Neurologic monitoring in the intensive care unit (ICU) is used either in a general sense as part of a system-based approach to assess one of the major bodily systems or with the specific intent to guide therapy and/or assess prognosis. Imaging studies of the central nervous system (CNS)—while not considered “monitoring” in the strict sense—play a central role in this assessment by establishing diagnoses and quantifying the extent of pathology. Important constraints for typical neuroradiologic imaging are presented in the first section below.

Many interventions in the ICU aimed at restoring or maintaining conditions that are favorable for recovery of the patient target the normal brain and, by extension, affect the results of neurologic monitoring. Therefore, an understanding of the parameters that affect the state of the brain is necessary as the context for interpreting the results of neurologic monitoring. These are presented in the second section, followed by a detailed discussion of available modalities for serial assessment or monitoring of the nervous system.

NEURORADIOLOGIC IMAGING

Routine imaging studies of the brain are important in the repeated assessment of a patient’s neurologic status. Objective information, particularly about structural abnormalities, is essential to the clinical diagnosis. Computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used studies. Continued or critically timed assessment may provide insight into the time course of an emergent or recovery from a pathologic process (1). Typical imaging studies of the brain are important in the repeated assessment of a patient target the normal brain and, by extension, affect the results of neurologic monitoring. Therefore, an understanding of the parameters that affect the state of the brain is necessary as the context for interpreting the results of neurologic monitoring. These are presented in the second section, followed by a detailed discussion of available modalities for serial assessment or monitoring of the nervous system.

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To maximize the utility of an imaging study, the requesting physician needs to be aware of the inherent strengths and weaknesses of the chosen imaging modality, as well as considerations such as morbid obesity, claustrophobia, the use of contrast agents, and metal implants (see www.mrisafety.com). Whereas the quality of CT images is simply degraded by patient movement, MRI images acquired in an uncooperative, moving patient may contain “spurious pathology” because of misregistration of anatomic structures. Contextual details of the clinical history should be provided to the interpreting radiologist so that the imaging protocol can be designed to optimize information. Finally, some thought should be given to the balance between the time spent obtaining the images and the risks to the patient from reduced, or delayed, care during imaging and transport. Given the rapid development in MRI modalities or in postacquisition processing, such a balance is frequently best achieved by consulting directly with the radiologist.

CT provides a map of the degree of radiographic absorption of intracranial structures. Generally, it is the test of choice for localizing blood and imaging bone. Newer, helical CT scanners make image acquisition a comparatively fast process. This allows the two- and three-dimensional reconstruction of arterial anatomy from images during the first pass of radiocontrast administration to obtain a CT arteriogram.

MRI provides a map of the response of hydrogen nuclei to external magnetic fields. It is more versatile than CT, provides better imaging of posterior fossa contents, and is considerably more time consuming. T1 weighting enhances the detection of lipids, methemoglobin (e.g., as the subacute residual of a hemorrhage), and concentrated protein (e.g., in a colloid cyst). A radiofrequency pulse prior to T1 image acquisition can suppress the enhancement of lipids (“fat suppression”) and is an example of a protocol change that affects the resulting image. T2 weighting enhances the detection of unbound water such as in cerebrospinal fluid (CSF) (Fig. 28.1). A radiofrequency pulse prior to T2 image acquisition (fluid attenuation inversion recovery [FLAIR] imaging) can suppress the enhancement of CSF and improve the detection of edema. MRI can also be focused to detect moving elements such as in MR arteriography or venography or CSF flow studies. Axoplasmic motion of bulk water can be imaged with MRI to obtain a diffusion image (apparent diffusion coefficient [ADC] map). This axoplasmic motion stops shortly after brain ischemia; therefore, diffusion images provide the earliest radiographic evidence for the core zone of an ischemic stroke.

Contrast media distribute with the blood flow and can therefore accentuate areas of increased vascularity such as in inflamed tissue or areas of tumor-induced angioneogenesis. Contrast media also distribute into—and thereby highlight—brain structures that are missing a blood–brain barrier such as the pineal gland or pituitary stalk, or brain areas where the blood–brain barrier has been disrupted. Brain perfusion can be imaged following a bolus administration of contrast medium by both MRI and CT. The resulting map of the time to peak concentration of the contrast medium currently provides qualitative information on cerebral blood flow (CBF), although quantitative approaches are under development. Qualitative differences in CBF can be used to identify the ischemic penumbra of a stroke.

CEREBRAL METABOLISM

The cerebral metabolic rate for oxygen (CMRO₂) of the brain averages 3.0 to 3.8 mL O₂/min/100 g. Although only 2% of body weight, the human adult brain accounts for 15% to 20% of the resting oxygen consumption and about 25% to 30% of the glucose consumption of the body. To meet this high demand for oxygen and glucose, the brain requires a relatively high level of brain tissue perfusion (40 to 60 mL/min/100 g) of brain tissue. CBF is regulated by four primary factors: metabolic stimuli, chemical stimuli, perfusion pressure, and neural stimuli.
Flow–Metabolism Coupling

In the normal brain, an increase in cerebral metabolism is rapidly matched by local increases in CBF. This is referred to as regional flow–metabolism coupling or cerebral metabolic autoregulation (2). CBF is thus linked to brain function and metabolism so that CBF varies in parallel with CMRO$_2$ (Fig. 28.2). Autoregulation and increased oxygen extraction are two compensatory responses to acute reductions in CBF (3–5). Oxygen extraction is able to vary within a narrow range. Misery perfusion occurs when oxygen extraction is increased as a response to increased CMRO$_2$, either when autoregulatory CBF compensation has been exceeded or uncoupling has occurred (6). As cerebral perfusion pressure (CPP) falls, CBF is maintained initially by resistance arteriole vasodilation (7). Severe ischemia results as CPP is further reduced; the capacity of CBF autoregulation and increased oxygen extraction is exhausted, and CBF falls as a function of pressure. Positron emission tomography (PET) studies indicate that this occurs with relatively preserved CMRO$_2$ in the penumbra of a focal ischemic area.

Several vasoactive metabolic mediators have been proposed for cerebral regulation, including hydrogen ion, potassium, CO$_2$, adenosine, glycolytic intermediates, phospholipid metabolites (2), and, more recently, nitric oxide (8). In humans, flow–metabolism coupling is evident during a variety of motor and cognitive tasks that can be mapped using CBF techniques (9).

The global relationship between CBF and CMRO$_2$ can be expressed by the Fick equation where $D_{ajO_2}$ is the arteriojugular difference in oxygen content:

$$CMRO_2 = D_{ajO_2} \times CBF$$

or

$$D_{ajO_2} = CMRO_2/CBF$$

In brain injury, during hypothermia, and under the influence of anesthetic agents, CBF and metabolism may become dissociated. In a series of 109 severe head injury patients, Bouna et al. reported that CBF measured within the first 6 hours after trauma was less than 18 mL/min/100 g (i.e., the threshold for cerebral ischemia) in one-third of the patients (10). Arterial vasospasm was an independent predictor of poor outcome (11). Secondary ischemic neurologic damage associated with systemic factors (e.g., hypotension or hypoxemia) and local factors (e.g., intracranial hypertension, hypoperfusion) worsened outcome. Disruption of normal homeostatic mechanisms such as pressure autoregulation (see below) may also aggravate cerebral ischemia. Mechanical hyperventilation used to reduce intracranial pressure (ICP) may be deleterious by decreasing CBF, and may thus also lead to ischemia (12).

**Hypothermia**

Cerebral protection by hypothermia is commonly attributed to cerebral metabolic suppression. The temperature coefficient (Q$_{10}$) is the factor by which CMRO$_2$ is decreased by a 10°C decrease in temperature. Between 37°C and 27°C, the temperature coefficient is 2.2, but between 27°C and 17°C—a temperature range during which electroencephalographic activity ceases—the temperature coefficient doubles to 4.5. Below 17°C, the Q$_{10}$ returns to near 2.0 (Fig. 28.3). In the absence of electroencephalographic activity (e.g., during barbiturate coma), however, the Q$_{10}$ remains near 2.0 over the entire temperature range. With moderate hypothermia (i.e., above 27°C), both CO$_2$ reactivity and autoregulation are intact while CBF and CMRO$_2$ remain coupled (13). Evidence suggests that there is a change in
the coupling of blood flow and metabolism during deep cerebral hypothermia (below 25°C). Nonetheless, metabolic regulation remains a main determinant of CBF even during deep cerebral hypothermia (14).

**Anesthetics**

With the exception of ketamine, most intravenous and inhalational anesthetics depress cerebral metabolism (15,16), with consequent reductions in oxygen consumption (CMRO₂), CBF, and ICP with intact autoregulation (17). As CMRO₂ decreases, CBF is reduced proportionately because of flow–metabolism coupling. Flow–metabolism coupling usually remains intact after the administration of sodium thiopental and propofol (17), and cerebral oxygen saturation is expected to remain unaltered or improve. Etomidate, in contrast, can produce a rapid reduction in CBF accompanied by a slower reduction in CMRO₂ (18,19). This flow–metabolism coupled mismatch, resulting from a greater reduction in flow than demand, may induce significant, albeit transient, cerebral oxygen desaturation.

Propofol is believed to maintain cerebral autoregulation, and even high doses of this drug do not obviate autoregulation or carbon dioxide reactivity (20). The effect of propofol on flow–metabolism coupling is more controversial, with at least one study demonstrating intact coupling (21). Both increased and decreased cerebral oxygen extraction have been demonstrated with propofol, suggesting CBF–CMRO₂ uncoupling (22,23). Despite the fact that the retention of normal flow–metabolism coupling is thought to occur in only a proportion of head-injured patients, there is a paucity of data regarding the influence of propofol on flow–metabolism coupling after traumatic brain injury (TBI). It has been demonstrated that after TBI, flow–metabolism coupling remains intact during a step increase in propofol infusion rates (24), as is the case in noninjured patients (25).

Benzodiazepines and opiates appear to have limited intrinsic effects on CBF, CMRO₂, and CBF–CMRO₂ coupling (26,27). Because of their sedative properties, they cause a decrease in CBF and ICP that parallels the sedation-induced decrease in CMRO₂. As with all anesthetics, the decreased sympathetic tone caused by the sedation, on the other hand, risks a decrease in mean arterial pressure that may in fact diminish cerebral perfusion. Dexmedetomidine, an α₂-receptor agonist, is a recent and relatively expensive sedative. Similar to opiates and benzodiazepines, its effects on cerebral physiology appear to be caused by the sedation (28). Limited experience in traumatic brain-injured patients did not reveal any adverse effects (29).

