Mini Review

Frontiers in Anesthesia: Old Acquaintances and New Perspectives in Brain Monitoring of General Anesthesia

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Abstract

Until a few years ago to determine the depth of anesthesia, the anesthetists exploited only a series of physical signs of the patient. In 1994, Sigland Chamoun described a novel measure of the level of consciousness during general anesthesia: the Bispectral (BIS) analysis. It was the beginning of a revolution in anesthesia monitoring, indeed during the last 15-20 years a number of EEG-based technologies have become commercially available. Unfortunately, none of these technologies has definitively solved the problem of the anesthesia awareness, thus assessment of depth of anesthesia is still a serious problem. Through these considerations this work focuses on new perspectives in brain monitoring.

Introduction

A bit of history

Despite significant steps have been taken by neuroscience and the knowledge of pharmacodynamics have been fine-tuned [1], we do not have a comprehensive view of what happens to the brain during General Anesthesia (GA). Thus, in 2005, Science considered understanding anesthetic mechanisms to be one of the important unsolved mysteries of modern medicine [2]. As a consequence, there has always been great uncertainty in Depth of Anesthesia (DOA) monitoring. In 1937, Arthur E. Guedel gave the classic description of clinical signs of ether anesthesia, including 4 stages: analgesia, delirium, surgical anesthesia and respiratory paralysis (till death) [3]. In 1954, Joseph F. Artusio further divided the first stage in Guedel's classification into three planes: no amnesia and analgesia; complete amnesic but only partial analgesia; complete analgesia and amnesia [4]. This is the history of DOA clinical monitoring. However, until a few years ago to determine the lightening of DOA, anesthetists exploited only a series of physical signs of the patient, including sudden hypertension, tachycardia, sweating, tearing or mydriasis [5]; indeed during the years, while the research enhanced standard monitoring, like pulse oximeter, electrocardiographic monitor, capnograph, and spirometer [6], assessment of DOA with specific instrumental tools was still a serious problem (Figure 1).

In 1984, Evans et al., [7] speculate that the activity of the lower esophagus could be a useful guide to the adequacy of anesthesia status because, as they stated, deepening anesthesia resulted in progressive suppression of lower esophageal contractility. Nevertheless, the groundlessness of this technique was quickly proven [8]. The same Evans proposed a scoring system called the 'patient response to surgical stimulus score', based on hemodynamic parameters (pressure and pulse rate), sweating and tearing [9]. As well demonstrated, this score is a poor indicator of DOA, in as much as hemodynamic responsiveness to noxious stimuli does not necessarily signify awareness, nor does lack of hemodynamic changes guarantee unconsciousness [10].

Because the actions of general anesthetics impact the brain's electrical activity, the possibility of analyzing data reflecting specific changes in the Electroencephalogram (EEG), could be a good way forward for DOA monitoring. Thus, in 1994, Sigland Chamoun described on the pages of Journal of Clinical Monitoring the Bispectral (BIS) analysis as a novel measure of the level of consciousness during general anesthesia [11]. The calculated BIS index was a statistical index based on a combination of time, frequency domain, and high-order spectral subparameters. It reflected the awake state, providing the activity of brain, ranged from 0 to 100 (40~60: adequate general anesthesia; under 40: deep hypnotic state).

Because the Anesthesia Awareness (AA) phenomenon has historically been the mean fear in anesthesiology, it seemed to have discovered the philosopher's stone of the anesthesia monitoring. Thus, BIS was initially considered the best tool for monitoring cerebral activity during anesthesia [12]. However, some scientists began to doubt the effectiveness of BIS, and Avidan et al., in a capital study on the topic, reported the same incidence of AA independently from BIS monitoring [13].

Figure 1: Depth anesthesia monitoring (1937-2015).
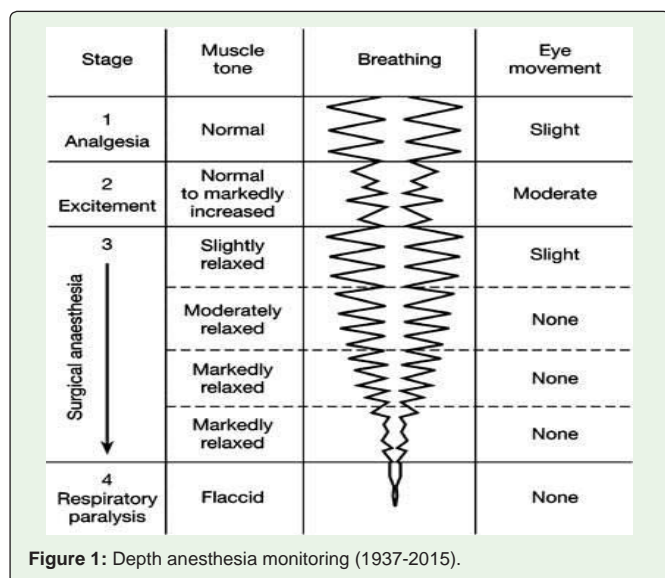
The Avidan's study also found that patients can become aware even when BIS values are within the target range (i.e., 40 to 60), and thus concluded that the BIS monitoring should not be used as part of standard practice of anesthesia [13]. It was the beginning of a hard fought battle on the pages of scientific journals, and according to Lang, today the BIS monitor has become the most controversial medical device in anesthesiology [14].

The current status

BIS monitor was the first Electroencephalography (EEG) - DOA monitor. It is the most widely used system to assess the monitoring of DOA, nevertheless during the last 15-20 years a number of EEG-based technologies have become commercially available. In addition to BIS, and based on different algorithms, there are the E-Entropy (previously known as M-Entropy) and the Narcotrend. The Entropy system was introduced by the Datex-Ohmeda Company in 2003 [15]. The founding principle behind this theory is that the irregularity within an EEG signal decreases with increasing brain levels of anesthetics. It uses a specific algorithm to process EEG and frontal electromyography data to produce two values that indicate the depth of anesthesia. The first value, response entropy, is based on both EEG and frontal electromyography signals and provides an indication of the patient's responses to external stimuli and may signal early awakening. The second value, state entropy, is a stable parameter based on EEG and may be used to assess the hypnotic effect of anesthetic agents on the brain [16].

Narcotrend has been developed at the University Medical School of Hannover, Germany and its algorithm is based on old studies on cerebral states during sleep [17]. The raw EEG signal is recorded by a single or double-channel. After a Fourier transformation, the algorithm state six stages of anesthesia and a series of sub stages. Less common DOA monitors are the Cerebral State Index, the Patient State Index and Neuro SENSE.

What is the clinical effectiveness and cost-effectiveness of EEG-based technologies compared with standard clinical monitoring? A significant systematic review of Shepherd and colleagues demonstrated that the impact of the technologies on reducing the

incidence of AA is limited. However, the authors concluded that the use of DOA monitoring can reduce the consumption of general anesthetic drugs [18].

Unfortunately, none of these technologies has definitively solved the problem of the AA. Thus, the current status is that EEG devices can be used in conjunction with observation of clinical signs and instrumental parameters (i.e. the End-tidal anesthetic gas concentrations) to titrate anesthetic dose, especially in particular clinical situation, like burns [19], as well as pediatric patients with congenital disease [20] or during the sedation even in children [21] and in dentistry [22].

Expert opinion suggests that anesthetists primarily use clinical signs with EEG values as an additional source of information. If there is a difference between them the priority must be given to the clinical signs [18].

Auditory evoked potentials and combination of parameters

A field of research in brain monitoring of anesthesia is the study of the Auditory Evoked Potentials (AEP). The rationale is that while BIS value is an index of hypnosis, AEP shows response to stimuli. The BIS and AEP measure different aspects of brain activity. In other words, BIS refers to cortical EEG, while AEP is the expression of the subcortical activity. In an attempt to combine the two aspects of the brain activity some authors have been developed a specific index, the Composite Auditory Evoked Potentials Index (cAAI), which uses both cortical EEG and AEP [23]. This composite index was considered a measure of overall balance between noxious stimulation, analgesia, and hypnosis. Nevertheless, the results of the studies are contradictory. While Horn et al., [24] demonstrated that a combination of EEG and AEP parameters can be used to differentiate degrees of anesthetic effects over a wide range of hypnosis, from the conscious state to deep anesthesia, however Nishiyama showed in propofol-fentanyl anesthesia that AEP alone might be better to discriminate DOA than cAAI and BIS [25]. The same author showed that cAAI was inferior to AAI and BIS to discriminate different anesthetic effect in a sevoflurane anesthesia, and he concluded that the cAAI had larger inter-individual variation than the AAI and BIS [26].

For these reasons the use of AEP (and derived indices) is not universally spread. Nevertheless, recently there is a growing interest on the impact of auditory perception and auditory information processing for the genesis of the AA phenomena. So, according to Dong et al., conscious and subconscious auditory processing during GA could be prevented using auditory evoked potential, especially the mid-latency auditory evoked potentials [27].

The main limitations of DOA monitoring are that various physiological factors influence EEG, such as age, gender, low body temperature, acid base imbalances, low blood glucose, or cerebral ischemia. Thus, scientific research is enabling the development of more reliable technologies based on the analysis and processing of data of brain activity.

