Review Article

Cerebral Blood Flow and Metabolism:
Effects of Anesthetic Drugs and Techniques

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It is our goal to review recent information concerning cerebral circulation and metabolism in man. Results in unanesthetized man are considered first, then the effects of anesthetic drugs, adjuvants, and special procedures. Normal values, units and abbreviations for the measurements discussed are shown in table 1.24, 96, 182

Methodology and Normal Values

The two techniques most commonly used for determination of cerebral blood flow (CBF) in man are Kety-Schmidt inert-gas-uptake method, which required blood sampling, and the tissue-clearance technique, which does not. When the Kety-Schmidt method is employed, the inert tracer gas is usually inhaled. Blood samples are withdrawn from an artery and the superior bulb of one jugular vein (assumed to contain representative cerebral venous blood) at intervals of 0.75–5 minutes and analyzed for the tracer. Curves showing the increases of arterial and cerebral venous blood tracer concentrations toward their eventual equilibrium values are obtained. CBF is then calculated from the area between these curves. When the technique was introduced, 15 percent N₂O was used as the tracer gas, and a normal CBF value of 54 ml/100 g/min was reported. The normal CMRO₂ was 3.3 ml/100 g/min.77 Later, the technique was modified to employ ⁸⁵Kr as the tracer and to include extrapolation of arterial and venous curves to their equilibrium values at infinite time.24 The modifications improved accuracy and resulted in the lower CBF and CMRO₂ values accepted today 62, 96, 97, 182: 44 ml/100 g/min and 3.0 ml/100 g/min, respectively. The Kety-Schmidt technique is well suited to the study of cerebral metabolism, since the sampled blood is available for chemical analysis, and the jugular venous blood is from the areas of brain included in the CBF measurement. Cerebral metabolic rates may be calculated as the product of CBF and the appropriate arteriovenous difference (A-V). The method yields average CBF and metabolic rates (i.e., overall values for the whole brain).

Tissue-clearance techniques for CBF determination employ either inhalation or intracarotid injection of a radioactive substance, typically ¹³³Xe.57 CBF is calculated from the decay of radioactivity in the brain, detected by external solid scintillation counting. Average CBF's determined by this technique and by the modified Kety-Schmidt method are similar.87 The intracarotid-injection technique is not well suited for metabolic studies, since representative blood samples cannot be obtained from the brain area being monitored.

CBF is normally nonuniform, varying both with histologic tissue type (grey vs. white matter) and with anatomic area of the brain. Regional flows from different anatomic areas of the brain (rCBF) can be obtained by using multiple external detectors.58, 62 This technique is useful for detecting areas of abnormal CBF, especially in infarction, tumor, and cerebrovascular disease.

Mathematical analysis of the clearance curves obtained with the intracarotid-injection tech-
CEREBRAL BLOOD FLOW AND METABOLISM

TABLE 1. Normal Values, Units and Abbreviations

<table>
<thead>
<tr>
<th>Full Name</th>
<th>Abbreviation</th>
<th>Normal Values and Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral blood flow</td>
<td>CBF</td>
<td>44 ml/100 g/min</td>
</tr>
<tr>
<td>Regional cerebral blood flow</td>
<td>rCBF</td>
<td>20–80 ml/100 g/min</td>
</tr>
<tr>
<td>Cerebral perfusion pressure*</td>
<td>PP</td>
<td>80 torr</td>
</tr>
<tr>
<td>Cerebrovascular resistance†</td>
<td>CVR</td>
<td>1.8 torr/ml/100 g/min</td>
</tr>
<tr>
<td>Arteriovenous oxygen content difference</td>
<td>(A-V)O₂</td>
<td>6.8 ml/100 ml</td>
</tr>
<tr>
<td>Cerebral metabolic rate for oxygen</td>
<td>CMRO₂</td>
<td>3.0 ml/100 g/min</td>
</tr>
<tr>
<td>Cerebral metabolic rate for glucose</td>
<td>CMRglucose</td>
<td>4.5 mg/100 g/min</td>
</tr>
<tr>
<td>Cerebral metabolic rate for lactate</td>
<td>CMRLactate</td>
<td>2.3 mEq/100 ml/min</td>
</tr>
<tr>
<td>Cerebral venous oxygen tension</td>
<td>PVO₂</td>
<td>35–40 torr</td>
</tr>
<tr>
<td>Oxygen-glucose index</td>
<td>OGI</td>
<td>90–100 per cent</td>
</tr>
<tr>
<td>Lactate-glucose index</td>
<td>LGI</td>
<td>0–10 per cent</td>
</tr>
<tr>
<td>Cerebral blood flow equivalent</td>
<td>CBF/CMRO₂</td>
<td>14–15 ml blood/ml O₂</td>
</tr>
</tbody>
</table>

* Defined as mean arterial minus mean cerebral venous pressure or mean arterial pressure minus intracranial pressure.
† Defined as PP/CBF.

tique permits partition of the tissue into slow- and fast-flow areas. This technique has yielded average flows of 18.7–21.1 ml/100 g/min for white matter and 78.0–80.5 ml/100 g/min for grey matter.52 The brain mass was evenly divided between fast- and slow-flow areas. Comparable figures were obtained from a similar analysis of 85Kr uptake curves with the Kety-Schmidt technique.185

The metabolic pattern of normal brain is described in table 1 by the relative values of the CMR's. Glucose is the usual substrate. Its aerobic utilization or combination with oxygen is represented by the oxygen-glucose index of 90–100 per cent.52–24 That is, nearly all the glucose utilized by brain tissue is combined with oxygen to yield CO₂, water, and energy. The small amount of glucose which is converted anaerobically to lactate is represented by the lactate-glucose index of 0–10 per cent.52–24 This metabolic disposition of glucose yields less energy, but the utilization of this pathway for a small fraction of glucose metabolism is not abnormal.

The adequacy of the cerebral oxygen supply may be estimated from the ratio of flow to a metabolic rate. Typically the ratio CBF/CMRO₂ is chosen, as CMRO₂ can be easily measured and is not seriously affected by any but the most rapid alterations in flow or metabolic rate.52 The ratio CBF/CMRO₂, the cerebral blood flow equivalent (table 1), is equal to 1/(A-V)O₂.27 It can thus be determined from (A-V)O₂ without measurement of either CBF or CMRO₂. In conditions where CMRO₂ is known to be stable, the CBF equivalent has been used to estimate relative changes in CBF.

