CHAPTER

26

Neurophysiology & Anesthesia

KEY CONCEPTS

1. Cerebral perfusion pressure is the difference between mean arterial pressure and intracranial pressure (or central venous pressure, whichever is greater).
2. The cerebral autoregulation curve is shifted to the right in patients with chronic arterial hypertension.
3. The most important extrinsic influences on cerebral blood flow (CBF) are respiratory gas tensions—particularly $Paco_2$. CBF is directly proportionate to $Paco_2$ between tensions of 20 and 80 mg Hg. Blood flow changes approximately 1–2 mL/100 g/min per mm Hg change in $Paco_2$.
4. CBF changes 5% to 7% per 1°C change in temperature. Hypothermia decreases both cerebral metabolic rate and CBF, whereas pyrexia has the reverse effect.
5. The movement of a given substance across the blood–brain barrier is governed simultaneously by its size, charge, lipid solubility, and degree of protein binding in blood.
6. The blood–brain barrier may be disrupted by severe hypertension, tumors, trauma, strokes, infection, marked hypercapnia, hypoxia, and sustained seizure activity.
7. The cranial vault is a rigid structure with a fixed total volume, consisting of brain (80%), blood (12%), and cerebrospinal fluid (8%). Any increase in one component must be offset by an equivalent decrease in another to prevent a rise in intracranial pressure.
8. With the exception of ketamine, all intravenous agents either have little effect on or reduce cerebral metabolic rate and CBF.
9. With normal autoregulation and an intact blood–brain barrier, vasopressors increase CBF only when mean arterial blood pressure is below 50–60 mm Hg or above 150–160 mm Hg.
10. The brain is very vulnerable to ischemic injury because of its relatively high oxygen consumption and near total dependence on aerobic glucose metabolism.
11. Hypothermia is the most effective method for protecting the brain during focal and global ischemia.

Anesthetic agents may have profound effects on cerebral metabolism, blood flow, cerebrospinal fluid (CSF) dynamics, and intracranial volume and pressure. In some instances, these alterations are deleterious, whereas in others they may be beneficial. This chapter reviews important physiological concepts in anesthetic practice and discusses the effects of commonly used anesthetics on cerebral physiology.

Cerebral Physiology

CEREBRAL METABOLISM

The brain normally consumes 20% of total body oxygen. Most cerebral oxygen consumption (60%) is used to generate adenosine triphosphate (ATP) to support neuronal electrical activity (Figure 26–1). The cerebral metabolic rate (CMR) is usually expressed in terms of oxygen consumption ($CMRO_2$) and averages 3–3.8 mL/100 g/min (50 mL/min) in adults. $CMRO_2$ is greatest in the gray matter of the cerebral cortex and generally parallels cortical electrical activity. Because of the relatively high oxygen consumption and the absence of significant oxygen reserves, interruption of cerebral perfusion usually results in unconsciousness within 10 sec, as oxygen tension rapidly drops below 30 mm Hg. If blood flow is not reestablished within 3–8 min under most conditions, ATP stores are depleted, and irreversible cellular injury begins to occur. The hippocampus and cerebellum seem to be most sensitive to hypoxic injury.

Neuronal cells normally utilize glucose as their primary energy source. Brain glucose consumption is approximately 5 mg/100 g/min, of which more than 90% is metabolized aerobically. $CMRO_2$ therefore normally parallels glucose consumption. This relationship is not maintained during starvation, when ketone bodies (acetoacetate and β-hydroxybutyrate) also become major energy substrates. Although the brain can also take up and metabolize lactate, cerebral function is normally dependent on a continuous supply of glucose. Acute sustained hypoglycemia is injurious to the brain. Paradoxically, hyperglycemia can exacerbate global and focal hypoxic brain injury by accelerating cerebral acidosis and cellular injury. Tight control of perioperative blood glucose concentration has been advocated in part because of adverse effects of hyperglycemia during ischemic episodes; however, overzealous blood glucose control can likewise produce injury through iatrogenic hypoglycemia.

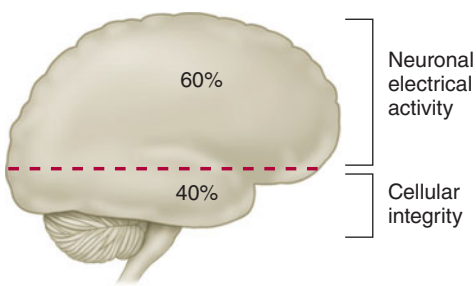

FIGURE 26–1 Normal brain oxygen requirements.

CEREBRAL BLOOD FLOW

Cerebral blood flow (CBF) varies with metabolic activity. There are a variety of methods available to directly measure CBF. These methods include: positron emission tomography, xenon enhanced computed tomography, single photon emission computed tomography, and computed tomography perfusion scans. These methods do not lend themselves to bedside monitoring of CBF. Blood flow studies confirm that regional CBF parallels metabolic activity and can vary from 10–300 mL/100 g/min. For example, motor activity of a limb is associated with a rapid increase in regional CBF of the corresponding motor cortex. Similarly, visual activity is associated with an increase in regional CBF of the corresponding occipital visual cortex.

Although total CBF averages 50 mL/100 g/min, flow in gray matter is about 80 mL/100 g/min, whereas that in white matter is estimated to be 20 mL/100 g/min. Total CBF in adults averages 750 mL/min (15% to 20% of cardiac output). Flow rates below 20–25 mL/100 g/min are usually associated with cerebral impairment, as evidenced by slowing on the electroencephalogram (EEG). CBF rates between 15 and 20 mL/100 g/min typically produce a flat (isoelectric) EEG, whereas rates below 10 mL/100 g/min are usually associated with irreversible brain damage.

Indirect measures are often used to estimate the adequacy of CBF and brain tissue oxygen delivery in clinical settings. These methods include:

- The velocity of CBF can be measured using transcranial Doppler (TCD); see Chapters 5 and 6 for a discussion of the Doppler effect. An ultrasound probe (2 mHz, pulse wave Doppler) is placed in the temporal area above the

zygomatic arch, which allows insonation of the middle cerebral artery. Normal velocity in the middle cerebral artery is approximately 55 cm/sec. Velocities greater than 120 cm/sec can indicate cerebral artery vasospasm following subarachnoid hemorrhage or hyperemic blood flow. Comparison between the velocities in the extracranial internal carotid artery and the middle cerebral artery (the Lindegaard ratio) can distinguish between these conditions. Middle cerebral artery velocity three times that of the velocity measured in the extracranial internal carotid artery more likely reflects cerebral artery vasospasm.

- Near infrared spectroscopy was discussed in Chapter 6. Decreased saturation is associated with impaired cerebral oxygen delivery, although near infrared spectroscopy primarily reflects cerebral venous oxygen saturation.
- Brain tissue oximetry measures the oxygen tension in brain tissue through placement of a bolt with a Clark electrode oxygen sensor. Brain tissue CO_2 tension can also be measured using a similarly placed infrared sensor. Normal brain tissue oxygen tension varies from 20–50 mm Hg. Brain tissue oxygen tensions less than 20 mm Hg warrant interventions, and values less than 10 mm Hg are indicative of brain ischemia.
- Intracerebral microdialysis can be used to measure changes in brain tissue chemistry that are indicative of ischemia and/or brain injury. Microdialysis can be used to measure cerebral lactate, neurotransmitters, markers of inflammation, and glucose concentration. Increases in the ratio of lactate/pyruvate have been associated with cerebral ischemia.

