Chapter 5

Important Issues in Coma and Neuromonitoring

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Additional information is available at the end of the chapter

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Abstract

Coma is defined as a state of unconsciousness and lack of response to noxious stimuli. The physiopathology of consciousness and coma is not entirely understood. On the other hand, clinical examination does not give us enough information in all types of coma states. In this chapter, some types of coma and their definition, the necessity of coma monitoring and what we can use for coma monitoring in ICU, algorithms for EEG monitoring, BIS, AppEntropy, permutation entropy and auditory evoked potentials are described. Burst suppression state new theories and cortical connectivity and reactivity during coma as a tool for coma prognosis will be on focus.

Keywords: coma status, burst suppression, cortical connectivity, cortical reactivity

1. Introduction

Coma is defined as a state of loss of consciousness and lack of response to external stimuli that occurs in pathological states and during anesthesia. The prognosis of coma patients is difficult to assess, as the mechanism through which coma occurs is not entirely understood. What we may do is evaluate cerebral function, through accurate and careful monitoring. Thus, the intensive care specialist requires one or several instruments to monitor the cerebral function of coma patients, as it is difficult to perform, even hourly, a clinical evaluation, taking into account the typical workload of the doctor.

In certain circumstances, a worsening neurological state does not manifest itself clinically—an example being nonconvulsive status, which has negative prognostic value in the case of traumatic brain injury (TBI), and can only be diagnosed through continuous electroencephalographic monitoring (EEG).

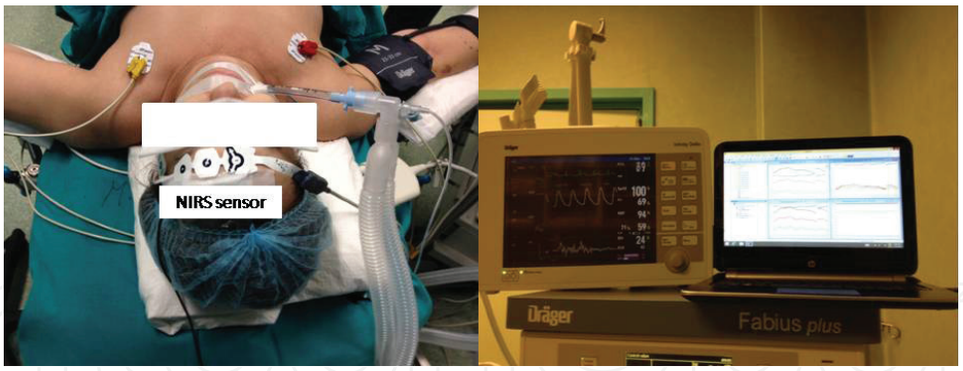

Figure 1. Continuous BIS (bispectral index) and NIRS (near-infrared spectroscopy) monitoring during anesthesia.

Continuous EEG monitoring and cerebral oximetry monitoring—through the NIRS (near-infrared spectroscopy) technique—are useful instruments that provide the doctor with real-time, vital information on the coma patient. These techniques have the advantage of noninvasivity, ease of use and they can provide the doctor with easily quantifiable scores. Perhaps most importantly, they can be made available continuously at the bedside (**Figure 1**).

Unfortunately, there is not one single standard monitor at this moment to accurately estimate what occurs in the brain of a coma patient. Therefore, in this chapter, we shall start with a brief exposition on coma physiopathology, insisting on burst suppression (BS) state, and we shall continue with the characteristics of the main coma states we might encounter in the intensive care unit (ICU). We will continue with the devices used to monitor anesthesia depth, which are used to monitor coma depth as well. These devices are based on EEG signal analysis. The main drawback of EEG signal analysis is noise: how shall we define and remove noise on an EEG?

A definitive answer is difficult to find, that is why "noise-resistant" mathematical algorithms have been developed. Thus, this chapter focuses on the mathematical algorithms used to interpret EEG signal, as it is important to know the basis of parameters and scores we receive from the devices we use. In the end, we describe new theories that might be standardized to evaluate coma state—such as cortical connectivity and reactivity.

