# 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, 183]

## 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 Blood samples are withdrawn from an artery and the superior bulb of one jugular vein (assumed to contain representative cerebral venous blood) at intervals of 0.75–5 minutes and analyzed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 per cent $N_2O$ was used as the tracer gas, and a normal CBF value of 54 ml/100 g/min was reported. The normal $CMR_{O_2}$ was 3.3 ml/100 g/min.[77] Later, the technique was modified to

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employ $^{85}Kr$ as the tracer and to include extrapolation of arterial and venous curves to their equilibrium values at infinite time.[94] The modifications improved accuracy and resulted in the lower CBF and $CMR_{O_2}$ values accepted today[63, 96, 97, 183]: 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 $^{133}Xe$.[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.[97] 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, 63] 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-

TABLE 1. Normal Values, Units and Abbreviations

| Full Name | Abbreviation | Normal Values and Units |
|---|---|---|
| Cerebral blood flow | CBF | 44 ml/100 g/min |
| Regional cerebral blood flow | rCBF | 20–80 ml/100 g/min |
| Cerebral perfusion pressure* | PP | 80 torr |
| Cerebrovascular resistance† | CVR | 1.8 torr/ml/100 g/min |
| Arteriovenous oxygen content difference | $(A-V)_{O_2}$ | 6.8 ml/100 ml |
| Cerebral metabolic rate for oxygen | $CMR_{O_2}$ | 3.0 ml/100 g/min |
| Cerebral metabolic rate for glucose | $CMR_{glucose}$ | 4.5 mg/100 g/min |
| Cerebral metabolic rate for lactate | $CMR_{lactate}$ | 2.3 mм/100 g/min |
| Cerebral venous oxygen tension | $Pv_{O_2}$ | 35–40 torr |
| Oxygen–glucose index | OGI | 90–100 per cent |
| Lactate–glucose index | LGI | 0–10 per cent |
| Cerebral blood flow equivalent | $CBF/CMR_{O_2}$ | 14–15 ml blood/ml $O_2$ |

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

nique 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.[63] The brain mass was evenly divided between fast- and slow-flow areas. Comparable figures were obtained from a similar analysis of [85]Kr 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.[2, 24] That is, nearly all the glucose utilized by brain tissue is combined with oxygen to yield $CO_2$, 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.[2, 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 $CBF/CMR_{O_2}$ is chosen, as $CMR_{O_2}$ can be easily measured and is not seriously affected by any but the most rapid alterations in flow or metabolic rate.[76] The ratio $CBF/CMR_{O_2}$, the cerebral blood flow equivalent (table 1), is equal to $1/(A-V)_{O_2}$.[27] It can thus be determined from $(A-V)_{O_2}$ without measurement of either CBF or $CMR_{O_2}$. In conditions where $CMR_{O_2}$ 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 $CMR_{O_2}$ values given above were obtained in healthy young adults, but these vary considerably with age. Kennedy and Sokoloff, employing the $N_2O$-uptake method, reported a mean CBF of 106.4 ml/100 g/min and a mean $CMR_{O_2}$ of 5.17 ml/100 g/min for a group of children aged 3 to 10 years.[73] 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 $CMR_{O_2}$. It is likely that the high CBF and $CMR_{O_2}$ 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. Schieve and Wilson[150] and Sokoloff[166] found no significant differences in CBF and $CMR_{O_2}$ 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 72.2 years had the same CBF as young adults, but a slightly lower $CMR_{O_2}$.[96] The decrease in $CMR_{O_2}$ was probably due to the inclusion in the group of pa-

tients with mild organic brain disease, since CBF and $CMR_{O_2}$ are markedly decreased in persons who have suffered strokes or who have senile dementia,[93, 127, 150, 157] particularly in the frontotemporal areas.[127, 157]

Low $CMR_{O_2}$ 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 $CMR_{O_2}$ and there is a direct correlation between $CMR_{O_2}$ and mental ability.[44]

## Control of CBF in Unanesthetized Man

### EFFECTS OF CARBON DIOXIDE

$Pa_{CO_2}$ has the greatest effect on CBF. Within the range of 20 to 60 torr, CBF varies approximately linearly with $Pa_{CO_2}$. Each torr increase or decrease in $Pa_{CO_2}$ is associated with an increase or decrease in CBF of about 1 ml/100 g/min.[75, 76] Within the same range, $Pa_{CO_2}$ has no measurable effect on $CMR_{O_2}$.[76] The effect appears to be general throughout the central nervous system, since $Pa_{CO_2}$ affects spinal cord blood flow in a similar manner.[162]

The mechanism for the $Pa_{CO_2}$ 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 $Pa_{CO_2}$ changes CBF almost immediately, because $CO_2$ diffuses rapidly from blood vessels to affect the pH of the ECF.[154] In the presence of constant $Pa_{CO_2}$, 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 $Pa_{CO_2}$ 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 hypocarbia is limited, and minimal CBF in man is reached at a $Pa_{CO_2}$ of about 10–20 torr.[186] There is evidence to indicate that cerebral tissue hypoxia occurs at very low $Pa_{CO_2}$ levels and plays a role in limiting the decrease of CBF in hypocapnia.[3, 186] Functional changes, such as alterations in critical flicker fusion frequency[5] and in reaction time,[190] 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 $CMR_{O_2}$. However, changes in $CMR_{O_2}$ 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,[132] 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 EEG 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 proscribe extreme hypocapnia ($Pa_{CO_2}$ 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 $CMR_{O_2}$, and local $Pv_{O_2}$ is elevated. This phenomenon has been termed the "luxury perfusion syndrome."[98] 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 $Pv_{O_2}$ increase.

If patients with focal cerebral ischemia are given $CO_2$ to breathe, the resultant hypercarbia 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 $Pa_{CO_2}$. 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." [58] It has been observed clinically and in animals by several investigators,[56, 58, 100, 170, 191] although one laboratory was unable to demonstrate it in animals.[83]

The "inverse steal" or "Robin Hood" syndrome is postulated to occur in response to hypocarbia.[100] Arterioles in diseased areas of brain are under maximal stimulus to remain dilated. They may not constrict in response to low $Pa_{CO_2}$, 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 still incomplete. It is important to note that "steal" and "inverse steal" do not occur in every patient with regional abnormalities of the cerebral circulation when $Pa_{CO_2}$ is altered. Moreover, it is not yet possible to predict how a particular patient will react. Thus, the benefit of hypo- 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 $Pa_{CO_2}$.

## $CO_2$ AND INTRACRANIAL PRESSURE

Hypercarbia increases intracranial pressure (ICP) and hypocarbia decreases it.[102, 149, 155, 165] 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.[140, 141, 163] Unfortunately, the phenomenon has not been well quantitated in normal man. In animals the reduction in ICP obtained with hyperventilation to a $Pa_{CO_2}$ of 20 torr is small and transient, partly because the decreased blood volume is offset by an increase in CSF volume.[141] 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.[102, 149, 155] In one study, the mean CSF pressure in a group of patients with intracranial tumors was halved by hyperventilation to a mean $Pa_{CO_2}$ of 20 torr, using positive–negative ventilation.[119] Alternative techniques for decreasing intracranial pressure during neurosurgery can also be effective and recently have been reviewed elsewhere.[115, 155]

## HYPOXIA

If $Pa_{O_2}$ is lowered while $Pa_{CO_2}$ is maintained constant, CBF is unaffected until $Pa_{O_2}$ falls below 50 torr. At this point cerebral vasodilation occurs and CBF increases.[22] At a $Pa_{O_2}$ of 35 torr, mean CBF was increased to 77 ml/100 g/min in a group of healthy men. $CMR_{O_2}$ was unchanged, but increases in $CMR_{lactate}$ and the glucose–lactate index suggested cellular hypoxia.[24] Jugular bulb $P_{O_2}$ was 27 torr, not so low as the value of 17 torr observed during extreme hypocarbia.[3] However, the severity of the metabolic changes in hypoxia and hypocarbia were about the same. Thus, jugular bulb $P_{O_2}$ is not always a useful indicator of the severity of cerebral hypoxia. Cerebral capillary or tissue $P_{O_2}$, cerebral function, or metabolic pattern is far superior.

