Reading Your Mind: Monitoring the Brain Under Anesthesia

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"Notwithstanding weaknesses of current devices, a window into the anesthetized brain, albeit a foggy one, may still be useful, in conjunction with information from other monitors, as a generic, all-purpose index of the brain’s response to powerfully sedating drugs." - Gregory Crosby

ELECTROENCEPHALOGRAPHY (EEG)

As early as 1937, Gibbs, Gibbs and Lennox proposed, “The anesthetist and surgeon could have before them on tape or screen a continuous record of the electric activity of both heart and brain.” Heuristically, this notion is compelling for several reasons. Although the brain is a primary target organ of general anesthesia, the field has not established a standard monitor for the brain. The EEG provides useful information during anesthesia, including surrogacy of unawareness. Today, EEG plug and play modules are available for most intraoperative monitors.

The EEG measures spontaneous electrical activity from neurons near the surface of the cortex. The EEG has excellent temporal resolution, but poor spatial resolution. The EEG montage refers to where the electrodes are placed. A standard EEG has 20 electrodes and 10 channels (10/20 system). With a bipolar montage, there are two electrodes per channel, with one of the two electrodes serving as a reference electrode in relation to the other. With a referential montage, there is a common reference electrode for all the channels. Electrodes are labeled according to their anatomical placement (e.g., frontal pole, frontal, central, parietal, temporal and occipital) and according to laterality (even numbers are right sided and odd numbers are left sided).

The EEG has a complex waveform that is typically far less organized and regular than the ECG waveform. The EEG waveform is made up of several waves, and can be broken down into the component waves through Fourier analysis. Typically all the component waves contribute to the overall waveform, but different waves predominate during different states (e.g., wakefulness, relaxation, REM sleep, non-REM sleep, sedation, general anesthesia, coma). The higher frequency waves (gamma [>30 Hz.] and beta [12-30 Hz.]) have relatively low amplitude and are arrhythmic. These waves are more prominent during wakefulness. With sleep, sedation and general anesthesia, the slower waves (alpha [8-12 Hz.], theta [4-8 Hz.] and delta [0-4 Hz.]) become more prominent. With deeper anesthesia and coma, burst suppression can occur (a suppressed EEG with sporadic burst of EEG activity). An introduction the EEG, including video clips, can be found on the website www.icetap.org (International Consortium for Electroencephalography Training of Anesthesia Practitioners).

Full montage EEG is generally not practical in the operating room. Anesthesia practitioners have typically used limited frontal montages (on the forehead) with one or two channels (e.g., FP1 to F7 and FP2 to F2). Despite the limitations of single area EEG monitoring, frontal montages are useful for anesthesia practitioners in that they display beta waves prominently during wakefulness, and delta waves prominently during general anesthesia (and sleep). An EEG pattern showing an underlying delta rhythm with spindles of concurrent waves at 7-14 Hz. might be reflective of hyperpolarization of the cortex and thalamus, which implies that the cortex could be disconnected from the environment (i.e., external sensory signals are blocked) and noxious stimuli might not be transmitted centrally. Recent research has shown that with relatively brief, structured training, anesthesiologists can learn to recognize important EEG patterns that occur during wakefulness and anesthesia.

PROCESSED ELECTROENCEPHALOGRAPHY AND AWARENESS

A practitioner cannot spend all her time scrutinizing a complex EEG trace and most anesthesia practitioners have not received formal instruction in EEG interpretation. The introduction of processed EEG devices that displayed a scaled index from 100 to 0 to reflect anesthetic depth was therefore appealing and enjoyed widespread and perhaps uncritical adoption among practitioners. With limited evidence of clinical utility, processed EEG devices garnered FDA approval, which legitimized their use in clinical practice.

