Chapter 17
Cerebral Physiology and the Effects of Anesthetic Drugs

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Key Points

• The brain has a high metabolic rate and receives approximately 15% of cardiac output. Under normal circumstances, cerebral blood flow (CBF) is approximately 50 mL/100 g/min. Gray matter receives 80% and white matter receives 20% of this blood flow.

• Approximately 60% of the brain’s energy consumption supports electrophysiologic function. The remainder of the energy consumed by the brain is involved in cellular homeostatic activities.

• CBF is tightly coupled to local cerebral metabolism. When cerebral activity in a particular region of the brain increases, a corresponding increase in blood flow to that region takes place. Conversely, suppression of cerebral metabolism leads to a reduction in blood flow.

• CBF is autoregulated and remains constant over a mean arterial pressure (MAP) range estimated at 65 to 150 mm Hg, given normal venous pressure. Appreciable intersubject variability exists. CBF becomes pressure passive when MAP is either less than the lower limit or more than the upper limit of autoregulation.

• CBF is also under chemical regulation. CBF varies directly with arterial carbon dioxide tension in the arterial partial pressure of carbon dioxide ($P_{aCO_2}$) range of 25 to 70 mm Hg. When arterial partial pressure of oxygen ($P_{aO_2}$) decreases to less than 60 mm Hg, CBF dramatically increases. Reductions in body temperature influence CBF primarily by suppression of cerebral metabolism.

• Systemic vasodilators (e.g., nitroglycerin, nitroprusside, hydralazine, calcium channel blockers) vasodilate the cerebral circulation and can, depending on the MAP, increase CBF. Vasopressors such as phenylephrine, norepinephrine, ephedrine, and dopamine do not have direct effects on the cerebral circulation. Their effect on CBF is via their effect on arterial blood pressure. When the MAP is less than the lower limit of autoregulation, vasopressors increase the MAP and thereby increase CBF. If the MAP is within the limits of autoregulation, then vasopressor-induced increases in systemic pressure have little effect on CBF.

• All volatile anesthetics suppress the cerebral metabolic rate (CMR) and, with the exception of halothane, can produce burst suppression of the electroencephalogram. At that level, the CMR is reduced by approximately 60%. Volatile anesthetics have dose-dependent effects on CBF. In doses less than the minimal alveolar concentration (MAC), CBF is modestly decreased. In doses larger than 1 MAC, direct cerebral vasodilation results in an increase in CBF and cerebral blood volume.

• Barbiturates, etomidate, and propofol decrease the CMR and can produce burst suppression of the electroencephalogram. At that level, the CMR is reduced by approximately 60%. Because blood flow and metabolism coupling are preserved, CBF is decreased. Opiates and benzodiazepines effect minor decreases in CBF and CMR. In contrast, ketamine can significantly increase the CMR with a corresponding increase in blood flow.

• Brain stores of oxygen and substrates are limited, and the brain is extremely sensitive to decreases in CBF. Severe decreases in CBF (less than 6 to 10 mL/100 g/min) lead to rapid neuronal death. Ischemic injury is characterized by early excitotoxicity and delayed apoptosis.
This chapter reviews the effects of anesthetic drugs and techniques on cerebral physiology, in particular, their effects on cerebral blood flow (CBF) and metabolism. The final section presents a brief discussion of pathophysiologic states, including cerebral ischemia and cerebral protection. Prime attention is directed to the immediate relevance of the rationale for use of the anesthetic and the intensive care management of patients with intracranial pathologic conditions. Chapter 70 presents the clinical management of these patients in detail. Neurologic monitoring, including the effects of anesthetics on the electroencephalogram (EEG) and evoked responses, is reviewed in Chapter 49.

**ANATOMY OF THE CEREBRAL CIRCULATION**

The arterial blood supply to the brain is composed of paired right and left internal carotid arteries, which give rise to the anterior circulation, and paired right and left vertebral arteries, which give rise to the posterior circulation. The connection of the two vertebral arteries forms the basilar artery. The internal carotid arteries and the basilar artery connect to form a vascular loop called the circle of Willis that permits collateral circulation between both the right and left and the anterior and posterior perfusing arteries. Three paired arteries that originate from the circle of Willis perfuse the brain: anterior, middle, and posterior cerebral arteries. The posterior communicating arteries and the anterior communicating artery complete the loop. The anterior and the posterior circulations contribute equally to the circle of Willis.

Under normal circumstances, blood from the anterior and posterior circulations does not admix because the pressures in the two systems are equal. Similarly, side-to-side admixing of blood across the circle is limited. The vessels that originate from the circle provide blood flow to well-delineated regions of the brain. However, in pathologic circumstances during which occlusion of one of the arterial branches occurs, the circle of Willis can act as an anteroposterior or side-to-side shunt to increase collateral blood flow to the region of the brain with reduced perfusion.

A complete circle of Willis is shown in Figure 17-1, A. However, substantial variability exists in the anatomy of the circle of Willis, and a significant proportion of individuals may have an incomplete circular loop. The variations in the circle and their prevalence are shown in Figure 17-1, B.

Three sets of veins drain blood from the brain. The superficial cortical veins are within the pia mater on the brain surface. Deep cortical veins drain the deeper structures of the brain. These veins drain into dural sinuses, of which the superior and inferior sagittal sinuses and the straight, transverse and sigmoid sinuses are the major dural sinuses. These ultimately drain into the right and left internal jugular veins. A schematic representation of the cerebral venous circulation is shown in Figure 17-1, C.

**REGULATION OF CEREBRAL BLOOD FLOW**

Anesthetic drugs cause dose-related and reversible alterations in many aspects of cerebral physiology, including CBF, cerebral metabolic rate (CMR), and electrophysiologic function (EEG, evoked responses). The effects of anesthetic drugs and techniques have the potential to adversely affect the diseased brain and are thus of clinical importance in patients with neurosurgical disease. Conversely, the effects of general anesthesia on CBF and CMR can be altered to improve both the surgical course and the clinical outcome of patients with neurologic disorders.

The adult human brain weighs approximately 1350 g and therefore represents approximately 2% of total body weight. However, it receives 12% to 15% of cardiac output. This high flow rate is a reflection of the brain’s high metabolic rate. At rest, the brain consumes oxygen at an average rate of approximately 3.5 mL of oxygen per 100 g of brain tissue per minute. Whole-brain oxygen consumption (50 mL/min) represents approximately 20% of total body oxygen utilization. Normal values for CBF, CMR, and other physiologic variables are provided in Box 17-1.

Approximately 60% of the brain’s energy consumption supports electrophysiologic function. The depolarization-repolarization activity that occurs, reflected in the EEG, requires expenditure of energy for the maintenance and restoration of ionic gradients and for the synthesis, transport, and reuptake of neurotransmitters. The remainder of the energy consumed by the brain is involved in cellular homeostatic activities. Local CBF and CMR within the brain are very heterogeneous, and both are approximately four times greater in gray matter than in white matter. The cell population of the brain is also heterogeneous in its oxygen requirements. Glial cells make up approximately one half of the brain’s volume and require less energy than neurons. Besides providing a physically supportive latticework for the brain, glial cells are important in the reuptake of neurotransmitters, in the delivery
The brain's substantial demand for substrate must be met by adequate delivery of oxygen and glucose. However, the space constraints imposed by the noncompliant cranium and meninges require that blood flow not be excessive. Not surprisingly, elaborate mechanisms regulate CBF. These mechanisms, which include chemical, myogenic, and neurogenic factors, are listed in Table 17-1.

**CHEMICAL REGULATION OF CEREBRAL BLOOD FLOW**

Several factors, including changes in CMR, arterial partial pressure of carbon dioxide ($\text{Paco}_2$), and arterial partial
precision mechanisms that mediate flow-metabolism coupling have not been defined, the data available implicate local by-products of metabolism (potassium ion [K\(^+\)], hydrogen ion [H\(^+\)], lactate, adenosine, and adenosine triphosphate [ATP]). Increased synaptic activity with the attendant release of glutamate leads to the downstream generation of a variety of mediators that affect vascular tone (Fig. 17-2). Glutamate, released with increased neuronal activity, results in the synthesis and release of nitric oxide (NO), a potent cerebral vasodilator that plays an important role in coupling of flow and metabolism. Glia play an important role in flow-metabolism coupling, and their processes make contact with neurons. These processes may serve as conduits for the coupling of increased neuronal activity to increases in blood flow. Glutamate activation of metabotropic glutamate receptors (mGluR) in astrocytes leads to arachidonic acid (AA) metabolism and the subsequent generation of prostaglandins and epoxyeicosatrienoic acids (EETs). Local by-products of metabolism (K\(^+\), H\(^+\), lactate, adenosine, and ATP) can also directly modulate vascular tone. Oxygen modulates the relative contribution of these pathways, and in the setting of reduced oxygen tension at the tissue level, the release of adenosine can contribute to vascular dilation. The net result therefore on vascular tone is determined by the relative contribution of multiple signaling pathways. In addition, nerves that innervate cerebral vessels release peptide neurotransmitters such as vasoactive intestinal peptide (VIP), substance P, cholecystokinin, somatostatin, and calcitonin gene–related peptide. These neurotransmitters may also potentially be involved in neurovascular coupling. Flow-metabolism coupling within the brain is a complex physiologic process that is regulated, not by a single mechanism, but by a combination of metabolic, glial, neural, and vascular factors.

CMR is influenced by several phenomena in the neurosurgical environment, including the functional state of the nervous system, anesthetic drugs, and temperature.

**FUNCTIONAL STATE.** CMR decreases during sleep and increases during sensory stimulation, mental tasks, or arousal of any cause. During epileptic activity, increases in the CMR may be extreme, whereas regionally after brain injury and globally with coma, the CMR may be substantially reduced.

**Anesthetic Drugs.** The effect of individual anesthetic drugs on the CMR is presented in greater detail in the second section of this chapter. In general, anesthetic drugs suppress the CMR, with the exception of ketamine and nitrous oxide (N\(_2\)O). The component of the CMR on which they act is electrophysiologic function. With several anesthetics, including barbiturates, isoflurane, sevoflurane, desflurane, propofol, and etomidate, increasing plasma concentrations cause progressive suppression of EEG activity and a concomitant reduction in the CMR. However, increasing the plasma level beyond what is required to first achieve suppression of the EEG results in no further depression of the CMR. The component of the CMR required for the maintenance of cellular integrity, the “housekeeping” component, is unaltered by anesthetic drugs (Fig. 17-3).

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### BOX 17-1 Normal Cerebral Physiologic Values

<table>
<thead>
<tr>
<th>Factor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global CBF</td>
<td>45-55 mL/100 g/min</td>
</tr>
<tr>
<td>Cortical (mostly gray matter) CBF</td>
<td>75-80 mL/100 g/min</td>
</tr>
<tr>
<td>Subcortical (mostly white matter) CBF</td>
<td>=20 mL/100 g/min</td>
</tr>
<tr>
<td>CMRO(_2)</td>
<td>3.3-3.5 mL/100 g/min</td>
</tr>
<tr>
<td>CVR</td>
<td>1.5-2.1 mm Hg/100 g/min</td>
</tr>
<tr>
<td>Cerebral venous Po(_2)</td>
<td>32-44 mm Hg</td>
</tr>
<tr>
<td>Cerebral venous So(_2)</td>
<td>55%-70%</td>
</tr>
<tr>
<td>SV/VO(_2)</td>
<td>=65%</td>
</tr>
<tr>
<td>ICP (supine)</td>
<td>8-12 mm Hg</td>
</tr>
</tbody>
</table>

**CBF,** Cerebral blood flow; **CMRO\(_2\),** cerebral metabolic rate of oxygen; **CVR,** cerebral vascular resistance; **ICP,** intracranial pressure; **Po\(_2\),** partial pressure of oxygen; **SV/VO\(_2\),** jugular venous oxygen saturation; **So\(_2\),** oxygen saturation.

### TABLE 17-1 FACTORS INFLUENCING CEREBRAL BLOOD FLOW

<table>
<thead>
<tr>
<th>Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical, Metabolic, Humoral</td>
<td>CMR influence assumes intact flow-metabolism coupling, the mechanism of which is not fully understood.</td>
</tr>
<tr>
<td>Anesthetics</td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
</tr>
<tr>
<td>Arousal; seizures</td>
<td></td>
</tr>
<tr>
<td>Pa(_{CO_2})</td>
<td></td>
</tr>
<tr>
<td>Pa(_{O_2})</td>
<td></td>
</tr>
<tr>
<td>Vasoactive drugs</td>
<td></td>
</tr>
<tr>
<td>Anesthetics</td>
<td></td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
</tr>
<tr>
<td>Vasopressors</td>
<td></td>
</tr>
<tr>
<td>Myogenic</td>
<td>The autoregulation mechanism is fragile; in many pathologic states, CBF is regionally pressure passive.</td>
</tr>
<tr>
<td>Autoregulation; MAP</td>
<td></td>
</tr>
<tr>
<td>Rheologic</td>
<td></td>
</tr>
<tr>
<td>Blood viscosity</td>
<td></td>
</tr>
<tr>
<td>Neurogenic</td>
<td>Contribution and clinical significance are poorly defined.</td>
</tr>
<tr>
<td>Extracranial sympathetic and parasympathetic pathways</td>
<td></td>
</tr>
<tr>
<td>Intraaxial pathways</td>
<td></td>
</tr>
</tbody>
</table>

*See text for discussion.

**CBF,** Cerebral blood flow; **CMR,** cerebral metabolic rate; **MAP,** mean arterial pressure; **Pa\(_{CO_2}\),** arterial partial pressure of carbon dioxide; **Pa\(_{O_2}\),** arterial partial pressure of oxygen.

pressure of oxygen (Pa\(_{O_2}\)), cause alterations in the cerebral biochemical environment that result in adjustments in CBF.

### Cerebral Metabolic Rate

Increased neuronal activity results in increased local brain metabolism, and this increase in the CMR is associated with a proportional change in CBF that is referred to as flow-metabolism coupling. The traditional view of this coupling is that it is a positive feedback mechanism wherein increased neuronal activity results in a demand for energy; this demand is met by an increase in CBF. More recent data indicate that coupling is based on a feed-forward mechanism wherein neuronal activity directly increases CBF, thereby increasing energy supply. Although the
When complete suppression of EEG is achieved, the cerebral metabolic rate of oxygen (CMRO₂) is similar irrespective of the anesthetic agent used to achieve EEG suppression. Yet, anesthetic-induced EEG suppression is not a single physiologic state and is influenced by the drug that is used to produce suppression. When barbiturates are administered to the point of EEG suppression, a uniform depression in the CBF and CMR occurs throughout the brain. When suppression occurs during the administration of isoflurane and sevoflurane, the relative reductions in the CMR and CBF are more intense in the neocortex than in other portions of the cerebrum. Electrophysiological responsiveness also varies. Cortical somatosensory-evoked responses to median nerve stimulation can be readily recorded at doses of thiopental far in excess of those required to cause complete suppression of the EEG but are difficult to elicit at concentrations of isoflurane associated with a burst-suppression pattern (∼1.5 MAC) (Fig. 17-4)⁴. In addition, the EEG characteristics of the burst-suppression states that occur just before complete suppression differ among anesthetic drugs. These differences may be of some relevance to discussions of differences in the neuroprotective potential of drugs that can produce EEG suppression.

**Temperature.** The effects of hypothermia on the brain have been reviewed in detail (also see Chapter 54). The CMR decreases by 6% to 7% per degree Celsius of temperature reduction. In addition to anesthetic drugs, hypothermia can also cause complete suppression of the EEG (at approximately 18°C to 20°C). However, in contrast to anesthetic drugs, temperature reduction beyond that at which EEG suppression first occurs does produce a further decrease in the CMR (Fig. 17-5). This decrease occurs because anesthetic drugs reduce only the component

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**Figure 17-2.** Cerebral flow-metabolism coupling. Synaptic activity leads to glutamate release, activation of glutamatergic receptors, and calcium entry in neurons. This results in a release of arachidonic acid (AA), prostaglandins (PGs), and nitric oxide (NO). Adenosine and lactate are generated from metabolic activity. These factors all lead to vascular dilation. Glutamate also activates metabotropic glutamate receptors (mGluR) in astrocytes, causing intracellular calcium entry, phospholipase A₂ (PLA₂) activation, release of AA and epoxyeicosatrienoic (EET) acid and prostaglandin E₂ (PGE₂). The latter two AA metabolites contribute to dilation. By contrast, AA can also be metabolized to 20-hydroxy-eicosatetraenoic acid (20-HETE) in vascular smooth muscle. 20-HETE is a potent vascular constrictor. cGMP, Cyclic guanosine monophosphate; eNOS, endothelial nitric oxide synthase; NMDAR, N-methyl D-aspartate glutamate receptor; nNOS, neuronal nitric oxide synthase. (Modified from Attwell D, Buchan AM, Charpak S, et al: Glial and neuronal control of brain blood flow, Nature 468(7321):232-243, 2010.)

