Abstract  Recent advances in computer technology have made it possible to perform prolonged digital continuous video EEG monitoring of many critically ill patients simultaneously. Recent studies using continuous EEG monitoring (cEEG) have found that these patients, especially those with coma, acute brain injury, or prior clinical seizures, often have nonconvulsive seizures (NCSz), and that these may contribute to secondary brain injury. The majority of seizures in the critically ill are nonconvulsive and can only be identified with EEG recording. Rapidly improving quantitative EEG (qEEG) software speeds data review to allow screening of multiple prolonged recordings to detect NCSz and has the potential to provide continuous information about changes in brain function in real time at the bedside. Optimal sensitivity and specificity of qEEG tools are obtained with full electrode montages and careful maintenance of scalp electrodes. New electrode technologies, such as MRI-compatible electrodes, help reduce the burden on EEG technologists while limiting interruptions in recordings. In addition to detecting NCSz, cEEG can also be used for dynamic detection of other changes in brain function such as ischemia, and can be coupled with other modalities of monitoring brain physiology such as microdialysis, tissue oximetry, and intracranial electrophysiology. Together, these tools can allow early detection of brain at risk for injury and alert the physician to intervene before the damage becomes irreversible.

Keywords  Continuous EEG monitoring, Intensive care unit, Neurotelemetry, Nonconvulsive seizures, Critical care, Status epilepticus

2.1. Introduction

Nonconvulsive seizures (NCSz) and nonconvulsive status epilepticus (NCSE) are increasingly recognized as common occurrences in the ICU where 8–48% of comatose patients undergoing continuous EEG monitoring (cEEG) may have
NCSz, depending on the study population (1–5) (Table 2-1). NCSz, as the term is used in this chapter, refers to electrographic seizures with little or no overt clinical manifestations. NCSE occurs when NCSz are prolonged; a common definition is continuous or near-continuous electrographic seizures lasting at least 30 min (2, 6, 7). Most patients with NCSz have purely electrographic seizures (1) (Table 2-1 and Fig. 2-1) but NCSz can be associated with other subtle signs such as face and limb twitching, nystagmus, eye deviation, pupillary abnormalities (including hippus), and autonomic instability (8–11). None of these signs is highly specific for NCSz and is often seen under other circumstances in the critically ill patient; thus, continuous EEG monitoring (cEEG) is necessary to diagnose NCSz. In this chapter, we will discuss the implementation of cEEG in the critically ill and how to review the data, including available quantitative EEG (qEEG) tools that enable efficient review of the vast amount of raw EEG generated by prolonged monitoring. We will also review which patients are appropriate candidates for cEEG, as well and the numerous EEG patterns that may be encountered. Finally, we will discuss future directions for cEEG and neurophysiological monitoring in the ICU.

2.2. How To Monitor

Obtaining high-quality cEEG recordings in the ICU is a challenge. Adequate technologist coverage is necessary to connect patients promptly, including on off-hours, and maintain those connections 24-h a day. Critically ill patients are frequently repositioned and transported to tests, which makes maintaining electrode integrity difficult. In our center, we employ collodion to secure disk electrodes, and check the electrodes twice daily, usually supplemented by keeping the live recordings visible remotely to see which patients require electrode maintenance. Newer electrodes, such as subdermal wires, which may be more secure and lead to less skin breakdown, may be appropriate for comatose patients who are expected to undergo cEEG for days to weeks (12). While these electrodes may take more time to apply, they require less maintenance and are MRI- and CT-compatible (both safe and not affecting image interpretation), thereby saving substantial technologist time. Concerns for image artifacts and patient safety make it necessary to remove and then reapply standard disk electrodes when patients undergo brain MRIs, but there has been some progress in creating practical MRI- and CT-compatible electrodes (13), including conductive plastic electrodes. These are now commercially available in the United States and have been safely used in MRI scanners with a field strength of up to 4 T (Fig. 2-2).