Since $CO_2$ has such a pronounced effect on CVR, it is not surprising that $Pa_{CO_2}$ 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 $Pa_{O_2}$ is below 35 torr.[22] It is not clear how hypoxemia dilates cerebral vessels, but accumulation of acid metabolites in the ECF around cerebral arterioles may be involved.[85]

## HYPEROXIA

The increase in $Pa_{O_2}$ induced by breathing 100 per cent oxygen at 1 atmosphere absolute (ATA), causes slight cerebral vasoconstriction.[165] Turner and associates believe that much of this constriction can be accounted for by alterations in $Pa_{CO_2}$.[173] At 2 ATA, the effect is more pronounced, and CBF is decreased 21 per cent from the normoxic state at constant $Pa_{CO_2}$.[65] Experimentally raised ICP is also decreased by oxygen at 2 ATA.[121]

TABLE 2. Cerebral Blood Flow and Metabolism in Anesthetized Man during Normocarbia*

| Anesthetic Agent | Concentration (per cent) | CBF | | CMRo₂ | | CVR torr/ml/ 100 g/min | CBF/ CMRo₂ | Reference |
|---|---|---|---|---|---|---|---|---|
| | | ml/100 g/min | Per cent Change | ml/100 g/min | Per Cent Change | | | |
| N₂O, thiopental induction | 70 | 40.5 | (− 9) | 2.39 | (−23) | 2.17 | 17.0 | 2, 184 |
| | 70 | 45.4 | (+ 1) | 3.02 | (− 2) | 1.97 | 15.0 | 3, 186 |
| N₂O, no thiopental | 70 | 45.4 | (+ 2) | 2.38 | (−23) | 2.0 | 19.0 | 164 |
| Halothane | 1.2 | 50.8 | (+14) | 2.80 | (− 9) | 1.1 | 18.1 | 21, 183 |
| | 1.2† | 54.4 | (+27) | 2.19 | (−26) | 1.4 | 24.8 | 20 |
| Cyclopropane | 5 | 26.2 | −36 | 1.68 | −40 | 3.30 | 15.6 | 4, 189 |
| | 13 | 34.3 | −25 | 2.27 | −29 | 2.39 | 15.1 | 4, 189 |
| | 20 | 66.0 | +61 | 2.50 | −11 | 1.74 | 26.4 | 4, 189 |
| | 20 | 67.2 | (+51) | 2.40 | (−23) | 1.59 | 27.9 | 164 |
| | 37 | 75.6 | +66 | 2.24 | −30 | 1.50 | 33.7 | 4, 189 |
| Diethyl ether | 2.4 | 38.8 | − 6 | 1.75 | −34 | 1.91 | 22.2 | 187 |
| | 4.5 | 67.5 | +56 | 2.24 | −11 | 0.99 | 30.1 | 187 |
| Ethrane | 0.85 | 39.0 | (− 5) | 2.28 | (−25) | 2.92 | 17.1 | ‡ |
| | 2.0 | 40.6 | (+ 2) | 2.00 | (−33) | 1.55 | 20.2 | ‡ |
| | 3.0 | 40.0 | − 3 | 1.53 | −50 | 1.34 | 26.2 | 188 |
| | 3.2 | 40.8 | (+ 2) | 1.84 | (−40) | 0.90 | 22.2 | ‡ |

* 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.[95] Autoregulation is not an instantaneous phenomenon; it may take as long as two minutes for CVR to change in response to altered perfusion pressure.[84, 211] 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 48–55 torr.[37, 123]

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.[45, 78, 156] At a CSF pressure of 920 mm H₂O, mean CBF is decreased by about 25 per cent.[48]

Autoregulation is disturbed in certain disease states. Following a grand mal seizure, CBF is elevated and increases passively if blood pressure increases.[133] Loss of autoregulation in tissue in and around areas of cerebral infarction has been alluded to in the discussion of vasomotor paralysis.[36, 160] Conditions which cause cerebral vasodilation, such as hypercarbia[133] and hypoxia,[41, 54] also disrupt autoregulation. In chronic hypertension, 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.[54]

### 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,[92, 112, 119] while others find no physiologic effect of the autonomic nervous system on CBF control.[99, 159, 165] The occasionally-suggested therapeutic procedure of bilateral stellate-ganglion block did not appear to affect CBF or $CMR_{O_2}$ in either normal subjects or stroke patients.[53] The effects of this block on the $CO_2$ 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.[101] Mean CBF was about 10 per cent higher during sleep, while $CMR_{O_2}$ and $Pa_{CO_2}$ were unchanged. Increased CBF has also been observed in animals during both rapid-eye-movement and slow-wave sleep.[128]

## 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).[50, 145, 146]

Seventy per cent nitrous oxide caused a slight, questionably significant fall in CBF in one study and no change from normal in two others.[164, 184, 186] 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.[20, 153] 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.[107] Thus, halothane appears to be a cerebral vasodilator at

most clinically useful concentrations. In contrast, the effects of cyclopropane on CBF are biphasic.[159] 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.[187]

The new anesthetic Ethrane (Ohio 347; 2-chloro-1,1,2 trifluoroethyl difluoromethyl ether) is interesting in that concentrations of 0.85 to 3.2 per cent (0.59 to 2.2 MAC) have no effect on CBF despite the EEG abnormalities that occur.[188] † 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.[105] 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.[105] The effects of inhalation anesthetics on the distribution of regional flows have not been determined.

### Effects on $CMR_{O_2}$

$CMR_{O_2}$ 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 $CMR_{O_2}$ by 2 per cent in one study and by 23 per cent in two others.[164, 184, 186] Halothane, 1.2 per cent, was found to decrease $CMR_{O_2}$ by 9 per cent in one study and 26 per cent in another.[20, 21] The differences between studies must be accounted for by differences in awake values (which were not measured), slight decreases in body

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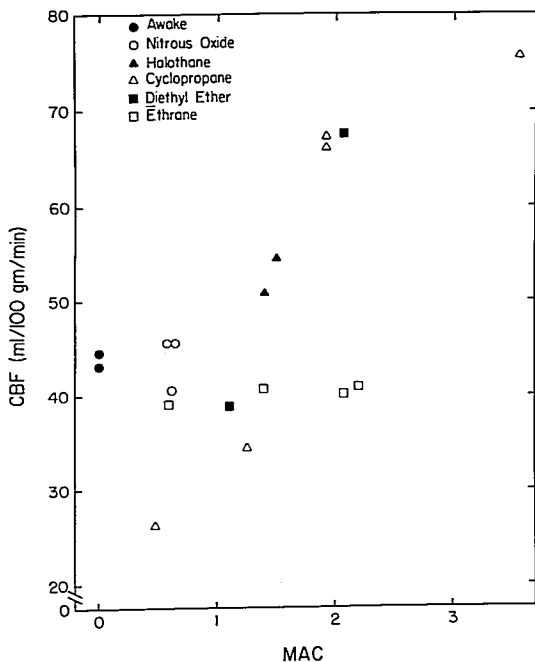† Also, unpublished data from the authors' laboratory.

Fig. 1. Cerebral blood flow as a function of MAC in awake and anesthetized man. Each point represents the mean of a group of at least six individuals.[164]

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 $CMR_{O_2}$.

Larger changes in $CMR_{O_2}$ were observed during cyclopropane anesthesia in a study in which each subject acted as his own awake control.[4] Concentrations of 5 to 36 per cent of this agent depressed $CMR_{O_2}$ 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 $CMR_{O_2}$ was obtained during anesthesia with the lowest cyclopropane concentration studied. It also seems odd that there was so little decrease in $CMR_{O_2}$ with 20 per cent cyclopropane. Another study reported a somewhat

greater depression of $CMR_{O_2}$ (23 per cent) with 20 per cent cyclopropane, but is less reliable for comparison, since it did not awake controls.[164]

The depression of $CMR_{O_2}$ with diethyl ether also is greater during light anesthesia. A 34 per cent decrease in $CMR_{O_2}$ was found during anesthesia with 2.4 per cent ether and an 11 per cent decrease in $CMR_{O_2}$ found with 3 per of men with 4.5 per cent ether.[187]

Although it has little effect on CBF, Ethrane (Ohio 347) depresses $CMR_{O_2}$; the depression increases with depth of anesthesia. The 50 per cent decrease in $CMR_{O_2}$ found with 3 per cent Ethrane makes this agent the most potent depressor of cerebral metabolism among the inhalation agents.[188]
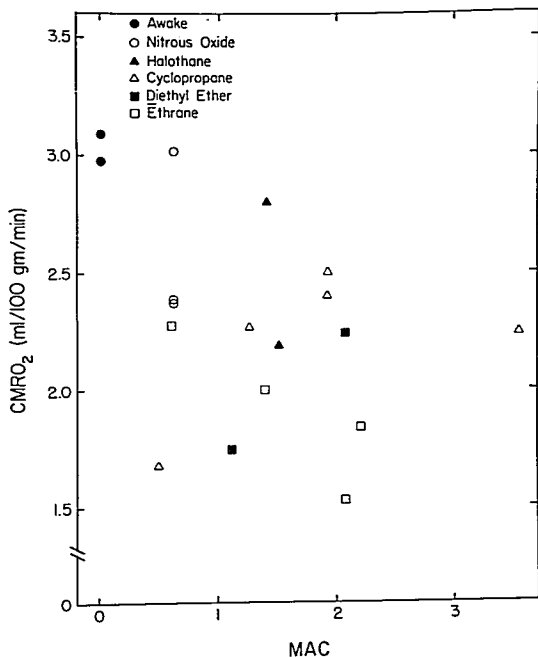
FIG. 2. Cerebral metabolic rate for oxygen as a function of MAC.

