Anesthesiology
V 39, No 6, Dec 1973

The Mechanism of Cerebral Vasodilation by Halothane

*Allan L. Smith, M.D.**

The moment-to-moment responses of cerebral blood flow (CBF), cerebral oxygen consumption (CMR_{O_2}), and cerebral arteriovenous oxygen content difference [$(a-v)_{O_2}$] following a step (sudden) increase in arterial halothane content from 1.29 ± 0.14 (mean ± SE) to 3.77 ± 0.21 vol per cent were studied in nine dogs. CBF increased from 52.8 ± 9.0 to 94.3 ± 17.1 ml/100 g/min during the 5-minute period following the halothane step-up, then declined to 87.4 ± 14.8 ml/100 g/min by the eighth minute. CMR_{O_2} decreased from 3.37 ± 0.44 to 2.35 ± 0.28 ml/100 g/min. Changes in CMR_{O_2} paralleled changes in brain halothane content. $(a-v)_{O_2}$ declined from 7.03 ± 0.68 to 3.30 ± 0.45 ml/100 g/min with the same time course as the decline of cerebral venous halothane content. If halothane acted principally as a direct dilator of cerebral vessels, CBF should have increased with the same rapid time course that arterial halothane content followed. The good correlations of $(a-v)_{O_2}$ and CMR_{O_2} with halothane concentration, and the poor correlation of CBF with changes in arterial halothane content, suggest that if direct cerebral vasodilation occurs with halothane, it is modest in intensity and is modified by metabolic effects. Alterations in CMR_{O_2} and control of $(a-v)_{O_2}$ are probably more important than direct effects on vascular smooth muscle in determining CBF during halothane anesthesia. (Key words: Cerebral blood flow; Cerebral oxygen consumption; Cerebral arteriovenous oxygen content difference; cerebral halothane uptake; Halothane.)

THE MECHANISM by which halothane increases cerebral blood flow (CBF) is unknown. Halothane may directly dilate cerebral vessels or may increase CBF indirectly through alterations in metabolism or metabolic control. Depression of cerebral oxygen consumption (CMR_{O_2}) is probably a direct cellular effect, and the cerebral arteriovenous oxygen content difference, $(a-v)_{O_2}$, varies inversely with anesthetic depth.[1] Since metabolism and flow are related by the equation $CMR_{O_2} = CBF \times (a-v)_{O_2}$, the effects of halothane on each of these variables cannot be independent. In an attempt to define the variables on which halothane acts directly, we determined the temporal responses of CBF, $(a-v)_{O_2}$, and CMR_{O_2} to a step (sudden) increase in arterial halothane concentration. If halothane affects CBF by direct dilation of cerebral arterioles, the time course of CBF increase should parallel the rapidly increasing time course of arterial halothane concentration. If halothane indirectly influences CBF by altering metabolic factors, then the time course of CBF increase might not correlate with the arterial halothane increase. In this circumstance, $(a-v)_{O_2}$ and CMR_{O_2} should follow the slower rate of increase of brain halothane content.

Methods

Nine mongrel dogs (both sexes), mean weight 20.2 kg, were studied. Anesthesia was begun with ketamine, 2 mg/kg, and continued with 1 to 1.5 per cent halothane in 30 per cent O_2–70 per cent N_2. Ventilation was controlled via an endotracheal tube. End-tidal P_{CO_2} was maintained at 35–40 torr during surgical preparations. A brachial artery was cannulated for blood sampling and the left femoral artery was cannulated for pressure measurements. A cannula was also placed in the right femoral artery for later connection to a blood reservoir. Infusion of 0.9 per cent NaCl was begun in a femoral vein.

The posterior portion of the superior sagittal sinus was exposed by a craniotomy 3 cm long and 2 cm wide. Bone between the craniotomy and the frontal air sinus was thinned to 1 mm to exclude bone venous blood from the sagittal sinus. A plastic cannula with a tip diameter of 0.7 mm was placed in the saggital sinus for sampling and pressure measurements. We then positioned a Doppler flow probe (Parks Electronics) over the exposed sagittal sinus and fixed it in place with dental cement. A thermistor 5 mm in diam-

* Assistant Professor of Anesthesia.

Received from the Department of Anesthesia, University of California, San Francisco, California 94122. Accepted for publication May 15, 1973. Supported in part by USPHS Grant 5POI-GM-15571.

TABLE 1. Experimental Conditions*

	Time (Minutes)		
	0	4-5	8-9
Arterial blood			
Halothane concentration, vol per cent	1.29 ± 0.14	3.77 ± 0.23	3.77 ± 0.21
Mean blood pressure, torr	126 ± 7	98 ± 6	98 ± 7
P_{CO_2}, torr	33.8 ± 1.8	33.6 ± 1.7	34.2 ± 1.8
P_{O_2}, torr	172 ± 5	176 ± 4	175 ± 5
*p*H	7.410 ± 0.017	7.426 ± 0.014	7.419 ± 0.020
Oxygen content, vol per cent	16.37 ± 0.89	16.41 ± 1.03	16.39 ± 1.02
Venous blood			
Halothane concentration, vol per cent	1.31 ± 0.16	3.51 ± 0.23	3.58 ± 0.21
Mean blood pressure, torr	12 ± 2		
P_{CO_2}, torr	48.1 ± 1.5	40.2 ± 1.4	40.9 ± 1.6
P_{O_2}, torr	36.2 ± 2.0	50.5 ± 2.6	52.0 ± 2.6
*p*H	7.331 ± 0.012	7.367 ± 0.015	7.372 ± 0.018
Oxygen content, vol per cent	9.33 ± 0.92	12.89 ± 1.19	13.08 ± 1.26
Rectal temperature (C)	37.6 ± 0.1		
Epidural temperature (C)	36.5 ± 0.2		

* Values are means ± SE.

eter was placed between bone and dura to measure epidural temperature.

Tracheal CO_2 and halothane concentrations were continuously monitored with infrared analyzers, and arterial and venous pressures were measured with strain gauges. Gas concentrations and pressures were recorded on a polygraph, together with the output of the flow probe.

After completion of the surgical procedure, the dog was paralyzed with 60 to 100 mg of gallamine. End-tidal halothane concentration was adjusted to 0.6 per cent and held constant at that level for at least 60 min. End-tidal CO_2 was set at 30 to 35 torr. Thirty minutes before the step increase in halothane concentration (see below), heparin, 1.5 mg/kg, was administered. To keep blood pressure constant, a reservoir bottle was connected to the cannula in the right femoral artery. The height of the reservoir was adjusted so that the animal shed blood when mean arterial pressure was above 120 torr and absorbed blood when pressure fell below 120 torr. Immediately prior to connecting the reservoir bottle, the animal's blood volume was expanded by intravenous infusion of 300 ml of 7-day-old, untyped dog blood.

To achieve the step increase, 8 per cent halothane was delivered initially. We subsequently reduced and adjusted the inspired concentration as needed to maintain end-tidal halothane constant at 1.6 per cent. Carbon dioxide was added to the inspired gas to keep end-tidal P_{CO_2} constant. Sampling for blood halothane content was performed at the following times after the step increase: arterial: 0, 0.3, 0.7, 1, 2.5, 4.5, 8, and 15.5 minutes; cerebral venous: 0, 0.7, 1.5, 2.5, 3.5, 4.5, 8, and 15.5 minutes. Samples were drawn for duplicate measurements of P_{CO_2}, *p*H, P_{O_2}, and oxygen content as follows: arterial: 0, 1.3, 3, 4, 5, 8.3, and 15 minutes; cerebral venous: 0, 0.3, 1, 2, 3, 5, 6.5, 8.3, and 15 minutes. In three of the nine dogs, sampling was carried to 8 minutes only. Total blood loss from the surgical procedure and sampling was about 150 ml. After the last sample had been drawn, autoregulation of CBF was tested in five animals by raising arterial blood pressures 25–40 torr with phenylephrine.

At the end of each study the Doppler flow probe was calibrated. A cannula was occlusively placed into the sagittal sinus and flow was measured by time blood collections. CBF was varied by changing P_{CO_2} or halothane concentration, and the relation between sagittal

TABLE 2. Cerebral Blood Flow and Metabolism*

	Time (Minutes)		
	0	4–5	8–9
CBF, ml/100 g/min	52.8 ± 9.0	94.3 ± 17.1	87.4 ± 14.8
CMR_{O_2}, ml/100 g/min	3.37 ± 0.44	2.60 ± 0.32	2.35 ± 0.28
$(a-v)_{O_2}$, ml/100 ml	7.03 ± 0.68	3.52 ± 0.38	3.30 ± 0.45

* Values are means ± SE.

sinus flow and Doppler frequency shift was established. This relation was always linear. The brain then was removed and weighed. CBF, in ml/100 g/min, was calculated from the relation described by Michenfelder and Theye, CBF = sagittal sinus flow × 100/0.43 × brain weight.[2] CBF values determined by the Doppler and ^{133}Xe-washout techniques were compared in preliminary experiments.

Blood oxygen content was determined using a carbon monoxide displacement technique,[3] halothane content by gas chromatography, and P_{O_2}, P_{CO_2}, and *p*H by electrodes.

Time plots of arterial and cerebral venous oxygen contents, cerebral venous P_{O_2} (Pv_{O_2}), and arterial and venous halothane contents were prepared, and smooth curves were drawn through the data points. Values of the arteriovenous halothane content difference (AVH) and $(a-v)_{O_2}$ were obtained from the appropriate curves at 0.25- to 1-minute intervals. Assuming that brain oxygen stores are negligible, CMR_{O_2} was calculated as the product of CBF and $(a-v)_{O_2}$. Brain halothane uptake at any time was obtained from the expression $\int_0^t (AVH)\cdot(CBF)\cdot dt$ by numerical integration. Halothane uptake to equilibrium was obtained by assuming that after the last minute of the study CBF was constant and AVH declined monoexponentially.

To facilitate comparisons among curves, all variables were expressed on a percentage change basis. The value at zero time was defined as the "equilibrium" value in the case of halothane, or the value of the greatest change for the other variables.

Results

Arterial oxygen content fell between the eighth and fifteenth minutes in five of the six dogs studied for 15 minutes. Since this could conceivably have affected control of CBF, results from the first eight minutes of the study only are presented. Mean experimental conditions at the start, midpoint, and end of the step increase are given in table 1. The exigencies of blood sampling prevented us from obtaining temperatures and venous pressures after zero time. The arterial halothane concentrations at 0 and 8 to 9 minutes were equivalent to gas partial pressures of 0.56 and 1.63 vol per cent, respectively, assuming a blood/gas partition coefficient of 2.3. Mean arterial blood pressure fell from 126 to 98 torr in spite of the arterial reservoir. Elevation of arterial pressure with phenylephrine after the last blood sample had been drawn did not increase CBF in any animal. The mean arterial pressure change with phenylephrine was from 98 to 128 torr. Arterial P_{CO_2}, P_{O_2}, and *p*H all were constant during the study period.

Absolute values for CBF and CMR_{O_2} are given in table 2. Percentage changes in mean anesthetic and cerebral hemodynamic variables are shown in table 3 and figures 1 and 2. At 8 minutes, cerebral venous blood and brain had achieved 92.9 and 78.6 per cent equilibrium with the new arterial halothane level, respectively. Initially, the CBF increase lagged behind the arterial halothane increase by about a minute. Mean CBF reached a maximum at the fifth minute, then declined. A mean value of 100 per cent was not achieved, since CBF values in all dogs did not reach their maximums at exactly the same time. Data from six animals suggest that CBF leveled off at about the twelfth minute at a value of 55 per cent, or 75.6 ml/100 g/min. CMR_{O_2} and $(a-v)_{O_2}$ decreased with the sudden increase in halothane. Note that the increases of these variables in figure 2 reflect rate of approach to equilibrium, *not* increases in CMR_{O_2} and (a–

TABLE 3. Percentage Changes in Response to a Step Increase in Halothane Concentration*

	Time (Minutes)				
	0	2	4	6	8
Arterial halothane	0	83.4 ± 4.4	100.0 ± 3.2	99.2 ± 2.8	99.5 ± 1.2
Venous halothane	0	62.4 ± 2.8	86.2 ± 3.9	91.3 ± 2.5	92.9 ± 1.7
Brain halothane	0	39.7 ± 2.9	61.1 ± 3.1	71.8 ± 3.2	78.6 ± 2.8
CBF	0	70.8 ± 8.7	86.6 ± 6.2	90.7 ± 4.0	77.2 ± 5.1
CMR_{O_2}	0	39.2 ± 7.5	64.2 ± 5.0	75.1 ± 6.6	83.2 ± 4.4
$(a-v)_{O_2}$	0	63.6 ± 7.6	85.4 ± 4.2	93.1 ± 6.4	93.4 ± 2.3
Pv_{O_2}	0	63.1 ± 7.7	87.1 ± 2.9	93.8 ± 1.5	95.0 ± 3.2

* Values are means ± SE.

$v)_{O_2}$. The time course of CMR_{O_2} change closely followed the time course of brain halothane concentration, and $(a-v)_{O_2}$ followed the same time course as venous halothane level. Pv_{O_2} followed almost exactly the same time course as $(a-v)_{O_2}$ (table 3).

Correlation between pairs of curves in each individual study were examined, using the "correlation index" criterion.[4] In every animal, the correlation of CMR_{O_2} with brain halothane and the correlation $(a-v)_{O_2}$ with venous halothane were better than the correlation of CBF with arterial halothane.

Eighteen paired measurements of CBF by the Doppler and ^{133}Xe-washout methods yielded the regression equation: ^{133}Xe CBF = 3.3 + 0.951 × Doppler CBF ($r = 0.91$). The slope was not significantly different from unity.

Discussion

The responses of the cerebral circulation to a step increase in halothane concentration were studied to help define the mechanism by which this anesthetic increases CBF. The implications of our data must be considered in the light of current concepts of cerebral circulatory control. Most workers agree that this is a local phenomenon.[5, 6, 7] Arteriolar smooth muscle is the effector organ. Some metabolite, probably CO_2 acting through periarteriolar extracellular fluid *p*H, forms a feedback control loop. CBF affects the metabolite washout from the brain and metabolite concentration "feeds back" to control arteriolar diameter. The sensitivity of CBF to changes in metabolite level might be referred to as the "gain" of the system. Several such systems may be acting simultaneously on the effector organ or may interact with each other; for example, Pv_{O_2} also may be related to CBF control. A perturbation of the control system might alter the feedback loop itself and thus affect its gain; for example, a decrease in metabolic CO_2 production should result in a lower gain. On the other hand, the perturbation could affect the effector organ, for instance, by changing intrinsic muscle tone. If the feedback loop is unaffected, the latter type of perturbation might be difficult to observe, since it could be compensated by the control loop.

Halothane probably alters the control loop gain by decreasing CO_2 production. Halothane also could affect CBF control in at least two other ways. The drug might have such a large *direct* relaxing effect on arterial smooth muscle that the metabolic control systems cannot compensate for it. Alternately, the direct effect could be relatively small, so that the feedback control system could easily compensate for it. CBF alterations would then be largely "indirect," or secondary to perturbation in the brain's normal feedback control loops.

Since halothane is a smooth-muscle relaxant, the "obvious" interpretation of the biphasic response of CBF to the step increase of halothane (fig. 1) would be: Halothane has a large direct relaxing effect on cerebral arterioles, which initially overrides metabolic flow control and produces an early rise in CBF. Halothane also directly reduces CMR_{O_2} at the cellular level. This is consistent with the parallel time courses of CMR_{O_2} and brain halothane content (fig. 2). As CBF increased, CMR_{O_2} decreased. Metabolic regulation, the feedback loop, caught up in 5 minutes, coun-

teracted the direct dilation produced by halothane, and reduced CBF.

This theory is appealing in its simplicity, but leaves a number of observations unexplained. Why did the CBF increase lag behind the arterial halothane increase by a whole minute? One would expect an immediate effect, if halothane is a "direct" cerebral vasodilator. Why was CBF increasing between the second and fifth minutes, when arterial halothane was constant? Neither of these questions can be answered by assuming a long delay in halothane uptake by arteriolar smooth muscle. Calculations based on known partition [8] and diffusion [9] coefficients suggest that arteriolar muscle should reach 90 per cent equilibrium with blood halothane in less than a second. CBF regulation occurs within seconds in response to perturbations such as a change in perfusion pressure or P_{CO_2}.[10] Why, then, did it take 5 minutes for the brain's metabolic or "feedback" control mechanisms to "correct" for the halothane-induced vasodilation?

A final deficiency of the "direct arteriolar dilation" explanation of the data is its failure to account for the behavior of Pv_{O_2} and $(a-v)_{O_2}$. Previous work has suggested that

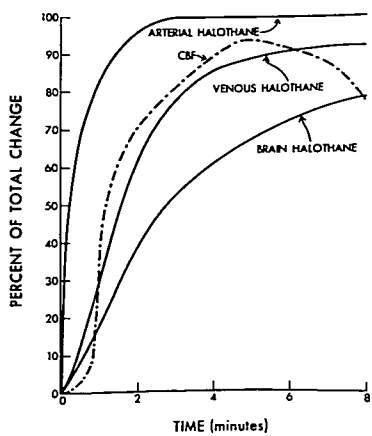

FIG. 1. Response of CBF to a sudden increase in arterial halothane concentration.

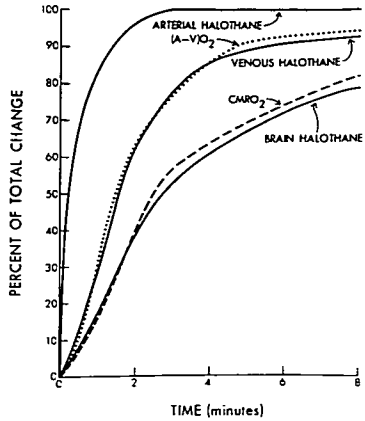

FIG. 2. Responses of CMR_{O_2} and $(a-v)_{O_2}$ to a sudden increase in arterial halothane concentration.

for all inhalation anesthetics, Pv_{O_2} depends on anesthetic dose only.[1] Consistent with this, Pv_{O_2} and $(a-v)_{O_2}$ were functions of halothane concentration in the present study (fig. 2). It is difficult to ascribe these correlations to coincidence alone. Pv_{O_2} is related to, and $1/(a-v)_{O_2}$ is equal to, the ratio CBF/CMR_{O_2}. If halothane directly affected only CBF and CMR_{O_2}, then Pv_{O_2} and $(a-v)_{O_2}$ would be dependent variables. How would we then explain the observed correlation of anesthetic dose with Pv_{O_2}?

Before discussing an alternate theory for the effects of halothane on cerebral hemodynamics, let us consider the possibility that halothane might affect control of brain tissue P_{O_2} and hence, Pv_{O_2}. That the time course of Pv_{O_2} was the same as that of venous halothane concentration is interesting, and might be explained in several ways. We could speculate that a metabolite whose time course after a step change in halothane concentration is the same as that of venous halothane content acts within a CBF control loop and thus indirectly regulates CBF/CMR_{O_2} and Pv_{O_2}. Another indirect form of Pv_{O_2} regulation might result if the anesthetic altered capillary-to-

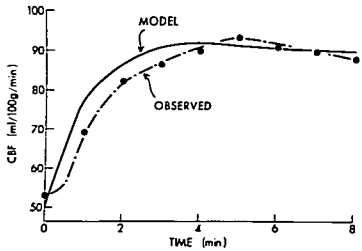

FIG. 3. Observed time course of CBF following a step increase in arterial halothane compared with that predicted from a mathematical model.

mitochondria oxygen transport gradients. Indirect tissue P_{O_2} or Pv_{O_2} regulation could occur if small amounts of acid metabolites were produced in the presence of anesthetics. These would act within the CO_2–H+ control loop to increase CBF, and thus Pv_{O_2}.

Finally, one might postulate that the brain regulates tissue P_{O_2} or Pv_{O_2} directly: that is, a control loop for Pv_{O_2} exists. Regulation within the loop might be modified by halothane or by an undetermined metabolite whose concentration is proportional to venous halothane content. The concept of regulation of Pv_{O_2} should not be surprising. CBF and CMR_{O_2} are affected very differently by the various inhalation anesthetics.[11] If Pv_{O_2} is not regulated either directly or indirectly, the observation that equivalent doses of all agents raise Pv_{O_2} to exactly the same level would be difficult to explain.

I suggest the following speculation on how halothane produces cerebral vasodilation. Halothane may relax arteriolar smooth muscle, but the brain's metabolic control loop opposes and compensates for any such effect. The primary effects of halothane are to depress CMR_{O_2} and to alter the mechanism which controls cerebral P_{O_2}. Depression of CMR_{O_2} is directly related to cerebral anesthetic concentration, and halothane resets the level at which Pv_{O_2} is maintained, by one of the mechanisms suggested above. These mechanisms all involve secondary changes in cerebrovascular resistance. CBF alterations are thus produced as secondary responses which adjust tissue P_{O_2} and thus $(a\text{–}v)_{O_2}$ and Pv_{O_2}. A biphasic CBF response to a sudden rise in arterial halothane occurs as the $CMR_{O_2}/(a\text{–}v)_{O_2}$ ratio is continuously altered. This theory offers no explanation for how anesthetics depress CMR_{O_2} or elevate Pv_{O_2}, but it is consistent with the observed effects on CBF, CMR_{O_2}, and Pv_{O_2}. In summary, the theory and data suggest that changes in Pv_{O_2} and CMR_{O_2} are "primary" and changes in CBF are "secondary" effects of halothane.

We may test the tenability of the above speculation, although not prove it, with a mathematical model of the cerebral circulatory effects of a step increase in halothane concentration. The model must predict a biphasic CBF response without assuming that halothane has direct vascular effects. The following assumptions were made: 1) CMR_{O_2} is a function of brain-tissue halothane concentration only; 2) $(a\text{–}v)_{O_2}$ is a function of cerebral venous halothane concentration only; 3) CBF is determined entirely by the ratio $CMR_{O_2}/(a\text{–}v)_{O_2}$. 4) Any *direct* effects of halothane on cerebral arterioles are immediately compensated for by the brain's metabolic control loops.

Data for CMR_{O_2} and $(a\text{–}v)_{O_2}$ were taken from unpublished studies; blood halothane concentrations from the present study were used. Details of the calculation are given in the Appendix. The mathematical model (fig. 3) predicts a biphasic CBF response which corresponds remarkably well to the observed curve. Although the correspondence is consistent with the author's speculations, the conclusions to be drawn from the model are permissive.

Some possible criticisms of the experiment should be considered. It is unlikely that the changes in arterial pressure significantly affected CBF in the 5–8-minute period of the halothane step-up. Autoregulation is not affected by anesthesia so long as the physiologic limit of vessel dilation is not exceeded.[12] These limits were not reached, as indicated by the lack of CBF change in response to a phenylephrine challenge. Furthermore, the peak of mean CBF occurred at 4 to 5 minutes, when the mean blood pressure had already reached its lowest level (table 3), and mean arterial blood pressure was constant during the period of subsequent CBF decrease. Although cerebral venous P_{CO_2} fell initially, it too was

constant during the period of CBF decrease. Thus, a changing tissue P_{CO_2} is not likely to have caused the CBF decrease. Ketamine, used as an induction agent, has effects on CBF and CMR_{O_2} which are completely dissipated within 30 minutes; the drug has no residual effect on the cerebral circulation like those of thiopental.[13]

Drs. J. W. Severinghaus and E. I. Eger, II, provided helpful suggestions for the preparation of the manuscript. The author appreciates the excellent technical assistance of Ms. Edwyna Von Gal and Ms. Merry Nishimura. Halothane was supplied by Ayerst Laboratories.