EFFECTS OF AGE AND ARTERIOSCLEROSIS

The normal CBF and CMRO₂ values given above were obtained in healthy young adults, but these vary considerably with age. Kennedy and Sokoloff, employing the Na-O₂ uptake method, reported a mean CBF of 106.4 ml/100 g/min and a mean CMRO₂ of 5.17 ml/100 g/min for a group of children aged 3 to 10 years.72 Corresponding values for young adults were 60.1 ml/100 g/min and 4.18 ml/100 g/min, respectively. Among the children, there was no correlation of age with CMRO₂. It is likely that the high CBF and CMRO₂ of childhood are not present at birth, since in dogs the neonatal CBF is low and does not reach its puppyhood peak until 2–8 weeks of age.74

Old age per se does not seem to affect CBF. Scheive and Wilson159 and Sokoloff166 found no significant differences in CBF and CMRO₂ among normal adults of any age group, although arteriosclerosis was associated with decreased CBF.166 Lassen et al. reported that normal people of mean age 72.3 years had the same CBF as young adults, but a slightly lower CMRO₂.166 The decrease in CMRO₂ was probably due to the inclusion in the group of pa-
tients with mild organic brain disease, since CBF and CMRO₂ are markedly decreased in persons who have suffered strokes or who have senile dementia,²³,¹⁵⁷,¹⁵⁰,¹⁵⁷ particularly in the frontotemporal areas.²¹,¹⁵⁷

Low CMRO₂ is probably usual in organic brain disease, since it occurs even in children. In this age group, hydrocephalus, mental retardation, and epilepsy are associated with decreased CMRO₂ and there is a direct correlation between CMRO₂ and mental ability.⁴¹

Control of CBF in Unanesthetized Man

Effects of Carbon Dioxide

Paco₂ has the greatest effect on CBF. Within the range of 20 to 60 torr, CBF varies approximately linearly with Paco₂. Each torr increase or decrease in Paco₂ is associated with an increase or decrease in CBF of about 1 ml/100 g/min.⁵²,⁷⁶ Within the same range, PaCO₂ has no measurable effect on CMRO₂.⁷⁸ The effect appears to be general throughout the central nervous system, since PaCO₂ affects spinal cord blood flow in a similar manner.¹⁲

The mechanism for the Paco₂ effect on CBF seems to be control of vascular tone by the pH of extracellular fluid (ECF) near cerebral arterioles.¹₅,¹₅₄,¹₅₈,¹₇₅ An alteration in Paco₂ changes CBF almost immediately, because CO₂ diffuses rapidly from blood vessels to affect the pH of the ECF.¹₄ In the presence of constant PaCO₂, acute changes in arterial [H⁺] or [HCO₃⁻] have little immediate effect on CBF, since these ions enter the ECF slowly.

Extremes of CO₂ Tension

As PaCO₂ is increased to very high values, CBF reaches a plateau. It is not clear at what point this occurs in man, but in the monkey CBF begins to level out at about 2.5 times its normocarbic value, 80–120 torr.¹³⁷ Presumably, maximum vasodilatation (minimal CVR) is reached at this point.

The decrease in CBF with hypocapnia is limited, and minimal CBF in man is reached at a PaCO₂ of about 10–20 torr.¹₅⁶ There is evidence to indicate that cerebral tissue hypoxia occurs at very low PaCO₂ levels and plays a role in limiting the decrease of CBF in hypocapnia.⁹,¹₅⁶ Functional changes, such as alterations in critical flicker fusion frequency⁹ and in reaction time,¹²⁰ have been demonstrated in man following hyperventilation. Metabolic pathways are altered as well. The deficient supply of oxygen is associated with decreased aerobic utilization of glucose and thus, decreased CMRO₂. However, changes in CMRO₂ are more difficult to measure and are usually not observed until hypoxia is severe. As glucose supply is not a limiting factor, even when CBF is low, anaerobic utilization of glucose is increased and CMR lactate rises. The oxygen–glucose index decreases and the lactate–glucose index increases.³

Metabolic abnormalities are mitigated if hyperventilation is carried out during hyperbaric oxygenation,¹²² presumably because even a low CBF then provides a sufficient oxygen supply. Further evidence for the presence of cerebral hypoxia during hyperventilation is given by the ECG changes of hyperventilation, which resemble those of arterial hypoxemia and can be reversed by hyperbaric oxygenation.²³ All the changes associated with hyperventilation seem to be reversible and therefore not dangerous in young, healthy persons.

One might wish to prescribe extreme hypocapnia (Paco₂ levels below 20 torr) in the aged, arteriosclerotic, hypotensive, or febrile patient, and in those with known cerebrovascular disease. However, the peculiar phenomena of regional cerebral circulation require a closer look before the effects of moderate hypocapnia can be fully evaluated in the patient with localized cerebrovascular disease.

Abnormalities of Response to CO₂

Control of CBF in areas around cerebral infarctions or tumors is sometimes lost.³⁶ The blood supply to these surrounding regions may be supranormal relative to CMRO₂, and local Pvo₂ is elevated. This phenomenon has been termed the "luxury perfusion syndrome."²⁸ A local accumulation of metabolic products is assumed to provide a maximum vasodilatory stimulus. The blood vessels in these areas are fully dilated and further local decrease in CVR is not possible. Vasomotor paralysis may also occur within ischemic areas of brain, without a local Pvo₂ increase.

If patients with focal cerebral ischemia are given CO₂ to breathe, the resultant hypercapnia increases rCBF in normal areas of brain,
as normal cerebral arterioles are dilated. But vessels in ischemic areas may be unable to dilate further and thus fail to respond to increased $P_aCO_2$. Since CVR does not decrease in the abnormal areas, but does in the normal ones, blood is shunted away from the abnormal areas and their flow decreases. This phenomenon has been termed the "intracerebral steal syndrome." It has been observed clinically and in animals by several investigators although one laboratory was unable to demonstrate it in animals.

The "inverse steal" or "Robin Hood" syndrome is postulated to occur in response to hypocarbia. Arterioles in diseased areas of brain are under maximal stimulus to remain dilated. They may not constrict in response to low $P_aCO_2$, while CVR is increased in normal areas of brain. Thus, blood would be shunted into ischemic areas. This argument suggests that hypocarbia can be beneficial, but the clinical evidence in its favor is not convincing. It is important to note that "steal" and "inverse steal" do not occur in every patient with regional abnormalities of the cerebral circulation when $P_aCO_2$ is altered. Moreover, it is not yet possible to predict how a particular patient will react. Thus, the benefit of hypocarbia or hypercarbia in patients with regional cerebrovascular disease remains a question. A trial of each in individual patients may be necessary if one wishes to attempt treatment of regional cerebrovascular disease with alteration of $P_aCO_2$.

CO$_2$ AND INTRACRANIAL PRESSURE

Hypocarbia increases intracranial pressure (ICP) and hypocarbia decreases it. Changes in cerebral blood volume may be involved in the mechanism of this phenomenon, since hypercarbia is associated with increased cerebral blood volume and hypocarbia decreases cerebral blood volume. Unfortunately, the phenomenon has not been well quantitated in normal man. In animals the reduction in ICP obtained with hyperventilation to a $P_aCO_2$ of 20 torr is small and transient, partly because the decreased blood volume is offset by an increase in CSF volume. However, in many patients with space-occupying cerebral lesions, hyperventilation has been clinically effective in lowering increased ICP and producing a "relaxed brain" at operation. In one study, the mean CSF pressure in a group of patients with intracranial tumors was halved by hyperventilation to a mean $P_aCO_2$ of 20 torr, using positive-negative ventilation. Alternative techniques for decreasing intracranial pressure during neurosurgery can also be effective and recently have been reviewed elsewhere.