2. Coma state

2.1. Coma—definition and theories

Coma is defined as a state of unconsciousness and lack of response to noxious stimuli. The physiopathology of consciousness and coma state is not entirely understood. It is not clear if a "coma center" exists or if the diverse pathological states that induce coma do so through different mechanisms. From this perspective, coma is similar to the anesthetic state, which is caused by several pharmacological agents, with different chemical structures. It is also unclear if a common center, on which all anesthetics act, exists. Based on histology and physiology, Sir Francis Crick postulated that the claustrum has a central role in maintaining consciousness (as it is connected with nearly all cerebral structures), like the conductor of an orchestra [1]. Recent studies have shown that during isoflurane anesthesia on the rat,

functional connectivity of the claustrum with medial prefrontal cortex and mediodorsal thalamus decreased [2]. As for coma state, there are no definitive studies proving the role of the claustrum in its physiopathology.

Regarding EEG activity, comas are different. The same coma state, defined by a lack of consciousness and of response to external pain stimuli may exhibit different EEG aspects. Thus, there are comas with prevalent alpha waves (alpha comas), beta waves (beta comas), theta waves (theta comas) or delta waves (delta comas). A common characteristic of these coma states is that if they are secondary to intoxication or metabolic encephalopathies, they have a positive prognosis, regardless of the EEG pattern, with response to external pain stimuli. If there are secondary to brain stem lesions or hypoxic ischemic encephalopathies and lacking response to external pain stimuli, comas bring a negative prognosis [3].

Comas secondary to TBI are caused by diffuse axonal injury (DAI) and by hemorrhages that compress the brain stem. Diffuse axonal injury occurs due to rapid (rotational) acceleration, which causes lacerations in the neuronal cytoskeleton and therefore block neuronal transport [4]. Hameroff and Penrose support the hypothesis that conscious processes are based in the microtubules of the neuronal cytoskeleton [5, 6]. Furthermore, it is known that volatile anesthetics interfere with the function of these microtubules. Nevertheless, if this theory proves true—that consciousness is based on and influenced by neuronal cytoskeleton microtubules—that might explain loss of consciousness secondary to diffuse axon injury.

Another etiology of coma is nonconvulsive status, defined as prolonged seizures there are not clinically manifested and associate altered mental status [7], secondary to TBI (8–16%), to stroke—HAS (3–31%) and craniotomy [8]. The mechanism of loss of consciousness during epilepsy is not entirely understood. Blumenfeld Hal et al. affirm that a common mechanism exists—a cortico-subcortical network dysfunction. Therefore, a decrease in cerebral blood flow (CBF) was noticed in frontoparietal association areas and the anterior and posterior interhemispheric regions with (CBF) increases in bilateral midline subcortical structures [9].

Besides, a loss of connectivity between medial and lateral frontoparietal association areas and upper brainstem/medial diencephalon was observed [10]. They state that these cortico-subcortical connectivity malfunctions (occurring in generalized tonic-clonic seizures, complex partial seizures and temporal lobe seizures) are caused either by indirect inhibition or by convulsions initiated in these structures.

2.2. Burst suppression (BS) state

Burst suppression is a cortical electrical activity defined by the existence of high-amplitude and variable frequency waves discharge, followed by a period of electrical activity suppression. BS is an intermediate state between slow waves EEG pattern and an isoelectric line. This BS pattern is present in several conditions, such as Ohtahara syndrome, TBI, hypoglycemia, hypoxia, hypothermia and anesthesia [11]. As for anesthesia bursts, they have a wave morphology specific to each anesthetic compound, and a different duration as well. In addition, the length of the burst decreases as the anesthesia depth increases [12]. Not only is the burst length variable, but so is its structure, according to its length. Thus, we have noticed [13] that for isoflurane anesthesia in rat, 4-seconds bursts and 1-second bursts have different aspects

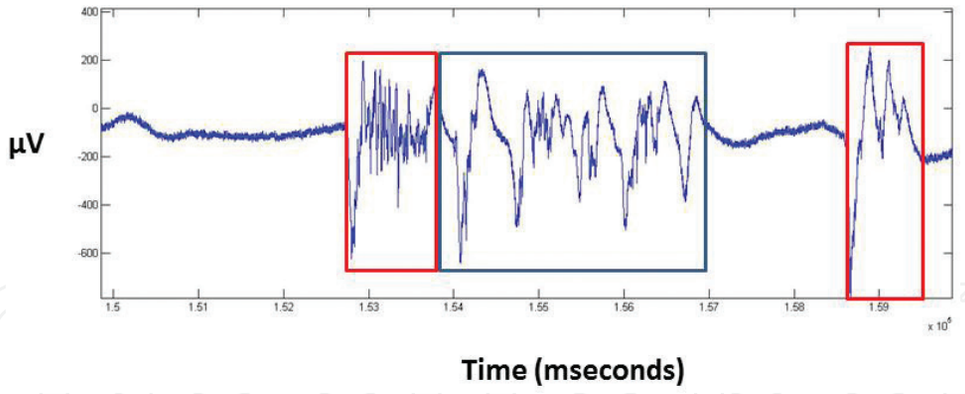

Figure 2. Burst aspects according to its length (local-field potential—LFP—recording). The first burst lasts almost 4 seconds and presents high-frequency waves at the beginning followed by slow waves. The second burst is short (almost 1 second) and presents slow waves.