References

1. Smith AL: Dependence of cerebral venous oxygen tension on anesthetic depth. ANESTHESIOLOGY 39:291–298, 1973
2. Michenfelder JD, Messick JM, Theye RA: Simultaneous cerebral blood flow measured by direct and indirect methods. J Surg Res 8:475–481, 1968
3. Klingenmaier CH, Behar MG, Smith TC: Blood oxygen content measured by oxygen tension after release by carbon monoxide. J Appl Physiol 26:653–655, 1969
4. Ostle B: Statistics in Research. Ames, Iowa, Iowa State University Press, 1963, pp 222–225
5. Betz E: Cerebral blood flow: Its measurement and regulation. Physiol Rev 52:595–630, 1972
6. Wahl M, Deetjen P, Thuran K, et al: Micropuncture evaluation of the importance of perivascular pH for the arteriolar diameter on the brain surface. Pfluegers Arch 316: 152–163, 1970
7. Skinhoj E: Regulation of cerebral blood flow as a single function of the interstitial pH in the brain. Acta Neurol Scand 42:604–607, 1966
8. Larson CP, Eger EI II, Severinghaus JW: The solubility of halothane in blood and tissue homogenates. ANESTHESIOLOGY 23:349–355, 1962
9. Cullen BF, Eger EI II: Diffusion of nitrous oxide, cyclopropane, and halothane through human skin and amniotic membrane. ANESTHESIOLOGY 36:168–173, 1972
10. Severinghaus JW, Lassen NA: Step hypocapnia to separate arterial from tissue P_{CO_2} in the regulation of cerebral blood flow. Circ Res 20:272–278, 1967
11. Smith AL, Wollman H: Cerebral blood flow and metabolism: Effects of anesthetic drugs and techniques. ANESTHESIOLOGY 36:378–400, 1972
12. Smith AL, Neigh JL, Hoffman JC, et al: Effects of general anesthesia on autoregulation of cerebral blood flow in man. J Appl Physiol 29:665–669, 1970
13. Dawson B, Michenfelder JD, Theye RA: Effects of ketamine on canine cerebral blood flow and metabolism: Modification by prior administration of thiopental. Anesth Analg (Cleve) 50:443–447, 1971

APPENDIX

A mathematical model was used to predict the time course of CBF. We assumed that CMR_{O_2} is a linear function of brain halothane concentration and that $(a\text{–}v)_{O_2}$ is a linear function of cerebral venous halothane concentration over the range 0.6 to 1.6 per cent end-tidal. Let H_a, H_v, and H_b represent halothane content in arterial blood, cerebral venous blood, and brain tissue, respectively, in ml/100 ml. Let t represent time in minutes. Twenty-seven CMR_{O_2} and $(a\text{–}v)_{O_2}$ values, obtained during equilibrium conditions in the author's laboratory, yielded these relationships:

$$CMR_{O_2} = 4.26 - 0.240H_b \quad (1)$$

$$(a\text{–}v)_{O_2} = 9.23 - 1.42H_v \quad (2)$$

Arterial and venous halothane uptake curves in the present study were fit by the following equations:

$$H_a = 0.129 + 0.248(1 - e^{-1.67t}) \quad (3)$$

$$H_v = 0.129 + 0.248(1 - 0.84e^{-.707t} - 0.16e^{-.092t}) \quad (4)$$

Mass balances for halothane and oxygen across the brain give

$$(CBF)(H_a - H_v) = \frac{dH_b}{dt} \quad (5)$$

$$(CBF)(a\text{–}v)_{O_2} = CMR_{O_2} \quad (6)$$

These six equations were used to eliminate the five variables CMR_{O_2}, $(a\text{–}v)_{O_2}$, H_a, H_v, and H_b. Combining the equations, adding factors to correct for units and solubilities, and performing the indicated operations yielded the sought-for relation between CBF and t in the form of a differential equation:

$$\frac{d(CBF)}{CBF} = \frac{1.97e^{-.707t} - 0.307e^{-0.92t} + 0.421e^{-1.67t}}{2.73 + 2.08e^{-.707t} + 0.398e^{-.092t}} dt \quad (7)$$

Equation 7 was solved numerically to yield the predicted time course of CBF shown in figure 3.