There are no data from studies of humans for methoxyflurane, chloroform, and trichloroethylene, but these agents depress canine $CMR_{O_2}$ 10 to 20 per cent.[105]

## EFFECTS ON $CBF/CMR_{O_2}$

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 $CMR_{O_2}$. Consistency improves, however, with consideration of the effect of deepening anesthesia on the ratio of CBF to $CMR_{O_2}$, i.e., the CBF equivalent (fig. 3). There is a clear trend for $CBF/CMR_{O_2}$ to increase as anesthetic depth is increased, thus providing higher tissue and venous $P_{O_2}$ values. Data for all agents lie close

together, so that $CBF/CMR_{O_2}$ seems to depend more on MAC than on the agent used. This correlation raises a number of questions. Does increased $CBF/CMR_{O_2}$ with deep anesthesia indicate an improved safety margin? Or is the higher tissue $P_{O_2}$ 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
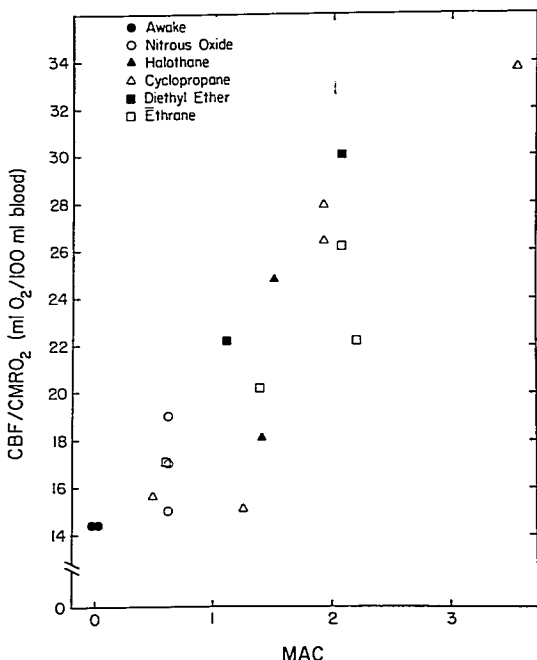
Fig. 3. The effect of anesthetic depth (MAC) on the cerebral blood flow equivalent, calculated from the data of figures 1 and 2.

production.[4] 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.[134]

### ANESTHESIA AND THE CBF–CO₂ RESPONSE

The responsiveness of CBF to changes of $Pa_{CO_2}$ 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.[154] Halothane, 1.2 per cent,

seems to increase the sensitivity of CBF to $Pa_{CO_2}$.[1] Christensen *et al.*, using another technique, also found that hypercarbia potentiated the cerebral vasodilatory effect of halothane.[20] The $Pa_{CO_2}$ 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 $Pa_{CO_2}$'s the CBF values with all agents approach each other (fig. 4); at a $Pa_{CO_2}$ 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

§ Unpublished data from the authors' laboratory.

suddenly added to an established nitrous oxide anesthetic.[28, 71, 106] 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 $H_2O$, respectively.[71] In patients with intracranial tumors, mean CSF pressure was increased 179 and 279 mm $H_2O$, respectively, after 10 minutes of administration of 0.5 per cent halothane and 0.9 per cent trichloroethylene.[71] The administration of 1.5 per cent methoxyflurane for only 10 minutes to five patients with intracranial space-occupying lesion markedly increased mean CSF pressure from 171 to 561 mm $H_2O$.[28] 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.[28]

The mechanism of ICP changes with the volatile agents is probably as follows: these drugs produce cerebral vasodilatation and thus increase cerebrovascular volume.[71, 140, 163] 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 within 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 ex-

ample, has an effect little different from that of 0.7 MAC nitrous oxide.

Langfitt and associates have studied the relation between a space-occupying lesion and CBF in an animal model.[90, 91] 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.[91] 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.[81, 82] In addition, cortical ATP and phosphocreatine concentrations are decreased in intracranial hypertension.[193, 194]

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.[28] 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 apneic period associated with endotracheal intubation are associated with further increases in CSF pressure.[168]

## 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 $CMR_{O_2}$.[79,

[104, 165] In contrast, anesthesia with thiopental has marked effects on cerebral hemodynamics. A dose of thiopental which still permitted some muscular response to pain reduced $CMR_{O_2}$ by 36 per cent.[56] The same metabolic depression resulted from a 0.5–1.6-g dose of this drug.[178] 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 $N_2O$-uptake technique to study cerebral hemodynamics.[130] During normocarbia, mean CBF was decreased to 27.6 ml/100 g/min and mean $CMR_{O_2}$ was decreased to 1.5 ml/100 g/min. When $Pa_{CO_2}$ was 17.5 torr, mean CBF was only 16.4 ml/100 g/min and $CMR_{O_2}$ was similar to that during normocarbia. Thus, although CBF was decreased, sensitivity to alterations in $Pa_{CO_2}$ 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.[5] The depression of CBF and $CMR_{O_2}$ 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.[59]

Thiopental and pentobarbital administration are associated with unchanged or decreased CSF pressure if $CO_2$ retention is prevented.[60, 168] 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.[165] Even morphine, 20–30 mg, given subcutaneously, has a negligible effect.[103] The slight increase in CBF found after morphine, 60 mg, given intravenously to normal men was probably the result of an increase in $Pa_{CO_2}$.[125] However, the decrease in mean $CMR_{O_2}$ from 3.2 to 1.9 ml/100 g/min was significant; furthermore, the

subjects who became most somnolent had the greatest declines in $CMR_{O_2}$. The metabolic depression found in this study could be partially reversed by 25 mg of n-allylnormorphine (Nalline).[125] 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 $Pa_{CO_2}$ is maintained constant.[72, 179]

Small doses of neuroleptanesthetic agents, such as 5 mg droperidol with 1.5 mg phenoperidine, do not affect CBF,[10] and this combination has been used for sedation in clinical CBF studies.[9] 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 $CMR_{O_2}$.[118] Fentanyl, 0.006 mg/kg, decreased CBF and $CMR_{O_2}$ by 47 and 18 per cent, respectively, 15 minutes after administration.[118] The combination drug, Innovar, decreased canine CBF 50 per cent and $CMR_{O_2}$ 23 per cent.[118] The data suggest that Innovar decreases cerebral venous oxygen content, and this has been confirmed by others.[57, 120] Innovar has also been found to decrease the response of CBF to alterations in $Pa_{CO_2}$.[118]

The effects of the neuroleptic agents on CSF pressure contrast with those of the volatile agents. Droperidol, 5 mg, plus phenoperidine, 1.5 mg, produced variable small changes in CSF pressure of normal patients.[39] 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.[39] 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 $Pa_{CO_2}$ "awake" and anesthetized. The "awake" line was adapted from the data of Kety et al.[75, 76] Modification was necessary because those workers reported higher normocarbic CBF's and $CMR_{O_2}$'s with the older form of the nitrous oxide-uptake technique for CBF determination than those presently obtained using $^{85}Kr$ and venous extrapolation. Their CBF values, therefore, were multiplied by the factor: $CMR_{O_2}$ with extrapolation technique/$CMR_{O_2}$ with original technique = 0.658, so that comparison on the same basis would be possible. "Awake" data obtained with the modified technique are not available.
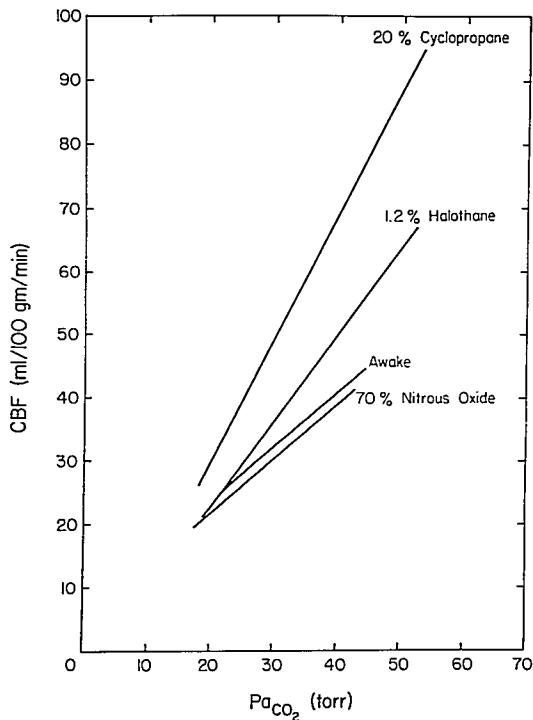
basal nitrous oxide anesthesia. Immediately following the injection of 2 mg/kg, CBF increased 80 per cent and $CMR_{O_2}$ increased 16 per cent.[29] These values returned to control levels during the subsequent 20–30 minutes. The increase in $CMR_{O_2}$ suggests that ketamine should be used cautiously in patients with cerebrovascular disease, since these individuals may not be able to compensate for the increased $CMR_{O_2}$ by increasing CBF.