**Arterial Carbon Dioxide and Oxygen**

Carbon dioxide is a potent cerebral vasodilator and thus a major determinant of CBF (Fig. 28.4) (30). At normotension, CBF increases almost linearly when the arterial partial pressure of carbon dioxide (PaCO₂) increases from 25 to 80 mmHg. Global CBF varies 2% to 4% for each millimeter of mercury change in PaCO₂ (31). The effects of PaCO₂ on cerebral circulation are regulated by a complex and interrelated system of mediators. The initial stimulus of CO₂-induced vasodilation is a decrease in brain extracellular pH (32), further mediated by nitric oxide, prostanoids, cyclic nucleotides, potassium channels, and a decrease in intracellular calcium concentration as a final common pathway.

Arterial tone has an important influence on how PaCO₂ affects CBF. Moderate hypotension impairs the response of the cerebral circulation to changes in PaCO₂, while severe hypotension abolishes it altogether (33). Similarly, PaCO₂ modifies pressure autoregulation, and from hypercapnia to hypocapnia, there is a widening of the autoregulation plateau (34). The response of cerebral vessels to CO₂ can be used therapeutically by instituting hyperventilation to decrease CBF, in turn...
Pressure Autoregulation

Pressure autoregulation refers to the ability of the brain to maintain total and regional CBF nearly constant despite large changes in systemic arterial blood pressure (Fig. 28.5), independent of flow–metabolism coupling (34). Autoregulation is generally expressed as the relationship between CBF and arterial blood pressure when cerebral venous and CSF pressures are low. It can be more precisely defined using the relationship between CBF and CPP that represents the difference between mean systemic arterial pressure and cerebral outflow pressure.

Because the cerebral venous system is compressible and may act as a “Starling resistor” or waterfall phenomenon (38), outflow resistance is governed by whichever pressure is higher—CSF pressure (ICP) or venous outflow pressure (jugular bulb pressure).

The cerebral vascular resistance (R) can be expressed as:

\[ R = \frac{CPP}{CBF} = \frac{8\pi}{h} \times b \times (\frac{l}{r^4}) \]

where \((\frac{8\pi}{h})\) is a constant for calculation, \(b\) = blood viscosity, \(l\) = length, and \(r\) = radius of the vessel. Importantly, the radius enters to the fourth power in the equation, making it the most efficient means of controlling vascular resistance.

In adults under normal conditions, CBF remains constant between a CPP of roughly 60 and 150 mmHg (34). The autoregulation curve is shifted to the right in hypertensive patients and to the left in neonates. At the lower limit of autoregulation, cerebral vasodilation is maximal, and below this level, CBF falls passively with CPP. Beyond the upper limit where vasoconstriction is maximal, the elevated intraluminal pressure may force the vessels to dilate, leading to an increase in CBF and damage to the blood–brain barrier (34,39). Metabolic mediators, such as adenosine, can also be involved in the low-pressure range of autoregulation (39).

Pressure autoregulation can be impaired in many pathologic conditions, including brain tumor, subarachnoid hemorrhage, stroke, or head injury. A loss of CBF regulatory capacity may be attributed to damage of the control system (e.g., cerebral vessels)—usually referred to as “paralysis” in the clinical literature (40)—or of the feedback mechanisms involved in the brain’s hemodynamic control. Changes in the normal feedback mechanisms may include tissue acidosis, extracellular potassium increase, or alterations in cerebral neural pathways. Neuropeptides can reach vasoactive levels in perivascular CSF as a result of synaptic overflow during neuronal activation or in pathologic conditions.

Neurogenic Regulation

A major difference between other systemic circulations and the cerebral circulation is the relative lack of humoral and autonomic control on normal cerebrovascular tone. Hence, a maximal stimulation of the sympathetic or parasympathetic nerves alters CBF only slightly (41). Furthermore, there is considerable evidence that indicates the existence of age-related differences in cerebral resistance vessels to neural stimuli. For example, both in vivo and in vitro, cerebrovascular constrictor responses to noradrenaline or electrical transmural stimuli are greater in fetal and neonatal animals than in adult animals. The mechanism for the age-related decrease is unclear, but could be the result of such factors as loss of number or affinity of \(\alpha\)-adrenergic receptors with development. However, changes in cerebrovascular sensitivity to \(\alpha\)-adrenergic stimuli may not occur with age in all species. Electrical or reflex activation of sympathetic nerves reduces CBF in adult rabbits. Sympathetic stimulation may protect the cerebral circulation from hyperemia associated with even modest elevations in arterial blood pressure.

Other Factors Regulating Cerebral Blood Flow

Although cardiac output hardly influences CBF in normal conditions, it may significantly influence flow to ischemic regions...
or sedation will alter the neurologic examination to varying degrees, making differentiation between drug effect and clinical deterioration very difficult. In an intubated patient who is treated with neuromuscular-blocking agents, the only evidence of recurrent generalized seizure activity may be increased ICP, while the postictal alteration of consciousness and the motor manifestations of the seizure go unnoticed. Finally, neurologic evaluations are performed intermittently and by examiners of variable skill, raising problems of reliability and reproducibility. Despite these limitations, the clinical examination forms the cornerstone of the neurologic assessment of ICU patients and typically directs further diagnostic or therapeutic interventions.

While a comprehensive discussion of a clinical neurologic examination is beyond the scope of this chapter, two aspects of the examination that are particularly pertinent to the ICU environment will be discussed in some detail. The first is the assessment of the level of consciousness, because of its ties to patient outcome for many different neurologic diseases. The second is the examination for assessing brain death, not only because it is a graded assessment of brainstem function, but also because it illustrates sources of error that may impact the results of the clinical neurologic examination in the ICU environment in general.

**Level of Consciousness: Glasgow Coma Scale**

The level of consciousness is typically assessed by the Glasgow coma scale (GCS). Numerical scores are assigned for best responses in the categories of eye opening, motor response, and verbal response (Table 28.2). The GCS was originally described more than 30 years ago for the continuous assessment of patients with TBI after the initial period of stabilization (46). Because its assessment is quick, objective, and relatively reliable (47), and because the resulting score is easily documented and communicated, the GCS has gained widespread use in emergency medicine and critical care patients. It has been incorporated into the Acute Physiology and Chronic Health Evaluation (APACHE) score (48) and the World Federation of Neurosurgical Societies (WFNS) grading of subarachnoid hemorrhage (49).

The level of consciousness is a reflection of the severity of many different disease states, and can be compromised not just by diseases of the CNS, but also at the extremes of a wide

---

**TABLE 28.2 Glasgow Coma Scale**

<table>
<thead>
<tr>
<th>Category</th>
<th>Grading</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye opening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>4</td>
<td>Swelling may interfere with testing.</td>
</tr>
<tr>
<td>To voice</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>To pain</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Motor response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follows commands</td>
<td>6</td>
<td>Avoid description of flexion as decorticate and extension as decerebrate because those terms denote an anatomic location of a lesion.</td>
</tr>
<tr>
<td>Localizes pain</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Withdraws to pain</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Flexion to pain</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Extension to pain</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Flaccid</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Verbal response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oriented</td>
<td>5</td>
<td>Impossible to assess in intubated patients. Some centers determine the response by inference and designate the final score with the subscript &quot;t.&quot;</td>
</tr>
<tr>
<td>Confused</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Inappropriate</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Incomprehensible</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

The Glasgow coma score is the sum of the best attainable subscores in the categories of eye opening (E), motor (M), and verbal (V) responses. It ranges from 15 (E4 + M6 + V5) to 3 (E1 + M1 + V1).
variety of other organ dysfunctions common in critical care. Not surprisingly, therefore, the scores from a tool such as the GCS that assesses the level of consciousness may be associated with prognosis and outcome. For the GCS, an association of lower scores with worsened outcome has been shown for TBI (50), subarachnoid hemorrhage (51), brain abscess (52), survival after cardiac arrest (53,54), and septic encephalopathy (55). For example, in TBI, a GCS score greater than 7 suggests a 90% likelihood of an outcome of moderate disability or better, whereas a score less than 7 suggests an increased risk of death or persistent vegetative state that approaches 60% to 90% for a GCS score of 3 (50,56,57). New data suggest that, at least in children, early decompressive craniectomy significantly increases the likelihood of better outcome (only mild disability) (58). In aneurysmal subarachnoid hemorrhage, a GCS score less than 13 after initial treatment of increased ICP (i.e., WFNS grade 4 or 5) corresponds to a 60% to 90% chance of a poor functional outcome or death, whereas such outcomes only affect 14% of patients whose level of consciousness is unaffected (GCS 15, WFNS grade 1 or 2) (51).

Despite its widespread use and appeal, the GCS has several important limitations, even if applied correctly. One is the information loss inherent in reducing a graded assessment of three responses into a single number. The second is that mechanical problems such as swelling and endotracheal intubation may prevent proper assessment of eye opening and verbal response. In this setting, some clinicians assign the lowest component score, whereas others try to infer the “true” score from related neurologic findings, and still others add the subscript “T” to indicate an intubated patient. Third, sedatives and neuromuscular-blocking agents affect the GCS score upon repeated assessment. Finally, although the degree of brainstem involvement may reflect the severity of coma, the GCS provides limited information about brainstem function.

**Determination of Brain Death**

The determination of brain death for purposes of organ donation or withdrawal of life support is an area that has brought both the merits and the limitations of the neurologic examination into clear focus. Because the clinical determination of brain death requires a comprehensive and methodical assessment of the patient (59), its steps may serve as a guide to the neurologic examination of a comatose patient. An algorithm for the determination of brain death is shown in Figure 28.6. Given the gravity of the “therapeutic” consequences of the diagnosis of brain death, a prerequisite to its determination is a clinical picture, typically supported by imaging studies, that is consistent with the occurrence of brain death.

