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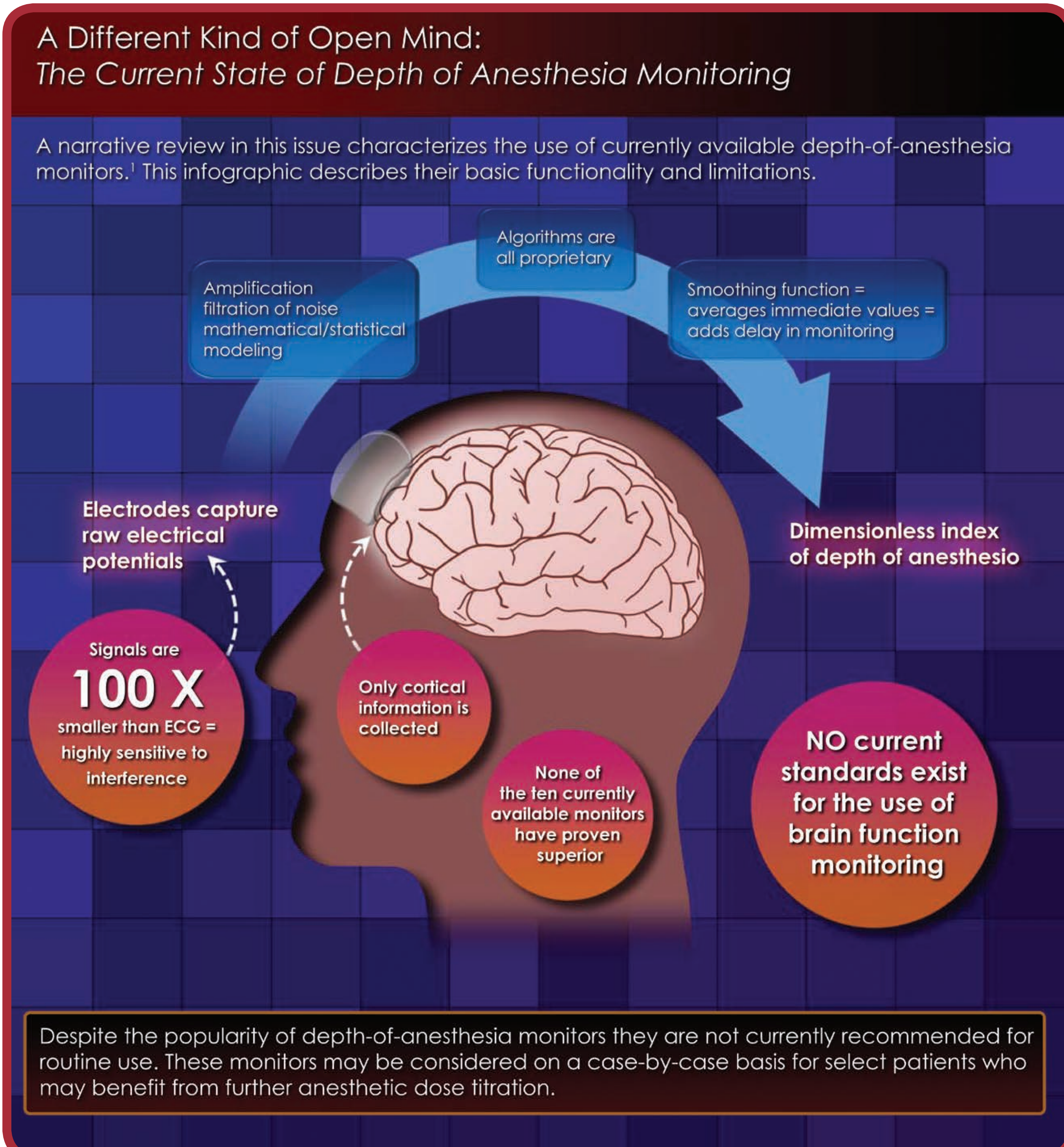

A narrative review in this issue brings us up to date on our current understanding and usage of processed electroencephalography monitors during anesthesia. Ten commercially available products exist that convert cortical, electrical signals into a dimensionless index as a gauge of anesthetic depth. Limitations of these monitors include (1) exclusively proprietary algorithms specific to each device, rendering comparisons between devices inherently difficult, (2) confinement to frontal lobe activity and lack of penetration into deeper, subcortical structures, and (3) sensitivity to a variety of sources of interference during monitoring. An American Society of Anesthesiologists practice advisory recommends against the routine use of these monitors, instead favoring their utilization for patients that may benefit from reduced anesthetic doses (eg, geriatric patients at risk for postoperative cognitive dysfunction).