HYPOXIA

If $P_aO_2$ is lowered while $P_aCO_2$ is maintained constant, CBF is unaffected until $P_aO_2$ falls below 50 torr. At this point cerebral vasodilation occurs and CBF increases. At a $P_aO_2$ of 35 torr, mean CBF was increased to 77 ml/100 g/min in a group of healthy men. CMRO$_2$ was unchanged, but increases in $CMR_lactate$ and the glucose-lactate index suggested cellular hypoxia. Jugular bulb $P_aO_2$ was 27 torr, not so low as the value of 17 torr observed during extreme hypocarbia. However, the severity of the metabolic changes in hypoxia and hypocarbia were about the same. Thus, jugular bulb $P_aO_2$ is not always a useful indicator of the severity of cerebral hypoxia. Cerebral capillary or tissue $P_aO_2$, cerebral function, or metabolic pattern is far superior.

Since CO$_2$ has such a pronounced effect on CVR, it is not surprising that $P_aCO_2$ modifies the effects of hypoxia on CBF. If hyperventilation is permitted to occur in response to hypoxia, the resultant hypocarbia counteracts the cerebrovascular dilating effect of hypoxia and CBF may not increase until $P_aO_2$ is below 35 torr. It is not clear how hypoxemia dilates cerebral vessels, but accumulation of acid metabolites in the ECF around cerebral arterioles may be involved.

HYPEROXIA

The increase in $P_aO_2$ induced by breathing 100 per cent oxygen at 1 atmosphere absolute (ATA), causes slight cerebral vasoconstriction. Turner and associates believe that much of this constriction can be accounted for by alterations in $P_aCO_2$. At 2 ATA, the effect is more pronounced, and CBF is decreased 21 per cent from the normoxic state at constant $P_aCO_2$. Experimentally raised ICP is also decreased by oxygen at 2 ATA.
## Table 2. Cerebral Blood Flow and Metabolism in Anesthetized Man during Normocarbia*

<table>
<thead>
<tr>
<th>Anesthetic Agent</th>
<th>Concentration (per cent)</th>
<th>CBF ml/100 g/min</th>
<th>CBF Percentage Change</th>
<th>CMHI02 ml/100 g/min</th>
<th>CVR torr/ml CMHI02</th>
<th>CBF/CMHI02</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>N₂O, thiopental induction</td>
<td>70</td>
<td>40.5 (-9)</td>
<td>2.39 (-23)</td>
<td>2.17</td>
<td>17.0</td>
<td>2, 184</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>43.4 (+1)</td>
<td>3.02 (-2)</td>
<td>1.97</td>
<td>15.0</td>
<td>3, 186</td>
<td></td>
</tr>
<tr>
<td>N₂O, no thiopental</td>
<td>70</td>
<td>45.4 (+2)</td>
<td>2.38 (-23)</td>
<td>2.0</td>
<td>19.0</td>
<td>164</td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>1.2</td>
<td>50.8 (+14)</td>
<td>2.80 (-9)</td>
<td>1.1</td>
<td>18.1</td>
<td>21, 183</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.2†</td>
<td>54.4 (+27)</td>
<td>2.19 (-26)</td>
<td>1.4</td>
<td>24.8</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Cyclopropane</td>
<td>5</td>
<td>26.2 -36</td>
<td>1.68 -40</td>
<td>3.30</td>
<td>15.6</td>
<td>4, 189</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>34.3 -25</td>
<td>2.27 -29</td>
<td>2.39</td>
<td>15.1</td>
<td>4, 189</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>66.0 +11</td>
<td>2.50 -11</td>
<td>1.74</td>
<td>26.4</td>
<td>4, 189</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>67.2 (+31)</td>
<td>2.40 (-23)</td>
<td>1.50</td>
<td>27.9</td>
<td>164</td>
<td></td>
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<tr>
<td></td>
<td>37</td>
<td>75.6 +60</td>
<td>2.24 -30</td>
<td>1.50</td>
<td>33.7</td>
<td>4, 189</td>
<td></td>
</tr>
<tr>
<td>Diethylether</td>
<td>2.4</td>
<td>38.8 -6</td>
<td>1.75 -34</td>
<td>1.91</td>
<td>22.2</td>
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<tr>
<td></td>
<td>4.5</td>
<td>67.5 +56</td>
<td>2.24 -11</td>
<td>0.99</td>
<td>30.1</td>
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<tr>
<td>Éther</td>
<td>0.85</td>
<td>39.0 (-5)</td>
<td>2.28 (-25)</td>
<td>2.92</td>
<td>17.1</td>
<td>‡</td>
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</tr>
<tr>
<td></td>
<td>2.0</td>
<td>40.6 (+2)</td>
<td>2.00 (-33)</td>
<td>1.55</td>
<td>20.2</td>
<td>‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>40.0 -3</td>
<td>1.53 -50</td>
<td>1.34</td>
<td>26.2</td>
<td>188</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.2</td>
<td>40.8 (+2)</td>
<td>1.84 (-40)</td>
<td>0.90</td>
<td>22.2</td>
<td>‡</td>
<td></td>
</tr>
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</table>

*All values were obtained using the inert gas-uptake technique with extrapolation of venous concentration to infinite time. Parentheses refer to changes from assumed awake values. Other per cent changes refer to studies in which each subject acted as his own control.

† Corrected for assumed vaporizer characteristics.
‡ Unpublished data from the author's laboratory.

## Autoregulation

"Autoregulation" refers to the ability to keep blood flow constant in the face of alteration in perfusion pressure. This is accomplished by changes in vascular resistance. The capacity to autoregulate is present to a remarkable extent in the normal cerebral vasculature. Variations of mean perfusion pressure over the range of 60 to more than 150 torr have no significant effect on CBF. At very low arterial blood pressures, autoregulation finally fails as the limits of cerebrovascular dilation are reached. CBF decreases and clinical signs of ischemia (nausea, fainting, dizziness, dimmed vision, etc.) occur when mean arterial blood pressure is 40-55 torr.

Increased intracranial pressure decreases cerebral perfusion pressure, but because of autoregulation CBF does not decrease until CSF pressures of 380-450 mm H₂O are reached. At a CSF pressure of 920 mm H₂O, mean CBF is decreased by about 25 per cent.

Autoregulation is disturbed in certain disease states. Following a grand mal seizure, CBF is elevated and increases passively if blood pressure increases. Loss of autoregulation in tissue in and around areas of cerebral infarction has been alluded to in the discussion of vasomotor paralysis. Conditions which cause cerebral vasodilation, such as hypercarbia and hypoxia, also disrupt autoregulation. In chronic hypertensive, autoregulation of CBF is present, but the range over which CBF is maintained constant may be smaller. Thus, the CBF's in some hypertensive patients may be very sensitive to small decreases in perfusion pressure.
AUTONOMIC INFLUENCES

It has long been known that cerebral vessels are supplied with autonomic nerves, but the significance of these nerves in control of the cerebral circulation remains questionable. Some authors believe that autonomic influences exert important modifying effects on the other factors controlling cerebral circulation, while others find no physiologic effect of the autonomic nervous system on CBF control. The occasionally-suggested therapeutic procedure of bilateral stellate-ganglion block did not appear to affect CBF or CMRO\textsubscript{2} in either normal subjects or stroke patients. The effects of this block on the CO\textsubscript{2} response of CBF and on autoregulation were not determined.