REGULATION OF CEREBRAL BLOOD FLOW

1. Cerebral Perfusion Pressure

1 Cerebral perfusion pressure (CPP) is the difference between mean arterial pressure (MAP) and intracranial pressure (ICP) (or central venous pressure [CVP], if it is greater than ICP). MAP – ICP (or CVP) = CPP. CPP is normally 80–100 mm Hg. Moreover, because ICP is normally less than 10 mm Hg, CPP is primarily dependent on MAP.

Moderate to severe increases in ICP (>30 mm Hg) can compromise CPP and CBF, even in the presence of a normal MAP. Patients with CPP values less than 50 mm Hg often show slowing on the EEG, whereas those with a CPP between 25 and 40 mm Hg typically have a flat EEG. Sustained perfusion pressures less than 25 mm Hg may result in irreversible brain damage.

2. Autoregulation

Much like the heart and kidneys, the brain normally tolerates a wide range of blood pressure, with little change in blood flow. The cerebral vasculature rapidly (10–60 s) adapts to changes in CPP. Decreases in CPP result in cerebral vasodilation, whereas elevations induce vasoconstriction. In normal individuals, CBF remains nearly constant between MAPs of about 60 and 160 mm Hg (**Figure 26–2**). Beyond these limits, blood flow becomes pressure dependent. Pressures above 150–160 mm Hg can disrupt the blood–brain barrier (see below) and may result in cerebral edema and hemorrhage.

2 The cerebral autoregulation curve (Figure 26–2) is shifted to the right in patients with chronic

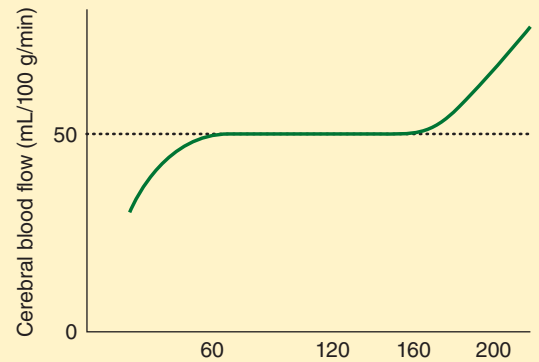

FIGURE 26–2 Normal cerebral autoregulation curve.

arterial hypertension. Both upper and lower limits are shifted. Flow becomes more pressure dependent at low "normal" arterial pressures in return for cerebral protection at higher arterial pressures. Studies suggest that long-term antihypertensive therapy can restore cerebral autoregulation limits toward normal.

Both myogenic and metabolic mechanisms may explain cerebral autoregulation. Myogenic mechanisms involve an intrinsic response of smooth muscle cells in cerebral arterioles to changes in MAP. Metabolic mechanisms indicate that cerebral metabolic demands determine arteriolar tone. Thus, when tissue demand exceeds blood flow, the release of tissue metabolites causes vasodilation and increases flow. Whereas hydrogen ions were once thought to mediate this response, other metabolites are likely involved.

3. Extrinsic Mechanisms

Respiratory Gas Tensions

3 The most important extrinsic influences on CBF are respiratory gas tensions—particularly $Paco_2$. CBF is directly proportionate to $Paco_2$ between tensions of 20 and 80 mm Hg (Figure 26–3). Blood flow changes approximately 1–2 mL/100 g/min per mm Hg change in $Paco_2$. This effect is almost immediate and is thought to be secondary to changes in the pH of CSF and cerebral tissue. Because ions do not readily cross the blood–brain barrier (see below) but CO_2 does, acute changes in $Paco_2$ but not HCO_3^- affect CBF. Thus, acute metabolic acidosis has little effect on CBF because hydrogen ions (H^+) cannot readily cross the blood–brain barrier. After 24–48 hr, CSF HCO_3^- concentration adjusts to compensate for the change in $Paco_2$, so that the effects of hypocapnia and hypercapnia are diminished. Marked hyperventilation ($Paco_2$ < 20 mm Hg) shifts the oxygen–hemoglobin dissociation curve to the left, and, with changes in CBF, may result in EEG changes suggestive of cerebral impairment, even in normal individuals.

Only marked changes in Pao_2 alter CBF. Whereas hyperoxia may be associated with only minimal decreases (–10%) in CBF, severe hypoxemia (Pao_2 < 50 mm Hg) greatly increases CBF (Figure 26–3).

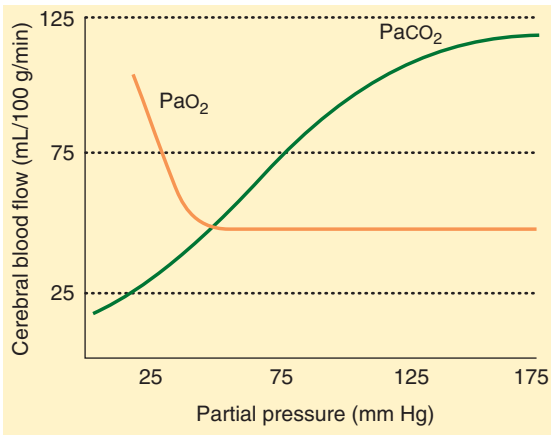

FIGURE 26–3 The relationship between cerebral blood flow and arterial respiratory gas tensions.

Temperature

4 CBF changes 5% to 7% per 1°C change in temperature. Hypothermia decreases both CMR and CBF, whereas hyperthermia has the reverse effect. Between 17°C and 37°C, the Q10 for humans is approximately 2—that is, for every 10° increase in temperature, the CMR doubles. Conversely, the CMR decreases by 50% if the temperature of the brain falls by 10°C (eg, from 37°C to 27°C) and another 50% if the temperature decreases from 27°C to 17°C. At 20°C, the EEG is isoelectric, but further decreases in temperature continue to reduce CMR throughout the brain. Hyperthermia (above 42°C) may result in neuronal cell injury.

Viscosity

The most important determinant of blood viscosity is hematocrit. A decrease in hematocrit decreases viscosity and can improve CBF; unfortunately, a reduction in hematocrit also decreases the oxygen-carrying capacity and thus can potentially impair oxygen delivery. Elevated hematocrit, as may be seen with marked polycythemia, increases blood viscosity and can reduce CBF. Some studies suggest

that optimal cerebral oxygen delivery may occur at hematocrits of approximately 30%.

Autonomic Influences

Intracranial vessels are innervated by the sympathetic (vasoconstrictive) and parasympathetic (vasodilatory) systems, Intense sympathetic stimulation induces vasoconstriction in these vessels, which can limit CBF. Autonomic innervation may also play an important role in cerebral vasospasm following brain injury and stroke.

BLOOD–BRAIN BARRIER

Cerebral blood vessels are unique in that the junctions between vascular endothelial cells are nearly fused. The paucity of pores is responsible for what is termed the blood–brain barrier. This lipid barrier allows the passage of lipid-soluble substances, but restricts the movement of those that are ionized or have large molecular weights. Thus, the movement of a given substance across the blood–brain barrier is governed simultaneously by its size, charge, lipid solubility, and degree of protein binding in blood. Carbon dioxide, oxygen, and lipid-soluble molecules (such as most anesthetics) freely enter the brain, whereas most ions, proteins, and large substances (such as mannitol) penetrate poorly.

5

Water moves freely across the blood–brain barrier as a consequence of bulk flow, whereas movement of even small ions is impeded (the equilibration half-life of Na^+ is 2–4 h). As a result, rapid changes in plasma electrolyte concentrations (and, secondarily, osmolality) produce a transient osmotic gradient between plasma and the brain. Acute hypertonicity of plasma results in net movement of water out of the brain, whereas acute hypotonicity causes a net movement of water into the brain. These effects are short-lived, as equilibration eventually occurs, but, when marked, they can cause rapid fluid shifts in the brain. Mannitol, an osmotically active substance that does not normally cross the blood–brain barrier, causes a sustained decrease in brain water content and is often used to decrease brain volume.