**Figure 17-3.** Interdependency of cerebral electrophysiologic function and cerebral metabolic rate (CMR). Administration of various anesthetics, including barbiturates, results in a dose-related reduction in the CMR of oxygen (CMRO₂) and cerebral blood flow (CBF). The maximum reduction occurs with the dose that results in electrophysiologic silence. At this point, the energy utilization associated with electrophysiologic activity has been reduced to zero, but the energy utilization for cellular homeostasis persists unchanged. Additional barbiturates cause no further decrease in CBF or CMRO₂. EEG, Electroencephalogram.
of the CMR associated with neuronal function, whereas hypothermia decreases the rate of energy utilization associated with both electrophysiologic function and the basal component associated with the maintenance of cellular integrity. Mild hypothermia preferentially suppresses the basal component of the CMR. The CMRO$_2$ at 18° C is less than 10% of normothermic control values, which may explain the brain’s tolerance for moderate periods of circulatory arrest at these and cooler temperatures.

Hyperthermia has an opposite influence on cerebral physiologic function. Between 37° C and 42° C, CBF and CMR increase. However, above 42° C, a dramatic reduction in cerebral oxygen consumption occurs, an indication of a threshold for a toxic effect of hyperthermia that may occur as a result of protein (enzyme) denaturation.

Paco$_2$. CBF varies directly with Paco$_2$ (Fig. 17-6), especially within the range of physiologic variation of Paco$_2$. CBF changes 1 to 2 mL/100 g/min for each 1 mm Hg change in Paco$_2$ around normal Paco$_2$ values. This response is attenuated at a Paco$_2$ less than 25 mm Hg. Under normal circumstances, the sensitivity of CBF to changes in Paco$_2$ (ΔCBF/ΔPaco$_2$) is positively correlated with resting levels of CBF. Accordingly, anesthetic drugs that alter resting CBF cause changes in the response of the cerebral circulation to carbon dioxide (CO$_2$). The magnitude of the reduction in CBF caused by hypocapnia is more intense when resting CBF is rapid (as might occur during anesthesia with volatile agents). Conversely, when resting CBF is slow, the magnitude of the hypocapnia-induced reduction in CBF is decreased. However, CO$_2$ responsiveness has been observed in normal brain during anesthesia with all of the anesthetic drugs that have been studied.

The changes in CBF caused by Paco$_2$ are dependent on pH alterations in the extracellular fluid of the brain. NO, in particular NO of neuronal origin, is an important nonexclusive mediator of CO$_2$-induced vasodilation. The vasodilatory response to hypercapnia is also mediated in part by prostaglandins. The changes in extracellular pH and CBF rapidly occur after Paco$_2$ adjustments because CO$_2$ freely diffuses across the cerebrovascular endothelium. In contrast with respiratory acidosis, acute systemic metabolic acidosis has little immediate effect on CBF because the BBB excludes H$^+$ from the perivascular space. The CBF changes in response to alterations in Paco$_2$ rapidly occur, but they are not sustained. Despite the maintenance of an increased arterial pH, CBF returns toward normal over a period of 6 to 8 hours because the pH of cerebrospinal fluid (CSF) gradually returns to normal levels as a result of extrusion of bicarbonate (see Fig. 70-6). Consequently, a patient who has had a sustained period of hyperventilation or hypoventilation deserves special consideration. Acute restoration of a
normal $P_{CO_2}$ value will result in a significant CSF acidosis (after hypopcapnia) or alkalosis (after hypercapnia). The former results in increased CBF with a concomitant increase in intracranial pressure (ICP) that depends on the prevailing intracranial compliance. The latter conveys a theoretic risk for ischemia.

$P_{O_2}$. Changes in $P_{O_2}$ from 60 to more than 300 mm Hg have little influence on CBF. Less than a $P_{O_2}$ of 60 mm Hg rapidly increases CBF (see Fig. 17-6). The mechanisms mediating cerebral vasodilation during hypoxia may include neurogenic effects initiated by peripheral and neuraxial chemoreceptors, as well as local humoral influences. At least part of the hyperemic response to hypoxia is mediated by NO of neuronal origin. Hypoxia-induced opening of ATP-dependent K+ channels in vascular smooth muscle also leads to hyperpolarization and vasodilation. The rostral ventrolateral medulla (RVM) serves as an oxygen sensor within the brain. Stimulation of the RVM by hypoxia results in an increase in CBF (but not the CMR), and lesions of the RVM suppress the magnitude of the CBF response to hypoxia. The response to hypoxia is synergistic with the hyperemia produced by hypercapnia and acidosis. At high $P_{O_2}$ values, CBF modestly decreases. At 1 atmosphere of oxygen, CBF is reduced by 12%.

**MYOGENIC REGULATION (AUTOREGULATION) OF CEREBRAL BLOOD FLOW**

Autoregulation refers to the capacity of the cerebral circulation to adjust its resistance to maintain CBF constant over a wide range of mean arterial pressure (MAP) values. In normal human subjects, the limits of autoregulation likely occur at MAP values of approximately 70 and 150 mm Hg (see Fig. 17-6). The lower limit of autoregulation (LLA) may be a MAP value of 50 mm Hg. Although this number was derived from animal studies, the LLA is likely higher in humans. The units used on the x axis of autoregulation curves will influence the correct inflection points of the curve. When the x axis is the MAP, the normal average LLA is not less than 70 mm Hg (with considerable interindividual variation). Because ICP is not usually measured in normal subjects, cerebral perfusion pressure (CPP) (MAP − ICP) is rarely available. Assuming a normal ICP of 5 to 10 mm Hg in a supine subject, an LLA of 65 mm Hg expressed as MAP corresponds to an LLA of 55 to 60 mm Hg expressed as CPP.

Above and below the autoregulatory plateau, CBF is pressure dependent (pressure passive) and linearly varies with CPP. Autoregulation is influenced by various pathologic processes, as well as the time course over which the changes in CPP occur. Even within the range over which autoregulation normally occurs, a rapid change in arterial pressure will result in a transient (i.e., 3 to 4 minutes) alteration in CBF.

The limits of autoregulation are conceptual constructs for the purpose of analysis. They do not represent physiologic “all-or-none” responses. A continuum of vascular responsiveness in both the lower and upper limits probably exists as the ability of the arteriolar bed to dilate or constrict is exhausted. Furthermore, the morphologic form of the autoregulation is strongly influenced by the background level of vasodilation or vasoconstriction (e.g., $P_{CO_2}$ or anesthetic conditions).

The precise mechanisms, by which autoregulation is accomplished and its overlap with flow-metabolism coupling are not known. According to the myogenic hypothesis, changes in CPP lead to direct changes in the tone of vascular smooth muscle; this process appears to be passive. NO may participate in the vasodilation associated with hypotension (also see Chapter 104). Autonomic innervation of cerebral blood vessels may also contribute to the autoregulation of blood flow (discussed in the next section).

**NEUROGENIC REGULATION OF CEREBRAL BLOOD FLOW**

The cerebral vasculature is extensively innervated. The density of innervation declines with vessel size, and the greatest neurogenic influence appears to be exerted on larger cerebral arteries. This innervation includes cholinergic (parasympathetic and nonparasympathetic), adrenergic (sympathetic and nonsympathetic), serotoninergic, and VIPergic systems of extraaxial and intraaxial origin. An extracranial sympathetic influence via the superior cervical ganglion, as well as parasympathetic innervation via the sphenopalatine ganglion, certainly exists in animals. The intraaxial pathways likely result from innervation arising from several nuclei in animals, including the locus coeruleus, the fastigial nucleus, the dorsal raphe nucleus, and the basal magnocellular nucleus of Meynert. Evidence of the functional significance of neurogenic influences has been derived from studies of CBF autoregulation and ischemic injury. Hemorrhagic shock, a state of high sympathetic tone, results in less CBF at a given MAP than occurs when hypotension is produced with sympatholytic drugs. During shock, a sympathetically mediated vasoconstrictive effect shifts the lower end of...
the autoregulatory plateau to the right. It is not clear what the relative contributions of humoral and neural mechanisms are to this phenomenon; however, a neurogenic component certainly exists because sympathetic denervation increases CBF during hemorrhagic shock. Moreover, sympathetic denervation produced by a blockade of the stellate ganglion can increase CBF in humans.9 Activation of cerebral sympathetic innervation also shifts the upper limit of autoregulation to the right and offers some protection against hypertensive breakthrough of the BBB. Experimental interventions that alter these neurogenic control pathways influence outcome after standardized ischemic insults, presumably by influences on vascular tone and therefore CBF. The nature and influence of such pathways in humans are not known, and their manipulation for the purposes of clinical management remains to be systematically investigated.

EFFECTS OF BLOOD VISCOSITY ON CEREBRAL BLOOD FLOW

Blood viscosity can influence CBF. Hematocrit is the single most important determinant of blood viscosity.10 In healthy humans, variation of the hematocrit within the normal range (33% to 45%) probably results in only modest alterations in CBF. Beyond this range, changes are more substantial. In anemia, cerebral vascular resistance is reduced and CBF increases. However, this may result not only from a reduction in viscosity but also as a compensatory response to reduced oxygen delivery.11 The effect of a reduction in viscosity on CBF is more important with focal cerebral ischemia, a condition in which vasodilation in response to impaired oxygen delivery is probably already maximal. In this situation, reducing viscosity by hemodilution increases CBF in the ischemic territory. In patients with focal cerebral ischemia, a hematocrit of 30% to 34% will result in optimal delivery of oxygen. However, manipulation of viscosity in patients with acute ischemic stroke is not of benefit in reducing the extent of cerebral injury.12 Therefore viscosity is not a target of manipulation in patients at risk as a result of cerebral ischemia, with the possible exception of those with hematocrit values higher than 55%.

VASOACTIVE DRUGS

Many drugs with intrinsic vascular effects are used in contemporary anesthetic practice, including both anesthetic drugs and numerous vasoactive drugs specifically used for hemodynamic manipulation. This section deals with the latter. The actions of anesthetics are discussed in the section, “Effects of Anesthetics on Cerebral Blood Flow and Cerebral Metabolic Rate.”

Systemic Vasodilators

Most drugs used to induce hypotension, including sodium nitroprusside, nitroglycerin, hyaluradone, adenosine, and calcium channel blockers, also cause cerebral vasodilation. As a result, CBF either increases or is maintained at prehypotensive levels. In addition, when hypotension is induced with a cerebral vasodilator, CBF is maintained at lower MAP values than when induced by either hemorrhage or a noncerebral vasodilator. In contrast to direct vasodilators, the angiotensin-converting enzyme (ACE) inhibitor enalapril does not have any significant impact on CBF.13 Anesthetics that simultaneously vasodilate the cerebral circulation cause increases in cerebral blood volume (CBV) with the potential to increase ICP. The effects of these anesthetics on ICP are less dramatic when hypotension is slowly induced, which probably reflects the more effective interplay of compensatory mechanisms (i.e., shifts in CSF and venous blood) when changes occur more slowly.

Catecholamine Agonists and Antagonists

Numerous drugs with agonist and antagonist activity at catecholamine receptors (α1, α2, β1, β2, and dopamine) are in common use. The effects of these vasoactive drugs on cerebral physiology are dependent on basal arterial blood pressure, the magnitude of the drug-induced arterial blood pressure changes, the status of the autoregulatory mechanism, and the status of the BBB. A drug may have direct effects on cerebral vascular smooth muscle or indirect effects mediated by the cerebral autoregulatory response to changes in systemic blood pressure (or both types of effects). When autoregulation is preserved, increases in systemic pressure should increase CBF if basal blood pressure is outside the limits of autoregulation. When basal pressure is within the normal autoregulation range, an increase in systemic pressure does not significantly affect CBF because the normal autoregulatory response to a rising MAP entails cerebral vasoconstriction (i.e., an increase in cerebral vascular resistance) to maintain a constant CBF. When autoregulation is defective, CBF will vary in direct relation to arterial pressure. The information in the following paragraphs and in Table 17-2 emphasizes data obtained from investigations of vasopressors in intact preparations and gives priority to the results obtained in humans and higher primates.

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Cerebral Blood Flow</th>
<th>Cerebral Metabolic Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α1</td>
<td>0/−</td>
<td>0</td>
</tr>
<tr>
<td>α2</td>
<td>−</td>
<td>+</td>
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<td>β</td>
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<td>Fenoldopam</td>
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</tr>
<tr>
<td>Epinephrine (BBB open)</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

BBB, Blood-brain barrier; +, increase; −, decrease; 0, no effect.
*Where species differences occurred, data from primates were given preference. See text for complete discussion.
The number of symbols indicates the magnitude of the effect.
**α1-Agonists.** Will the administration of α1-agonists (phenylephrine, norepinephrine) reduce CBF?

Studies in humans and nonhuman primates do not confirm this concern. Intracarotid infusions of norepinephrine in doses that significantly increase the MAP result in no change in CBF. Administration of phenylephrine to patients undergoing cardiopulmonary bypass does not decrease CBF. There are, however, some species differences with regard to the CBF response to α-agonists. α1-Agonists also do not cause cerebral vasocostriction in rats but do produce modest decreases in CBF in dogs and goats; this decrease in CBF can be blocked by α1-antagonists (also see Chapter 16).

Norepinephrine can increase CBF. Such increases might occur if autoregulation were defective or its limit exceeded. In some instances the increases may be the result of abnormalities in the BBB. β-Mimetic drugs (norepinephrine has β1-activity) may cause activation of cerebral metabolism with a coupled increase in CBF. This effect is more apparent when these drugs can gain greater access to the brain parenchyma via a defective BBB (see Table 17-2).

The traditional view that CBF can be maintained by the administration of α1-agonists without any adverse effect on cerebral oxygenation has been challenged. In anesthetized patients, phenylephrine administration by bolus modestly reduced cerebral oxygen saturation (S\text{CO}_2), measured by near-infrared oximetry. Ephedrine, although increasing arterial blood pressure to a similar extent as phenylephrine, did not reduce S\text{CO}_2, presumably because of its ability to maintain cardiac output. In human volunteers, a norepinephrine-induced increase in arterial blood pressure slightly reduced middle cerebral artery (MCA) flow velocity and S\text{CO}_2 and jugular venous oxygen saturation (SJV\text{O}_2). By contrast, although phenylephrine decreased S\text{CO}_2, MCA flow velocity was increased and SJV\text{O}_2 was unchanged. Do phenylephrine and norepinephrine administration negatively impact cerebral oxygenation? Several factors argue against this possibility. The first concern is methodology. Near-infrared spectroscopy (NIRS) measures oxygenated and deoxygenated blood in a defined region of brain and is a composite of arterial, capillary, and venous blood. Vasopressors affect both arterial and venous tone. Even a minor change in the volume of arterial and venous volumes within the region of the brain can affect the S\text{CO}_2 measurement. Moreover, extracranial contamination is a significant component of the S\text{CO}_2 values reported by the currently available NIRS monitors. This contamination is more important than the slight reduction in S\text{CO}_2 observed in these investigations. In the absence of direct measurement of brain tissue oxygenation, a modest reduction in S\text{CO}_2 in the face of increasing arterial blood pressure cannot be taken as evidence of impairment of cerebral oxygenation. In addition, phenylephrine did not decrease SJV\text{O}_2, a more global measurement of cerebral oxygenation. Although norepinephrine decreased SJV\text{O}_2 by approximately 3% (a mild reduction at best), its administration has been previously shown to increase the CMRO\text{O}_2. Finally, the minor reduction in S\text{CO}_2 effected by phenylephrine is no longer apparent when an increase in the CMRO\text{O}_2 is concurrent. Phenylephrine apparently does not prevent an increase in CBF when such an increase is warranted by increased brain metabolism.

These studies were conducted in patients with a normal central nervous system (CNS). Although unlikely, the concern is that α1-agonists might reduce cerebral perfusion in the injured brain. For example, in patients with a head injury, the administration of phenylephrine increased CPP and did not reduce regional CBF. Transient changes may occur in CBF and S\text{CO}_2 (on the order of 2 to 5 minutes) in response to bolus doses of phenylephrine; however, with a continuous infusion, α1-agonists have little direct influence on CBF and cerebral oxygenation in humans. Thus maintenance of CPP with these vasopressors does not have an adverse effect on the brain.

**α2-Agonists.** α2-Agonists have both analgesic and sedative effects. This class of drugs includes dexmedetomidine and clonidine, with the latter being a significantly less specific and less potent α2-agonist. Two investigations in human volunteers have confirmed the ability of dexmedetomidine to decrease CBF. Dexmedetomidine dose-dependently decreased MCA flow velocity, with the maximum reduction being approximately 25%. Dexmedetomidine (1-μg/kg loading dose and infusion at either 0.2 or 0.6 μg/kg/hr) decreased CBF by approximately 30% in healthy human volunteers. In both these investigations, the CMR was not measured; whether the reduction in CBF was due to a direct vasconstrictor activity of dexmedetomidine or to suppression of the CMR with a corresponding reduction in CBF is not clear. In a more recent study of dexmedetomidine during which both MCA flow velocity and the CMR were measured in healthy humans, dexmedetomidine decreased MCA flow velocity in parallel with a reduction in the CMR. The effects of dexmedetomidine on CBF were primarily mediated by its ability to suppress the CMR. The well-known effect of dexmedetomidine to decrease arterial blood pressure merits careful consideration if used in patients who are critically dependent on collateral perfusion pressure, especially in the recovery phase of an anesthetic.

**β-Agonists.** β-Receptor agonists, in small doses, have little direct effect on the cerebral vasculature. In larger doses and in association with physiologic stress, they can cause an increase in the CMR with an accompanying increase in CBF. The β1-receptor is probably the mediator of these effects. In doses that do not result in substantial changes in the MAP, intracarotid epinephrine does not change CBF in unanesthetized humans. However, with larger doses that lead to an increase in the MAP, both CBF and CMRO\text{O}_2 can increase by approximately 20%.