Ketamine increased lumbar CSF pressure an average of 253 mm $H_2O$ in a group of patients without neurologic disease.[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.[49, 123] An intramuscular dose without pressor effect does not alter CBF or $CMR_{O_2}$.[153] A continuous intravenous infusion of epinephrine, at a mean rate of 28.9 µg/min, increased blood pressure and did not measurably affect CBF or $CMR_{O_2}$.[35] With a larger intravenous dose of epinephrine, 36.9 µg/min, CBF and $CMR_{O_2}$ were augmented by 22 and 23 per cent, respectively.[80] 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 $CMR_{O_2}$ via unknown mechanisms.

Mephentermine, in a dose which raises mean arterial blood pressure only 10 torr, increased $CMR_{O_2}$ in normal subjects by 24 per cent; a compensatory increase in CBF did not occur.[139] 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,[49, 128] both norepinephrine and metaraminol appear to be mild cerebral vasoconstrictors when administered systemically to normotensive persons.[50, 126, 153]   In contrast to epinephrine and mephentermine, these drugs do not alter $CMR_{O_2}$. Norepinephrine and metaraminol have been utilized to treat the low CBF associated with hypotension. However, because of their cerebral vasoconstricting effect, blood pressure must be elevated to slightly supranormal levels in order to obtain a near-normal CBF.[126]

Neither angiotensin nor phenylephrine affects CBF or $CMR_{O_2}$ in normal man.[49, 128, 164] Theoretically, 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 $CMR_{O_2}$ so long as blood pressure remains normal.[22, 124] A small dose of ethyl alcohol (22 ml) has no effect on CBF or $CMR_{O_2}$.[11] However, stupor or coma due to acute ethyl alcohol intoxication (mean blood level 320 mg/100 ml) was found to decrease $CMR_{O_2}$ 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 $Pa_{CO_2}$.[11]

d-Tubocurarine in modest doses, 40–75 mg, has no effect on CBF or $CMR_{O_2}$.[153] 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 $CMR_{O_2}$.[6, 12, 152] However, general anesthesia produced by intravenous administration of the steroid 21-hydroxypregnanedione

3,20 caused a 19 per cent decrease in mean $CMR_{O_2}$ and a 31 per cent decrease in mean CBF.[47]

No cerebral hemodynamic or metabolic changes were found after intravenous infusion of 750 mg procaine over a 20-minute period.[147]

In normal dogs, 1.5 g/kg of urea, given intravenously, did not affect CBF or $CMR_{O_2}$, although the brain was observed to shrink markedly.[54] 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; $CMR_{O_2}$ was unchanged.[46] Mannitol, 0.7 g/kg, caused mean CBF to increase from 36 to 53 ml/100 g/min and augmented mean $CMR_{O_2}$ from 2.0 to 2.5 ml/100 g/min in six brain-tumor patients.[46] 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,[165] histamine,[165] papaverine,[67] and nylidrin[33] have cerebral vasodilating properties. Some of these have been tested for treatment of cerebrovascular disorders, but the results have been mixed.[108, 110] 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 $CMR_{O_2}$ in man,[169] but quantitative data with controlled $Pa_{CO_2}$ are scanty. Cohen et al. correlated $CMR_{O_2}$ with body temperature over the small range 34–38 C during halothane anesthesia and reported log $CMR_{O_2} = 0.073$ T $- 2.23$.[21] Extrapolation of these data would yield the rather high $Q_{10}$ of 5.¶

¶ $Q_{10}$ 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. $CMR_{O_2}$ fell with hypothermia, with a $Q_{10}$ of about 3.[141] Michenfelder and Theye reported a $Q_{10}$ of 2.23 in dogs.[114] In monkeys, Bering found that $CMR_{O_2}$ decreased with hypothermia ($Q_{10}$ 3.5).[14] 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.[60] 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.[60, 114]

Two reports have noted that $(A-V)_{O_2}$ was unaltered by hypothermia.[60, 141] A third reported a decrease in $(A-V)_{O_2}$ with hypothermia, but this may have been due to alterations in $Pa_{CO_2}$.[114] Thus, it appears that during hypothermia per cent decreases in CBF and $CMR_{O_2}$ are similar and arteriovenous oxygen difference remains unchanged. However, $Pv_{O_2}$ decreases, because the solubility of oxygen in blood increases at lower temperatures.[60]

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, 117, 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.[164] Since the drugs commonly used to induce hypotension during anesthesia have no important direct effects on CBF or $CMR_{O_2}$,[165] 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 48–55 torr,[37, 123]

healthy anesthetized patients seem to tolerate even lower pressures. Eckenhoff *et al.* studied 42 patients made hypotensive for surgical operations.[20] 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 $Pv_{O_2}$ observed was 27 torr in one patient; in all of the others, $Pv_{O_2}$'s were greater than 30 torr. In another study of hypotensive anesthesia, Schettini and associates reported a $Pv_{O_2}$ 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 $CMR_{O_2}$ 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 $CMR_{O_2}$, including $Pa_{CO_2}$, 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

| Author | Paco₂ | Anesthetic Drug | Blood Pressure Support* | Awake Test Clamping | Shunt | Hyperbaric Oxygenation |
|---|---|---|---|---|---|---|
| Bloodwell[16] | Induced hypercarbia | $C_3H_6$, 20 per cent | Yes | No | No | No |
| Coleman[25] | Spontaneous respiration | Methohexitone drip | † | Yes | Yes | No |
| Connolly[26] | Induced hypercarbia | Methoxyflurane | No | Yes | No | No |
| Ehrenfeld[21] | Induced hypocarbia | Halothane, 0.58–0.85 per cent | Yes | No | No | No |
| Homi[59] | Induced hypercarbia | $C_3H_6$, 20–30 per cent | Yes | † | † | Yes |
| Jacobson[66] | Normocarbia | Halothane, 1 per cent | † | No | No | Yes |
| Jenkins[65] | Induced hypercarbia | Halothane ± $N_2O$ | Yes | No | Yes | No |
| Jennett[70] | Normocarbia | Trichloroethylene | † | † | † | Yes |
| Ranier[125] | Spontaneous respiration | Local | No | Yes | Yes | No |
| Thompson[171] | Induced hypocarbia | † | No | No | Yes | No |
| White[181] | Induced hypercarbia | Halothane, 0.4–1.5 per cent in $N_2O$ | No | No | No | No |

    * 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/$CMR_{O_2}$. 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 $P_{CO_2}$'s were associated with larger infarctions.[12, 167] 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.[170] Brawley and associates also observed this phenomenon and found, in addition, that in five of seven cases rCBF in the ischemic area decreased as $Pa_{CO_2}$ increased.[15] A decrease in the availability of oxygen in ischemic areas (measured polarographically) when carbon dioxide was administered has also been reported.[52] 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.[83]

Boysen et al. studied patients during carotid endarterectomy at various levels of $Pa_{CO_2}$.[17] They measured rCBF in 14 areas of the operated side, as well as carotid arterial blood pressure distal to the surgical clamp (stump pressure).** Hypercapnia, in contrast to normocapnia and hypocapnia, was associated with decreases in both stump pressure and efficiency of autoregulation. Although hypercapnia increased overall CBF, it reduced rCBF to ischemic areas in five of 21 patients studied. Pistolese et al. found that increased $Pa_{CO_2}$ 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.[131] Fourcade et al. have also reported studies of stump pressure during surgery.[40] They observed the effects of alterations in $Pa_{CO_2}$ and systemic arterial pressure. In most patients, the highest stump pressures were associated with the lowest $Pa_{CO_2}$'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.[19] 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 $Pa_{CO_2}$ 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 $Pa_{CO_2}$ levels in carotid surgery and to maintain either normocarbia or mild hyperventilation ($Pa_{CO_2} = 30$ torr), perhaps with the aid of end-tidal $P_{CO_2}$ monitoring. In this $Pa_{CO_2}$ range, the theoretical problems that hyperventilation causes hypoxia and that hypoventilation 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 $Pa_{CO_2}$ 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.[12] Hypertension was also observed to reverse neurologic symptoms in four patients with cerebrovascular insufficiency, while $CO_2$ inhalation and papaverine failed.[34] 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.[131] In two studies there were consistent increases in pressure distal to the arterial occlusion when systemic hypertension was induced.[18, 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.[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.[28, 45, 151, 182] Possibly increased tolerance has been demonstrated in man,[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,[191] no change,[103] and improvement[103] of flow to ischemic areas. Furthermore, aminophylline, a constrictor of normal cerebral vessels, increases rCBF in focally diseased areas in some patients.[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 $CMR_{O_2}$ the most? Figure 2 shows that the differences among available anesthetics in quantity of $CMR_{O_2}$ reduction are small. Furthermore, we do not know whether a decreased $CMR_{O_2}$ is beneficial. It has been suggested that the decrease in $CMR_{O_2}$ 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.[217] Evidence for this statement was obtained in a study of anoxia and cerebral tissue ATP levels.[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 $CMR_{O_2}$ depression. This implies that the protective action of anesthetics against anoxia is not correlated with $CMR_{O_2}$. 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 $CBF/CMR_{O_2}$ and cerebral venous oxygen saturation more than light anesthesia (fig. 3). However, jugular venous oxygen tension or saturation is an average over the whole brain, and it has not proven useful in predicting the occurrence of focal neurologic defects.[93] 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.[42, 68, 174] Perhaps the electroencephalogram [55] or even rCBF monitoring [69] 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.[59, 70] However, the safe period of cerebral circulatory arrest in animals is only slightly prolonged by 100 per cent oxygen at 3 ATA.[122, 129] At a $Pa_{O_2}$ of about 1,000 torr, mean cerebral venous $P_{O_2}$ 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.[70]

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.[145] 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.[8, 129] Polarographic measurements in the human cortex during carotid clamping have indicated augmented $O_2$ availability at 29 C.[109] Wylie discussed a series of 24 patients, most of whom showed intolerance to carotid clamping while normothermic.[192] 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.[142] 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.