NORMAL SLEEP

A group of healthy volunteers was studied while awake but tired, and later when sleep spindles appeared in the electroencephalogram. Mean CBF was about 10 per cent higher during sleep, while CMRO\textsubscript{2} and Pa\textsubscript{tr} were unchanged. Increased CBF has also been observed in animals during both rapid-eye-movement and slow-wave sleep.

Inhalation Anesthetics

EFFECTS ON CBF

The effects of the common inhalational anesthetics on human CBF are shown in table 2. The effects of the anesthetics on CBF are graphed in figure 1 as a function of minimum alveolar concentration (MAC).

Seventy per cent nitrous oxide caused a slight, questionably significant fall in CBF in one study and no change from normal in two others. The mild cerebrovascular effects of this agent make it useful as the background anesthetic for investigations involving the cerebral circulation.

Halothane produces different results. Increases in human CBF to 50.8 and 54.4 ml/100 g/min have been reported with 1.2 per cent of this anesthetic. Although studies of other concentrations have not been reported for man, CVR in the dog was found to decrease progressively at increasing halothane levels from 0.5 to 4.0 per cent. Thus, halothane appears to be a cerebral vasodilator at most clinically useful concentrations. In contrast, the effects of cyclopropane on CBF are biphasic. Five per cent cyclopropane, a subanesthetic concentration, caused CBF to fall 36 per cent in a group of normal men. During light (13 per cent) cyclopropane anesthesia, CBF was depressed 25 per cent below its awake value. However, deep cyclopropane anesthesia was a potent cerebral vasodilator; CBF was increased 61 per cent and 65 per cent, respectively, by 20 per cent and 37 per cent of this drug.

Diethyl ether seems to behave like cyclopropane with respect to the cerebral circulation, over the range for which data are available. There was a small decrease in CBF to a mean of 38.8 ml/100 g/min during 2.4 per cent ether and an increase to 67.5 ml/100 g/min with 4.5 per cent ether.

The new anesthetic Ethane (Ohio 347; 2-chloro-1,1,2 trifluoroethyl difluoromethyl ether) is interesting in that concentrations of 0.55 to 3.2 per cent (0.59 to 2.2 MAC) have no effect on CBF despite the EEG abnormalities that occur. The authors are aware of no CBF determination in man during anesthesia with trichloroethylene, fluroxene, chloroform, or methoxyflurane. However, trichloroethylene had no effect on canine cortical flow. Chloroform (0.5–1.0 per cent) was found to increase the cortical flow of dogs by 19 per cent, and methoxyflurane (0.5 per cent) given to dogs for 30 minutes produced a 19 per cent decrease in flow. The effects of inhalation anesthetics on the distribution of regional flows have not been determined.

EFFECTS ON CMRO\textsubscript{2}

CMRO\textsubscript{2} values for the agents discussed above appear in table 2 and are shown in figure 2 as a function of MAC. Seventy per cent nitrous oxide decreased CMRO\textsubscript{2} by 2 per cent in one study and by 23 per cent in two others. Halothane, 1.2 per cent, was found to decrease CMRO\textsubscript{2} by 9 per cent in one study and 26 per cent in another. The differences between studies must be accounted for by differences in awake values (which were not measured), slight decreases in body

\footnote{Also, unpublished data from the authors' laboratory.}
temperature during anesthesia, and variability in responses to anesthesia. In any case, it seems reasonable to conclude that 70 per cent nitrous oxide and 1.2 per cent halothane are both mild depressants of CMRO₂.

Larger changes in CMRO₂ were observed during cyclopropane anesthesia in a study in which each subject acted as his own awake control. Concentrations of 5 to 36 per cent of this agent depressed CMRO₂ from 11.3 to 40.4 per cent, but the amount of depression was not related to anesthetic depth in a simple manner, as figure 2 shows. In fact, the lowest CMRO₂ was obtained during anesthesia with the lowest cyclopropane concentration studied. It also seems odd that there was so little decrease in CMRO₂ with 20 per cent cyclopropane. Another study reported a somewhat greater depression of CMRO₂ (23 per cent) with 20 per cent cyclopropane, but is less reliable for comparison, since it did not awake controls.¹⁶⁴

The depression of CMRO₂ with diethyl ether also is greater during light anesthesia. A 34 per cent decrease in CMRO₂ was found during anesthesia with 2.4 per cent ether and an 11 per cent decrease in CMRO₂ found with 3 per cent of men with 4.5 per cent ether.¹⁶⁷

Although it has little effect on CBF, Êthran (Ohio 347) depresses CMRO₂; the depression increases with depth of anesthesia. The 50 per cent decrease in CMRO₂ found with 3 per cent Êthran makes this agent the most potent depressor of cerebral metabolism among the inhalation agents.¹⁶⁸
Fig. 2. Cerebral metabolic rate for oxygen as a function of MAC.

There are no data from studies of humans for methoxyflurane, chloroform, and trichloroethylene, but these agents depress canine CMRO₂ 10 to 20 per cent.¹⁰⁵

Effects on CBF/CMRO₂

It may not be proper to treat figures 1 and 2 as dose–response curves,¹⁷⁷ and perhaps this is why there is a rather dissatisfying lack of uniformity in the manner in which the inhalation anesthetics affect CBF and CMRO₂. Consistency improves, however, with consideration of the effect of deepening anesthesia on the ratio of CBF to CMRO₂, i.e., the CBF equivalent (fig. 3). There is a clear trend for CBF/CMRO₂ to increase as anesthetic depth is increased, thus providing higher tissue and venous Pₐ values. Data for all agents lie close together, so that CBF/CMRO₂ seems to depend more on MAC than on the agent used. This correlation raises a number of questions. Does increased CBF/CMRO₂ with deep anesthesia indicate an improved safety margin? Or is the higher tissue Pₐ somehow necessitated by a block in oxygen utilization or uptake? Is the mechanism of this phenomenon similar to the luxury perfusion syndrome? These questions remain unanswered.

Metabolic Pathways during Anesthesia

With a single exception, no changes from the normal patterns of cerebral carbohydrate metabolism have been observed with normoxic, normocarbic general anesthesia. The exception is 5 per cent cyclopropane, which was associated with increased cerebral lactate
production. The question whether 5 per cent cyclopropane causes cerebral hypoxia is interesting, since low cyclopropane concentrations must be present in the brain at least transiently during induction and emergence.

The effects of anesthetics on the response of CBF to arterial hypoxemia have not been determined in man. However, pentobarbital anesthesia has been found not to alter this response in the monkey.

**Anesthesia and the CBF–CO₂ Response**

The responsiveness of CBF to changes of \( P_{\text{aCO}_2} \) in the awake state and during anesthesia is shown in figure 4. During anesthesia with 70 per cent nitrous oxide, the response of CBF to hypercarbia is almost identical to that in the awake state. Halothane, 1.2 per cent, seems to increase the sensitivity of CBF to \( P_{\text{aCO}_2} \). Christensen et al., using another technique, also found that hypercarbia potentiated the cerebral vasodilatory effect of halothane. The \( P_{\text{aCO}_2} \) sensitivity of CBF is clearly greater during anesthesia with 20 per cent cyclopropane than in the awake state. However, hyperventilation will produce a low CBF even with cyclopropane anesthesia. At low \( P_{\text{aCO}_2} \) and the CBF values with all agents approach each other (fig. 4); at a \( P_{\text{aCO}_2} \) of 20 torr, the CBF's with all anesthetics shown span a range of only 8 ml/100 g/min.