(**Figure 2**). Long bursts start with high-frequency high-amplitude waves, followed by low-frequency high-amplitude waves, while short bursts present low-frequency high-amplitude waves as it is seen on power spectral density graphics (**Figure 3**).

Even though a BS presenting coma state is considered deep, BS is deemed a state of hyper-excitability, as bursts can be evoked by subliminal stimuli [14] and BS electrical activity is correlated with cerebral blood flow changes as well [15].

The mechanism supporting this phenomenon remains incompletely explained. We have two theories attempting an explanation at the moment. The metabolic theory of Emery Brown [11]

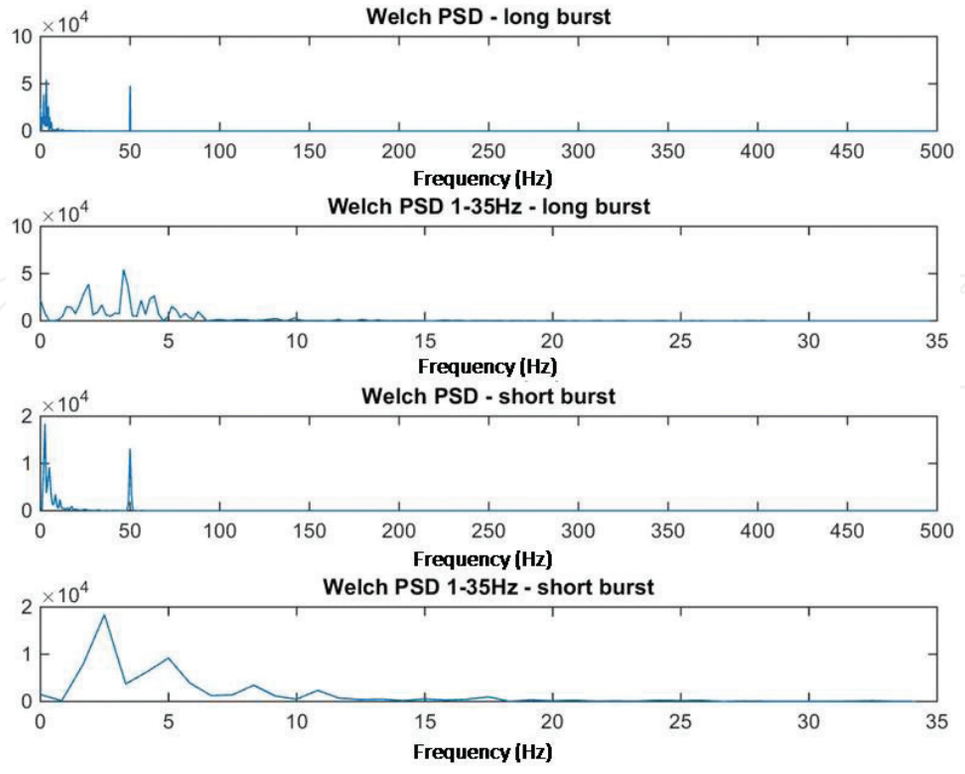

Figure 3. Power spectral density during the long burst versus the short burst. Two peaks of frequencies can be observed in the long burst.

is based on the fact that BS states correlate with low metabolism states (with low metabolic rate), such as hypothermia, anesthesia and hypoglycemia. The link between the electrical and the metabolic activity is the KATP channels, so during the burst, ATP concentration decreased which induces an increase in the conductance of KATP and thus a neuronal membrane hyperpolarization occurs (flat-line EEG). The theory of Amzica [16] states that BS activity is modulated by extracellular calcium concentration variations, thus the depletion of the extracellular cortical calcium during the burst is responsible for the EEG silence (flat line) after that. The basis of this phenomenon is unclear as well. It is regarded that bursts are caused by internal input, modulated by neural networks. On the other hand, the cortex has been proven to exhibit BS activity, without the intervention of subcortical structures [17].