**FIGURE 28.6.** Evaluation of a patient in a coma.
TABLE 28.3 Neurologic States Resembling Brain Death

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Diagnostic Aids</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia</td>
<td>Core temperature &lt;32°C</td>
<td>May cause CNS depression up to clinical brain death</td>
</tr>
<tr>
<td></td>
<td>Osborne waves on ECG&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug screening</td>
<td></td>
</tr>
<tr>
<td>Acute poisoning</td>
<td>Serum concentration measurements</td>
<td>In differentiating from brain death, consider antidote and/or document subtherapeutic drug concentration and/or wait for four elimination half-lives</td>
</tr>
<tr>
<td>Metabolic encephalopathy</td>
<td>Laboratory testing</td>
<td>Direct CNS depressants may confound confirmatory testing of brain death because of cMRo&lt;sub&gt;2&lt;/sub&gt;-cBF coupling</td>
</tr>
<tr>
<td>Akinesic mutism</td>
<td>Intact lower brainstem function</td>
<td>Imaging studies should document structural CNS changes</td>
</tr>
<tr>
<td>Locked-in syndrome</td>
<td>Intact sleep–wake cycle</td>
<td>Imaging studies should document structural CNS changes</td>
</tr>
<tr>
<td></td>
<td>Clinical course and imaging studies</td>
<td>Imaging study shows frontal or mesencephalic brain lesion</td>
</tr>
</tbody>
</table>

<sup>1</sup>ECG: electrocardiogram; cMRo<sub>2</sub>, cerebral metabolic requirement for oxygen; cBF, cerebral blood flow; CNS, central nervous system.

The first step in the neurologic examination for the determination of brain death is the determination of coma (i.e., lack of responsiveness to external stimuli due to unconsciousness as discussed above). Motor responses elicited by the examination need to be differentiated from spontaneous movements during the examination. The latter are typically brief, slow movements that originate from the spinal cord and do not become integrated into decerebrate or decorticate responses. Only rarely are they reproducible upon repeat testing. Reproducible partial eye opening that failed to reveal the iris has been described in response to a peripheral painful stimulus in a patient who fulfilled clinical criteria of brain death (60). Conditions that may confound the clinical diagnosis of brain death are listed in Table 28.3. In addition to considering such confounding conditions, the diagnosis of brain death should be consistent with imaging studies and/or the overall clinical picture before the formal determination of brain death is considered.

The next step in the neurologic examination is the assessment of brainstem function. As in the assessment of the level of consciousness, direct trauma to either afferent or efferent structures needs to be considered before any of the tests of brainstem function are interpreted as negative. Typical tests, their afferent and efferent pathways, and potentially interfering clinical conditions are summarized in Table 28.4.

To complete the diagnosis of brain death, an apnea test is performed to test the response to an acute decrease in the pH of CSF due to hypercarbia. Hypercarbia is induced by disconnection of mechanical ventilation while continued oxygenation is assured by both preoxygenation and apneic oxygenation. Absence of respiratory movements at an arterial PCO<sub>2</sub> of 60 mmHg or after an increase in PCO<sub>2</sub> of 20 mmHg is consistent with brain death. Apnea testing may be complicated by arterial hypotension due to loss of arterial and autonomic tone (61). While such hypotension corroborates the diagnosis of brain death, it makes the hemodynamic stability required for apnea testing difficult to attain. The apnea test may trigger movement responses, which reflect residual spinal activity (62).

Once all these criteria for brain death are met, an observation period followed by repeat assessment or a confirmatory test is used to reach a final diagnosis (see Fig. 28.6). Cerebral angiography is the gold standard among confirmatory tests. Contrast media is injected into the aortic arch and distributes to the external carotid circulation, whereas the internal carotid and vertebral arteries fill only to the level of the skull base and atlanto-occipital junction, respectively. Similar findings can be obtained with MR angiography or with single photon emission CT. Electroencephalography (EEG) and transcranial Doppler (TCD) are also frequently used as confirmatory tests. Their role will be discussed in greater detail below.

<table>
<thead>
<tr>
<th>Brainstem Reflex</th>
<th>Afferent Path</th>
<th>Efferent Path</th>
<th>Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pupillary light reaction</td>
<td>II</td>
<td>III</td>
<td>Not confounded by systemic drugs; absence may be caused by prolonged administration of neuromuscular-blocking agents</td>
</tr>
<tr>
<td>Ocular movements (oculocerephal reflex or caloric nystagmus)</td>
<td>VIII</td>
<td>III, VI</td>
<td>Contoured by damage from ototoxic drugs; cervical spine trauma may preclude testing of the oculocephalic reflex; voluntary ocular movements are sometimes the only finding that differentiates a &quot;locked-in&quot; syndrome from brain death</td>
</tr>
<tr>
<td>Corneal reflex / pressure on supraorbital nerve</td>
<td>V</td>
<td>VII</td>
<td></td>
</tr>
<tr>
<td>Gag</td>
<td>IX</td>
<td>IX, X</td>
<td>May be difficult to assess in orotracheally intubated patient</td>
</tr>
<tr>
<td>Cough</td>
<td>X</td>
<td>X, cervical roots</td>
<td>Best tested by assessing the response to tracheal suctioning</td>
</tr>
</tbody>
</table>

*CT<sup>99mTc</sup>-HMPAO. Electroencephalography (EEG) and transcranial Doppler (TCD) are also frequently used as confirmatory tests. Their role will be discussed in greater detail below.
Electrophysiologic Techniques

Neurophysiologic function testing has been used for more than 20 years as a diagnostic/prognostic tool in the ICU (63–66). Snapshots of function of different parts of the nervous system have been used to predict the most likely long-term function of the nervous system as a whole. This information helps the intensivist determine whether continued aggressive intensive care is appropriate given the patient’s most likely long-term neurologic outcome. To a much lesser extent, neurophysiologic testing modalities have been used as continuous monitors of neurologic function in the patient who cannot be assessed neurologically, primarily because of the need for sedation (67–69). There are two main modalities of neurophysiologic function testing used in the intensive care unit: EEG and evoked potentials (EPs). For each modality, the theoretical basis for use and utility will be reviewed.

Electroencephalography

To understand how EEG can be used in the ICU, the clinician must first understand how scalp-recorded EEG is produced and what factors may affect the recordings. EEG activity is generated by neurons in the pyramidal layer of the cerebral cortex. The scalp-recorded EEG is produced by a summation of excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs), not actual cellular depolarization. EPSPs and IPSPs are produced by the spontaneous release of small packets of excitatory or inhibitory neurotransmitters from a nerve terminal that produce only very small changes in the postsynaptic membrane potential, insufficient to cause depolarization. As a result, the amplitude (voltage) of EEG electrical activity is much smaller than the electrocardiogram, ranging from less than 5 μV in the elderly to over 100 μV in the teenager. As a result, the EEG signal cannot be recorded remotely from the generator site, and practically speaking, EEG activity recorded from a single electrode only reflects cortical activity directly beneath the recording site. In addition, because the EEG signal is so small, poor electrode contact with the scalp may result in significant loss of signal.

Maintenance of ion fluxes associated with the production of the EEG is an energy-requiring process. Pharmacologic total suppression of the EEG will result in a 50% to 60% decrease in CMRO₂ (70,71). The decrease in oxygen requirement parallels the suppression of the EEG in cases of lesser suppression. An EEG that is merely slowed pharmacologically will be associated with a higher CMRO₂ than an EEG that is totally suppressed or flat.

The EEG is organized spatially and temporally, but patterns of organization are much more difficult for the clinician to recognize, primarily because few clinicians have significant experience with normal EEG patterns, pathologic EEG patterns, or drug-induced EEG patterns. EEG patterns are described primarily in terms of frequency (how fast voltage oscillations occur) and amplitude (size or voltage). Slower frequency ranges include δ (3 Hz or slower) and θ (3.5 to 7.5 Hz). These frequencies are not seen in the normal awake adult but are commonly seen in the naturally asleep adult or in the adult who is receiving therapeutic doses of sedative-hypnotic and/or analgesic drugs. Faster frequency ranges include α (8 to 13 Hz) and β (>13 Hz). Alpha frequencies (8 to 13 Hz) tend to be present on the posterior part of the head and are most prominent with the eyes closed. Alpha activity disappears with attention and concentration, replaced with faster β activity.

Beta frequencies are commonly seen more toward the front of the head and are associated with increased “function” of a particular part of the brain. In the neurologically abnormal patient, θ and δ frequencies may be focal, associated with a specific loss of function, or more global, associated with generalized neurologic dysfunction. Generally, the more severe the neurologic damage/dysfunction, the slower the recorded EEG activity will be. For example, a patient with a receptive and expressive aphasia will likely demonstrate EEG slowing (θ and δ waves) over the dominant temporal lobe.

Sedative-hypnotic drugs produce a change in neurologic function that is likewise paralleled by EEG changes. The EEG changes associated with sedative-hypnotic drugs are predictable, related both to the drug used and the dosage of drug given. The vast majority of sedative-hypnotic drugs used in the ICU will produce identical, dose-related changes in the EEG. Table 28.5 shows EEG pattern changes associated with most drugs that would be used in the ICU environment. Dexmedetomidine sedation produces EEG patterns indicating that patients are more sedated than they actually are. Even a low-dose infusion produces a combination of slow delta oscillations with bursting 9- to 15-Hz spindles (72). Combinations of drugs, of course, will have different effects than when either drug is used alone. Specific data regarding the effect of combinations of drugs is limited and beyond the scope of this chapter. However, in general, both sedative and analgesic drugs will increase the primary effect of the drug being used in the higher dose as well as add effects of their own.

In summary, the scalp-recorded EEG reflects the function of closely underlying neuronal tissue. These functions may be altered by neurologic damage, pharmacologic means, normal changes in function associated with changes in alertness or sleep, or any combination of these factors. Thus, whether the EEG is used as a monitor or a diagnostic/prognostic tool, interpretation of data without a thorough knowledge of all factors that could influence recordings is not possible.

Diagnostic Electroencephalography in the Intensive Care Unit

Diagnostic EEG studies or EEG monitoring in the ICU is done primarily for one of three purposes: Brain death determination, monitoring for evidence of seizure activity or cerebral ischemia, and determination of drug effect for the purposes of titrating sedative and analgesic drugs or control of ICP.