## References

1. Alexander SC, Wollman H, Cohen PJ, et al: Cerebrovascular response to $Pa_{CO_2}$ during halothane anesthesia in man. J Appl Physiol 19:561–565, 1964

2. Alexander SC, Cohen PJ, Wollman H, et al: Cerebral carbohydrate metabolism during hypocarbia in man. ANESTHESIOLOGY 26:624–631, 1965

3. Alexander SC, Smith TC, Strobel GE, et al: Cerebral carbohydrate metabolism of man during respiratory and metabolic alkalosis. J Appl Physiol 24:66–72, 1968

4. Alexander SC, Colton ET, Smith AL, et al: The effects of cyclopropane on cerebral and systemic carbohydrate metabolism. ANESTHESIOLOGY 32:236–245, 1970

5. Allen CD, Morris LE: Central nervous system effects of hyperventilation during anesthesia. Br J Anaesth 34:296, 1962

6. Alman RW, Fazekas JC: Effects of ACTH on cerebral blood flow and oxygen consumption. Arch Neurol Psychiatr 65:680–682, 1951

7. Altenburg BM, Michenfelder JD, Theye RA: Acute tolerance to thiopental in canine oxygen consumption studies. ANESTHESIOLOGY 31:443–448, 1969

8. Anabtawi IN, Brockman SK: Protective effects of hypothermia on total occlusion of the cerebral circulation: A quantitative study. Ann Surg 155:312–315, 1962

9. Barker J, Jennet WB: Neuroleptanalgesia for cerebral blood flow studies in patients undergoing carotid ligation. Acta Anaesth Scand suppl 24:47–50, 1966

10. Barker J, Harper AM, McDowall DG, et al: Cerebral blood flow, cerebrospinal fluid pressure, and EEG activity during neuroleptanalgesia induced with dehydrobenzperidol and phenoperidine (abstract). Br Anaesth 40:143–144, 1968

11. Battey LL, Heyman A, Patterson JL: Effects of ethyl alcohol on cerebral blood flow and metabolism. JAMA 152:6–10, 1953

12. Battistini N, Casacchia M, Bartolini A, et al: Effects of hyperventilation on focal brain

damage following middle cerebral artery occlusion, Cerebral Blood Flow. Edited by M Brock, C Fieschi, DH Ingvar, et al. Berlin, Springer-Verlag, 1969, pp 249–253

13. Bentick RC, Gordan GS, Adams JE, et al: Effect of desoxycorticosterone glucoside upon cerebral blood flow and metabolism of normal subjects. J Clin Invest 30:200–204, 1951

14. Bering EA: Effect of body temperature change on cerebral oxygen consumption of the intact monkey. Am J Physiol 200:417–419, 1961

15. Betz E, Heuser D: Cerebral cortical blood flow during changes of acid–base equilibrium of the brain. J Appl Physiol 23:726–733, 1967

16. Bloodwell RD, Hallman GL, Keats AS, et al: Carotid endarterectomy without a shunt. Arch Surg 96:644–652, 1968

17. Boysen G, Ladegaard-Pedersen HJ, Hendriksen H, et al: The effects of $Pa_{CO_2}$ on regional cerebral blood flow and internal carotid arterial pressure during carotid clamping. ANESTHESIOLOGY 35:286–300, 1971

18. Brawley BW, Strandness P, Kelly WA: The physiologic response to therapy in experimental cerebral ischemia. Arch Neurol 17:180–187, 1967

19. Brock M, Hadjidimos A, Schurmann K: Possible adverse effects of hyperventilation on rCBF during the acute phase of total proximal occlusion of a main cerebral artery, Cerebral Blood Flow. Edited by M Brock, C Fieschi, D Ingvar, et al. Berlin, Springer Verlag, 1969, pp 254–257

20. Christensen MS, Hoedt-Rasmussen K, Lassen NA: Cerebral vasodilation by halothane anesthesia in man and its potentiation by hypotension and hypercapnia. Br J Anaesth 39:927–934, 1967

21. Cohen PJ, Wollman H, Alexander SC, et al: Cerebral carbohydrate metabolism during halothane anesthesia. ANESTHESIOLOGY 25:185–191, 1964

22. Cohen PJ: The effects of decreased oxygen tension on cerebral circulation, metabolism, and function, Proceedings of the International Symposium on the Cardiovascular and Respiratory Effects of Hypoxia. Basel, Karger, 1966, pp 81–104

23. Cohen PJ, Reivich M, Greenbaum L: The electroencephalogram of awake man during hyperventilation: Effects of oxygen at three atmospheres (absolute) pressure. ANESTHESIOLOGY 27:211–212, 1966

24. Cohen PJ, Alexander SC, Smith TC, et al: Effects of hypoxia and normocarbia on cerebral blood flow and metabolism in man. J Appl Physiol 23:183–189, 1967

25. Coleman J, Gillespie JA: Management of carotid endarterectomy with special reference to anesthesia. Br J Surg 50:856–857, 1963

26. Connelly JE: Discussion at Society for Vascular Surgery meeting, New York, 1969. Surgery 67:94–95, 1970

27. Cotev S, Lee J, Severinghaus J: The effects of acetazolamide on cerebral blood flow and cerebral tissue $P_{O_2}$. ANESTHESIOLOGY 29:471–477, 1968

28. Cox JMR, Catton DV, Spoerel WE: The effect of halothane on cerebral ischemia in rabbits. ANESTHESIOLOGY 26:242–243, 1965

29. 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

30. Eckenhoff JE, Enderby GEH, Larson A, et al: Human cerebral circulation during deliberate hypotension and head-up tilt. J Appl Physiol 18:1130–1138, 1963

31. Ehrenfeld WK, Hamilton FN, Larson CP, et al: Effect of $CO_2$ and systemic hypertension on downstream arterial pressure during carotid endarterectomy. Surgery 67:87–96, 1970

32. Ehrmantraut WR, Shea JG, Ticktin HE, et al: Influence of promazine and methylphenidate on cerebral hemodynamics and metabolism. Arch Intern Med 100:66–69, 1957

33. Eisenberg S: The effect of nylidrin hydrochloride (Arlidin) on the cerebral circulation. Am J Med Sci 240:85–92, 1960

34. Farhat SM, Schneider RC: Observations on the effect of systemic blood pressure on intracranial circulation in patients with cerebrovascular insufficiency. J Neurosurg 27:441–445, 1967

35. Fazekas JF, Thomas A, Johnson J, et al: Effect of arterenol (norepinephrine) and epinephrine on cerebral hemodynamics and metabolism. Arch Neurol 2:435–438, 1960

36. Fieschi C, Agnoli A, Battistini N, et al: Derangement of regional cerebral blood flow and its regulatory mechanisms in acute cerebrovascular disease. Neurology 18:1166–1179, 1968

37. Finnerty FA, Witkin L, Fazekas JF: Cerebral hemodynamics during cerebral ischemia induced by acute hypotension. J Clin Invest 33:1227–1232, 1954

38. Fitch W, Barker J, McDowall DG, et al: The effect of methoxyflurane on cerebrospinal fluid pressure in patients with and without intracranial space-occupying lesions. Br J Anaesth 41:564–572, 1969

39. Fitch W, Barker J, Jennett WB, et al: The influence of neuroleptanalgesic drugs on cerebrospinal fluid pressure. Br J Anaesth 41:800–806, 1969

40. Foureade HE, Larson CP, Ehrenfeld WK, et al: The effects of $CO_2$ and systemic hypertension on cerebral perfusion during carotid endarterectomy. ANESTHESIOLOGY 33:383–390, 1970

41. Freeman J, Ingvar DH: Elimination by hypoxia of cerebral blood flow autoregulation and EEG relationship. Exp Brain Res 5: 61–71, 1968