Evidence suggests that a defect in the BBB enhances the effect of β-agonists. Intracarotid norepinephrine, which does not normally affect CBF and CMR, increases CBF and CMR when BBB permeability is increased with hypertonic drugs. Epinephrine caused an elevation in the CMRO\text{O}_2, but only when the BBB was made permeable. These observations beg the interpretation that β-agonists will increase CBF and CMR only when the BBB is injured. However, when epinephrine was given in doses that did not significantly increase the MAP, increases in CBF and CMR occurred. Accordingly, BBB injury may exaggerate...
but not be a necessary condition in humans for the occurrence of β-mediated increases in CBF and CMR.

**β-Blockers.** β-Adrenergic blockers either reduce or have no effect on CBF and CMR. In two investigations in humans, propranolol, 5 mg intravenously, and labetalol, 0.75 mg/kg intravenously, had no effect on CBF and cerebral blood flow velocity (CBFV), respectively. Modest reductions in CBF occur after the administration of labetalol to patients undergoing craniotomy who become hypertensive during emergence from anesthesia. Esmolol shortens seizures induced by electroconvulsive therapy (ECT), which suggests that esmolol does cross the normal BBB. Catecholamine levels at the time of β-blocker administration or the status of the BBB (or both) may influence the effect of these drugs. β-Adrenergic blockers are unlikely to have adverse effects on patients with intracranial pathologic abnormalities, other than effects secondary to changes in perfusion pressure.

**Dopamine.** Dopamine can treat hemodynamic dysfunction. It also augments the function of the normal cardiovascular system when an increase in the MAP is desired as an adjunct to the treatment of focal cerebral ischemia, especially in the setting of vasospasm. Nonetheless, its effects on CBF and CMR have not been defined with certainty. The likely predominant effect of dopamine in the normal cerebral vasculature, when administered in small doses, is probably slight vasodilation with a minimal change in the CMR. Increased CMR in discrete regions of the brain, such as the choroid plexus and basal ganglia, can occur. However, overall cortical blood flow is not influenced. Vasoconstriction of the cerebral circulation is not observed even when dopamine is administered in doses of up to 100 μg/kg/min. In that same investigation, dobutamine increased CBF and CMR by 20% and 30%, respectively. Fenoldopam is a dopamine agonist with activity at the D₃-receptor and α₂-receptor. The administration of fenoldopam leads to systemic vasodilation and a decrease in arterial blood pressure. In humans, fenoldopam decreased systemic blood pressure to a level that was above the LLA; however, a modest (≈15%) reduction was observed in CBF that did not increase to normal levels when systemic blood pressure was supported. This reduction in CBF was attributed to the α₂ activity of fenoldopam; its effect on the injured brain is not known.

**Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Antagonists.** Both ACE inhibitors and angiotensin-receptor antagonists (ARAs) are commonly used to treat hypertension. In the surgical setting and in the neurocritical care unit, these drugs are administered to control arterial blood pressure acutely. ACE inhibitors and ARAs reduce arterial blood pressure when hypertension is present. However, they do not affect resting CBF, and autoregulation is maintained. In patients with acute stroke, ACE inhibitors and ARAs reduce arterial blood pressure but do not acutely affect CBF. Apparently, these drugs did not reduce CBF when arterial blood pressure modestly decreased (also see Chapter 16).

**AGE**

The loss of neurons is progressive in the normally aging brain from young adulthood to advanced age. Initial studies showed a reduction in neuronal density of as much as 60%. More recent investigations reveal neuronal loss of approximately 10%. The loss of myelinated fibers results in reduced white matter volume. By contrast, the loss of synapses in the aged brain is considerably greater. The majority of excitatory synapses in the brain are on dendritic spines. Dendrite branching and volume progressively decrease, and the number of dendritic spines is reduced by approximately 25% to 35%. Attendant with the loss of neuropil, both CBF and CMRO₂ decrease by 15% to 20% at the age of 80 years (also see Chapters 80 and 93).

**EFFECTS OF ANESTHETICS ON CEREBRAL BLOOD FLOW AND CEREBRAL METABOLIC RATE**

This section discusses the effects of anesthetic drugs on CBF and CMR. It includes limited mentions of the influences on autoregulation, CO₂ responsiveness, and CBV. Effects on CSF dynamics, the BBB, and epileptogenesis are discussed in the section, “Epileptogenesis.”

In neuroanesthesia, the manner in which anesthetic drugs and techniques influence CBF receives prime attention. The rationale is twofold. First, the delivery of energy substrates is dependent on CBF, and modest alterations in CBF can substantially influence neuronal outcome in the setting of ischemia. Second, control and manipulation of CBF are central to the management of ICP because CBF varies in response to vasoconstrictor-vasodilator influences. CBV varies with it. With respect to ICP, CBV is the more critical variable. In the normal brain, CBV is approximately 5 mL/100 g of brain, and over a PaCO₂ range of approximately 25 to 70 mm Hg, CBV changes by approximately 0.049 mL/100 g for each 1 mm Hg change in PaCO₂. In an adult brain weighing approximately 1400 g, this change can amount to 20 mL in total CBV for a PaCO₂ range of 25 to 55 mm Hg. Because CBV is more difficult to measure than CBF, few data exist, especially in humans.

Although CBV and CBF usually vary in parallel, the magnitude of change in CBV is less than the magnitude of change in CBF (Fig. 17-7). In addition, CBV and CBF independently vary under some circumstances. During cerebral ischemia, for example, CBV increases, whereas CBF is significantly reduced. Autoregulation normally serves to prevent MAP-related increases in CBV. In fact, as the cerebral circulation constricts to maintain a constant CBF in the face of an increasing MAP, CBV actually decreases. When autoregulation is impaired or its upper limit (≈150 mm Hg) is exceeded, CBF and CBV then increase in parallel as arterial blood pressure increases (see Fig. 17-6). A declining MAP results in a progressive increase in CBV as the cerebral circulation dilates to maintain constant flow, and exaggerated increases in CBV occur as the MAP decreases to less than the LLA. In normal subjects, the initial increases in CBV do not increase ICP because there...
The “compliance” curve that is commonly drawn to describe the ICP-volume relationship (see Fig. 70-3) actually depicts the relationship ΔP/ΔV (elastance) and not ΔV/ΔP (compliance). The reference to “reduced compliance” in this text is more correctly described as “increased elastance.” However, because the existing literature most commonly uses the “compliance” terminology, the authors have left the misuse uncorrected herein.

**INTRAVENTOUS ANESTHETIC DRUGS**

The action of most intravenous anesthetics leads to parallel reductions in CMR and CBF. Ketamine, which causes an increase in the CMR and CBF, is the exception. The effects of selected intravenous anesthetic drugs on human CBF are compared in Figure 17-8.25,47-59 (also see Chapter 30).

Changes in CBF induced by intravenous anesthetics are largely the result of the effects on the CMR with parallel (coupled) changes in CBF. If this were the entire explanation, then the CBF/CMR ratio would be the same for all anesthetics. Unfortunately, it is not. In addition, direct effects on cerebral vascular smooth muscle (e.g., vasoconstriction, vasodilation, alteration of autoregulatory function) contribute to the net effect. For instance, barbiturates are cerebral vasoconstrictors, yet some barbiturates actually cause relaxation of cerebral vascular smooth muscle in isolated vessel preparations.60 However, a substantial reduction in the CMR occurs in vivo, and the net effect at the point of EEG suppression is vasoconstriction and a substantial decrease in CBF.61 In general, autoregulation and CO₂ responsiveness are preserved during the administration of intravenous anesthetic drugs.

*Note a well-entrenched misuse of terminology.206 The “compliance” terminology, the authors have left the misuse uncorrected herein.

**Barbiturates**

A dose-dependent reduction in CBF and CMR occurs with barbiturates. With the onset of anesthesia, both CBF and CMRO₂ are reduced by approximately 30%.62 When large doses of thiopental cause complete EEG suppression, CBF and CMR are reduced by approximately 50%.61,63 Further increases in the barbiturate dose have no additional effect on the CMR.61 These observations suggest that the major effect of nontoxic doses of depressant anesthetics is a reduction in the component of cerebral metabolism that is linked to electrical brain function (e.g., neurophysiologic activity) with only minimal effects on the second component, which is related to cellular homeostasis (see Fig. 17-3).

Tolerance to the CBF and CMR effects of barbiturates may quickly develop.64 In patients with severe head injury in whom barbiturate coma was maintained for 72 hours, the blood concentration of thiamylal required to maintain EEG burst suppression was observed to be increased by the end of the first 24 hours and continued to increase over the next 48 hours.65 During deep pentobarbital anesthesia, autoregulation is maintained at mean arterial pressures as low as 60 mm Hg, CO₂ responsiveness also persists.
Propofol

The effects of propofol (2,6-diisopropylphenol) on CBF and CMR are similar to those of barbiturates. Both CBF and CMR decrease after the administration of propofol in humans.66 In healthy volunteers, surgical levels of propofol reduced regional CBF by 53% to 79% in comparison with the awake state.67,68 Alkire and co-workers69 assessed cerebral glucose metabolism in volunteers by positron-emission tomography (PET) before and during infusion of propofol to the point of unresponsiveness. The whole-brain metabolic rate decreased by 48% to 58%, with limited regional heterogeneity observed. When compared with isoflurane-fentanyl or sevoflurane-fentanyl anesthesia, a combination of propofol and fentanyl decreased subdural pressure in patients with intracranial tumors and decreased the arteriovenous oxygen content difference (AVDO2).70 Collectively, these investigations in human subjects indicate that propofol effects reductions in the CMR and secondarily decreases CBF, CBV, and ICP.

Both CO2 responsiveness and autoregulation are preserved in humans during the administration of propofol,71,72 even when administered in doses that produce burst suppression of the EEG.73 The magnitude of the reduction in CBF during hypocapnia is decreased during propofol administration. This effect is probably due to the cerebral vasoconstriction induced by suppression of CMR, which further limits hypocapnia-mediated vasoconstriction.

Etomidate

The effects of etomidate on CBF and CMR are also similar to those of barbiturates. Roughly parallel reductions in CBF and CMR occur in humans,47,74 and, in general, they are accompanied by progressive suppression of the EEG. Induction of anesthesia with either thiopental or etomidate resulted in a similar reduction in MCA flow velocity of approximately 27%.75 The changes in CBF and CMR are substantial. Renou and colleagues47 administered approximately 0.2 mg/kg of etomidate to adults and observed mean reductions in CBF and CMR of 34% and 45%, respectively. As is the case with barbiturates, no further reduction in the CMR occurs when additional drug is administered beyond a dose sufficient to produce EEG suppression. This latter phenomenon has not been demonstrated in humans. However, Bingham and associates14 observed that etomidate lowered ICP when administered to patients with severe head injuries in whom EEG activity was well preserved but was ineffective when substantial antecedent EEG suppression existed. The global CMR suppression attainable with etomidate is slightly less profound than that achieved with isoflurane and barbiturates. This finding is consistent with the observation that unlike barbiturates, which cause CMR suppression throughout the brain, the CMR suppression caused by etomidate is regionally variable and predominantly occurs in forebrain structures.

Etomidate is effective in reducing ICP without causing a reduction in CPP in patients with intracranial tumors77 and patients with head injuries.78 However, the administration of etomidate resulted in an exacerbation of brain tissue hypoxia and acidosis in patients in whom the MCA was temporarily occluded during surgery.79 Additional concerns regarding the occurrence of adrenocortical suppression caused by enzyme inhibition and renal injury caused by the propylene glycol vehicle80 will probably preclude more than episodic use.

Reactivity to CO2 is preserved in humans during the administration of etomidate.47,74 Autoregulation has not been evaluated. Myoclonus and epileptogenesis are discussed in the section, “Epileptogenesis.”

Narcotics

Inconsistencies can be found in the available information, but narcotics likely have relatively little effect on CBF and CMR in the normal, unstimulated nervous system. When changes do occur, the general pattern is one of modest reductions in both CBF and CMR. The inconsistencies in the literature probably largely arise because the control states entailed paralysis and nominal sedation in many studies, often with N2O alone. In these studies, in which substantial reductions in CBF and CMR were frequently observed, the effect of the narcotic was probably a combination of the inherent effect of the drug plus a substantial component attributable to reduction of arousal. Comparable effects related to reduction of arousal may occur and can be clinically important. However, they should be viewed as nonspecific effects of sedation or pain control, or both, rather than specific properties of narcotics. The following discussion emphasizes investigations in which control measurements were unlikely to have been significantly influenced by arousal phenomena.

Morphine. When morphine (~1 mg/kg) was administered as the sole drug to humans, Moyer and associates81 observed no effect on global CBF and a 41% decrease in the CMR. The latter is a substantial reduction, and the absence of a simultaneous adjustment in CBF is surprising. No other investigations of morphine have been conducted in humans alone. Jobes and co-workers48 gave morphine (1 and 3 mg/kg) with 70% N2O to patients and observed no significant change in CBF or CMR. The N2O that was used might be expected to have caused a tendency toward increases in CBF and CMR. The relative absence of net changes in these variables from awake control measurements suggests a small-to-moderate depressive effect of morphine on CBF and CMR at this large dose. However, morphine can cause a substantial release of histamine in individual patients. Histamine is a cerebral vasodilator that will cause an increase in CBV and a CBF effect that will vary, depending on the systemic blood pressure response.

Autoregulation was observed to be intact between MAP values of 60 and 120 mm Hg in human volunteers anesthetized with morphine, 2 mg/kg, and 70% N2O.82

Fentanyl. Limited human data are available. Vernhiet and colleagues49 measured CBF and CMR before and during anesthesia with 12 to 30 (mean, 16) µg/kg of fentanyl and 50% N2O in patients about to undergo cerebral angiography. Atropine and pancuronium were the only other agents administered. Neither CBF nor CMR significantly changed from awake control values in their group of six subjects. However, one of the patients (with epilepsy and with normal results on computed tomography
[CTJ) had dramatic and unexplained increases in both CBF and CMRO_{2}. For the remaining five patients, CBF and CMRO_{2} decreased by 21% and 26%, respectively (P < .05). The data for fentanyl-N_{2}O presented in Figure 17-8 are derived from these patients, who received an average of 17 μg/kg of fentanyl. Murkin and associates measured CBF before and after induction of anesthesia with high-dose fentanyl, 100 μg/kg, and diazepam, 0.4 mg/kg. CBF fell by 25%, although part of this effect may well have been a result of benzodiazepine (see later discussion in the section, “Benzodiazepine”) rather than fentanyl. Firestone and co-workers, using PET, observed a heterogeneous CBF response to 1.5 μg/kg of fentanyl in healthy volunteers. Increases occurred in the frontal, temporal, and cerebellar areas simultaneous with decreases in discrete areas associated with pain-related processing. CO_{2} responsiveness and autoregulation are unaffected, and the hyperemic CBF response to hypoxia remains intact.

In conclusion, fentanyl will cause a moderate global reduction in CBF and CMR in the normal quiescent brain and will, similar to morphine, cause larger reductions when administered during arousal.

**ALFENTANIL.** McPherson and associates administered alfentanil, 320 μg/kg, to pentobarbital-anesthetized dogs. They observed no changes in CBF, CMR, CO_{2} responsiveness, autoregulation, or CBF response to hypoxia. No studies of the effects of alfentanil on the CMR in humans have been conducted. Schregel and colleagues administered 25 to 50 μg/kg of alfentanil to patients receiving 60% N_{2}O after induction of anesthesia with thiopental. CBF transiently decreased. A Doppler measure of MCA diameter was simultaneously unchanged, thus suggesting that the reduction in CBF was indicative of a decrease in CBF. Mayberg and co-workers also observed no change in CBF in response to 25 to 50 μg/kg of alfentanil given to patients during maintenance of anesthesia with isoflurane-N_{2}O.

Although data are few, the general pattern is similar and the conclusions should be the same as for sufentanil (see the next paragraph). Alfentanil was included with fentanyl and sufentanil in two of the investigations of conditions in the surgical field mentioned in connection with sufentanil. No adverse effects were noted.

**SUFENTANIL.** Studies in animals and humans indicate that sufentanil causes, depending on the dose, either no change or a reduction in CBF and CMR. Stephan and colleagues measured CBF and CMRO_{2} in patients before and after induction of anesthesia with 10 μg/kg of sufentanil. They observed a 29% reduction in CBF and a 22% reduction in CMRO_{2}. Murkin and co-workers, in a study involving the same dose of sufentanil and a similar design, made essentially identical observations. Mayer and associates gave 0.5 μg/kg of sufentanil to volunteers and observed no change in CBF. Weinstabl and co-workers observed reductions in CBFV when 1.0 and 2.0 μg/kg of sufentanil were given to patients with increased ICP who were in the intensive care unit (ICU). Neither Weinstabl and colleagues nor Mayer and associates who administered sufentanil to healthy volunteers, observed changes in CBFV after 0.5 μg/kg of sufentanil.