Criteria for brain death vary from state to state, but in most states, a 16- to 32-channel isoelectric EEG on two consecutive recordings at least 24 hours apart can provide strong corroborating evidence for cessation of brain function (see Fig. 28.6). Because other factors affecting the EEG can produce an isoelectric EEG in the absence of brain death, the EEG cannot be used as the sole evaluation for brain death. Although it is likely that drug levels (see Table 28.5) will decline significantly over a 24-hour period, patients with massive drug overdose or impaired metabolic pathways may show an isoelectric EEG for much longer than 24 or 48 hours. In these cases, the neurologic examination may also not be useful because high drug levels may suppress even the most resistant reflex responses. Fortunately, other diagnostic testing methods, including other electrophysiologic and nonelectrophysiologic methods, may be helpful. EPs (see below), for example, are more resistant to drug effects than the EEG and can frequently be used to demonstrate brainstem and cortical function, even in the face
of an isoelectric EEG (73,74). In addition, an EEG recorded immediately after cardiac arrest may show an isoelectric pattern that subsequently recovers (75). Cortical EPs have also been demonstrated to be more reliable in assessing neurologic function immediately after an ischemic/anoxic insult (75). In summary, a scalp-recorded, 16- to 32-channel EEG is a helpful adjunct to the diagnosis of brain death, provided all other factors influencing the EEG are understood and controlled.

Continuous EEG monitoring in the ICU or, alternatively, sequential diagnostic EEG studies, have been described for detection of nonconvulsive seizure (NCS) activity (or seizure activity in the pharmacologically paralyzed patient) and for detection of cerebral ischemia (67–69,76–78). This type of monitoring requires multiple channels of information to obtain adequate monitoring coverage of the entire brain. A highly trained technologist observes the patient simultaneously with the EEG recording and operates the equipment and maintains recording electrodes during nursing care that will commonly dislodge them. The technologist also provides real-time neurophysiologic data to the clinicians caring for the patient. Processed EEG algorithms have been developed to facilitate detection of ischemia epileptiform and frank seizure activity during continuous EEG monitoring (79,80). Although the technology shows promise even in the hands of nonneurophysiologists (81), this technique has not yet evolved enough to eliminate the need for an on-site technologist with monitoring experience.

Continuous EEG monitoring in the ICU has demonstrated that NCSs are much more common than previously thought (77,78,82). NCSs have been reported following neurosurgical procedures, subarachnoid hemorrhage, CNS infection, head injury, and other conditions. In addition, there is evidence using neuron-specific enolase as a marker of neurologic injury that NCSs may produce neurologic damage and that seizure duration and time to diagnosis are significantly related to the extent of damage and long-term outcome. Without continuous EEG monitoring, NCSs cannot be detected, as they are not consistently and specifically associated with other findings such as hypertension and tachycardia (82).

The personnel and fiscal costs of continuous EEG monitoring have made it unfeasible except in the larger neurologic and neurosurgical ICUs, where many patients with conditions amenable to continuous monitoring require care (76). In addition, very little outcome data exist to demonstrate that such monitoring is overall cost effective. When considering real-time neurologic monitoring in the patient whose neurologic examination cannot be assessed, much work needs to be done to determine how continuous EEG monitoring will mesh with other neurologic monitoring modalities such as ICP, CBF, brain tissue P02 monitoring, TCD, and microdialysis monitoring. Theoretically and based on limited clinical data (76–81), there is much promise for continuous EEG monitoring when used as a part of a multimodality neurologic monitoring program.

### Monitoring of Sedation by Processed Electroencephalography

The use of the EEG to monitor the depth of sedation in patients in the ICU has been described extensively in the literature, and nearly all techniques utilize processed EEG rather than the

<table>
<thead>
<tr>
<th>Drug and Dose</th>
<th>Effect on EEG Dominant Frequency</th>
<th>Effect on EEG Amplitude</th>
<th>Burst Suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Barbiturates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>Fast frontal β activity</td>
<td>↑</td>
<td>↑↑↑ → 0</td>
</tr>
<tr>
<td>Moderate dose</td>
<td>Frontal α-frequency spindles</td>
<td>↑</td>
<td>↑↑↑ → 0</td>
</tr>
<tr>
<td>High dose</td>
<td>Diffuse δ → burst suppression → silence</td>
<td>↑</td>
<td>↑↑↑ → 0</td>
</tr>
<tr>
<td><strong>Etomidate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>Fast frontal β activity</td>
<td>↑</td>
<td>↑↑↑ → 0</td>
</tr>
<tr>
<td>Moderate dose</td>
<td>Frontal α-frequency spindles</td>
<td>↑</td>
<td>↑↑↑ → 0</td>
</tr>
<tr>
<td>High dose</td>
<td>Diffuse δ → burst suppression → silence</td>
<td>↑</td>
<td>↑↑↑ → 0</td>
</tr>
<tr>
<td><strong>Propofol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>Loss of α, ↑ frontal β</td>
<td>↑</td>
<td>Yes, with high doses</td>
</tr>
<tr>
<td>Moderate dose</td>
<td>Frontal δ, waxing/waning α</td>
<td>↑</td>
<td>Yes, with high doses</td>
</tr>
<tr>
<td>High dose</td>
<td>Diffuse δ → burst suppression → silence</td>
<td>↑</td>
<td>↑↑↑ → 0</td>
</tr>
<tr>
<td><strong>Dexmedetomidine</strong></td>
<td>Early appearance of high-amplitude δ frequency</td>
<td>↑</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>that increases with dose, similar to opiates</td>
<td>↑</td>
<td>No</td>
</tr>
<tr>
<td><strong>Ketamine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>Loss of α, ↑ variability</td>
<td>↑↓</td>
<td>No</td>
</tr>
<tr>
<td>Moderate dose</td>
<td>Frontal rhythmic delta</td>
<td>↑</td>
<td>No</td>
</tr>
<tr>
<td>High dose</td>
<td>Polymorphic δ, some β</td>
<td>↑↑</td>
<td>(β is low amplitude)</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td>Loss of α, increased frontal β activity</td>
<td>↑</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Frontally dominant δ and β</td>
<td>↑</td>
<td>No</td>
</tr>
<tr>
<td><strong>Opiates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>Loss of β, α slows</td>
<td>↑↑↑↑</td>
<td>No</td>
</tr>
<tr>
<td>Moderate dose</td>
<td>Diffuse δ, some β</td>
<td>↑↑↑↑</td>
<td>No</td>
</tr>
<tr>
<td>High dose</td>
<td>δ, often synchronized</td>
<td>↑↑↑↑</td>
<td>No</td>
</tr>
</tbody>
</table>

8, <3-Hz frequency; 0, 3.5–7.5-Hz frequency; α, 8–13-Hz frequency; β, >13-Hz frequency.
unprocessed analog signal. Drug effect monitoring is generally accomplished using one or two channels of EEG information, generally recorded over the frontopolar region of the cerebral cortex. This location is chosen because application of surface recording electrodes is easy in this location (no hair) and most devices designed for this purpose have been validated using frontopolar recording locations. Usage of this smaller number of channels is based on the assumption that the drug effect will be similar in all areas of the brain. This assumption is generally valid except in the case of a patient with focal brain damage. In areas of damage, the drug effect will generally be greater than usual and must be interpreted in light of the abnormal baseline recording. None of the commercially available devices for monitoring drug effects on the EEG has been calibrated or validated appropriately for monitoring drug effects in the patient with the abnormal EEG, and relatively limited information is available on the use of EEG to monitor drug effects in neurologically damaged patients (83–86).

EEG drug effect monitoring is used most commonly for titrating sedative drugs, particularly in the pharmacologically paralyzed patient, but also for titration of barbiturate drugs or propofol used to control ICP (67–69,87,88). Devices used to monitor the drug effect utilize unprocessed, raw analog EEG in a fashion similar to ECG monitoring in the ICU or utilize one of three signal processing techniques: Power spectrum analysis, bispectral analysis (BIS), or EEG entropy analysis. Examples of commercial monitors include the BIS, the patient state index, SEDline, and entropy. Although the BIS monitor has been used and studied most widely among these monitors, the concepts discussed below should apply to other EEG-based monitors of sedation as well.

BIS (Aspect Medical Systems, Inc., Natick, MA) monitoring has been used in the intensive care setting to guide dosing of sedatives and reassure clinicians that paralyzed or agitated patients are amnestic but not excessively sedated (89). The BIS monitor processes EEG signals that are recorded from a self-adhesive electrode strip placed on the forehead. It calculates and displays a BIS value, a dimensionless number ranging from 0 to 100 that is derived from highly processed EEG data that includes EEG power, frequency, and bicoherence (90). Low BIS numbers indicate strong relationships among the EEG frequencies and reflect a condition consistent with a deep hypnotic state (Table 28.6). This relationship is valid despite the effects of age and infirmity on sensitivity to sedation (91,92).

Despite its obvious clinical utility, the aspects of imperfect performance of the BIS monitor are well known. For example, the BIS can decrease to numbers (20 to 50) consistent with deep general anesthesia during natural sleep without sedation (93). Moreover, although memory is less likely to form at lower BIS values, memory has been demonstrated even at a BIS in a range (40 to 60) associated with general anesthesia (94). Additionally, artifact from electromyographic, electrooculographic (95), or pacemaker generators (96) can produce significant but spurious BIS increases (from 50s to 80s), although the algorithm has been improved in the last decade to reduce the effects of such artifacts. This finding raises the possibility of overdosing nonrelaxed or paced patients when attempting to maintain a given BIS range. BIS values can also be driven higher by medications that are CNS stimulants, such as ketamine or methylphenidate (97). Dexmedetomidine, as discussed earlier, may produce EEG patterns that will result in lower BIS values at a comparable level of sedation (71,95).

In such cases, the BIS may not reflect the level of hypnosis or sedation experienced by the patient. Therefore, when the sedative dosages required to achieve a desired BIS range exceed normal expectations, the possibility of an artifactual interference deserves consideration.

Perhaps the most significant issue with BIS or other monitors of cortical anesthetic drug effect are their inability to differentiate deep sedation from cerebral ischemia. Both conditions cause loss of higher frequency EEG waves (α and β slowing and δ and θ wave intrusion) and, in extreme states, both can produce burst suppression or isoelectric EEG patterns with a low BIS. When O2 delivery decreases below a level sufficient to meet the CMRO2, electrical function fails and BIS decreases. This may partly explain improved ICU outcomes when the BIS is maintained above 60 (98). Therefore, the determination that sedation is adequate based on having achieved a target BIS value should only be made when one is confident that cerebral perfusion is adequate.

