The last few decades have yielded significant insights into the mechanisms of acute cerebral injury. The most important finding has been that a significant proportion of neurologic damage after injury occurs secondarily and, thus, is potentially preventable or treatable. This discovery has altered the approach to acute neurologic injury and, coupled with improved diagnostic techniques, has reversed the therapeutic nihilism that had previously marked the field. In this chapter, we will attempt to provide a foundation in the basics of cerebrovascular physiology. Based on these foundations, we will attempt to outline a rational approach to the treatment of both general and specific neurologic emergencies.
Approximately 20% of the cardiac output and oxygen consumption is utilized by the human brain, which accounts for only 2% of the total body mass (1). The majority of cerebral oxygen consumption occurs at the highly metabolically active gray matter structures of the brain. The relatively high metabolic activity of these cells is needed to sustain the electrical gradients of neurons needed to transmit electrical signals, synthesize transmitters, and maintain the infrastructure of the cell (2).

The central nervous system utilizes intracellular stores of phosphocreatine and adenosine triphosphate (ATP) as its energy source. These stores are constantly replenished through the aerobic oxidative phosphorylation of glucose at the inner membrane of the neuronal mitochondria. Glucose is the main substrate for brain metabolism, with specific glucose trans- 

fersases in the capillary endothelium providing entry into the neuronal cytoplasm. Brain energy reserves are limited. Electrical activity is inhibited within seconds, and cellular breakdown occurs within minutes of lack of oxygen delivery to the neurons. Anaerobic metabolism provides only a small amount of energy needed to maintain neuronal cellular activity (2).

Under normal conditions, cerebral blood flow (CBF) and regional distribution of oxygen are tightly coupled. Increases in cerebral metabolism lead to an increase in the delivery of oxygen and glucose to metabolically active tissue. Cerebral blood flow is, by convention, measured in milliliters of flow per 100 g of tissue per minute. Normal CBF ranges between 30 and 70 mL/100 g/min. The cerebral metabolic rate of oxygen consumption (CMRO\textsuperscript{2}) is the rate of oxygen utilized by cerebral tissue. It is calculated by the Fick method of measuring the product of CBF and the cerebral oxygen arterial–venous difference of an inert nondiffusible substance. Direct and indirect methods exist to estimate both CBF and CMRO\textsuperscript{2}. Cerebral oxygen delivery (CDO\textsuperscript{2}) is the product of CBF and the oxygen-carrying capacity of hemoglobin. The normal mean capillary partial pressure of oxygen (PO\textsubscript{2}) is approximately 65 mm Hg, representing a difference between normal arterial PO\textsubscript{2} (90–95 mm Hg) and venous PO\textsubscript{2} (35–40 mm Hg). Normal values for standard measures of CBF, CMRO\textsuperscript{2}, and CDO\textsuperscript{2} are detailed in Table 43.1.

Cerebral ischemia develops if cerebral oxygen utilization cannot meet metabolic demands. This can result from problems with cerebral oxygen delivery, increased metabolic demands, or impaired oxygen utilization. Decreases in CDO\textsuperscript{2} can occur with decreases in cerebral blood flow due to stroke, increased intracranial pressure (ICP), decreased cardiac output, or hypotension. The cerebral metabolic rate increases with increased cerebral activity, seizures, or hyperthermia. Blood loss or carbon monoxide poisoning can decrease the oxygen-carrying capacity (3).

Inadequate oxygen delivery due to decreased CBF is the most common cause of cerebral ischemia. Synaptic transmission, and hence electrical activity, discontinues at CBF below 15 to 20 mL/100 g/min. Further decreases in CBF lead to ionic pump failure and membrane destabilization (3). Cerebral oxygen delivery can also be affected by changes in the concentration of oxygen bound to hemoglobin. Hemoglobin has a high affinity for binding oxygen, with greater than 90% of the hemoglobin binding sites for oxygen saturated at arterial partial pressures of oxygen (P\textsubscript{a}O\textsubscript{2}) greater than 70 mm Hg. Increasing P\textsubscript{a}O\textsubscript{2} with increases in inspired oxygen above this level, therefore, has little effect on oxygen delivery. However, a large oxygen gradient is needed at the cellular level to provide an adequate pressure gradient for the oxygen molecule to diffuse to the mitochondrial inner membrane. The critical required P\textsubscript{a}O\textsubscript{2} at the level of the mitochondria is estimated at 5 mm Hg, hence, at low oxygen gradients (venous P\textsubscript{a}O\textsubscript{2} levels below 30 mm Hg), cerebral insufficiency will develop (2).

Several mechanisms exist to maintain oxygen delivery to the brain. Cerebral hyperperfusion will lead to the depolarization of medullary neurons mediating sympathetic output, which consequently results in a compensatory increase in blood pressure and heart rate. Decreased cerebral perfusion leading to decreased arterial oxygen delivery to the cerebral capillary bed will lead to venodilation lowering of the postcapillary pressure and increasing flow across the capillary bed. Oxygen extraction bound to hemoglobin is increased across the capillary bed as CBF continues to decrease. This increase in oxygen extraction can be detected by measuring jugular venous blood and comparing it to its arterial oxygen content. Finally, increases in local hydrogen ion concentration will occur as ischemia develops, presumably due to lactate production from anaerobic metabolism. The resultant shift in the oxygen displacement curve of hemoglobin to the right will result in increased oxygen release from hemoglobin to the local cerebral tissue.

Cerebral ischemia can be categorized into focal and global causes. Focal ischemia occurs when there is severe or complete reduction of blood flow to one of the major arteries of the brain. Neurologic impairment develops in functional patterns attributable to the particular arterial distribution that is involved. This most commonly is seen secondary to embolic or atherosclerotic large vessel occlusion. Global ischemia refers to severe reductions or cessation of blood flow to the entire brain. This most commonly occurs after cardiac arrest but can be seen in any condition that leads to global cerebral hyperperfusion or hypoxia (2,3).

Cerebral tissues exhibit selective vulnerability to ischemia. Neurons are the least resistant to cerebral ischemia, followed by oligodendroglia, astrocytes, and endothelial cells in order of

### Table 43.1

<table>
<thead>
<tr>
<th>NORMAL VALUES FOR CEREBRAL BLOOD FLOW AND METABOLISM</th>
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<tr>
<td>Cerebral blood flow (CBF)</td>
</tr>
<tr>
<td>Systemic arterial oxygen content (CaO\textsubscript{2})</td>
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<tr>
<td>Jugular venous oxygen content (C\textsubscript{v}O\textsubscript{2})</td>
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<tr>
<td>Cerebral oxygen delivery (CDO\textsuperscript{2})</td>
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<tr>
<td>Cerebral arterial–venous oxygen content difference</td>
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<td>Cerebral metabolic rate of oxygen consumption</td>
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<td>CMRO\textsuperscript{2}</td>
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susceptibility. Specific neuronal populations also exhibit selective vulnerability to ischemia and hypoxia. The most susceptible neurons to anoxia are the CA1 and CA3 cells, located in the medial hippocampus. These cells are the most widely connected and have the highest resting metabolic rate of all neurons. Similarly, highly metabolically active cells with high susceptibility to ischemia include the cerebellar Purkinje cells, cortical cell levels 3 and 5, and the medium-size neurons of the strata (2,4).

Vascular patterns of neuronal injury encountered with cerebral anoxia can be attributed to the selective ischemic vulnerability of varying cerebral cell types, coupled with the different mechanisms by which ischemia or hypoxia can occur. Watershed or border zone infarctions occur at the boundary between the perfusion territories of the large cerebral arteries. Hypoxygenation after cardiac, septic, or hemorrhagic shock is the most common etiology for this phenomenon. Selective loss of neurons in the hippocampus, basal ganglia, cortex, and cerebellum can lead to laminar necrosis of these tissues, and may occur after ischemia leads to cell death in these cells, but circulation is restored prior to involvement of other neuronal cell populations. Dysfunction of the central white matter can develop in the setting of hypoxia where hypoxia does not occur. Cerebral white matter is believed to be selectively vulnerable to this condition due to its decreased resting regional CBF compared to the more metabolically active gray matter (2).