There are numerous sources of artifact in the ICU environment that make cEEG challenging. Some are easily identified and filtered out such as 60 Hz (or 50 Hz in Europe) line noise from nearby electrical equipment. Others, however, such as pacemaker artifact, chest percussion, vibrating beds, respirator activity, and intravenous drips, may be difficult to distinguish from seizures or other cerebral activity (14, 15) (Fig. 2-3). Simultaneous digital video recording is useful for distinguishing brain signals from artifacts, especially rhythmic patterns such as those seen with chest percussion. In addition, video recording helps correlate EEG patterns with patient behaviors. In some cases, periodic EEG patterns can be determined to be ictal if they are time-locked to subtle patient movements (16). In addition, some significant
<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>EEG type</th>
<th>Design</th>
<th>N</th>
<th>Percentage of patients with any seizures</th>
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<tr>
<td>Privitera et al. (5)</td>
<td>Patients with altered level of consciousness or suspected subclinical seizures anywhere in medical center.</td>
<td>Routine EEG</td>
<td>Prospective</td>
<td>198</td>
<td>37</td>
<td>100 (32% had no subtle clinical signs)</td>
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<tr>
<td>Jordan (104)</td>
<td>Patients admitted to neuro-ICU undergoing cEEG.</td>
<td>cEEG</td>
<td>Retrospective</td>
<td>124</td>
<td>35</td>
<td>74</td>
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<td>DeLorenzo et al. (35)</td>
<td>All patients with prior convulsive SE and altered level of consciousness without clinical seizure activity.</td>
<td>cEEG</td>
<td>Prospective</td>
<td>164</td>
<td>48</td>
<td>100 (29% NCSE)</td>
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<td>Vespa et al. (105)</td>
<td>All patients with moderate to severe traumatic brain injury admitted to the neuro-ICU.</td>
<td>cEEG</td>
<td>Retrospective</td>
<td>94</td>
<td>22</td>
<td>52</td>
</tr>
<tr>
<td>Towne et al. (4)</td>
<td>ICU patients in coma without clinical seizure activity.</td>
<td>Routine EEG</td>
<td>Retrospective</td>
<td>236</td>
<td>8</td>
<td>100 (NCSE)</td>
</tr>
<tr>
<td>Vespa et al. (78)</td>
<td>Patients admitted to neuro-ICU with stroke or intracerebral hemorrhage.</td>
<td>cEEG</td>
<td>Prospective</td>
<td>109</td>
<td>19</td>
<td>79</td>
</tr>
<tr>
<td>Claassen et al. (1)</td>
<td>Patients of all ages with unexplained decreased level of consciousness or suspected subclinical seizures</td>
<td>cEEG</td>
<td>Retrospective</td>
<td>570</td>
<td>19</td>
<td>92</td>
</tr>
<tr>
<td>Pandian et al. (3)</td>
<td>Neuro-ICU patients undergoing cEEG for diagnostic purposes or for titration of intravenous therapy for SE</td>
<td>cEEG</td>
<td>Retrospective</td>
<td>105</td>
<td>68</td>
<td>27 (NCSE)</td>
</tr>
<tr>
<td>Jette et al. (33)</td>
<td>Patients &lt;18 years admitted to ICU with unexplained decreased level of consciousness or suspected subclinical seizures.</td>
<td>cEEG</td>
<td>Retrospective</td>
<td>117</td>
<td>44</td>
<td>75</td>
</tr>
<tr>
<td>Claassen et al. (51)</td>
<td>Patients with intracerebral hemorrhage with unexplained decreased level of consciousness or suspected subclinical seizures</td>
<td>cEEG</td>
<td>Retrospective</td>
<td>102</td>
<td>31</td>
<td>58</td>
</tr>
<tr>
<td>Oddo et al. (36)</td>
<td>Medical ICU patients without known brain injury undergoing with unexplained decreased level of consciousness or suspected subclinical seizures</td>
<td>cEEG</td>
<td>Retrospective</td>
<td>201</td>
<td>10 (additional 17% with PEDs)</td>
<td>67</td>
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EEG patterns in the critically ill appear after the patient is stimulated, which is easily determined by reviewing the video (17, 18).

The number of electrodes used in cEEG studies varies considerably. In our center, we typically perform “full electrode” recordings using 16 or more active electrodes in addition to 1 or 2 reference electrodes and cardiac leads. Other authors have used reduced electrode configurations (19). The advantage of a reduced electrode system is that it is faster to apply and easier to maintain. It is also easier to work around other neuro-monitoring devices, surgical wounds, or ventricular drains common in NICU patients.
Fig. 2-3. Common ICU EEG artifacts. (a) Rhythmic bitemporal artifact due to chest compression in a medical ICU patient (arrow). (b) Respirator artifact due to fluid collecting in the tubing (arrow). These patterns are easily recognized on simultaneous video recording, as they are synchronized with respirations. (c) Left temporal rhythmic waveforms (arrow) due to patting in an infant. This pattern is sometimes easy to confuse with seizures without video, as it often shows a physiological field with evolution in frequency and amplitude. (d) Semirhythmic right temporal artifact (black arrow) due to chest percussion mimicking right PLEDs or potentially ictal activity in a patient with true left hemisphere PLEDs (white arrows). (e) Right occipital 5-Hz rhythmic artifact (arrow) due to percussion bed activity. (f) Rhythmic 1–1.5-Hz artifact (arrow) due to chewing in an edentulous patient.
However, a full electrode configuration improves the ability to distinguish brain signals from artifacts, aids in spatial localization of pathological activity, and provides a safety factor in case one or more leads fail, including allowing qEEG calculations and alarms to continue to function adequately (20). In addition, reduced electrode methods, especially when coupled to qEEG tools, may miss clinically significant events. For instance, Shellhaas et al. (21) found that neonatologists evaluating amplitude-integrated EEG using only two electrodes for seizure detection, a technique employed in purpose-built devices common in neonatal ICUs, detected only 12–38% of seizures identified using conventional electrode arrangements. Although emergent below-the-hairline EEG recordings have only moderate sensitivities and specificities (22), they are almost certainly better than no EEG at all; a full EEG should be done when possible to confirm or refute the results.