**Intracranial Pressure**

Halothane, trichloroethylene, and methoxyflurane all increase intracranial pressure when

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\( \text{\S} \) Unpublished data from the authors' laboratory.
suddenly added to an established nitrous oxide anesthetic. The magnitude of the increase seems related to the concentration of the agent administered. The changes are seen in people with normal CSF dynamics, but are greater in the presence of intracranial space-occupying lesions. In groups of normal persons, the administration for 10 minutes of 0.5 per cent halothane, 1.5 per cent methoxyflurane, and 0.9 per cent trichloroethylene raised mean CSF pressure 68, 57, and 105 mm H₂O, respectively. In patients with intracranial tumors, mean CSF pressure was increased 179 and 279 mm H₂O, respectively, after 10 minutes of administration of 0.5 per cent halothane and 0.9 per cent trichloroethylene. The administration of 1.5 per cent methoxyflurane for only 10 minutes to five patients with intracranial space-occupying lesions markedly increased mean CSF pressure from 171 to 561 mm H₂O. Since halothane and methoxyflurane also decrease arterial pressure, these agents can cause greater decreases in cerebral perfusion pressure (measured as mean arterial less intracranial pressure) in tumor patients than in normal individuals. The intracranial pressures observed in patients under nitrous oxide-oxygen-relaxant anesthesia were only slightly elevated.

The mechanism of ICP changes with the volatile agents is probably as follows: these drugs produce cerebral vasodilatation and thus increase cerebrovascular volume. In the normal person, compensation for the increased cerebrovascular volume occurs by displacement of intracranial CSF to the spinal subarachnoid space. The compensatory mechanism is already at least partly exhausted in the tumor patient, so that with the closed skull, small increases in blood volume may induce large increases in ICP. If this explanation is correct, then when anesthesia is very light and CBF is normal or decreased there might be little or no effect on ICP. The studies of volatile anesthetics and CSF pressure quoted above were done with nitrous oxide as the background anesthetic. Since nitrous oxide itself causes a slight increase in ICP, the effects observed may have resulted from summation of nitrous oxide and volatile anesthetic actions. It is possible that 0.7 MAC halothane, for example, has an effect little different from that of 0.7 MAC nitrous oxide.

Langfit and associates have studied the relation between a space-occupying lesion and CBF in an animal model. They found that rapid inflation of an intracranially-placed balloon decreased CBF. They also reported that in chronic intracranial hypertension CBF was maintained by vasodilation. However, any additional vasodilation could cause a further rise in ICP and thereby impede flow. The volatile anesthetic agents may produce such undesirable vasodilation, particularly when anesthesia is deep. It is very likely, therefore, that the acute increase in ICP with administration of vasodilating anesthetics in patients with space-occupying lesions quickly results in decreased CBF. The increased ICP and decreased CBF probably cause cerebral hypoxia in man, since in animals this situation is associated with increased cerebral venous blood lactate and CSF lactate concentrations and elevated lactate/pyruvate ratios. In addition, cortical ATP and phosphocreatine concentrations are decreased in intracranial hypertension.

At present, it would seem wise to avoid anything but the lowest concentrations of volatile anesthetics in patients with intracranial space-occupying lesions. Although hyperventilation may mitigate the effects of the volatile agents on ICP, this maneuver should not be relied upon to prevent them. Hyperventilation may not counteract anesthetic-induced cerebral vasodilation in the patient with an intracranial space-occupying lesion, as it does in normal individuals. Last, we must stress the importance of smooth anesthesia in patients with increased ICP. Struggling and irregular respiration during induction and a long gaugne period associated with endotracheal intubation are associated with further increases in CSF pressure.

Intravenous Anesthetics and Adjuvant Drugs

BARBITURATES

Sedation with the barbiturates thiopental, phenobarbital, and amytal in doses which do not cause loss of consciousness is not associated with alterations in CBF or CMRO₂.
In contrast, anesthesia with thiopental has marked effects on cerebral hemodynamics. A dose of thiopental which still permitted some muscular response to pain reduced CMRo2 by 36 per cent. The same metabolic depression resulted from a 0.5–1.6 g dose of this drug. In neither of these two studies was respiration controlled, so that the CBF values reported are difficult to evaluate. Pierce et al. gave a larger dose of thiopental (mean 35 mg/kg), controlled respiration, and used the Kety-Schmidt N2O-uptake technique to study cerebral hemodynamics. During normocarbia, mean CBF was decreased to 27.6 ml/100 g/min and mean CMRo2 was decreased to 1.5 ml/100 g/min. When PaCO2 was 17.5 torr, mean CBF was only 16.4 ml/100 g/min and CMRo2 was similar to that during normocarbia. Thus, although CBF was decreased, sensitivity to alterations in PaCO2 remained intact during thiopental anesthesia.

It is well known that acute tolerance to the anesthetic effects of thiopental occurs. In addition, acute tolerance to the cerebral hemodynamic effects of the drug has been demonstrated in animals. Altenberg et al. studied dogs with halothane as the background anesthetic. The depression of CBF and CMRo2 caused by thiopental infusion was mitigated when the animals were given a bolus of thiopental two hours before the infusion. Barbiturate anesthesia has also been shown, in animals, to reduce the regional differences in CBF which are normally present in the awake state.

Thiopental and pentobarbital administration are associated with unchanged or decreased CSF pressure if CO2 retention is prevented. The magnitude of the effect has not been well defined.

**Narcotics and Neuroleptics**

Small doses of narcotics, such as might be used for premedication, have no significant effect on the cerebral circulation. Even morphine, 20–30 mg, given subcutaneously, has a negligible effect. The slight increase in CBF found after morphine, 60 mg, was given intravenously to normal men was probably the result of an increase in PaCO2. However, the decrease in mean CMRo2 from 3.2 to 1.9 ml/100 g/min was significant; furthermore, the subjects who became most somnolent had the greatest declines in CMRo2. The metabolic depression found in this study could be partially reversed by 25 mg of n-allylnormorphine (Nalline). The effects of anesthetic doses of narcotics on the cerebral circulation have not yet been investigated. The increase in intracranial pressure that occurs after morphine administration is due to respiratory depression and can be prevented if PaCO2 is maintained constant.

Small doses of neuroleptanesthetic agents, such as 5 mg droperidol with 1.5 mg pheno- peridine, do not affect CBF, and this combination has been used for sedation in clinical CBF studies. Anesthetic doses of neuroleptics have not been investigated in man, but in a group of dogs droperidol, 0.3 mg/kg, decreased CBF 40 per cent without affecting CMRo2. Fentanyl, 0.006 mg/kg, decreased CBF and CMRo2 by 47 and 18 per cent, respectively, 15 minutes after administration. The combination drug, Innovar, decreased canine CBF 50 per cent and CMRo2 23 per cent. The data suggest that Innovar decreases cerebral venous oxygen content, and this has been confirmed by others. Innovar has also been found to decrease the response of CBF to alterations in PaCO2.