The Infographic is composed by Naveen Nathan, MD, Northwestern University Feinberg School of Medicine (n-nathan@northwestern.edu). Illustration by Naveen Nathan, MD.

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REFERENCE

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IARS International Anesthesia Research Society

CME

The Technology of Processed Electroencephalogram Monitoring Devices for Assessment of Depth of Anesthesia

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Commercial brain function monitors for depth of anesthesia have been available for more than 2 decades; there are currently more than 10 devices on the market. Advances in this field are evidenced by updated versions of existing monitors, development of new monitors, and increasing research unveiling the mechanisms of anesthesia on the brain. Electroencephalography signal processing forms an integral part of the technology supporting the brain function monitors for derivation of a depth-of-anesthesia index. This article aims to provide a better understanding of the technology and functionality behind these monitors. This review will highlight the general design principles of these devices and the crucial stages in electroencephalography signal processing and classification, with a focus on the key mathematical techniques used in algorithm development for final derivation of the index representing anesthetic state. We will briefly discuss the advantages and limitations of this technology in the clinical setting as a tool in our repertoire used for optimizing individualized patient care. Also included is a table describing 10 available commercial depth-of-anesthesia monitors. (Anesth Analg 2018;126:111–7)

Brain function monitors for assessing depth of anesthesia or hypnosis have been commercially available since the 1990s. Promoted to measure anesthetic effects on the brain, the purpose of these devices is to improve anesthetic titration to provide adequate anesthetic depth for each patient. Clinical application would hopefully translate by providing appropriate depth during administration of general anesthesia to avoid the consequences of insufficient anesthetic depth (eg, intraoperative awareness) or excessive anesthetic depth (eg, delayed emergence, postoperative delirium, and cognitive issues). Currently, no standards exist for intraoperative brain monitoring of anesthetic effects with full-montage electroencephalogram (EEG), the most widely accepted modality for cerebral function monitoring, including for the anesthetic effects on brain function.[1] Interpretation of a full-montage EEG during anesthesia requires additional specialized training, which not all anesthesia providers have. All depth-of-anesthesia monitors utilize processed EEG (pEEG) signals to derive numerical indices representing the depth of anesthesia. Initially, the simple application of this noninvasive technology and the potential benefit to prevent intraoperative awareness led to rapid clinical adoption. Further research revealed important limitations of this technology; so, the need continues for an effective brain function monitor to guide anesthetic titration for optimal clinical care and improved patient outcomes. The purpose of this article is to review the technology behind the commercially available depth-of-anesthesia monitors, briefly summarize their advantages and limitations in the clinical setting, and assess the current barriers and opportunities for improvement toward a gold standard in state-of-anesthesia brain monitoring.

PRINCIPLES OF EEG MONITORING

The EEG represents the net summation of postsynaptic cortical neuronal potentials. To be registered by the sensors, the total current generated must penetrate several tissue layers and the monitoring electrodes. The signals received at the skin surface are approximately 100 times smaller than electrocardiographic signals and, as a result, are very sensitive to electrical interference and artifacts.[2] The close proximity of the sensor to the rostral structures of the brain allows it to detect the EEG signals correlated with neural functions of the cerebral cortex, which relate to wakefulness, awareness, and memory. An EEG recording comprises various waveforms with different characteristics containing a large amount of information for interpretation. Advantages of the EEG as a monitor are that changes can be captured milliseconds after occurrence, and that it has a capacity to reflect both normal and aberrant aggregated electrical activity of different brain regions.

Anesthesia and other processes that inhibit higher cortical function decrease overall neuronal firing, slowing the waveforms and increasing its synchrony. Although the mechanism of anesthesia in the brain is unclear, progressive anesthetic depth is associated with both behavioral phenomena and characteristic EEG changes. The observed behavioral and EEG correlation with anesthetic depth are generally consistent and reproducible, and they provide the basis for EEG-based depth-of-anesthesia monitoring.

Currently available depth-of-anesthesia monitoring devices measure limited EEG activity from forehead electrodes and then process and analyze these signals with highly complex mathematical methods; the most promising correlating parameters are then compared with empirical data (a database of EEG and

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behavioral correlates mostly obtained from healthy patients) and tested clinically using various iterations that incorporate learned information in developing a depth-of-anesthesia monitor (Figure 1A). The complete algorithms for many monitors are proprietary. Advances in complex mathematical tools, coupled with improved computing power and speed, now allow for real-time processing of raw EEG signals.