6

The blood–brain barrier may be disrupted by severe hypertension, tumors, trauma, strokes, infection, marked hypercapnia, hypoxia, and sustained seizure activity. Under these conditions, fluid movement across the blood–brain barrier becomes dependent on hydrostatic pressure rather than osmotic gradients.

CEREBROSPINAL FLUID

CSF is found in the cerebral ventricles and cisterns and in the subarachnoid space surrounding the brain and spinal cord. Its major function is to protect the central nervous system (CNS) against trauma.

Most of the CSF is formed by the choroid plexuses of the cerebral (mainly lateral) ventricles. Smaller amounts are formed directly by the ventricles' ependymal cell linings, and yet smaller quantities are formed from fluid leaking into the perivascular spaces surrounding cerebral vessels (blood–brain barrier leakage). In adults, normal total CSF production is about 21 mL/hr (500 mL/d), yet total CSF volume is only about 150 mL. CSF flows from the lateral ventricles through the intraventricular foramina (of Monro) into the third ventricle, through the cerebral aqueduct (of Sylvius) into the fourth ventricle, and through the median aperture of the fourth ventricle (foramen of Magendie) and the lateral apertures of the fourth ventricle (foramina of Luschka) into the cerebellomedullary cistern (cisterna magna) (**Figure 26–4**). From the cerebellomedullary cistern, CSF enters the subarachnoid space, circulating around the brain and spinal cord before being absorbed in arachnoid granulations over the cerebral hemispheres.

CSF formation involves active secretion of sodium in the choroid plexuses. The resulting fluid is isotonic with plasma despite lower potassium, bicarbonate, and glucose concentrations. Its protein content is limited to the very small amounts that leak into perivascular fluid. Carbonic anhydrase inhibitors (acetazolamide), corticosteroids, spironolactone, furosemide, isoflurane, and vasoconstrictors decrease CSF production.

Absorption of CSF involves the translocation of fluid from the arachnoid granulations into the cerebral venous sinuses. Smaller amounts are absorbed at nerve root sleeves and by meningeal lymphatics.

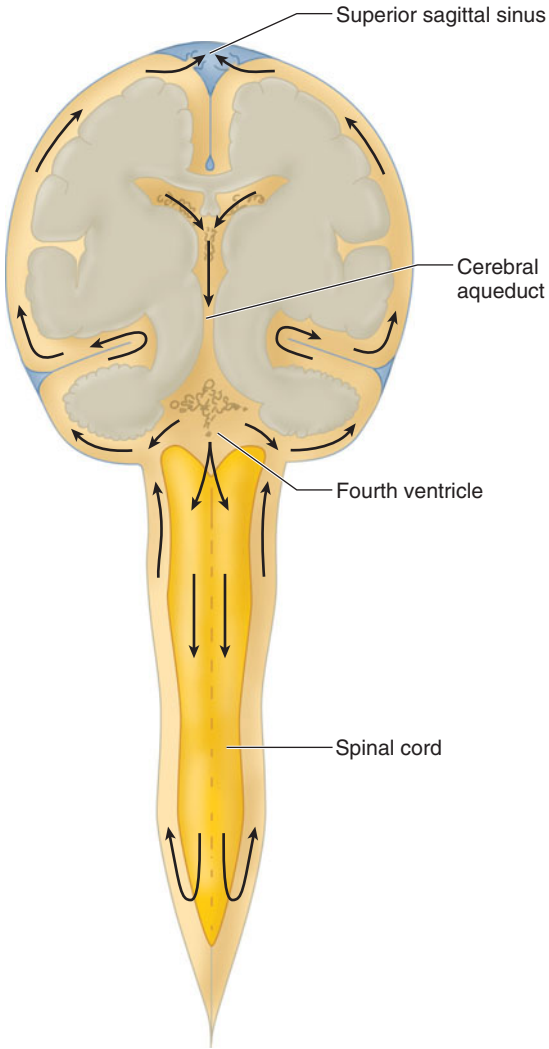

FIGURE 26–4 The flow of cerebrospinal fluid in the central nervous system. (Reproduced, with permission, from Waxman SG: *Correlative Neuroanatomy*, 24th ed. McGraw-Hill, 2000.)

Because the brain and spinal cord lack lymphatics, absorption of CSF is also the principal means by which perivascular and interstitial protein is returned to the blood.

INTRACRANIAL PRESSURE

7 The cranial vault is a rigid structure with a fixed total volume, consisting of brain (80%), blood (12%), and CSF (8%). Any increase in one component must be offset by an equivalent decrease in another to prevent a rise in ICP. By convention, ICP means supratentorial CSF pressure measured in the lateral ventricles or over the cerebral cortex and is normally 10 mm Hg or less. Minor variations may occur, depending on the site measured, but, in the lateral recumbent position, lumbar CSF pressure normally approximates supratentorial pressure.

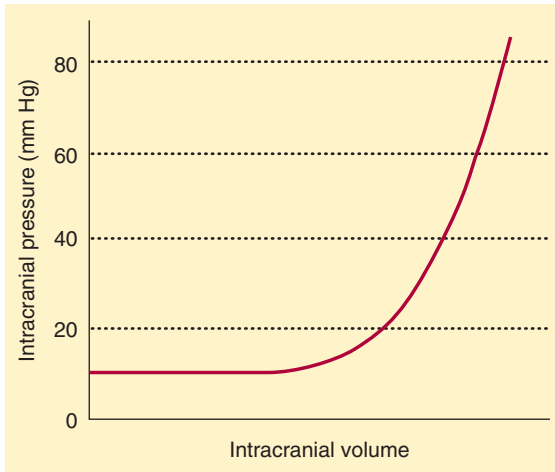

FIGURE 26–5 Normal intracranial elastance.

Intracranial elastance is determined by measuring the change in ICP in response to a change in intracranial volume. Normally, small increases in volume of one component are initially well compensated (Figure 26–5). A point is eventually reached, however, at which further increases produce precipitous rises in ICP. Major compensatory mechanisms include: (1) an initial displacement of CSF from the cranial to the spinal compartment, (2) an increase in CSF absorption, (3) a decrease in CSF production, and (4) a decrease in total cerebral blood volume (primarily venous).

The concept of total intracranial compliance is useful clinically, even though compliance probably varies in the different compartments of the brain and is affected by arterial blood pressure and $Paco_2$. Cerebral blood volume is estimated to increase 0.05 mL/100 g of brain per 1 mm Hg increase in $Paco_2$. Blood pressure effects upon cerebral blood volume are dependent on the autoregulation of CBF.

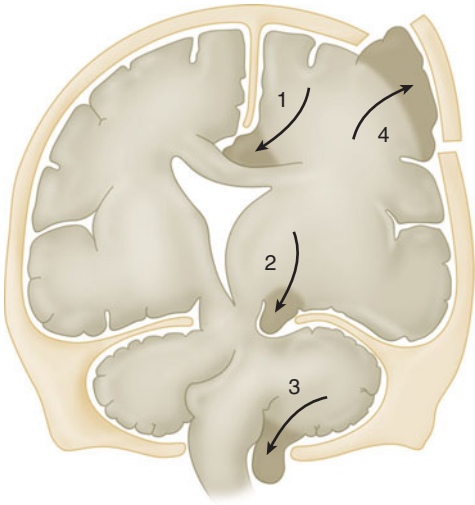

FIGURE 26–6 Potential sites of brain herniation. (Reproduced, with permission, from Fishman RA: Brain edema. N Engl J Med 1975;293:706.)