2.3. Data Analysis

Several days of cEEG generates gigabytes of data that, in its raw form, are time-consuming for a neurophysiologist to review, especially if many patients are being monitored simultaneously. Furthermore, the raw EEG may be difficult for nonexperts, such as ICU physicians and nurses, to interpret at the bedside. Therefore, concerning electrographic events may not be noticed until several hours later, when the file is reviewed by the neurophysiologist. Computing advances have enabled the use of qEEG algorithms to reduce the data and provide graphical representation of significant patterns and trends to speed up review. Some of the commonly employed qEEG methods are discussed below (see (23) for a detailed review).

Many qEEG data reduction and trending tools are based on transforming the raw cEEG into a time–frequency series using algorithms such as short time Fourier transform or continuous wavelet transform. Several hours of cEEG recordings can be reduced to a single screen of time–frequency values using a compressed spectral array or density spectral array. The time–frequency data can be averaged over scalp regions or hemispheres to further reduce the data. Using these techniques, the abrupt changes in cEEG spectral power in a relatively narrow frequency range during seizures are highlighted, allowing quick assessment of seizure frequency and duration (Fig. 2-4). Time–frequency transformation of the cEEG can be further manipulated to provide a single scalar value for each epoch of time. For instance, Claassen et al. (24) showed that the ratio of total hemispheric power in the alpha frequency band (8–13 Hz) to the total power in the delta frequency band (1–4 Hz) after maximal alerting, or post-stimulation alpha–delta ratio (ADR), was the most useful qEEG parameter for detecting delayed cerebral ischemia in patients with high-grade subarachnoid hemorrhage (SAH). Hemispheric asymmetries in spectral power, computed as ratio of left and right total power for all EEG frequencies or as relative differences at each frequency, can be used to quickly identify focal seizures (e.g., Fig. 2-4). The greatest utility of reducing the cEEG to single scalar values is that these values can easily be displayed and interpreted on bedside monitors like heart rate and blood pressure. This could allow early identification of neurophysiological events by the ICU staff and alarms to trigger patient examination and could lead to more responsive treatment.
Fig. 2-4. Using quantitative EEG tools to aid review and interpretation in a 7-year-old with viral encephalitis and refractory nonconvulsive status epilepticus with cyclic alternating seizures. (a) Typical qEEG display showing long-term trends in spectral power between 0 and 18 Hz for both hemispheres (top two panels), relative interhemispheric asymmetry index (middle; up=right on relative asymmetry tracing, and red=more power on right on asymmetry spectrogram), and hemispheric amplitude-integrated EEG (bottom two panels) for five hours of recoding. (b) enlargement of the region in a marked by the dash line. There is an alternating pattern of increased spectral power at all frequencies on the right (R), and then the left (L) hemispheres.
Other trending algorithms highlight amplitude measures, which can also be used to detect seizures. Amplitude-integrated EEG (aEEG) computes statistical measures such as mean, maximum, minimum, and percentiles of the smoothed and full-wave-rectified EEG signal (Figs. 2-4 and 2-5). These tools are commonly used in commercial devices in neonatal ICUs (25) to assess the background EEG and occasionally to detect seizures, although these qEEG-based devices may be insensitive for detecting seizures (21). Reliance on qEEG tools without the ability to review the raw EEG
for noncerebral signals can also lead to false positive seizure detections (Fig. 2-5); thus, qEEG should only be interpreted in conjunction with the raw EEG wave forms and confirmed by electroencephalographers whenever possible.

Fig. 2-5. Limits of seizure detection using amplitude-integrated EEG in a 64-year-old man with central nervous system lymphoma and altered mental status. (a) A plot of the average amplitude-integrated EEG (aEEG) for the left (top) and right (bottom) hemispheres demonstrates frequent transient elevations in the EEG amplitude (open arrows) that correspond to left temporal electrographic seizures. A typical seizure is shown in (b) with the onset indicated by the arrows. At times, similarly shaped peaks in the aEEG trend (solid arrows) occurred that correspond to movement/muscle artifact such as that seen in (c). It is not possible to differentiate seizures from artifact by the aEEG tracing alone.
Quantitative EEG tools can also calculate the degree of burst-suppression of the EEG background to allow for easy titration of medication to induce coma, a common treatment of status epilepticus (SE), or refractory elevated intracranial pressure (ICP) (26). EEG-based monitors such as bispectral index (27), patient state index (28), and Narcotrend (29) have been in use in operating rooms and ICUs for over a decade to monitor depth of sedation. While these single-purpose devices use proprietary algorithms, evaluation of the raw cEEG or qEEG measures can also provide information about arousal in the paralyzed patient (30). Unlike cEEG, these devices cannot detect seizures, and their performance has not been tested adequately in brain-injured patients.

In our experience, no one qEEG tool is appropriate for all patients or even for the same patient at all times. Situations may occur where one tool is more susceptible to certain artifacts or is less sensitive to the seizures the individual patient may have. Instead, we employ multiple tools simultaneously to screen the initial cEEG record and focus particularly on reviewing the raw EEG data at times where there appear to be clear changes in the qEEG measures from baseline (Fig. 2-4). Once the patient’s seizure pattern is identified, the parameters of the qEEG tools can be further refined to highlight this pattern and improve the recognition of subsequent seizures.