Interpretation of BIS or, for that matter, any EEG-based monitor of sedation is best accomplished when the patient’s pharmacologic support remains stable in the face of changing CPP or, conversely, the CPP remains adequate and stable during pharmacologic adjustments and BIS changes. As a corollary, the BIS can assist with guiding therapy when the adequacy of O2 supply to the CNS is in question (99).

In summary, other than for drug effect monitoring, use of the EEG in the ICU remains relatively limited, primarily because of personnel costs and difficulty in maintaining stable technical conditions for monitoring multiple channels of information. As our understanding of underlying mechanisms for neurologic injury improves, we may be able to learn which monitoring modalities are most useful for a given clinical scenario and which can more specifically target EEG monitoring to a smaller area of the brain. In addition, as computing power continues to improve, signal processing technology will likewise improve, and EEG monitoring equipment that recognizes artifact and self-corrects technical problems may reduce the need for the continuous presence of highly trained personnel to operate the EEG in the ICU environment.

### Peripheral Nerve Stimulation

The rate of recovery from neuromuscular-blocking agents depends upon the neuromuscular-blocking agent chosen, its dosing pattern (intermittent or continuous infusion), and numerous patient factors (e.g., pseudocholinesterase deficiency, hepatic or renal dysfunction, induced cytochrome P450 enzyme, organophosphate toxicity, among many others) (100). The suitability for extubation following prolonged

<table>
<thead>
<tr>
<th>Value</th>
<th>Clinical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Awake patient, amnesia unlikely</td>
</tr>
<tr>
<td>80</td>
<td>Sedated responsive patient, amnesia prominent unless significant event</td>
</tr>
<tr>
<td>70</td>
<td>Heavily sedated or unconscious patient, amnesia probable</td>
</tr>
<tr>
<td>60</td>
<td>General anesthesia, unresponsive to verbal stimuli</td>
</tr>
<tr>
<td>40</td>
<td>Deep hypnotic state</td>
</tr>
<tr>
<td>20</td>
<td>Burst suppression</td>
</tr>
<tr>
<td>0</td>
<td>Isoelectric electroencephalogram</td>
</tr>
</tbody>
</table>
neuromuscular blockade has traditionally relied upon functional strength testing, such as an ability to produce a negative inspiratory force or to sustain a head lift. Incomplete patient cooperation caused by sedation or confusion, among other reasons, can adversely affect these tests. Peripheral nerve stimulation (PNS), used for “muscle twitch” testing, or acceleromyography, complements such functional assessments by objectively revealing the condition of the neuromuscular junction, independent of patient participation.

Reliable interpretation of nerve stimulation requires uniform form stimulation and placement parameters. Conventional PNS delivers current—adjustable up to 80 mA—in a train-of-four (TOF) series at 2 Hz as double-burst stimulation, as single shocks at 1.0 or 0.1 Hz, or by tetanic stimuli of 50 or 100 Hz. When tolerated, maximal current settings assure the best chance of delivering supra-threshold stimuli and activation of the greatest percentage of motor fibers despite changes of impedance or proximity, as can occur with electrode separation or desiccation, skin cooling, or peripheral edema. TOF and double-burst stimulation patterns do not require comparison to earlier responses for interpretation, and are therefore well suited for use in the ICU setting where recovery of neuromuscular function may take hours to days and may involve assessments by multiple providers.

Muscle twitch testing measures the force of muscle contractions in response to PNS. The ratio of the force between the last and first stimuli in a series (TOF or double-burst stimulation) best defines the percentage of acetylcholine receptors occupied by nondepolarizing neuromuscular-blocking agents in the neuromuscular junction, but is cumbersome to perform (101). Counting the loss of twitches in a TOF is a simpler method for assessing the level of block and has greater bedside utility (Table 28.7). In contrast, the TOF ratio does not change following the administration of a depolarizing neuromuscular-blocking agent such as succinylcholine. When depolarizing neuromuscular-blocking agents are used, the force of contraction diminishes equally across all stimuli and disappears altogether with sufficient dose. If an excessive depolarizing neuromuscular-blocking agent is administered, a prolonged phase II block emerges. TOF responses during a phase II block behave similarly to responses obtained following nondepolarizing neuromuscular-blocking agents.

The peripheral nerve stimulator is attached to a patient using two pre-gelled electrocardiogram electrodes, although needle electrodes can also be used. The electrodes should be placed closely (without the gels touching) to one another over a site where a nerve with motor function lies relatively superficial to the skin. Antegrade nerve conduction is improved if the positive lead is applied to the proximal electrode. The current path between electrodes should not contain the muscle whose movement is being monitored. Separation of electrodes beyond several centimeters increases the probability that the PNS current may depolarize muscle directly, causing movement unrelated to conduction through the neuromuscular junction and thus, misinterpretation of the level of neuromuscular blockade.

Common sites for electrode placement are over the course of the ulnar nerve at the medial aspect of the wrist or over the ulnar groove at the elbow. Stimulation of the ulnar nerve activates the m. adductor pollicis and twitches the thumb. Placement of the electrodes anterior to the tragus will stimulate the facial nerve, which innervates the m. corrugator supercilii and furrows the eyebrow. Stimulation of the posterior tibial nerve posterior to the medial malleolus causes the m. flexor hallucis brevis and great toe to move.

Cold will weaken muscle strength even in the absence of neuromuscular-blocking agents, making PNS testing valuable in patients recovering from hypothermia (102). Patients who have had a stroke will experience an upregulation of acetylcholine receptor density on the muscle membrane as the affected muscles denervate. As a result, PNS on an affected limb will produce a TOF response that exceeds the response seen from the same site PNS on a normal limb. To avoid overdosing or prematurely extubating a patient based on TOF testing, PNS should be performed on sites unaffected by prior nerve injury.

PNS is particularly helpful for monitoring the level of relaxation achieved during the infusion of neuromuscular-blocking agents. PNS monitoring can help direct the rate of infusion and avoid excessive administration. Pharmacokinetic and pharmaco-dynamic models that illustrate the TOF response to PNS with succinylcholine and rocuronium neuromuscular-blocking infusions can be found at http://vam.anest.ufl.edu/simulations/simulationportfolio.php.

**TABLE 28.7 Percentage of Neuromuscular Junction Blockade with Nondepolarizing Neuromuscular-Blocking Agents and Corresponding Train-of-Four and Clinical Responses**

<table>
<thead>
<tr>
<th>Response</th>
<th>% Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Train-of-four (0/4)</td>
<td>95</td>
</tr>
<tr>
<td>Train-of-four (1/4)</td>
<td>90</td>
</tr>
<tr>
<td>Train-of-four (2/4)</td>
<td>85</td>
</tr>
<tr>
<td>Train-of-four (3/4)</td>
<td>80</td>
</tr>
<tr>
<td>Train-of-four (4/4)</td>
<td>75</td>
</tr>
<tr>
<td>Sustained (≥ 5 sec) tetanus</td>
<td>50</td>
</tr>
<tr>
<td>Sustained (≥ 5 sec) head lift</td>
<td>25</td>
</tr>
</tbody>
</table>

**EVOKEPOTENTIALS**

The EEG is a recording of the spontaneous electrical activity of the cerebral cortex. In contrast, EPs are recordings of the electrical activity occurring within parts of the nervous system produced by activation of either sensory or motor systems. With the exception of motor-evoked responses recorded from muscle, EPs are much smaller than background EEG or muscle electrical activity, and the responses from repetitive stimuli must be averaged to be able to discern the responses from other background biologic signals and environmental noise. Auditory responses are very small (generally <0.5 μV) and require as many as 2,000 averaged responses to resolve the signal. Somatosensory responses are larger (0.5 to 10 μV) and require fewer responses to be visible. EPs are described in terms of latency (conduction time [milliseconds]) from stimulus application to arrival at a generating site with onset or peak of response), amplitude (microvolts), and morphology (Fig. 28.7). Conceptually, amplitude is the more important parameter for ICU studies because voltage is related to the amount of functional neural tissue generating the response. With a nerve injury, however, signals will be conducted more slowly through the most damaged fibers. This situation spreads out the arrival times of conducted signals, desynchronizing the evoked response, decreasing its amplitude, and broadening its morphology.
In comparison with the EEG, EPs are much less susceptible to the effects of intravenous sedative-hypnotic drugs and are not significantly affected by intravenous analgesics (103). Auditory EP responses will not be altered significantly by any sedating or analgesic regimen used in the ICU today. Notably, based on known effects of opiates and sedatives on brainstem auditory-evoked potentials (BAEPs), patients admitted with opiate or sedative drug overdose and an isoelectric EEG will not show any significant abnormality of waves I through V related to the drug effect alone (73,74,103). Somatosensory evoked potentials (SEPs) are somewhat more susceptible to the effects of sedative drugs. Cortical SEPs do show significant increases in latency and decreases in amplitude with sedating medications (103), but generally, they will not be completely abolished even by enough sedative medication to render the EEG isoelectric (73,74,103). This is important to remember for the patient with drug overdose.

Table 28.8 is a summary of the different types of EPs that may be recorded or monitored in the ICU. The results of these tests are frequently used as prognostic indicators of intermediate and long-term neurologic function. Some large neurologic or neurosurgical ICUs are able to provide continuous real-time EP monitoring. Unlike EEG, which reveals only electrical function of the cortex, EPs reflect the function of nervous system tissue along the entire signal conduction pathway. The response to an electrical stimulus applied to a distal peripheral nerve is typically recorded as it is conducted centrally from the peripheral nerve, over the spinal cord (usually the cervical region), and over the cerebral cortex. Thus, the peripheral nervous system, spinal cord, brainstem, thalamus, internal capsule, and cerebral cortex are assessed with a single test. Generally, EPs are assumed to reflect the function of the surrounding neural tissue, whether cortical, subcortical, or spinal cord (Fig. 28.8). Where conduction times differ from normal or are observed to change helps to locate the stressed or damaged structure. Although it is possible to have unchanged EPs with very focal lesions in the brain or spinal cord causing profound neurologic deficit, this is uncommon. EPs usually reflect the function of the surrounding neural tissue and have been demonstrated as very effective at detecting a developing injury and in prognosticating the long-term effects of an existing neurologic injury. This section of the chapter will examine BAEPs, SEPs, and transcranial motor-evoked potentials (MEPs) and their use as diagnostic, prognostic, and monitoring tools in the ICU.