Sustained elevations in ICP can lead to catastrophic herniation of the brain. Herniation may occur at one of four sites (Figure 26–6): (1) the cingulate gyrus under the falx cerebri, (2) the uncinate gyrus through the tentorium cerebelli, (3) the cerebellar tonsils through the foramen magnum, or (4) any area beneath a defect in the skull (transcalvarial).

Effect of Anesthetic Agents on Cerebral Physiology

Overall, most general anesthetics have a favorable effect on the CNS by reducing electrical activity. Determination of the effects of the specific agents is complicated by the concomitant administration of other drugs, surgical stimulation, intracranial compliance, blood pressure, and CO_2 tension. For example, hypocapnia blunts the increases in CBF and ICP that usually occur with ketamine and volatile agents.

This section describes the changes generally associated with each drug when given alone. Table 26–1 summarizes and compares the effects of the various anesthetics. The effects of vasoactive agents and neuromuscular blocking agents are also discussed.

TABLE 26–1 Comparative effects of anesthetic agents on cerebral physiology.[1]

Agent	CMR	CBF	CSF Production	CSF Absorption	CBV	ICP
Halothane	↓↓	↑↑↑	↓	↓	↑↑	↑↑
Isoflurane	↓↓↓	↑	±	↑	↑↑	↑
Desflurane	↓↓↓	↑	↑	↓	↑	↑
Sevoflurane	↓↓↓	↑	?	?	↑	↑
Nitrous oxide	↓	↑	±	±	±	↑
Barbiturates	↓↓↓↓	↓↓↓	±	↑	↓↓	↓↓↓
Etomidate	↓↓↓	↓↓	±	↑	↓↓	↓↓
Propofol	↓↓↓	↓↓↓↓	?	?	↓↓	↓↓
Benzodiazepines	↓↓	↓	±	↑	↓	↓
Ketamine	±	↑↑	±	↓	↑↑	↑↑
Opioids	±	±	±	↑	±	±
Lidocaine	↓↓	↓↓	?	?	↓↓	↓↓

[1]↑, increase; ↓, decrease; ±, little or no change; ?, unknown; CMR, cerebral metabolic rate; CBF, cerebral blood flow; CSF, cerebrospinal fluid; CBV, cerebral blood volume; ICP, intracranial pressure.

EFFECT OF INHALATION AGENTS

1. Volatile Anesthetics

Cerebral Metabolic Rate

Halothane, desflurane, sevoflurane, and isoflurane produce dose-dependent decreases in CMR. Isoflurane produces the greatest maximal depression (up to 50% reduction), whereas halothane has the least effect (<25% reduction). The effects of desflurane and sevoflurane seem to be similar to that of isoflurane. No further reduction in CMR is produced by doses of anesthetics or other drugs greater than the doses that render the EEG isoelectric.

Cerebral Blood Flow & Volume

At normocarbia, volatile anesthetics dilate cerebral vessels and impair autoregulation in a dose-dependent manner (Figure 26–7). Halothane has the greatest effect on CBF; at concentrations greater than 1%, it nearly abolishes cerebral autoregulation. Moreover, the increase in blood flow is generalized throughout all parts of the brain. At an equivalent minimum alveolar concentration (MAC) and blood pressure, halothane increases CBF up to 200%, compared with 20% for isoflurane. Qualitatively and quantitatively, desflurane may be closest to isoflurane. Sevoflurane produces the least cerebral vasodilation. The effect of volatile agents on CBF also seems to be time dependent, because, with continued administration (2–5 h), blood flow begins to return to normal.

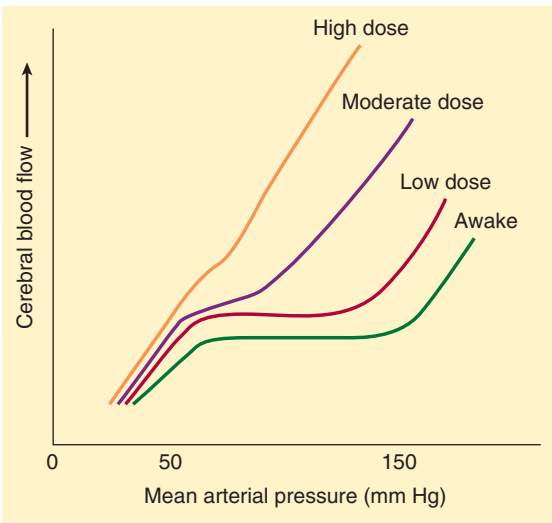

FIGURE 26–7 Dose-dependent depression of cerebral autoregulation by the volatile anesthetics.

The response of the cerebral vasculature to CO_2 is generally retained with all volatile agents. Hyperventilation (hypocapnia) can therefore abolish or blunt the initial effects of these agents on CBF. With halothane, the timing of the hyperventilation is important. Only if hyperventilation is initiated prior to the administration of halothane will halothane-induced increases in CBF be prevented. In contrast, simultaneous hyperventilation with administration of either isoflurane or sevoflurane can prevent increases in CBF and ICP.

Increases in cerebral blood volume (10% to 12%) generally parallel increases in CBF, but the relationship is not necessarily linear. Expansion of cerebral blood volume can markedly elevate ICP in patients with reduced intracranial compliance. Hypocapnia can blunt the increase in cerebral blood volume associated with volatile anesthetic administration.

Altered Coupling of Cerebral Metabolic Rate & Blood Flow

As is apparent from the discussion above, volatile agents alter, but do not uncouple, the normal relationship of CBF and CMR. The combination of a decrease in neuronal metabolic demand with an increase in CBF (metabolic supply) has been termed luxury perfusion. In contrast to this potentially beneficial effect during global ischemia, a detrimental **circulatory steal phenomenon** is possible with volatile anesthetics in the setting of focal ischemia. Volatile agents can increase blood flow in normal areas of the brain, but not in ischemic areas, where arterioles are already maximally vasodilated. The end result may be a redistribution ("steal") of blood flow away from ischemic to normal areas.

Cerebrospinal Fluid Dynamics

Volatile anesthetics affect both formation and absorption of CSF. Halothane impedes absorption

of CSF, but only minimally retards formation. Isoflurane, on the other hand, facilitates absorption and is therefore an agent with favorable effects on CSF dynamics.

Intracranial Pressure

The net effect of volatile anesthetics on ICP is the result of immediate changes in cerebral blood volume, delayed alterations on CSF dynamics, and arterial CO_2 tension. Based on these factors, isoflurane and sevoflurane seem to be the volatile agents of choice in patients with decreased intracranial compliance.

2. Nitrous Oxide

The effects of nitrous oxide are influenced by other agents or changes in CO_2 tension. Thus, when combined with intravenous agents, nitrous oxide has minimal effects on CBF, CMR, and ICP. Adding this agent to a volatile anesthetic, however, can further increase CBF. When given alone, nitrous oxide causes mild cerebral vasodilation and can potentially increase ICP.

EFFECT OF INTRAVENOUS AGENTS

1. Induction Agents

8 With the exception of ketamine, all intravenous agents either have little effect on or reduce CMR and CBF. Moreover, with some exceptions, changes in blood flow generally parallel those in metabolic rate. Cerebral autoregulation and CO_2 responsiveness are preserved with all agents.