With Internet-based networking, it is now practical to monitor dozens of patients in multiple ICUs. If there is sufficient network capability in the hospital, cEEG can be streamed live over the network and can be interpreted in real time if needed (and personnel are available). In addition, cEEG can be reviewed remotely from home or from a distant hospital site using virtual private networks and virtual network computing (20). However, in current practice, cEEG is not yet a truly real-time technology at most centers. In our center, records are routinely reviewed by neurophysiologists or technologists three times daily. Records can be reviewed more frequently if there are suspicious clinical events or medications are being titrated. However, as most NCSz have little or no detectable clinical correlate, they may go unrecognized for several hours with only intermittent review. It is clear that we need to move towards continuous real-time monitoring via use of quantitative EEG alarms and around-the-clock “neurotelemetrists” to respond to the alarms and review the long-term trends.

2.4. Who To Monitor

Recent studies using routine and cEEG monitoring have helped to identify which patients are at risk for NCSz and, therefore, may benefit from cEEG. The causes of NCSz and NCSE in ICU patients are similar to the causes of convulsive seizures in these patients. These include acute structural lesions, infections, metabolic derangements, toxins, withdrawal, and epilepsy, all common diagnoses in the critically ill patient (31). However, NCSz are the more common ictal manifestation (or lack thereof) in ICU patients (1–5). NCSz are even more common in the pediatric population, especially in infants (1, 20, 32, 33). Recent prospective studies using cEEG have indentified the incidence of NCSz and NCSE in various patient populations. These studies are summarized in Table 2-1.

While it may not be surprising that patients with acute brain injuries (1, 34) and recent convulsive SE (35) have a high risk of NCSz, NCSz also occur in
medical or surgical ICU patients, including in those without known structural brain injury. Critically ill medical and surgical patients are susceptible to many toxic, electrolyte, and metabolic abnormalities that may cause both mental status changes and seizures. In the Columbia series, 21% of patients monitored with cEEG with toxic-metabolic encephalopathy as their primary neurologic diagnosis had NCSz. In other series, 5–25% of patients with acute NCSz had metabolic derangements as the likely etiology of their seizures (4, 6). In a recent study of 201 medical ICU patients without known brain injury that underwent cEEG monitoring, 22% of patients had periodic epileptiform discharges (PEDs) or seizures; sepsis and acute renal failure were significantly associated with both PEDs and seizures (36).

2.5. What To Look For

The background, interictal, and ictal EEG patterns of the critically ill patient are significantly different from those encountered in ambulatory patients (37, 38). Ictal patterns may include rhythmic epileptiform discharges or rhythmic waves at greater than 3 Hz. However, in critically ill patients, rhythmic or periodic patterns occurring at a rate of less than 3 per second can be ictal as well. One set of criteria for defining NCSz is shown in Table 2-2. It should be noted that these criteria reflect expert consensus and there are periodic patterns common to critically ill patients where the relationship to seizures is unknown (39). In practice, it is often difficult to determine whether periodic activity in a comatose patient reflects seizure activity, a brain at risk for seizures, or, perhaps, has no relationship to seizures (as is widely thought to be the case with triphasic waves seen in metabolic encephalopathy).

Table 2-2. Criteria for Diagnosing Nonconvulsive Seizures (adapted from (39), Who Modified the Criteria of (6)).

Any pattern lasting at least 10 s satisfying any one of the following three primary criteria

Primary criteria

• Repetitive generalized or focal spikes, sharp-waves, spike-and-wave complexes at ≥ 3/s

• Repetitive generalized or focal spikes, sharp-waves, spike-and-wave, or sharp-and-slow wave complexes at < 3/s and the secondary criterion

• Sequential rhythmic, periodic, or quasi-periodic waves at ≥1/s and unequivocal evolution in frequency (gradually increasing or decreasing by at least 1/s, e.g., 2–3/s), morphology, or location (gradual spread into or out of a region involving at least two electrodes). Evolution in amplitude alone is not sufficient. Change in sharpness without other change in morphology is not enough to satisfy evolution in morphology

Secondary criterion

Significant improvement in clinical state or appearance of previously absent normal EEG patterns (such as posterior-dominant “alpha” rhythm) temporally coupled to acute administration of a rapidly acting antiepileptic drug. Resolution of the “epileptiform” discharges leaving diffuse slowing without clinical improvement and without appearance of previously absent normal EEG patterns would not satisfy the secondary criterion.
While certain periodic discharges may be more closely related with systemic metabolic abnormalities, such as triphasic waves in hepatic encephalopathy, others may reflect injured tissue at risk for seizures such as periodic lateralized epileptiform discharges (PLEDs) and generalized periodic epileptiform discharges (GPEDs) (40–42) (Fig. 2-6). There is convincing evidence to suggest that PLEDs are sometimes ictal. For instance, PLEDs can be time-locked to focal clonic movements in some patients with focal motor SE (16). Positron emission tomography in a patient with frequent PLEDs demonstrated increased regional glucose metabolism similar to what is seen with focal seizures (43). Single-photon emission CT (SPECT) imaging in patients with PLEDs demonstrated increased regional cerebral perfusion that normalized when the PLEDs resolved (44, 45). In addition, frequent PLEDs in elderly patients have been associated with a confusional state that resolves spontaneously or with diazepam treatment (46). However, other studies have described cases where PLEDs are clearly non-ictal such as in some epilepsy patients with chronic interictal PLEDs (47). In addition, when some patients with PLEDs and acute brain injury demonstrate seizures, the EEG pattern is often faster and with different morphology (48). Given the close association with seizures and the fact they are at times clearly associated with behavioral changes, some authors view PLEDs as an unstable state in an “irritable” brain, lying along an ictal–interictal continuum (39, 42).

A common practice used to distinguish ictal from non-ictal periodic EEG patterns in the critically ill is to see whether they are abolished by a trial of short-acting benzodiazepines (Table 2-3 and Fig. 2-7). However, almost all periodic discharges, including triphasic waves seen in metabolic encephalopathy and the discharges of Creutzfeldt-Jakob Disease, are attenuated by benzodiazepines (49). Thus, unless there is clinical improvement accompanying the EEG change, the test is not helpful. Unfortunately, improvement can take substantial time even if the activity represents NCSE and is aborted with benzodiazepines. However, a substantial portion of ICU patients with nonconvulsive seizures or NCSE will improve neurologically, and usually within a day of treatment. For example, Drislane et al. (50) showed that 56% of critically ill patients without anoxic injury treated for NCSzs demonstrated mental status improvement. Although noncomatose patients were more likely to improve (81%), 48% of comatose patients improved as well. Our protocol for attempting to prove the presence of NCSE is shown in Table 2-3. It is important to recognize that lack of clinical improvement does not exclude NCSE – it simply does not help determine its presence or absence.

While there is consistent evidence that the presence of PEDs (and nonconvulsive seizures) are an independent risk factor for worse prognosis in intracerebral hemorrhage (ICH) (51), SAH, (52), sepsis(36), and after GCSE (35, 53), it is unclear whether these and other periodic discharges require treatment and how aggressive this treatment should be. Laboratory studies and computer modeling are beginning to probe the network mechanisms that mediate periodic discharges in the injured brain (54).

Another common pattern in encephalopathic ICU patients is epileptiform activity triggered by stimulation or arousals. The evoked activity may be anywhere on the interictal to ictal spectrum and we have termed it “stimulus-induced rhythmic, periodic, or ictal discharges” (SIRPIDs). There is usually no clinical correlate, as with most ICU seizures, but a small number of patients will have
Fig. 2-6. Periodic discharges in critically ill patients. (a) Right frontal PLEDs occurring at 1 Hz (arrow) in an 82-year-old man after resection of a bifrontal meningioma. The patient subsequently developed right frontal electrographic seizures. (b) Generalized periodic discharges at 1–2 Hz in a 79-year-old patient with dementia, renal disease, and altered mental status. Although these waveforms have a triphasic morphology at times, the pattern subsequently evolved to 2.5–3 Hz GPEDs consistent with NCSz and was associated with modest elevations in neuron-specific enolase, a marker of neuronal injury, to 14 (reference range 3.7–8.9).
Table 2-3. Benzodiazepine Trial for the Diagnosis of Nonconvulsive Status Epilepticus (adapted from Jirsch and Hirsch (11)).

Appropriate patients have rhythmic or periodic focal or generalized epileptiform discharges on EEG with altered level of consciousness

Need to monitor EEG, pulse oximetry, blood pressure, ECG, and respiratory rate with dedicated nurse

Antiepileptic drug trial

- Sequential small doses of rapidly acting short-duration benzodiazepine such as midazolam at 1 mg/dose
- Between doses, repeated clinical and EEG assessment
- Trial is stopped after any of the following
  1. Persistent resolution of the EEG pattern (and exam repeated)
  2. Definite clinical improvement
  3. Respiratory depression, hypotension, or other adverse effect
  4. A maximum dose is reached (such as 0.2 mg/kg midazolam, though higher may be needed if the patient is on chronic benzodiazepines)

Test is considered positive if there is resolution of the potentially ictal EEG pattern AND either an improvement in the clinical state or the appearance of previously absent normal EEG patterns (e.g., posterior-dominant “alpha” rhythm). If EEG improves but patient does not, the result is equivocal.

Fig. 2-7. Benzodiazepine trial in a 51-year-old man with multiple medical problems including chronic liver disease and HIV who was admitted to the medical ICU with sepsis. Despite treatment, he continued to have poor mental status. (a) Initial cEEG monitoring showed GPEDs at 1–2 Hz. (b) Following the administration of lorezapam 1 mg IV, the GPEDs became less frequent and the patient became responsive and followed commands, strongly suggesting that the initial pattern was ictal.
focal motor seizures consistently elicited by alerting stimuli (18). This is most likely a result of hyperexcitable cortex that is activated by the usual arousal pathways, which involve the upper brainstem, thalamus, and widespread thalamo-cortical projections. This epileptiform activity may become clinically apparent if it causes synchronous activation of motor pathways. At our center, technologists stimulate patients twice daily to assess for the presence of SIRPIDs.