In the clinical practice, finding BS patterns in coma patients presents a negative prognostic value, if the BS ratio (BSR = suppression time/epoch duration * 100) is over 20–23% [18].

3. EEG monitoring and interpretation

3.1. Continuous EEG monitoring

Continuous EEG monitoring is the most used and, perhaps, the most efficient method of evaluating coma patients in the ICU. The advantage is the electrode placing: it is noninvasive (or minimally invasive), can be easily applied on the scalp of the patient and requires a minimal qualification of the ICU staff. Most EEG recording devices include software for mathematically processing the signal, and generating scores or frequencies.

The acquisition system 10–20, that is classically used, provides an overview of the main cortical areas. Placing the electrodes and fastening them with a specialized helmet may facilitate CT or MRI transportation, in order to obtain a complex imagistic and electroencephalographic representation. Standard EEG monitoring provides information on the onset of epileptic seizures, is useful in detecting nonconvulsive status and in detecting early and late ischemia, secondary to subarachnoid hemorrhage. Furthermore, it provides useful information (based on prevailing EEG patterns and reactivity) for the prognostic of the coma patient [19].

The following chapter will describe the main mathematical algorithms that are used in analyzing EEG signal, as well as the devices used for monitoring coma and anesthesia depth.

3.2. EEG signal analysis

3.2.1. Spectral analysis

Spectral analysis of EEG signal is based on the fast Fourier transformation (FFT), which decomposes the signal according to the mean amplitude of each frequency in the signal. By applying second-order FFT, the result is the spectral power graphic, which decomposes the signal based on amplitude squared/frequency (microvolts^2/Hz). Analyzing this graphic provides very important parameters to estimate the depth of sedation/anesthesia.

Median frequency (MEF) represents the value of frequency whose perpendicular meets Ox in the point that splits equally the area under the spectral power graphic.

Spectral edge frequency (SEF) is the value of frequency from which we can draw a perpendicular to Ox that leaves 90 or 95% of the spectral power function under graphic area to the left [20] (**Figure 4**).

If the patient is anesthetized, the values of these parameters will decrease proportionally with the degree of sedation (they will shift to the left), because during sedation, the high-frequency fast waves EEG activity ceases [21]. Surgical anesthesia is performed at the moment the EEG shows mostly theta waves.

3.2.2. EEG signal entropy

Entropy represents the degree of disorder in a system. Ludwig Boltzmann defines entropy as the logarithmic function of the number of microstates corresponding to a macrostate. In 1949, Claude Shanon defines information entropy as being:

$$S = \sum_{i=1}^{n} P(x)\log P(x) \quad (1)$$

where S = entropy,

P = apparition probability,

log = binary logarithm.

As EEG is a signal composed of several types of waves, with a disorderly aspect, the more disorderly (more types of waves), the higher the entropy. An isoelectric EEG signal has a null entropy. This type of entropy, applied to EEG signals, was used to monitor anesthetic depth during desflurane anesthesia [22]. The Datex-Ohmeda company (now acquired by GE) developed a device that analyzes EEG signal entropy and displays it as a score.

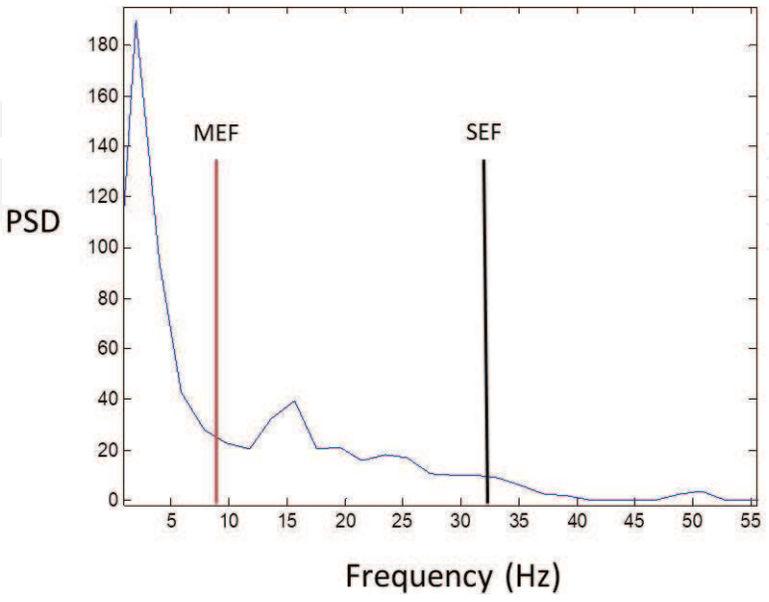

Figure 4. EEG power spectrum density (PSD). In this figure, median frequency (MEF) and spectral edge frequency (SEF) are displayed on the PSD graph.