Neuronal cell death is a product of both the severity and time of ischemia; thus, incomplete degrees of ischemia can be tolerated for longer periods of time. However, there is some critical threshold of ischemia that will ultimately lead to necrosis. The duration and severity of ischemia needed to reach a critical threshold can be modified by metabolic factors such as hyperpyrexia, temperature, and metabolic activity. Critical reductions of oxygen, therefore, produce significant but nonfatal degrees of ischemia and neuronal functional death. Lethal reductions of oxygen imply that some threshold has been crossed that will lead to a series of events, and ultimately to cell death (2).

Oxygen deprivation leading to neuronal cell death proceeds through several distinctive steps. The high metabolic activity of neurons rapidly depletes oxygen-derived ATP and phosphocreatine stores, resulting in failure of synaptic transmission the electroencephalogram (EEG) at this point becomes flat, and consciousness is lost. Electrical failure occurs as CBF falls below 16 to 20 ml/100 g tissue/minute and cerebral oxygen consumption falls below one third of its normal resting metabolism, but restoration of CBF after electrical failure will allow functional recovery of the cell. Further decreases in CBF to less than 10 ml/100 g tissue/minute will lead to failure of the energy needed to maintain the activity of the mitochondrial enzymes potassium pump. As flow continues to decrease, membrane depolarizations occur, and ischemic gradients are lost as potassium effluxes from the cell and sodium and water enter the cells, leading to the development of cytotoxic edema (Fig. 43.1). Release of excessive amounts of glutamate is believed to mediate the process of excitatory cell death after ischemia. Normally, glutamate, an excitatory neurotransmitter, is released into the synaptic cleft and rapidly cleared by energy-dependent cellular uptake mechanisms. In the setting of energy failure, extracellular glutamate levels increase. Most glutamate neurotoxicity is mediated through N-methyl-D-aspartate (NMDA) receptors. Stimulation of these receptors activates calcium channel-mediated entry into the cell. Intracellular calcium subsequently activates a number of destructive enzymatic processes, including protease destruction of structural proteins and phospholipase destruction of plasma membranes, with release of arachidonic acid and endonucleases capable of fragmenting DNA repair mechanisms. Mitochondrial uptake of calcium leads to the interruption of electron transport and the development of oxygen-free radicals (1,3,5,6).

The above process leads to necrosis of brain tissue with distinctive neuropathologic features. Necrosis is characterized by cellular swelling, membrane wall lysis, and a resultant inflammatory reaction to clear the necrotic tissue. Cells die in groups, leaving large areas of necrotic tissue (7). Apoptosis, or programmed cell death, also occurs in cerebral ischemia. Apoptosis is an organized and regulated form of cell death where intra- and extracellular signals lead to a programmed process of cell death with preservation of the mitochondria. Pathologically, apoptosis leads to cell shrinkage, chromatin condensation, and dissolution of the cell membrane. Inflammation is not commonly seen. These two distinctive forms of cell death probably represent a spectrum of the biochemical and morphologic changes that can occur in cerebral ischemia (1).

In focal ischemia and infarction, a central region of necrosis can be surrounded by a potentially viable area of tissue described as the ischemic penumbra. The ischemic penumbra can be defined through CBF measurements and electrophysiology or biochemical and genetic methods. The penumbra, by definition, is tissue that is potentially salvageable if circulation is restored. Neurocritical care focuses on methods to restore flow to the ischemic penumbra and potentially limit the extent of neuronal cell death.
REGULATION OF CEREBRAL CIRCULATION

Methods of Cerebral Blood Flow Measurements

The study of modern cerebrovascular physiology began in the 1940s when Kety and Schmidt described a direct method for quantifying CBF based on the Fick principle (8). The original Fick equation stated that oxygen uptake in the lung was equal to the product of cardiac output and the arteriovenous difference of oxygen (9). Kety substituted nitrous oxide, an inert, nonmetabolizable, diffusible tracer in place of oxygen (10), and thus, the accumulation of nitrous oxide in the brain was substituted for the absorption of oxygen in the lungs (11). This technique is still considered the gold standard for quantifying CBF, but is invasive and limits measurements only to global CBF (12).

The development of external detection systems allowed for the use of radioactive tracers to measure regional areas of CBF. Focal perfusion and washout of substances could be used to determine flow into local brain regions. Xenon\(^{133}\), a diffusible \(\gamma\)-emitting substance, was used initially as an injection and later through inhalation. Perfusion and washout were calculated using a rotating \(\gamma\)-counter. Later, the application of computed tomographic techniques (Xenon CT) allowed for improved resolution of regional areas of cerebral blood flow (rCBF) (13). Single photon emission computed tomography (SPECT) uses technetium\(^{99m}\) as a ligand to measure rCBF, and is the most commonly used technique to measure CBF. Technetium\(^{99m}\) crosses the blood-brain barrier and is trapped within cells. The tracer accumulates in varying brain regions according to the rate of delivery, and thus is a marker for rCBF. Multidetector systems are used to quantify the accumulation of tracer (14). Positron emission tomography (PET) is similar to SPECT in that an external detector is used to measure an accumulated radioactive substance. The generation and use of positrons, however, significantly improve resolution. A positron is an electron with a positive charge formed by the decay of radioisotopes. It requires a cyclotron or linear accelerator for its production. The collision of a positron with an electron produces two photons that are sent off at 180 degrees. The simultaneous detection of these photons allows for improved resolution and three-dimensional reconstruction of rCBF. In addition to measuring CBF, different radiotabeled ligands can be used to measure cerebral blood volume (CBV), glucose metabolism, or cerebral oxygen extraction. PET provides the highest quanitative measure of rCBF and can be used for a variety of physiologic experiments (15). However, it is expensive, requires a cyclotron, and is limited to a few academic centers (Fig. 43.2).

New techniques of bolus tracking with magnetic resonance imaging (MRI) and computed tomography (CT) have allowed for acute assessments of cerebral perfusion. In these techniques, a bolus of a contrast agent is detected either through changes in the \(T_2\) signal or Hounsfield units. Estimations of CBF can be made by measuring the transit time required for these boluses to pass through cerebral tissue. These techniques are being used widely for the acute assessments of cerebral infarctions (16,17).

Factors that Regulate Cerebral Blood Flow

Cerebral autoregulation refers to the capacity of CBF to remain constant despite changes in cerebral perfusion pressure. It is a pressure phenomenon that needs to be differentiated from the effect of carbon dioxide and arterial oxygen tension on CBF. This control, and thus the shape of the autoregulatory curve, can be modified by a number of extrinsic factors. Hypertension, hypercapnia, and increased sympathetic nervous activity will increase both the upper and lower ranges of autoregulation. Chronic hypotension, hypocapnia, and parasympathetic activity will lower the set points of autoregulation. The autoregulatory curve will shift upward with advancing age. In the healthy, normotensive individual, CBF is a pressure-passive phenomenon below perfusion pressures of 50 to 60 mm Hg and above perfusion pressures of 150 to 160 mm Hg. Between these broad parameters, CBF increases only slightly (18,19) (Fig. 43.3).

In most vascular beds, autoregulation occurs at the level of the arterioles. A significant proportion of vascular resistance in the cerebral circulation, however, is modulated at the level of the cerebral arteries. In cats, dogs, and monkeys, approximately 40% of the cerebral vascular resistance is mediated by changes in the baseline psal artery diameter of vessels greater than 400 \(\mu\)m in diameter (20).