The ideal DOA monitor

According to Jagadeesan et al., [28] an ideal DOA monitor would have several specific attributes. For example, it should have a rapid response time without any delay, and its function should not

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Table 1: Features of an ideal DOA monitor.

Features of an ideal DOA monitor
Economic
Easy to use and interpreter
Safe, non-invasive and reliable
Portable and/or compatible with other anaesthesia devices
Suitable for every types of general anaesthesia (intravenous or inhaled) and for all anaesthetics
It must suggest the dosage of anaesthetic agents
Accurately reflecting the depth of anaesthesia
Ability to function according to the neurophysiological bases of consciousness (and anaesthesia)
Sensitive to various stimuli (e.g. intubation, skin incision)
Accurately filtering artefacts generated either by the patient (e.g. by eye movements and muscle activity) or external sources (poor skin contact, mains or power line interference, electrocautery)
Suitable also in clinical situations impacting the raw EEG (e.g. seizures, age, race, gender, low core body temperature, acid-base imbalances, low blood glucose, drugs administered to the patient or brain ischemia)
No delay in response between the event (e.g. sudden arousal or loss of responsiveness) and the value (index) or wave displayed

be altered by artifacts and drugs. However, the main feature of an ideal device for monitoring DOA is its ability to function according to the neurophysiological bases of consciousness (and anesthesia). It is well known that the state of consciousness requires connectivity among various brain regions, and a transition in the anesthesia status involves a loss of connectivity [29]. So, an ideal DOA monitor would have good spatial resolution and would target several brain regions, like the frontal cortex, the posterior cortical regions, subcortical areas and deep brain structures, like the thalamus and hippocampus. Furthermore, this device should be economic, easy to use and interpreter, safe, non-invasive and reliable, as well as suitable for every types of general anesthesia (intravenous or inhaled) and for all anesthetics. Since a DOA device is designed with the purpose of monitoring the impact of anesthetics on consciousness, it must suggest the exact dosage of anesthetic agents (Table 1).

Future directions for research in the field of brain monitoring during anesthesia

Nowadays, we are witnessing a rapid evolution of the brain monitoring EEG-based techniques [30]. The right way is the research on the neurophysiological bases of consciousness, as well as the mechanisms underlying anesthesia-induced Loss of Consciousness (LOC). In this direction the studies of Boly et al., [31] on the spectral EEG changes after propofol administration are very important. These evidences underline the importance of recurrent corticocortical communication in the maintenance of consciousness, suggesting a direct effect of anesthetics on cortical dynamics. Indeed, if it is obvious that the anesthetic effect is realized through the ligand-receptors interacting in different brain areas, it remains to be analyzed the exact physical mechanism (or operating mechanism) of the general anesthetics, namely the neural correlates of anesthetic-induced unconsciousness. In other words, the understanding of the physiological mechanisms by which the anesthetics interfere with cortical and subcortical signals is the key to develop one or more accurate algorithms for DOA monitoring.

For instance Purdon and the Emory Brown's team [32] published their fascinating research explaining that EEG pattern (and its changing) is indicative in real time of the patient transaction from consciousness to the anesthesia status. Moreover, the analysis of the tracks has allowed to identify some characteristic trends; in particular, the LOC is marked by an increase of the waves of low frequency (less than 1 herz) associated with a decrease in the coherence of the oscillations of the alpha occipital area (an index of the synchronization of the neuronal activation in this region of the brain), and to the appearance of oscillations alpha consistent in the frontal area. The changes of cerebral activation were reversed in the phase of recovery of consciousness. These EEG markers represent specific 'signatures' to precisely trace the transitions to and from the consciousness in GA. The Brown's methodology is a combination of likelihood, Bayesian, state-space, time-series and point process approaches, used to develop statistical methods and signal-processing algorithms for neuroscience data analysis. This field of study is also a brilliant example of transactional research, involving experts in functional magnetic resonance imaging, EEG, neurophysiological recordings, and researchers experienced in microdialysis methods, as well as in statistic and mathematical [33].

Conclusion

Measuring DOA remains one of the most controversial and subjective aspect of modern anesthesia. Is it possible integrating the new derived EEG markers into strategies for patient monitoring during GA? We hope that these technologies are perfected and soon large-scale distributed to permanently solve the AA problem. Furthermore, in addition to the AA, a reliable brain monitoring could help to avoid other significant clinical manifestations, including the emergence delirium in children, the adverse developmental effects in neonates and infants, and the wide spectrum of postoperative cognitive disorders in the elderly.

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