Cerebral Circulation of Man During Halothane Anesthesia

Effects of Hypocarbia and of d-Tubocurarine

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Cerebral circulatory measurements were made in 13 young normal male volunteers anesthetized with 1.2 per cent halothane in oxygen. Studies were performed at normal and at low Pa_{CO_2} with intravenous d-tubocurarine and at low Pa_{CO_2} without d-tubocurarine. During halothane anesthesia the cerebral vasculature was shown to constrict when Pa_{CO_2} was lowered, a response similar to that which has been observed in awake man. Halothane in the concentration studied was demonstrated to be a mild cerebral vasodilator. d-Tubocurarine was shown not to affect either cerebral blood flow, cerebral vascular resistance, or cerebral oxygen consumption. The relation of cerebral blood flow to the more easily measured jugular venous P_{O_2} is demonstrated and discussed.

KNOWLEDGE of the effects of anesthetic agents on the cerebral circulation of man is sparse. Information is lacking in the following areas: (1) The effects of the anesthetic agents on cerebral vascular resistance and cerebral blood flow. (2) The effects on the cerebral circulation of common anesthetic events, such as deliberate hyperventilation, the use of muscle relaxants, and changes in blood pressure.

Information on some of these points has been obtained during various levels of thiopental narcosis in man.[1-4] These studies suggest that thiopental causes cerebral vasoconstriction, the effect probably being more marked with larger doses. The same work

also indicates that thiopental significantly depresses cerebral oxygen consumption, an effect which again seems to be dose-related.

In this study, some of the effects of halothane anesthesia on the cerebral circulation and oxygen consumption of normal man were investigated at normal and at lower than normal Pa_{CO_2}. In addition, the effects of d-tubocurarine on the cerebral circulation were measured. All measurements were performed at approximately the same depth of halothane anesthesia.

Methods

Thirteen normal, unpremedicated male volunteers were studied during halothane anesthesia without operation. All had refrained from smoking for at least 36 hours. Following induction of anesthesia with nitrous oxide, oxygen, and halothane, a single dose of 60 mg. of succinylcholine was given, and an endotracheal tube was inserted. The subjects were then given 1.2 per cent halothane in oxygen delivered through a calibrated Fluotec vaporizer in a nonrebreathing system. Ventilation was controlled with a Bird respirator at minute volumes sufficient to lower arterial P_{CO_2} to 20–25 mm. of mercury. Normal levels of arterial P_{CO_2} were obtained in some cases by adding CO_2 to the inhaled gases, while the ventilatory pattern remained unchanged. d-Tubocurarine in intravenous doses of 40 to 75 mg. was administered when CO_2 was added, in order to prevent spontaneous respirations. d-Tubocurarine was given to half of the hypocarbic subjects and omitted in the other half in order to determine if the drug affected cerebral blood flow or oxygen consumption.

TABLE 1. Experimental Conditions

	Hypocarbia without d-Tubocurarine		Hypocarbia with d-Tubocurarine		Normocarbia with d-Tubocurarine	
	6*		6*		6*	
	Mean	S.E.	Mean	S.E.	Mean	S.E.
Age	28.7	2.8	27.0	1.4	24.7	1.2
Weight (pounds)	163	6.5	165	9.8	162	6.8
Height (inches)	71.2	0.7	71.3	1.1	70.4	0.9
End-Tidal Halothane (%)	0.94	0.06	1.00	0.04	1.03	0.04
Peak Insp. Pressure (cm. H_2O)	15.7	0.8	14.3	0.6	15.9	0.8
Peak Exp. Pressure (cm. H_2O)	−3.2	0.2	−3.1	0.2	−3.1	0.1
$\dot{V}$ (liters/minute)	12.22	0.78	11.84	0.53	13.08	0.94
V_T (ml.)	874	61	818	44	847	59
f (breaths/minute)	14.2	1.1	14.5	0.4	15.7	1.1
Temperature (°C.)	36.0	0.3	35.7	0.4	36.4	0.4

* Number of studies.

No other drug was administered. Normal saline was given intravenously in amounts sufficient to replace the blood removed for samples.

Gases from within the endotracheal tube were sampled continuously and passed through appropriate infrared analyzers for the determination of end-tidal CO_2 and halothane concentrations. Expired minute ventilation was measured with a Wright anemometer. Body temperature was measured in the mid esophagus with a calibrated thermistor probe.

Blood samples were drawn anaerobically from needles placed in a femoral artery, and in the superior bulb of the jugular vein.[5] Pressures in both of these vessels were measured with Statham transducers. Cerebral blood flow was measured by a modification of the Kr^{85} method of Lassen and Munck,[6] sampling intermittently over periods varying from 14 to 23 minutes.

Blood pH, P_{CO_2}, and P_{O_2} were measured in appropriate electrodes, making corrections for temperature, electrode drift, and metabolic changes in blood with the passage of time.[7] Oxygen content of venous blood was determined spectrophotometrically,[8] the method having been previously calibrated by manometric Van Slyke analyses.[9] Oxygen contents of arterial and venous blood were determined as the sum of hemoglobin oxygen capacity determined spectrophotometrically and dissolved oxygen, as estimated from P_{O_2} and oxygen solubility in blood.