In response to hypotension, both cerebral arteries and arterioles will dilate to maintain constant CBF. Vessel dilatation progresses from the largest vessels to the smallest with decreases in cerebral perfusion pressure (21). Cerebral arterioles will also continue to dilate below the lower limit of autoregulation (19). Further drops in pressure flow slowly across the capillary bed and lead to an increase in the oxygen extraction coefficient...
The metabolic theory of pressure autoregulation postulates that the local changes in cerebral blood flow found with changes in cerebral metabolic activity are mediated through the release of local neurochemical substances from the nonvascular cells of the central nervous system (18). The tight coupling of flow to metabolism and the timing of autoregulation suggest that this postulated mechanism. Several substances have been suggested including hydrogen ion concentrations, carbon dioxide, nitric oxide, adenosine, potassium, and calcium (27). Experimental evidence exists in favor of and against all of the postulated mediators (18, 28–30). Varying combinations have also been suggested. Most recently, changes in potassium levels mediated through alterations in calcium gene-related peptides have been suggested as a mechanism of arteriolar dilation (31). Changes in cerebral perfusion pressure have been observed that alter the degree of endothelial oxygen tension, and have been suggested as an important mechanism for autoregulation (32).

Neurogenic Influences. The role of direct neurogenic influences on cerebral autoregulation is limited. As mentioned, the sympathetic and parasympathetic nervous system plays a role in modulating the cerebral autoregulatory curve. However, direct neural control over small arteries or arterioles that regulate focal changes in CBF does not occur, and other intrinsic nerve fibers may be in a position to regulate vascular tone (33). The localization or central control of these nerves has a far more potent elusive (18, 34).

**Regulation of Cerebral Blood Flow by Carbon Dioxide and Oxygen**

Changes in the partial pressure of carbon dioxide (\(\text{PCO}_2\)) have significant effects on CBF. A 1-mm Hg change in \(\text{PCO}_2\) results in an approximately 2.5% to 4% change in CBF. This effect is more pronounced in the gray matter than white matter. The response curve of \(\text{PCO}_2\) is sigmoidal, with the CBF response flattening below 15 to 20 mm Hg and above 100 mm Hg. The vasodilation occurs in all vessel sizes but is most pronounced on the smaller arterioles (31) (Fig. 43.4).

Changes in vessel diameter are mediated through alterations in cerebrospinal hydrogen ion concentrations (CSF pH). The direct application of \(\text{CO}_2\) or bicarbonate to pial arterioles does not affect vessel diameters. Since \(\text{CO}_2\) is freely diffusible across the blood-brain barrier, changes in \(\text{PaCO}_2\) will affect both cerebrospinal fluid hydrogen ion and bicarbonate concentrations (35). The response of changes in hydrogen ion concentration is relatively short-lived, lasting only a few hours, as the choroid plexus of the brain will compensate for changes in hydrogen ion concentration by adjusting the production of cerebrospinal fluid bicarbonate (36).

At partial pressures of oxygen below 50 mm Hg, there is a rapid increase in CBF. Again, this is more significant in gray, as opposed to white, matter. There is a linear relationship between...
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FIGURE 43.4. Alterations in cerebral blood flow with changes in the partial pressure of carbon dioxide. Note the S-shaped curve, with flat portions at the extremes of the curve. Data obtained from normotensive dogs. (From Harper AM, Glass HI. Effect of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial pressures. J Neurol Neurosurg Psychiatry. 1965;28:449–452.)

the arterial oxygen content and CBF in hypoxia (Fig. 43.5) (21,37). Vasoactive effects may be mediated directly through oxygen or adenosine A₂ receptors (11).

Cerebral Blood Volume and Intracranial Hemodynamics

Normal ICP measures between 5 and 8 mm Hg, with statistical variations ranging as high as 15 mm Hg. Beyond this level, some degree of intracranial pathology should be suspected (38). Normal ICP fluctuates rhythmically, approximately 3 to 5 mm Hg. The sinusoidal pattern of this fluctuation can be seen on ICP pressure traces and was originally described by Traube and Hering (39). The origin of the ICP waves is unknown, but may have to do with phasic constriction and dilation of the cerebral arterioles (40). Cerebral perfusion pressure (CPP) is the perfusion pressure of blood through the brain. This is defined as the pressure difference between mean arterial pressure (MAP) and mean jugular venous pressure. However, when ICP is greater than jugular venous pressure, ICP is substituted for jugular venous pressure, and hence, CPP is typically reported as MAP – ICP (36).

The intracranial pressure volume curve demonstrates a relatively flat portion where increases in volume are accommodated with little change in pressure. At some inflection point, these processes are exhausted, and small changes in volume lead to larger increases in ICP (Fig. 43.6). This pressure volume curve may, thus, represent the displacement of various fluids from the intracranial space.

The approximate contents of the intracranial cavity consist of the brain parenchyma (75%), blood (20%), and CSF (5%). Most of the intracranial blood resides on the venous side of the circulation (38). According to the Monroe doctrine, the overall volume of the contents of the intracranial cavity must remain constant. Accordingly, any increase in the intracranial contents from venous engorgement, intracerebral hemorrhage, tumors, edema, etc., must be compensated by an equal displacement of fluids or tissue. Monroe postulates that the flat portion of the ICP volume curve represents displacement of CSF into the more compliant spinal subarachnoid space. Progressive increases in volume lead to further displacement of venous and arterial blood. Finally, brain tissue is displaced and herniation will occur (Fig. 43.6) (41).

Intracranial compliance can be determined by measuring the speed and duration of changes that occur in the intracranial cavity. Tumors, for example, can grow to large volumes before becoming problematic. The slow-growing process allows for a gradual increase in intracranial compliance. Similarly, an acute hemorrhage of the same size will not be tolerated.

Intracranial compliance can be determined by measuring the change in ICP to a given volume. A volume pressure response (VPR) is estimated by measuring the ICP response to an infusion of 1 mL of sterile saline into an intraventricular catheter (42). Small changes in response to this increased volume suggest that the patient was on the flat portion of the volume pressure curve. Increases in ICP greater than 4 mm Hg in response to 1 mL of fluid would suggest that intracranial reserve was limited. A more widely used index to measure intracranial compliance has been the pressure volume index (PVI). This index estimates the volume needed to increase ICP by a factor of 10 (43).

Spontaneous and sustained elevations in ICP were noted by Lunberg early in the study of cerebral hemodynamics (44). The origin of these “plateau waves” had been speculative until the 1980s when Rosner et al. provided a potential rationale as to how these could develop. Rosner accounted for these waves through the observation of subtle changes in MAP and ICP, and their effect on CBV and ICP. Rosner observed that plateau waves were always preceded by subtle drops in CPP. As previously noted, decreases in CPP will lead to cerebral vasodilation of the cerebral arteries and arteries, which consequently

FIGURE 43.5. Alterations of regional cerebral blood flow to changes in arterial oxygen tension. Note oxygen tensions below approximately 50 lead to a sharp increase in regional cerebral blood flow (rCBF); regional areas of cerebral blood flow. (From Golmanov EV, Rees DJ. Oxygeon and cerebral blood flow. In: Welch KMA, Caplan LR, Reis DJ, et al., eds. Primer on Cerebrovascular Disease. San Diego: Academic Press; 1997:58-60.)
result in an increase in total CBV through an increase of blood in the cerebral venous system. At some point, however, continued decreases in CBF will lead to a decrease in CBV (Fig. 43.3) (45). The cerebral engorgement of blood that occurs with the initial decrease in MAP increases ICP and decreases CPP, thus initiating a cycle of decreasing CPP, increasing CBV, and increasing ICP. The process is spontaneously reversed by an acute elevation of blood pressure from a Cushing response. This sympathetic response occurs in the setting of decreased CPP as the brainstem center’s modulating sympathetic activity becomes oligemic (46). Rosner has used these observations as the basis for management of cerebral perfusion pressure due to head trauma (41).