Fig. 2-8. Testing for stimulus induced rhythmic, periodic, or ictal discharges in critically ill patients. (a) EEG technologist demonstrating the cotton applicator used to provide nasal noxious stimulation to comatose patients undergoing cEEG twice daily. (b) SIRPIDs induced following noxious stimulation (black arrow) in an 84-year-old woman who was comatose following evacuation of a large right subdural hematoma. Shortly after stimulation, right frontal periodic discharges are seen. After several seconds, repetitive left hand movements emerge (red arrow) that are time-locked to the discharges. She subsequently became more responsive following treatment with anticonvulsants.
The treatment and prognostic implications of SIRPIDs are currently unknown, but the relationship between ictal discharges and arousals raises the possibility that limiting unnecessary stimulation in patients with SIRPIDs may be beneficial. This can be studied fairly easily, particularly when cerebral microdialysis is being utilized.

2.6. Why Monitor

While NCSz are common in the critically ill, the evidence that they worsen outcomes and require prompt identification and treatment is mixed (55, 56). In several studies, the presence of NCSE and delay to diagnosis and treatment were each associated with significantly higher mortality (6, 57), though mortality in patients with NCSE may be most related to the underlying cause (58). In addition, while NCSE may be associated with poor prognosis in the critically ill elderly (59), one retrospective study showed that aggressive treatment of NCSz and NCSE was associated with worse outcomes in this population (60). Because of the conflicting outcome data, much of the justification for identifying and treating NCSz in the critically ill comes from human and animal data demonstrating that seizures can lead to neuronal injury. To date, there has not been a prospective controlled trial to determine whether treating NCSz or NCSE improves neurologic outcomes.

There is a large body of evidence that prolonged seizures, even if non-convulsive, can lead to neuronal damage in several animal models. In a seminal study, Meldrum et al. (61) found that paralyzed and artificially ventilated baboons had hippocampal cell loss after treatment with a convulsant. Cell death occurred after 60 min of continuous electrographic seizures despite careful control of oxygenation, temperature, and metabolic status. In rodent models, electrical and chemiconvulsant-induced SE is associated with cell loss, free-radical production, inflammation, gliosis, and synaptic reorganization (62). Pathological changes can be seen in the absence of overt convulsions and can have profound long-term effects such as impaired performance on cognitive tasks (63) and the development of epilepsy (64). There is also some evidence from animal models that even single or multiple brief seizures may lead to cell death and cognitive impairment (65, 66). Even in the absence of cell death, brief seizures in certain animal models can lead to alterations in gene expression (67), impaired long-term potentiation which is related to memory (68), and reduced threshold for subsequent seizures (69). SE in humans has also been associated with hippocampal cell loss in postmortem studies (70). In hospitalized patients, SE is associated with neuronal injury as demonstrated by elevated levels of serum neuron-specific enolase (NSE), including in patients without detectable acute brain injury (e.g., from seizure activity alone) (71, 72). In fact, even complex partial seizures in ambulatory patients with epilepsy can lead to elevated NSE (73). While the sequelae of NCSz and NCSE are not as well understood, evidence suggests that they can lead to neuronal damage in humans. DeGiorgio et al. (74) showed that NSE levels, though elevated after all seizures, were especially high following NCSz and seizures of partial onset even in absence of acute brain injury.

In addition to direct pathological effects of seizures themselves, seizure may also worsen the extent of injury from the inciting neurological injury. Seizures
can place increased metabolic, excitotoxic, and oxidative stress on at-risk brain leading to irreversible injury. For instance, microdialysis studies in patients with TBI demonstrated increases of extracellular glutamate to excitotoxic levels following NCSz (75) as well as associated elevated lactate/pyruvate ratios and ICP (76). Glycerol, a marker of cellular breakdown, has also been found to be elevated in the microdialysate after NCSz in TBI patients (77). Compared to patients without NCSz who had similar injuries, impaired brain metabolism and increased ICP could be seen up to 100 h after injury (76). As mentioned above, NCSz in ICH were associated with increased mass effect on serial imaging, as well as worse NIHSS (National Institutes of Health Stroke Scale) scores in one study (78) and expansion of hematoma size in another (51); there was a trend towards worse outcomes in those with NCSzs in both studies. Seizures are also associated with increased metabolic demand, which may worsen injury to ischemic brain, particularly the penumbra. NCSz were associated with increased infarct volumes and higher mortality rates following middle cerebral artery occlusion in rats, (79) and treatment resulted in reduced volumes (80). In addition, even brief seizures can lead to hemodynamic changes, such as increased cerebral blood flow (CBF) (81), which may lead to transient and potentially injurious elevations in ICP even in the absence of tonic-clonic activity (82, 83). Finally, seizures are associated with peri-injury depolarizations, a process related to cortical spreading depression and which seems to be very common and to contribute to secondary neuronal injury itself (84, 85).