Many subjects were studied twice—either at low and at normal Pa_{CO_2}—or at low Pa_{CO_2}, first without and then with d-tubocurarine. The first measurements were made 90 or more minutes after the start of halothane anesthesia, and the second measurements 30 or more minutes after the first were completed.

Results

The measurements were divided into three groups—those made at normal Pa_{CO_2}; those made at low Pa_{CO_2} in curarized subjects; and those at low Pa_{CO_2} in non-curarized subjects. The experimental conditions are shown in table 1. There were no significant differences among the three groups in any of the variables shown in table 1.*

In table 2 are shown the values of arterial and jugular venous P_{O_2}, P_{CO_2} and pH. No significant differences appeared between the two groups of hypocarbic subjects, indicating that d-tubocurarine had no effect on these variables. However, both hypocarbic groups differed significantly from the normocarbic group ($P < 0.05$) in all variables except arterial P_{O_2}.

The results obtained for some cerebral circulatory and metabolic parameters are shown in table 3. The two hypocarbic groups did not differ significantly in cerebral blood flow (CBF) or cerebrovascular resistance (CVR),

* The statistical method used in these comparisons was the Link and Wallace analysis of variance.[10]

TABLE 2.   Blood Gas Measurements

Situation	Number	Arterial						Jugular Venous					
		P_{O_2} (mm. Hg)		P_{CO_2} (mm. Hg)		pH		P_{O_2} (mm. Hg)		P_{CO_2} (mm. Hg)		pH	
		Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
Hypocarbia without d-tubocurarine	6	545	31	23.7	1.3	7.608	0.025	31.7	2.3	36.2	2.4	7.510	0.026
Hypocarbia with d-tubocurarine	6	604	28	23.2	1.2	7.631	0.012	30.4	4.3	37.8	1.1	7.508	0.014
Normocarbia with d-tubocurarine	6	566	15	37.3	0.8	7.449	0.019	53.7	5.1	45.8	1.2	7.399	0.015

although CBF and CVR in both hypocarbic groups differed significantly from those of the normocarbic group ($P < 0.01$). Cerebral oxygen consumption (CMR_{O_2}) did not differ significantly among the three anesthetized groups. Thus, Pa_{CO_2} was shown to affect both CBF and CVR, but not CMR_{O_2} during halothane anesthesia; and d-tubocurarine was demonstrated to be without effect on CBF, CVR, or CMR_{O_2}.

In table 3 are also shown normal values obtained in this laboratory in awake man. CBF and CVR in the anesthetized normocarbic group differed from the values obtained in normal awake man ($P < 0.1$),† indicating a cerebral vasodilating effect of halothane. CMR_{O_2} was somewhat lower in all three groups of anesthetized subjects than it was in awake man.

There were no significant differences in perfusion pressure among the anesthetized groups, but perfusion pressure was lower in all three anesthetized groups than it was in the awake subjects ($P < 0.05$). It was possible to demonstrate in an analysis of the individual data, that CBF in the anesthetized subjects was independent of perfusion pressure of the brain. Over the range of perfusion pressures found in this study (41 to 81 mm. of mercury), there was no significant relation between perfusion pressure and CBF.

The relation between jugular venous P_{O_2} and CBF in subjects anesthetized with 1.2 per cent halothane is shown in figure 1. Though the scatter is considerable, a linear regression relating CBF and jugular venous P_{O_2}, and its formula are shown in figure 1.

Discussion

The results obtained during anesthesia were not influenced by the inhalation of nearly 100 per cent oxygen, for it has been shown that the inhalation of oxygen does not affect CBF or CVR, provided that the Pa_{CO_2} does not vary.[11, 12]

The absence of any differences in CBF, CVR, and CMR_{O_2} between the hypocarbic subjects given d-tubocurarine and those who were not is strong evidence that d-tubocurarine has no important effects on the cerebral circulation of man, even in the relatively large intravenous doses used in this study. The question of the effects of curarization on the cerebral circulation of man was raised, but not answered, in the work of Pierce et al.,[3] where large doses of both d-tubocurarine and thiopental were administered. Now it seems reasonable to attribute Pierce's results solely to the effects of thiopental anesthesia. The findings of marked cerebral vasoconstriction and greatly depressed CMR_{O_2} during thiopental anesthesia stand in sharp contrast to the effects of anesthesia with 1.2 per cent halothane observed in this study—cerebral vasodilatation and a small decrease in CMR_{O_2}. The relation of lowered body temperature to the change in CMR_{O_2} is fully discussed elsewhere.[13]

During halothane anesthesia at least three factors affected the cerebral vascular response.

† Student's t-test.