**Cerebral Edema**

Intracranial hypertension can be caused by expanding masses, cerebral engorgement, or the development of cerebral edema. Cerebral edema may compress brain structures, leading to herniation, or reduce cerebral perfusion with subsequent infarction (47). Cerebral edema is roughly defined as an increase in the brain tissue water and sodium content of the extravascular space (48). Cerebral edema, therefore, different from brain engorgement, which represents an increase in the blood volume of the intravascular space (49).

Cerebral edema can be defined according to its location or mechanism of production. According to location, edema can occur either inside the brain cells (intracellular) or outside the cells and the intravascular space in the interstitium (interstitial). While certain forms of cerebral edema may predominate, pure forms of either type of edema rarely exist. Cytotoxic edema is the term employed to describe the intracellular edema that develops after the loss of cell wall integrity (50). The terminology implies a toxic etiology, but it is most often seen in cellular energy failure due to ischemia or hypoxia. Vasogenic edema represents an expansion of the interstitium due to disruption of the capillary blood-brain barrier, which allows the extravasation of fluid from the intravascular space. Interstitial edema develops secondary to increases in the hydrostatic pressures of the ventricular system draining the CSF. Osmotic edema refers to the intracellular swelling that occurs due to rapid changes in brain sodium concentrations or the osmotic disequilibrium syndromes (48).

**MECHANISMS OF BRAIN INJURY AND THERAPEUTIC CONCERNS**

**Immediate Concerns**

The most important features in managing acute neurologic injury are rapid transport to a trauma center or stroke center, management of airway, oxygenation, and circulation issues; careful and repeated monitoring; and prompt head imaging, with immediate medical or surgical management of expanding mass lesions (51). The mechanisms of neurologic injury will, of course, vary depending upon the nature of the injury, but all will include—to some degree—secondary injury caused by cerebral ischemia. In head trauma, shearing injury develops due to different deceleration rates of gray and white matter. The resultant disruption of neurologic tracts is followed by a period of ischemia and secondary injury. Prolonged seizure activity in status epilepticus leads to hippocampal ischemia, cell death, and atrophy (52). A zone of ischemia surrounds all areas of cerebral infarction and cerebral hemorrhage (53).

The primary goal of acute neurologic management is to prevent secondary injury. This is attained by initiating measures...
to support cerebral oxygen delivery and limit cerebral metabolism. Hypoxemia, hypotension, expanding mass lesions, persistent fever, and intracranial hypertension all potentially worsen secondary injury by limiting cerebral oxygen delivery and increasing cerebral metabolism. Immediate attention and correction of the above problems can have a significant impact on both immediate and long-term outcome (51–53). A sense of urgency of the treating team is critical to providing early and aggressive resuscitative efforts (53).

The specific management of acute neurologic emergencies will vary according to the nature of the illness or injury, but some general concepts can be applied to all neurologic emergencies. The basics of all life support protocols focus on the initiation of adequate airway control, restoration of adequate respiration, and circulation. Loss of pharyngeal tone leading to airway obstruction can occur in patients with a depressed level of consciousness. Impairment of respiratory drive can occur after seizures, head trauma, anoxic injury, stroke, or metabolic disturbances. Decreases in cerebral perfusion are common after head or multisystem injury, shock, sepsis, and hemorrhage.

The acute management of neurologic injury must focus on the maintenance of cerebral oxygen delivery. To accomplish this goal, adequate oxygenation, respiration, and blood pressure must be ensured. Airway control via endotracheal intubation for the neurologic patient should be performed immediately in all patients with a Glasgow coma score (GCS) of 8 or less. Supplemental oxygenation and red blood cell transfusions should be given to provide adequate oxygenation. Once the basics of life support have been secured, a rapid history should be obtained from supporting personnel or family. In many circumstances, the patient will be unable to provide an adequate history. The immediate details surrounding the incident are crucial to understanding the nature or type of injury. A general physical exam prior to the neurologic assessment should focus on possible trauma or other medical conditions. Raccoon eyes or a Battle sign (bruising of the orbits and mastoid region respectively) is evidence for a basilar skull fracture. In head trauma with loss of consciousness, neck injury should be assumed and cervical stabilization provided. A fundoscopic exam may reveal papilledema or subhyaloid hemorrhages. Underlying body or breath odors may suggest intoxication. New onset atrial fibrillation may be the only clue to the mechanism of a cerebral infarct. Sudden eye, finger, or limb movements may be the only indication for subclinical seizure activity. A rapid neurologic assessment focusing on the level of consciousness, the cranial nerve exam, and any localizing features can be obtained within minutes. The GCS is commonly used as a quantitative assessment of neurologic function (54).

More recently, a new coma score has been developed that has been validated in the neurointensive care unit (55) (Fig. 43.7). Further validations of this scale are under way in nonneurologic staff and intensive care units.

Emergent head imaging is obtained as soon as the patient is considered hemodynamically stable to leave the emergency room or intensive care unit. CT is the usual initial choice due to accessibility. A head CT without contrast is the best test to assess for skull or bone fractures and the possibility of acute intracranial blood. Large intracerebral, epidural, or subdural hematomas may need emergent evacuation. New imaging techniques such as CT perfusion and MRI for perfusion diffusion imaging may be able to identify specific salvageable ischemic brain regions that are at risk for infarction. New portable CT scanners hold promise for even earlier assessment, as these do not require the often risky movement of the patient to the radiology area.

Baseline laboratories to be obtained include electrolytes, complete blood count, prothrombin and activated partial prothrombin times, liver function tests, blood urea nitrogen, and creatinine levels.

The Brain Trauma Foundation guidelines recommend ICP monitoring for patients with severe head injury (defined as a GCS of 8 or less) and an abnormal CT scan. ICP monitoring is additionally recommended for severe head trauma and a normal CT scan if two or more of the following are present (56):

- Abnormal motor posturing
- Age older than 40 years
- Systolic blood pressure less than 90 mm Hg (56)

Specific treatment can be initiated once cardiopulmonary status has been stabilized and general and neurologic assessments have been completed. Guidelines and protocols currently exist for prehospital management of head trauma, intravenous and intra-arterial lysis of cerebral thrombosis, intracerebral hemorrhage, and status epilepticus (32,57–60).

General Therapeutic Considerations

In addition to the above measures designed to maintain adequate cerebral oxygen delivery, there has been a growing interest in the role of temperature, glucose, and blood pressure modulation in the management of neurologic injury. There is a large body of evidence in standardized laboratory animal models of cerebral ischemia that elevations in brain temperature both increase the amount of neuropathologic damage to injured tissue and induce damage to brain areas not usually involved (61). Excitotoxicity is believed to be the most likely mechanism for induction of these changes.

Hyperthermia

Hyperthermia increases both glutamate release and extracellular concentration. Free radical production is accelerated, and the sensitivity of neurons to excitotoxic injury is increased (62, 63). The role for excitotoxicity is corroborated by a noted increase in cellular acidosis and depolarization in the ischemic penumbra. Other postulated mechanisms for neurologic damage with hyperthermia include inhibition of protein kinases responsible for synaptic transmission and cellular repair, and the release of neuronal proteases. The latter is believed to be the mechanism for worsening cerebral edema at higher brain temperatures (64–67). Hyperthermia worsens outcomes in ischemic stroke patients (68), with a 2.2-fold increase in morbidity and mortality for every 1°C increase in temperature above 37.5°C (69). Similarly, these results have been extended to the neurologic intensive care unit population. Hyperthermia in this population both worsened outcome and increased length of stay (70).

