Noninvasive Monitoring in the Neurointensive Care Unit: EEG, Oximetry, TCD

7

Christoph N. Seubert, Jean E. Cibula, and Michael E. Mahla

Contents

Abstract

Noninvasive monitoring modalities in the neurointensive care unit fall into two broad categories. The first aims to assess function of the nervous system. Examples of such monitoring modalities are the clinical exam, the electroencephalogram, and the recording of evoked potentials. Since neurological function is disrupted before cellular integrity is lost, monitors of function provide early warning of inadequate oxygen supply and provide opportunity to correct this problem before irreversible damage occurs. The second category aims to determine the adequacy of cerebral perfusion. Examples are transcranial Doppler ultrasonography, near-infrared spectroscopy, tissue pO_2, and brain or jugular venous oximetry. No single monitoring technique is without its limitations or addresses all questions raised by a given patient.

Keywords

Electroencephalography • EEG • Transcranial Doppler • TCD • Jugular bulb oximetry • Brain tissue oxygen • Brain death • Coma • Prognosis

Introduction

Monitoring the brain is a natural extension of medical care in neurointensive care units (NICU). Careful, repeated, and reliable assessment of the patient's neurological status underlies therapeutic decisions and thus underpins ultimate outcome. Improvements in the disease process present opportunities to decrease the level of physiologic support and to initiate interventions aimed towards rehabilitation. Conversely, progression of the disease processes may necessitate increased levels of physiologic support and additional medical or neurosurgical interventions in order to mitigate secondary injury to the central nervous system (CNS).

C.N. Seubert, MD, PhD (✉)
Division of Neuroanesthesia, Department of Anesthesiology,
University of Florida College of Medicine,
1600 SW Archer Rd, Rm M509, 100254,
Gainesville, FL 32610-0254, USA

Intraoperative Neurophysiologic Monitoring Laboratory,
Shands Hospital, Gainesville, FL, USA
e-mail: cseubert@anest.ufl.edu

J.E. Cibula, MD
Department of Neurology,
University of Florida College of Medicine,
Gainesville, FL 32611, USA
e-mail: jean.cibula@neurology.ufl.edu

M.E. Mahla, MD
Division of Neuroanesthesia, Department of Anesthesiology,
University of Florida College of Medicine,
1600 SW Archer Rd, Rm M509, 100254,
Gainesville, FL 32610-0254, USA
e-mail: mahla@ufl.edu

A.J. Layon et al. (eds.), *Textbook of Neurointensive Care*,
DOI 10.1007/978-1-4471-5226-2_7,

Neurophysiologic monitoring is done on the premise that normal function and the ability to compensate for pathophysiologic processes cease *before* irreversible structural damage ensues. Removal of the secondary insult should allow continued structural integrity and eventual recovery of function. In the CNS, this therapeutic window may extend from a few minutes to a few hours depending on the pathophysiologic reason why function failed and on the monitoring modality used to assess the change.

Monitoring modalities fall into two broad categories. The first aims to assess function of the nervous system. Examples of such monitoring modalities are the clinical exam, the electroencephalogram, and the recording of evoked potentials. The second category aims to determine the adequacy of cerebral perfusion. Examples are transcranial Doppler ultrasonography, near-infrared spectroscopy, tissue pO_2, and brain or jugular venous oximetry. No single monitoring technique is without its limitations or addresses all questions raised by a given patient. As clinicians decide what monitoring is used to help with patient management, neurological monitoring should not be held to a higher standard than other monitors. In fact, no monitor in either operating room or ICU has been shown to change outcome. Multimodal approaches that combine assessment of cerebral blood flow, cerebral function, and intracranial pressure with appropriate imaging and respiratory and cardiac monitoring show the greatest promise of prospectively aiding therapeutic decision making. Ultimately, any contribution made by monitoring will be tied to implementation of appropriate therapies.

Monitoring of Neurological Function

When O_2 delivery to the brain falls below a level sufficient to meet the cerebral metabolic requirement for oxygen ($CMRO_2$), function fails. Since function is disrupted *before* cellular integrity is lost, monitors of function provide early warning of inadequate O_2 supply and provide opportunity to correct this problem before irreversible damage occurs. Such monitors can be used to guide therapy when the CNS may be compromised by the natural progression of a disease process, e.g., worsening cerebral edema after cardiac arrest or head trauma, or by a complication of a disease, e.g., vasospasm in the wake of a subarachnoid hemorrhage.

Alternatively, brain function may be abnormal despite adequate O_2 supply due to factors intrinsic or extrinsic to the brain. Examples of the former include convulsive or nonconvulsive seizures and postictal states; examples of the latter include metabolic abnormalities such as hepatic encephalopathy or intoxications. In a given patient, such depressant factors may coexist with inadequate O_2 supply. For example, seizure activity, which frequently occurs after delayed resuscitation from cardiac arrest, may coexist with and compound post-hypoxic cerebral edema.

The Neurological Examination

Overview

Of all neurophysiologic monitoring modalities, the neurological examination of an awake and cooperative patient allows for the most comprehensive assessment of CNS function. It requires no special equipment or technologists to operate the equipment and can be applied continually, as needed. It should include a repeated focused assessment of CNS structures at risk in a given patient and a general overview such as the documentation of the level of consciousness, e.g., by the Glasgow Coma Scale, motor responses to verbal and/or painful stimuli, and evaluation of brainstem reflexes.

In practice, however, the neurological examination has important limitations. First, patients in neurointensive care frequently present in an altered state or with diseases that severely limit the information obtainable by a neurological exam. Second, neurological evaluations are usually done discontinuously and by examiners of varying skill or may be variably documented. Therefore, they may miss evolving changes and/or give variable results. Third, the results of neurological exams are confounded and constrained by therapeutic interventions that are frequently used in the ICU such as endotracheal intubation, sedatives/hypnotics, analgesics, or neuromuscular blocking agents. For example, the decrease and eventual absence of a pupillary light response in the syndrome of a transtentorial herniation will be preceded by extensive changes in the level of consciousness and higher cortical functions, which will be missed in an intubated patient treated with neuromuscular blocking agents.

Level of Consciousness

The first step in the neurological examination is the assessment of the level of consciousness. The standard tool is the *Glasgow Coma Scale* (*GCS*), which grades the patient's best efforts in the categories of *eye opening* (4–1 points), *motor response* (6–1 point), and *verbal response* (5–1 points), with higher scores indicating better CNS function. One obvious limitation in the use of the GCS for repeated assessments is the requirement of a verbal response, which will be unobtainable in intubated patients. Clinicians have devised various ways to overcome this limitation, such as a combined eye opening/motor response score marked with a "T" subscript to indicate endotracheal intubation or a best clinical guess at the response that a patient would give, if he/she were extubated. Regardless of the method used to adapt the GCS to intubated patients, it retains most of its diagnostic and prognostic utility [1].

Because of the limitations of the GCS for repeated assessment, a host of other scales have been developed to grade

disorders of consciousness, with a particular emphasis on the potential for rehabilitation. Their utility has been systematically reviewed recently [2], but their detailed discussion exceeds the scope of this chapter.

Brain Death

One area, which has brought both the merits as well as the limitations of the neurological exam into clear focus, is determination of brain death for purposes of organ donation or withdrawal of support, which is discussed in detail in Chap. 44. Because the clinical determination of brain death requires a comprehensive and methodical clinical assessment of the patient [3], it may also serve as a guide to the neurological exam of a comatose patient in the NICU. Its steps, with the exception of the apnea test, will be briefly summarized here.

In the case of brain death, the GCS by definition assumes the lowest possible value, because brain death is characterized by coma and unresponsiveness [4–6]. Motor responses *elicited by the exam* need to be differentiated from spontaneous movements *during the exam*. The latter are typically brief, slow movements, which 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 [4, 6]. Conditions that may confound the clinical diagnosis of coma are listed in Table 7.1 [5]. In addition to considering such confounding conditions, the diagnosis of coma should be consistent with imaging studies and/or the overall clinical picture.

The next step in the neurological 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 consistent with brain death. Typical tests, their afferent and efferent pathways, and potentially interfering clinical conditions other than direct trauma to the tested pathways are summarized in Table 7.2.

Monitoring Spontaneous Electrical Activity: Electroencephalography

Theory

Electroencephalography (EEG) is a graphical representation of voltage differences over certain areas of the cortex over time. The electrical signal is a summation of the excitatory postsynaptic potentials and the inhibitory postsynaptic potentials under each electrode and may be recorded anywhere from the scalp over the cerebral cortex. Each EEG channel has two input electrodes, the second of which is subtracted from the first by inverting the signal polarity of the second input, which is known as differential amplification. If the voltage difference is negative, the tracing goes upward, and if the difference is positive, the tracing is deflected downward by convention. In modern digital recordings, all of the electrodes are recorded with respect to a particular referential electrode and are subsequently digitally processed into montages, or combinations, of electrodes, some of which are referential (where the second input is a common electrode that minimizes local input such as one placed on the ipsilateral

Table 7.1 Neurological states resembling brain death

Disease state	Diagnostic aids	Comments
Hypothermia	Core temperature <32 °C Osborne waves on ECG	May cause central nervous system depression up to clinical brain death
Acute poisoning	Drug screening	In differentiating from brain death, consider antidote and/or document subtherapeutic drug concentration and/or wait for four elimination half-lives
	Serum concentration Measurements	Direct central nervous system depressants may confound confirmatory testing of brain death because of $CMRO_2$/CBF coupling
Metabolic encephalopathy	Laboratory testing	Imaging studies should document structural central nervous system changes
Akinetic mutism	Intact lower brainstem function Intact sleep-wake cycle	Imaging study shows frontal or mesencephalic brain lesion
Locked-in syndrome	Clinical course and imaging studies	Central locked-in syndrome: corticobulbar and corticospinal tracts are interrupted at the level of the base of the pons; vertical eye movements are intact Peripheral locked-in syndrome: Guillain-Barré syndrome, advanced amyotrophic lateral sclerosis, neuromuscular blocking agents, organophosphate poisoning

Data from Wijdicks [5]. Reproduced with permission from Seubert and Mahla [92]

Abbreviations: *$CMRO_2$* cerebral metabolic requirement for oxygen, *CBF* cerebral blood flow, *ECG* electrocardiogram

Table 7.2 Neurological exam of brainstem function

Brainstem reflex	Afferent path	Efferent path	Caveats
Pupillary light reaction	II	III	Not confounded by systemic drugs, absence may be caused by prolonged administration of neuromuscular blocking agents [6]
Ocular movements (oculocephalic reflex or caloric nystagmus)	VIII	III, VI	Confounded 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 "locked-in" syndrome from brain death
Corneal reflex/pressure on supraorbital nerve	V	VII	
Gag	IX	IX, X	May be difficult to assess in orotracheally intubated patient
Cough	X	X, cervical roots	Best tested by assessing the response to tracheal suctioning

Reproduced with permission from Seubert and Mahla [92]

ear or in the sagittal midline) or differential (where there may be a chain or sequence of electrodes comparing EEG signals point to point). In the former, the amplitude differences provide localizing information, and in the latter, localization is by phase reversals where polarity changes. The interpreting physician may change from one montage to another while reading the study in order to assess artifact or polarity, an ability not found in the old analog/paper EEG machines. The EEG technologist is an essential part of the team, monitoring signals, monitoring electrode integrity, and ensuring that impedances are balanced between electrodes. Failure to maintain good impedances can result in significant contamination by artifact, which may obscure important findings or lead to a false interpretation of the EEG. Differential amplification (see previous discussion) allows for common mode rejection: the elimination of identical signals from the output if they are present in both inputs. Common mode rejection assists with the elimination of 60 Hz artifact from an electrical device at the bedside that is poorly shielded. Mismatch of impedances impairs the ability of common mode rejection to eliminate some artifacts. Proper grounding also aids in reducing electrical interference. Grounding also reduces the risk of direct electrical shock to the patients and caregivers. The ICU electrical environment is particularly challenging, with multiple monitors, IV pumps, ventilators, specialty beds, and cardiac equipment all providing potential artifact sources. Since intracranial electrodes tend to be less subject to environmental artifact and record from a much more localized area, some centers use invasive electrodes and monitors routinely for patients in the ICU [7].