### Brainstem Auditory-Evoked Potentials

The stimulus for the BAEP is a repetitive loud click applied via headphone or ear inserts. To interpret the information provided by BAEPs, the clinician must be aware of modes by which testing can fail. For example, cerumen in the ear canal may muffle the applied stimulus; trauma may anatomically disrupt the auditory apparatus (damage to the external auditory canal, tympanic membrane, middle ear apparatus; aminoglycoside antibiotics may damage the inner ear transduction system). Fortunately, the eighth nerve itself produces a recordable action potential (Fig. 28.9), and presence of this response confirms that the auditory stimulus has actually reached the nervous system. Confirmation of nervous system activation is an essential first step for all EPs and should precede any interpretation of waveforms. This step guards against equipment malfunction, technical issues, and incorrectly optimistic and
pessimistic interpretations. Without the presence of an eighth nerve action potential on the BAEP, no conclusions about the functioning of the more rostral auditory pathway can be made.

Figure 28.8 is a schematic representation of the auditory pathway in relationship to important brainstem and midbrain structures. The entire BAEP is generally completed within 10 milliseconds of the stimulus application. Because the auditory pathway has multiple synapses that produce recordable responses from the lower pons through the midbrain, if the recorded response demonstrates abnormalities at any level, significant neurologic impairment of the patient is likely because of the functional significance of nearby motor, sensory, autonomic, cranial nerve, and reticular activating system structures. Based on results from multiple studies, if the BAEP beyond the cochlear nerve action potential (wave I) is absent bilaterally, the CNS prognosis is grave with clinical and/or angiographic criteria often establishing brain death (63,66,104–106). Figure 28.10 shows BAEP and SEP recordings from three different patients who were comatose following trauma or surgery and were being evaluated for CNS function with EP recordings in the surgical ICU. Patient A had absent BAEPs beyond wave I and absent SEPs, and was determined to be brain dead within 24 hours of the EP studies. Patient B had a normal recording

![Figure 28.9. Normal brainstem auditory-evoked response. Note the presence of wave I, the eighth nerve action potential, which confirms that the auditory apparatus is being properly stimulated.](image1)

![Figure 28.10. Neurophysiologic studies from three comatose patients. A: Brain-dead patient. This patient has no recordable evoked auditory response after wave I and no recordable somatosensory response after the cervical response. (continued)](image2)
of waves I through V, but SEPs were absent. This patient had a prolonged hospital course and never recovered any higher neurologic function. Patient C had normal BAEPs and SEPs despite a severely impaired neurologic examination and difficult-to-control seizures at the time of the SEP study. Subsequent EP studies continued to show intact BAEPs and SEPs despite abnormal posturing and difficult-to-control seizures. This patient went on to recover independent neurologic function after many months of rehabilitation (107). These three patients exemplify the most common usage of EPs in the ICU, and their studies and outcome reflect what is documented in the literature. In summary, absent BAEPs beyond wave I indicate a high likelihood of a brain death outcome. Intact and normal BAEPs may indicate a good outcome, especially in the face of normal SEPs. If SEPs are absent bilaterally, the best likely outcome is a chronic vegetative state, even with normal BAEP waves I through V.

The stimulus for the SEP is repetitive electrical stimulation delivered to a peripheral nerve, most commonly the median nerve at the wrist or the posterior tibial nerve at the ankle, using surface electrodes or subdermal needle electrodes. The first response (a nerve action potential confirming pathway activation) is recorded proximally over the peripheral nerve or appropriate nerve plexus (Fig. 28.11). The next recorded response is generated in the lower brainstem and recorded with a surface electrode placed over the upper cervical spine. The primary initial cortical response at the rostral end of the somatosensory pathway is recorded over the cortex, contralateral to the side of stimulus application. Median nerve cortical SEPs usually occur 25 milliseconds from stimulus application or 50 milliseconds from stimulus application at the posterior tibial nerve. The normal SEP also contains responses that are later than the primary response. These responses, also generated by cortical neurons, are considered to be related to higher cognitive function. Most studies where SEPs are monitored or used for diagnosis and prognosis only analyze the initial primary cortical response occurring prior to 25 milliseconds. A few studies have also examined the prognostic significance of the later SEP or auditory responses (108,109), but the

![Figure 28.10](image-url)
FIGURE 28.11. Normal median nerve somatosensory response. Reproducible responses at the brachial plexus and cervical levels confirm that a somatosensory stimulus is reaching the central nervous system. Without responses at both these levels, conclusions about cortical functions cannot be made.
clinician should be aware that all of these later responses are highly influenced and easily abolished by any of the drugs used for sedation and analgesia in the ICU. In fact, later auditory responses have been used to gauge the depth of sedation in a fashion similar to the EEG bispectral index (109).

Figure 28.8 shows the somatosensory pathway schematically, together with the auditory pathway and nearby brainstem, midbrain, and cortical structures, in a single slice through the pons. As shown in the figure, the auditory and somatosensory pathways are separated far enough to include multiple important structures in the territory between them. The anatomic locations of the two separated pathways explain why neurologic outcome is usually better when both evoked response modalities show a normal response. The presence of cortical responses to a peripheral stimulus indicates that the involved subcortical nervous pathway is intact and that cortical neurons are still functional enough to be activated and produce a measurable electrical response, both of which are necessary for a good long-term neurologic outcome.

In summary, the presence of normal SEPs bilaterally, based on all available literature, is an excellent prognostic sign. The absence of any SEP cortical response is a poor prognostic indicator. The degree of bad outcome can be predicted by the BAEP. Intact and normal BAEPs with absent cortical SEPs predict a best outcome of a chronic vegetative state. Outcome may be worse, however, as BAEPs commonly deteriorate later with rostral-to-caudal CNS deterioration. Absent BAEP responses beyond wave I predict a high likelihood of brain death. Present but abnormal SEPs are associated with intermediate outcomes between good/high function and a chronic vegetative state (63,65,66,104–106,109–112).

The motor pathway may be tested by transcranial stimulation of the motor cortex. The cortex may be activated by a magnetic or electrical stimulus. A descending response may then be recorded over the spinal cord at multiple levels: The peripheral nerve and (most commonly) the muscle. Cortical stimulation, either electrical or magnetic, commonly activates the motor cortex governing the upper and lower extremities and produces a myogenic response that does not need to be modified by Cushing at the turn of the 19th century, states that any increase in volume of one intracranial component may overwhelm the compensatory mechanisms and produce a rapid increase in ICP; whereas a slowly growing brain tumor may produce a gradual displacement of structures within the cranial vault without a significant increase in ICP. ICP is not static. Pressure fluctuations occur with cardiac systole due to distention of the intracranial arteriolar tree and respiration (i.e., ICP falling with each inspiration and rising with expiration). Straining or compression of neck veins can also cause a rise in pressure. A value in excess of 20 mmHg is almost always abnormal and should be treated. As the ICP increases, the cerebral venous pressure increases in parallel so as to remain 2 to 5 mmHg higher, or else the venous system would collapse. Because of this relationship, CPP can be satisfactorily estimated from mean arterial pressure at the external auditory meatus minus ICP.

Intracranial Pressure Monitoring and Waveform Interpretation

In cases of intracranial disease, the relevant pressure opposing adequate perfusion is the ICP. ICP reflects the dynamic interaction of tissues and fluids within a fixed volume, hard cranial shell of approximately 1,400 mL in an adult. Its contents can be divided into cerebral parenchyma, arterial and venous blood, and CSF components. The cerebral parenchyma accounts for 80% to 90% of the contents and includes intra- and extracellular fluid as well as cellular membranes. The volume of the blood together with the CSF makes up the remaining 10% to 20%. The Monroe–Kellie doctrine, as modified by Cushing at the turn of the 19th century, states that any increase in volume of one intracranial component occurs at the expense of another. Normal ICP in adults is 8 to 15 mmHg, and in babies, the pressure is 10 to 20 mmHg (less when measured through a lumbar puncture). Compensatory mechanisms stabilize ICP in response to slight changes in CBF, as well as CSF production and absorption. In the absence of effective compensatory mechanisms, an increase in the volume of any one of the components will lead to an exponential increase in pressure, as illustrated by the pressure–volume relationship (Fig. 28.12) described by Langh (117). Compensation may be achieved by any of the following: changes in the volume of CSF; the slight distention of the dura; changes in the intravascular volume, particularly in the venous channels; and compression or swelling of the brain. The rate of change in the volume of intracranial contents is important. For example, a rapid increase in volume produced by an epidural hematoma may overwhelm the compensatory mechanisms and produce a rapid increase in ICP, whereas a slowly growing brain tumor may produce a gradual displacement of structures within the cranial vault without a significant increase in ICP.

CEREBRAL PERFUSION

This section of the chapter will examine methods that are available to monitor the adequacy of CBF. These monitors provide information that is complementary to the functional assessment discussed above, because function only becomes altered when CBF decreases by more than half.

The most common clinical measure aimed at ensuring adequate CBF is to maintain the CPP above the lower limit of cerebral autoregulation. Cerebral arterial circulation is normally autoregulated to maintain a constant CBF for a CPP between 70 and 150 mmHg. The accuracy of the CPP measurement should be confirmed in every patient. Because patients in the ICU are often positioned with their head elevated, calculating blood pressure goals that are corrected for the difference in vertical height between the external auditory meatus (as a landmark for the circle of Willis) and the blood pressure zero point (cuff, or arterial line zero point) are essential to defending the desired CPP. For every centimeter in vertical height between the two, the true blood pressure is approximately 0.75 mmHg lower in the head than displayed. Even in a semirecumbent adult, the height difference from the heart to the head can reach 27 cm, representing an arithmetic correction downward of 20 mmHg for blood pressure and CPP in the brain. Zero arterial transducers at the external auditory meatus or calculate the correction to achieve the target CPP.
Clinical deterioration in neurologic status is widely considered a sign of increased ICP. Bradycardia, increased pulse pressure, and pupillary dilation are accepted as signs of increased ICP.