The effects of the neuroleptic agents on CSF pressure contrast with those of the volatile agents. Droperidol, 5 mg, plus phenergan, 1.5 mg, produced variable small changes in CSF pressure of normal patients. However, droperidol, 5 mg, plus fentanyl, 0.1 mg, decreased intracranial pressures in all patients with normal CSF pathways and in all but one of a group of patients with intracranial space-occupying lesions. Since mean arterial blood pressure fell in the latter group, cerebral perfusion pressure was essentially unchanged. Decreased CSF pressure along with reduction in CBF suggests that cerebrovascular volume is decreased by these agents. Thus, the fentanyl-droperidol combination, or perhaps thiopental, would seem superior to the volatile agents as a supplement to nitrous oxide anesthesia in patients with head injuries or tumors.

**Ketamine**

The cerebral hemodynamic effects of ketamine have been investigated in the dog with
Fig. 4. The sensitivity of CBF to \( P_{\text{CO}_2} \) "awake" and anesthetized. The "awake" line was adapted from the data of Kety et al.\textsuperscript{25,74} Modification was necessary because those workers reported higher noncarboxric CBF's and \( \text{CMR}_{\text{O}_2} \)'s with the older form of the nitrous oxide-uptake technique for CBF determination than those presently obtained using \( ^{3} \text{Kr} \) and venous extrapolation. Their CBF values, therefore, were multiplied by the factor: \( \text{CMR}_{\text{O}_2} \) with extrapolation technique/ \( \text{CMR}_{\text{O}_2} \) with original technique = 0.659, so that comparison on the same basis would be possible. "Awake" data obtained with the modified technique are not available.

Basal nitrous oxide anesthesia. Immediately following the injection of 2 mg/kg, CBF increased 80 per cent and \( \text{CMR}_{\text{O}_2} \) increased 16 per cent.\textsuperscript{29} These values returned to control levels during the subsequent 20-30 minutes. The increase in \( \text{CMR}_{\text{O}_2} \) suggests that ketamine should be used cautiously in patients with cerebrovascular disease, since these individuals may not be able to compensate for the increased \( \text{CMR}_{\text{O}_2} \) by increasing CBF.

Ketamine increased lumbar CSF pressure an average of 253 mm H\(_2\)O in a group of patients without neurologic disease.\textsuperscript{43} It is likely that even greater increases in ICP would be produced by this drug in patients with intracranial space-occupying lesions.

Vasoactive Drugs

A single intracarotid injection of epinephrine does not affect CBF.\textsuperscript{19,129} An intramuscular dose without pressor effect does not alter CBF or \( \text{CMR}_{\text{O}_2} \).\textsuperscript{122} A continuous intravenous infusion of epinephrine, at a mean rate of 28.9 \( \mu \text{g} / \text{min} \), increased blood pressure and did not measurably affect CBF or \( \text{CMR}_{\text{O}_2} \).\textsuperscript{25} With a larger intravenous dose of epinephrine, 36.9 \( \mu \text{g} / \text{min} \), CBF and \( \text{CMR}_{\text{O}_2} \) were augmented by 22 and 23 per cent, respectively.\textsuperscript{50} Evidently, the effect of this drug on cerebral vessels is
dose-related. Moderate amounts of epinephrine have no measurable effect. Large doses increase CBF and CMRO₂ via unknown mechanisms.

Mephenetermine, in a dose which raises mean arterial blood pressure only 10 torr, increased CMRO₂ in normal subjects by 24 per cent; a compensatory increase in CBF did not occur. This suggests that care should be exercised when using the drug in patients with cerebral circulatory disease.

Although intracarotid norepinephrine is without effect on CBF, both norepinephrine and metaraminol appear to be mild cerebral vasconstrictors when administered systemically to normotensive persons. In contrast to epinephrine and mephenetermine, these drugs do not alter CMRO₂. Norepinephrine and metaraminol have been utilized to treat the low CBF associated with hypertension. However, because of their cerebral vasconstricting effect, blood pressure must be elevated to slightly supranormal levels in order to obtain a near-normal CBF.

Neither angiotensin nor phenylephrine affects CBF or CMRO₂ in normal man. These drugs might be superior to other pressors for the treatment of decreased CBF due to hypotension.

OTHER DRUGS

Neither promazine, 50–200 mg iv, nor chlorpromazine, 50 mg im or iv, has any effect on CBF or CMRO₂ so long as blood pressure remains normal. A small dose of ethyl alcohol (22 ml) has no effect on CBF or CMRO₂. However, stupor or coma due to acute ethyl alcohol intoxication (mean blood level 320 mg/100 ml) was found to decrease CMRO₂ by 31 per cent. This degree of inebriation was also associated with a 21 per cent increase in CBF, which could be partially accounted for by a slight increase in PaCO₂.

d-Tubocurarine in modest doses, 40–75 mg, has no effect on CBF or CMRO₂. The cerebral metabolic effects of succinylcholine have not been reported.

Neither ACTH nor cortisone, 100–200 mg, nor desoxycorticosterone glucoside, 50 mg, alters CBF or CMRO₂. However, general anesthesia produced by intravenous administration of the steroid 21-hydroxyprogrenedione 3,20 caused a 19 per cent decrease in mean CMRO₂ and a 31 per cent decrease in mean CBF.

No cerebral hemodynamic or metabolic changes were found after intravenous infusion of 750 mg procaine over a 20-minute period.

In normal dogs, 1.5 g/kg of urea, given intravenously, did not affect CBF or CMRO₂, although the brain was observed to shrink markedly. A decrease in CSF pressure would not be expected to affect CBF in normal brain, because of autoregulation. However, only 0.63 g/kg urea increased CBF in three of four patients with brain tumors; CMRO₂ was unchanged.

Mannitol, 0.7 g/kg, caused mean CBF to increase from 36 to 53 ml/100 g/min and augmented mean CMRO₂ from 2.0 to 2.5 ml/100 g/min in six brain-tumor patients.

The patients probably had low CBF because perfusion pressure, at least in some regions, had been reduced below autoregulatory limits by increased ICP. When the osmotic agents decreased CSF pressure, cerebral perfusion pressure increased and blood flow and metabolism returned towards normal.

A number of unrelated drugs, including the nitrates, histamine, papaverine, and nylidrin have cerebral vasodilating properties. Some of these have been tested for treatment of cerebrovascular disorders, but the results have been mixed. Often extracerebral vascular dilation decreases cerebral perfusion pressure, and sclerotic vessels which cannot autoregulate may suffer a decrease in flow. One would suspect that the success of these drugs might be further limited by intracerebral steals.

Special Techniques and Procedures

HYPOTHERMIA

Hypothermia decreases CBF and CMRO₂ in man, but quantitative data with controlled PaCO₂ are scanty. Cohen et al. correlated CMRO₂ with body temperature over the small range 34–38 °C during halothane anesthesia and reported log CMRO₂ = 0.073 T − 2.23. Extrapolation of these data would yield the rather high Q₁₀ of 5.5.

