23 per cent. Two thirds of this decrease was probably caused by 70 per cent nitrous oxide, one third by a small decline in body temperature.

When mean Pa_{CO_2} was lowered to 18.3 mm. of mercury cerebral blood flow was halved; but cerebral oxygen consumption did not decrease further, even though mean jugular venous P_{O_2} was only 19.8 mm. of mercury.

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