TABLE 3. Cerebral Circulatory Measurements

Situation	No.	CBF (ml./100 g./min.)		CVR (mm. Hg/ ml./100 g./min.)		CMRo₂ (ml./100 g./min.)		Perfusion Pressure* (mm. Hg)	
		Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
Hypocarbia without d-tubocurarine	6	27.2	1.4	2.4	0.13	2.45	0.31	65.1	5.4
Hypocarbia with d-tubocurarine	6	23.1	2.6	2.6	0.31	2.56	0.36	55.3	3.3
Normocarbia with d-tubocurarine	6	50.8	2.7	1.1	0.14	2.80	0.23	56.0	4.8
Awake†	6	44.4	2.2	1.9	0.16	3.09	0.19	82.1	4.8

 * Mean arterial pressure minus mean jugular venous pressure.
 † Mean arterial $P_{CO_2} = 41.4$ mm. of mercury.

One of these, the arterial P_{CO_2}, affected CVR in the same manner as it does in awake man and in man during thiopental anesthesia. As Pa_{CO_2} decreased, the CVR increased and the CBF decreased. A second factor was the lower perfusion pressure of the brain, resulting from the lower arterial pressure which occurred during halothane anesthesia. The cerebral vessels appear to dilate when blood pressure decreases during halothane anesthesia; and therefore CBF tends to remain constant over a considerable range of perfusion pressures. A similar phenomenon has been observed by others in conscious man.[14, 15] The third effect on CVR was that of halothane itself, which appeared to produce a moderate amount of cerebral vascular dilatation, as evidenced by the CBF of 50.8 ml./100 g./minute during normocarbia and halothane anesthesia. This is significantly greater $(P < 0.10)$ than the normal value in awake man (44.4 ml./ 100 g./minute).

McDowall, Harper and Jacobson,[16] studying the effects of less than 0.5 per cent halothane in dogs, found large decreases in both CBF and CMR_{O_2}, accompanied by a greatly increased CVR. It is difficult to reconcile these results with those obtained in this study. However, a number of differences can be pointed out between these two studies. First, the drugs used were different: McDowall and associates induced anesthesia with unspecified amounts of thiopental, a drug known to have marked effects on cerebral circulation and oxygen utilization[3]; they also employed unspecified amounts of succinylcholine, a drug whose effects on the cerebral circulaiton are un-

known. In addition, their animals inhaled N_2O during parts of the study, and again the effects of this agent on the cerebral circulation are not known. Second, they were studying the effects of a lower halothane concentration than was employed here. The length of time halothane was inhaled is not specified. Furthermore, it seems unusual that the effects of halothane on CBF, CVR, and CMR_{O_2} were independent of the inspired concentration of halothane, between 0.5 and 3.0 per cent in that study. It must also be pointed out that the former studies were performed in dogs, while the present were on man. The temperature of their animals is not specified, and therefore evaluation of the measured CMR_{O_2} is difficult. Lastly, the "CBF" measurement from which McDowall and his colleagues cal-
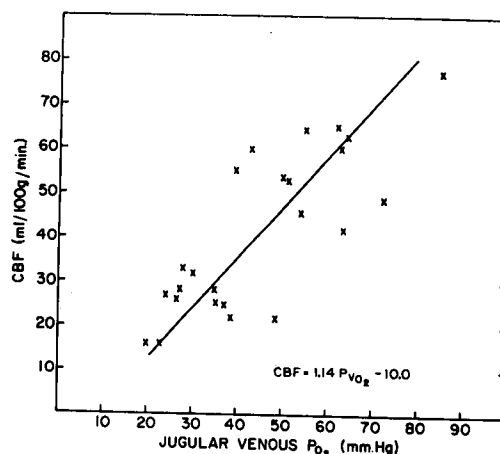

FIG. 1. Cerebral blood flow as a function of jugular venous P_{O_2} during halothane anesthesia.

culate their "CVR" and "CMRo$_2$" actually measures the flow of blood in only a small area of superficial cortex, whereas the "CBF" measured in this laboratory yields an average figure for the whole brain. Perhaps this difference in what is actually measured lies at the root of the differing results in these two investigations.

The relation of CBF and jugular venous P$_{O_2}$ shown in figure 1 might be of clinical use in estimating CBF from the more easily made measurement of jugular venous P$_{O_2}$ if certain reservations are kept in mind. The errors in estimating CBF from jugular venous P$_{O_2}$ arise from the fact that jugular venous P$_{O_2}$ is determined not only by CBF, but also by CMRo$_2$, which in turn is affected by many other variables, such as age, temperature, anesthetic drugs, and the depth of anesthesia. Therefore, estimation of CBF from figure 1 might be attempted in young normal patients, so long as the procedure was limited to halothane anesthesia of roughly the same depth as was employed here, and so long as the rather wide scatter of the data is kept in mind.

Summary

Cerebral blood flow, cerebral vascular resistance, and cerebral oxygen consumption were measured in normal male volunteers during the inhalation of 1.2 per cent halothane in oxygen. Studies were performed at low and at normal Pa$_{CO_2}$, and with and without intravenous d-tubocurarine.

The cerebral vasculature was shown to respond to lowering of Pa$_{CO_2}$ with constriction, during halothane anesthesia, as it does in awake man. Halothane in the concentration studied was demonstrated to be a mild cerebral vasodilator. d-Tubocurarine was shown not to affect any of the variables measured.

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