2.7. How Long To Monitor

Several recent studies have address the duration of cEEG monitoring required to diagnose NCSz in critically ill patients. In their study of NICU patients, Pandian et al. (3) found that routine EEGs (30 min) detected seizures in only 11% of patients, while subsequent cEEG (mean duration of 2.9 days) detected seizures in 28%. In 110 critically ill patients with seizures detected by eEEG (92% of patients had purely nonconvulsive seizures), Claassen et al. (1) found that only half of patients had their first seizure within the first hour of monitoring. Although 95% of noncomatose patients had their first seizure within 24 h, only 80% of comatose patients had a seizure by this time (Fig. 2-9). After 48 h of monitoring, the first seizure had occurred in 98% of noncomatose versus 87% of comatose patients. Coma and the presence of PEDs predicted a delay in the time to first seizure (>24 h). Similarly, Jette et al. (33) found that 50% of 51 children with nonconvulsive seizures had their first seizure within 1 h, and 80% within 24 h. Therefore, we feel monitoring for 24 h is probably sufficient to rule out NCSz in noncomatose patients without PEDs, but longer periods may be required for comatose patients or those with epileptiform discharges.

2.8. Future Directions

In addition to detecting seizures, cEEG can be used to identify other changes in brain physiology. In recent years, there has been renewed interest in using cEEG for the detection of brain ischemia. It has been known for some time that EEG changes occur within seconds of reduction in CBF (86, 87), which is the basis for intraoperative EEG monitoring of ischemia during carotid
endarterectomy (88–90). In these patients, as CBF falls below 25–30 mL/100 g/min, there is a progressive loss of higher frequencies and prominent slowing of background EEG activity. When CBF falls below 8–10 mL/100 g/min, which is low enough to cause irreversible cell death, all EEG frequencies are suppressed (91, 92). Therefore, cEEG can detect a window where intervention can potentially prevent permanent brain injury.

Recent advances in computing have allowed for the real-time application of qEEG tools for extracting time–frequency data to measure changes in the background EEG rhythms. The ability to reduce EEG patterns usually identified by visual review to scalar values allows for prolonged use of cEEG monitoring in the ICU to detect cerebral hypoperfusion or other acute processes, especially in comatose or sedated patients where clinical examination is limited. In a study of 32 primarily good-grade SAH patients, Vespa et al. (19) found that a reduction in the variability of relative alpha frequency (a visual scoring of a tracing displaying 6–14 Hz expressed as a percentage of total power between 1–20 Hz) was 100% sensitive and 50% specific for vasospasm as detected by transcranial Doppler (TCD) or angiography. In the majority of patients, qEEG changes preceded the diagnosis of vasospasm by over 2 days. In a study of 34 poor-grade SAH patients (Hunt–Hess grade 4 and 5), Claassen et al. (93) found that the post-stimulation alpha/delta ratio was the most useful qEEG parameter for detection of delayed cerebral ischemia: a reduction in the post-stimulation ratio of alpha to delta frequency power of >10% relative to baseline in six consecutive epochs of cEEG was 100% sensitive and 76% specific for delayed cerebral ischemia. A reduction of >50% in a single epoch was 89% sensitive and 84% specific. However, these studies examined the use of qEEG for ischemia detection in a retrospective manner, and the performance of these tools in patient management has yet to be tested rigorously; this is largely due to the lack of practical software to detect these changes in

![Fig. 2-9. Summary plot of time to detect first seizure in 110 critically ill patients undergoing continuous EEG monitoring who had convulsive or nonconvulsive seizures (>90% were nonconvulsive). (Reproduced with permission from Claassen et al. 2004)]](image.png)
an automated fashion and alert ICU staff in a timely manner. In addition to ischemia, cEEG monitoring can be used to detect evolving intracranial hemorrhages or masses (94) and systemic metabolic changes.

Real-time application of cEEG monitoring – neurotelemetry – including using automated alarm systems at the bedside, as exists with cardiac telemetry in almost all hospitals today, is becoming an approachable goal. Reducing the raw cEEG to a few displayed variables using qEEG tools will make it a practical tool that can be interpreted by nurses and intensivists or by neurotelemetry technicians. In addition, trend and critical value alarms can be used to alert staff to changes in neurological status (23). Computer algorithms have been successfully used to detect ongoing seizures in patients in epilepsy monitoring units (95). Because seizure patterns in the critically ill are different from ambulatory patients, new algorithms must be designed to detect seizures in this patient population (23). Refining techniques to help identify patterns of interest is an area of active research (96, 97). Improvement is needed, as many qEEG and data reduction tools are not sufficiently specific (98) and are susceptible to contamination by artifacts (Fig. 2-5). While ICU staff can be easily trained to review raw cEEG traces for obvious artifacts and even pathological patterns (94), a neurophysiologist must still be available to verify the interpretation.

In parallel with these technical advancements, continued research is needed to confirm that real-time monitoring is a necessary goal. Further studies need to be performed in both laboratory models and in prospective clinical trials to examine whether identifying and treating NCSz early improves outcomes, though this is already known for ischemia and is likely to be the case for other acute brain processes such as elevated ICP. It is also necessary to determine the relationship of the different periodic and rhythmic EEG patterns in the critically ill to ongoing brain injury to identify targets for intervention (39). Studies are also needed to determine whether using cEEG to detect ischemia improves patient outcomes and to identify the time window for intervention after a change is detected by cEEG.