The five methods most commonly used to monitor ICP are an intraventricular catheter, a subarachnoid or subdural bolt, a subdural catheter, an intraparenchymal fiberoptic filament sensor, an extradural fiberoptic sensor. Each of these has its advantages and disadvantages. The intraventricular catheter is typically considered the gold standard. Its advantages include easy recalibration and a means to treat ICP elevations by removing CSF. However, it is the most invasive method and distorted intracranial pathology may necessitate several insertion attempts. The other devices are easier to place, but the accuracy of the recorded values may be more difficult to verify. All ICP monitors share a risk of infection of about 5%.

Patients who require ICP monitoring are generally considered to be those with a closed head injury and a GCS less than or equal to 8; in whom a CT scan shows significant brain distortion; with worsening neurologic status; in whom there is a need to sedate, paralyze, or operate in the context of an abnormal brain; with postoperative complications; and who are unconscious or in shock. The ICP data derived from such monitoring can serve as a useful therapeutic guide to clinical care.

The normal ICP waveform has three characteristic peaks (P1, P2, and P3) of decreasing height that correlate with the arterial pulse waveform (Fig. 28.13). The P1 (or percussion) wave originates from arterial systole and has a sharp peak and constant amplitude. The P2 (or tidal) wave is more variable and ends on the dicrotic notch. Elevation of the P2 component of the ICP waveform is thought to reflect decreased intracranial adaptive capacity and impaired autoregulation. However, sustained increases in ICP can occur without P2 elevation. The P3 (or dicrotic) wave follows the dicrotic notch and is venous in origin.

When consecutive ICP waveforms are observed over time, three distinct patterns—first described by Lundberg in 1960 as A, B, and C waves—may be observed (118). A waves, now more commonly referred to as plateau waves, are pathologic (Fig. 28.14). There is a rapid rise in ICP up to 50 to 100 mmHg, followed by a variable period during which the ICP remains elevated ("plateau"), followed by a rapid fall to the baseline. These plateau waves typically last from 5 to 20 minutes. They are generally seen in patients with already elevated ICP. During a series of plateau waves, amplitude and duration may increase, leading to a "terminal" wave in which ICP may rise to levels that impede CBF. "Truncated" or atypical plateau waves that do not exceed 50 mmHg are early indicators of neurologic deterioration. B and C waves are smaller fluctuations in ICP thought to be related to respiration and autonomic fluctuations in blood pressure (Traube-Hering-Mayer waves), respectively. They are of little clinical significance.

Observing a normal CPP may be reassuring but must not be assumed to reflect normal CBF. Increased cerebrovascular resistance (e.g., because of carotid stenosis, cerebral vasospasm, or microcirculatory compromise) may cause ischemia despite normal CPP. Similarly, normal CPP may coexist with hyperemia in settings such as posttraumatic vasoparalysis, normal perfusion pressure breakthrough after resection of an arteriovenous malformation, or following carotid endarterectomy.

**DIRECT CEREBRAL BLOOD FLOW MEASUREMENT**

Several methods for determination of CBF exist (Table 28.9). They have the potential to provide insights into the pathophysiologic events in head injury or stroke, and help to direct therapeutic interventions.
TABLE 28.9 Techniques for Measuring Cerebral Blood Flow

<table>
<thead>
<tr>
<th>Category</th>
<th>Technique</th>
<th>Resolution</th>
<th>Invasiveness</th>
<th>Cost</th>
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<tr>
<td>Bedside</td>
<td>Kety-Schmidt</td>
<td>Thermal clearance, 15 min</td>
<td>Hemispheric</td>
<td>Jugular catheter, +</td>
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<td>133Xenon wash-out</td>
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<td>Arteriovenous difference in oxygen</td>
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<td>content, jugular venous oxygen</td>
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<td>Double indicator dilution</td>
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<td>Near-infrared spectroscopy</td>
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<td>Thermal clearance probe</td>
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<td>Position emission tomography</td>
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<td>Stable Xenon computed</td>
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<td>Single photon emission tomography</td>
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<td>Magnetic resonance imaging</td>
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Direct measurement of CBF is possible by determining the kinetics of wash-in or wash-out of an inert tracer compound in a variation of the method originally described by Kety and Schmidt (119). The most widely used measurement involves the administration of a radioactive isotope of 133Xe per inhalation or intravenously, followed by measurement of the radioactivity wash-out, with γ detectors placed over specific areas of the brain. This method provides a spatial resolution of about 3 to 4 cm, depending on the number of detectors. In the normal brain, flow at different depths may be inferred from the early wash-out, which should reflect high-perfusion cortical gray matter and low-perfusion deeper white matter. An important disadvantage of the technique is its lack of sensitivity for focal areas of hypoperfusion, which are obscured by adjacent areas of adequate flow—a phenomenon described as “look-through.”

Radiologic methods like SPECT, PET, Xenon-enhanced CT or perfusion CT, and MRI provide excellent spatial resolution, but are not available at the bedside. Some are used clinically as confirmatory tests in the determination of brain death. SPECT and magnetic resonance angiography, for example, show a “hollow skull phenomenon” and absent intracranial flow, respectively. Xenon-enhanced CT, and recently, perfusion CT scans have been used to obtain prognostic information and withhold unnecessarily aggressive therapy by assessing the severity of the decrease in CBF during stroke (120). Perfusion imaging allows the detection of a viable penumbra around areas of ischemia, which may be restored to normal function if the relative ischemia can be reversed.

Transcranial Doppler

An easy-to-apply, noninvasive bedside monitor that provides information on CBF is TCD ultrasound (121). The many applications of ultrasound imaging in the ICU setting have brought modern instrumentation to the ICU bedside, allowing TCD to be acquired based on color flow images of intracranial arteries against a backdrop of other intracranial structures as transcranial color-coded sonography (TCCS).

In TCD, ultrasound waves are used to measure the velocity of blood flow in the basal arteries of the brain and the extracranial portion of the internal carotid artery. These waves are transmitted through the relatively thin temporal bone, the orbit, or the foramen magnum (122). When they contact moving red blood cells, they are reflected at a changed frequency through the brain and skull back to a detector. The change in frequency as blood cells move toward or away from the ultrasound transmitter and detector is an example of the Doppler effect, and is related to velocity and direction of flow. Velocity increases during systole and decreases during diastole; blood in the center of the lumen moves faster than that near the vessel wall, producing a spectrum of flow velocities. This spectrum resembles the shape of the waveform produced by an intra-arterial pressure transducer (Fig. 28.15). The TCD probe emits ultrasound waves as short pulses. Because ultrasound travels through tissue at a constant velocity, assessment of flow at different distances from the transducer becomes possible by varying the time window during which the reflected ultrasound waves are received. Thus, each arterial segment at the base of the brain has a distinct signature in terms of depth of insonation and direction of flow. TCD measurements are most commonly (and easily) made in the middle cerebral and internal carotid arteries, but may also be measured in other vessels, including the anterior cerebral, anterior communicating, posterior cerebral, posterior communicating, and basilar arteries. In approximately 10% of patients, particularly elderly females, technically satisfactory recordings cannot be obtained because of increased skull thickness (122).

Although TCD allows the interrogation of all arteries that supply the brain, it cannot provide a simple assessment of global or hemispheric CBF. In the setting of acute stroke or traumatic arterial dissection, the mere patency of a vessel is an important question that has diagnostic, therapeutic, and prognostic implications (121–123). For example, the presence of blood flow indicates recanalization of a vessel and may be used to spare a patient the risks associated with thrombolytic therapy. Beyond the question of vessel patency, the link between TCD measurements and CBF is indirect and subject to one technical limitation and two principal assumptions inherent in the link. The technical limitation is that the accuracy with which the flow velocity can be determined depends on the
angle of insonation. The variability of repeated measurements can be minimized by using a single examiner, provided a shift in brain structures caused by a mass lesion does not displace the artery. The two principal assumptions that have to be met for TCD-measured blood flow velocity to correspond to CBF are as follows:

1. Flow and flow velocity are directly related only if the diameter of the artery remains constant.
2. Second, the blood flow in the basal arteries of the brain must be directly related to cortical CBF.

These assumptions likely represent an oversimplification and have not been supported adequately by evidence. Specifically, radioactive Xenon-measured CBF does not correlate well with TCD-derived middle cerebral artery velocity during carotid endarterectomy or cardiopulmonary bypass (124–126). Likewise, normal variations in blood flow velocities are large (125).

Detection of Cerebral Vasospasm

TCD has been helpful in identifying vasospasm following aneurysmal subarachnoid hemorrhage and is typically used daily in these patients (127). As the diameter of the arterial lumen decreases with vasospasm, the velocity of blood flowing through the narrowed vessel must increase if flow is to be maintained. Using absolute flow velocity alone, detection and documentation of the severity and duration of vasospasm are possible, with a specificity that approaches 100% but with limited sensitivity. Flow velocities greater than 120 and 85 cm/sec identify patients at risk for angiographic vasospasm in middle cerebral and basilar artery territories, respectively (128). One important setting where absolute TCD flow velocity may underestimate the severity of vasospasm is that of increased ICP (129). Increases in ICP, however, lead to characteristic changes in the TCD waveform and increase the pulsatility index (see Fig. 28.15 and the following Section). Therapeutic dilation of stenotic arteries may not normalize TCD flow velocities immediately because of impaired autoregulation in the poststenotic vascular bed (130). Likewise, TCD cannot assess isolated distal vasospasm, which may account for as much as one-third of all cases of vasospasm (131).

Assessment of Intracranial Pressure and Confirmation of Brain Death

The TCD-generated waveform exhibits characteristic sequential changes as ICP increases (see Fig. 28.15) (132). As ICP increases, the systolic waveform becomes more peaked. As ICP nears diastolic blood pressure, diastolic flow diminishes and subsequently ceases. Once ICP exceeds diastolic blood pressure, TCD shows a pattern of to-and-fro movement of blood that indicates imminent intracranial circulatory arrest. This change in waveforms can be used to calculate a pulsatility index by relating the difference between peak systolic and end-diastolic velocity to the mean or to the systolic velocity. Such waveform analyses correlate well with ICP (133) but cannot replace ICP monitoring because autoregulation, vasospasm, or proximal arterial stenosis may alter the TCD signal independent of the ICP (121).