A penetrating question that many asked was whether the use of processed EEG devices during general anesthesia would prevent unintended intraoperative awareness. An important observational study suggested that routine processed EEG monitoring might be associated with a dramatic 82% reduction in awareness, but, as an observational cohort study, the results had to be interpreted with caution. The B-Aware investigators argued that in order to adopt processed EEG devices in routine anesthesia practice, convincing proof of efficacy was necessary. They suggested that short of yielding a 0.9% reduction (minimum clinically important effect) in awareness in high-risk (for awareness) patients, such devices could not be recommended for routine use. The B-Aware trial randomized 2,500 patients to a protocol based on a currently used processed EEG monitoring
or to routine clinical practice.\textsuperscript{7} The processed EEG protocol was associated with a 0.74\% (95\% CI, 0.14\% to 1.4\%) reduction in awareness.\textsuperscript{7} Thus the B-Aware trial did not demonstrate a reduction commensurate with the pre-specified minimum clinically important effect. Furthermore, it was difficult to know whether the reduction in awareness was attributable to the monitor or to a protocol that increased clinical vigilance in the experimental group. Finally, about half the patients in the B-Aware trial received total intravenous anesthesia, which is associated with a higher risk for intraoperative awareness.

The B-Unaware and the BAG-RECALL clinical trials enlarged on the results of previous studies. The single center 2,000 patient B-Unaware trial tested a protocol based on a currently used processed EEG device against a protocol based on end tidal anesthetic concentration (ETAC).\textsuperscript{8} There was no difference in the incidence of definite awareness between the protocols (0\%; 95\% CI, -0.56\% to 0.57\%). Similar to the B-Aware trial, the B-Unaware trial was imprecise (i.e., had wide confidence intervals around the point estimate), which meant that it could rule out potentially clinically relevant benefit (in terms of awareness) of either protocol. However, the results of the B-Unaware trial did suggest that compared with a protocol based on ETAC, a protocol based on processed EEG would not decrease awareness by the minimum clinically important effect pre-specified by the B-Aware investigators. Interestingly, the B-Unaware trial was heavily criticized for its imprecision, whereas the B-Aware trial, which was similarly imprecise, did not face similar censure. This is probably because the B-Unaware trial was a “negative” trial, while the B-Aware trial was a “positive” study. In the B-Unaware trial fewer patients had possible awareness in the ETAC group than in the processed EEG group.

The 6,000 patient, multi-center BAG-RECALL trial was methodologically similar to the B-Unaware trial.\textsuperscript{9} This follow-up study showed convincingly that for patients at high risk for awareness, a protocol based on a currently used processed EEG device was not superior to a protocol based on ETAC.\textsuperscript{10} Interestingly, and contrary to the hypothesis of the trial, there was a higher incidence of definite awareness, possible awareness and traumatic awareness among patients who were randomized to the processed EEG group.\textsuperscript{10}

To help complete the picture somewhat, a recent multi-center study from China showed that for patients receiving total intravenous anesthesia, a protocol based on processed EEG was associated with a dramatic decrease in the incidence of awareness.\textsuperscript{11} However, similar to the B-Aware trial, it is unclear how much of the benefit in this trial was attributable to the monitor, and how much to a protocol designed to increased clinical vigilance. Taking all the studies together, it is likely that a protocol based on processed EEG is effective in reducing awareness, especially compared with routine care and in patients receiving total intravenous anesthesia. On the other hand, a processed EEG based protocol is not superior to a protocol based on ETAC in preventing intraoperative awareness.

**LIMITATIONS OF EEG AND PROCESSED EEG**

There are several possible explanations for the lack of an advantage of a processed EEG based protocol over an ETAC based protocol. Conceptually, it is not clear that anesthesia deepens smoothly or linearly, in which case “depth of anesthesia” might be a problematic concept. In a recent study, Whitlock and colleagues showed that the processed EEG index does not always change predictably with changes in ETAC.\textsuperscript{12} This could mean that titrating volatile anesthetic administration according to currently used processed EEG indices might be inappropriate. Other potential reasons why a protocol based on currently available processed EEG devices might be imperfect in preventing awareness include:

- Current devices are not designed based on neurobiological principles of anesthesia or unconsciousness.\textsuperscript{13}
- Awareness can occur when processed EEG indices suggest that patients are unaware.\textsuperscript{8-10}
- There is lack of intra-patient reproducibility in currently used processed EEG indices, which brings into question their reliability.\textsuperscript{14}
- There is lack of inter-patient reproducibility in currently used processed EEG indices, which also brings into question their reliability. For example young people and older people can have shifts in levels of consciousness at very different values of the processed EEG indices.\textsuperscript{15}
- Ketamine and NMDA antagonists (e.g., nitrous oxide) do not produce the typical EEG changes that are seen during general anesthesia.
- As single or dual channel devices, limited montage EEG and currently available processed EEG monitors are unable to assess relational assessments among brain regions (e.g., by transfer entropy).
- State transitions occur rapidly; however, currently used processed EEG devices have a median delay of about 1 minute before they reflect state shifts (e.g., unaware to wakeful).\textsuperscript{16}
- Currently available monitors are not specific for anesthesia (e.g., they cannot distinguish general anesthesia from sleep). As such they cannot predict whether a patient will respond to a particular stimulus.
- Electromyography and other artifacts contaminate the EEG trace and might confound clinical interpretation.

**IMPROVING OTHER OUTCOMES WITH PROCESSED EEG MONITORING**

“An ETAC protocol may inadvertently result in overdosing of the brain in cognitively vulnerable persons. This is worrisome because deep sedation is associated with a higher incidence of postoperative delirium, other adverse cognitive outcomes, and increased mortality in elderly surgical and critically ill patients.” - Gregory Crosby.\textsuperscript{1}
It has been suggested that use of a processed EEG index to guide anesthetic administration decreases anesthetic administration and improves patient outcomes, compared with an ETAC guided approach. There are three assumptions underpinning this perspective. First, that an ETAC protocol results in increased anesthetic administration in real world clinical practice. Second, than an ETAC protocol results in worse patient outcomes in real world clinical practice. Third, an increased anesthetic dose within a clinically relevant range results in worse patient outcomes. Recent evidence from large clinical trials does not support any of these three assumptions. In the B-Aware, B-Unaware and BAG-RECALL trials, there was no real difference in anesthetic administration when a processed EEG guided practice. This is unsurprising considering the recent study by Whitlock et al., which showed that, during anesthetic maintenance, a processed EEG index is frequently invariant over a clinically relevant range of volatile anesthetic concentrations.12 Other investigators have demonstrated this invariance for both volatile anesthetic agents and for propofol.17-19 Large clinical trials have also not demonstrated clinically relevant outcomes benefits with processed EEG based protocols.7,8,10,20-22 Although one study did show that patients who received general anesthesia had a higher delirium incidence than patients who were sedated,23 two targeted studies have not shown that a processed EEG monitor decreases postoperative (early) cognitive decline following general anesthesia.24,25 There is no compelling evidence that a slight increase in anesthetic dose (e.g., 0.9 MAC rather than 0.6 MAC) during a singly anesthetic worsens patient’s outcomes. Data from the B-Unaware trial suggests that patients who received higher anesthetic concentrations did not have worse postoperative complications or outcomes.20,21

GOING FORWARD WITH EEG MONITORING

Clearly there is a long way to go with brain monitoring in the operating room and in the intensive care unit. But EEG has become much more popular among anesthesia practitioners in recent years and might become a standard monitor in future. All anesthesia practitioners should seek to increase their knowledge of EEG, and should exploit existing educational resources, such as www.icetap.org. It is important that future candidate depth of anesthesia monitors should be conceived according to neurobiological principles and theories of anesthetic-induced unconsciousness. The algorithms defining the monitors should be open source, allowing clinician scientists to evaluate and improve them. Many of the limitations of current devices (e.g., significant delays in response to state changes) can easily be addressed in the new generation of brain monitors.

REFERENCES:


