New neurophysiology and central nervous system dysfunction
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Purpose of review
The goal of this article is to summarize very recent technologic advances in neurophysiologic monitoring and to illustrate their potential benefit to critical care medicine.

Recent findings
Simplified, computer-processed electroencephalography devices now permit cost-effective, long-term critical care monitoring. They may be used alone to objectively assess sedation or coma level. In addition, these monitors serve as screening tools for more detailed electrophysiologic characterization of cortical dysfunction resulting from seizures, ischemia, or hypoxia. Somatosensory potentials broaden these capabilities to the entire neuraxis, whereas long-latency auditory evoked potentials facilitate measurement of changes in vigilance and cognition. Motor evoked potentials offer a sensitive and reliable method to determine the function of descending motor pathways in uncooperative or unresponsive patients. They may also yield a new measure of cortical excitability. New developments with transcranial Doppler ultrasonography promise noninvasive measures of cerebral perfusion pressure and particulate embolization. Near-infrared spectroscopy appears to enable noninvasive measurement of regional tissue oxygenation in both the brain and spinal cord.

Summary
When used together, these continuous measures of synaptic function, cerebral perfusion, and oxygenation give the clinician a vast amount of otherwise unobtainable information regarding the functional status of the central nervous system.

Keywords
electroencephalography, cerebral oximetry, motor evoked potentials, somatosensory-evoked potentials, transcranial Doppler ultrasonography

This article describes some of the very recent advances in neurophysiologic monitoring and their application in the management of central nervous system dysfunction in the critical care environment.

Electroencephalography
Growing recognition of the importance of nonconvulsive seizures in the etiologic factors of secondary brain injury has stimulated interest in long-term care electroencephalographic recording. An additional impetus is a new appreciation of the vital role of adequate sedation in the recovery process. Unfortunately, reliance on traditional electroencephalographic records for either of these applications is often impractical and economically unfeasible.

The cerebral function monitor, introduced in the early 1980s, was an early attempt at electroencephalographic compression. This single-channel device presented the rectified, amplitude-integrated, and logarithmically transformed bihemispheric signal in a time-compressed 6-cm/h format. The processed electroencephalographic display was categorized by the absence of sleep/wakefulness cycles and patterns signifying hyperexcitability (paroxysm, sawtooth) and synaptic depression (burst-suppression, flat line) [1].

Limitations hampered its acceptance as a replacement for traditional multilead electroencephalography. Now, however, there appears to be a resurgent interest in this device as a trigger for traditional electroencephalographic recording [2]. When used in this way, perhaps half of the compressed tracings may be immediately interpretable at the bedside [1]. Thus, the monitor may shorten the therapeutic response time and improve the use of expensive diagnostic resources.

The success of this simple approach to critical care electroencephalographic analysis has spawned several variants. In each, complex electroencephalographic amplitude and frequency information is reduced to a linear scale [3]. All provide probability estimates of patient responsiveness. The Bispectral Index is an empirically derived discriminant function containing four distinct electroencephalographic features. It is obtained from a single electroencephalographic channel, whereas the patient state index uses a four-channel system to measure changes in the topographic distribution of a different set of electroencephalographic features [4]. The third
approach applies physics to electroencephalographic analysis. Spectral entropy is used to measure the degree of electroencephalographic orderliness. Patient responsiveness appears to be directly related to electroencephalographic disorder.

These numeric indices have successfully guided sedation in critical care patients [5–10]. In addition, they have aided our understanding of neurophysiologic substrates of consciousness and its alteration [11•]. Studies are also beginning to examine their strengths and limitations in monitoring other states of heightened (i.e., seizures) and depressed (i.e., ischemia, hypoxia) cortical responsiveness. Gunawardane et al. [12] found that postictal electroencephalographic slow waves may result in low Bispectral Index values that do not correspond with the patient’s level of responsiveness. Merat et al. [13] demonstrated low Bispectral Index values during regional and global cerebral ischemia. Anecdotal experience from our monitoring service is consistent with this finding (Fig. 1). Vivien et al. [14] used the Bispectral Index as a screening tool to initiate a formal evaluation of brain death.