Hypothermia

Hypothermia may have a neuroprotective role in preventing many of the neuropathologic changes described with hyperthermia. Early applications of hypothermia protocols were problematic, with significant cardiac complications occurring below temperatures of 30°C. Most protocols were used during
### Chapter 43: Central Nervous System


**Eye response**
- E4: Eyelids open or opened, tracking, or blinking to command
- E3: Eyelids open but not tracking
- E2: Eyelids closed but open to loud voice
- E1: Eyelids closed but open to pain
- E0: Eyelids remain closed with pain

**Motor response**
- M4: Thumbs-up, fist, or peace sign to command
- M3: Locating to pain
- M2: Flexion response to pain
- M1: Extensor posturing
- M0: No response to pain or generalized myoclonic status epilepticus

**Brainstem reflexes**
- B4: Pupil and corneal reflexes present
- B3: Pupil wide and fixed
- B2: Pupil or corneal reflexes absent
- B1: Absent pupil, corneal, and cough reflex
- B0: Absent pupil, corneal, and cough reflex (using tracheal suctioning) are absent

**Respiration**
- R4: Not intubated, regular breathing pattern
- R3: Not intubated, Cheyne-Stokes breathing pattern
- R2: Not intubated, irregular breathing pattern
- R1: Breaths above ventilator rate
- R0: Breaths at ventilator rate or apnea

**Eye response (E)**
Grade the best possible response after at least 3 trials in an attempt to elicit the best level of alertness. A score of E4 indicates at least 3 voluntary excursions. If eyes are closed, the examiner should open them and examine tracking of a finger or object. Tracking with the opening of 1 eyelid will suffice in cases of eyelid edema or facial trauma. If tracking is absent horizontally, examine vertical tracking. Alternatively, 2 blinks on command should be documented. This will recognize a locked-in syndrome (patient is fully aware). A score of E3 indicates the absence of voluntary tracking with open eyes. A score of E2 indicates eyelids opening to loud voice. A score of E1 indicates eyelids open to pain stimulus. A score of E0 indicates no eyelids opening to pain.

**Motor response (M)**
Grade the best possible response of the arms. A score of M4 indicates that the patient demonstrated at least 1 of 3 hand positions (thumbs-up, fist, or peace sign) with either hand. A score of M3 indicates that the patient touched the examiner’s hand after a painful stimulus compressing the temporomandibular joint or supraorbital nerve (localization). A score of M2 indicates any flexion movement of the upper limbs. A score of M1 indicates extensor posturing. A score of M0 indicates no motor response or myoclonic status epilepticus.

**Brainstem reflexes (B)**
Grade the best possible response. Examine pupillary and corneal reflexes. Preferably, corneal reflexes are tested by instilling 2-3 drops of sterile saline on the cornea from a distance of 4-6 inches (this minimizes corneal trauma from repeated examinations). Cotton swabs can also be used. The cough reflex to tracheal suctioning is tested only when both of these reflexes are absent. A score of B4 indicates pupil and cornea reflexes are present. A score of B3 indicates one pupil wide and fixed. A score of B2 indicates either pupil or cornea reflexes are absent. B1 indicates both pupil and cornea reflexes are absent, and a score of B0 indicates pupil, cornea, and cough reflex (using tracheal suctioning) are absent.

**Respiration (R)**
Determine spontaneous breathing pattern in a nonintubated patient and grade simply as regular R4, irregular R2, or Cheyne-Stokes R3 breathing. In mechanically ventilated patients, assess the pressure waveform of spontaneous respiratory pattern or the patient triggering of the ventilator R1. The ventilator monitor displaying respiratory patterns is used to identify the patient-generated breaths on the ventilator. No adjustments are made to the ventilator while the patient is graded, but grading is done preferentially with Pao2 within normal limits. A standard apnea (oxygen-diffusion) test may be needed when patient breathes at ventilator rate R0.
cardiac arrest with cardiac and neurosurgical procedures with varying results (71). Moderate hypothermia (33°C) has been employed successfully, with significant improvements in neurologic outcome in two randomized trials for global cerebral ischemia after cardiac arrest (72,73). In both of these protocols, hypothermia was induced early—within 2 to 8 hours—and maintained for 12 to 24 hours before passive rewarming. Sedation and pharmacologic paralysis were instituted to prevent the hypermetabolism and hypothermia that occurs with shivering. Hypothermia, however, failed to improve outcome in a randomized trial of patients with severe head trauma (74). Subgroup analysis revealed worse outcomes in patients older than 45 years and in spontaneous hypothermic patients who were actively rewarmed. It is speculated that the lack of efficacy was due to the delay in the initiation of treatment (71). Hypothermia has been applied to patients with ischemic stroke in a small case series with promising results (75). A multicenter trial using a randomized application of hypothermia for large hemispheric infarcts is currently under way.

Hyperglycemia

Glucose control in patients with neurologic injury has recently received a considerable amount of attention. Hyperglycemia has been well documented to increase infarct size and worsen outcome in ischemic stroke (76,77). More recent studies in patients treated with thrombolytics have supported these observations (78–81). The negative effects of hyperglycemia may be limited to large-vessel ischemia or occlusions (82). Hyperglycemia has also been associated with a worsened outcome in subarachnoid hemorrhage (83), and results in head trauma have been inconsistent (84–86).

Hyperglycemia in acute neurologic injury may be attributed to several different mechanisms. The most common proposed mechanism for the development of hyperglycemia is a hormonally induced stress response that occurs with neurologic injury, thus leading to an increase in catecholamine and cortisol release. Other proposed means by which hyperglycemia can occur in neurologic injury include pituitary ischemia, direct irritation of glucose regulatory centers, and the discovery of latent hypothalamic damage, or a physiologic response to volume depletion. The center of the controversy, thus, is determining whether the hypertension encountered during neurologic injury is pathologic or a normal compensatory and protective physiologic response. In addition, cerebral autoregulation is disturbed to varying degrees after brain injury; after the completion of autoregulation, CBF directly correlates with MAP. Disturbances in cerebral autoregulation can be global or focal, involving only areas adjacent to the damaged brain.

The controversy surrounding the optimal blood pressure after neurologic injury is based on competing processes. In areas surrounding neurologic injury, the blood-brain barrier is often damaged. In these areas, hypertension can lead to the development of cerebral edema by increasing the intravascular Starling forces, driving fluid into the interstitium of the brain. Brain area surrounding tumors, arteriovascular malformations, or local areas of trauma or infarction are particularly susceptible. Blood pressure management is often titrated to maintain systolic pressures below 140 mm Hg after neurosurgery to avoid the complications of postoperative edema and breakthrough hemorrhage. In severe carotid stenosis, the CPP to the affected cerebral hemisphere may be compromised, leading to a shift of the cerebral autoregulatory curve to lower blood pressures. Hypertension after carotid endarterectomy may need to be treated to avoid the similar complications of breakthrough hemihypomia and hemorrhage. Large cerebral infarcts similarly have a tendency for hemorrhagic conversion with sustained hypertension.

Alternatively, overly aggressive management of hypertension after neurologic injury can be potentially deleterious. Brain areas with disturbed autoregulation may require a specific pressure to maintain adequate perfusion. An example of this is the development of plateau waves after head trauma that represents cerebral vasodilation in response to inadequate cerebral perfusion. Cerebral vasospasm after subarachnoid hemorrhage (SAH) is treated with induced hypertension. In selected small case series, induced hypertension has been used in the treatment of stroke (97). Optimal blood pressure may need to be titrated to the individual patient and disease process.