Barbiturates

Barbiturates have four major actions on the CNS: (1) hypnosis, (2) depression of CMR, (3) reduction of CBF due to increased cerebral vascular resistance, and (4) anticonvulsant activity. Barbiturates produce dose-dependent decreases in CMR and CBF until the EEG becomes isoelectric. At that point, maximum reductions of nearly 50% are observed; additional barbiturate dosing does not further reduce metabolic rate. Unlike isoflurane, barbiturates reduce metabolic rate uniformly throughout the brain. CMR is depressed slightly more than CBF, such that metabolic supply exceeds metabolic demand (as long as CPP is maintained). Because barbiturate-induced cerebral vasoconstriction occurs only in normal areas, these agents tend to redistribute blood flow from normal to ischemic areas in the brain (Robin Hood, or reverse steal phenomenon). The cerebral vasculature in ischemic areas remains maximally dilated and is less affected by the barbiturate because of ischemic vasomotor paralysis.

Barbiturates also seem to facilitate absorption of CSF. The resultant reduction in CSF volume, combined with decreases in CBF and cerebral blood volume, makes barbiturates highly effective in lowering ICP. Their anticonvulsant properties are also advantageous in neurosurgical patients who are at increased risk of seizures.

Opioids

Opioids generally have minimal effects on CBF, CMR, and ICP, unless $Paco_2$ rises secondary to respiratory depression. Increases in ICP have been reported in some patients with intracranial tumors following administration of sufentanil and to a lesser degree, alfentanil. The mechanism seems to be a precipitous drop in blood pressure; reflex cerebral vasodilation likely increases intracranial blood volume and potentially ICP. Significant decreases in blood pressure can adversely affect CPP, regardless of the opioid selected. In addition, small doses of alfentanil (<50 mg/kg) can activate seizure foci in patients with epilepsy. Morphine is generally not considered optimal as a component of anesthesia for intracranial surgery. Morphine's poor lipid solubility results in slow CNS penetration and prolonged sedative effects. Normeperidine, a metabolite of meperidine, can induce seizures, particularly in patients with renal failure. The accumulation of normeperidine and the associated cardiac depression limit the use of meperidine, except in small doses to treat shivering.

Etomidate

Etomidate decreases the CMR, CBF, and ICP in much the same way as thiopental. Its effect on CMR

is nonuniform, affecting the cortex more than the brainstem. Its limited effect on the brainstem may be responsible for greater hemodynamic stability during anesthesia induction, compared with that of barbiturates. Etomidate also decreases production and enhances absorption of CSF.

Induction with etomidate is associated with a relatively high incidence of myoclonic movements, but these movements are not associated with seizure activity on the EEG in normal individuals. The drug has been used to treat seizures, but reports of seizure activity following etomidate suggest that the drug is best avoided in patients with a history of epilepsy. In fact, small doses of etomidate can activate seizure foci in patients with epilepsy.

Propofol

Propofol reduces CBF and CMR, similar to barbiturates and etomidate; however, the decrease in CBF may exceed that in metabolic rate. Although it has been associated with dystonic and choreiform movements, propofol seems to have significant anticonvulsant activity. Moreover, its short elimination half-life makes it a useful agent for neuroanesthesia. Propofol infusion is commonly used for maintenance of anesthesia in patients with or at risk of intracranial hypertension. Propofol is by far the most common induction agent for neuroanesthesia.

Benzodiazepines

Benzodiazepines lower CBF and CMR, but to a lesser extent than barbiturates, etomidate, or propofol. Benzodiazepines also have useful anticonvulsant properties. Midazolam is the benzodiazepine of choice in neuroanesthesia because of its short half-life. Midazolam used as an induction agent frequently causes decreases in CPP in elderly and unstable patients and may result in prolonged emergence.

Ketamine

Ketamine is the only intravenous anesthetic that dilates the cerebral vasculature and increases CBF (50% to 60%). Selective activation of certain areas (limbic and reticular) is partially offset by depression of other areas (somatosensory and auditory) such that total CMR does not change. Seizure activity in thalamic and limbic areas is also described. Ketamine may also impede absorption of CSF without affecting formation. Increases in CBF, cerebral blood volume, and CSF volume can potentially increase ICP markedly in patients with decreased intracranial compliance. However, ketamine administration does not increase ICP in neurologically impaired patients under controlled ventilation with concomitant administration of propofol or a benzodiazepine. Additionally, ketamine may offer neuroprotective effects, according to some investigations. Ketamine's blockade of the *N*-methyl-D-aspartate (NMDA) receptor during periods of increased glutamate concentrations, as occurs during brain injury, may be protective against neuronal cell death (**Figure 26–8**).

2. Anesthetic Adjuncts

Intravenous lidocaine decreases CMR, CBF, and ICP, but to a lesser degree than other agents. Its principal advantage is that it decreases CBF (by increasing cerebral vascular resistance) without causing other significant hemodynamic effects. Lidocaine may also have neuroprotective effects. Lidocaine infusions are used in some centers as a supplement to general anesthesia to reduce emergence delirium and the requirement for opioids.

Droperidol has little or no effect on CMR and minimally reduces CBF. When used in larger doses with an opioid as part of a neuroleptic technique, droperidol may sometimes cause undesirable prolonged sedation. Droperidol and narcotics were once mainstays of neuroanesthesia. Droperidol's prolongation of the QT interval and risk of fatal arrhythmia, as well as official warnings related to the drug, have retarded its use.

Reversal of opioids or benzodiazepines with naloxone or flumazenil, respectively, can reverse any beneficial reductions in CBF and CMR. Reversal of narcotics or benzodiazepines in chronic users can lead to symptoms of substance withdrawal.