Clinical brain death demonstrates a characteristic blood flow velocity pattern (134,135). There is a short systolic inflow of blood, followed by an exit of blood (flow direction reverses) from the cranium during diastole. TCD is a validated confirmatory test in the diagnosis of brain death.
with a sensitivity that exceeds 90% and a specificity of 100% (136,137). Although TCD can ascertain the diagnosis in most patients at the bedside, a large craniotomy or an inadequate bone window may preclude the complete examination necessary to confirm brain death.

**Jugular Venous Oxygen Saturation Monitoring**

Jugular venous oxygen saturation (SjvO₂) monitoring has been touted as an indicator of cerebral oxygen homeostasis. Changes in SjvO₂ from the normal range (60% to 70%) provide indirect information on the state of CMRO₂, and because blood flow is normally linked to CMRO₂, indirect information on CBF as well. Approximately 50% to 70% of patients with severe head trauma (GCS ≤ 8) will have an episode of desaturation (SjvO₂ < 50%). Despite an ischemic threshold widely accepted to be SjvO₂ > 50% during the early hyperemic conditions following head injury, the clinical utility of SjvO₂ monitoring remains unsettled (138).

The complexity of catheter placement, robustness of data acquisition, sample collection, and results interpretation contribute to a limited utilization of SjvO₂ monitoring in victims of moderate to severe head injury (139). SjvO₂ is preferentially measured from the flow-dominant internal jugular vein (right 60%, left 25%, equal 15%) (140) to provide the best estimate of whole brain CMRO₂ conditions. Internal jugular vein size on ultrasound or CT provides a reasonable estimate of hemispheric dominance.

An increase in SjvO₂ indicates lowered CMRO₂ (less extraction) and/or increased or hyperemic CBF. A decrease in SjvO₂ (greater extraction) indicates increased CMRO₂, hypoxia/aneemia, or oligemia. Observed changes in SjvO₂ might then help guide therapeutic interventions.

Abundant experience validates the association of jugular venous desaturation (SjvO₂ < 50%) with worsened neurologic outcome. Conversely, mortality in TBI was reduced 66% when monitoring and managing the cerebral extraction of oxygen with SjvO₂ in addition to CPP compared to management by CPP alone (141). CMRO₂ increased in patients with elevated ICP (ICP ≥ 20 mmHg) and normal to decreased cerebral extraction (“luxury perfusion”) of oxygen with hyperventilation therapy. Elevated ICP associated with normal to increased cerebral extraction of oxygen was treated with mannitol, resulting in improved ICP and cerebral oxygenation.

Profound neurologic deterioration occurs with SjvO₂ desaturation to 30% or less (142). As cerebral circulatory arrest develops, the external carotid artery increasingly provides the blood sampled at the jugular bulb, and SjvO₂ then increases. In the clinical setting where brain death is expected, a ratio of mixed venous blood saturation to SjvO₂ less than 1 has been found to be highly sensitive (95%), specific (100%), and predictive (92%) for cerebral circulatory arrest (143).

The limitations of SjvO₂ monitoring may partly explain its decreasing use. Admixture of extracranial blood through collateral venous drainage into the superior sagittal, sigmoid, and cavernous sinuses or directly into the jugular bulb is believed to occur even when the catheter is correctly placed into the jugular bulb (144). When samples are drawn faster than 2 mL/min (145) or the catheter tip lies too far short of the jugular bulb, extracranial blood may further contaminate the specimen and spuriously elevate SjvO₂. Even a “clean” SjvO₂ sample does not distinguish between lateralizing differences in flow, metabolism, or brain injury. Thus, because SjvO₂ reflects a global average from a variety of brain regions, marked regional hypoperfusion may not be reflected by a change in SjvO₂ (146). Although SjvO₂ and brain tissue oxygen pressure (PbrO₂), a measure of regional ischemia, usually track in the same direction, maintaining SjvO₂ above conventional thresholds did not reliably protect against the occurrence of regional ischemic insults. Consequently, SjvO₂ cannot be used alone to direct hyperventilation or to alert clinicians to evolving hypcapnia-induced regional cerebral ischemia. It is now clear that “acceptable” hyperventilation may cause harm that remains clinically undetected by SjvO₂ (147).

SjvO₂ monitoring may be most useful as a trend monitor in patients with diffuse global brain injury and when it identifies saturations below the ischemic threshold. Normal range SjvO₂ can represent a “false-negative” measurement insofar as areas of regional ischemia may be present. Currently, the best technique for guiding therapy to a regional area of concern is with PbrO₂ monitoring.

**Near-Infrared Spectroscopy**

Near-infrared spectroscopy (NIRS) utilizes the minimal absorption and greater penetration of wavelengths in the infrared portion of the electromagnetic spectrum to evaluate changes in CBF and cerebral oxygenation. NIRS uses light with a wavelength between 700 and 1,300 nm to penetrate the scalp, skull, and brain (148) and offers the advantage of continuous, noninvasive monitoring of the cerebral cortex; it is typically done with one sensor each for the right and the left hemisphere of the brain. NIRS is currently best established for intraoperative use in cardiac surgery where neither confounding by intracranial pathology (edema, hematoma, or subarachnoid blood) nor strict differentiation between intracranial and extracranial contribution is of significant concern (149). In ideal circumstances, NIRS may be as sensitive in detecting progressive cerebral hypoxia as EEG (150), but spatial resolution is limited by the number of detectors. Further development in the technology will be required for NIRS to find a role in the ICU setting (128).

**Brain Oxygen Monitoring**

In contrast to most other techniques for evaluating brain oxygenation, tissue level monitoring offers both the advantage and disadvantage of robustly and continuously monitoring a very discrete region of tissue (151). Intraparenchymal direct oxygen partial pressure measurements (PbrO₂) are valuable in the management of cerebral perfusion and as well as with patients with TBI (152,153). They vary with CPP and can be used to define a physiologic lower limit of the CPP (154). The variability of PbrO₂ with cerebral perfusion can be used to define an oxygen reactivity index, which appears to reflect autoregulation. Diminished reactivity correlates with poorer outcome in subarachnoid hemorrhage and TBI (155,156).

In the 2007 Guidelines for the Management of Severe Head Injury (157), a brain tissue oxygenation threshold of less than 15 mmHg was adopted as a level III recommendation. Subthreshold levels of PbrO₂, particularly if severe or persistent, have been associated with increased morbidity and mortality in patients with severe brain injury. Van den Brink et al. studied...
101 comatose, nonpenetrating head injury patients whose GCS score was greater than 8. Despite aggressive management of ICP and CPP, brain tissue hypoxia frequently occurred (158). The depth and duration of tissue hypoxia was associated with an unfavorable outcome and death at 6 months after injury. Such studies have recently been synthesized in a systematic review that confirmed the value of brain tissue oxygen monitoring (159). Research on optimal management strategies in the face of degraded PbrO2 are still an active area of research (160,161). Giri et al. described that increases in inspiratory oxygen have little effect on PbrO2 in normal tissue, whereas in the injured brain, PbrO2 is increased as long as blood flow is present (162). Stiefel et al. reported in 2005 a management strategy in severe TBI that included PbrO2 monitoring and therapy directed at maintaining brain oxygenation greater than 25 mmHg (163). Using this multimodal approach, they observed reduced patient mortality compared to CPP-directed therapy.

Cerebral Microdialysis
Microdialysis is a technique that can be combined with brain tissue oxygen monitoring within the same highly localized probe (164,165). Therefore, interpretation of the data will also be influenced by its location either in the penumbra of a lesion or in relatively normal brain. The intracerebral probe consists of a fluid path surrounded by a semipermeable membrane. This fluid path is perfused with a balanced salt solution that equilibrates with interstitial fluid from the brain. Therefore, the fluid returned from that fluid path contains substances from the brain in proportion to their local concentration, their specific membrane permeability, and the perfusate flow rate. Because the latter two do not change, the concentration of substances of interest can be followed over time. In the research context, this technique has been used to study topics as diverse as the role of excitotoxicity (166) or the proteomics of brain ischemia in stroke (167,168). The monitoring application closest to clinical utility, however, sets its sights considerably lower. It aims to determine the state of aerobic glucose utilization by following glucose concentrations directly or the ratio of metabolic intermediary products such as the pyruvate-to-lactate ratio. Ratiometric determinations of chemically similar molecules obviate the need to calibrate the probe based on the permeability of the substance(s) of interest. A decrease in the pyruvate-to-lactate ratio indicates an increase in anaerobic metabolism and/or mitochondrial dysfunction consistent with ischemia (166). Threshold values concerning for excessive substrate use of inadequate substrate delivery are a lactate/pyruvate ratio greater than 40 or a glucose concentration of less than 0.7 to 1 mmol/L (154). At this time, microdialysis is mostly used in conjunction with other monitors rather than as a stand-alone technique (128).

SUMMARY

Technologic advances in neurointensive care medicine have allowed for the successful treatment of severely injured patients. Early detection of the magnitude of the injury, damage control of coexisting diseases, prevention of secondary injury, and, ultimately, pharmacologic or surgical correction of neurodisorders are all primary objectives of the focused neurointensive care team. Effective neuromonitoring techniques are fundamental tools to achieve these goals. As the field of neurocritical care continues to emerge as a subspecialty dedicated to the treatment of critically ill patients with neurologic diseases, the neuromonitoring level of sophistication will increase in parallel, and so will our ability to monitor cerebral physiology and pathophysiology in real time.

Key Points

- Neuromonitoring requires an in-depth appreciation of neuroanatomy and neurophysiology.
- The foundation of monitoring is applied clinical evaluation.
- It is important to recognize the difference between systemic and cerebral circulation regulation to maintain neurologic integrity, autoregulation, and coupling of metabolism and oxygen delivery.
- Neuromonitoring has utility in determination of brain death, neurologic integrity, blood flow, and evaluation of blood flow.
- Continuous EEG may be used to evaluate seizure activity and depth of sedation.
- ICP monitoring provides dynamic information of compliance and pressure, which is useful following an intracranial insult.
- By providing complementary information about function, metabolism, and perfusion, multimodality monitoring may allow earlier identification of clinically important trends.
- Normal neurophysiologic monitoring signals are reassuring for current state and a patient’s future recovery. Abnormal waveforms can be caused by a variety of benign or pathologic conditions and require investigation to interpret their significance.

References

CHAPTER 28  Neurologic Monitoring