It is generally impractical for the ICU staff to be expected to interpret the raw EEG signal except for a few select cases, such as the monitoring of burst suppression (Fig. 7.1) and when titration of sedation such as in pentobarbital coma is required. Reviewing the entire EEG takes a significant amount of time for the skilled technologist or physician, and, typically, the technologist will review the data and sample them for the physician's review. A two-channel EEG may not record over an area of interest, and artifact identification may be problematic. When more electrodes are used, there is greater sensitivity for detecting abnormalities and spatial localization of abnormalities, but the review and interpretation of such a record require more time and expertise. Changes that occur over hours may be subtle and missed on a raw EEG. Reviews may only be performed once or twice a day, and, thus, feedback may be delayed. In large centers, technologists may be able to watch live streaming EEG remotely, but since they may be watching multiple patients, some events may be missed even in this setting [8].

Drug Effects

It is crucial for the physician interpreting the EEG to know the medications the patient is receiving, as they may have a profound effect on the EEG patterns observed. Medications such as carbapenems or fluoroquinolones may lower the seizure threshold. Levetiracetam may cause EEG changes resembling subclinical seizures. Prominent, so-called drug spindles, for example, are seen with benzodiazepines, propofol, and other sedating medications. Withdrawal from pentobarbital coma can result in a transiently sharply contoured background which can be of concern for seizures in the unwary. Sedation with anesthetics such as pentobarbital and propofol can cause burst-suppression patterns, which carry a grave prognosis if seen in unmedicated patients following cardiopulmonary arrest [9].

Clinical Applications

Monitoring

Nevertheless, if the patient has persistently altered mental status or develops clinical seizures, EEG monitoring is an important component of patient care and should be considered early in the patient's ICU stay [10]. A routine EEG (less than 1 h) may be sufficient if the patient is neurologically stable. In the patient with an unstable or deteriorating neurological examination, a prolonged EEG study, even lasting overnight or days (long-term EEG), may be needed to determine whether or not subclinical seizures or nonconvulsive status epilepticus may be the culprit. Please see Chap. 39

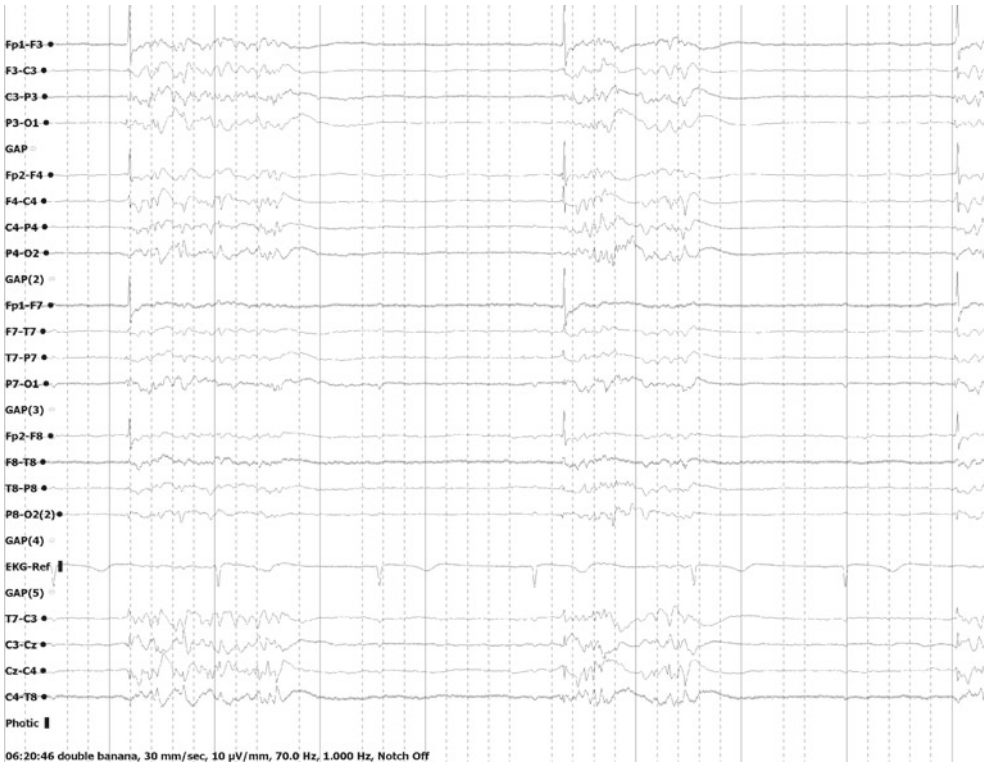

Fig. 7.1 Electroencephalogram recorded from a patient in a pharmacologic coma. All channels show a pattern of burst suppression, i.e., periods of EEG activity followed by periods of EEG silence

on Seizures for further discussion of seizures and status epilepticus, which is considered a neurological emergency requiring immediate intervention. Other clinical events that are reflected in the EEG are sedative drugs, physiological states such as sleep and arousal, as well as pathological states such as sleep deprivation or cerebral ischemia [11]. Of note, both ischemia and increasing concentrations of anesthetics cause a slowing of EEG activity and ultimately burst suppression (Fig. 7.2). Conversely, EEG reactivity to environmental stimuli and persistence or reappearance of sleep architecture portend a better neurological prognosis. When in doubt, discuss the testing with the monitoring neurologist to determine what type of EEG study best fits the patient's needs. Some tertiary centers routinely use long-term EEG monitoring on alert patients for 24 h and stuporous or comatose patients for 48 h on admission to the neuro-ICU, particularly those with hemorrhages in order to detect subclinical seizures or status epilepticus. A normal EEG does not exclude the possibility of a seizure, but a longer study (and larger sample size) may help ensure that a subclinical presentation is not missed.

In order to improve bedside utility of ICU EEG recording, trending software has been developed using quantitative EEG techniques to provide an overview of the EEG which may be interpretable at the bedside with relatively minimal training. Most currently available digital EEG machines can have such software added if it is not available as an initial option. Hirsch and Brenner's *Atlas of EEG in Critical Care* provides an excellent overview and detailed introduction to this topic and methods [12]. The displayed options can be customized for the patient, so that a continuous overview of the EEG data is readily seen. These techniques do not replace the expert review of the raw EEG data because the software is not able to completely address artifact or detect more subtle abnormalities. Quantitative bedside EEG analysis may, however, help improve timeliness of feedback to the patient care team and responsiveness to changes in the patient's condition. Commonly used quantitative techniques include:

- *Fourier transform* changes the EEG displayed from amplitude over time to frequency over time and displays the resulting data as a *power spectrum* where the frequencies making up a particular segment of EEG are displayed. *Compressed spectral arrays* may represent these data as a stack of successive tracings and can also use colored bands to represent the EEG power at different frequencies as a *color density spectral array*. Individual EEG channels are typically displayed, but topographical maps may also be used.
- *Envelope trending* uses the median peak-to-peak amplitude in a particular block of time to create a graph over time for a specific electrode pair. Selection of the area of interest is crucial to detecting changes.
- *The spectral edge frequency* is the frequency below which a predetermined percentage of the study's EEG power lies.

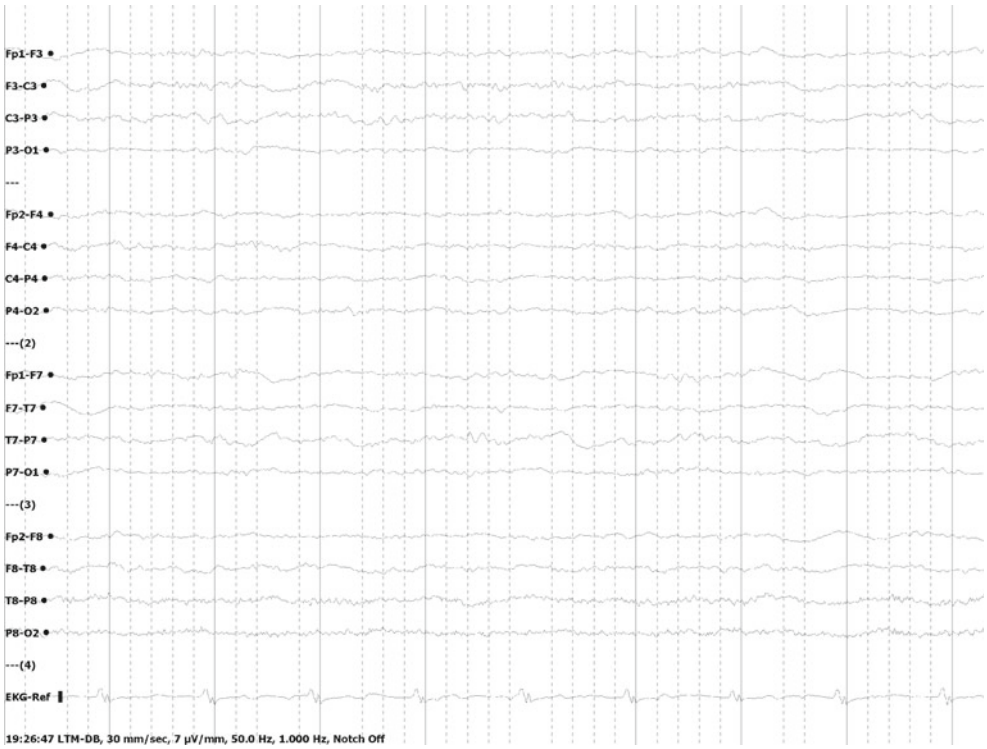

Fig. 7.2 EEG ischemia. This is part of the long-term EEG performed on a 68-year-old patient with severe neurovascular disease. The patient was admitted to the neuro ICU because of a thrombosis of the mid-basilar artery resulting in midbrain and bilateral thalamic infarcts. The patient had a prior history of a left internal carotid artery occlusion and an old left cortical stroke in the territory of the posterior middle cerebral artery The EEG shows a poorly organized background with some degree of generalized slowing, likely due to the new thalamic strokes. EEG slowing is maximal in the area of old infarction on the left

- *Asymmetry indices* may be used in a patient at high risk for vasospasm, for example, and compares the EEG frequency of homologous pairs of electrodes averaged over the entire hemisphere. A shift from one side to another could indicate vasospasm or ischemia from another cause [13, 14].
- The *brain symmetry index* (*BSI*) is a numerical value between 0 (perfect symmetry) and 1 (maximal asymmetry) over all frequencies at a homologous electrode pair which has been shown to correlate with stroke scales and has been used to follow progress after tPA administration [15, 16].
- *Automated spike and seizure detection* is available on digital EEG systems, but since these largely rely on frequency and amplitude algorithms, artifact may have a significant impact and the study must still be reviewed by an expert. Seizures without an EEG correlate are not detected by such software, and many will falsely detect a seizure if the patient is moving or being moved [17].

Brain Death

Because EEG monitors only the cerebral cortex, other types of neurodiagnostic tools must be used to evaluate subcortical structures. In general, the best tool is the neurological examination itself, performed by an experienced clinician. For cerebral death evaluations, evidence has not shown that electrophysiologic tools are necessary for the diagnosis and, thus, they are considered confirmatory or ancillary only [3]. While both somatosensory evoked potentials (SSEPs) and bispectral index (BIS) will typically show specific patterns associated with brain death, there is insufficient evidence to show that these modalities will accurately document cessation of the function of *the entire* brain. The ancillary tests most commonly used in this clinical setting include EEG, cerebral angiography, nuclear perfusion scanning, transcranial Doppler (TCD), CT angiography (CTA), and magnetic resonance imaging and angiography (MRI/MRA). Ancillary tests do not replace the core examination but may help shorten the observation period and are often used if there is uncertainty regarding the neurological examination.

Sedation

Sedation of patients in the ICU is done to relieve patient's anxiety and discomfort and facilitate supportive care. Recent work highlighting the morbidity and cost of excessive sedation has led to the adoption of sedation protocols that incorporate interruption of sedation, efforts towards weaning from mechanical ventilation, and mobilization [18, 19]. Such an approach needs to be adapted to patients in the NICU, because the pharmacologic target of the sedatives – the brain – is frequently affected by the disease process that brought the patient to intensive care in the first place [20]. For example, sedation of NICU patients interferes on the one hand with their neurological exam, while on the other hand, sedation is a therapeutic intervention in the setting of elevated intracranial pressure.

Assessment of the adequacy of sedation is typically done clinically by applying sedation scales such as the Richmond Agitation-Sedation Scale, which assesses the spectrum from

sedation to agitation over a range from unarousable (a value of −5) to alert/calm (a value of 0) to combative (a value of +5) [21]. Processed frontal EEG in the form of the "depth-of-anesthesia" monitors such as the bispectral index (BIS) or EEG-entropy has also been studied as a tool to facilitate appropriate titration of sedation. While these monitors may accurately reflect anesthetic drug effect [22] – a BIS value <30, for example, predominately reflects the degree of EEG suppression [23] – level of sedation includes parameters other than measurable drug effects on the frontal cortex. For example, analgesia, a very important component of sedation, is not well monitored by either BIS or EEG-entropy [24]. The main utility of EEG-based monitors of sedation may therefore lie in guiding administration of sedatives, if patients require deep sedation or administration of neuromuscular blocking agents. In both these settings, artifacts that typically confound EEG recording are reduced, and standard sedation scales are of limited utility.

Evoked Electrical Activity

Theory

Evoked potentials can be used to evaluate the sensory and motor systems. Motor evoked potentials are recorded at the level of the muscles and do not have to be extracted from background EEG activity. Sensory evoked potentials, in contrast, are recorded from scalp surface electrodes placed in standard EEG positions. They represent the response to a series of repeated sensory stimuli and are signal averaged over time to extract the evoked response from the EEG background. Signal averaging is necessary because evoked potentials are typically one to two orders of magnitude smaller than EEG. Thus, the signal-to-noise ratio precludes recording of responses evoked by individual stimuli. Characteristic waves are produced, and then latencies are measured which can be compared to normative data in order to provide localizing information for neurological deficits. Naming conventions vary, but generally they are based on latency of the response and designated positive or negative polarity (Fig. 7.3). Sensory evoked responses are generally much less vulnerable to medication/sedation effects (but are reduced or absent in hypothermia) and are most frequently used for specific diagnostic questions.

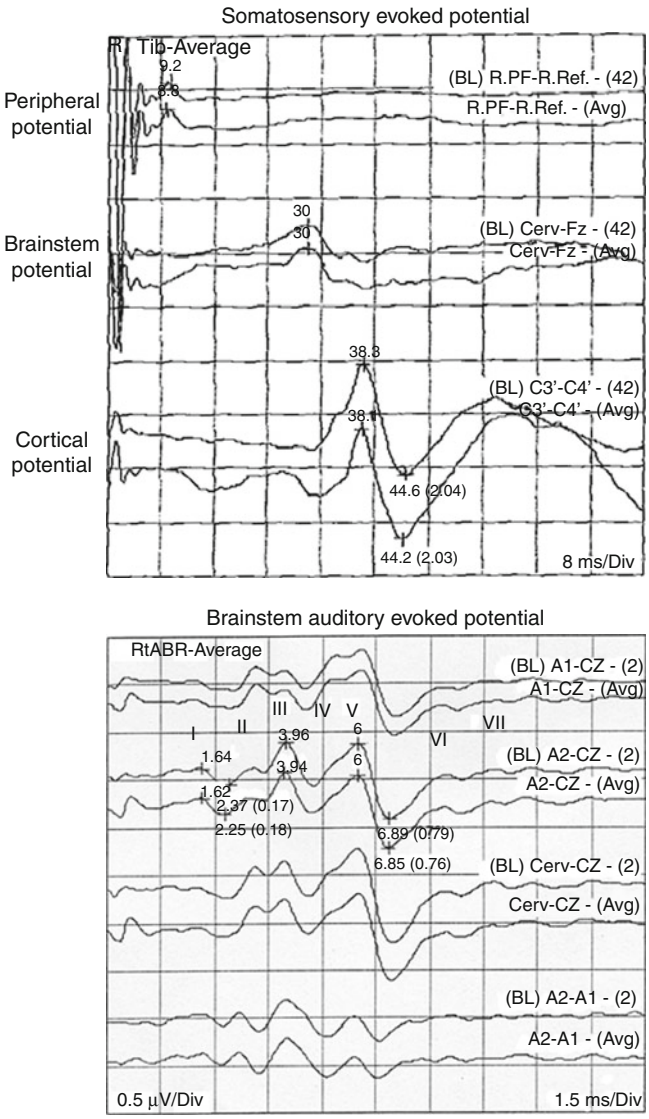

Fig. 7.3 Sensory evoked potentials in response to somatosensory and auditory stimulation. The *top panel* shows three pairs of traces in response to posterior tibial nerve stimulation. Potentials are recorded along the somatosensory pathway peripherally in the popliteal fossa, at the level of the brainstem, and over the contralateral somatosensory cortex. The *bottom panel* shows brainstem auditory evoked potentials along the neural pathway of the brainstem recorded from different electrodes. Wave I represents neural activity in the inner ear. Waves III–V represent rostral conduction of the auditory impulse in the brainstem

VEPs

For example, visual evoked potentials (VEPs) are commonly used to evaluate the visual pathways in patients with demyelinating disorders. The patient focuses on the center of a screen showing an alternating checkerboard pattern. The latency of the responses produced can help to demonstrate the presence of a lesion in the optic pathway, even in the absence of a deficit in visual acuity. VEPs are not commonly used in the ICU setting.

AEPs

Brainstem auditory evoked potentials (BAEPs) are used routinely to test hearing in infants but can also be used intraoperatively for brainstem and cranial nerve VIII surgeries and in comatose patients as a prognostication tool (see section "Clinical Application"). The sensory stimulus for BAEPs is a brief "click" applied via headphones at a volume that exceeds the hearing threshold. If hearing is intact, changes may be seen after brainstem compression or infarction [25].

SSEPs

Somatosensory evoked potentials (SSEPs) are evoked by electrical stimulation of median and posterior tibial nerves and recorded along the conducting pathway as well as over the contralateral somatosensory cortex (Fig. 7.3). SSEPs have been studied in the setting of anoxic-ischemic encephalopathy, and the absence of the bilateral N20 with median nerve stimulation 1–3 days after CPR was predictive of a poor outcome [26]; however, the hypothermia protocol may confound the predictive value of this, as can other metabolic derangements. Conversely, the bilateral persistence of a cortical response to SSEPs from median nerve stimulation has so far consistently predicted eventual awakening (albeit with varying degrees of function) from hypoxic coma [27].

MEPs

Motor evoked potentials (MEPs) may be used in spinal cord or aortic surgeries where the anterior spinal artery may be threatened. Traditional SSEP monitoring serves as a surrogate for monitoring the motor pathways but may not always detect motor deficits, so MEPs have been used in parallel [28]. Transcranial stimulation is the preferred method, which produces D waves by direct pyramidal cell activation and I waves by indirect activation through interneurons as well as polyphasic compound muscle action potentials [29]. MEP recording can be performed outside the operating room setting using a magnetic coil but is impossible in patients requiring complete neuromuscular blockade and may be more difficult in children. There is ongoing interest in magnetic stimulation in the field of neurorehabilitation research, but use in the ICU is investigational.

Clinical Application

As the use of evoked potentials spread from the diagnostic setting to the operating room, there was also enthusiasm for evaluating their role in the neuro-ICU. Because continuous high-quality recordings require the presence of trained technologists and because evoked potentials can only be recorded from selected pathways of the CNS, their adoption as monitors of subcortical function to complement EEG was not realized. Their current clinical application is restricted to specific diagnostic questions and to prognostication in coma.

Somatosensory evoked potentials in combination with brainstem auditory evoked potentials are helpful in the management of comatose patients [30–38]. In general, if both brainstem auditory evoked potentials and cortical somatosensory evoked potentials are intact at presentation and remain intact, ultimate outcome is good. A relatively good outcome may occur in this case even if all clinical signs indicate a very poor prognosis [31]. If the cortical somatosensory evoked potentials at presentation are absent and the brainstem auditory evoked potentials are present, the best outcome expected is a chronic vegetative state. If both cortical somatosensory evoked potentials and all brainstem auditory evoked potential waves beyond wave I are absent, brain death is very likely. It is important to note that drug overdose will not eliminate either the brainstem auditory evoked potential or the early and intermediate latency components of the somatosensory evoked potential. While the electroencephalogram may be entirely absent in the case of drug overdose or therapy such as in barbiturate coma, the brainstem auditory evoked potential and somatosensory evoked potential should be present if the patient has brain function.

Slight differences in sensitivity, specificity, and predictive value of evoked potentials exist that depend on the etiology of the comatose state. In anoxic-ischemic coma, absence of cortical SEPs 24 h after the precipitating event was found to be the best method to predict poor outcome [27]. Similarly, bilateral loss or absence of cortical SEPs is always associated with a poor outcome in comatose patients, whose EEG reveals alpha, theta, or alpha-theta coma [38]. Conversely, presence of cortical SEPs is associated with a favorable outcome. Auditory evoked potentials are less useful in anoxic-ischemic coma. Brainstem responses may initially be absent, due to cochlear ischemia, but are otherwise only affected very late in the course of anoxia/ischemia. Presence of mid-latency or late auditory potentials is predictive of a good outcome but is subject to the same modulating influences as the EEG. In coma due to head trauma, both the cerebral hemispheres and the brainstem may be involved in a pattern of lesions that reflects more the mechanism of injury and less the intrinsic tolerance to hypoxia/ischemia of a given brain structure. Presence of cortical EPs such as the N20 of the median SSEP or mid-latency AEPs is still associated with favorable outcomes even if the latency of the peaks is increased [39]. Conversely, absence of cortical peaks and progressive rostro-caudal deterioration of BAEPs, as occurs with transtentorial herniation, leads to brain death [40]. The decreased predictive power of absent cortical responses in posttraumatic coma is demonstrated by the fact that all cases of good clinical outcomes despite absent cortical SSEPs stem from such trauma patients [41, 42].

Monitors of Cerebral Blood Flow

Cerebral ischemia is one of the most common pathophysiologic mechanisms of secondary injury in NICU patients with a variety of CNS diseases. Therefore, maintenance of adequate cerebral blood flow is a critical therapeutic objective. The most frequent modality used is the invasive measurement of arterial blood pressure either by itself or augmented by simultaneous measurement of intracranial pressure, as discussed in Chaps. 8 and 35. Patient management

Table 7.3 Techniques for measuring cerebral blood flow

Category	Technique	Resolution		Invasiveness	Cost
		Temporal	Spatial		
Indirect	Neurological exam	>3 min	Eloquent areas	No	+
	Electroencephalogram/evoked potentials	1–3 min	Cortex/sensory pathway	No	++
	Cerebral perfusion pressure	<1 min	Global	Subdural, intraventricular, or intraparenchymal probe	+
Bedside	Kety-Schmidt	15 min	Hemispheric	Jugular catheter	+
	^{133}Xenon washout	3–15 min	3–4 cm	Jugular catheter, radiation	+
	$AVDO_2$, jugular venous oxygen saturation ($S_{JV}O_2$)	<1 min	Global	Jugular catheter	+
	Double indicator dilution	3 min	Global	Jugular catheter, descending thoracic aortic catheter	+
	Near-infrared spectroscopy	<1 min	Local, bifrontal	No	+
	Thermal clearance probe	<1 min	Local, 1–2 cm	Exposed cortex	+
	Laser Doppler flow probe	<1 min	Local, 1–2 cm	Exposed cortex	+
Tomographic	Positron emission tomography (PET)	4–6 min/section	<1 cm	Radiation from positron emitter	+++++
	Stable xenon computed tomogram (CT)	4–6 min/section	<1 cm	Radiation from CT scan	+++
	Single-photon emission tomography (SPECT)	4–6 min/section	<1 cm	Radiation from gamma emitter	+++
	Magnetic resonance imaging (MRI)	4–6 min/section	<1 cm	No	+++

Data from Martin and Doberstein [43], Madsen and Secher [44], Cottrell [45], and Keller et al. [46]. Reproduced with permission from Seubert and Mahla [92]

according to the principle of maintaining cerebral perfusion pressure is, however, limited to a global approach that accounts neither for the specific needs of an individual patient nor for regional variation within a given patient's brain. Regional variation in perfusion can be assessed through the imaging of the transit of a bolus of contrast medium during CT or MRI imaging. While the great benefit of imaging is its good spatial resolution, a significant downside of imaging is the increase in the risk of complications associated with the need to move critically ill patients to the scanners. Conversely, the prominent role of imaging is confirmed by the trend to make CT scanners sufficiently portable to allow deployment at the bedside and to move MRI scanners close to neuro-ICUs. Details on neuroradiological techniques are provided in Chap. 40.

Indicator Dilution Methods

Bedside techniques of determining cerebral blood flow rely on a variety of techniques and provide either crude estimates of global cerebral blood flow or highly localized information. They measure cerebral blood flow by determining either the wash-in or washout of a relatively inert indicator substance such as a dye, isotope, or a pulse of heat, in a variation of an idea that dates back to the early studies of Kety and Schmidt. Available techniques are summarized in Table 7.3 [43–46]. Some modalities that are in more widespread use will be discussed next in some detail.

Transcranial Doppler

A unique bedside approach to the study of cerebral perfusion is the determination of cerebral blood flow velocities in major intracranial arteries using transcranial Doppler ultrasound. Older instrumentation was restricted to measurements of flow velocity at a particular depth and required the operator to assemble a mental image of the intracranial circulation as successive arterial segments were interrogated. Newer machines combine pulsed-wave Doppler measurements of flow velocity with ultrasound imaging capacities, which greatly facilitates anatomic orientation, correct attribution of flow velocities to particular vessels, and correction of flow velocities for the angle of insonation [47]. Transcranial Doppler studies are typically done once daily during vulnerable periods in the course of a CNS disease but can also be used continuously, for example, to detect embolic events.

Theory

Transcranial Doppler (TCD) uses ultrasound waves to measure the velocity of blood flow in the basal arteries of the brain and the extracranial internal carotid artery. Ultrasound is transmitted through the relatively thin temporal bone and

at reduced intensity through the orbit or the foramen magnum [48]. In approximately 10 % of patients, particularly elderly females, technically satisfactory recordings cannot be obtained because of a limited temporal bone window [48].

When the ultrasound waves contact moving red blood cells, they are reflected back towards the transducer at a changed frequency. The change in frequency 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 cells in the center of the lumen move faster than blood cells near the vessel wall, producing a spectrum of flow velocities. This flow spectrum resembles the shape of the waveform produced by an intra-arterial pressure transducer (Fig. 7.4). The TCD probe emits ultrasound waves as short pulses and thus represents an application of pulsed-wave Doppler. 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 segment of the arteries at the base of the brain has a distinct signature in terms of depth of insonation, direction of flow, and shape of the waveform (Fig. 7.4).

Although TCD allows interrogation of all arteries that supply the brain, TCD cannot provide a simple assessment of global or hemispheric blood flow. 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 [48, 49]. Beyond the question of vessel patency, the link between TCD measurements and cerebral blood flow is indirect. From a technical point of view, the angle of insonation needs to be kept constant between assessments. Furthermore, two assumptions have to be met for TCD-measured blood flow velocity to correspond to CBF: First, the diameter of the artery must remain constant. Only then is flow proportional to flow velocity. 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 MCA velocity during carotid endarterectomy or cardiopulmonary bypass [50–52]. Likewise, normal variations in blood flow velocities are large [53]. Despite this limitation, TCD has found many applications in the NICU, particularly in combination with other monitoring modalities that assess CBF.

Clinical Applications

Vasospasm

TCD has been very helpful in identifying vasospasm following aneurysmal subarachnoid hemorrhage. 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 (Fig. 7.5). Importantly, such increases in flow velocity precede neurological deficits and thus provide a window of opportunity for intervention. Using absolute flow velocity alone, detection and documentation of the severity and duration of vasospasm is possible with a specificity that approaches 100 % but with limited sensitivity [53–55]. Sensitivity may be improved by normalizing the flow velocity to a patient-specific baseline measured prior to the time of vasospasm [53]. A way of accounting for changes in global cerebral blood flow, e.g., during induced hypertension, the intracranial flow velocity of the middle cerebral artery can be divided by the flow velocity of the ipsilateral extracranial internal carotid artery (Lindegaard ratio) [56]. A Lindegaard ratio greater than 3 is consistent with the presence of vasospasm. One important setting, wherein absolute TCD flow velocity may underestimate the severity of vasospasm, is that of increased ICP [57]. Increases in ICP, however, lead to characteristic changes in the TCD waveform and increase the pulsatility index, which relates the difference between peak systolic and end-diastolic velocity either to the mean or to the systolic velocity. Interpreting TCD flow velocities also needs to take localized therapeutic interventions into account. Specifically, TCD flow velocities may remain elevated despite successful dilation as a result of impaired autoregulation in the poststenotic vascular bed [58].

TBI

TCD in combination with determinations of CBF has identified phases of hyperemia and cerebral arterial vasospasm in traumatic brain injury as important mechanisms that underlie increased ICP and secondary injury, respectively [59–62]. Similar to vasospasm after aneurysmal subarachnoid hemorrhage, the severity of posttraumatic vasospasm correlates with the radiological severity of tissue damage, although the onset of posttraumatic vasospasm may be earlier than that after subarachnoid hemorrhage [63]. TCD has also been used in traumatic brain injury to assess the degree to which cerebral blood flow regulation is disrupted. Whereas normal CO_2-reactivity, pressure autoregulation, and flow/metabolism coupling are associated with a good outcome, disrupted CBF regulation carries a bad prognosis [64, 65].

Brain Death

The TCD-generated waveform exhibits sequential characteristic changes as intracranial pressure increases (Fig. 7.4) [66]. 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 (Fig. 7.6). This change in waveforms can be used to calculate a pulsatility index by relating the difference between peak systolic and end-diastolic velocity either to the mean or to the systolic velocity. Such waveform analyses

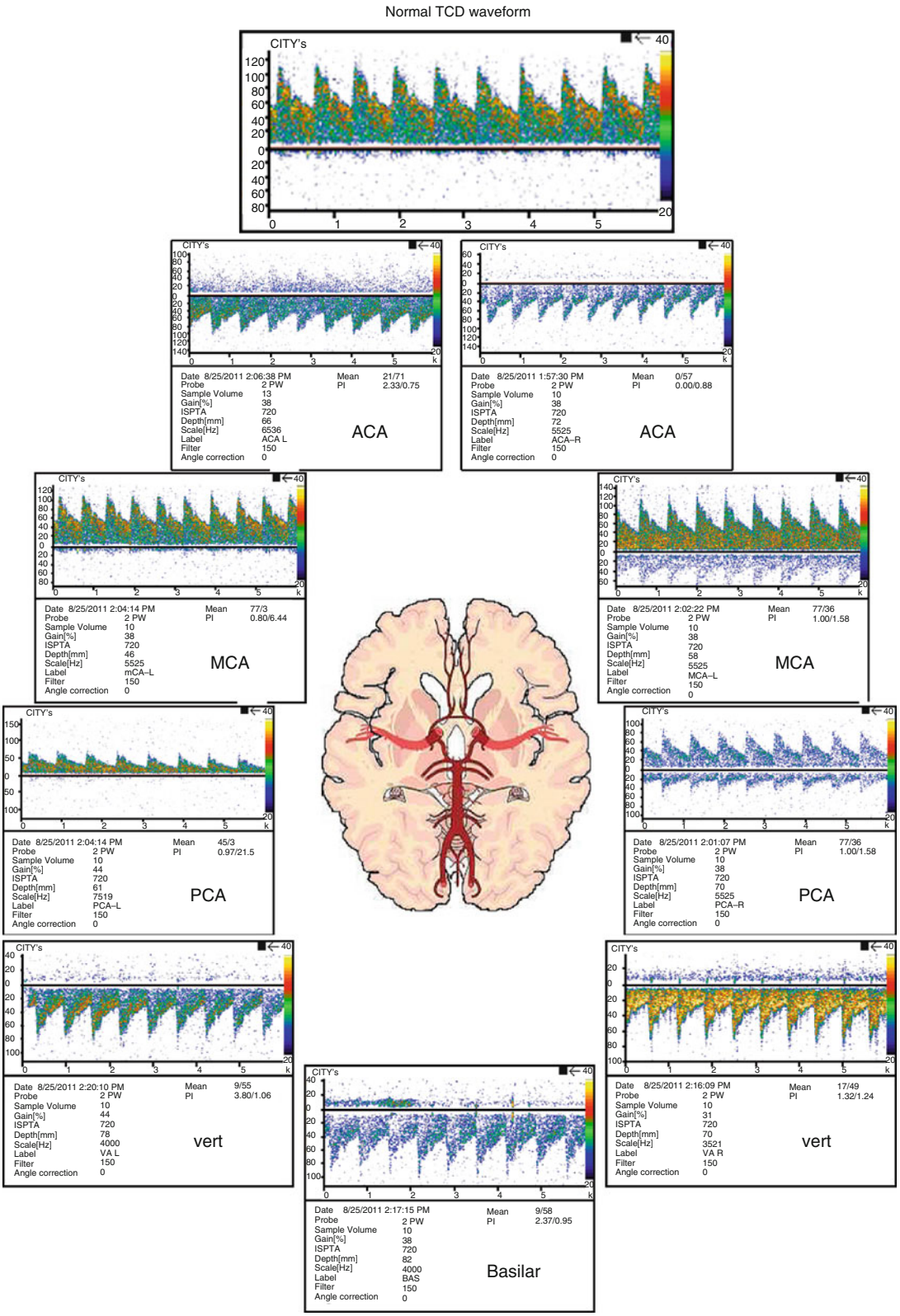

Fig. 7.4 Normal transcranial Doppler (TCD) exam. The *top panel* shows a normal flow pattern in a middle cerebral artery (MCA) with a spectrum of flow velocities. The *bottom panel* shows a complete exam of anterior (ACA), middle (MCA), and posterior (PCA) cerebral arteries insonated through a temporal bone window. From the temporal window flow in posterior and middle cerebral arteries is towards the transducer (depicted as positive values), and flow in the anterior cerebral arteries is away from the transducer (depicted as negative values). Vertebral arteries (vert) and basilar artery are insonated from the back of the flexed neck through the foramen magnum. All flow is away from the transducer, depicted as negative values (Courtesy of Michael Waters, MD)

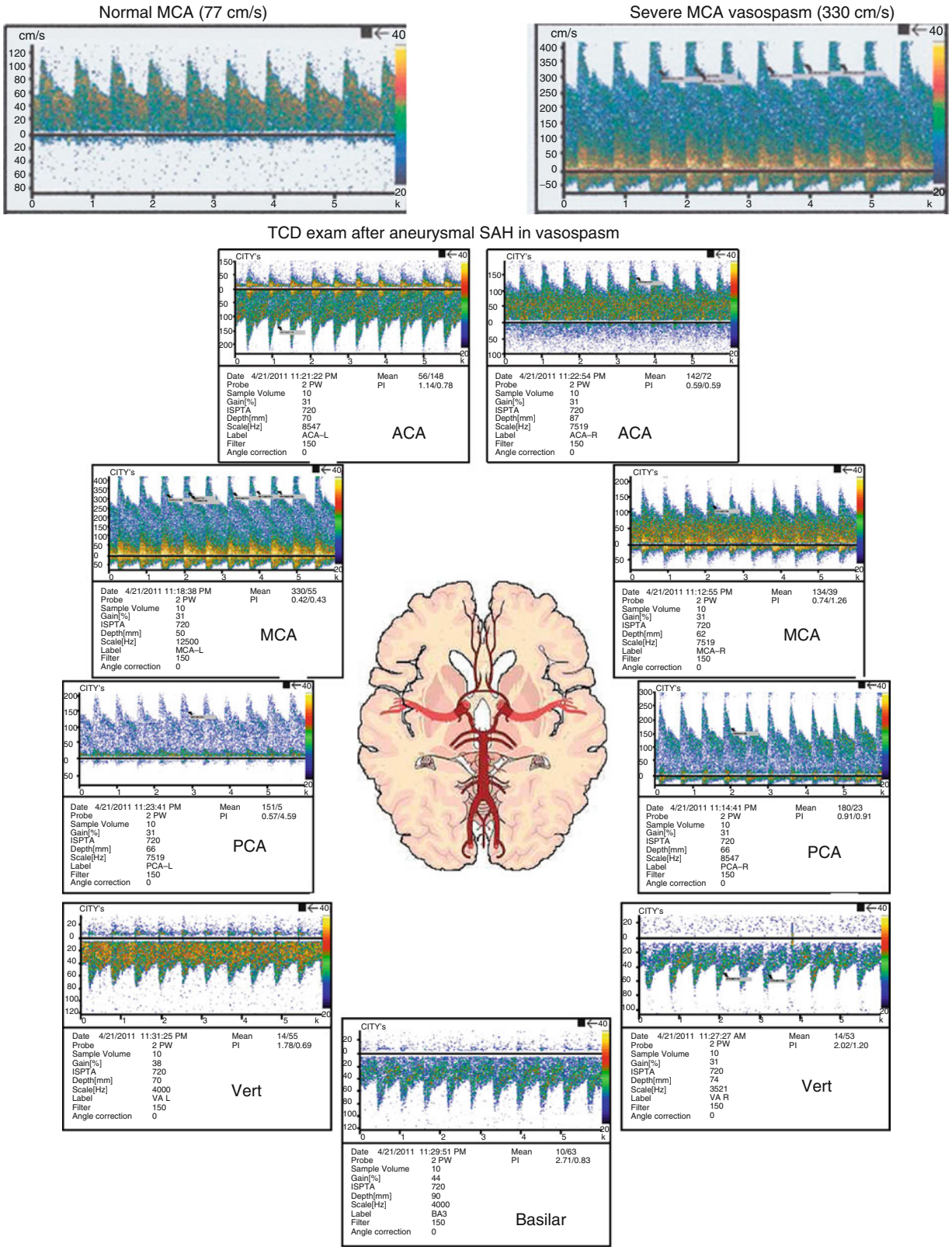

Fig. 7.5 Transcranial Doppler (TCD) exam in severe vasospasm. The *top panel* compares flow velocities in normal and severely narrowed middle cerebral arteries. Note the different velocity scales. The *bottom panel* shows the complete exam with vasospasm in the left posterior, middle, and anterior cerebral arteries as well as the right posterior and middle cerebral arteries. The exam also illustrates the operator dependence of the exam, because the right anterior cerebral artery is not captured (Courtesy of Michael Waters, MD)

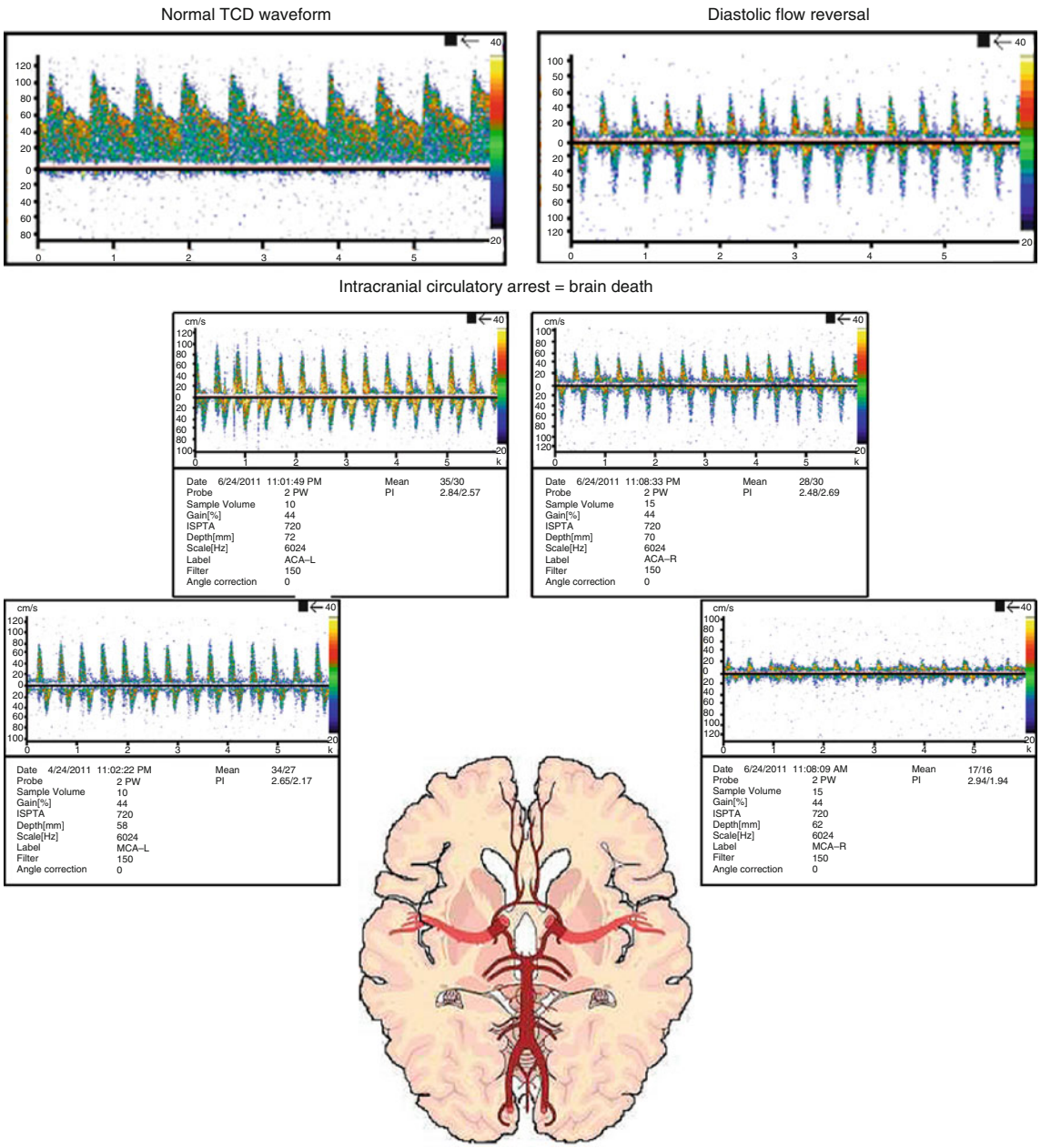

Fig. 7.6 Transcranial Doppler (TCD) exam in brain death. As intracranial pressure rises, diastolic flow becomes compromised first, resulting in a more peaked appearance of the TCD waveform. Once intracranial exceeds diastolic pressure, flow reverses during diastole (Courtesy of Michael Waters, MD)

correlate well with the intracranial pressure [57, 67, 68], especially if they take the arterial blood pressure curve into account [69]. However, serial TCD cannot replace ICP monitoring because, in a given patient, factors such as autoregulation, vasospasm, or proximal arterial stenosis may alter the TCD signal independent of the ICP [48].

Clinical brain death demonstrates a characteristic blood flow velocity pattern (Fig. 7.6). 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 near 100 % [70]. While 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.

Thermal Diffusion Flowmetry

Thermal diffusion flowmetry measures local cerebral blood flow through a probe inserted into the white matter. The

probe consists of two thermistor elements. One thermistor measures brain temperature. The other is held at a slightly higher temperature than the first thermistor. The energy required to maintain the temperature differential between the two thermistors is proportionate to the heat-conducting properties of white matter, which stays constant as long as the probe is properly placed and does not move, and to the convective cooling of cerebral blood flow, which is reported in the conventional units of ml/100 g/min. Local CBF measured by thermal diffusion agrees well with CBF measured by stable xenon CT [71]. An example of a clinical application of thermal diffusion flowmetry is the determination of presence or absence of cerebral autoregulation in traumatic brain injury [72], which may impact the management strategy and ultimately outcome in these patients [73]. One limitation of thermal diffusion flowmetry is that the measurement will cease if the patient becomes febrile beyond a temperature of 39.5 °C. This reflects a built-in safety feature that prevents tissue heating beyond 41 °C.

Laser Doppler Flowmetry

The second technique that is transitioning from bench to bedside is the measurement of local CBF by using a fiberoptic laser Doppler flow probe. Because it measures local blood flow velocity based on the Doppler principle discussed previously, it only presents relative cerebral blood flow and thus gives just trending information.

Monitors of Oxygen Supply/Demand Balance

The average oxyhemoglobin saturation can be used, in a manner analogous to mixed venous oxygen saturation, to determine whether oxygen supply and demand are in balance. As long as changes in $CMRO_2$ are matched by concomitant changes in cerebral blood flow, oxygen extraction will stay the same as will oxyhemoglobin saturation. If demand outstrips supply, oxygen extraction will increase, thereby decreasing oxyhemoglobin saturation. Jugular bulb oximetry and cerebral oximetry are two approaches that aim to measure oxygen saturation. Both technologies use reflectance oximetry to determine saturation values. Reflectance oximetry relies on the fact that near-infrared light penetrates tissue for several centimeters and that hemoglobin, in its oxygenated and deoxygenated form, is the major tissue compound absorbing near-infrared light [44]. Near-infrared light of at least two different wavelengths is emitted, and the reflected light of each wavelength is quantified to determine an oxygen saturation value. While the technologies of jugular bulb oximetry and cerebral oximetry are similar in concept, different assumptions underlie the validity of jugular bulb oximetry and cerebral oximetry as monitors of global and regional oxygen supply/demand balance, respectively.

Direct measurements of oxygen partial pressure in brain tissue (PbO_2) can be derived from a modified Clark electrode implanted into the brain. The technology is relatively robust and provides information about actual tissue oxygenation, albeit only from a highly localized area of metabolically heterogeneous brain. If the probe is situated in normal brain, PbO_2 correlates with jugular bulb saturation [74]. Severe or prolonged tissue hypoxia is associated with worse functional outcomes [75]. As familiarity with this technique improves, it may supplant jugular bulb oximetry, which has greater rates of failure and complications.

Jugular Venous Oximetry ($S_{JV}O_2$)

The measurement of jugular bulb oxygen saturation requires placement of a catheter into the jugular vein. That catheter is advanced from a puncture site in the neck retrograde under fluoroscopic guidance until its tip lies in the jugular bulb. Oxygen saturation can be determined continuously by using a fiberoptic catheter or intermittently by blood gas analysis. Due to its invasive nature and potential interference with cerebral venous drainage, cannulation is usually only done on one side.

There are several theoretical problems with this technique. The measurement technique evaluates the *global* balance between cerebral O_2 supply and demand. The amount of brain that must be affected for $S_{JV}O_2$ to change is thought to be on the order of 10–15 %. Inadequate CBF to a small area of cortex may be masked by blood, which has a higher SvO_2 from areas of adequately perfused brain in either hemisphere. Thus, a high saturation can be falsely reassuring. Similarly, admixture of extracerebral venous blood e.g., through catheter malposition, may falsely increase $S_{JV}O_2$. Although virtually all blood from the brain drains via the jugular veins, mixing of venous blood is incomplete and results in differences between right- and left-sided measurements [76–78]. Specifically, the dominant jugular vein, i.e., the right jugular vein in the majority of patients, drains predominantly cortical venous blood, whereas the contralateral jugular vein drains mostly blood from subcortical structures [78, 79]. To account for this asymmetry, many clinicians cannulate the jugular bulb on the side where jugular vein compression causes the largest increase in intracranial pressure [78, 79]. Placement of a catheter in the jugular vein may diminish jugular outflow or cause thrombosis after prolonged use and thus raise ICP in patients with decreased intracranial elastance. However, in clinical practice, such complications are rare [80, 81] and should be weighed against the benefit of the information obtained. Despite these limitations, $S_{JV}O_2$ monitoring is an integral part of multimodality monitoring in many NICUs.

Although $S_{JV}O_2$ monitoring has been used after cardiac surgery and subarachnoid hemorrhage, most reports involve management of severely head-injured patients. In head-injured patients, $S_{JV}O_2$ values of <50 or >75 % are associated with worse outcomes. Episodes of jugular venous oxygen desaturation, thought to reflect episodes of relative ischemia, were associated with worse neurological deficits even after adjusting for confounding factors such as age, Glasgow Coma Scale, or type of injury [82, 83]. Similarly, $S_{JV}O_2$ values of >75 %, which may reflect the decreased demand of traumatized tissue rather than true hyperemia, were associated with worse patient outcomes [84, 85]. $S_{JV}O_2$ monitoring appears to be helpful in detecting cerebral ischemia associated with excessive hyperventilation. Although hyperventilation may lower ICP, the accompanying decrease in CBF can cause O_2 delivery to fall below demand. Falling $S_{JV}O_2$ suggests that another technique to control ICP, e.g., drug-induced reduction of $CMRO_2$ or CSF drainage, might be safer. The prompt feedback and straightforward conceptual framework for interpretation provided by $S_{JV}O_2$ monitoring has played an important role in limiting hyperventilation and shifting the focus away from controlling ICP towards maintaining CPP.

Cerebral Oximetry

The cerebral oximeter was developed as a noninvasive assessment of the adequacy of cerebral oxygenation [85]. In addition to the brain tissue underlying the oximetry probe, the light also passes through the scalp and skull. The exact light path is not known. Therefore, the relative contribution of extracranial and intracranial blood to the measured saturation may vary according to sensor design and placement. The sensor is usually placed on the skin overlying the frontopolar portion of the cerebral cortex (forehead). Arterial, capillary, and venous hemoglobin within the light path contributes to the measured saturation value. Because two-thirds to four-fifths of the cerebral blood volume is on the venous side, cerebral oximetry determines predominantly local S_VO_2 [44].

Cerebral oximetry is most widely used in the care of cardiac surgery patients, particularly during complex surgical procedures such as those requiring circulatory arrest. The perceived utility in this setting may derive from the fact that the majority of changes seen in cardiac surgery affect all of the cerebral inflow and hence overcome some of the conceptual limitations of the device. More germane to the situation in the NICU may be the experience with cerebral oximetry during carotid endarterectomy. Cerebral oximetry has been compared to transcranial Doppler and $S_{JV}O_2$ as a means to assess global cerebral perfusion [86, 87]. While neither of these monitors is currently considered a gold standard for measuring the adequacy of CBF during carotid endarterectomy, the relationships demonstrated were interesting. Decreases in cerebral oxygen saturation were accompanied by significant decreases in middle cerebral artery flow velocity (MCAv). The converse was not always true, however. Significant falls in MCAv could occur without any change in oxygen saturation at all, suggesting the presence of collateral circulation. There was also a strong correlation between JvO_2 and cerebral oxygen saturation. The degree of change in the two monitors was not necessarily similar, however. Placement of the probe over the parietal cortex produced a more similar degree of change in the two monitors than the standard frontal placement. Compared to accepted tests of adequate cerebral blood flow during carotid artery occlusion such as the neurological exam of the awake patient, the EEG, or SSEPs, cerebral oximetry showed good sensitivity but relatively poor specificity. The poor specificity makes it difficult to define a relative or absolute threshold below which cerebral oxygen saturation indicates ischemia [88].

Perhaps the greatest limitation of this monitor is the lack of multichannel capability. There is no reason to expect that oxygen saturation in one portion of the brain would reflect oxygen saturation in other areas of the brain. Indeed, EEG changes during ischemia are sometimes limited to a few channels. Likewise, many patients in the NICU are at risk for secondary focal or multifocal rather than generalized damage to CNS structures. Studies of cerebral oximetry in patients with traumatic brain injury failed to document consistent utility of the monitor. Thus, although $S_{JV}O_2$ and cerebral oximetry provide complementary information on the cerebral oxygen supply/demand balance, further study and technical development will be required before cerebral oximetry can claim a place in the multimodal assessment of NICU patients.

Tissue Probes

In contrast to most other techniques for evaluating brain oxygenation, tissue monitoring and microdialysis offer both the advantage and disadvantage of monitoring a very discrete region of tissue. Most centers place such probes into uninjured white matter on the side of the brain with more severe pathology [89]. Continuous brain tissue oxygen monitoring measures the balance of oxygen delivery and cerebral metabolism by reporting the partial pressure of oxygen at the probe site [89]. The value thus differs from both arterial and mixed venous oxygen partial pressures. Normal values are between 20 and 50 mmHg. Values less than 20 mmHg identify cerebral hypoxia and ischemia in patients with brain injury, aneurysmal subarachnoid hemorrhage, malignant stroke, or other patients at risk for secondary brain injury. Intraparenchymal direct oxygen partial pressure measurements ($PbrO_2$) have been shown to be of value in the management of cerebral perfusion and management of patients with traumatic brain injury [90].

Many studies over the past decade support that subthreshold levels of $PbrO_2$ are associated with increased morbidity and mortality in patients with severe brain injury. In 2007, Guidelines for the Management of Severe Head Injury [91] (intervention based on a brain tissue oxygenation threshold of less than 15 mmHg) were adopted as a level III recommendation. While the exact significance of local partial pressure of brain tissue oxygen continues to be debated, evidence for inclusion in multimodal monitoring is increasing.

Brain microdialysis can also be performed through an implanted tissue probe. Energy metabolites such as the lactate to pyruvate ratio, neurotransmitters involved in excitotoxicity, or molecules indicative of cell damage can be measured over time. This monitor provides the unique opportunity to interrogate the pathophysiologic process that underlies changed neurological function. It is currently used mostly in the context of research protocols.

References

1. Kornbluth J, Bhardwaj A. Evaluation of coma: a critical appraisal of popular scoring systems. Neurocrit Care. 2011;14:134–43.
2. Seel RT, Sherer M, Whyte J, Katz DI, Giacino JT, Rosenbaum AM, Hammond FM, Kalmar K, Bender-Pape TL, Zafonte R, Biester RC, Kaelin D, Kean J, Zasler N. Assessment scales for disorders of consciousness: evidence-based recommendations for clinical practice and research. Arch Phys Med Rehabil. 2010;91:1795–813.
3. Wijdicks EF, Varelas PN, Gronseth GS, Greer DM. Evidence–based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2010;74:1911–8.
4. Santamaria J, Orteu N, Iranzo A, Tolosa E. Eye opening in brain death. J Neurol. 1999;246:720–2.
5. Wijdicks EF. Brain death. Philadelphia: Lippincott Williams & Wilkins; 2001.
6. Schmidt JE, Tamburro RF, Hoffman GM. Dilated nonreactive pupils secondary to neuromuscular blockade. Anesthesiology. 2000;92:1476–80.
7. Fisch BJ. Digital and analog EEG instruments: parts and functions, chapter 3. In: Fisch BJ, editor. Fisch and Spehlmann's EEG primer. Amsterdam: Elsevier; 1999.
8. Pauri F, Pierelli F, et al. Long-term EEG-video-audio monitoring: computer detection of focal EEG patterns. Electroencephalogr Clin Neurophysiol. 1992;82:1–9.
9. Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe S. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;67:203–10.
10. Hirsch LJ. Continuous EEG, monitoring in the ICU. J Clin Neurophysiol. 2004;21:332–40.
11. Friedman D, Claasen J, Hirsch LJ. Continuous electroencephalogram monitoring in the intensive care unit. Anesth Analg. 2009;109:506–23.
12. Hirsch L, Brenner RP. Atlas of EEG in critical care. Hoboken: Wiley-Blackwell; 2010.
13. Claasen J, Mayer SA, Hirsch LJ. Continuous EEG monitoring in patients with subarachnoid hemorrhage. J Clin Neurophysiol. 2005;22:92–8.
14. Vespa P, Nuwer MR, et al. Early detection of vasospasm after acute subarachnoid hemorrhage using continuous EEG ICU monitoring. Electroencephalogr Clin Neurophysiol. 1997;103:607–15.
15. van Putten MJ. The revised brain symmetry index. Clin Neurophysiol. 2007;118:2362–7.
16. de Vos CC, van Maarseveen SM, Brouwers PJ, van Putten MJ. Continuous EEG monitoring during thrombolysis in acute hemispheric stroke patients using the brain symmetry index. J Clin Neurophysiol. 2008;25:77–82.
17. Scheuer ML, Wilson SB. Data analysis for continuous EEG monitoring in the ICU: seeing the forest and the trees. J Clin Neurophysiol. 2004;21:353–78.
18. Morandi A, Brummel NE, Ely EW. Sedation, delirium and mechanical ventilation: the "ABCDE" approach. Curr Opin Crit Care. 2011;17:43–9.
19. Jackson DL, Proudfoot CW, Cann KF, Walsh T. A systematic review of the impact of sedation practice in the ICU on resource use, costs and patient safety. Crit Care. 2010;14:R59. 1–12.
20. Beretta L, DeVitis A, Grandi E. Sedation in neurocritical patients: is it useful? Minerva Anestesiol. 2011;77:828–34.
21. Ely EW, Truman B, Shintani A, Thomason JWW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: the reliability and validity of the Richmond Agitation Sedation Scale (RASS). JAMA. 2003;289:2983–91.
22. Cottenceau V, Petit L, Masson F, Guehl D, Asselineau J, Cochard JF, Pinaquy C, Leger A, Sztark F. The use of bispectral index to monitor barbiturate coma in severely brain injured patients with refractory intracranial hypertension. Anesth Analg. 2008;107:1676–82.
23. Bruhn J, Bullion TW, Shafer SL. Bispectral Index (BIS) and burst suppression: revealing a part of the BIS algorithm. J Clin Monit Comput. 2000;16:593–6.
24. Sackey PV. Frontal EEG, for intensive care unit sedation: treating numbers or patients? Crit Care. 2008;12:186.
25. Legatt AD, Arezzo JC, Vaughn Jr HG. The anatomic and physiologic basis of brainstem auditory evoked potentials. Neurol Clin. 1988;6:681–704.
26. Young GB. Clinical practice. Neurologic prognosis after cardiac arrest. N Engl J Med. 2009;361:605–11.
27. Zandbergen EG, de Haan RJ, Stoutenbeek CP, Koelman JH, Hijdra A. Systematic review of early prediction of poor outcome in anoxic-ischaemic coma. Lancet. 1998;352:1808–12.
28. Legatt A, Ellen R. Grass lecture: motor evoked potential monitoring. Am J Electroneurodiagnostic Technol. 2004;44:223–43.
29. Hallett M. Transcranial magnetic stimulation: a primer. Neuron. 2007;55:187–99.
30. Goodwin SR, Toney KA, Mahla ME. Sensory evoked potentials accurately predict recovery from prolonged coma caused by strangulation. Crit Care Med. 1993;21:631–3.
31. Goodwin SR, Friedman WA, Bellefleur M. Is it time to use evoked potentials to predict outcome in comatose children and adults? Crit Care Med. 1991;19:518–24.
32. Greenberg RP, Newlon PG, Hyatt MS, Narayan RK, Becker DP. Prognostic implications of early multimodality evoked potentials in severely head-injured patients. A prospective study. J Neurosurg. 1981;55:227–36.
33. Greenberg RP, Becker DP, Miller JD, Mayer DJ. Evaluation of brain function in severe human head trauma with multimodality evoked potentials. Part 2: localization of brain dysfunction and correlation with posttraumatic neurological conditions. J Neurosurg. 1977;47:163–77.
34. Greenberg RP, Mayer DJ, Becker DP, Miller JD. Evaluation of brain function in severe human head trauma with multimodality evoked potentials. Part 1: evoked brain-injury potentials, methods, and analysis. J Neurosurg. 1977;47:150–62.
35. Greenberg RP, Newlon PG, Becker DP. The somatosensory evoked potential in patients with severe head injury: outcome prediction and monitoring of brain function. Ann N Y Acad Sci. 1982;388:683–8.

36. Machado C. Multimodality evoked potentials and electroretinography in a test battery for an early diagnosis of brain death. J Neurosurg Sci. 1993;37:125–31.
37. Machado C, Valdes P, Garcia-Tigera J, Virues T, Biscay R, Miranda J, Coutin P, Roman J, Garcia O. Brain-stem auditory evoked potentials and brain death. Electroencephalogr Clin Neurophysiol. 1991;80:392–8.
38. Guerit JM, Fischer C, Facco E, Tinuper P, Murri L, Ronne-Engstrom E, Nuwer M. Standards of clinical practice of EEG and EPs in comatose and other unresponsive states. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl. 1999;52:117–31.
39. Guerit JM, de Tourtchaninoff M, Soveges L, Mahieu P. The prognostic value of three-modality evoked potentials (TMEPs) in anoxic and traumatic comas. Neurophysiol Clin. 1993;23:209–26.
40. Sleigh JW, Havill JH, Frith R, Kersel D, Marsh N, Ulyatt D. Somatosensory evoked potentials in severe traumatic brain injury: a blinded study. J Neurosurg. 1999;91:577–80.
41. Schwarz S, Schwab S, Aschoff A, Hacke W. Favorable recovery from bilateral loss of somatosensory evoked potentials. Crit Care Med. 1999;27:182–7.
42. Lindsay K, Pasaoglu A, Hirst D, Allardyce G, Kennedy I, Teasdale G. Somatosensory and auditory brain stem conduction after head injury: a comparison with clinical features in prediction of outcome. Neurosurgery. 1990;26:278–85.
43. Martin NA, Doberstein C. Cerebral blood flow measurement in neurosurgical intensive care. Neurosurg Clin N Am. 1994;5: 607–18.
44. Madsen PL, Secher NH. Near-infrared oximetry of the brain. Prog Neurobiol. 1999;58:541–60.
45. Cottrell JE. Cerebral blood flow. In: Cottrell JE, editor. Anesthesia and neurosurgery. New York: Mosby Year Book, Inc; 2001. p. 800–25.
46. Keller E, Wietasch G, Ringleb P, Scholz M, Schwarz S, Stingele R, Schwab S, Hanley D, Hacke W. Bedside monitoring of cerebral blood flow in patients with acute hemispheric stroke. Crit Care Med. 2000;28:511–6.
47. Nedelmann M, Stolz E, Gerriets T, Baumgartner RW, Malferrari G, Seidel G, Kaps M. Consensus recommendations for transcranial color-coded duplex sonography for the assessment of intracranial arteries in clinical trials on acute stroke. Stroke. 2009;40:3238–44.
48. Manno EM. Transcranial Doppler ultrasonography in the neurocritical care unit. Crit Care Clin. 1997;13:79–104.
49. Ringelstein EB, Biniek R, Weiller C, Ammeling B, Nolte PN, Thron A. Type and extent of hemispheric brain infarctions and clinical outcome in early and delayed middle cerebral artery recanalization. Neurology. 1992;42:289–98.
50. Halsey JH, McDowell HA, Gelmon S, Morawetz RB. Blood velocity in the middle cerebral artery and regional cerebral blood flow during carotid endarterectomy. Stroke. 1989;20:53–8.
51. Nuttall GA, Cook DJ, Fulgham JR, Oliver Jr WC, Proper JA. The relationship between cerebral blood flow and transcranial Doppler blood flow velocity during hypothermic cardiopulmonary bypass in adults. Anesth Analg. 1996;82:1146–51.
52. Weyland A, Stephan H, Kazmaier S, Weyland W, Schorn B, Grune F, Sonntag H. Flow velocity measurements as an index of cerebral blood flow. Validity of transcranial Doppler sonographic monitoring during cardiac surgery. Anesthesiology. 1994;81:1401–10.
53. Sloan MA, Haley Jr EC, Kassell NF, Henry ML, Stewart SR, Beskin RR, Sevilla EA, Torner JC. Sensitivity and specificity of transcranial Doppler ultrasonography in the diagnosis of vasospasm following subarachnoid hemorrhage. Neurology. 1989;39:1514–8.
54. Wozniak MA, Sloan MA, Rothman MI, Burch CM, Rigamonti D, Permutt T, Numaguchi Y. Detection of vasospasm by transcranial Doppler sonography. The challenges of the anterior and posterior cerebral arteries. J Neuroimaging. 1996;6:87–93.
55. Sloan MA, Burch CM, Wozniak MA, Rothman MI, Rigamonti D, Permutt T, Numaguchi Y. Transcranial Doppler detection of vertebrobasilar vasospasm following subarachnoid hemorrhage. Stroke. 1994;25:2187–97.
56. Lindegaard KF, Nornes H, Bakke SJ, Sorteberg W, Nakstad P. Cerebral vasospasm after subarachnoid haemorrhage investigated by means of transcranial Doppler ultrasound. Acta Neurochir Suppl (Wien). 1988;42:81–4.
57. Klingelhofer J, Dander D, Holzgraefe M, Bischoff C, Conrad B. Cerebral vasospasm evaluated by transcranial Doppler ultrasonography at different intracranial pressures. J Neurosurg. 1991;75:752–8.
58. Giller CA, Purdy P, Giller A, Batjer HH, Kopitnik T. Elevated transcranial Doppler ultrasound velocities following therapeutic arterial dilation. Stroke. 1995;26:123–7.
59. Kelly DF, Kordestani RK, Martin NA, Nguyen T, Hovda DA, Bergsneider M, McArthur DL, Becker DP. Hyperemia following traumatic brain injury: relationship to intracranial hypertension and outcome. J Neurosurg. 1996;85:762–71.
60. Kordestani RK, Counelis GJ, McBride DQ, Martin NA. Cerebral arterial spasm after penetrating craniocerebral gunshot wounds: transcranial Doppler and cerebral blood flow findings. Neurosurgery. 1997;41:351–9.
61. Lee JH, Martin NA, Alsina G, McArthur DL, Zaucha K, Hovda DA, Becker DP. Hemodynamically significant cerebral vasospasm and outcome after head injury: a prospective study. J Neurosurg. 1997;87:221–33.
62. Martin NA, Patwardhan RV, Alexander MJ, Africk CZ, Lee JH, Shalmon E, Hovda DA, Becker DP. Characterization of cerebral hemodynamic phases following severe head trauma: hypoperfusion, hyperemia, and vasospasm. J Neurosurg. 1997;87:9–19.
63. Sander D, Klingelhofer J. Cerebral vasospasm following posttraumatic subarachnoid hemorrhage evaluated by transcranial Doppler ultrasonography. J Neurol Sci. 1993;119:1–7.
64. Lee JH, Kelly DF, Oertel M, McArthur DL, Glenn TC, Vespa P, Boscardin WJ, Martin NA. Carbon dioxide reactivity, pressure autoregulation, and metabolic suppression reactivity after head injury: a transcranial Doppler study. J Neurosurg. 2001;95:222–32.
65. Klingelhofer J, Sander D. Doppler CO2 test as an indicator of cerebral vasoreactivity and prognosis in severe intracranial hemorrhages. Stroke. 1992;23:962–6.
66. Hassler W, Steinmetz H, Gawlowski J. Transcranial Doppler ultrasonography in raised intracranial pressure and in intracranial circulatory arrest. J Neurosurg. 1988;68:745–51.
67. Goraj B, Rifkinson-Mann S, Leslie DR, Lansen TA, Kasoff SS, Tenner MS. Correlation of intracranial pressure and transcranial Doppler resistive index after head trauma. AJNR Am J Neuroradiol. 1994;15:1333–9.
68. Klingelhofer J, Conrad B, Benecke R, Sander D, Markakis E. Evaluation of intracranial pressure from transcranial Doppler studies in cerebral disease. J Neurol. 1988;235:159–62.
69. Schmidt B, Klingelhofer J, Schwarze JJ, Sander D, Wittich I. Noninvasive prediction of intracranial pressure curves using transcranial Doppler ultrasonography and blood pressure curves. Stroke. 1997;28:2465–72.
70. Monteiro LM, Bollen CW, van Huffelen AC, Ackerstaff RG, Jansen NJ, van Vught AJ. Transcranial Doppler ultrasonography to confirm brain death: a meta-analysis. Intensive Care Med. 2006; 32:1937–44.
71. Vajkoczy P, Roth H, Horn P, Luecke T, Thomé C, Huebner U, Martin GT, Zappletal C, Klar E, Schilling L, Schmiedek P. Continuous monitoring of regional cerebral blood flow—experimental and clinical validation of a novel thermal diffusion microprobe. J Neurosurg. 2000;93:265–74.
72. Rosenthal G, Sanchez-Mejia RO, Phan N, Hemphill 3rd JC, Martin C, Manley GT. Incorporating a parenchymal thermal diffusion cerebral blood flow probe in bedside assessment of cerebral

autoregulation and vasoreactivity in patients with severe traumatic brain injury. J Neurosurg. 2011;114:62–70.
73. Howells T, Elf K, Jones PA, Ronne-Engström E, Piper I, Nilsson P, Andrews P, Enblad P. Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma. J Neurosurg. 2005;102:311–7.
74. Gupta AK, Hutchinson PJ, Al Rawi P, Gupta S, Swart M, Kirkpatrick PJ, Menon DK, Datta AK. Measuring brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. Anesth Analg. 1999;88:549–53.
75. Valadka AB, Gopinath SP, Contant CF, Uzura M, Robertson CS. Relationship of brain tissue PO2 to outcome after severe head injury. Crit Care Med. 1998;26:1576–81.
76. Latronico N, Beindorf AE, Rasulo FA, Febbrari P, Stefini R, Cornali C, Candiani A. Limits of intermittent jugular bulb oxygen saturation monitoring in the management of severe head trauma patients. Neurosurgery. 2000;46:1131–8.
77. Lam JM, Chan MS, Poon WS. Cerebral venous oxygen saturation monitoring: is dominant jugular bulb cannulation good enough? Br J Neurosurg. 1996;10:357–64.
78. Macmillan CS, Andrews PJ. Cerebrovenous oxygen saturation monitoring: practical considerations and clinical relevance. Intensive Care Med. 2000;26:1028–36.
79. Goetting MG, Preston G. Jugular bulb catheterization does not increase intracranial pressure. Intensive Care Med. 1991;17: 195–8.
80. Coplin WM, O'Keefe GE, Grady MS, Grant GA, March KS, Winn HR, Lam AM. Thrombotic, infectious, and procedural complications of the jugular bulb catheter in the intensive care unit. Neurosurgery. 1997;41:101–7.
81. Gopinath SP, Robertson CS, Contant CF, Hayes C, Feldman Z, Narayan RK, Grossman RG. Jugular venous desaturation and outcome after head injury. J Neurol Neurosurg Psychiatry. 1994;57: 717–23.
82. Fandino J, Stocker R, Prokop S, Trentz O, Imhof HG. Cerebral oxygenation and systemic trauma related factors determining neurological outcome after brain injury. J Clin Neurosci. 2000;7: 226–33.
83. Cormio M, Valadka AB, Robertson CS. Elevated jugular venous oxygen saturation after severe head injury. J Neurosurg. 1999;90:9–15.
84. Macmillan CS, Andrews PJ, Easton VJ. Increased jugular bulb saturation is associated with poor outcome in traumatic brain injury. J Neurol Neurosurg Psychiatry. 2001;70:101–4.
85. Highton D, Elwell C, Smith M. Noninvasive cerebral oximetry: is there light at the end of the tunnel? Curr Opin Anaesthesiol. 2010;23:576–81.
86. Cho H, Nemoto EM, Yonas H, Balzer J, Sclabassi RJ. Cerebral monitoring by means of oximetry and somatosensory evoked potentials during carotid endarterectomy. J Neurosurg. 1998;89:533–8.
87. Duffy CM, Manninen PH, Chan A, Kearns CF. Comparison of cerebral oximeter and evoked potential monitoring in carotid endarterectomy. Can J Anaesth. 1997;44:1077–81.
88. Pennekamp CW, Bots ML, Kappelle LJ, Moll FL, de Borst GJ. The value of near-infrared spectroscopy measured cerebral oximetry during carotid endarterectomy in perioperative stroke prevention. A review. Eur J Vasc Endovasc Surg. 2009;38:539–45.
89. Maloney-Wilensky E, Le Roux P. The physiology behind direct brain oxygen monitors and practical aspects of their use. Childs Nerv Syst. 2010;26:419–30.
90. Maloney-Wilensky E, Gracias V, Itkin A, Hoffman K, Bloom S, Yang W, Christian S, LeRoux PD. Brain tissue oxygen and outcome after severe traumatic brain injury: a systematic review. Crit Care Med. 2009;37:2057–63.
91. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care, AANS/CNS, Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW. Guidelines for the management of severe traumatic brain injury. X. Brain oxygen monitoring and thresholds. J Neurotrauma. 2007;24 Suppl 1:S65–70.
92. Seubert CN, Mahla ME. Neurologic monitoring in the neurointensive care unit. In: Layon AG, Gabrielli A, Friedman WA, editors. Textbook of neurointensive care. Philadelphia: WB Saunders; 2004.