Endotracheal Intubation

Medical complications are common after neurologic injury and worsen outcome (98,99). The risk of aspiration pneumonia is increased in patients with a depressed level of consciousness. Early recognition and treatment of this complication are needed. Endotracheal intubation is required for neurologic patients who are unable to maintain airway patency or protect their airway from secretions. Endotracheal intubation provides...
a poor outcome for patients with ischemic and hemorrhagic stroke (100). The timing of extubation in the neurologic pa-
tient is controversial, since many patients remain intubated solely for airway protection. Dogma mandates that patients remain intubated until their GCS improves to greater than 8. However, a more recent prospective study has suggested that prolonged intubation in neurologic patients increases the rate of ventilator-acquired pneumonias, increases length of stay, and worsens outcomes. The authors recommended early extubation based on the patient’s ability to control secretions (101). Alter-
natively, early tracheostomy may be considered.

Cardiac Stunning and Neurogenic Pulmonary Edema

Cardiac stunning and neurogenic pulmonary edema can oc-
cur after acute neurologic catastrophes. This is most com-
monly seen after severe head trauma, subarachnoid hemor-
rhage, status epilepticus, or intracerebral hemorrhage. The
mechanism of cardiopulmonary damage is believed to occur through massive catecholamine release mediated through the sympathetic nervous system (102). In neurogenic pulmonary edema, sympathetic-mediated pulmonary venoconstriction is believed to create the Starling forces necessary to develop pul-
monary edema (103). The sympathetic nervous system also in-
nervates the contractile elements of the pulmonary endothelial
cells. Catecholamine-mediated contraction of these cells can lead to opening of the tight junctions of the capillaries, allow-
ing protein to flux into the pulmonary parenchyma (104). The
process is self-limited, and aggressive diuresis and high levels of positive end-expiratory pressure (PEEP) are usually adequate to improve oxygenation.

Sympathetically-induced cardiac changes may be more se-
vere. The sympathetic innervation of the heart parallels the
cardiovascular reflex arc, which probably accounts for the
noted electrocardiogram (ECG) changes that can occur with
severe neurologic injury. Deep T-wave inversions are usually
reported as “cerebral T waves”; however, the spectrum of sym-
pathetically induced ECG changes is broad, and includes ST
elevations and depressions (102). Pathologically, cardiac con-
traction bands are seen surrounding the entry zone of the sym-
pathetic endplates into the myocardium. These bands represent
reperfusion injury from ischemic cardiac muscle. The muscle
dies in a hypercontracted state and ultimately becomes cal-
cified (105). Cardiac enzymes are elevated, but this finding
does not necessarily implicate coronary artery disease. Clini-
cally, myocardial contraction is impaired, and cardiac output and ejection fraction are decreased. Pulmonary edema is com-
mon, complicating an oftentimes concurrent process of neuro-
genic pulmonary edema. More recently, apical ballooning has
been described with catecholamine excess, the so-called “Tako-
Tsubo” cardiomyopathy (106). Serial echocardiography sug-
gests that cardiac function usually improves over the course of
a week, although it is important to note that the diagnosis of
catecholamine-induced cardiac stunning implies a more severe
neurologic injury, complicates medical management, and may
portend a worse outcome (99).

Sodium Metabolism and Homeostasis

Disturbances in sodium metabolism and homeostasis are found in a variety of neurologic diseases. The syndrome of inap-
propriate antidiuretic hormone (SIADH) may be seen early in
head trauma. Circulating levels of antidiuretic hormone (ADH)
are elevated in a number of acute neurologic emergencies sec-
ondary to a catecholamine-induced stress response. This raises
the question of whether the hyponatremia encountered is itself
due to inappropriate ADH release or simply represents an ap-
propriate but significant release of the hormone. In either case,
the release of ADH has significant implication for the manage-
ment of the neurologic patient. Acute hyponatremia leads to
the development of intracellular edema, with expansion of the
size of the neuronal cell body. Unlike other cells in the body, the
neuron needs to maintain its cell size and integrity in order to
transmit electrical signals. The cellular response of the neu-
ron to intracellular edema is to extrude intracellular osmoles
to reduce the intracellular osmolality and return the cell size
to normal (107). Thus, chronic hyponatremia can be tolerated
well. However, cellular swelling in response to acute hypona-
trema will lead to mental obtundation and seizures. Due to
these considerations, normal saline is the preferred intravenous
solution in the neurologic intensive care unit.

Salt-wasting Nephropathy

A self-limited, salt-wasting nephropathy can develop after
SAH. This process will lead to hyponatremia and volume de-
pletion if not recognized and treated (108). The etiology re-
mains somewhat difficult to identify. In dogs and guinea pigs, the
process is mediated through the renal sympathetic nerve.

Transsection of this nerve will prevent salt wasting. This re-
sponse is species specific, and is not true for rats; the human
response is unknown (109). A variety of circulating hormones or
substances have been proposed to initiate this response. The
leading candidate is the B isoform of atrial natriuretic peptide
(ANP), which has been found in some series to be elevated prior
to the development of hyponatremia and cerebral vasospasm
(110).

Diabetes insipidus (DI) leading to hyponatremia is expected
after pituitary surgery, and is seen in any process that affects
the hypothalamus or pituitary stalk. Head trauma leading to shearing
injury of the pituitary stalk is a common cause for delayed
DI. The diagnosis is made by the development of hyponatremia
in the setting of hypotonic diuresis that is not induced by diuret-
ics. This process must be differentiated from a postoperative
diuresis. Normal postoperative diuresis will not spontaneously
develop hyponatremia. Correction of the hyponatremia must be
achieved slowly if hyponatremia has been present for more than
a few hours (107).

Chapter 43: Central Nervous System

### SPECIFIC THERAPEUTIC CONCERNS AND TREATMENT OPTIONS

#### Head Trauma and Intracranial Hypertension

Severe head trauma remains a significant source of morbidi-
ty and mortality in the United States, accounting for approxi-
mately 50,000 deaths a year. It is the leading source of death for
people younger than 44 years of age (51). Historically, treat-
ment has focused on the management of sustained intracra-
nial hypertension, and was based largely on retrospective data
obtained from the National Traumatic Coma data bank. Sur-
vival was greater than 80% in patients who were able to have
their ICP maintained at less than 20 mm Hg compared with more than 90% mortality for patients who had uncontrollable sustained intracranial hypertension (53,111). Therefore, treat-
ment was focused on measures to decrease ICP, which might include diuresis, aggressive treatment of hypertension, keeping the patient relatively hypovolemic, and elevation of the head of bed.

The work by the Richmond group in the 1970s and 1980s largely changed the focus on head trauma treatment from using measures designed to lower ICP to those designed to maintain adequate CPP. As previously described, in some circumstances, elevations in ICP may be related to inadequate perfusion (41). Treatment thus shifted to include maintaining adequate blood volume and cerebral perfusion, as well as treating sustained elevations in ICP. What constitutes an adequate CPP has been debated and may vary under different conditions; however, the most recent Brain Trauma Foundation guidelines have rec-

ommended a minimum CPP of 60 mm Hg (112).

In addition to maintaining adequate cerebral perfusion, a treatment strategy has been proposed that tailors hyperventi-
lation based on the results of jugular venous O$_2$ (SjvO$_2$) mon-

itoring (113). In some circumstances, elevated ICP can be at-
tributed to cerebral hypoxemia. In this condition, a narrow ar-
terial venous gradient can be normalized by inducing cerebral 
vasoconstriction through hyperventilation. Similarly, widened arterial venous gradients would suggest a high risk of cere-
bral ischemia and prompt efforts to increase cerebral perfu-

sion. Both methods have their proponents, but most agree that attend-
tion to details and standardization of care in the severely injured neurologic patient are crucial (114,115).