42. Galbraith JG: Monitoring of brain oxygenation during carotid ligation. J Neurosurg 27:102–104, 1967

43. Gardner AE, Olson BE, Lichtiger M: Cerebrospinal-fluid pressure during dissociative anesthesia with ketamine. ANESTHESIOLOGY 35:226–228, 1971

44. Gerfinkel JM, Baird HW, Ziegler J: The relationship of oxygen consumption to cerebral functional activity. J Pediat 44:64–71, 1954

45. Goldstein A, Wells BA, Keats AS: Effect of anesthesia on the tolerance of dog brain to anoxia. ANESTHESIOLOGY 25:98, 1964

46. Goluboff B, Shenkin H, Haft H: The effects of mannitol and urea on cerebral hemodynamics and cerebrospinal fluid pressure. Neurology 14:891–898, 1964

47. Gordon GS, Guadagni N, Picchi J, et al: Steroid anesthesia in man: Clinical and cerebral metabolic effects. J Int Coll Surg 25:9–12, 1956

48. Greenfield JC, Tindall GT: Effect of acute increase in intracranial pressure on blood flows in the internal carotid artery of man. J Clin Invest 44:1343–1351, 1965

49. Greenfield JC, Tindall GT: Studies of the effects of vasopressor drugs on internal carotid artery blood flow in man, Blood Flow Through Organs and Tissues. Edited by WH Bain and AM Harper. Edinburgh, Livingstone, 1968, pp 336–348

50. Gregory GA, Eger EI II, Munson ES: The relationship between age and halothane requirement in man. ANESTHESIOLOGY 30: 488–491, 1969

51. Haggendal E, Winso I: Influence of hypoxia on the response of CBF to hypocapnia, Cerebral Blood Flow. Edited by M Brock, C Fieschi, D Ingvar, et al. Berlin, Springer-Verlag, 1969, pp 70–74

52. Halsey JH, Clark LC: Some regional circulatory abnormalities following experimental cerebral infarction. Neurology 20:238–246, 1970

53. Harmel MH, Halkenshiel JH, Auslin GM, et al: The effect of bilateral stellate ganglion block on the cerebral circulation in normal and hypertensive patients. J Clin Invest 28:415–418, 1949

54. Harper AM, Bell RA: The failure of intravenous urea to alter the blood flow through the cerebral cortex. J Neurol Neurosurg Psychiatry 26:69–70, 1963

55. Harris EJ, Brown WH, Pavy RN, et al: Continuous electroencephalographic monitoring during carotid artery endarterectomy. Surgery 62:441–447, 1967

56. Himwich WA, Homburger E, Maresca R, et al: Brain metabolism in man: Unanesthetized and in Pentothal narcosis. Am J Psychiatry 103:689–696, 1947

57. Hoedt-Rasmussen K, Sveinsdottir E, Lassen NA: Regional cerebral blood flow in man determined by intra-arterial injection of radioactive inert gas. Circ Res 18:237–247, 1966

58. Hoedt-Rasmussen K, Skinhoj E, Paulson O, et al: Regional cerebral blood flow in acute apoplexy. Arch Neurol 17:271–281, 1967

59. Homi J, Humphries AW, Young JR, et al: Hyperbaric anesthesia in cerebrovascular Surgery. Surgery 59:57–65, 1966

60. Hornbein TF, Fortner RWF, Casselle DC: The effect of ventilation on cerebral oxygenation during hypothermia. ANESTHESIOLOGY 30:342, 1969

61. Horsley JS: The intracranial pressure during barbital narcosis. Lancet 232:141–143, 1937

62. Hurwitz BS, Wolfson SK: Brain lactate in anoxia and hypothermia: Relationship to brain viability. Expl Neurol 23:426–434, 1969

63. Ingvar DH, Cronqvist S, Ekberg R, et al: Normal values of regional cerebral blood flow in man, including flow and weight estimates of gray and white matter. Acta Neurol Scand suppl 14:39–45, 1965

64. Ingvar DH, Lundmark T, Risberg J, et al: Recording of multiple clearance curves by means of a magnetic core memory. Scand J Clin Lab Invest suppl 102:XI:H, 1968

65. Jacobson I, Harper AM, McDowall DG: The effects of oxygen under pressure on cerebral blood flow and cerebral venous oxygen tension. Lancet 2:549, 1963

66. Jacobson J: Discussion at Society for Vascular Surgery meeting, New York, 1969. Surgery 67:95–96, 1970

67. Jayne HW, Scheinberg P, Rich M, et al: The effect of intravenous papaverine hydrochloride on the cerebral circulation. J Clin Invest 31:111–114, 1952

68. Jenkins LC, Chung WB: A clinical appraisal of the adequacy of brain circulation during anesthesia, with particular reference to carotid thromboendarterectomy. Canad Anaesth Soc J 16:461–476, 1969

69. Jennett WB, Harper AM, Gillespie FC: Measurement of regional cerebral blood flow during carotid ligation. Lancet 2:1162–1163, 1966

70. Jennett WB, Ledingham I, Harper AM, et al: The effect of hyperbaric oxygen during carotid surgery, Cerebral Blood Flow. Edited by M Brock, C Fieschi, D Ingvar, et al. Berlin, Springer Verlag, 1969, pp 159–160

71. Jennett WB, Barker J, Fitch W, et al: Effects of anesthesia on intracranial pressure in patients with intracranial space-occupying lesions. Lancet 1:61–64, 1969

72. Keats AS, Mithoefer JC: The mechanism of increased intracranial pressure induced by

morphine. N Engl J Med 252:1110–1113, 1955

73. Kennedy C, Sokoloff L: An adaptation of the nitrous oxide method to the study of the cerebral circulation in children; normal values for cerebral blood flow and metabolic rate in childhood. J Clin Invest 36: 1130–1137, 1967

74. Kennedy C, Crave GD, Jelle JW, et al: Blood flow to white matter during maturation of the brain. Neurology 20:613–618, 1970

75. Kety SS, Schmidt CF: The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output, and blood pressure of normal young men. J Clin Invest 25:107–119, 1946

76. Kety SS, Schmidt CF: The effects of altered tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. J Clin Invest 27:487–492, 1948

77. Kety SS, Schmidt CF: The nitrous oxide method for the quantitative determination of cerebral blood flow in man: Theory, procedure, and normal values. J Clin Invest 27:476–483, 1948

78. Kety SS, Shenkin HA, Schmidt CF: The effects of increased intracranial pressure on cerebral circulatory functions in man. J Clin Invest 27:493–499, 1948

79. Kety SS, Woodford RB, Harmel MH, et al: Cerebral blood flow and metabolism in schizophrenia. The effects of barbiturate semi-narcosis, insulin coma, and electroshock. Am J Psychiatry 104:765–770, 1948

80. King B, Sokoloff D, Wechsler RL: The effects of l-epinephrine and l-norepinephrine upon cerebral circulation and metabolism in man. J Clin Invest 31:273–279, 1952

81. Kjallquist A, Siesjo BK, Zwetnow N: Effects of increased intracranial pressure on cerebral blood flow and on cerebral venous $P_{O_2}$, $P_{CO_2}$, pH, lactate, and pruvate in dogs. Acta Physiol Scand 75:267–275, 1969

82. Kjallquist A, Siesjo BK, Zwetnow N: Effects of increased intracranial pressure on cerebral blood flow and on cerebrospinal fluid $HCO_3$, pH, lactate, and pyruvate in dogs. Acta Physiol Scand 75:345–352, 1969

83. Kogure K, Fujishima M, Scheinberg P, et al: Effects of changes in carbon dioxide pressure and arterial pressure on blood flow in ischemic regions of the brain in dogs. Circ Res 24:557–565, 1969

84. Kogure K, Scheinberg P, Fujishima M, et al: Effects of hypoxia on cerebral autoregulation. Am J Physiol 219:1393–1396, 1970

85. Kogure K, Scheinberg P, Reinmuth OM, et al: Mechanisms of cerebral vasodilation in hypoxia. J Appl Physiol 29:223–229, 1970

86. Kramer RS, Sanders AP, Lesage AM, et al: The effect of profound hypothermia on preservation of cerebral ATP content during circulatory arrest. J Thorac Cardiovasc Surg 56:699–709, 1968

87. Kreuscher H: Die Hirndurchblutung Unter Neuroleptanaesthesie. Berlin, Springer-Verlag, 1967

88. Kreuscher H, Grote J: Die Wirkung des Phencyclidinderivates Ketamine (Cl 581) auf die Durchblutung und Sauerstoffaufnahme des Gihirns beim Hund. Anaesthesist 16:304–308, 1967

89. Landau WH, Freygang WH, Rowland LP, et al: The local circulation of the living brain; values in the unanesthetized and anesthetized cat. Trans Am Neurol Assoc 80: 125–129, 1955

90. Langfitt TW, Weinstein JD, Kassel NF: Cerebral vasomotor paralysis produced by intracranial hypertension. Neurology 15: 622–641, 1965