3. Vasopressors

9 With normal autoregulation and an intact blood–brain barrier, vasopressors increase

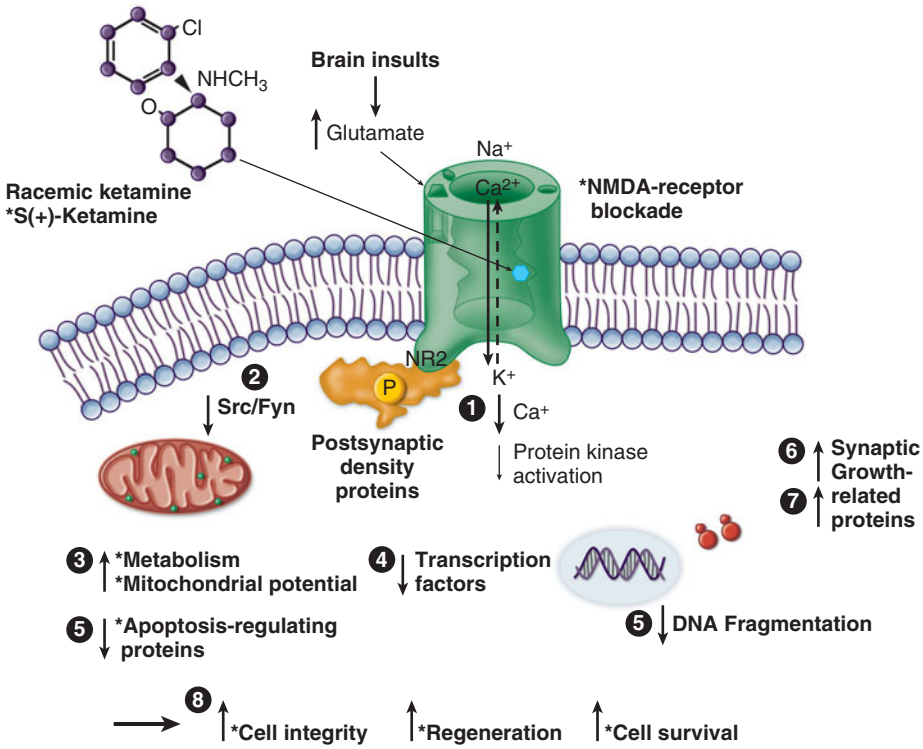

FIGURE 26–8 Pharmacological effects reported for racemic and S(+)-ketamine which are presumed to be relevant for neuroprotection. After onset of brain injury, blockade of excessive stimulation of *N*-methyl-D-aspartate (NMDA) receptors by ketamine reduces calcium influx through the receptor channel (1). This attenuates supraphysiological increases in the assembly and interaction of NMDA receptor subunits, postsynaptic density proteins, and other intracellular signaling systems such as protein kinases (2). Thus, several kinase transduction cascades become less activated. This improves preservation of metabolism and maintenance of the mitochondrial transmembrane potential (3). This, in turn, reduces pathological activation of transcription factors (4). Proteins involved in apoptosis are less activated, which is associated with less DNA fragmentation (5). A better preservation of synaptic proteins occurs, and the expression of growth proteins indicating regeneration in adult neurons is enhanced. The prevention of pathological amplification of NMDA receptor signaling finally results in increased cellular survival, preserved cellular and synaptic integrity, and regenerative efforts. *Superiority of effects induced by S(+)-ketamine, only. (Reproduced, with permission, from Himmelseher S, Durieux ME: Revising a dogma: ketamine for patients with neurological injury? Anesth Analg 2005:101:524.)

CBF only when mean arterial blood pressure is below 50–60 mm Hg or above 150–160 mm Hg. In the absence of autoregulation, vasopressors increase CBF by their effect on CPP. Changes in CMR generally parallel those in blood flow. β-Adrenergic agents seem to have a greater effect on the brain when the blood–brain barrier is disrupted; central β_1-receptor stimulation increases CMR and blood flow. β-Adrenergic blockers generally have no direct effect on CMR or CBF, whereas α_2-adrenergic agonists produce cerebral vasoconstriction. Excessive elevations in blood pressure with any agent can disrupt the blood–brain barrier.

4. Vasodilators

In the absence of hypotension, most vasodilators induce cerebral vasodilation and increase CBF in a

dose-related fashion. When these agents decrease blood pressure, CBF is usually maintained and may even increase. The resultant increase in cerebral blood volume can significantly elevate ICP in patients with decreased intracranial compliance. Of this group of drugs, only the ganglionic blocker trimethaphan has little or no effect on CBF and cerebral blood volume. Trimethaphan is no longer available in the United States.

5. Neuromuscular Blocking Agents

Neuromuscular blockers (NMBs) lack direct action on the brain but can have important secondary effects. Hypertension and histamine-mediated cerebral vasodilation increase ICP, whereas systemic hypotension (from histamine release or ganglionic blockade) lowers CPP. Succinylcholine can increase ICP, possibly as a result of cerebral activation associated with enhanced muscle spindle activity, but the increase is generally minimal and clinically unimportant, if an adequate dose of propofol is given and hyperventilation is initiated at induction. Moreover, a small (defasciculating) dose of a nondepolarizing NMB seems to blunt the increase, at least partially. In the majority of instances, increases in ICP following administration of an NMB are the result of a hypertensive response due to light anesthesia during laryngoscopy and tracheal intubation. Acute elevations in ICP will also be seen, if hypercapnia or hypoxemia results from prolonged apnea.

Physiology of Brain Protection

PATHOPHYSIOLOGY OF CEREBRAL ISCHEMIA

10 The brain is very vulnerable to ischemic injury because of its relatively high oxygen consumption and near total dependence on aerobic glucose metabolism (above). Interruption of cerebral perfusion, metabolic substrate (glucose), or severe hypoxemia rapidly results in functional impairment; reduced perfusion also impairs clearance of potentially toxic metabolites. If normal oxygen tension, blood flow, and glucose supply are not reestablished within 3–8 min under most conditions, ATP stores are depleted, and irreversible neuronal injury begins. When CBF decreases below 10 mL/100 g/min, cell function is deranged, and ion pumps fail to maintain cellular vitality. The ratio of lactate to pyruvate is increased secondary to anaerobic metabolism. During ischemia, intracellular K^+ decreases, and intracellular Na^+ increases. More importantly, intracellular Ca^{2+} increases because of failure of ATP-dependent pumps to either extrude the ion extracellularly or into intracellular cisterns, increased intracellular Na^+ concentration, and release of the excitatory neurotransmitter glutamate. Glutamate acts at the NMDA receptor, further enhancing Ca^{2+} entry into the cell, hence the potential benefit of NMDA blockers for neuroprotection.

Sustained increases in intracellular Ca^{2+} activate lipases and proteases, which initiate and propagate structural damage to neurons. Increases in free fatty acid concentration and cyclooxygenase and lipoxygenase activities result in the formation of prostaglandins and leukotrienes, some of which are potent mediators of cellular injury. Accumulation of toxic metabolites, such as lactic acid, also impairs cellular function and interferes with repair mechanisms. Lastly, reperfusion of ischemic tissues can cause additional tissue damage due to the formation of oxygen-derived free radicals. Likewise, inflammation and edema can promote further neuronal damage, leading to cellular apoptosis.

STRATEGIES FOR BRAIN PROTECTION

Ischemic brain injury is usually classified as focal (incomplete) or global (complete). Global ischemia includes total circulatory arrest as well as global hypoxia. Cessation of perfusion may be caused by cardiac arrest or deliberate circulatory arrest, whereas global hypoxia may be caused by severe respiratory failure, drowning, and asphyxia (including anesthetic mishaps). Focal ischemia includes embolic, hemorrhagic, and atherosclerotic strokes, as well as blunt, penetrating, and surgical trauma.

In some instances, interventions aimed at restoring perfusion and oxygenation are possible; these include reestablishing effective circulation, normalizing arterial oxygenation and oxygen-carrying capacity, or reopening an occluded vessel. With focal ischemia, the brain tissue surrounding a severely damaged area may suffer marked functional impairment but still remain viable. Such areas are thought to have very marginal perfusion (<15 mL/100 g/min), but, if further injury can be limited and normal flow is rapidly restored, these areas (the "ischemic penumbra") may recover completely. When the above interventions are not applicable or available, the emphasis must be on limiting the extent of brain injury.

From a practical point of view, efforts aimed at preventing or limiting neuronal tissue damage are often the same whether the ischemia is focal or global. Clinical goals are usually to optimize CPP, decrease metabolic requirements (basal and electrical), and possibly block mediators of cellular injury. Clearly, the most effective strategy is prevention, because once injury has occurred, measures aimed at cerebral protection become less effective.

Hypothermia

11 Hypothermia is an effective method for protecting the brain during focal and global ischemia. Indeed, profound hypothermia is often used for up to 1 hr of total circulatory arrest. Unlike anesthetic agents, hypothermia decreases both basal and electrical metabolic requirements throughout the brain; metabolic requirements continue to decrease even after complete electrical silence. Additionally, hypothermia reduces free radicals and other mediators of ischemic injury. Induced hypothermia has shown benefit following cardiac arrest and is a routine part of most postarrest protocols for comatose patients.

Anesthetic Agents

Barbiturates, etomidate, propofol, and isoflurane can produce complete electrical silence of the brain and eliminate the metabolic cost of electrical activity; unfortunately, these agents have no effect on basal energy requirements. Furthermore, with the exception of barbiturates, their effects are nonuniform, affecting different parts of the brain to variable extents.