Q₁₀ is the factor by which a metabolic rate is altered when temperature changes 10 °C.
Rosomoff and Holaday reported that in dogs CBF fell linearly with temperature to 25 C at the rate of 6.7 per cent per degree C. CMRO_2 fell with hypothermia, with a Q_10 of about 3_111. Michenfelder and Theye reported a Q_10 of 2.23 in dogs. In monkeys, Bering found that CMRO_2 decreased with hypothermia (Q_10 3.5). Hornbein et al. observed a mean Q_10 of only 2.07 in this species and a decrease in CBF of 55 per cent over the range 37–27 C. From these data it may be conjectured that Q_10 for the human brain is in the range of 2–3. In neither the dog nor the monkey was evidence of anaerobic metabolism seen during hypothermia_114.

Two reports have noted that (A-V)O_2 was unaltered by hypothermia_90, 111. A third reported a decrease in (A-V)O_2 with hypothermia, but this may have been due to alterations in PaCO_2. Thus, it appears that during hypothermia per cent decreases in CBF and CMRO_2 are similar and arteriovenous oxygen difference remains unchanged. However, PvO_2 decreases, because the solubility of oxygen in blood increases at lower temperatures.

Additional metabolic effects which serve to protect the brain against anoxia have been observed during hypothermia. Processes which occur during cerebral anoxia, including ATP depletion, decrease in the ATP/ADP ratio, increase in inorganic phosphate, and accumulation of lactate, are all slowed in the presence of hypothermia_62, 86, 111, 172. Furthermore, hypothermia may reduce the quantity of oxygen necessary to maintain cerebral cellular integrity, as well as that necessary to maintain function_117.

**Deliberate Alterations of Blood Pressure**

Autoregulation of CBF is intact during general anesthesia, so that the normal brain can compensate for either hypertension or hypotension_114. Since the drugs commonly used to induce hypotension during anesthesia have no important direct effects on CBF or CMRO_2_115, the cerebral vasculature autoregulates and maintains CBF constant over a wide range of pressures when deliberate hypotension is induced. Although in normal awake man signs of cerebral ischemia occur at mean arterial blood pressures in the range of 45–55 torr_27, 123, healthy anesthetized patients seem to tolerate even lower pressures. Eckenhoff et al. studied 42 patients made hypotensive for surgical operations_26. The mean arterial pressure at heart level was as low as 40 torr (systolic pressure about 50 torr), but since head-up tilts averaging 24 degrees were used, pressures at the base of the skull must have been even less. The lowest PvO_2 observed was 27 torr in one patient; in all of the others, PvO_2’s were greater than 30 torr. In another study of hypotensive anesthesia, Schettini and associates reported a PvO_2 range of 29–46 torr with head-up tilt and a mean arterial blood pressure of 49 torr_145. No patient in either group suffered permanent neurologic or psychologic deficits. Perhaps the decreased CMRO_2 occurring during general anesthesia was responsible in part for the apparent protection. Perhaps a small temperature decrease resulting from heat loss due to peripheral vasodilation was protective. It should be emphasized that the above results pertain to normal, nonarteriosclerotic man. The situation may be very different when there are mechanical limitations to flow, cerebrovascular disease, or a hypermetabolic state (e.g., fever). In such cases deliberate hypotension of any degree may be extremely hazardous.

**Anesthesia for Carotid-artery Surgery**

Patients about to undergo carotid endarterectomy are frequently elderly and hypertensive, and may have generalized arterial disease. If a temporary shunt is not utilized and arterial occlusion is necessary, the remaining cerebral arteries, which often are diseased themselves, must then supply the tissue previously nourished by the occluded vessel. The exquisite sensitivity of brain tissue to hypoxia is well known. Can the anesthesiologist do anything to reduce the chance of permanent neurologic damage secondary to cerebral ischemia? The answer is probably yes, through control of the factors that affect CBF and CMRO_2, including PaCO_2, arterial blood pressure, body temperature, and type and depth of anesthesia.

That there is no general agreement about the best combination of these variables is illustrated in table 3, which lists the techniques used by a representative sample of workers in carotid-artery surgery.
### Table 3. Techniques for Management of Carotid Artery Surgery

<table>
<thead>
<tr>
<th>Author</th>
<th>Paco₂</th>
<th>Anesthetic Drug</th>
<th>Blood Pressure Support*</th>
<th>Awake Test Clamping</th>
<th>Shunt</th>
<th>Hyperbaric Oxigenation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloodwell</td>
<td>Induced hypercarbia</td>
<td>C₂H₄, 20 per cent</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Coleman</td>
<td>Spontaneous respiration</td>
<td>Methohexiteone drip</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Connolly</td>
<td>Induced hypercarbia</td>
<td>Methoxyflurane</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ehrenfeld</td>
<td>Induced hypercarbia</td>
<td>Halothane, 0.58–0.85 per cent</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Homi</td>
<td>Induced hypercarbia</td>
<td>C₂H₄, 20–30 per cent</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Jacobson</td>
<td>Normocarbia</td>
<td>Halothane, 1 per cent</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Jenkins</td>
<td>Induced hypercarbia</td>
<td>Halothane ± N₂O</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Jennett</td>
<td>Normocarbia</td>
<td>Trichloroethylene</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ranier</td>
<td>Spontaneous respiration</td>
<td>Local</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Thompson</td>
<td>Induced hypercarbia</td>
<td>Halothane, 0.4–1.5 per cent in N₂O</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>White</td>
<td>Induced hypercarbia</td>
<td>Halothane, 0.4–1.5 per cent in N₂O</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* Raising arterial pressure with drugs to above the resting level or above 140 torr systolic.
† Not reported.

The evidence favoring hypercarbia is straightforward—it increases CBF and the ratio CBF/CMRO₂. Against hypercarbia is the fact that it sometimes causes an intracerebral steal, worsening ischemia. In animals subjected to ligation of the middle cerebral artery, higher PaCO₂'s were associated with larger infarctions. Additional evidence for the deleterious effects of hypercarbia has been obtained in similar middle cerebral artery-ligation preparations. Symon found that arteriolar pressure distal to the occlusion was decreased by carbon dioxide administration. Brawley and associates also observed this phenomenon and found, in addition, that in five of seven cases rCBF in the ischemic area decreased as PaCO₂ increased. A decrease in the availability of oxygen in ischemic areas (measured polarographically) when carbon dioxide was administered has also been reported. A fourth laboratory, again using a middle cerebral artery-ligation preparation, obtained the opposite result, and reported increases in flow to ischemic areas with carbon dioxide administration. Boysen et al. studied patients during carotid endarterectomy at various levels of PaCO₂. They measured rCBF in 14 areas of the operated side, as well as carotid arterial blood pressure distal to the surgical clamp (stump pressure). Hypercarbia, in contrast to normocapnia and hypocapnia, was associated with decreases in both stump pressure and efficiency of autoregulation. Although hypercarbia increased overall CBF, it reduced rCBF to ischemic areas in five of 21 patients studied. Pistolese et al. found that increased PaCO₂ augmented CBF in endarterectomy patients before carotid-artery clamping, but after clamping hypercarbia caused either no change in CBF or a steal from the ischemic areas. Fourcade et al. have also reported studies of stump pressure during surgery. They observed the effects of alterations in PaCO₂ and systemic arterial pressure. In most patients, the highest stump pressures were associated with the lowest PaCO₂'s. Unfortunately, the situation is far from clear-cut. One of Fourcade's patients had the greatest stump pressure during hypercarbia. Another exception is a case of acute middle cerebral artery occlusion in a 9-year-old girl. Thirty-six hours after the occlusion, hyperventilation decreased flow in the ischemic area, while four days later hyperventilation improved CBF in the ischemic area.