91. Langfitt TW, Kassel NF, Weinstein JD: Cerebral blood flow with intracranial hypertension. Neurology 15:761–773, 1965

92. Langfitt TW, Kassel NF: Cerebral vasodilatation produced by brain stem stimulation: Neurogenic control vs. autoregulation. Am J Physiol 215:90–97, 1968

93. Larsen CP, Ehrenfeld WK, Wade JG, et al: Jugular venous oxygen saturation as an index of adequacy of cerebral oxygenation. Surgery 62:31–39, 1967

94. Lassen NA, Munck O: The cerebral blood flow in man determined by the use of radioactive krypton. Acta Physiol Scand 33: 30–49, 1955

95. Lassen NA: Cerebral blood flow and oxygen consumption in man. Physiol Rev 39:183–238, 1959

96. Lassen NA, Feinberg I, Lane MH: Bilateral studies of cerebral oxygen uptake in young and aged subjects and in patients with organic dementia. J Clin Invest 39:491–500, 1960

97. Lassen NA, Hoedt-Rasmussen K: Human cerebral blood flow measured by two inert gas techniques. Circ Res 19:681–688, 1966

98. Lassen NA: The luxury perfusion syndrome and its possible relation to acute metabolic acidosis localized within the brain. Lancet 2:1113–1115, 1966

99. Lassen NA: Neurogenic control of CBF. Scand J Clin Lab Invest suppl. 102:VIF, 1968

100. Lassen NA, Palvalgyi R: Cerebral steal during hypercapnia and the inverse reaction during hypocapnia observed by the $^{133}$xenon technique in man. Scand J Clin Invest suppl. 102:XIIID, 1968

101. Mangold R, Sokoloff L, Conner E, et al: The effects of sleep and lack of sleep on the cerebral circulation and metabolism of normal young men. J Clin Invest 34:1092–1100, 1955

102. Marrubini MB, Rossanda M, Tretola L: The role of artificial hyperventilation in the control of brain tension during neurosurgical operations. Br J Anaesth 36:415–431, 1964

103. McCall ML, Taylor HW: The effects of morphine sulfate on cerebral circulation and metabolism in normal and toxemic pregnant women. Am J Obstet Gynecol 64:1131–1136, 1952

104. McCall ML, Taylor HW: Effects of barbiturate sedation on the brain in toxemia of pregnancy. J Am Med Soc 149:51–54, 1952

105. McDowall DG, Harper AM: Blood flow and oxygen uptake of the cerebral cortex of the dog during anesthesia with different volatile agents. Acta Neurol Scand suppl 14:146–151, 1965

106. McDowall DG, Barker J, Jennet WB: Cerebrospinal pressure measurements during anesthesia. Anaesthesia 21:189–201, 1966

107. McDowall DG: The effects of clinical concentrations of halothane on the blood flow and oxygen uptake of the cerebral cortex. Br J Anaesth 39:186–196, 1967

108. McHenry LC, Jaffe ME, Kawamura J, et al: Effect of papaverine on regional blood flow in focal vascular disease of the brain. N Engl J Med 282:1167–1170, 1970

109. Meyer JS, Hunter J: Effects of hypothermia on local blood flow and metabolism during cerebral ischemia and hypoxia. J Neurosurg 14:210–227, 1957

110. Meyer JS, Gotoh F, Gilroy J: Improvement in brain oxygenation and clinical improvement in patients with strokes treated with papaverine hydrochloride. JAMA 194:957–961, 1965

111. Meyer JS, Handa J, Huber P, et al: Effects of hypotension on internal and external carotid blood flows. J Neurosurg 23:191–198, 1965

112. Meyer JS, Yoshida K, Sakamoto K: Autonomic control of cerebral blood flow measured by electromagnetic flowmeters. Neurology 17:638–649, 1967

113. Meyer JS, Ryu T, Toyoda M, et al: Evidence for a Pasteur effect regulating cerebral oxygen and carbohydrate metabolism in man. Neurology 19:954–962, 1969

114. Michenfelder JC, Theye RA: Hypothermia: Effect on canine brain and whole-body metabolism. ANESTHESIOLOGY 29:1107–1112, 1968

115. Michenfelder JD, Gronert GA, Rehder K: Neuroanesthesia. ANESTHESIOLOGY 30:65–100, 1969

116. Michenfelder JD, Van Dyke RA, Theye RA: The effects of anesthetic agents and techniques on canine cerebral ATP and lactate levels. ANESTHESIOLOGY 33:315–321, 1970

117. Michenfelder JD, Theye RA: The effects of anesthesia and hypothermia on canine cerebral ATP and lactate during anoxia produced by decapitation. ANESTHESIOLOGY 33:430–439, 1970

118. Michenfelder JD, Theye RA: Effects of fentanyl, droperidol, and Innovar on canine cerebral metabolism and blood flow. Br J Anaesth 43:630–635, 1971

119. Millar RA: Neurogenic control of the cerebral circulation, Cerebral Circulation. Edited by DG McDowall. Boston, Little, Brown, 1969, pp 539–556

120. Miller JD, Barker J: The effect of neuroleptanalgesic drugs on cerebral blood flow and metabolism. Br J Anaesth 41:554–555, 1969

121. Miller JD, Ledingham I: Reduction of increased intracranial pressure. Arch Neurol 24:210–216, 1971

122. Moor GF, Fruson RL, Margolis G, et al: An evaluation of the protective effect of hyperbaric oxygenation on the central nervous system during circulatory arrest. J Thorac Cardiovasc Surg 52:618–628, 1966

123. Moyer JH, Morris G: Cerebral hemodynamics during controlled hypotension induced by the continuous infusions of ganglionic blocking agents (hexamethonium, Pendiomid, and Arfonad). J Clin Invest 33: 1081–1088, 1954

124. Moyer JH, Morris G, Pontius R, et al: Effect of chlorpromazine on cerebral hemodynamics and cerebral oxygen metabolism in man. Circulation 14:380–385, 1956

125. Moyer JH, Pontius RP, Morris G, et al: Effect of morphine and n-allylnormorphine on cerebral hemodynamics and oxygen metabolism. Circulation 15:379–384, 1957

126. Moyer JH, Morris G, Snyder H: A comparison of the cerebral hemodynamic response to aramine and norepinephrine in the normotensive and hypotensive subject. Circulation 10:265–270, 1964

127. Obrist WD, Chivian E, Cronqvist S, et al: Regional cerebral blood flow in senile and presenile dementia. Neurology 20:315–322, 1970

128. Olesen J: The effect of intracarotid infusion of adrenaline, noradrenaline and angiotensin on the regional cerebral blood flow in man. Presented at the International Cerebral Blood Flow Symposium, London, Sept. 18, 1970

129. Patterson RH, McSherry CK, Schwartz MS: Hyperbaric oxygen, hypothermia, and cerebral ischemia in the dog. J Surg Res 8:279–285, 1968

130. Pierce EC, Lambertsen CJ, Deutch S, et al: Cerebral circulation and metabolism during thiopental anesthesia and hyperventilation in man. J Clin Invest 41:1664–1671, 1962

131. Pistolese GR, Citone C, Faraglia V, et al: Effects of hypercapnia on cerebral blood flow during clamping of the carotid arteries in surgical management of cerebro-

vascular insufficiency. Neurology 20:95–100, 1971

132. Plum F, Posner JB, Smith WW: Effect of hyperbaric–hyperoxic hyperventilation on blood, brain, and CSF lactate. Am J Physiol 215:1240–1244, 1968

133. Plum F, Posner JB, Troy B: Cerebral metabolic and circulatory responses to induced convulsions in animals. Arch Neurol 18:1–13, 1968

134. Powers SR, Roe CM, Creel W: Relation between regional cerebral blood flow and cerebral function. Surgery 61:74–82, 1967

135. Ranier WG, Guellen J, Bloomquist CD, et al: Carotid artery surgery. Am J Surg 116:678–681, 1968

136. Rapela CE, Machowicz PP, Freeman G: Effects of $CO_2$ on autoregulation of cerebral blood flow (abstract). Fed Proc 22:344, 1963

137. Reivich M: Arterial $P_{CO_2}$ and cerebral hemodynamics. Am J Physiol 206:25–35, 1964

138. Reivich M, Isaacs G, Evarts E, et al: The effect of slow wave and REM sleep on regional cerebral blood flow in cats. J Neurochem 15:301–306, 1968

139. Richardson DW, Ferguson RW, Patterson JL: Effects of mephentermine on cerebral metabolism and circulation. J Pharmacol Exp Ther 119:219–224, 1957

140. Risberg J, Ancri D, Ingvar DH: Correlation between cerebral blood volume and cerebral blood flow in the cat. Exp Brain Res 8:321–326, 1969

141. Rosomoff HL, Holaday DA: Cerebral blood flow and oxygen consumption during hypothermia. Am J Physiol 179:85–88, 1954

142. Rosomoff HL, Gilbert R: Brain volume and cerebrospinal fluid pressure during hypothermia. Am J Physiol 183:19–25, 1955

143. Rosomoff HL: Protective effects of hypothermia against pathological processes of the nervous system. Ann NY Acad Sci 80:475–486, 1959

144. Rosomoff HL: Distribution of intracranial contents with controlled hyperventilation. ANESTHESIOLOGY 24:640–649, 1963

145. Saidman LJ, Eger EI II, Munson ES, et al: Minimum alveolar concentrations of methoxyflurane, halothane, ether, and cyclopropane in man: Correlation with theories of anesthesia. ANESTHESIOLOGY 28:994–1002, 1967

146. Saidman LJ: The effects of Ethrane (letter to the editor). ANESTHESIOLOGY 31:386, 1969

147. Scheinberg P, Jayne HW, Blackburn MA, et al: Studies of cerebral circulatory functions following intravenous administration of procaine hydrochloride. Arch Neurol Psychiatry 68:815–818, 1952

148. Schettini A, Freund HR, Owre ES: Deliberate hypotension with halothane/oxygen in head and neck surgery. Am J Surg 114:543–550, 1967

149. Schettini A, Cook AW, Owre ES: Hyperventilation in craniotomy for brain tumor. ANESTHESIOLOGY 28:363–371, 1967

150. Schieve JF, Wilson WP: The influence of age, anesthesia, and cerebral arteriosclerosis on cerebral vascular activity to $CO_2$. Am J Med 15:171–174, 1953

151. Secher O, Wilhjelm B: The protective action of anesthetics against hypoxia. Canad Anaesth Soc J 15:423–440, 1968

152. Sensenbach W, Madison L, Ochs L: The effects of ACTH and cortisone on cerebral blood flow and metabolism. J Clin Invest 32:372–380, 1953

153. Sensenbach W, Madison L, Ochs L: A comparison of the effects of l-nor-epinephrine, synthetic l-epinephrine, and U.S.P. epinephrine upon cerebral blood flow and metabolism in man. J Clin Invest 32:226–232, 1953

154. 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

155. Shenkin HA, Bouzarth WF: Clinical methods of reducing intracranial pressure. N Engl J Med 282:1465–1471, 1970

156. Shulman K, Verdier GR: Cerebral vascular resistance changes in response to cerebrospinal fluid pressure. Am J Physiol 213:1084–1088, 1967

157. Simard D, Olesen J, Paulson OB, et al: Regional cerebral blood flow and its regulation in dementia. Brain 94:273–288, 1971

158. Skinhoj E: Regulation of cerebral blood flow as a single function of the interstitial $pH$ of the brain. Acta Neurol Scand 42:604–607, 1966

159. Skinhoj E, Paulson OB: Carbon dioxide and cerebral circulatory control. Arch Neurol 20:249–252, 1969

160. Skinhoj E, Hoedt-Rasmussen K, Paulson OB, et al: Regional cerebral blood flow and its autoregulation in patients with transient focal cerebral ischemic attacks. Neurology 20:485–493, 1970

161. Skinhoj E, Paulson OB: The mechanism of action of aminophylline upon cerebral vascular disorders. Acta Neurol Scand 46:129–140, 1970

162. Smith AL, Pender JW, Alexander SC: Effects of $P_{CO_2}$ on spinal cord blood flow. Am J Physiol 216:1158–1163, 1969

163. Smith AL, Neufeld GR, Ominsky AJ, et al: Interrelations among cerebral blood flow, mean transit time, and vascular volume (abstract). Fed Proc 29:519, 1970

164. 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

165. Sokoloff L: The action of drugs on the cerebral circulation. Pharmacol Rev 11:1–85, 1959

166. Sokoloff L: Cerebral circulatory and metabolic changes associated with aging. Res Publ Assoc Res Nerve Ment Dis 41:237–254, 1966

167. Soloway M, Nadel W, Albin M, et al: The effect of hyperventilation on subsequent cerebral infarction. ANESTHESIOLOGY 29:975–980, 1968

168. Sondergard W: Intracranial pressure during general anesthesia. Dan Med Bull 8:18–25, 1961

169. Stone HH, Donnelly C, Frobese AS: The effect of lowered body temperature on the cerebral hemodynamics and metabolism of man. Surg Gynecol Obstet 103:313–317, 1956

170. Symon L: Regional cerebrovascular responses to acute ischaemia in normocapnia and hypercapnia. J Neurol Neurosurg Psychiatry 83:756–762, 1970

171. Thompson JE: Cerebral protection during carotid endarterectomy (editorial). JAMA 202:1046–1047, 1967

172. Thorn W, Scholl H, Pfleiderer G, et al: Stoffwechselvorange im Gihirn bei normaler und herabgesetzter Korpertenperatur unter ischamischer un anoxischer Belastung. J Neurochem 2:150–165, 1958

173. Turner J, Lambertsen CJ, Owen SG, et al: Effects of .08 and .8 atmospheres of inspired $P_{O_2}$ upon cerebral hemodynamics at a constant alveolar $P_{CO_2}$ of 43 mm Hg (abstract). Fed Proc 16:130, 1967

174. Viancos JG, Sechser PH, Keats AS, et al: Internal jugular venous oxygen tension as an index of cerebral blood flow during carotid endarterectomy. Circulation 34:875–882, 1966

175. Wahl M, Dectjen 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

176. Waltz AG: Effect of blood pressure on blood flow in ischemic and nonischemic cerebral cortex: Phenomena of autoregulation and luxury perfusion. Neurology 18:613–621, 1968

177. Waud BE, Waud DR: On dose-response curves and anesthetics (editorial). ANESTHESIOLOGY 33:1–4, 1970

178. Wechsler RL, Dripps RD, Kety SS: Blood flow and oxygen consumption of the human brain during anesthesia produced by thiopental. ANESTHESIOLOGY 12:308–314, 1951

179. Weitzner SW, McCoy GT, Binder LS: Effects of morphine, levallorphan, and respiratory gases on increased intracranial pressure. ANESTHESIOLOGY 24:291–298, 1963

180. Wells BA, Keats AS, Cooley DA: Increased tolerance to cerebral ischemia produced by general anesthesia during temporary carotid occlusion. Surgery 54:216–223, 1963

181. White CW, Allarde RR, McDowell HA: Anesthetic management for carotid artery surgery. JAMA 202:1023–1027, 1967

182. Wilhjelm BJ, Arnfred I: Protective action of some anesthetics against anoxia. Acta Pharmacol Toxicol (Kbh) 22:93–98, 1965

183. Wollman H, Alexander SC, Cohen PJ, et al: Cerebral circulation of man during halothane anesthesia. ANESTHESIOLOGY 25:180–184, 1964

184. Wollman H, Alexander SC, Cohen PJ, et al: Cerebral circulation during general anesthesia and hyperventilation in man. ANESTHESIOLOGY 26:329–334, 1965

185. Wollman H, Alexander SC, Cohen PJ, et al: Two compartment analysis of the blood flow in the human brain. Acta Neurol Scand suppl 14:49–52, 1965

186. Wollman H, Smith TC, Stephen GW, et al: Effects of extremes of respiratory and metabolic alkalosis on cerebral blood flow in man. J Appl Physiol 24:60–65, 1968

187. Wollman H, Smith AL, Pender JW, et al: Cerebral circulation and metabolism in man during general anesthesia with diethyl ether. Presented at the American Society of Anesthesiologists' meeting, Washington, D. C., Oct. 1968

188. Wollman H, Smith AL, Hoffman JC: Cerebral blood flow and oxygen consumption during electroencephalographic seizure patterns induced by anesthesia with Ethrane (abstract). Fed Proc 28:356, 1969

189. Wollman H, Smith AL, Alexander SC: Effects of general anesthetics in man on the ratio of cerebral blood flow to cerebral oxygen consumption, Cerebral Blood Flow. Edited by M Brock, C Fieschi, D Ingvar, et al. Berlin, Springer-Verlag, 1969, pp 242–243

190. Wollman SB, Orkin LR: Postoperative human reaction time and hypocapnia during anesthesia. Br J Anaesth 40:920–925, 1968

191. Wullenweber R: Intracerebral steal in man recorded by a heat clearance technique. Scand J Clin Lab Invest suppl 102:XIII C, 1968

192. Wylie EJ: Discussion at the 1965 meeting of the Society for Vascular Surgery, New York. Surgery 59:65–66, 1966

193. Zwetnow NN: The influence of increased intracranial pressure on the lactate, pyruvate, bicarbonate, phosphocreatine, ATP, ADP, and AMP concentrations of the cerebral cortex of dogs. Acta Physiol Scand 79:158–166, 1970

194. Zwetnow NN: Effects of increased cerebrospinal fluid pressure on the blood flow and on the energy metabolism of the brain. Acta Physiol Scand suppl 339:1–31, 1970