Ketamine may also have a protective effect because of its ability to block the actions of glutamate at the NMDA) receptor.

No anesthetic agent has consistently been shown to be protective against global ischemia. The ever increasing number of studies highlighting the potential neurotoxicity of anesthetics (especially in infants) also questions the role of volatile anesthetics in neuroprotection.

Specific Adjuncts

Nimodipine plays a role in the in the treatment of vasospasm associated with subarachnoid hemorrhage. Studies are ongoing to discern the roles of various NMDA receptor antagonists, erythropoietin, Ca^{2+} antagonists, and free radical scavengers to mitigate ischemic neuronal injury.

General Measures

Maintenance of a satisfactory CPP is critical. Thus, arterial blood pressure should be normal or slightly elevated, and increases in venous and ICP should be avoided. Oxygen-carrying capacity should be maintained and normal arterial oxygen tension preserved. Hyperglycemia aggravates neurological injuries following either focal or global ischemia, and blood glucose should be maintained at less than 180 mg/dL. Normocarbia should be maintained, as both hypercarbia and hypocarbia have no beneficial effect in the setting of ischemia and could prove detrimental; hypocarbia-induced cerebral vasoconstriction may aggravate the ischemia, whereas hypercarbia may induce a steal phenomenon (with focal ischemia) or worsen intracellular acidosis.

EFFECT OF ANESTHESIA ON ELECTROPHYSIOLOGICAL MONITORING

Electrophysiological monitors are used to assess the functional integrity of the CNS. The most commonly used monitor for neurosurgical procedures is evoked potentials. EEG is much less commonly used. Proper application of these monitoring modalities

TABLE 26–2 Electroencephalographic changes during anesthesia.

Activation	Depression
Inhalational agents (subanesthetic)	Inhalation agents (1-2 MAC)
Barbiturates (small doses)	Barbiturates
Benzodiazepines (small doses)	Opioids
Etomidate (small doses)	Propofol
Nitrous oxide	Etomidate
Ketamine	Hypocapnia
Mild hypercapnia	Marked hypercapnia
Sensory stimulation	Hypothermia
Hypoxia (early)	Hypoxia (late) Ischemia

is critically dependent on monitoring the specific area at risk and recognizing anesthetic-induced changes. Both monitoring modalities are described in Chapter 6.

The effects of anesthetic agents on the EEG are summarized in Table 26–2.

ELECTROENCEPHALOGRAPHY

EEG monitoring is useful for assessing the adequacy of cerebral perfusion during carotid endarterectomy (CEA), as well as anesthetic depth (most often with processed EEG). EEG changes can be simplistically described as either activation or depression. EEG activation (a shift to predominantly high-frequency and low-voltage activity) is seen with light anesthesia and surgical stimulation, whereas EEG depression (a shift to predominantly low-frequency and high-voltage activity) occurs with deep anesthesia or cerebral compromise. **Most anesthetics produce an EEG consisting of an initial activation (at subanesthetic doses) followed by dose-dependent depression**.

Inhalation Anesthetics

Isoflurane can produce an isoelectric EEG at high clinical doses (1–2 MAC). **Desflurane and sevoflurane produce a burst suppression pattern at high doses (>1.2 and >1.5 MAC, respectively) but not electrical silence**. Nitrous oxide is also unusual in that it increases both frequency and amplitude (high-amplitude activation).

Intravenous Agents

Benzodiazepines can produce both activation and depression of the EEG. Barbiturates, etomidate, and propofol produce a similar pattern and are the only intravenous agents capable of producing burst suppression and electrical silence at high doses. In contrast, opioids characteristically produce only dose-dependent depression of the EEG. Lastly, ketamine produces an unusual activation consisting of rhythmic high-amplitude theta activity followed by very high-amplitude gamma and low-amplitude beta activities.

EVOKED POTENTIALS

Somatosensory evoked potentials test the integrity of the spinal dorsal columns and the sensory cortex and may be useful during resection of spinal tumors, instrumentation of the spine, CEA, and aortic surgery. The adequacy of perfusion of the spinal cord during aortic surgery is probably better assessed with motor evoked potentials (which assess the anterior part of the spinal cord). Brainstem auditory evoked potentials test the integrity of the eighth cranial nerve and the auditory pathways above the pons and are used for surgery in the posterior fossa. Visual evoked potentials may be used to monitor the optic nerve and occipital cortex during resections of large pituitary tumors.

Interpretation of evoked potentials is more complicated than that of the EEG. Evoked potentials have poststimulus latencies that are described as short, intermediate, and long. Short-latency evoked potentials arise from the nerve stimulated or the brain stem. Intermediate- and long-latency evoked potentials are primarily of cortical origin. In general, short-latency potentials are least affected by anesthetic agents, whereas long-latency potentials are affected by even subanesthetic levels of most agents. Visual evoked potentials are most affected by anesthetics, whereas brain stem auditory evoked potentials are least affected.

Intravenous agents in clinical doses generally have less marked effects on evoked potentials than do volatile agents, but, in high doses, can also decrease amplitude and increase latencies (see Chapter 6).

CASE DISCUSSION

Postoperative Hemiplegia

A 62-year-old man has undergone a right carotid endarterectomy (CEA). Immediately following surgery, in the recovery room, he is noted to be weak on the contralateral side.

How is a patient undergoing CEA evaluated preoperatively?

Patients with cerebrovascular disease, and, in particular, carotid stenosis are at very high risk of coronary artery and peripheral arterial disease. It would be unusual for a patient to have carotid stenosis who did not have evidence of atherosclerosis elsewhere. Patients undergoing CEA, therefore, require a preoperative cardiac evaluation, according to American College of Cardiology/American Heart Association guidelines.

With respect to patient risk factors, the guidelines provide algorithms for how patients should be evaluated and managed intraoperatively. As part of this patient's preoperative evaluation, a thorough neurological examination should have been performed with special attention paid to motor function. This patient may well have been weak on the left side prior to surgery, in which case the hemiparesis might be due to a preexisting condition. If this is a new finding, it requires aggressive management.

Is general or regional anesthesia the optimal anesthetic technique for managing patients undergoing CEA?

For the past several decades, the majority of patients undergoing CEAs in the United States have had general anesthesia. General anesthesia was chosen because many surgeons operating in the neck area felt more comfortable if the airway was controlled, and the patient was completely anesthetized should evidence of cerebral ischemia develop.

More recently, regional anesthesia has been advocated as providing an adequate surgical field, a comfortable and relaxed patient (if done with monitored anesthesia care), stable hemodynamics, and ideal monitoring of cerebral function during crossclamping because an awake patient provides the best evidence of adequate cerebral perfusion. The patient can indicate or be observed for evidence of aphasia, facial droop, or hemiparesis. Regional anesthesia is usually performed with superficial cervical plexus blocks.

How should cerebral function be monitored intraoperatively in this patient?

When the carotid is crossclamped, the ability to identify inadequate cerebral circulation in the ipsilateral hemisphere is critical, as there is a window of opportunity for immediate intervention and correction of any deficit.

Global and focal neurological status can continuously be assessed in awake patients, if the patient is mildly sedated when undergoing regional anesthesia. In such a situation, practical assessment consists of frequent (every 2–5 min) examination of strength using the contralateral handgrip and maintenance of constant verbal contact with the patient to assess level of consciousness.