More recently, brain tissue oxygen monitoring has been used in head trauma to guide therapy. Brain tissue oxygen tension is measured by placement of a small flexible probe, usually through a cranial bolt directly into the brain parenchyma. CBF and PET studies have reported that low oxygen tensions corre-
late with low CBF measures and high oxygen extraction ratios (116,117). Two small observational studies have suggested an improved neurologic outcome with therapies designed to main-
tain brain tissue oxygen tensions greater than 10 mm Hg (118); however, to date, no randomized trials have been completed (119).

Intracranial hypertension is treated through the removal of space-occupying lesions, decreasing cerebral edema or venous engorgement, or expanding the cranial vault. Expanding brain masses—tumors, subdural or epidural hematomas—need to be evacuated as soon as possible to avoid cerebral herniation and damage to important brain structures. Removal of CSF through an external ventricular drain is a means to reduce the volume of the intracranial contents. Placement of an external ventricular drain also allows for the direct measurement of ICP.

Hyperventilation is useful for the acute management of in-
tracranial hypertension. Intracranial hypertension is treated through decreases in CBF that are mediated through arte-

riolar vasoconstriction. Chronic hyperventilation is generally avoided due to concerns that prolonged vasoconstriction may worsen cerebral ischemia (120). The effect of hyperventilation on ICP is also self-limited, generally lasting only 3 to 6 hours; thus, hyperventilation is usually used for ICP control in the acute setting until a longer-acting strategy can be employed.

Osmotic agents are typically employed to lower ICP. Man-

nitol, given in boluses of 0.25 to 1.0 g/kg, is the most commonly used agent in the United States. Mannitol lowers ICP through a number of mechanisms. The intravascular osmotic gradient created by mannitol can lead to extracellular fluid being drawn into the intravascular space and removed through osmotic di-
uresis. Paczynski et al. were able to demonstrate a decrease in hemispheric brain water in a rat stroke model with large bolu-

ses of mannitol, although the effect was small and delayed for several hours (121). More likely, mannitol exerts its effect on ICP by decreasing CBV. According to this theory, the os-

motnic gradient initiated by an infusion of mannitol causes an influx of extravascular water into the intravascular space. This leads to a decrease in blood viscosity due to a hemodilution of red blood cell mass and fibrinogen. The decrease in ICP can be explained through the use of the Hagen-Poiseuille equation. In this equation, flow is indirectly related to serum viscosity and a constant—a product of r (p) times the length of the vessel (Fig. 43.8). Assuming constant cerebral blood flow and cerebral vessel reactivity, according to this equation, the radius of this vessel must decrease in response to both an increase in CPP and a decrease in viscosity (48). Rosner describes this as passive vasoconstriction (41).

Hypertonic saline in place of mannitol has been recently advocated. Hypertonic saline may have an advantage of less nephrotoxicity, although this has not been studied. Theoret-
ically, its mechanism of action should be the same as mannitol. Widespread use of hypertonic saline, however, has been limited by a lack of a standardized dosing regimen (122,123).

An overall strategy for treating intracranial hypertension is to attempt to maintain the most optimal CPP at the lowest pos-
ible ICP. To attain this goal, other maneuvers may be necessary. Sedation and paralysis can be helpful to decrease ICP if chest wall compliance is high or if the patient is exhibiting respira-
tory dyssynchrony with the ventilator. Since the spinal venous plexus lacks valves, there is a theoretical concern that eleva-
tions in PEEP could be transmitted directly to the brain, thus increasing ICP. This is rarely problematic in noncompliant pul-

monary states, but can occur if PEEP is elevated—some would say at a value of greater than 20 cm H$_2$O—under conditions of increased pulmonary and decreased intracranial compliance (125).

Corticosteroids are useful in treating the vasogenic edema from tumors and meningitis. The use of glucocorticoids in head trauma, though, is not recommended as several randomized trials have found no therapeutic benefit (124–127). Barbitalates are effective in lowering ICP by decreasing cere-
bral metabolism. Their use is generally reserved for cases of

\[
F = \frac{8\rho p r^4}{\eta l}
\]

where $F =$ flow, $p =$ pressure gradient (CPP), $r =$ vessel diameter, $n =$ viscosity, $l =$ vessel length.
refractory intracranial hypertension, and dosing is often titrated to a burst suppression pattern monitored on the EEG. One randomized trial reported improved mortality (128) with barbiturate use, although in head trauma, this remains debatable due to the limited quality of life of survivors (129).

Early hemi-craniectomy—defined as occurring within 48 hours—with duraplasty is gaining recognition as a possible alternative for treatment of recalcitrant traumatic cerebral edema (130). Future randomized trials will need to be performed for further research.

Seizure Control and Status Epilepticus

Seizures are common after neurologic injury and can worsen outcome by increasing metabolic demands beyond oxygen delivery capabilities. Anticonvulsant prophylaxis may be employed for patients with subarachnoid hemorrhage, or intracerebral hemorrhages that abut the cortical surface of the brain. Anticonvulsants are recommended during the first week after severe head trauma to prevent posttraumatic epilepsy (131). Immediate treatment of seizures should utilize generous dosing of benzodiazepines.

Status epilepticus (SE) is a neurologic emergency that is associated with significant morbidity and mortality. Traditional definitions of SE that require 30 minutes of sustained seizure activity or nonarousal between sequential seizures have proved impractical to initiating timely treatment. A new operational definition suggests the immediate treatment of all seizures that last more than 5 minutes (52). Protocols have been developed for the management of anticonvulsants (52). Aggressive early initiation of treatment is important, as SE becomes more difficult to control as seizures continue. It is important to treat that SE is often underrecognized. Generalized tonic-clonic movements during electrical seizure activity evolve through a progression of clinical stages where a form of electrical dissociation can occur. Over time, physical movements become progressively more subtle and are manifested only by slight movements of the lips, fingers, or eyelids. A common mistake is to assume that seizures have discontinued after loading with anticonvulsants and initiating pharmacologic paralysis. This underscores the importance of EEG monitoring to ensure that seizures have been adequately treated. Attention to airway management and hemodynamics is important, as many of the anticonvulsants will have respiratory and cardiovascular depressant effects.

Refractory SE is defined as SE that has not responded to the usual first-line medications. Propofol, midazolam, and thiopental—or pentobarbital infusions under EEG monitoring—are required for treatment. However, propofol use has fallen into relative disfavor due to several case reports of deaths during infusions (132,133). It is not used in children with SE due to concerns over the development of a propofol infusion syndrome (134).

Subarachnoid Hemorrhage

Mortality from aneurysmal SAH remains high, with 15% of patients dying before getting medical attention (135). The care of patients with SAH can be divided into management before and after a cerebral aneurysm is secured. Management prior to aneurysmal treatment is designed to prevent rebleeding. Rebleeding occurs in approximately one third of all patients with aneurysmal SAH, and is highest within a few days after SAH. Neurosurgeons and neurointensivists will treat acute hypertension in patients with unsecured aneurysms. The rationale for treatment is based on the International Cooperative Aneurysmal trial (136) and, more recently, on a large Japanese observational study that noted a higher incidence of rebleeding in patients with sustained systolic elevations in blood pressure of more than 160 mm Hg (137). Blood pressure is preferentially treated with β-blockers, which do not significantly affect CBF and can narrow the pulse pressure. Hydralazine and angiotensin-converting enzyme (ACE) inhibitors have minimal effects on CBF. In general, nitroprusside is avoided due to concerns that it may induce cerebral vasoconstriction and increase ICP. Intravenous nicardipine is the drug of choice if intravenous infusion is needed to control blood pressure (135).

The use of antifibrinolytic agents to prevent rebleeding is controversial. Previously a mainstay of treatment, the use of antifibrinolytic agents was largely abandoned after studies revealed increased mortality from the development of cerebral vasospasm. More recently, however, a randomized nonblinded study suggested that rebleeding rates could be decreased without increasing the rate of cerebral vasospasm (138). This study awaits further confirmation. Severe cerebral vasospasm occurs after SAH and requires the placement of an external ventricular drain.