A logical conclusion is that no change and no reduction in ICP occurs as a result of the administration of either sufentanil or alfentanil. However, in some investigations in humans, sufentanil was associated with modest increases in ICP. The increases in ICP associated with sufentanil are likely the consequence, in part, of a normal autoregulatory response to the sudden reduction in the MAP that can occur as a consequence of sufentanil administration. Therefore sufentanil and fentanyl should be administered in a manner that does not produce a sudden reduction of MAP. Such a decrease will reduce CPP and may increase ICP, each of which, in sufficient extreme, may be deleterious. However, ICP increases attributed to sufentanil are small. Furthermore, four investigations that compared conditions in the surgical field, including pressure under brain retractors, identified no adverse influences attributable to sufentanil. Accordingly, sufentanil need not be viewed as contraindicated in any way, although its effect on the MAP should be closely followed.

**REMIFENTANIL.** Investigations of moderate doses of remifentanil in patients have revealed similar effects to that of other synthetic narcotics (with the exception of its substantially shorter duration of action). In patients undergoing craniotomy for supratentorial space-occupying lesions, 1 μg/kg of remifentanil caused no change in ICP. In a second investigation in patients undergoing craniotomies, approximately 0.35 μg/kg/min of remifentanil resulted in CBF values comparable to those observed with moderately deep anesthesia with either isoflurane-N_{2}O or fentanyl-N_{2}O. CO_{2} responsiveness was preserved. Greater doses of remifentanil may have more substantial effects. CBFV in the MCA decreased 30% in response to 5 μg/kg, followed by 3 μg/kg/min of remifentanil at a constant MAP in patients being anesthetized for bypass surgery. A lower dose of 2 μg/kg, followed by an infusion of 3 μg/kg/min, however, did not affect CBFV. Quantitatively similar observations were made after a large dose of sufentanil in patients undergoing cardiac anesthesia (see earlier discussion in the section, “Sufentanil”). Remifentanil was administered with other drugs that might influence cerebral hemodynamics. More recent studies in human volunteers have demonstrated that the infusion of small (sedative) doses of remifentanil can increase CBF. A PET study in human subjects to whom remifentanil, 0.05 and 0.15 μg/kg/min, was administered revealed increases in CBF in the prefrontal, inferior parietal, and supplementary motor cortices; reductions in CBF were observed in the cerebellum, superior temporal lobe, and midbrain gray matter. The relative increase in CBF was greater with the administration of the larger dose of remifentanil. Similar data were obtained by Lorenz and colleagues, who used magnetic resonance imaging (MRI) to determine CBF. In a PET investigation in human volunteers, Kofke and co-workers observed remifentanil-induced increases in regional CBF within the limbic system. Although the underlying mechanisms of the increases in CBF are not clear, disinhibition produced by the small-dose remifentanil infusion, or perhaps the sensation of side effects (e.g., warmth, comfort, pruritus), may have contributed. When combined with
N\textsubscript{2}O, CBF and CO\textsubscript{2} reactivity is similar in patients given remifentanil or fentanyl.\textsuperscript{109} In conclusion, sedative doses of remifentanil alone can cause minor increases in CBF. With larger doses or with the concomitant administration of anesthetic adjuvants, CBF is either unaltered or modestly reduced.

**Benzodiazepines**

Benzodiazepines cause parallel reductions in CBF and CMR in humans. CBF and CMRO\textsubscript{2} decreased by 25% when 15 mg of diazepam was given to patients with head injuries.\textsuperscript{52} The effects of midazolam on CBF (but not on CMR) have also been studied in humans. Forster and associates\textsuperscript{33,112} observed a 30% to 34% reduction in CBF after the administration of 0.15 mg/kg of midazolam to awake healthy human volunteers. Veselis and coworkers,\textsuperscript{113} using PET, observed a global 12% reduction in CBF after a similar dose and noted that the decreases preferentially occurred in the brain regions associated with arousal, attention, and memory. CO\textsubscript{2} responsiveness was preserved.\textsuperscript{114}

In conclusion, benzodiazepines cause a moderate reduction in CBF in humans, which may be metabolically coupled. The extent of the maximal reductions of CBF and CMR produced by benzodiazepines is probably intermediate between the decreases caused by narcotics (modest) and barbiturates (substantial). It appears that benzodiazepines should be safe to administer to patients with intracranial hypertension, provided that respiratory depression and an associated increase in PaCO\textsubscript{2} do not occur.

**Flumazenil**

Flumazenil is a highly specific, competitive benzodiazepine receptor antagonist. It had no effect on CBF when administered to unanesthetized human volunteers.\textsuperscript{112,115} However, flumazenil reverses the CBF-, CMR-, and ICP-lowering effects of midazolam. Whereas Knudsen and colleagues\textsuperscript{116} observed no change in either CBF or CMR when patients were aroused from midazolam anesthesia with flumazenil at the conclusion of craniotomy for brain tumor resection, Chiolero and coauthors\textsuperscript{117} reported severe increases in ICP when flumazenil was given to patients with head injuries who were sedated with midazolam and in whom ICP was poorly controlled before the administration of flumazenil. These latter observations are consistent with animal investigations during which flumazenil not only reversed the CBF and CMR effects of midazolam, but it also caused a substantial, although short-lived, overshoot above premidazolam levels in both CBF and ICP by 44% to 56% and 180% to 217%, respectively. The CMR did not rise above control levels, thus indicating that the increase in CBF was not metabolically coupled. The CBF overshoot effect is unexplained, but it may be a neurogenically mediated arousal phenomenon. Flumazenil should be very cautiously used to reverse benzodiazepine sedation in patients with impaired intracranial compliance.

**Droperidol**

No human investigations of the CBF and CMR effects of droperidol have been conducted in isolation. However, the information available from animal investigations and combination drug administration in humans\textsuperscript{118,119} taken together, suggests that droperidol is not a cerebral vasodilator and probably has little effect on CBF and CMR in humans. The occasional increases in ICP that have been observed\textsuperscript{118} probably reflect normal autoregulation-mediated vasodilation in response to an abrupt decrease in the MAP.

**Ketamine**

Among the intravenous anesthetics, ketamine is unique in its ability to cause increases in both CBF and CMR.\textsuperscript{120} Animal studies indicate that the changes in the CMR are regionally variable. In rats, substantial increases occur in limbic system structures with modest changes or small decreases in cortical structures.\textsuperscript{121} PET studies in humans have demonstrated that subanesthetic doses of ketamine (0.2 to 0.3 mg/kg) can increase global CMR by approximately 25%.\textsuperscript{122} The greatest increase in the CMR occurred in the frontal and anterior cingulate cortex. A relative reduction in the CMR in the cerebellum was also observed. Commercially available formulations of ketamine contain both the (S)- and (R)-ketamine enantiomers. The (S)-ketamine enantiomer substantially increases CMR, whereas the (R) enantiomer tends to decrease the CMR, particularly in the temporo-medial cortex and in the cerebellum.\textsuperscript{123} These changes in the CMR are accompanied by corresponding changes in CBF.\textsuperscript{124} Global, as well as regional, increases in CBF in humans that were not accompanied by similar increases in the CMRO\textsubscript{2} after the administration of (S)-ketamine enantiomer have been observed. Both subanesthetic and anesthetic doses of ketamine increased global CBF by approximately 14% and 36%, respectively, without altering global CMRO\textsubscript{2}. As expected, the oxygen extraction ratio was reduced, considering the unchanged CMR and increased CBF. CBV increased by approximately 50%.\textsuperscript{59} The majority of investigations indicate that autoregulation is maintained during ketamine anesthesia,\textsuperscript{125} and CO\textsubscript{2} responsiveness is preserved.

The anticipated ICP correlate of the increase in CBF and CBV has been confirmed to occur in humans. However, anesthetic drugs (e.g., diazepam, midazolam, isoflurane-N\textsubscript{2}O, propofol) blunt or eliminate the increases in ICP or CBV associated with ketamine.\textsuperscript{120,126,127} In fact, decreases in ICP occur when relatively large doses of ketamine (1.5 to 5 mg/kg) are administered to patients with head injuries who are sedated with propofol.\textsuperscript{128} Accordingly, although ketamine is probably best avoided as the sole anesthetic drug in patients with impaired intracranial compliance, it may be cautiously given to patients who are simultaneously receiving the drugs mentioned earlier (e.g., propofol, opioids).

**Lidocaine**

Lidocaine produces a dose-related reduction in the CMRO\textsubscript{2} in experimental animals.\textsuperscript{129} In dogs, 3 mg/kg decreased the CMRO\textsubscript{2} by 10%, and 15 mg/kg decreased it by 27%. When very large doses (160 mg/kg) were given to dogs maintained on cardiopulmonary bypass, the reduction in the CMRO\textsubscript{2} was apparently more than that observed with large-dose barbiturates.\textsuperscript{130} In addition, the membrane-stabilizing effect of lidocaine likely reduces
the energy required for the maintenance of membrane integrity. In unanesthetized human volunteers, Lam and colleagues observed reductions in CBF and CMR of 24% and 20%, respectively, after the administration of 5 mg/kg of lidocaine over a 30-minute period, followed by an infusion of 45 μg/kg/min.

Bedford and co-workers compared the effectiveness of bolus doses of thiopental, 3 mg/kg, and lidocaine, 1.5 mg/kg, in controlling the acute increase in ICP that occurred after the application of a pin head holder or skin incision in patients undergoing craniotomies. The two regimens were equally effective in causing a reduction in ICP. However, the decrease in the MAP was greater with thiopental. Accordingly, a bolus dose of lidocaine is a reasonable adjunct to the prevention or treatment of acute increases in ICP and can prevent increases in ICP associated with endotracheal suctioning. Although large doses of lidocaine can produce seizures in humans and in some experimental animals, lidocaine-induced seizures have not been reported in anesthetized humans. Nonetheless, lidocaine doses should be adjusted to those that achieve serum levels less than the seizure threshold (>5 to 10 μg/mL) in awake humans. After a 2-mg/kg bolus, peak serum concentrations of 6.6 to 8.5 μg/mL are below the seizure threshold. Bolus doses of 1.5 to 2.0 mg/kg therefore seem appropriate.

**INHALED ANESTHETICS**

**Volatile Anesthetics**

The pattern of volatile anesthetic effects on cerebral physiology is quite different than the pattern from intravenous anesthetics, which generally cause parallel reductions in CMR and CBF. All volatile anesthetics, similar to intravenous sedative-hypnotic drugs, suppress cerebral metabolism in a dose-related manner. Volatile anesthetics also possess intrinsic cerebral vasodilatory activity as a result of direct effects on vascular smooth muscle. The net effect of volatile anesthetics on CBF is therefore a balance between a reduction in CBF caused by CMR suppression and an augmentation of CBF caused by the direct cerebral vasodilation. When administered at a dose of 0.5 MAC, CMR suppression–induced reduction in CBF predominates, and net CBF decreases in comparison with the awake state. At 1 MAC, CBF remains unchanged; at this dose, CMR suppression and vasodilatory effects are in balance. Beyond 1 MAC, the vasodilatory activity predominates, and CBF significantly increases, even though the CMR is substantially reduced (Fig. 17-9). Vasodilation with increasing doses of volatile agents leads to an attenuation of cerebral autoregulation. With large doses, autoregulation is abolished and cerebral perfusion becomes pressure passive (Fig. 17-10).

The increase in CBF produced by volatile anesthetics at doses larger than 1 MAC could reflect uncoupling of flow and metabolism. However, coupling (CBF adjustments paralleling changes in the CMR) persists during anesthesia with volatile anesthetics. Accordingly, the conclusion should be that the CBF/CMR ratio is altered (increased) by volatile anesthetics. This alteration is dose related, and, under steady-state conditions,
increasing doses of volatile agents lead to greater CBF/CMRO₂ ratios\textsuperscript{134,142}; that is, higher MAC levels cause more \textit{luxury} perfusion.

The important clinical consequences of the administration of volatile anesthetics are derived from the increases in CBF and CBV—and consequently ICP—that can occur. Of the commonly used volatile anesthetics, the order of vasodilating potency is approximately halothane $\gg$ enflurane $\gg$ desflurane $\approx$ isoflurane $> sevoflurane$.

**Effects on Cerebral Blood Flow.** Volatile anesthetics possess intrinsic vasodilatory activity, and they not only modify cerebral autoregulation, but they also produce a dose-dependent decrease in arterial blood pressure. Hence, their effects on CBF and CMR are best evaluated when arterial blood pressure is maintained at the same level. In addition, the cerebrovascular effects of volatile anesthetics are modulated by the simultaneous administration of other CNS-active drugs. The control state, awake, sedated, or anesthetized, against which the CBF and CMR effects of volatile anesthetics are compared, is important to recognize. The best information concerning the cerebrovascular effects of volatile anesthetics is obtained in studies during which a nonanesthetized awake control state is used.

Data on the cerebrovascular effects of halothane and enflurane are limited. Initial studies in humans demonstrated that the administration of 1 MAC halothane significantly increases CBF, even when systemic blood pressure is substantially reduced, in comparison with preanesthetic CBF\textsuperscript{143}. The same investigators subsequently showed that in humans, when the MAP is maintained at 80 mm Hg, 1.1 MAC levels of halothane increase CBF by as much as 191\% and decrease the CMR by approximately 10\% (Fig. 17-11).\textsuperscript{143,144,146,148} When compared with awake values, 1.2 MAC enflurane also increased CBF and decreased CMR by 45\% and 15\%, respectively.\textsuperscript{145} The dramatic increases in CBF with a simultaneous modest reduction in the CMR attest to the cerebral vasodilatory properties of halothane and enflurane. Isoflurane, by contrast, does not increase CBF as much as halothane or enflurane. At doses of 1.1 MAC, isoflurane increases CBF by approximately 19\% when arterial blood pressure is maintained within the normal range. The CMR is reduced by approximately 45\%.\textsuperscript{141}

Both sevoflurane and desflurane can significantly reduce CBF in humans when compared with CBF in awake, nonanesthetized patients. At 1 MAC concentrations, sevoflurane\textsuperscript{147} and desflurane\textsuperscript{145} decreased CBF by 38\% and 22\% and CMR by 39\% and 35\%, respectively. These results, which suggest that the cerebral vasodilatation produced by isoflurane is greater than that produced by sevoflurane and desflurane, were obtained with CBF measured by the inert gas technique. This technique primarily measures CBF within the cortex and therefore may have substantially underestimated global CBF. PET studies in healthy humans have shown that sevoflurane dose-dependently suppresses the CMRO₂ and CBF; at 1 MAC levels, the reduction in CBF and CMRO₂ is approximately 50\% and 50\% to 60\%, respectively.\textsuperscript{67,68} Even with a significant reduction in CBF, the administration of sevoflurane does not cause a decrease in CBV. In addition, other investigations in humans, most using the measurement of MCA flow velocity by transcranial Doppler, indicate that differences in the effects of isoflurane, desflurane (Fig. 17-12, A), and sevoflurane are, at best, modest.\textsuperscript{149-151} Unfortunately, a strictly quantitative comparison among these volatile anesthetics is not possible, considering the variations in arterial blood pressure among study group patients. In addition, some discrepancy exists among studies in the literature regarding the magnitude of the effects of volatile anesthetics on CBF. Much of this inconsistency may occur as a result of the interaction of regionally selective CBF methods with the heterogeneity within the cerebrum of the CBF effects of volatile anesthetics. (See the later section, "Distribution of Changes in Cerebral Blood Flow/Cerebral Metabolic Rate.")

The anesthetic properties of xenon were recognized several decades ago, but this anesthetic is only now being evaluated for possible use in patients. The MAC of xenon has been estimated to be 63\% to 71\%, with female patients having significantly lower MAC values (51\%).\textsuperscript{152} Xenon primarily exerts its anesthetic effect via noncompetitive antagonism of the N-methyl-D-aspartate receptor (NMDAR),\textsuperscript{153} although activation of the TREK two-pore
K⁺ channel might also play a role. In healthy humans, the administration of 1 MAC xenon resulted in a reduction in CBF by approximately 15% in the cortex and by 35% in the cerebellum; interestingly, CBF in white matter increased by 22%. This reduction in CBF is accompanied by a parallel reduction of the cerebral metabolic rate of glucose (CMRg) by 26%. Cerebral autoregulation and CO₂ reactivity are preserved during xenon anesthesia in animals. Under background pentobarbital anesthesia in an experimental model of increased ICP, the administration of xenon did not increase ICP, and the response to both hypocapnia and hypercapnia was preserved. Diffusion of xenon into air-containing spaces such as the bowel does occur, although the magnitude of air expansion is considerably less than that with N₂O. Accordingly, caution will have to be exercised with the use of xenon in patients with intracranial air. These data indicate that it has a favorable profile for neuroanesthesia.

**Effects on Cerebral Metabolic Rate.** All of the volatile anesthetics cause reductions in the CMR. The degree of reduction in the CMRO₂ that occurs at a given MAC is less with halothane than with the other four anesthetics. Sevoflurane’s effect on the CMRO₂ is very similar to that of isoflurane. The available information, derived in separate investigations, suggests that desflurane causes slightly less suppression of the CMRO₂ than isoflurane, especially at concentrations above 1 MAC. Although a direct comparison of the CMRO₂ effects of all of the volatile anesthetics has not been performed in humans, doses of 1 MAC isoflurane, sevoflurane, and desflurane clearly reduce the CMRO₂ (AVDO₂ in arterial and jugular bulb blood samples) by 25%, 38%, and 22%, respectively. Halothane (0.9 MAC) and isoflurane (0.5 MAC) can decrease the CMRg by 40% and 46%, respectively, in PET studies. The decrease in the CMRO₂ is dose related. With isoflurane (and almost certainly desflurane and sevoflurane as well), the maximal reduction is simultaneously attained with the occurrence of EEG suppression, which occurs at clinically relevant concentrations, such as 1.5 to 2 MAC in humans. Additional isoflurane up to 6% end-tidal volume results in no further reduction in the CMR and no indication of metabolic toxicity. Halothane presents a contrast to this pattern. Halothane concentrations in excess of 4 MAC are required to achieve EEG suppression in animals, and additional halothane causes a further reduction in the CMRO₂ in concert with alterations in energy charge. The latter changes, which are reversible, suggest interference with oxidative phosphorylation. These data indicate that, unlike isoflurane, halothane can produce reversible toxicity when administered in very high concentrations.