In patients undergoing general anesthesia, indirect cerebral monitoring techniques have been used to assess the adequacy of the cerebral circulation. These techniques include stump bleeding, stump pressure, jugular venous oxygen saturation, EEG, a processed EEG (such as the bispectral index or evoked potentials), TCD, arteriography, and measurement of blood flow using xenon. Back bleeding of the distal carotid artery following crossclamp and incision of the artery suggests reasonable collateral circulation above the clamp. It is very subjective and nonquantitative.

To better qualify and quantify the adequacy of collateral perfusion (**Figure 26–9**), stump pressure measurements can be used. Some surgeons

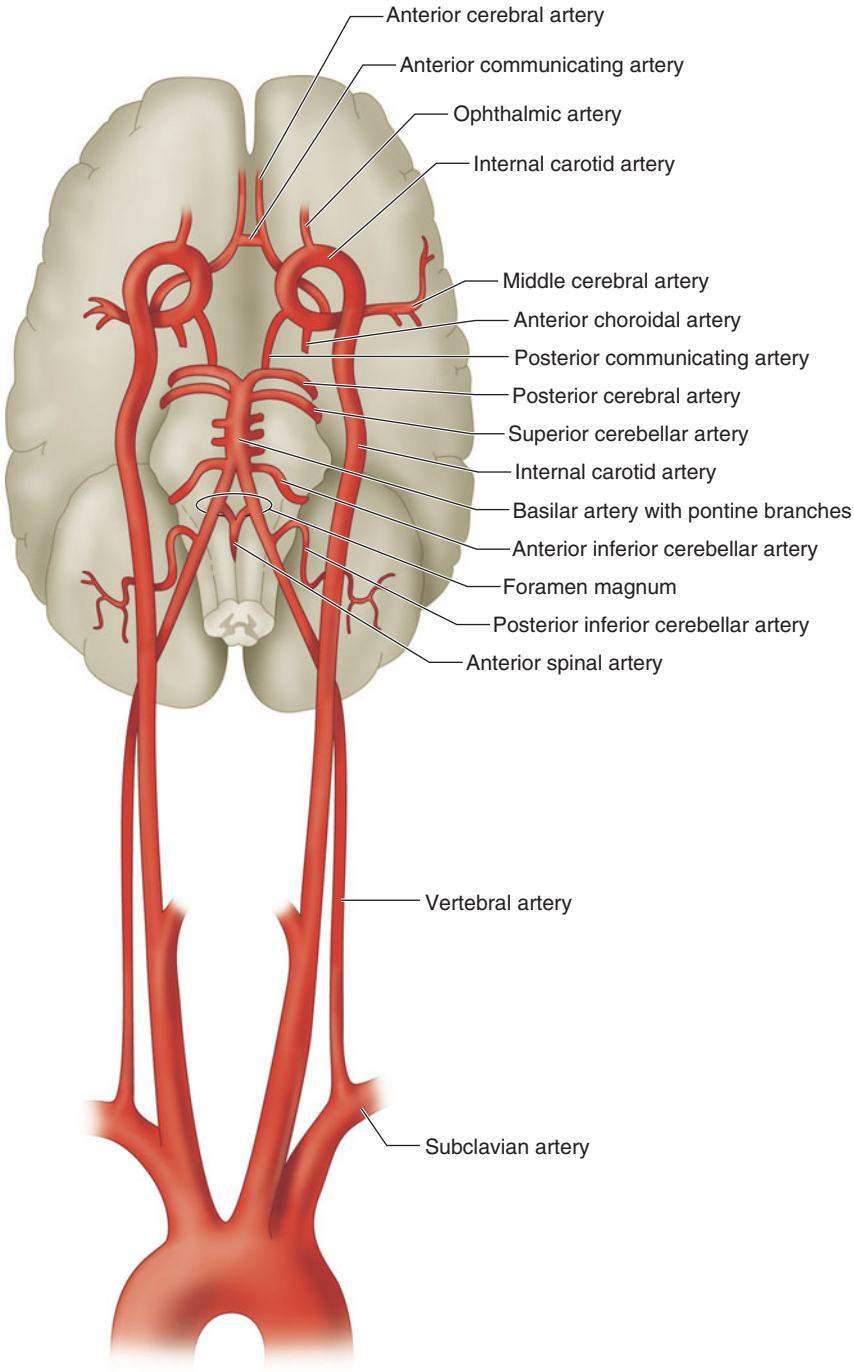

FIGURE 26–9 The cerebral circulation.

believe that a shunt should be used in all patients with a previous cerebrovascular accident, independent of stump pressure, and for any patient whose stump pressure is less than 25 mm Hg. However, this is controversial, as many neurosurgeons and vascular surgeons use 50 mm Hg as a cutoff.

The EEG is sometimes used for monitoring patients undergoing CEA under general anesthesia. In such a circumstance, inhalation or intravenous anesthesia can influence the EEG, but gross changes associated with carotid clamping can be detected. However, analyzing the EEG is labor and technology intensive and requires interpretation of the data.

For this reason, techniques that employ a processed EEG (eg, the bispectral index monitor) are being explored as a monitor for cerebral ischemia. Evoked potentials, such as auditory and visual evoked potentials, have also been examined, but do not seem to have significant clinical application.

Jugular venous oxygen saturation has been studied in an attempt to identify the acute onset of cerebral ischemia. Because it is a global measure, it does not reflect regional, or, in particular, focal cerebral ischemia and therefore is not used for routine clinical practice. TCD ultrasonography provides noninvasive assessment of blood flow in the middle cerebral artery.

How should hemodynamics be controlled intraoperatively?

During carotid clamping and immediately afterward in the recovery room, patients are often hemodynamically labile. **Bradycardia can develop during surgical manipulation of the carotid sinus because of the direct stimulation of the vagus nerve.** Tachycardia may develop as a result of stress or pain or as a direct result of manipulation of the carotid sinus with release of catecholamines into the circulation.

Hypotension is also observed because of the direct vasodilating and negative ionotropic effects of anesthetic agents. Hypotension following carotid unclamping is common, particularly in patients with more severe carotid stenosis. This could be due to a cerebral protective process. Cerebral autoregulation protects the brain from reperfusion by reducing cerebral production of renin, vasopressin, and norepinephrine, which results in hypotension. Hypertension is also a frequent finding in patients undergoing CEA. Many patients have hypertension as a comorbid condition, which is often further exacerbated by the surgical stress and manipulation of the carotid body, which causes release of catecholamines and sympathetic stimulation.

Invasive arterial pressure monitoring and suitable venous access to infuse vasoactive medications are necessary during carotid surgery.

What is the most likely etiology of this patient's findings?

This patient most likely has had a cerebrovascular accident due to an arterio-to-arterial embolus; more than 95% of patients will fit into this category. Weakness can also develop as a result of a hyperperfusion syndrome, which occurs in patients with severe carotid stenosis who have now reestablished flow to the affected cerebral hemisphere. Such patients usually have a greater than 95% carotid stenosis with a less than 1-mm channel in the affected carotid artery. Typically, the syndrome does not develop in the postoperative anesthesia care unit (PACU), but several hours afterward when the patient begins complaining of a headache, and, in severe cases, develops hemiparesis.

Because a cerebrovascular accident is most likely, when the anesthesiologist is called to see such a patient in the PACU, a thorough neurological examination quantifying any cranial nerve involvement and the degree of weakness on the contralateral side should be performed. Any hemodynamic changes need to be treated immediately, with assurance of adequate hemoglobin and oxygenation levels. Ultrasonic evaluation of the carotid artery is frequently required. The surgeon needs to be notified at once, as it may be necessary to return to the operating room to explore the carotid artery.

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