Once the aneurysm is secured, care focuses on the evaluation and treatment of cerebral vasospasm. Cerebral vasospasm is a pathologic narrowing of the basal cerebral arteries that occurs after SAH. Pathologically, the cerebral vessels display intimal hyperplasia, collagen remodeling, and a diffuse cellular infiltrate (139). The process takes approximately 4 days to develop and resolves after approximately 2 weeks. This process is initiated by a breakdown product of hemoglobin found in the subarachnoid space. The likelihood of developing cerebrovascular vasospasm is predicted by the amount of subarachnoid blood visualized on a 24-hour CT scan (140). Larger amounts of blood predict a higher likelihood of vasospasm, and the location of the clot usually correlates with the site of most severe vasospasm (141). Cerebral vessel narrowing can be monitored by the use of transcranial Doppler ultrasonography (TCD). Rising flow velocities may precede the development of neurologic deficits but, oftentimes, will ideally need to be verified by CBF measures to verify the significance of TCD findings (139). The onset of vasospasm is treated with intravascular fluid expansion and hemodynamic augmentation. Cerebral salt wasting can occur, and is best treated with hypertonic solutions and fluid restriction. Cerebral autoregulation is impaired in cases of cerebral vasospasm and may require induced hypertension to treat neurologic deficits. There is a theoretical advantage to the use of phenylephrine since there are decreased α-receptors in the cerebral vasculature, although this has not been verified with CBF studies (139,142). Some studies have advocated the use of dobutamine to increase cardiac index in patients with vasospasm (143). Nonrandomized studies have shown reversal
Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) is bleeding that occurs directly into the brain parenchyma. ICH is classified as primary, secondary to underlying lesions, or spontaneous. The most common etiology of ICH is hypertension, which weakens and ruptures the small perforating vessels of the basal cerebral arteries. A growing source of ICH is secondary to long-term anticoagulant use (145).

Clinically, ICH presents with severe headaches and focal neurologic deficits, usually prompting an immediate transfer to an emergency room. Serial head CT studies have revealed that hematoma expansion occurs in approximately 40% of patients with ICH within the first 6 hours (146). A double-blinded randomized trial suggested that recombinant factor VIIa used within the first 4 hours of ictus decreased the hematoma expansion and improved outcome (147), but questions still remain, since an increase in thrombotic complications was noted in the treatment group. Acute hypertension is, again, common after ICH, and blood pressure control is controversial since aggressive management may extend the ischemic penumbra surrounding the hematoma. Conversely, PET studies suggest that modest control of hypertension is safe (148). A large randomized study evaluating the surgical evacuation of supratentorial ICH did not report a benefit over medical management. However, subgroup analysis did suggest a benefit to evacuation of primarily cortical hematomas (149). A subsequent study is currently ongoing. Corticosteroids have not shown any benefit in the treatment of ICH (150).

Ischemic Stroke

The use of thrombolytics has dramatically changed the management of acute ischemic stroke. The National Institute of Neurological Disorders and Stroke (NIH) trial demonstrated improved 3-month outcomes in patients treated within 3 hours of onset with intravenous tissue plasminogen activator (tPA) (59). Intracerebral lysis of clots has been successfully used in small trials and has extended the treatment windows up to 6 hours for the anterior circulation and 12 hours for the posterior circulation (58). Most recently, devices used for direct mechanical disruption and removal of intra-arterial clots have been approved (151).

Hypertension is common in the setting of an acute stroke, but usually resolves within a few hours of ictus, and treatment is controversial. Hemorrhagic conversion of ischemic infarctions is increased with sustained systolic pressures greater than 180 mm Hg; blood pressure must be below this limit prior to tPA administration (59). However, overly aggressive treatment of blood pressure is commonplace and may actually result in extension of the primary ischemic insult. Large hemispheric infarctions—defined as strokes involving more than 50% of the middle cerebral artery (MCA) territory—are at risk for the subsequent development of cerebral edema and herniation (152). Close neurologic monitoring is required to identify any signs of deterioration. Treatments designed to lower ICP can be effective but act only as temporizing measures, since cerebral tissue shifts and not increased ICP are most likely to be the source of neurologic deterioration (153). Hemispherectomy has been successfully used in a small case series and one pilot trial (154–156). The application and timing of this procedure, however, remain debatable.

SUMMARY

This chapter has attempted to provide an overview of cerebral vascular physiology and cerebral ischemia. A grasp of these principles is vital to understanding the nature of treatments designed to maintain adequate CBF and prevent secondary neurologic injury. Future treatments that focus on the details of critical care and maintaining tissue oxygenation show promise in improving outcome after neurologic injury.

PEARLS

Cerebral ischemia develops if oxygen utilization cannot meet the metabolic requirements of the tissue. This most commonly occurs due to a decrease in oxygen delivery to the cell. Ischemia is categorized into focal and global etiologies, with varying brain cell subtypes and neurons displaying selective vulnerability to ischemia. Neuronal cell death is a product of the degree and time of ischemic insult. In focal ischemia, a core of central necrotic tissue is surrounded by ischemic but potentially viable tissue.

Cerebral Circulation

Various methods to measure CBF and CMRO2 have been developed and utilized to study cerebrovascular physiology. Newer perfusion techniques involving magnetic resonance and computed tomography perfusion may expand clinical applications.

Cerebral autoregulation refers to the ability of the cerebral vasculature to maintain constant CBF over a range of CPP. Cerebral autoregulation is maintained through a variety of proposed mechanisms that lead to vasodilatation and dilatation of both the cerebral arteries and arterioles. Cerebral autoregulation is disturbed in most neurologic processes and increases the risk of secondary ischemic insult. Carbon dioxide and oxygen tensions have distinctive effects on CBF. The effects of carbon dioxide are mediated through changes in CSF hydrogen ion concentration. Intracranial pressure volume curves may reflect the pressure needed to displace various cerebral contents from the intracranial cavity.
Acute elevations in ICP, known as plateau waves, can be explained by cerebral vasodilatation induced by decreases in CPP. Cerebral edema is described by its location and mechanism of production.

**Treatment Issues**

Secondary injury accounts for a significant proportion of the neurologic injury that occurs after stroke, trauma, or seizures.

Secondary injury can be reduced by:
- Prompt transport to a trauma or stroke center
- Initiation of brain resuscitative measures designed to improve cerebral oxygen delivery
- Emergent brain imaging with available neurological procedures as needed
- Serial neurologic assessment and monitoring
- Specific protocols exist for treatment of specific neurologic emergencies.

**General Therapeutic Considerations**

Hyperthermia and hyperglycemia extend neurologic damage in animal models of ischemia and are associated with worse neurologic outcomes.

Moderate hyperthermia improved neurologic outcomes in patients with cerebral anoxia after cardiac arrest and may be helpful for other types of neurologic injury.

Control of hyperglycemia may lead to improved outcomes in neurologic injury.

Blood pressure management after acute neurologic injury needs to be titrated to maintain adequate cerebral perfusion, but not worsen the development of cerebral edema.

Medical complications are frequent after acute neurologic injury and need to be treated aggressively.

**Specific Treatment Options**

Management of head trauma has expanded from the primary focus on lowering ICP to maintaining adequate CPP. Attention to oxygen extraction ratios and brain tissue oxygenation may also improve outcome.

Status epilepticus is an emergency that can be successfully treated if recognized and treated early.

Treatment of aneurysmal SAH focuses on methods to prevent rebleeding prior to aneurysmal repair and methods to increase CBF during cerebral vasospasm after aneurysm repair.

Early strategies to lyse clots in ischemic stroke and prevent hemotoma expansion after ICH have changed the acute management of stroke.

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