Continuous EEG monitoring is just one of the modalities available to evaluate brain physiology in the ICU. ICP monitoring using intraventricular catheters or intraparenchymal probes, brain tissue oxygenation monitors, CBF monitoring and brain metabolism monitoring using microdialysis probes (99), all provide critical data about brain physiology. The use of these methods in combination with cEEG may help further understanding of the complex relationships between CBF, tissue oxygenation, cerebral metabolism, and neuronal activity in the injured brain (Fig. 2-10). In addition, the combined use of these methods may be able to compensate for some of the shortcomings of the individual methods. For instance, microdialysis and tissue oxygenation probes sample only the immediate area of brain into which they are inserted and can miss new injury to a remote area of the brain that may be detected by cEEG because of the wide spatial coverage. Conversely, there are situations, such as barbiturate coma, where the relationship between EEG activity and tissue ischemia is limited and other methods may be necessary to detect new ischemic injury (90).

Finally, new research is examining the utility of electrophysiological monitoring beyond conventional scalp EEG. Recent studies in patients with severe trauma brain injury (TBI) using subdural electrodes found episodes of cortical spreading depression, i.e., slow and prolonged peri-injury depolarizations
lasting several minutes or longer, near injured brain (84). Similar types of cortical depolarizations have been observed in animal models of stroke where they are associated with infarct enlargement due to NMDA (N-methyl D-aspartate)-receptor-mediated injury (100). Recently, these events have also been demonstrated in patients with large middle cerebral artery strokes (101) and in patients with SAH (102), where they have been associated with delayed cerebral ischemia. Preliminary studies at our center (103) demonstrated that a small depth electrode inserted near injured cortex in severely brain injured patients was able to detect seizures and other epileptiform activity (Fig. 2-10) as well as changes in background activity from ischemia or hemorrhage that was not apparent on scalp EEG. It is possible that many focal seizures occurring across the cerebral cortex, but not synchronized sufficiently to generate scalp EEG changes, may contribute to impaired consciousness in some comatose patients without evidence of seizures on cEEG. Whether targeting these events for therapy improves patient outcomes needs to be determined. When possible, we use individualized, physiology-driven data (such as the lactate/pyruvate ratio and glutamate on microdialysis) to decide which EEG patterns require additional treatment and which do not.

2.9. Summary

Nonconvulsive seizures are common in brain injured patients with altered mental status and even in critically ill patients without structural brain injury. Seizures can contribute to depressed level of consciousness and cause secondary neuronal injury. Therefore, in our center, we recommend cEEG for all critically ill patients with acute brain injury and altered mental status and for patients with fluctuating or unexplained impaired mental status. Patients who are encephalopathic but not comatose are typically monitored for 24 h to exclude NCSz. However, patients who are comatose, who have PEDs, or who are having sedation/antiepileptic drugs withdrawn should undergo at least 48 h of cEEG. Once NCSz or equivocal periodic patterns are identified, monitoring can continue for several days. If NCSz are identified, cEEG is necessary to monitor the response to treatment and, more importantly, correlate improvement in the cEEG findings with improvement in the patient’s clinical status. If the cEEG demonstrates periodic activity that is suspicious for, but not definitively, seizure activity, further monitoring can help the neurophysiologist gather additional evidence for or against the ictal nature of the pattern (e.g., to see whether there are unequivocal seizures). This monitoring requires 24-h technician coverage to connect patients and perform maintenance; appropriate information technology infrastructure; neurophysiologists available to review the data; and tools to speed up data review. While this requires a substantial amount of resources, it is feasible.

Fig. 2-10. (continued) glutamate and lactate and decrease in pyruvate. The lactate/pyruvate ratio increased dramatically to greater than 700 (normal <30; >40 associated with neuronal injury) suggesting significantly increased brain metabolic stress. (b) Scalp (black traces) and miniature depth electrode (blue traces) recording prior to meperidine (open arrow) demonstrates diffuse attenuation and slowing over the scalp and at the depth electrode. (c) During the period after meperidine administration when lactate/pyruvate ratio peaked (closed arrow), the scalp EEG was obscured by artifact. However, depth electrode recordings demonstrated periodic discharges and rhythmic delta activity at some of the leads (red arrow)
Fig. 2-10. Multimodality monitoring in a 61-year-old with a Hunt–Hess grade 5 subarachnoid hemorrhage due to a ruptured right anterior communicating artery aneurysm, vasospasm, and coma. A “bundle” consisting of a microdialysis probe, brain tissue oximetry monitor, intracerebral pressure transducer, and an eight-contact miniature depth electrode was placed in the right frontal lobe at the bedside. Continuous EEG was recorded simultaneously. (a) Levels of major cerebral metabolites in the microdialysate over time including lactate (black line), pyruvate (blue line), glutamate (green line), and the lactate/pyruvate ratio (red line; note broken y-axis for clarity) as well as ICP (blue bars with area under the curve shaded gray). At approximately 1 a.m. on 6/26, the patient was given a bolus of meperidine for shivering, which was followed by a rapid increase in brain tissue
and cEEG is routinely employed in many neuroscience ICUs around the world. In addition, cEEG has applications outside of NCSz detection, which can expand the number of patients who may benefit from monitoring. Advances in the use of cEEG for ischemia detection and general brain function monitoring can make it a widely applicable tool for dynamic assessment of neurological function, in combination with other monitoring modalities, with the potential to detect brain injury moments after it occurs.

References

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