Some nonlinearity exists in the CBF and CMR dose-response relationships for volatile anesthetics. The initial appearance of an EEG pattern associated with the onset of anesthesia with halothane, enflurane, and isoflurane is accompanied by a precipitous decline in the CMRO₂. Thereafter, the CMRO₂ declines in a slower dose-dependent manner. Such an effect has also been demonstrated for sevoflurane. In a dose escalation study in humans, the greatest reduction in entropy (i.e., a measure of anesthetic depth) was observed with 1 MAC sevoflurane anesthesia, with lesser reductions occurring at increasing concentrations. Other studies during anesthetic induction with halothane found significant increases in CBF before any alteration in the CMR. This finding suggests that the direct effect of a volatile agent on smooth muscle may develop more rapidly than influences related to the depression of the CMR.

![Figure 17-12. Effect of volatile anesthetics on cerebral blood flow (CBF) (A) and the cerebral metabolic rate of oxygen (CMRO₂) (B) in awake humans.](image-url)
**PART II: Anesthetic Physiology**

**Distribution of Changes in Cerebral Blood Flow and Cerebral Metabolic Rate.** The regional distribution of anesthetic-induced changes in CBF and CMR significantly differs with halothane and isoflurane. Halothane produces relatively homogeneous changes throughout the brain. CBF is globally increased, and CMR is globally depressed. The changes caused by isoflurane are more heterogeneous. Increases in CBF are greater in subcortical areas and hindbrain structures than in the neocortex. In humans, 1 MAC sevoflurane (Fig. 17-13) results in a reduction in the neocortex than in the subcortex. The converse is true for the CMR, with a larger reduction in the neocortex than in the subcortex. In humans, 1 MAC sevoflurane (Fig. 17-13) results in a reduction in CBF within the cortex and the cerebellum. With an increase in sevoflurane dose, CBF within the cortex decreases further. By contrast, flow increases in the cerebellum with doses greater than 1.5 MAC. These effects of sevoflurane are similar to those produced by isoflurane. Desflurane has not been evaluated by local CBF studies. However, considering the similarity of its effects on the EEG (suggesting similar cortical CMR and CBF effects), the interim assumption of similar heterogeneity in CBF distribution seems reasonable. These distribution differences may explain certain apparent contradictions in reported CBF effects in the existing literature for isoflurane. Methods that assess global hemodynamic effects reveal greater changes than those that emphasize the cortical compartment. For instance, Eintrei and co-workers found no increase in CBF by surface xenon washout when isoflurane was administered to patients undergoing craniotomy, yet others have reported that the administration of isoflurane to normocapnic subjects with intracranial pathologic conditions can result in increases in CSF pressure.

**Time Dependence of Cerebral Blood Flow Effects.** The effects of volatile anesthetics on CBF are time dependent in animal investigations. After an initial increase, CBF substantially decreases and reaches a steady state near pre–volatile agent levels between 2.5 and 5 hours after exposure. The mechanism of this effect is not understood, and the phenomenon was not evident in humans studied during a 3- or 6-hour exposure to halothane, isoflurane, desflurane, or sevoflurane.

**Cerebral Blood Volume.** The extensive investigation of the influence of volatile anesthetics on CBF has been primarily based on the concern that the cerebral vasodilation produced by volatile anesthetics might increase ICP. However, it is CBV and not CBF, per se, that influences ICP. Most of the intracranial blood is within the cerebral venous circulation; although a reasonable correlation exists between vasodilation-induced increases in CBF and CBV, the magnitude of changes in CBV is considerably greater than that in CBF (see Fig. 17-7). Hence, changes in CBF do not reliably predict changes in CBV and, by extension, in ICP. Nonetheless, CBV is considerably greater during isoflurane anesthesia than during propofol or pentobarbital anesthesia. In human volunteers, 1 MAC sevoflurane reduced regional CBF but not regional CBV; by contrast, propofol reduced both regional CBF and regional CBV (Fig. 17-14). In addition, CBV responds to changes in PaCO₂ by a reduction in CBV with hypocapnia and an increase in CBV with hypercapnia. The magnitude of the change in CBV is, however, less than the change in CBF. In aggregate, although the effect of anesthetics and interventions on CBV may parallel the effect on CBF, substantial qualitative and quantitative differences may well be observed.

**Carbon Dioxide Responsiveness and Autoregulation.** CO₂ responsiveness is well maintained during anesthesia with all volatile anesthetics. As with all vasodilators, CBF is preserved up to lower MAP values during the administration of volatile anesthetics with no evidence of differences among the various anesthetics. Direct comparisons of CBF with isoflurane, desflurane, and sevoflurane anesthesia.
during hypotension are not available. By contrast, autoregulation of CBF in response to increasing arterial blood pressure is impaired, which is most apparent with the anesthetics that cause the most cerebral vasodilation and are dose related. Sevoflurane may cause less impairment of autoregulation than other volatile anesthetics. Recent studies surprisingly report no change in CBFV in response to phenylephrine-induced increases in the MAP during anesthesia with 1.2 to 1.5 MAC sevoflurane or in CBF during hemorrhagic hypotension. The autoregulatory response to increasing blood pressure may be pertinent during acute episodes of hypertension, such as during laryngoscopy or mismatch of surgical stimulation to anesthetic depth. Some relevance to hyperemic states after carotid endarterectomy (CEA) or resection of arteriovenous malformations might exist (also see Chapter 70).

Cerebral Vasodilation by Anesthetics—Clinical Implications. Isoflurane, desflurane, and sevoflurane may have a modest cerebral vasodilating effect in the human cortex when administered at doses of 1 MAC or less. In fact, the administration of volatile anesthetics can effect net decreases in CBF (see Fig. 17-12, A). These data, however, should be interpreted with considerable caution because the critical variable that is of interest in the clinical setting is CBV. Although a direct correlation exists between CBF and CBV, as noted earlier, the relationship is not strictly 1:1. The magnitude of the changes in CBV is significantly less than the magnitude of the changes in CBF, and modest reductions in CBF may not necessarily be accompanied by reductions in CBV. This finding is exemplified by clinical investigations in which a significant increase in ICP (and by extension, CBV) was observed in patients to whom isoflurane was administered at doses that should reduce CBF. Although induction of hypocapnia mitigated the increase in ICP, hyperventilation may not be effective in blunting isoflurane-induced increases in ICP in patients with intracranial tumors. In experimental investigations of cerebral injury, volatile anesthetics significantly increased ICP, which was not ameliorated by hypocapnia. Collectively, these data suggest that volatile anesthetics have minimal effects on cerebral hemodynamics in patients with normal intracranial compliance. However, in patients with abnormal intracranial compliance, the potential for volatile anesthetic–induced increases in CBV and ICP exist. Accordingly, volatile anesthetics should be used with caution in the setting of large or rapidly expanding mass lesions, unstable ICP, or other significant cerebral physiologic derangements in which CO₂ responsiveness and flow-metabolism coupling may be impaired. When they occur (e.g., a somnolent, vomiting patient with papilledema; a large mass; compressed basal cisterns), the clinician may well be advised to use a predominantly intravenous technique until such time when the cranium and dura are open and the effect of the anesthetic technique can be directly assessed. Such circumstances will be relatively rare in elective neurosurgery.

Situations in which the CMR has been decreased by drug administration or disease processes should also justify caution in the use of volatile anesthetics. If a volatile anesthetic has a substantial direct vasodilating effect on the cerebral vasculature that is normally offset by an opposing metabolically mediated vasoconstricting influence, then a near-maximal reduction of the CMR may have occurred; a volatile anesthetic will have a predominantly vasodilating effect. These data suggest that isoflurane is a significant cerebral vasodilator when administered in situations during which the component of the CMR that is associated with electrophysiologic function is already suppressed by other drugs or pathologic processes, such as traumatic brain injury.

The net vasodilating effects of equi-MAC concentrations of isoflurane, desflurane, and sevoflurane are less in

![Anesthetic Effects on CBF and CBV](image-url)

**Figure 17-14.** Effect of anesthetic drugs on cerebral blood flow (CBF) and cerebral blood volume (CBV). **A,** When compared with isoflurane, propofol and pentobarbital effected substantial reductions in CBF. However, reductions in CBV were more modest. **B,** Although sevoflurane effected a significant reduction in regional CBF (rCBF), regional CBV (rCBV) was unchanged; had blood pressure been supported to normal levels, rCBV may have been greater than the awake state. By contrast, propofol effected a significant reduction in both rCBF and rCBV. These data indicate that the magnitude of the effect of anesthetics on rCBF is substantially greater than on rCBV. Hence, decreases in rCBF may not lead to equivalent reductions in rCBV. MAP, Mean arterial pressure; N₂O, nitrous oxide.
humans than that of halothane, and the former are probably therefore preferable if a volatile anesthetic is to be used in the setting of impaired intracranial compliance. When hypocapnia is established before the introduction of halothane, the increases in ICP that might otherwise occur in a normocapnic patient with poor intracranial compliance can be prevented or greatly attenuated. Nonetheless, isoflurane, desflurane, or sevoflurane are preferred because the margin for error is probably wider than with halothane.

Nitrous Oxide

N₂O can cause increases in CBF, CMR, and ICP. At least a portion of the increases in CBF and CMR may be the result of a sympathoadrenal-stimulating effect of N₂O. The magnitude of the effect considerably varies according to the presence or absence of other anesthetic drugs (Fig. 17-15). When N₂O is administered alone, very substantial increases in CBF and ICP can occur. In sharp contrast, when N₂O is administered in combination with intravenous drugs, including barbiturates, benzodiazepines, narcotics, and propofol, its cerebral vasodilating effect is attenuated or even completely inhibited. The addition of N₂O to anesthesia established with a volatile anesthetic will result in moderate increases in CBF.

Nitrous Oxide Administered Alone. The most dramatic reported increases in ICP or CBF in humans and experimental animals have occurred when N₂O was administered alone or with minimal background anesthesia. For instance, Henriksen and Jorgensen recorded ICP before and during spontaneous breathing of 66% N₂O by patients with intracranial tumors. Mean ICP increased from 13 to 40 mm Hg. The increases in CBF observed in humans are more modest than those observed in animals but are still substantial. Whether these substantial increases represent the effects of N₂O, per se, or whether they reflect the nonspecific effects of a second-stage arousal phenomenon is not known.

Nitrous Oxide Administered With Intravenous Anesthetics. When N₂O is administered in conjunction with certain intravenous anesthetics, its CBF effect may be considerably attenuated. Phirman and Shaprio observed that a reproducible increase in ICP that occurred in response to the administration of 70% N₂O to a comatose patient was prevented by the previous administration of a combination of thiopental and diazepam, despite no change in baseline ICP. In an investigation of patients with intracranial tumors and poor intracranial compliance (mean preinduction ICP, 27 mm Hg), 50% N₂O introduced during barbiturate anesthesia and after the induction of hypocapnia had a negligible effect on ICP. Jung and associates compared lumbar CSF pressure in patients with brain tumors during the administration of 0.7% isoflurane or 70% N₂O after the induction of anesthesia with a barbiturate. Lumbar CSF pressure was modestly but significantly greater with N₂O. The fact that the increase was less dramatic than those cited earlier for N₂O alone may reflect the presence of residual barbiturate. Benzodiazepines administered alone have been shown to blunt the CBF response to N₂O in both animals and humans. Narcotics appear to have a similar effect. Jobes and coauthors reported that anesthesia with 1 mg/kg morphine plus 70% N₂O resulted in no change in CBF from awake control values. Because of the very minor effect of morphine on CBF, these data suggest that N₂O did not cause substantial cerebral vasodilation. Although the addition of N₂O to propofol anesthesia in children increased MCA flow velocity, such increases have not been demonstrated by other investigators (also see Chapter 93).

Nitrous Oxide Administered With Volatile Anesthetics. In most investigations, including several in humans, during which N₂O has been added to an anesthetic of 1 MAC or greater, substantial increases in CBF have been recorded. Algottsson and associates examined the effect of an approximately equi-MAC substitution of N₂O for isoflurane. They compared CBF in patients anesthetized with 1.5 MAC isoflurane and 0.75 MAC isoflurane with 65% N₂O. They observed 43% greater CBF with the latter, again consistent with a substantial vasodilating effect of N₂O in the presence of a volatile agent. Similar observations were made by Lam and coauthors and Strebel and colleagues. Several investigations have confirmed that CBF will be less with 1 MAC isoflurane than with a 1 MAC combination achieved with 50% to 65% N₂O and isoflurane.

This vasodilating effect of N₂O may be positively correlated with the concentration of inhaled drug and suggests that, in general, the increase in CBF caused by N₂O is exaggerated at higher concentrations of both halothane and isoflurane. Of importance, however, is the observation of Reinstrup and co-workers, who demonstrated that the administration of 50% N₂O to healthy volunteers did not significantly alter CBV. In support of this observation, Kais and colleagues did not observe any effect of N₂O on CBV when added to a background of 1 MAC sevoflurane anesthesia. Although N₂O can increase CBF, these data indicate that its effect on CBV is modest at best.

![Figure 17-15. Mean percent increases in cerebral blood flow velocity (CBFV) in the middle cerebral artery of normocapnic subjects exposed to 60% nitrous oxide (N₂O) after control recording in three conditions: awake, 1 MAC isoflurane (150 μg·kg⁻¹·min⁻¹), and propofol, 150 μg·kg⁻¹·min⁻¹.](image-url)
**Effects of Nitrous Oxide on Cerebral Metabolic Rate.** No uniform agreement has been reached concerning the effect of N₂O on the CMR. Parallel changes in CBF and CMR,²¹⁴ increases in CBF without alteration of the CMR,¹⁹⁶ and CMR alteration occurring without changes in CBF¹⁴³ have all been reported. These findings are, doubtless, the product of differences in species, methods, depth of background anesthesia, and interactions with simultaneously administered anesthetics. In a recent investigation in humans, the administration of 70% N₂O on a background of either sevoflurane or propofol anesthesia resulted in modest increases in the CMRO₂, thus indicating that N₂O does indeed increase cerebral metabolism.⁶⁸

The CBF response to CO₂ is preserved during the administration of N₂O.¹⁹⁷

**Clinical Implications.** Despite the inconsistencies that are evident, the vasodilatory action of N₂O can be clinically significant in neurosurgical patients with reduced intracranial compliance. However, N₂O-induced cerebral vasodilation may be considerably blunted by the simultaneous administration of intravenous anesthetics. By contrast, the addition of N₂O to a volatile drug–based anesthetic can modestly increase cerebral metabolism and blood flow. N₂O has been widely used in neurosurgery, and banning it is inconsistent with the accumulated experience. Nonetheless, in circumstances wherein ICP is persistently elevated or the surgical field is persistently tight, N₂O should be viewed as a potential contributing factor. Because N₂O rapidly enters a closed gas space, it should be avoided or omitted when a closed intracranial gas space may exist or intravascular air is a concern.

**Muscle Relaxants**

**Nondepolarizing Relaxants**

The only recognized effect of nondepolarizing muscle relaxants on the cerebral vasculature occurs via the release of histamine (also see Chapters 34 and 35). Histamine can result in a reduction in CPP because of the simultaneous increase in ICP (caused by cerebral vasodilation) and a decrease in the MAP.¹⁹⁸ When the BBB is intact, it is not entirely clear whether histamine directly causes cerebral vasodilation or whether it is a secondary (autoregulatory) response to a reduction in the MAP. d-Tubocurarine is the most potent histamine releaser among available muscle relaxants. Metocurine, atracurium, and mivacurium also release histamine in lesser quantities. This effect is likely to be clinically inconsequential unless these muscle relaxants are administered in the large doses necessary to achieve endotracheal intubating conditions rapidly. Of this group of drugs, cisatracurium has the least histamine-releasing effect. No evidence of histamine release was observed after the administration of 0.15 mg/kg (three times the 95% effective dose [ED₉₅] for twitch depression) of cisatracurium to neurosurgical patients in the ICU.¹⁹⁹ Yet, cisatracurium’s slow onset of action makes it not useful for a rapid-sequence induction of anesthesia.

Vecuronium, in relatively large doses of 0.1 to 0.14 mg/kg, had no significant effect on cerebral physiology in patients with brain tumors.²⁰⁰ The other aminosteroids, pipecuronium and rocuronium, should be similarly without direct effect, and no adverse events have been reported.

The indirect actions of relaxants may also have effects on cerebral physiology. Pancuronium given as a large bolus dose can cause an abrupt increase in arterial pressure, which might increase ICP in patients with impaired intracranial compliance and defective autoregulation; however, no significant clinical event has ever been reported. Muscle relaxation may reduce ICP because coughing and straining are prevented, which decreases central venous pressure with a concomitant reduction in cerebral venous outflow impedance.