EEG SIGNAL PROCESSING

The analog EEG signals received from the forehead surface electrodes are amplified and then filtered to remove noise and interference. Common interference includes electrical (eg, power line and electrocardiogram) and muscle activity (eg, eye and scalp movements). Forehead electromyograms (EMGs) contribute to the algorithm and are often isolated for separate display as another depth-of-anesthesia indicator.

During processing, EEG data are divided into time periods, or epochs. For digital conversion, the continuous analog signals are sampled at regular intervals and converted into discrete data points. Converting from a continuous signal to a series of discrete signals causes a loss of fidelity. To extract the desired from the undesired EEG signals, the data pass through additional filtering steps before undergoing mathematical processing. After artifact removal, the epoch is either salvaged, via approximation of missing data, or discarded if it is highly contaminated (Figure 1B).[1,3,4]

EEG ANALYSIS APPROACHES

Mathematical and statistical modeling is applied to the digitized raw EEG data to derive a depth-of-anesthesia measurement (Figure 2). This analysis involves EEG feature extraction and categorization into a final dimensionless index.

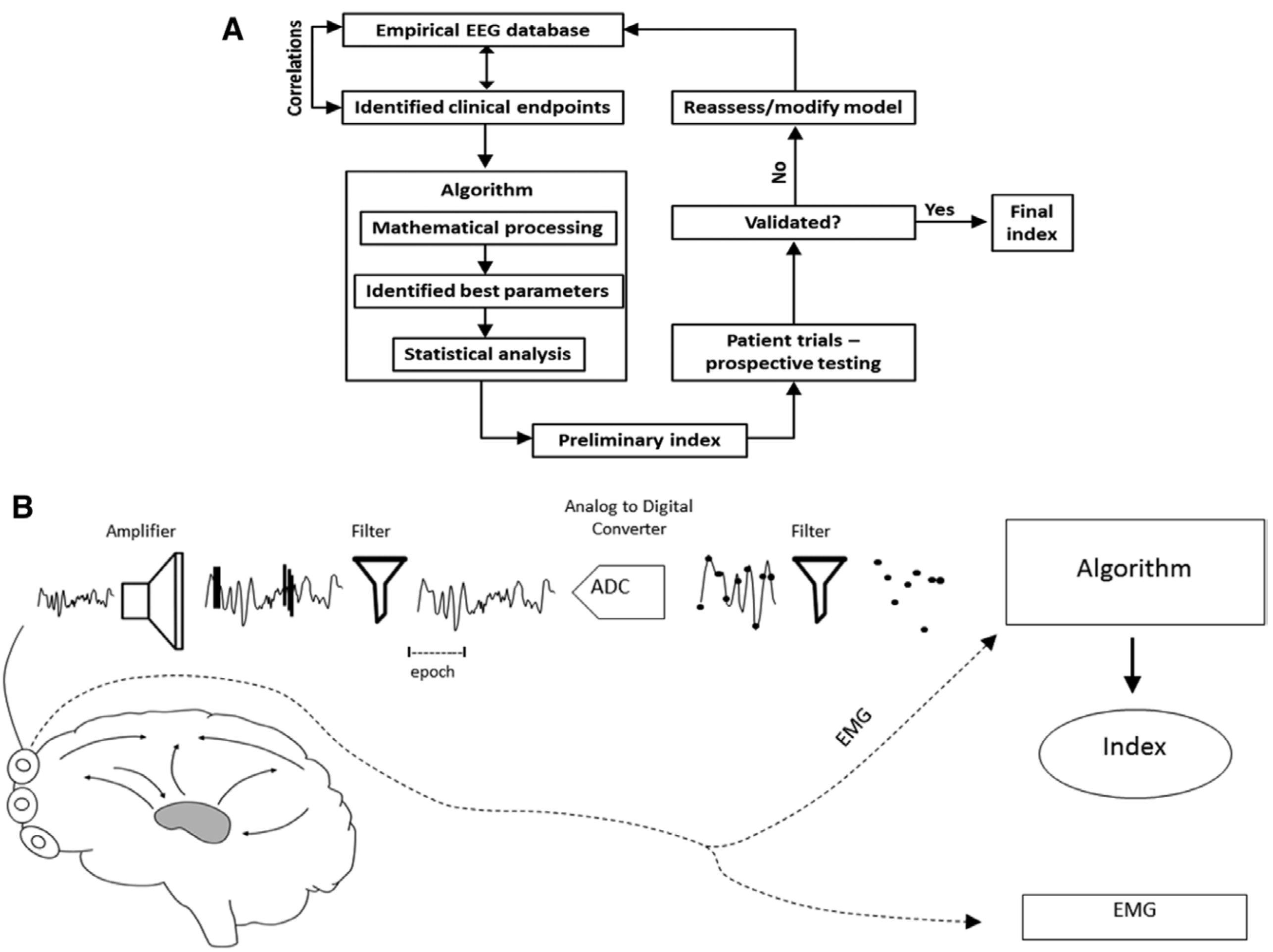

Figure 1. A, The conceptual design of current depth-of-anesthesia monitors. The basis for EEG-based depth-of-anesthesia monitoring is the behavioral correlates and EEG changes occurring with increasing anesthetic depth. The EEG signals and related behavioral response with increasing levels of anesthesia from healthy patients are collected to form a database for reference. Relevant clinical endpoints are identified (eg, loss of consciousness, loss of response to increasing levels of stimuli, return to wakefulness, etc). This database is analyzed; the most promising correlating parameters are extracted and categorized via highly complex mathematical methods for a preliminary depth-of-anesthesia index. This algorithm is then tested in clinical trials in which the performance of the index is scrutinized. If not satisfactory, changes are made where necessary, and the process is repeated until the algorithm is deemed validated. The complete algorithms for many monitors are proprietary. B, EEG signal processing involves the sensing and recording of raw EEG signals and the amplification and initial filtering of extraneous noise. The analog signals are then divided into epochs (time intervals) and converted to digital data. Note the loss of fidelity after the conversion. The data are further filtered for the desired signals before complex mathematical manipulation. The algorithm in each depth-of-anesthesia monitor will extract the relevant EEG features or parameters and will determine the final depth-of-anesthesia index based on statistical analysis and classification of those parameters. EMG data are often incorporated into the algorithms (most algorithms are proprietary). In addition, many monitors display EMG data separately from the depth-of-anesthesia index. EEG indicates electroencephalogram; EMG, electromyogram.

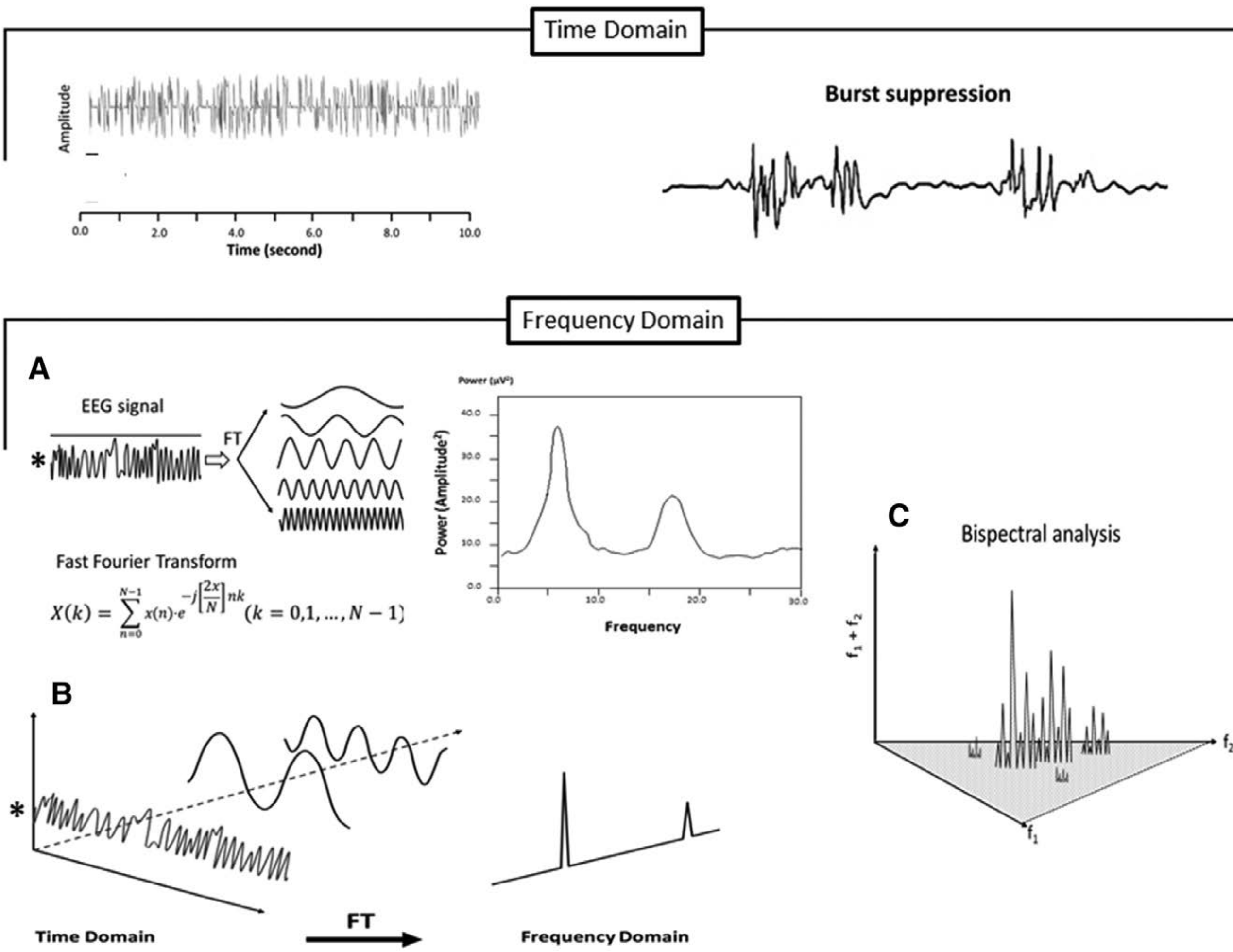

Figure 2. Examples of mathematical approaches used in depth-of-anesthesia algorithms for extraction of relevant EEG features for derivation of a final index. Time domain analysis (EEG signal analysis as a function of time) and frequency domain analysis (EEG signal analysis as a function of frequency) are illustrated. One of the most important time domain techniques in depth-of-anesthesia algorithm development is burst suppression, an EEG pattern associated with deep levels of anesthesia and pathology (eg, hypoxia). In frequency domain analysis, the FT is an important mathematical technique that converts time domain signals into the frequency domain. An analogy is a white light (raw EEG signals marked with an asterisk in A) passing through a prism (FT) and decomposing into a spectrum of separate colors (spectrum of frequencies) with different intensities (amplitudes). The fast FT (equation shown) is a manipulation of the FT to improve computational efficiency. B, The same raw EEG signals (marked with an asterisk) deconstructing into frequencies with specific amplitudes that are displayed in the frequency domain (power or amplitude squared versus frequency). Note that the deconstructed frequencies do not all start in synchrony with each other relative from the origin (phase). C depicts bispectral analysis, which quantifies the relationship between component EEG frequencies. The graph illustrates the values for bispectrum and bicoherence relationships at 2 primary frequencies ($f1$ and $f2$) along with their frequency sum ($f1 + f2$). The bispectrum is the product of the FT of each $f1$, $f2$, and $f1 + f2$. The bicoherence measures the degree of phase coupling of $f1$, $f2$ and $f1 + f2$. High values (peaks in the diagram) could imply that those component frequencies are correlated, maybe originating from the same neural pacemaker. EEG indicates electroencephalogram; FT, Fourier transform.

The following methods highlight the most common approaches applied by algorithms for the extraction of relevant EEG features.

Time Domain Analysis Methods

Time domain analysis examines EEG signals as a function of time. Characteristics of EEG morphology, associated randomness, and lack of precise predictability represent examples of important factors in algorithm development.

The algorithms used by the depth-of-anesthesia monitors often incorporate 1 or more time domain-based analytical approaches; examples include zero-order frequency, aperiodic analysis, wavelet analysis, rhythmicity autocorrelates, autoregressive models, and symbolic analysis, of which a detailed review is outside the scope of this article.[3,5,6]

Specifically, burst suppression rate is a very important time domain parameter used to quantify the time proportion spent in burst suppression; when seen on EEG during anesthesia, it indicates reduced cerebral activity and can represent deep anesthetic level or pathology (eg, ischemia).

Frequency Domain Analysis Methods

The analysis of complex biosignals is greatly enhanced by frequency domain analysis, which analyzes signals as a function of frequency with the following important techniques.

Fourier Transform. The fundamental mathematical basis for EEG signal processing is Fourier transformation, which deconstructs the original time domain waveforms into a series of individual sinusoidal waves of different frequencies (cycles per second, Hertz), amplitudes, and phase (shift relative from origin or synchrony). An analogy is that of white light passing through a prism and decomposing into a spectrum of separate colors (spectrum of frequencies) with different intensities (amplitudes). A power spectrum is generated when the amplitude of the signals in the frequency spectrum is squared for mathematical analysis. The fast Fourier transform significantly improves computing efficiency from the original Fourier transform, allowing digital spectral results in real time, including visual modalities such a compressed spectral arrays, density spectral arrays, and spectral edge frequency.[3]

Bispectral Analysis. Bispectral analysis, a higher-order mathematical manipulation, is used to gain additional useful information from the EEG power spectrum. The bispectrum quantifies the relationship between component EEG frequencies. The Fourier transform of waves at 2 primary frequencies (*f*1 and *f*2), along with their frequency sum (*f*1 + *f*2), forming a triplet (*f*1, *f*2, *f*1 + *f*2), are multiplied and the bispectrum magnitude is calculated. Additionally, the degree of phase coupling in that triplet (*f*1, *f*2, *f*1 + *f*2), called the bicoherence or bispectral coherence, is also quantified through further calculations. Although the physiologic significance of bispectral and bicoherence values is uncertain, high values would imply that those component frequencies are correlated, maybe originating from the same neural pacemaker. Also, bispectral analysis is useful to suppress certain sources of noise, thus improving the signal to noise ratio.[3]

Entropy

Entropy measures the randomness or irregularity of the signals. Increasing anesthesia depth correlates with decreased randomness, with the EEG signals displaying more regularity, implying more stability and predictability of the system. Entropy analysis can be performed in time or frequency domains (spectral entropy), and can also detect nonlinear signal correlations. Mathematical manipulations involving Fourier transform of the EEG signals produce a range from maximum irregularity to complete regularity, while operating in parallel with the time variable.[4,7]

Evoked Potentials

Auditory-evoked potentials (AEPs) measure time-locked EEG responses to repetitive auditory clicks, testing the neural pathways carrying information from the periphery to the cerebral cortex. The typical AEP response to increasing anesthetic concentrations is increased signal latency and decreased amplitude. The brainstem is relatively less sensitive to anesthetics, whereas the middle-latency AEPs or early cortical responses change predictably, with increasing concentrations of both volatile and intravenous anesthetics. The corresponding middle-latency AEP signals are discriminated from background EEG for index calculation[8] (Figure 3). Combining AEPs with complex EEG processing techniques may improve the predictability of anesthetic effects on the brain.[8]

The Table shows examples of available monitors. For each monitor, the extracted EEG parameters are chosen by their ability to correlate to different stages of anesthesia (eg, burst suppression rate correlates with deep anesthetic level, while EMG activity correlates to light anesthetic level). During depth-of-anesthesia monitoring, those parameters undergo classification analysis that determines the extent of contribution from each toward the index value at that time point. Examples of classification analysis techniques include weighted sum, plausibility analysis, fuzzy logic inference systems, and neural network classifier systems. Each approach has advantages, disadvantages, and accuracy rates for discrimination of anesthetic depth levels. A detailed review is outside the scope of this article. Finally, most algorithms include a smoothing function to decrease rapid fluctuations in the displayed index; this is done by averaging the new index with immediate past values, adding a delay in reflection of the clinical state.[5,6]

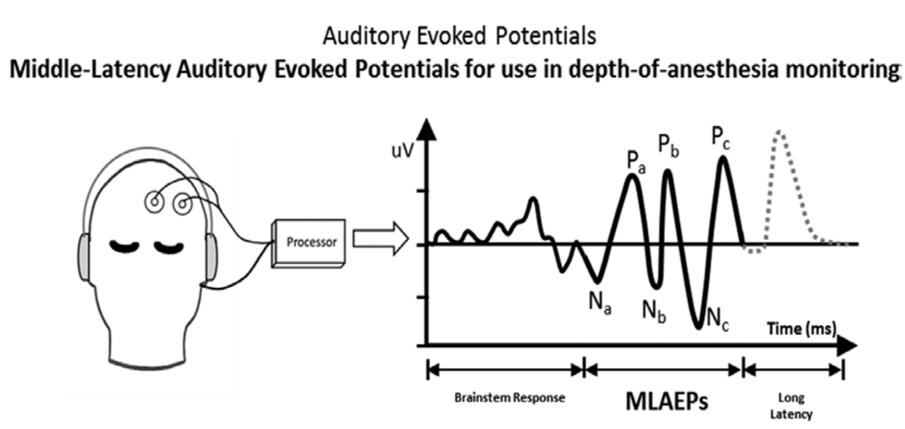

Figure 3. AEPs measure time-locked EEG responses to repetitive auditory clicks, testing the neural pathways carrying information from the periphery to the cerebral cortex. The typical AEP response to increasing anesthetic concentrations is increased latency and decreased amplitude of the signals. The brainstem is relatively less sensitive to anesthetics, whereas the MLAEPs or early cortical responses change predictably with increasing concentrations of both volatile and intravenous anesthetics, therefore the MLAEP waves are the portion of the AEPs specifically used for depth-of-anesthesia assessment. The MLAEP signals are detected and discriminated from background EEG signals, analyzed, and classified via the algorithm of the monitor for derivation of depth-of-anesthesia index. AEP indicates auditory-evoked potentials; EEG, electroencephalogram; MLAEP, middle-latency AEPs.

Table. Brief Description of Currently Available Processed EEG-Based Monitors in Alphabetical Order

Monitor	Features
AEP Monitor/2 (Danmeter A/S, Odense, Denmark)	The AEP index, the AAI, is an index relying on MLAEP and EEG signals. Bilateral click stimuli are delivered through headphones. The EEG signals after the stimuli are discerned from the background EEG noise and processed for MLAEPs, reflecting neural activity within the thalamus and primary auditory cortex. When the AEP signals are low in quality, the AAI is derived mainly from EEG-based spectral parameters. Burst suppression ratio and EMG data are also displayed. Two index scales: 0–60 and 0–100.[9]
BIS Monitor (Medtronic, Minneapolis, MN)	It utilizes an algorithm based on power spectral analysis, bispectral analysis, and burst suppression data. The derivation of the BIS index is achieved through a weighted sum of relevant subparameters. The BIS index scale is from 0 to 100. In addition to a single-channel EEG, it also offers a bilateral sensor for assessment of asymmetry. Density spectral arrays and spectral edge frequencies can be displayed as well as EMG activity and burst suppression information.[3]
Cerebral State Monitor (Danmeter A/S, Odense, Denmark)	The algorithm for the cerebral state index utilizes frequency domain analysis and burst suppression ratio processed with fuzzy logic methodology for inference of the index. It uses a single-channel EEG with an index scale of 0 to 100. In addition to the index, it also provides measures of burst suppression percentage and EMG activity.[10]
Entropy Module (GE Health care Technologies, Helsinki, Finland)	The algorithm uses spectral analysis to produce 2 main parameters for overall assessment of depth of anesthesia: the SE, for depth of hypnosis (index scale, 0–100), and RE, for indirect assessment of noniception/responsiveness to stimuli (derived from the frontal EMG; index scale, 0–91). A widening difference between SE and RE is deemed a likely indicator of inadequate anesthesia. In addition to the waveform display of SE and RE, a burst suppression ratio is also displayed. It uses a single-channel EEG.[7]
Index of consciousness monitor (Morpheus Medical, Barcelona, Spain)	The index of consciousness is derived via symbolic dynamics, a time domain method that divides the EEG signals into partitions and labels each partition with symbols of 1 and 0, depending on mathematical determination. It is conceptually similar to entropy. This approach can detect nonlinear EEG characteristics and assess levels of signal complexity. The algorithm also includes frequency domain methods and burst suppression analysis. A fuzzy logic inference system is used in index derivation. Burst suppression and EMG information are also displayed. Single-channel EEG with an index scale of 0 to 99.[11]
Narcotrend Monitor (MonitorTechnik, Bad Bramstedt, Germany)	The Narcotrend index is derived from a system developed for the visual classification of the EEG patterns associated with stages of natural sleep. It uses burst suppression, time, and frequency domain analysis to extract the relevant EEG parameters, which are then classified through plausibility testing into a total of 14 possible substages: A (awake) to F (deep) with further subdivisions. The most recent version also provides an index from 0 to 100. Uses 1- or 2-channel EEG. Also displays EMG information.[12]
NeuroSENSE Monitor (NeuroWave Systems Inc, Cleveland Heights, OH)	The WAVcns index is calculated via wavelet analysis of the EEG signals in the gamma frequency band, using a deterministic approach (a method that always produces the same output for a given EEG interval). This monitor was purposefully developed for use in anesthesia closed-loop delivery systems. It uses bilateral brain monitoring for derivation of index with a scale of 1 to 100.[13]
SEDline Monitor (Masimo, Irvine, CA)	The patient state index is calculated by a 4-channel EEG with an algorithm incorporating high heterogeneity of variance at different levels of sedation/hypnosis, taking into account anterior–posterior relationships in the brain and coherence between bilateral brain regions. Burst suppression data and plausibility analysis are applied for final index derivation. It also displays bilateral density spectral arrays, and bilateral 4 channels of raw EEG waveforms. Scale consists of 0–100, with optimal depth between 25 and 50 (in contrast to other monitors with similar scale and recommended anesthetic depth between 40 and 60).[14]
SNAPII Monitor (Stryker, Inc, Kalamazoo, MI)	The SNAP index is based on calculations involving power spectral analysis in the 0 to 18 and 80 to 420 Hz frequency ranges, called the low-frequency index and high-frequency index, respectively, for the derivation of the single index. It claims an algorithm that minimizes artifacts and a shorter lag time to detect patient awakening. It uses a single-channel EEG and an index scale of 0 to 99.[15]
qCON 2000 monitor (Quantium Medical, Barcelona, Spain)	The qCON index is derived from spectral analysis and burst suppression rate and processed through an artificial neural network and fuzzy logic system. Conceptually, it has similarities to the entropy approach. The qCON index is a measure of hypnosis, whereas the qNOX index is a measure of noniception, each similarly derived through different frequencies. Both indexes range from 0 to 99. The qNOX reference scale was derived through EEG signals in patients moving in response to nailbed pressure. Single-channel EEG. Also displays EMG and burst suppression data.[16]

This list is not intended to be all inclusive.

Abbreviations: AEP, auditory-evoked potential; EEG, electroencephalogram; EMG, electromyogram; MLAEP, middle-latency AEP; RE, response entropy; SE, state entropy.

ADVANTAGES AND INDICATIONS FOR pEEG MONITORS

Research suggests that depth-of-anesthesia monitors may reduce intraoperative awareness and may predict anesthesia outcomes in specific high-risk populations. At present, no monitor has been proven superior, and the current American Society of Anesthesiologists practice advisory on brain function monitoring says it "is not routinely indicated for patients undergoing general anesthesia, either to reduce the frequency of intraoperative awareness or to monitor depth of anesthesia … that the decision to use a brain function monitor should be made on a case-by-case basis by the individual practitioner for selected patients …"[17] These recommendations are also shared by other professional international organizations.[18,19] Depth-of-anesthesia monitoring has been recommended for those undergoing total intravenous anesthesia and neuromuscular-blocking agents for intraoperative awareness reduction.[19] It is also recommended for the elderly patient to minimize postoperative delirium[20,21] by avoiding deep anesthesia levels that may lead to unnecessary burst suppression, and recently received a grade A recommendation by the European Society of Anaesthesiologists.[21]

CHALLENGES OF pEEG MONITORS

The utilization of pEEG for brain monitoring has known limitations. Many factors can modulate the raw EEG signals during an anesthetic-induced altered state of consciousness, affecting the reliability of the EEG signals as indicators of anesthesia state. Some patient-dependent variables include age and pathophysiologic states (eg, hypothermia, hypoglycemia, acid-base abnormalities, previous brain pathology, brain ischemia, and seizures). Another challenge involves ketamine, nitrous oxide, and xenon not producing the typical EEG patterns seen during general anesthesia and with other agents (eg, opioids), although not significantly changing the pEEG index may significantly impact the anesthetic state of the patient. Other limitations include undetected artifacts and time lag for the index to display after changes in anesthesia affecting index reliability.

The most significant limitation resides in the neurophysiological basis of the effects of anesthesia and the associated end points of interest: unconsciousness/unawareness/amnesia, analgesia, and immobility. The EEG is deemed limited for spatial resolution and assessment of regional connectedness of brain processes. Currently, there is no unified standard to EEG features during anesthesia that correspond to all patients and anesthetic agents, hence the multiple unique algorithms. Although the correlation is positive, the EEG alone at this time seems improbable to provide all information needed to reliably and accurately assess unawareness and other anesthetic end points. Until the neurobiological principles of those end points are better understood, the devices can only indirectly infer the state of anesthesia through the EEG and surrogate parameters such as EMG. In addition, the definitions of unconsciousness and awareness need standardization across researchers and the published literature. Recent research in the biology of consciousness and anesthetic effects are yielding promising results for better understanding and development of a monitor.[22–24]

In conclusion, all current depth-of-anesthesia monitors rely on raw EEG signals for derivation of their indices. The technology behind these monitors is based on high-order mathematical analysis, using complex algorithms for processing the raw EEG signals enabled by gains in computing speed and power. As the understanding of the mechanisms of anesthesia on consciousness and related end points improves, a monitor that directly measures those neurobiological pathways can provide customized delivery of anesthesia for each patient with the goal of improving outcomes.

DISCLOSURES

Name: Brenda G. Fahy, MD, MCCM.
Contribution: This author helped write the manuscript.
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Contribution: This author helped write the manuscript.
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