** Stump pressure is a measure of cerebral perfusion pressure on the operated side. It is not a direct measure of CBF, since its value depends on patency of collateral arterial channels proximal to the occlusion, CVR of vessels distal to it, and cerebral venous pressure.
Although a decreased $P_a CO_2$ is often beneficial, the problem is that we cannot predict in advance what will happen in a given patient. It would seem most prudent, then, to avoid extreme $P_a CO_2$ levels in carotid surgery and to maintain either normocarbia or mild hyperventilation ($P_a CO_2 = 30$ torr), perhaps with the aid of end-tidal $PCO_2$ monitoring. In this $P_a CO_2$ range, the theoretical problems that hyperventilation causes hypoxia and that hyperventilation causes increased intracranial pressure are not considerations. This procedure should benefit some patients and harm few or none. It seems to be a logical middle ground to tread until we understand more about how to predict the effect of $CO_2$ in the presence of diseased cerebral vessels, or until we are prepared to make rapid measurements of regional CBF in the operating room as $P_a CO_2$ is altered.

The question of arterial blood pressure support is more easily resolved. In animals subjected to ligation of the middle cerebral artery, hypertension drastically reduced the area of ischemia.\textsuperscript{12} Hypertension was also observed to reverse neurologic symptoms in four patients with cerebrovascular insufficiency, while $CO_2$ inhalation and papaverine failed.\textsuperscript{24} In a group of patients prior to carotid clamping, hypertension did not affect CBF on the operated side; this indicated the presence of normal autoregulation. After clamping, hypertension augmented CBF, demonstrating loss of autoregulation on the clamped side; this vasomotor paralysis was probably due to ischemia.\textsuperscript{21} In two studies there were consistent increases in pressure distal to the arterial occlusion when systemic hypertension was induced.\textsuperscript{15, 40} Waltz cast a dissenting opinion. He observed that hypertension did not increase CBF in the ischemic region around the ligated middle cerebral artery in the cat.\textsuperscript{176} Although agreement on the use of hypertension is not complete, certainly no one advocates hypotension. Some who recommend hypercarbia are probably achieving concomitant hypertension.

The choice of anesthetic technique for carotid surgery first revolves about local or general anesthesia. Some prefer local anesthesia because if neurologic symptoms develop with carotid clamping they are immediately obvious. Others argue that general anesthesia seems to improve tolerance to cerebral ischemia in animals.\textsuperscript{29, 42, 121, 122} Possibly increased tolerance has been demonstrated in man,\textsuperscript{180} and we have noted the tolerance of the anesthetized brain to hypotension.

If general anesthesia is elected, the choice of agent and depth is a difficult one. There are no clinical studies comparing different agents, so we must proceed on theoretical grounds. The choice of anesthesia that markedly increases CBF, such as deep ether or cyclopropane anesthesia, is open to criticism. The agent may elevate ICP or may produce an intracerebral steal similar to that seen with hypercarbia. Although the steal phenomenon has not been investigated with anesthetics, other cerebral vasodilators like papaverine have been associated with worsening,\textsuperscript{191} no change,\textsuperscript{166} and improvement\textsuperscript{103} of flow to ischemic areas. Furthermore, aminophylline, a constrictor of normal cerebral vessels, increases rCBF in focally diseased areas in some patients.\textsuperscript{161} As in the case of $CO_2$, patient responses may differ, and it may be wise to employ agents such as nitrous oxide, which are not strong cerebral vasodilators. Furthermore, the use of explosive agents interferes with the cautery desired by many surgeons.

Is it worthwhile to choose the anesthetic which depresses CMRO$_2$ the most? Figure 2 shows that the differences among available anesthetics in quantity of CMRO$_2$ reduction are small. Furthermore, we do not know whether a decreased CMRO$_2$ is beneficial. It has been suggested that the decrease in CMRO$_2$ during anesthesia is secondary to a reduced level of brain function and does not indicate a change in the quantity of oxygen needed to maintain cellular integrity.\textsuperscript{217} Evidence for this statement was obtained in a study of anoxia and cerebral tissue ATP levels.\textsuperscript{116, 117} Tissue ATP concentration may be regarded as a measure of energy reserves. Groups of animals were anesthetized with different agents and various degrees of metabolic depression resulted. The cerebral ATP level before anoxia was produced and the rate of decrease of cerebral ATP during anoxia were unrelated to the amount of anesthetic-induced CMRO$_2$ depression. This implies that the protective action of anesthetics against anoxia is not correlated with CMRO$_2$. If it is desired to produce
the fewest physiologic changes and only mild effects on cerebral hemodynamics, then nitrous oxide anesthesia supplemented by small amounts of Innovar, narcotic, or muscle relaxant might be selected.

Deep anesthesia increases CBF/CMRO$_2$ and cerebral venous oxygen saturation more than light anesthesia (fig. 3). However, jugular venous oxygen saturation is an average over the whole brain, and it has not proven useful in predicting the occurrence of focal neurologic deficits. There is no way of determining whether potentially ischemic areas will be or can be luxury-perfused. In spite of this, several groups have recommended using jugular venous oxygen tension or saturation as a measure of CBF. Perhaps the electroencephalogram or even rCBF monitoring will prove more useful as a predictor of incipient neurologic damage during carotid clamping.

Hyperbaric oxygenation has been considered as an adjunct to management of carotid endarterectomy because of its potential to improve oxygen delivery during the period of decreased CBF. However, the safe period of cerebral circulatory arrest in animals is only slightly prolonged by 100 per cent oxygen at 3 ATA. At a PaO$_2$ of about 1,000 torr, mean cerebral venous PaO$_2$ in a group of patients was increased more than 30 torr; nevertheless, hyperbaric oxygenation should not be expected to be of benefit in regions of total ischemia.

Hypothermia is another technique that may be useful for carotid surgery, because of its metabolic effects. In dogs subjected to middle cerebral artery ligation, hypothermia decreased the sizes of the infarcts, compared with the normothermic state. The duration of circulatory arrest which produces permanent neurologic deficits in dogs is increased from 4–6 minutes during normothermia to 20–29 minutes at 28–29 C. Polarographic measurements in the human cortex during carotid clamping have indicated augmented O$_2$ availability at 29 C. Wylie discussed a series of 24 patients, most of whom showed intolerance to carotid clamping while normothermic. All but one underwent carotid operations without shunts at 30–31 C and suffered no neurologic complications. Additional salutary effects of hypothermia include reduction in brain volume and cerebrospinal fluid pressure.

The disadvantages of hypothermia are that it may considerably prolong anesthesia time and that it has its own morbidity. Complications of hypothermia include cardiac arrhythmias, heat or cold damage to skin and subcutaneous tissues, and impaired blood coagulation. Its place in anesthesia for carotid surgery is still being argued. Not many use or recommend it presently. Perhaps it should be reserved for the patient with severe disease who will not have a shunt placed during the operation.

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