A metabolite of atracurium, laudanosine, may be epileptogenic. However, although large doses of atracurium caused an EEG arousal pattern in dogs, CBF, CMR, and ICP were unaltered.²⁰¹ In rabbits, the administration of laudanosine did not increase the severity of the epileptoid activity caused by the direct application of a cephalosporin to the cortical surface.²⁰² It appears highly unlikely that epileptogenesis will occur in humans with atracurium.²⁰³

In summary, vecuronium, pipecuronium, rocuronium, atracurium, mivacurium, cisatracurium, metocurine, and pancuronium (if acute MAP increases are prevented with the latter) are all reasonable muscle relaxants for use in patients with or at risk for intracranial hypertension. Doses of metocurine, atracurium, and mivacurium should be limited to ranges not associated with hypotension.

Rocuronium will probably be increasingly used for the induction of anesthesia, as well as for intraoperative relaxation. It has the most rapid onset time of any nondepolarizing muscle relaxant. With sugammadex, even a profound neuromuscular blockade can be rapidly reversed (see Chapters 34 and 35).

**Succinylcholine**

Succinylcholine can produce modest increases (~5 mm Hg) in ICP in lightly anesthetized humans. This effect appears to be the result of cerebral activation (as evidenced by EEG changes and increases in CBF) caused by afferent activity from the muscle spindle apparatus.²⁰⁴ However, a poor correlation between the occurrence of visible muscle fasciculations and an increase in ICP have been noted. As might be expected with what appears to be an arousal phenomenon, deep anesthesia has been observed to prevent succinylcholine-induced increases in ICP in the dog. In humans, the increase in ICP is also blocked by paralysis with vecuronium and by defasciculation with metocurine, 0.03 mg/kg.²⁰⁵ The efficacy of other defasciculating anesthetics has not been examined in humans.

Although succinylcholine can produce increases in ICP, it can still be used for a rapid-sequence induction of anesthesia. Kovarik and coauthors²⁰⁶ observed no change in ICP after the administration of succinylcholine, 1 mg/kg, to 10 nonparalyzed, ventilated neurosurgical patients in the ICU, 6 of whom had sustained a head injury. Their observations are very relevant because it is in precisely this population of patients that the issue of the use of succinylcholine arises most frequently. Considering that the ICP effects of succinylcholine may be an arousal
phenomenon caused by increased afferent traffic from muscle spindles, it is not unreasonable to assume that disease processes that substantially blunt the level of consciousness might similarly blunt this response. As with many anesthetics, the concern should not be whether it is used but how it is used. If administered with proper attention to the control of CO₂ tension, arterial blood pressure, and depth of anesthesia and after defasciculation, then little hazard should attend its use.

### OTHER EFFECTS OF ANESTHETICS ON CEREBRAL PHYSIOLOGY

#### CEREBROSPINAL FLUID DYNAMICS

Approximately 150 mL of CSF is in the adult human, one-half within the cranium and one-half in the spinal CSF space. CSF, which is formed in the choroid plexuses and, to a lesser extent, in the brain’s interstitium with transepidermal diffusion into the ventricular system, is replaced approximately three to four times per day. It functions both as a cushion for the CNS and as an excretory pathway. Anesthetics have been shown to influence both the rate of formation and the rate of reabsorption of CSF. Table 17-3 provides nonquantitative information about the direction of the influences of common anesthetic drugs. All the information has been derived from animals and these processes have not been examined in humans. Of the volatile anesthetics, halothane decreases secretion of CSF, isoflurane has no effect, and enfurane and desflurane increase secretion. Absorption of CSF is reduced by halothane and enfurane, unchanged by desflurane, and increased by isoflurane. Although probably of minimal relevance to clinical practice, a theoretic concern might be in the setting of a prolonged closed-cranium procedure in a patient with poor intracranial compliance. The most deleterious potential combination of effects in a patient with poor intracranial compliance is increased CSF production and decreased reabsorption. This pattern occurs with enfurane in the dog, which is perhaps another reason (in addition to the potential for epileptogenesis in the presence of cerebral injury and hypocapnia) for omission of enfurane in this circumstance.

#### BLOOD-BRAIN BARRIER

In the majority of the body’s capillary beds, fenestrations between endothelial cells are approximately 65 Å in diameter. In the brain, with the exception of the choroid plexus, in the pituitary, and in the area postrema, tight junctions reduce this pore size to approximately 8 Å. As a result, large molecules and most ions are prevented from entering the brain’s interstitium (BBB). A limited number of studies of anesthetic effects on the BBB have been conducted. In experimental animals, 1% isoflurane leads to extravasation of albumin into the thalamus, indicating some compromise of the BBB integrity. At higher doses, isoflurane (3%) significantly increases protein extravasation, not only in the thalamus but also in the cortex. This disruption of the BBB is quantitatively similar to what is achieved by mannitol. In experimental models of brain injury, isoflurane has been reported to both exacerbate and ameliorate edema formation in the injured brain. Whether these effects are the result of isoflurane action at the BBB, per se, or to hemodynamic perturbations attendant with anesthesia is not known. The clinical relevance of the potential BBB modulation by anesthetics is not clear. To the authors’ knowledge, no peer-reviewed investigation has attempted a comparison of anesthetic effects on BBB function during anesthesia in normotensive humans.

### EPILEPTOGENESIS

An extensive review of the convulsant and anticonvulsant effects of anesthetics and adjuvants is available. Several commonly used anesthetics have some epileptogenic potential, particularly in predisposed individuals. A concern is that seizure activity may go unrecognized in an anesthetized and paralyzed patient and may result in neuronal injury if substrate demand (CMR) exceeds supply for a prolonged period. A second concern is that the epileptogenic effect will persist in the postanesthesia period when seizures may occur in less well-controlled circumstances than those that exist in the surgical unit. In practice, it appears that spontaneous seizures during or after anesthesia have been extremely rare events. Nonetheless, in patients with processes that might predispose them to seizures, the use of potentially epileptogenic drugs should be avoided in situations during which reasonable alternatives are available.

#### Volatile Anesthetics

Enflurane is potentially epileptogenic in the clinical setting. Of particular relevance to neuroanesthesia is the observation that hypocapnia potentiates seizure-type discharges during enflurane anesthesia. A 50% decrease in the CMRO₂ was noted in human volunteers anesthetized with 3% enflurane; however, with the onset of seizure activity, the CMRO₂ returned to normal, thus indicating preservation of flow-metabolism coupling. No evidence suggests that this type of EEG activity is deleterious when oxygen delivery is maintained during the event. However, because seizure activity can elevate brain metabolism by as much as 400%, the use of enflurane,

### TABLE 17-3 EFFECTS OF ANESTHETIC AGENTS ON THE RATE OF CSF SECRETION AND ABSORPTION

<table>
<thead>
<tr>
<th></th>
<th>Halothane</th>
<th>Enflurane</th>
<th>Isoflurane</th>
<th>Desflurane</th>
<th>Fentanyl</th>
<th>Etomidate</th>
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<tbody>
<tr>
<td>Secretion</td>
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<td>Absorption</td>
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Upward arrows indicate an increase in the rate of cerebrospinal fluid (CSF) absorption or secretion, and downward arrows indicate a decrease. The information is presented nonquantitatively, and effects may vary with dose.
especially at high doses and with hypocapnia, should probably be avoided in patients predisposed to seizures or those with occlusive cerebrovascular disease.

The EEG-activating property of enflurane has been intraoperatively used to activate and identify seizure foci that are to be surgically resected; and, in this situation, spike activity not preoperatively present has been observed to persist after surgery. In addition, two reports of seizures in the immediate postoperative period after enflurane anesthesia in both predisposed and nonpredisposed individuals have been recounted. No permanent sequelae appeared to occur as a result of these events, and, in fact, this association is not a rigorously proven one. At worst, such occurrences are extremely uncommon.

Isoflurane can cause EEG spiking and myoclonus, but it has not been associated in the experimental setting with the frank epileptoid activity induced by enflurane. The clinical experience with isoflurane is extremely large, and unexplained seizurelike activity has been reported in only two patients. One occurrence was intraoperative, and the other incidence was immediately postoperative. Therefore epileptogenesis does not appear to be a clinical concern with isoflurane. In fact, isoflurane has been successfully used to control EEG seizure activity in refractory status epilepticus.

Seizures occur during the induction of anesthesia with high concentrations of sevoflurane in children, including those without a recognized seizure diathesis. In two healthy humans, EEG burst suppression with 2 MAC sevoflurane was accompanied by epileptiform discharges that were observed during EEG monitoring. These discharges were associated with a significant increase in CBF, thus demonstrating that flow-metabolism coupling was preserved. In patients with temporal lobe epilepsy, the administration of 1.5 MAC sevoflurane elicited widespread paroxysmal EEG activity. Of note was the observation that paroxysmal activity was not restricted to the ictal focus and that the administration of sevoflurane did not provide any assistance in localizing the epileptogenic region of the brain. The development of tonic-clonic movements indicative of seizure activity has also been reported in otherwise healthy patients on emergence from sevoflurane anesthesia. In all of the reported cases of seizure activity attributable to sevoflurane anesthesia, untoward sequelae have not been documented. These reports highlight sevoflurane’s ability, albeit small, to evoke epileptiform activity; accordingly, the use of sevoflurane in patients with epilepsy should be undertaken with appropriate caution.

**Propofol**

Seizures and opisthotonos can occur after propofol anesthesia. However, systematic studies in both humans and animals, although identifying the occurrence of occasional dystonic and choreiform movements, have failed to confirm propofol as a proconvulsant. In fact, propofol appears to be anticonvulsant in mice. Furthermore, ECT seizures were shorter after induction with propofol than after induction with methohexital, which is more consistent with an anticonvulsant effect. In addition, propofol sedation has been widely used during awake resection of seizure foci and other intracranial lesions. Although pronounced high-amplitude beta-frequency activity in the EEG has been observed, unexpected incidences of seizures have not been reported.

**Narcotics**

Seizures or limbic system hypermetabolism (or both) can be readily elicited in some animal species with narcotics. Although an increase in CBF in deep brain...
structures associated with pain processing has been observed in human volunteers. Humans do not have a clinically apparent correlate of the hypermetabolism effect observed in animals. Several anecdotal accounts, unaccompanied by EEG recordings, have reported the occurrence of grand mal convulsions in patients who received both high and low doses of fentanyl. However, systematic investigations of EEG changes during the administration of relatively large doses of fentanyl, sufentanil, and alfentanil in humans have not documented neuroexcitatory activity, and the seizures may have been an exaggerated rigidity phenomenon. There are exceptions. Tempelhoff and coauthors reported partial complex seizures on the induction of anesthesia with fentanyl in patients undergoing anterior temporal lobectomy. Eight of the nine patients displayed electrical seizure activity at a range of clinically relevant fentanyl doses (mean, 26 μg/kg). Another study found that alfentanil, 50 μg/kg, augmented temporal lobe spike activity in patients with temporal lobe epilepsy. Untreated rigidity may, itself, also have important CNS consequences. ICP elevation can occur during narcotic-induced rigidity, probably as a consequence of cerebral venous congestion.

NEONATAL ANESTHETIC NEUROTOXICITY
This subject is discussed in detail in Chapter 93.

CEREBRAL PHYSIOLOGY IN PATHOLOGIC STATES

CEREBRAL ISCHEMIA—PATHOPHYSIOLOGIC CONSIDERATIONS

Critical Cerebral Blood Flow Thresholds
The brain has a high rate of energy utilization and very limited energy storage capacity. The brain is therefore extremely vulnerable in the event of interruption of substrate (e.g., oxygen, glucose) supply. Under normal circumstances, global CBF is maintained at approximately 50 mL/100 g/min. In the face of a declining CBF and therefore oxygen supply, neuronal function deteriorates in a progressive manner rather than in an all-or-none fashion (Fig. 17-16). There is substantial reserve below normal CBF levels, and not until EEG evidence of ischemia begins to appear is CBF decreased to approximately 20 mL/100 g/min. At a CBF level of approximately 15 mL/100 g/min, the cortical EEG is isoelectric. However, only when CBF is reduced to approximately 6 to 10 mL/100 g/min are indications of potentially irreversible membrane failure, such as increased extracellular potassium and a loss of the direct cortical response, rapidly evident. As CBF decreases in the flow range between 15 and 10 mL/100 g/min, a progressive deterioration in energy supply occurs and eventually leads to membrane failure and neuronal death at a time course that may last hours rather than minutes. The brain regions falling within this CBF range (6 to 15 mL/100 g/min) encompass brain tissue in which neuronal dysfunction is temporarily reversible but within which neuronal death will occur if flow is not restored; such regions are referred to as the ischemic penumbra. Studies defining progression to cerebral infarction within the penumbra have been principally performed in the cerebral cortex of primates, and the actual CBF levels at which the various decrements in function occur may vary with both anesthetic and species. However, in humans anesthetized with halothane and N2O, the CBF threshold for the initial EEG change is similar to that observed in the animal investigations.

Models of Cerebral Ischemia
How different is complete cerebral ischemia, as occurs during cardiac arrest, and incomplete cerebral ischemia, as may occur during occlusion of a major cerebral vessel or severe hypotension? From the clinician’s vantage, the important difference is that the residual (i.e., collateral) blood flow during incomplete ischemia may result in enough delivery of oxygen to allow some generation of ATP and thereby stave off the catastrophic irreversible membrane failure that occurs within minutes during normothermic complete cerebral ischemia. This difference in the rate of failure of the energy supply (Fig. 17-17) can result in significantly more apparent tolerance for focal or incomplete ischemia than for complete global ischemia (e.g., cardiac arrest).

Energy Failure and Excitotoxicity
Energy failure is the central event that occurs during cerebral ischemia. ATP is required for the maintenance of the normal membrane ionic gradient, and energy failure is rapidly attended by membrane depolarization and influx of sodium (Na+) and calcium (Ca2+) into the neuron. Voltage-dependent Ca2+ channels are then activated, and Ca2+ gains entry into the cytosol. Depolarization of presynaptic terminals also results in the release of massive quantities of excitatory neurotransmitters, particularly

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**Figure 17-16.** Relationships between cerebral perfusion, cerebral blood flow (CBF), the electroencephalogram (EEG), and the functional status and viability of neurons. Note that in the approximate CBF range of 6 to 12 mL/100 g/min, the energy supply is insufficient to support electrophysiologic activity (i.e., flat EEG) but can prevent complete membrane failure and neuronal death for extended periods. These areas are referred to as the ischemic penumbra. The data are derived from studies on the cerebral cortex of barbiturate-anesthetized baboons and unanesthetized monkeys. The CBF and mean arterial pressure thresholds may vary with anesthetic and species.
glutamate, into the synaptic cleft. Activation of glutamatergic receptors, the NMDAR and the \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid receptors (AMPAR), adds to the influx of Na\(^+\) and Ca\(^{2+}\) (Fig. 17-18). Initiation of cellular signaling by the activation of mGluR leads to the release of stored Ca\(^{2+}\) from the endoplasmic reticulum (ER) via inositol 1,4,5-triphosphate (IP\(_3\)) receptors. Ionic influx is accompanied by an influx of water, and neuronal swelling rapidly occurs after membrane depolarization. The injury that is initiated by excessive mGluR activity is referred to as excitotoxicity.

Ca\(^{2+}\) is a ubiquitous second messenger in cells and is a cofactor required for the activation of a number of enzyme systems. The rapid, uncontrolled increase in cytosolic Ca\(^{2+}\) levels initiates the activation of a number of cellular processes that contribute to injury. Cytoskeletal proteins such as actin are cleaved by activated proteases. These enzymes also degrade a number of the protein constituents of the neuron. Lipases attack cellular lipids and produce membrane damage. An important lipase, phospholipase \( A_2 \), releases fatty acids such as AA from membranes. Metabolism of AA to prostaglandins and leukotrienes by cyclooxygenase and lipoxygenase is accompanied by the generation of superoxide free radicals. The latter, in combination with other free radicals generated in response to mitochondrial injury, can lead to lipid peroxidation and membrane injury. Prostaglandins and leukotrienes also evoke an inflammatory response and are powerful chemotactic drugs. Activation of platelets within cerebral microvessels, as well as an influx of white blood cells into damaged areas, aggravates the ischemic injury by occluding the vasculature.

DNA damage is also an important event during ischemic neuronal injury. Generation of free radicals from AA metabolism, from injured mitochondria, and from the production of peroxynitrite from NO leads to oxidative injury to DNA. Activation of endonucleases also produces DNA strand breaks. Under normal circumstances, DNA injury results in the activation of poly–adenosine diphosphate [ADP]–ribose polymerase (PARP), an enzyme that participates in DNA repair. With excessive DNA injury,
PARP activity dramatically increases, which can lead to the depletion of nicotinamide adenine dinucleotide (NAD\(^+\)), a substrate of PARP. NAD\(^+\) is also an important coenzyme in energy metabolism, and its depletion further exacerbates energy failure.

Lactate formation is an additional element of the pathophysiologic process. Lactic acid is formed as a result of the anaerobic glycolysis that takes place after failure of the supply of oxygen. The associated decline in pH contributes to the deterioration of the intracellular environment. An increased preschismic serum glucose level may accelerate this process by providing additional substrate for anaerobic glycolysis.

NO, which has emerged as a probable mediator of CBF changes in many normal physiologic states (see the preceding section, “Cerebral Metabolic Rate”), is also of relevance to pathophysiologic ischemia. NO is, in fact, a weak free radical that in turn leads to the generation of a more reactive species (peroxynitrite), and it is the \textit{killer substance} used by macrophages. In cerebral ischemia, NO is probably both friend and foe. During a period of focal ischemia, the vasodilating effect of NO (probably constitutively elaborated NO of endothelial origin) likely serves to augment collateral CBF. However, in the postischemic phase, NO (probably derived from neurons or macrophages) contributes to neuronal injury.

Collectively, the simultaneous and unregulated activation of a number of cellular pathways overwhelms the reparative and restorative processes within the neuron and ultimately leads to neuronal death.

**Nature of Neuronal Death**

Neuronal death that occurs in response to these processes has been categorized as necrotic or apoptotic in nature. Necrotic death of neurons, mediated by excitotoxic injury, is characterized by rapid cellular swelling, condensation and pyknosis of the nucleus, and swelling of the mitochondria and ER. A characteristic of these necrotic neurons is the presence of acidophilic cytoplasm. \(^{261}\) Necrotic neuronal death results in local infiltration of the brain by inflammatory cells. A consequence of this inflammation is a considerable amount of collateral damage.

Neuronal apoptosis, a form of \textit{cellular suicide}, has also been demonstrated in a variety of models of cerebral ischemia. Apoptosis is characterized by chromatin condensation, involution of the cell membrane, swelling of mitochondria, and cellular shrinkage. In the later stages of apoptosis, neurons fragment into several apoptotic bodies, which are then cleared from the brain. \(^{261}\) The lack of a substantial inflammatory response to apoptotic death limits injury to surrounding neurons that have survived the initial ischemic insult.

A number of biochemical pathways that lead to apoptosis have been described. Initiation of apoptosis by the release of cytochrome \(c\) from injured mitochondria has been studied the most (Fig. 17-19). Cytochrome \(c\) is restricted from the cytoplasm by the outer mitochondrial membrane. \(^{262}\) When mitochondria are injured, pores within the outer membrane allow cytochrome \(c\) to be released into the cytoplasm, where it interacts with procaspase-9 and apoptosis-activating factor (APAF) to produce an apoptosome. Procaspase-9 undergoes activation by proteolytic cleavage. Activated caspase-9 then activates caspase-3. The latter serves as an executor of apoptosis by cleaving a number of protein substrates that are essential in DNA repair (such as PARP). Activation of caspase-3 can also occur by inflammatory signaling via tumor necrosis factor alpha (TNF-\(\alpha\)) and the activation of caspase-8. \(^{263}\) It should be noted that the neuronal injury that occurs in response to ischemia cannot be easily divided into necrosis or apoptosis. The nature of neuronal death probably encompasses a spectrum in which some neurons undergo necrosis or apoptosis whereas others undergo cell death that has features of both necrosis and apoptosis.

**Timing of Neuronal Death**

The traditional concept of ischemic injury was that neuronal death was restricted to the time of ischemia and during the early reperfusion period. However, more recent data indicate that postischemic neuronal injury is a dynamic process during which neurons continue to die for a long period after the initiating ischemic insult (Fig. 17-20). \(^{264}\) This delayed neuronal death, which was
first demonstrated in models of global cerebral ischemia, has been demonstrated during focal ischemia as well. The extent of delayed neuronal death depends on the severity of the ischemic insult. With severe ischemia, most neurons undergo rapid death. With more moderate insults, neurons that survive the initial insult undergo delayed death. This ongoing neuronal loss contributes to the gradual expansion of cerebral infarction after focal ischemia. In experimental studies, evidence of cerebral inflammation, which can theoretically contribute to further injury, has been demonstrated even 6 to 8 months after the primary ischemia.

The occurrence of delayed neuronal death has important implications for the evaluation of studies in which neuroprotective strategies are being investigated. A wide variety of interventions have shown neuroprotective efficacy in studies in which the extent of injury is evaluated within 3 to 4 days after ischemia. However, this neuroprotective efficacy may not be sustained. Recent data indicate that cerebral infarction undergoes gradual expansion and that a reduction in injury attributed to a particular therapeutic intervention is no longer apparent when the injury is evaluated after a long postischemic recovery period. Long-term (>1 month) evaluation of the efficacy of a particular intervention is therefore important.

Much of the literature on the pathophysiologic process of cerebral ischemia has primarily been focused on neuronal injury. However, recent work has highlighted the importance of the contribution of astrocytes, microglia, vascular cells (e.g., endothelium, smooth muscle cells, pericytes), basement membranes, and extracellular matrix to stroke. These individual components in aggregate form the neurovascular unit. A detailed understanding of the contribution of each component of the neurovascular unit is a prerequisite, not only for the protection of the brain against ischemic and traumatic injury, but also for therapeutic approaches for the regeneration of the CNS.

**BRAIN PROTECTION**

The literature on cerebral ischemia and brain protection is vast, and a detailed discourse on this topic is beyond the scope of the present discussion. A number of excellent recent reviews on the subject are available.

**Considerations Relevant to Complete Global Ischemia (Cardiac Arrest)**

Maintaining adequate perfusion pressure after cardiac arrest is of considerable importance. Hypotension developing after resuscitation from cardiac arrest may aggravate the microcirculatory and vasospastic processes occurring at this time and may increase brain damage. A late phase of intracranial hypertension may occur and is due to the development of extensive cerebral edema (probably both vasogenic and cytotoxic edema) associated with brain necrosis. Attempts to control this type of intracranial hypertension with osmotherapy usually fail. ICP monitoring is not generally used because the patients in whom these delayed increases in ICP develop have sustained massive tissue damage.

Both barbiturates and calcium channel blockers have been administered after cardiac arrest. The former are
ineffective.274 In a small cohort (51 patients) of patients after cardiac arrest, nimodipine was shown to improve CBF but not neurologic outcome.275 In a second trial with approximately 150 patients after cardiac arrest, no overall benefit in neurologic outcome was observed.276 However, a subset of patients in whom the initiation of advanced life support was delayed for longer than 10 minutes demonstrated improved survival. This single study cannot serve as justification for the administration of nimodipine after cardiac arrest, especially in the face of the unequivocally negative results of the multicenter lidoflazine cardiac arrest study.277 Once again, the important therapeutic objectives are the maintenance of normocapnia and normotension, normalization of systemic pH, avoidance of hyperthermia, and prevention and treatment of seizures.

Induced mild hypothermia is effective in reducing mortality and morbidity in patients who sustain a cardiac arrest that is followed by altered mental status with mortality and morbidity in patients who sustain a car-

hyperthermia, and prevention and treatment of seizures.

Before discussing individual anesthetics, it should be noted that anesthesia, per se, is protective. For undefined reasons, reducing the level of systemic stress associated with a standardized experimental insult results in an improved outcome.281,282 In reviewing the protection-by-anesthetics literature, readers should be conscious of the possibility that the protective benefit ascribed to an intervention with an anesthetic drug may, in fact, be the product of exaggeration of the injury in a high-stress control state, such as N2O sedation.

**Barbiturates.** Numerous demonstrations have revealed the protective efficacy of barbiturates in focal cerebral ischemia in animals,283-285 and a single demonstration confirmed the effectiveness in a human.286 The effect has been principally attributed to suppression of the CMR. However, the effects of CBF redistribution and free radical scavenging287 have been suggested to contribute, and evidence indicates that CMR suppression is not the sole mechanism.288 Suppression of the CMR might logically be expected to be of benefit to brain regions in which oxygen delivery is inadequate to meet normal demands but is sufficient to allow energy consumption by some ongoing electrophysiologic activity (i.e., in which the EEG was abnormal but not flat). Such regions are likely to be limited in size in the setting of focal ischemia, yet several of the animal investigations suggest a very substantial protective effect.283,284 Review of these experiments reveals that the methods used to monitor and maintain temperature, although accepted at the time, were below the standards that have evolved from a more recent understanding of the effects of both deliberate289,290 and inadvertent hypothermia. Unrecognized cerebral hypothermia may well have been a factor in some of the cited investigations, and it is therefore possible that the protective efficacy of barbiturates may have been overestimated. Although more recent publications involving suitable temperature control methods do, in fact, indicate a protective effect of barbiturates,289,291,292 the magnitude of that effect was modest when compared with the results of earlier studies. Barbiturate-induced EEG suppression in an already anesthetized patient may still be logical therapy when it can be applied before or early in the course of a period of temporary focal ischemia (e.g., temporary occlusion during aneurysm surgery). However, the decision to institute such therapy should be made only after considering the risk of the occlusive event, the patient’s cardiovascular status, and the physician’s willingness to accept the possibility of delayed emergence, together with an objective view of the probable magnitude of the protective effect.

Numerous investigations in animals and humans have failed to demonstrate any protective effect of barbiturates in the setting of global cerebral ischemia (e.g., cardiac arrest).274

Because CMR suppression has been the presumed mechanism of effect, barbiturates have traditionally been administered to produce maximal reduction of the CMR (which is nearly complete when EEG burst suppression has been achieved). However, data presented by Warner and colleagues288 demonstrated that the same protective benefit (expressed as a reduction of infarct volume) could be achieved with a third of the burst-suppression dose, which raises a clinically important issue. The various barbiturates (e.g., thiopental, thiamylal, methohexital, pentobarbital) have similar effects on the CMR and have generally been assumed to have equal protective efficacy. However, if the mechanism of protection is a pharmacologic effect other than a reduction in the CMR, then is it reasonable to assume equivalence among the barbiturates? Recent data suggest that the neuroprotective efficacy of barbiturates is not similar. In a direct comparison of three clinically used barbiturates, methohexital and thiopental, but not pentobarbital, reduced injury in an animal model of focal ischemia.293 These data suggest that mechanisms other than or at least in addition to metabolic suppression may contribute to the protective effect of barbiturates.

**Volatile Anesthetics.** Isoflurane is also a potent suppressant of the CMR in the cerebral cortex, and EEG evidence suggestive of a protective effect in humans has been reported.254 In comparison with the awake
or N₂O-fentanyl–anesthetized state, isoflurane is neuroprotective in models of hemispheric, focal, and nearly complete ischemia. Of interest is the recent observation that isoflurane’s neuroprotective efficacy is not sustained. When injury is evaluated 2 days after ischemia, a robust reduction in injury is observed with isoflurane anesthesia. However, by 14 days this reduction in injury was not apparent. These data indicate that neuronal injury continues well into the posts ischemic recovery period and that the neuroprotective benefit that is evident shortly after ischemia may not persist for the long term. More recent data have shown that isoflurane treatment can improve neuronal survival when the severity of ischemia is limited and the restoration of blood flow after ischemia is complete. The neuroprotective effect of isoflurane is not substantially different from that of other volatile anesthetics. Sevoflurane reduces ischemic injury in animal models of focal and hemispheric ischemia; its efficacy is not different from that of halothane. Desflurane also reduces neuronal injury to the same extent that isoflurane does. The available data therefore suggest that adequate anesthesia, per se, may have a protective effect versus the awake state, but there does not appear to be any difference in neuroprotective efficacy among the volatile anesthetics.

XENON. The inert gas xenon exerts its anesthetic action by noncompetitive blockade of NMDAR. As such, it is logical to suspect that it might provide neuroprotection against excitotoxic injury. The neuroprotective efficacy of xenon has been demonstrated against oxygen-glucose deprivation in vitro, focal ischemia in vivo in mice, and cardiopulmonary bypass–induced cognitive dysfunction in rats. Of interest are observations that simultaneous administration of subanesthetic doses of xenon in combination with either hypothermia or isoflurane significantly reduces neuronal injury and improves neurologic function in a neonatal rodent model of hypoxia-ischemia; this protective effect was apparent as late as 30 days after injury. Moreover, the administration of xenon has been shown to have a preconditioning effect on the brain, previous exposure reduces the vulnerability of the brain to ischemic injury. Anesthetic drugs that have activity at NMDAR (ketamine) and γ-aminobutyric acid A (GABA₅) receptors (e.g., volatile anesthetics, barbiturates, benzodiazepines, propofol) have been shown to cause neuronal injury in rodent neonatal pups during the critical period of synaptogenesis. Although xenon has antagonist activity at NMDAR, the evidence to date suggests that it does not lead to apoptosis in the developing brain. Note should be made, however, that long-term neuroprotection with xenon has not yet been demonstrated in experimental adult subjects. The specific use of xenon for the purpose of neuroprotection awaits results from outcome studies in humans.

PROPOFOL. EEG suppression can also be achieved with clinically feasible doses of propofol. Anecdotal information suggests that it is being used to provide protection during both aneurysm surgery and CEA. In experimental models of cerebral ischemia, the extent of neurologic injury in propofol-anesthetized animals was similar to that in halothane-anesthetized animals. Given the previous demonstration that halothane can reduce injury, these data provide indirect evidence of propofol’s neuroprotective efficacy. In a more recent investigation, cerebral infarction was significantly reduced in propofol-anesthetized animals in comparison with awake animals. Direct comparison of propofol to pentobarbital has also demonstrated that cerebral injury after focal ischemia is similar in animals anesthetized with the two drugs. Similar to the situation with volatile anesthetics, initial investigations revealed that propofol protection is not sustained. Durable protection with propofol is achievable if the severity of the ischemic insult is mild. Collectively, these data are consistent with the premise that propofol can reduce ischemic cerebral injury.

ETOMIDATE. Etomidate was proposed as a potential protective anesthetic in the setting of aneurysm surgery. It, too, produces CMR suppression to an extent equivalent to barbiturates, and, similar to the barbiturates, etomidate is an agonist at the (inhibitory) GABA₅ receptor. To the contrary, in an experimental model of focal ischemia, the volume of injury was not reduced by etomidate relative to a 1.2 MAC halothane-anesthetized control group. In fact, the volume of injury with etomidate was significantly larger than that in the control group. In patients subjected to temporary intracranial vessel occlusion, the administration of etomidate results in greater tissue hypoxia and acidosis than does equivalent desflurane anesthesia. The aggravation of injury produced by etomidate (an imidazole) may be related to direct binding of NO as a consequence of etomidate-induced hemolysis combined with direct inhibition of the NO synthase enzyme by etomidate. Therefore no scientific studies support the current use of etomidate for cerebral protection.

CALCIUM CHANNEL ANTAGONISTS. Orally administering nimodipine (the intravenous preparation is not approved for clinical use in North America) for 21 days beginning as soon as possible after subarachnoid hemorrhage (SAH) is now established clinical practice. Other calcium channel blockers have reduced vasospasm after SAH but have not improved patient outcome, suggesting that nimodipine’s benefit is a cellular rather than a vascular effect. However, routinely administering nimodipine or any other calcium channel blocker after neurologic stroke that has occurred in the surgical unit or in any other environment has not yet become standard practice. Despite favorable results in small trials, not all investigations of those who sustain stroke have confirmed the benefits of nimodipine.

OTHER ANESTHETICS. A remarkable number of anesthetics have shown neuroprotective efficacy in animal studies. However, to date, large-scale randomized trials of a variety of anesthetics in patients with stroke have not demonstrated neuroprotection for any drug. With the exception of tissue plasminogen activator (tPA) for thrombolysis and the calcium channel blockers nimodipine and nicardipine for the management of SAH, pharmacologic neuroprotective anesthetics are not available for the treatment of ischemic stroke.
of patients with cerebral ischemia. Details about drugs that have undergone clinical trials and those that are currently being investigated in humans can be found at the Stroke Trials Registry (www.strokecenter.org/trials/TrialDetail.aspx?tid=338) of Washington University in St. Louis.

Cerebral Ischemia: Influence of Physiologic Variables

Cerebral Perfusion Pressure. Measures designed to augment CBF (an important determinant of energy supply) are also important. In the ischemic penumbra (described in the section, “Critical Cerebral Blood Flow Thresholds”), small improvements in CBF have the potential to prolong neuronal survival substantially. Maintenance of high-normal CPP can augment collateral perfusion pressure and maintain CBF and has been shown to result in improvement in various neurophysiologic parameters, including neurologic function. By contrast, hypotension can reduce CBF and exacerbate injury. In trials of nimodipine in patients with acute stroke, a reduction in blood pressure of 10% to 20% increased the probability of an adverse outcome (either death or dependency) four-fold, thus emphasizing the adverse impact of blood pressure reduction on an injured brain. Therefore in patients with cerebral ischemia, hypotension should be promptly treated and normotension restored. Although the target MAP should obviously be based on knowledge of a patient’s preexisting blood pressure, data to provide specific guidelines are insufficient in humans. In the majority of patients, maintenance of the MAP in the 70 to 80 mm Hg range should be adequate. The available data provide support for reducing blood pressure to less than 180/105 mm Hg in patients with stroke who have been treated with tPA in the hope of reducing the incidence of hemorrhage into the ischemic brain. In addition, blood pressure augmentation to a systolic pressure of 180 to 220 mm Hg in patients with SAH-induced vasospasm and to a CPP greater than 60 mm Hg in patients with traumatic brain injury is reasonable. Note, however, that augmentation of CPP in the high-normal range carries the inadequately explored risks of increased edema and hemorrhagic infarction if used as support during more than brief periods of ischemia, particularly when several hours has elapsed since the onset of ischemia.

Carbon Dioxide Tension. Hypercapnia has the potential to cause intracerebral steal and may worsen intracellular pH. Despite some support for the occurrence of a favorable so-called Robin Hood or inverse steal, hypocapnia has not generally proved effective in either laboratory or clinical settings. Pending further information and in the absence of a means of verifying the perfusion response to the manipulation of PaCO2, normocapnia remains standard practice.

Temperature. Hypothermia is the principal cerebral protective technique for circulatory arrest procedures (also see Chapter 54). It unequivocally enhances cerebral tolerance for episodes of ischemia. For deep hypothermia, this effect is largely a function of the reduction in the CMR. Although barbiturates reduce only the component of the CMR associated with electrophysiologic work (approximately 60% of the CMRO2 in the awake state), hypothermia causes a reduction in both electrophysiologic energy consumption and energy utilization related to the maintenance of cellular integrity; mild hypothermia may preferentially suppress the latter. A substantial number of laboratory studies have demonstrated that mild degrees of hypothermia (2°C to 4°C) during an episode of ischemia can confer substantial protection as histologically measured. In addition, evidence from animal studies suggests that hypothermia initiated in the immediate postischemic period confers a protective benefit.

In light of this dramatic protective effect of mild hypothermia in the laboratory, its use in the surgical setting may be advocated. Proponents of its use argue that hypothermia is readily achieved and not accompanied by significant myocardial depression or arrhythmias. In addition, the patient can be easily rewarmed in the surgical unit after the risk of ischemia has subsided. Results of a pilot study clearly demonstrated a trend toward improved neurologic outcome in hypothermic patients undergoing intracranial aneurysm clipping. Unfortunately, the subsequent definitive trial did not demonstrate any improvement in outcome that could be attributable to hypothermia. However, it should be noted that the majority of the patients in that study had SAH of grades I, II, and III. In addition, the number of patients who had temporary clips applied in excess of 20 minutes was quite small (five to six patients). Consequently, an argument has been made that mild hypothermia may well be of benefit in patients with high-grade aneurysms or in those in whom the complexity of the aneurysm clipping is such that prolonged temporary clipping may be required. Considering that temperature reduction takes time, the decision to induce hypothermia must be made in advance. Therefore the therapeutic use of hypothermia may be considered in such high-risk patients.

The application of mild hypothermia after head injury reduced ICP and improved neurologic outcome in pilot trials. Of note is the finding that complications attributable to hypothermia were not observed. A subsequent multcenter trial of hypothermia in patients with head injuries, however, failed to confirm the findings of the pilot studies. Induction of mild hypothermia did not improve long-term neurologic outcome. Note should be made, however, of the post hoc finding that the outcomes in patients younger than 45 years of age who were initially hypothermic were worse if these patients were rewarmed; these data suggest that such patients should be rewarmed over a prolonged period.

A number of clinical trials of induced hypothermia in a limited number of patients with stroke have been conducted. To date, these trials have demonstrated the feasibility of inducing hypothermia in the range of 33°C to 35°C, even in patients who are not subjected to endotracheal intubation and mechanical ventilation. Hypothermia was associated with improved ICP and CPP. However, complications, particularly thrombocytopenia, bradycardia, ventricular ectopy, hypotension, and infection, are frequent. In addition, an intractable increase in ICP can occur during rewarming, even if the elevation in temperature is gradual and accomplished over a period of
several hours. These side effects attest to the need to conduct randomized trials to evaluate properly the efficacy of mild hypothermia in patients with stroke. Such trials are currently under way.

Data regarding the application of mild hypothermia in survivors of cardiac arrest are more positive. Two recent trials have demonstrated that the induction of hypothermia (32° C to 34° C) after successful resuscitation from cardiac arrest resulted in a significantly better neurologic outcome 6 months after the arrest.278,339 These studies demonstrate the clinical efficacy of hypothermia for the purposes of reducing ischemic cerebral injury and to provide support for the use of intraoperative hypothermia in patients who are considered to be at high risk.

By contrast, increases in brain temperature during and after ischemia aggravate injury.340 An increase of as little as 1° C can dramatically increase injury. Ischemia that normally results in scattered neuronal necrosis produces cerebral infarction when body temperature is elevated. Therefore avoiding hyperthermia in patients who have suffered an ischemic insult or in those who are at risk for cerebral ischemia seems prudent. In the surgical setting, hyperthermia is seldom a problem (witness the authors’ efforts to prevent hypothermia). One situation in which body temperature is often allowed to increase is during rewarming after hypothermic cardiopulmonary bypass. In this situation, hyperthermia (core body temperature in excess of 38° C) is not uncommon. The suggestion that increases in temperature in excess of 37° C to 38° C are detrimental is some merit, considering the recent information regarding the deleterious effect of hyperthermia.

Glucose. Withholding glucose-containing solutions in situations during which cerebral ischemia may occur is now an established practice. The practice is based on numerous demonstrations in animal models of brain and spinal cord ischemia that elevation of plasma glucose before episodes of either complete or incomplete ischemia results in aggravation of neurologic injury. However, it should be noted that the majority of investigations involved adult animals and that certainty concerning the adverse effects of hyperglycemia in immature subjects, such as neonates, is less.341 Furthermore, it should be noted that only some342,343 and not all344 of the investigations in humans have provided confirmation of an independent effect of serum glucose on neurologic outcome. Nonetheless, in long-term outcome studies, diabetic and nondiabetic hyperglycemia has been shown to be an independent predictor of poor outcome.345 In the National Institutes of Health–sponsored recombinant tPA stroke trial, hyperglycemia was associated with significantly lower odds for desirable clinical outcomes and a higher incidence of intracranial hemorrhage.346 These data prompted a randomized clinical trial of the efficacy of insulin administration to patients with acute stroke. Although the trial was underpowered, the results showed that the administration of insulin to control blood glucose levels in patients with stroke did not improve outcome 3 months after stroke.346 A recurrent theme in the discussion of these studies is that glucose elevation may be the result of the stress associated with a severe insult, either ischemic or traumatic, rather than its cause. In addition, the inevitable questions of whether and how quickly immediate prerisk treatment of an elevated plasma glucose level with insulin reduces risk to normoglycemic levels have not been thoroughly examined. It is the opinion of the authors that, at this juncture, acute insulin administration (with its attendant risk of hypoglycemia) in patients with modest glucose elevation (~150 mg/dL) in the surgical setting is not yet justified.

By contrast, hypoglycemia is also associated with cerebral injury. With a gradual reduction in blood glucose values to approximately 40 mg/dL, a shift in EEG frequencies occurs from alpha and beta toward delta and theta.347 Below a blood glucose level of 20 mg/dL, suppression of the EEG (flat) is observed. Persistence of this level of hypoglycemia results in seizure activity and neuronal injury, particularly to the hippocampus.

Seizures. Normalization of systemic pH, prevention and treatment of seizures, which dramatically increase the CMR, and control of the ICP and CPP are all important elements of brain protection and resuscitation, although mundane and lacking in appeal of the pharmacologic silver bullet.

Intravascular Volume and Hematocrit Manipulation. Although hemodilution has not proved effective in studies of human stroke, both laboratory and human data support the practice; hemodilution is an established part of the management of ischemia associated with vasospasm. However, the data do not currently justify routine hemodilution (a hematocrit of 30% to 35% is the theoretic optimum) in patients in whom focal ischemia might occur in the surgical unit.348 On the other hand, the potentially deleterious effects of hemocoencentration should help further suppress the out-of-date notion that neurosurgical patients should be run dry. An increased hematocrit, because of viscosity effects, reduces CBF.10 In anticipation of a procedure wherein incomplete ischemia might occur, such as CEA, a hematocrit in excess of 55% should be considered for decrease by preoperative phlebotomy.

Summary of Anesthetics and Neuroprotection

In comparison to the awake or lightly sedated state, the vulnerability of the brain to ischemic injury is reduced under anesthesia. Volatile anesthetics, barbiturates, propofol, xenon, and ketamine reduce injury in experimental models and may reduce injury in comparison with a pure N2O-narcotic anesthetic. However, direct comparison has not demonstrated the superiority of any one anesthetic (or combination of anesthetics) over another. Therefore, based on the available data, the use of a specific anesthetic or anesthetic regimen for the purpose of brain protection in the clinical setting cannot be recommended. There is a paucity of information about anesthetic neuroprotection in humans and the lack of clinical trials is understandable, considering the low frequency of stroke and ischemic injury in the perioperative setting. There are, however, a few clinical investigations from which inferences about anesthetic neuroprotection can be made. In the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST), a subset of patients received...
supplemental doses of thiopental, etomidate, or propofol for the purposes of neuroprotection. The neurologic outcome in these patients was no different than those who did not receive these anesthetics.349 In the general anesthesia versus local anesthesia trial,350 patients undergoing CEA were randomized to receive either general anesthesia or local anesthesia (also see Chapter 70); in the latter group, patients were lightly sedated but were arousable during surgery. The outcome between the two groups was not different, indicating that the general anesthetic state did not provide any protective benefit.350 Finally, in a recent retrospective trial of thrombolysis for acute stroke, patients who were anesthetized had a worse outcome than those who were only mildly sedated. Although the worse outcome with general anesthesia was attributed to a lower CPP in that group,351 the results do not provide evidence of anesthetic neuroprotection. In aggregate, these data suggest that supplemental drugs that produce burst suppression of the EEG do not provide protection in anesthetized patients and that the state of general anesthesia does not improve neurologic outcome.

The neuroprotective efficacy of anesthetic drugs in experimental studies is achieved only by strict attention to the maintenance of physiologic homeostasis; in fact, the potential for exacerbation of cerebral injury, either traumatic or ischemic, with physiologic mismanagement is significantly more likely than the modest protection afforded by pharmacologic drugs—these are important observations. Accordingly, with respect to brain protection, efforts should be focused on the maintenance of physiologic parameters (e.g., perfusion pressure, oxygenation, normocapnia, temperature management, control of hyperglycemia, seizure prophylaxis) within the appropriate ranges and less on pharmacologic or anesthetic drugs to reduce cerebral injury.

Deferring Elective Procedures After Stroke

The risk of extension of cerebral infarction in the event of subsequent anesthesia and surgery has not been systematically studied. In patients who have suffered a stroke, CBF undergoes significant changes. Areas of both high and low CBF occur, and stabilization of regional CBF and CMR is apparent after approximately 2 weeks.352 Loss of normal vasomotor responses (e.g., CO₂ responsiveness, autoregulation) in the early postinsult period is very common,353-355 and these changes persist beyond 2 weeks in a small percentage of patients with stroke.354,355 BBB abnormalities, as reflected by the accumulation of CT contrast material or brain scan isotopes, are still present 4 weeks after the insult,356 and the histologic resolution of large infarcts is not complete for several months. Early CEA after stroke in patients with large strokes and neurologic disability was accompanied by an increased risk of intracerebral hemorrhage.357 Based on early CEA experience, deferring CEA for 4 to 6 weeks after stroke is recommended.357 A 6-week delay should give some assurance of the probable recovery of autoregulation, CO₂ responsiveness, and BBB integrity.

A delay in CEA after stroke, however, poses risks. In patients who have sustained a stroke, the incidence of a second stroke is approximately 12%.358 The risk of a complete carotid occlusion is considerable with delayed surgery. In addition, early CEA can restore cerebral perfusion to the ischemic penumbra, possibly improving long-term functional recovery.359 However, the size and location of the infarction should be weighed. A small infarction in silent cortex may offer wider latitudes than a large lesion that has resulted in a paresis that is still resolving. A small prospective study suggests that in patients with nondisabling stroke, early CEA can be safely performed within 2 weeks of the stroke.360 Candidates for early CEA after stroke may include patients with relatively small cerebral infarctions, resolution (either complete or near complete) of neurologic symptoms, and ipsilateral carotid artery stenosis.361 Delaying CEA in patients who have had large strokes with significant neurologic disability, reduced level of consciousness, and displaying a midline shift on the CT scan is generally preferable.

Outcome data to inform the decision about surgery for the patient after stroke, other than CEA, is lacking. With the extrapolation of the information from the CEA studies, pending other information, deferring elective surgery for at least 4 weeks after a cerebral vascular accident and preferably for 6 weeks from the point at which a stable postinsult neurologic state has been achieved seems reasonable.

CHRONIC ARTERIAL HYPERTENSION

A recurrent concern is that of acceptable levels of arterial blood pressure reduction in patients who are chronically hypertensive. Firm guidelines have not been established. However, from the vantage of cerebral well-being, limiting elective MAP reduction to 30% to 35% of resting mean levels seems appropriate for both hypertensive and normotensive patients. The same guidelines might apply in both populations because in chronic hypertension, both the lower and upper limits of autoregulation are shifted to the right with apparently little distortion.362 The rationale for a limit of 30% to 35% is as follows. MAP reductions of 50% in nonanesthetized patients, both normotensive and hypertensive, will commonly produce reversible symptoms of cerebral hypoperfusion.362-364 Although even greater reductions will probably be tolerated provided that exposures are brief, the hematocrit is reasonable, and the cerebral vasculature is patent, the authors counsel against it. A reduction in the MAP of this magnitude will significantly increase the probability of CPP being close to or below the LLA, thereby reducing cerebrovascular reserve. It has been demonstrated that a 25% reduction in the MAP will bring both normotensive and hypertensive patients to the LLA.363 As the reduction in the MAP exceeds 25% of baseline, CBF values will be below normal, albeit in patients free of occlusive vascular disease, above the threshold for neurophysiologic dysfunction or injury (see Fig. 17-6). However, physiologic reserve is being encroached upon, thereby leaving little margin for error or for other causes of impaired cerebral oxygen delivery such as low hematocrit or unrecognized cerebrovascular disease.

In animals, treatment of chronic hypertension can restore the LLA to normal.365,366 A similar phenomenon has been observed in humans by Strandgaard, although restoration was incomplete and had failed to occur after...
as long as 12 months of treatment in some patients. It is an unexplored possibility that the extent of restoration of the LLA with antihypertensive therapy is agent dependent. Some may restore the LLA more effectively than others. In particular, ACE inhibitors have been shown to decrease the LLA acutely in both normotensive and hypertensive subjects.

**Intracranial Hypertension**

Control of intracranial hypertension is discussed in detail in Chapter 70.

**BRAIN TUMORS**

There are few data regarding the physiologic function of intracranial tumors. Arbit and colleagues measured CBF in cerebral tumors with laser Doppler technology. In general, they found that tumors had lower CBF than the normal brain. Autoregulation was occasionally apparent. Vascular responsiveness to changes in Pao2 and PacO2 are generally preserved in patients with gliomas. However, in some circumstances, hyperventilation can at times be associated with paradoxical increases in MCA flow velocity ipsilateral to the tumor. Measurement of regional CBF in the area of the tumor might also be a useful predictor of the grade of intracranial gliomas; both regional CBF and regional CBV are greater with high-grade gliomas. Considerable edema is often associated with intracranial tumors, and the radiologic extent of the edema, which presumably represents the extent of abnormal vessel leakiness, correlates with the severity of the elevation in ICP that occurs in association with intubation-related hypertension. Edema formation in the peritumoral region can be characterized as vasogenic with leakage of plasma proteins from the vascular space, hydrocephalic secondary to obstruction of CSF flow, or static as a result of venous obstruction by tumor. Although the precise mechanisms by which edema formation occurs are not clear, the loss of integrity of the tight junctions of components of the BBB, an increased permeability induced by vascular endothelial growth factor expressed by tumors, and an increased expression of leukotriene C4 in peritumoral fluid probably play a role. Osmotherapy with mannitol will affect a reduction in edema; it causes a reduction in edema formation with little effect on edema reabsorption, a reduction in permeability of the BBB that can be recognized as rapidly as 1 hour after administration and a modest reduction in tumor size. See Chapter 70 for a complete discussion.

**COMA AND EPILEPSY**

Regardless of its cause, coma reduces brain metabolism. In the case of lesions occurring in the reticular activating system, the reduction in the CMR probably represents a normal physiologic adjustment to reduced functional activity. During generalized seizure activity, CMR and CBF may dramatically increase. The intensive motor and brain activity associated with generalized seizures leads to the development of systemic and cerebral acidosis, often accompanied by a reduction in arterial oxygenation, an increase in PacO2, and peripheral lactic acidosis. If generalized seizure activity continues unabated, then arterial hypotension ensues. With muscular relaxation and measures ensuring adequate oxygenation and ventilation, the systemic acidosis and hypotension can be avoided and the severity of the cerebral acidosis diminished. During relatively brief episodes of continuous seizures, the brain seems able to meet the high metabolic demands. However, even with effective ventilation and maintenance of perfusion pressure, when seizures continue for a prolonged period, they can lead to the development of irreversible neuronal damage. Therapy aimed at interrupting the seizure and restoring a normal balance between cerebral metabolic demand and blood flow is indicated. Barbiturates, benzodiazepines, or other potent anticonvulsants are appropriate. Adequate relaxants must be viewed as purely symptomatic therapy because they do not alter the abnormal cerebral electrical activity.

The potentially injurious nature of seizures justifies attention to prevention. Practices vary. However, patients who have sustained a severe head injury or SAH and any patient on whom a substantial cortical incision is planned are at risk, and prophylactic anticonvulsants should be considered.

**Complete references available online at expertconsult.com**

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PART II: Anesthetic Physiology

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