Gilbert et al. [15] evaluated the Bispectral Index and a wide range of univariate electroencephalographic spectral indices as proxies for widely used assessment tools including the Acute Physiology and Chronic Health Evaluation III Neurologic Score, the Glasgow Coma Scale, the Reaction Level Scale, and the Modified Ramsay Sedation Scale. Bispectral Index was significantly correlated with all of these measures and showed better agreement than any of the univariate electroencephalographic parameters.

The recently renewed interest in critical care electroencephalography applications also encompasses more complex multichannel analysis systems. Nonconvulsive status epilepticus is associated with hypoxia and a variety of metabolic disturbances but is difficult to diagnose in the obtunded or comatose patient. Brenner [16] described the multilead electroencephalography patterns used in the detection of nonconvulsive seizures. However, the proposed diagnostic criteria and management strategy are controversial.

Peters et al. [17] described a real-time automatic electroencephalographic seizure detection system and demonstrated its effectiveness as a closed-loop controller of electrical brain stimulation. Miller et al. [18] found the incidence of clinical seizures in neonates with perinatal asphyxia to be 37%. Seizure severity was independently associated with brain injury and was not limited to structural damage detectable by magnetic resonance imaging (MRI). Scher [19] stated that electroencephalography should be used in addition to clinical criteria to limit both misdiagnosis and overtreatment of abnormal nonepileptic behaviors. Scherg et al. [20•] used an automated electroencephalographic seizure detection scheme based on spectral analysis with a correct detection rate of 93% and false detection rate of only 4%. Walder et al. [21] reviewed reports of seizure-like phenomena associated with propofol. They encompassed generalized tonic–clonic seizures, focal motor seizures, hypertonus, twitching, rhythmic movements, opisthotonos, and involuntary movements. The only factor common among the cases was a presumed abrupt change in brain propofol concentration.

Although electroencephalography is quite sensitive to small changes in excitability and has good spatial discrimination, it may tell us little about the underlying cause of cortical dysfunction. Other physiologic data are often required to identify the source of abnormality and assess initial therapeutic response.

**Sensory evoked potentials**

The near-exclusive focus of electroencephalography on cortical synaptic activity may be broadened with the use of sensory evoked potentials. These illuminate the entire pathway at risk, from the skin surface to the cortex. The wealth of information provided by these discrete potentials complements the continuous electroencephalography. For example, combined electroencephalography, sensory evoked potentials, and polysomnography may improve outcome prediction in comatose children [22]. Evoked potentials and sleep recordings may supplement functional status information provided by clinical evaluation and the Glasgow Coma Scale score.

Hattori et al. [23] used upper limb somatosensory evoked potentials (SSEPs) to objectively document traction effectiveness in patients with cervical myelopathy, radiculopathy, or sprain. With all three conditions, injury severity influenced the magnitude of pretraction...
prolongation of subcortical SSEP components and latency decreases with traction.

Fortunately, SSEPs appear to be only modestly altered by many new critical care management techniques. Bois-seau et al. [24] found stable low-limb cortical SSEPs with propofol anesthesia. Bloom et al. [25] recorded reproducible cortical SSEPs with anesthetic doses of the new short-acting agent dexmedetomidine. In the critical care unit, Lang et al. [26] showed that mild hypothermia (32°C) increased central conduction time by 7% per degree Celsius. However, in contrast to nonpulsatile perfusion, amplitude of the cortical components was significantly increased.

Somatosensory evoked potentials have also been used successfully to predict outcome in adult patients with traumatic brain injury [27]. On a more cautious note, Wohlrab et al. [28] reported posttraumatic recovery in a small number of children who initially presented with bilateral loss of median nerve SSEPs.

The P300 is a positive, scalp-derived auditory evoked potential with an approximately 300-millisecond latency. It is termed a cognitive evoked potential because it is typically produced in attendent subjects attempting to identify infrequent “oddball” acoustic stimuli. However, Cote et al. [29] have shown that it may also be present during rapid eye movement (REM) sleep. Thus, it may also have use in obtunded critical care patients to document subtle return of partial responsiveness to environmental stimuli.

Wiedemayer et al. [30] summarized their recent experience with sensory evoked potentials during neurosurgical procedures. True positive findings with intervention occurred in 10% of 423 cases, whereas presumed false-negative indications occurred in 4% of cases. Thus, the net benefit of monitoring was the prevention of postoperative deficit in 6% of cases. Considering the substantial costs associated with each deficit, neuromonitoring appeared to be justified, both clinically and economically. Comparable critical care studies are urgently needed.

Motor evoked potentials
In the past year, we have seen an explosive interest in the use of transcranial motor evoked potentials, culminating with the US Food and Drug Administration approval of the first monitoring device for high-intensity transcranial electric stimulation (TES). Because TES is painful, most of the studies to date have been conducted during general anesthesia. de Haan and Kalkman [31] showed that low-limb evoked electromyographic responses to trains of TES were reliable and were produced quickly enough to guide timely interventions aimed at preserving and/or restoring adequate spinal cord perfusion. Calancie et al. [32••] reported on TES and SSEPs in 194 spinal surgery patients. TES could not be produced in nine, and SSEPs could not be produced in 42. The investigators often observed SSEP failure to identify motor deficit. Multipulse TES was viewed as a simple, safe, and highly accurate technique to prevent motor deficit during surgery. Jacobs et al. [33•] used TES in 184 consecutive thoracoabdominal aneurysm repairs. Motor responses were successfully elicited in all but one case. This monitoring technique appeared to be largely responsible for a more than threefold reduction in the incidence of neurologic deficits. Jacobs et al. [33•] concluded that TES was a sensitive technique for the functional assessment of critical collateral spinal cord perfusion involving lumbar and pelvic arteries. Their conclusion was further supported by the work of MacDonald and Janusz [34], who also used TES and SSEPs during thoracoabdominal aneurysm repair. TES provided rapid and reliable differentiation of cord ischemia from confounding variables. Two infarctions were accurately predicted, and nine potential deficits were averted. Sueda et al. [35] perfused cold blood into aneurysms after clamping the aorta. Intercostal arteries were reimplanted into the graft if perfusion suppressed TES responses. After arterial reimplantation into the aortic graft, motor responses returned and there were no deficits.

For critical care applications, production of motor evoked potentials with transcranial magnetic stimulation (TMS) has the advantage of painlessness. Although magnetically evoked motor responses are more susceptible than TES to anesthetic and sedative suppression of α motor neurons, recordings are possible under these conditions. For example, Aglio et al. [36] used single-pulse TMS and SSEPs in 27 anesthetized patients. Evoked motor responses were successfully produced in 21 of 27. In their series, they noted two false-negative SSEP responses but none for TMS.

Anesthetic suppression may be overcome through the use of a TMS pulse train. Temporal summation of α motor neurons appears to partially negate suppressant anesthetic effects. Scheufler and Zentner [37,38] consistently produced high-amplitude, low-limb motor responses to repetitive TMS during general anesthesia with propofol, etomidate, midazolam, remifentanil, and ketamine. The observed optimal stimulation frequency of 100 Hz in awake patients increased to 200 Hz during anesthesia.

Recent critical care applications of TMS include those of Cantello et al. [39], who used TMS to demonstrate functionally intact corticospinal pathways in 21 cases of suspected psychogenic paralysis. In healthy volunteers, Maeda et al. [40] and Sommer et al. [41] found high interindividual but low intra-individual variability in motor responses to paired TMS. This suggests that for criti-
cal care applications, one should consider using these potentials as a trend monitor to document individualized change in the function of descending motor pathways. In this regard, Manganotti et al. [42] used TMS to assess intracortical inhibition in normal subjects and patients with progressive myoclonic epilepsy. A conditioning, digitally applied electrical stimulus inhibited the motor responses to paired TMS in normal subjects. In contrast, the sensory stimulus facilitated the motor responses in epileptics. The technique provided a direct objective measure of cortical hyperexcitability. It may one day offer valuable diagnostic and mechanistic information for patients suspected of having atypical nonconvulsive seizures. Pulse-train TMS is now achievable with commercially available stimulators. Figure 2 demonstrates upper and lower limb responses to a train of three pulses in a patient with an incomplete injury at the C7 level.

Transcranial Doppler ultrasonography
Despite the extensively publicized Brain Trauma Foundation guidelines for management of head injury [43,44], wide variations in practice pattern remain. For example, Bulger et al. [45] recently surveyed the care of patients with severe head injury among 31 US academic trauma centers. There was substantial variation in the application of intracranial pressure–directed therapy, with an intercenter range of 0 to 100% of patients with a Glasgow Coma Scale score less than 9.

Concern about the complications of invasive monitoring appears to be a major factor in the institution-specific low utilization of traditional cerebral perfusion pressure. A new development in transcranial Doppler ultrasonography (TCD) monitoring has addressed this issue and achieved promising results. Schmidt et al. [46] used mean arterial pressure and TCD-derived measurement of mean ($V_m$) and diastolic ($V_d$) middle cerebral artery flow velocity to estimate noninvasive cerebral perfusion pressure according to the formula:

$$\text{Noninvasive cerebral perfusion pressure} = \text{mean arterial pressure} \times \left(\frac{V_d}{V_m}\right) + 14 \text{ mm Hg}$$

Noninvasive cerebral perfusion pressure reliably detected the hemodynamic consequences of transitional changes in intracranial pressure, such as B waves and plateau waves. Additionally, there was a significant correlation between invasive and noninvasive estimates of cerebral perfusion. Confirmation of these preliminary results may stimulate a resurgent interest in the value of perfusion-directed therapy. This approach may also be useful in stroke management because Eames et al. [47] found with TCD that dynamic cerebral autoregulation is globally impaired after acute ischemic stroke.

Transcranial Doppler ultrasonography is of established value in the diagnosis and medical management of cere-
bral vasospasm. However, in a new application, Suarez et al. [48] demonstrated the effectiveness of TCD monitoring for the endovascular treatment of vasospasm. TCD was as sensitive as cerebral angiography in detecting symptomatic vasospasm. High TCD velocities often appeared before the appearance of symptoms.

Several life-threatening complications of sickle cell disease may lead to ICU admission. These include vasocclusive pain crises, cerebral vascular accidents, anemia, and multiorgan failure. Erythrocytapheresis appears to retard the development of these sequelae, but uniform transfusion criteria have not been established. Jenkins [49] reviewed the essential information provided by TCD in these high-risk patients. As an illustration of this application, Figure 3 depicts the typical high-velocity TCD tracing observed in a patient with sickle cell disease with middle cerebral artery stenosis.

Tinkler et al. [50] used TCD to measure embolic signals during nonvalvular atrial fibrillation. There was a significant reduction with anticoagulant therapy, suggesting a benefit of TCD assessment of antiplatelet and antithrombus therapy. A new development in TCD signal analysis may further this objective. When insonated at two ultrasonic frequencies, particulate emboli preferentially reflect the higher one, whereas the opposite is true for gaseous emboli. Russell and Brucher [51•] used this principle to successfully differentiate relatively benign gas bubbles from the more injurious particulate emboli.

**Figure 3. Transcranial Doppler ultrasonography quantifies the degree of intracranial vascular stenosis in sickle cell disease**

![Typical middle cerebral artery flow velocity spectra are shown from a normal adolescent (A) and from a patient with symptomatic sickle cell disease (B). The dramatic increase in peak and mean velocity with sickle cell disease indicates the presence of hemodynamically significant cerebrovascular stenosis.](image)

**Figure 4. Near-infrared spectroscopy identifies oxygen imbalance within brain and spinal cord**

Spatially resolved, near-infrared spectroscopy was used to measure oxygen saturation of the brain (thin line) and lower thoracic spinal cord (thick line) during repair of a thoracoabdominal aneurysm. Of the six such cases that we have monitored thus far, this was the only one to demonstrate precipitous and persistent spinal cord oxygen desaturation during aortic occlusion. The patient awoke paraplegic. (Inset) Graph shows the spinal cord oxygen profile on the fourth postoperative day that was generated by sequential measurements over each thoracic vertebra. Note the low saturation in the T9 region.
Cerebral oximetry
Brawanski et al. [52••] compared the information obtained from an invasive continuous measure of cerebral cortical oxygen tension with that provided noninvasively by transcranial dual-wavelength, spatially resolved, near-infrared spectroscopy (i.e., cerebral oximetry). Time series analysis in patients with head injury or aneurysmal subarachnoid hemorrhage showed generally good agreement but some discordant episodes. However, reexamination of the relation in the frequency domain through spectral analysis demonstrated that both technologies produced similar information, albeit in dissimilar formats. This important observation may foster a reinterpretation of some of the negative evaluations of the noninvasive method.

Dunham et al. [53] examined the relation between cerebral perfusion pressure and regional cerebral oxygen saturation measured transcranially with near-infrared spectroscopy. Although there was a direct relation between them, there were examples of low brain oxygen saturation with acceptable cerebral perfusion pressure (>70).

Spinal cord measurement with noninvasive tissue oximetry is also being tested. LeMaire et al. [54] evaluated spatially resolved tissue oximetry in a swine model of ischemic spinal cord injury that relied on sequential ligation of segmental intercostal arteries from T6 to L1. Complete ligation resulted in only a 6% decline in an oxygen sensor located over T6 but a 39% drop at the T11 level. The regional hypoxia was associated with a loss of SSEPs and, ultimately, histologic evidence of ischemic spinal cord injury. These investigators used intrathecal injection of infrared-absorbing dye to provide direct-evidence spinal cord measurement [55].

We have recently begun to use this technique in patients at risk for spinal cord ischemia. Figure 4 shows marked desaturation in the lower thoracic cord during repair of a thoracoabdominal aneurysm. The patient awoke paraplegic. The spinal oxygen profile in the insert in Figure 4 shows persistent desaturation in the T9 region.

Lack of a widely accepted gold standard appears to have impeded the clinical acceptance of noninvasive cerebral oximetry. Perhaps this limitation will be overcome soon with the introduction of functional MRI with blood oxygenation level–dependent contrast and arterial spin-labeling perfusion contrast [56••]. Blood oxygenation level–dependent functional contrast is based on the observation that the ferrous ion of heme in deoxyhemoglobin is paramagnetic. Increased signal strength reflects a local deoxyhemoglobin decrease, indicating that regional perfusion exceeds metabolic oxygen demand. Arterial spin-labeling perfusion contrast uses magnetically labeled arterial blood water as a diffusible tracer for cerebral blood flow measurements. The label decay time is long enough to permit imaging and short enough to quantify dynamic change.

Together, blood oxygenation level–dependent functional contrast and arterial spin-labeling perfusion contrast permit direct study of activation flow coupling, the coupling process of brain metabolism and blood flow originally described more than a century ago by Sherrington [57]. The functional MRI has shown interictal hypometabolism and hypoperfusion [58] and focal hyperfusion during epilepsy partialis continua. However, the functional MRI results also may force us to revise long-standing notions. For example, it now appears that cerebral blood flow changes are not regulated by glycolytic demands. Rather, flow seems to be dictated by the need for the removal of metabolic products such as lactate [59]. Furthermore, Mintun et al. [60] found that decreased tissue oxygen does not appear to be a key signal for cerebral blood flow increase.

Conclusions
The new developments described for each of the neurophysiologic technologies offer the promise of improved care for critically ill patients. However, the current emphasis on evidence-based medicine means that many of these innovations will not endure without adequate class I evidence. It is imperative that critical care specialists, biomedical statisticians, and ethicists work together to develop study designs that permit scientifically valid, single-site, prospective, controlled studies with reasonable cost and effort. Without this statistical innovation, many patients may suffer needlessly.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of special interest
•• Of outstanding interest


This page contains a mix of references and abstracts, likely from a scientific journal or conference proceedings. The text is a compilation of various studies and reports, focusing on neurological monitoring techniques and their applications. The authors discuss the use of neurophysiological and physiological monitoring methods in various clinical settings, such as during surgery, in intensive care units, and in the evaluation of neurological conditions. The references are cited extensively, indicating a thorough review of the literature on the subject. The text is dense with technical terms and specialized terminology, typical of a scientific document.


This report describes new functional MRI techniques that bridge the chasm between brain imaging and neurophysiology.