The EEG signal entropy calculation is based on the following algorithm:

$$SN[f1, f2] = \frac{S[f1, f2]}{\log(N[f1, f2])} \quad (2)$$

where [f1, f2] = frequencies between which the EEG signal is analyzed,

N[f1, f2] = number of frequencies between f1and f2.

The EEG signal is acquired at a frequency of 400 Hz, and to analyze it, several epochs (windows) are used, between 0.92 and 60.16 seconds, in order to cover all EEG signal frequencies. The shortest epoch is used to analyze frequencies between 32 and 47 Hz, and the 60.16 epoch to analyze frequencies under 2 Hz. The device provides two entropy indices: state entropy (SE) and response entropy (RE). SE analyzes EEG in the frequency domain 0.8–32 Hz, while RE in the 0.8–47 Hz frequency domain. The difference between RE and SE is given by the EMG activity: it is assumed that an increase of entropy in the 32–47 Hz domain corresponds to an increase of frontal electromyographic activity, and this difference shows indirectly the quality of intraoperative analgesia). SE is between 0 and 91, and RE is between 0 and 100.

During anesthesia, the values displayed by the entropy monitor must be in the range of 40–60 in order to prevent waking up during the intervention [23–25].

3.2.3. Bispectral index

The Aspect Medical company was the first to market a monitor for anesthesia depth, in 1994 [26]. It is based on the bispectral analysis of EEG signal [27]. The monitor analyzes the EEG recorded by prefrontal electrodes, based on an algorithm, undisclosed entirely up until today [28]. This algorithm calculates a score between 0 (isoelectric line) and 100 (patient awake). This algorithm was validated by correlating the clinical sedation score, lack of response to pain stimulation and EEG parameters for approximately 1500 patients (cumulating approximately 5000 hours of recordings). BIS monitoring evaluates well the degree of sedation/hypnosis of anesthesia, and not directly the anesthetic depth. It was validated for all volatile and intravenous anesthetic, except ketamine. As this generates thalamocortical dissociation, the EEG is similar to that of an awake patient. During sevoflurane anesthesia, ketamine may increase the BIS score, though anesthesia deepens [29]. In the case of propofol anesthesia, analgesic dose of ketamine does not influence the bispectral index [30–32]. Though xenon has a similar mechanism to ketamine and was not used in the validation process of the BIS monitor, it modifies the EEG similarly to propofol [33]. As for correlating the BIS score, older studies have stated that BIS under 50 does not ensure hypnosis [34]. A more recent study reveals that xenon anesthesia depth clinical signs correlate well with BIS score values [35].

The algorithm used incorporates spectral analysis, bispectral analysis and burst-suppression activity analysis (BS). Spectral analysis, described above, decomposes the signal based on the amplitude of each frequency, analyzing data individually and ignoring the relationship with other constituents. In the human brain, there are several EEG signal generators. While the patient is awake, the EEG signal is produced by the independently emitted activity of several generators, only slightly synchronized. As the patient falls asleep or is anesthetized,

the number of active generators decreases and they become more synchronized. Bispectral analysis quantifies the phase-phase coupling between these EEG signal generators.

BIS components are *beta ratio* and *SyncFastSlow*. Beta ratio is the logarithm of the ratio of two frequency components of the spectral power (30–47 Hz and 11–20 Hz), while *SyncFastSlow* is the logarithm of the bispectral ratio of 0.5–47 Hz and 40–47 Hz [36].

$$BetaRatio = \log\left(\frac{P\ 30-47}{P\ 11-20}\right) \tag{3}$$

$$SyncFastFlow = \log\left(\frac{B\ 0.5-47}{B\ 40-47}\right) \tag{4}$$

BIS monitors display several parameters, such as the BIS score value (between 0 and 100), which should be maintained during anesthesia between 40 and 60 to prevent waking up, signal quality index, suppression ratio for a 60 seconds epoch (SR), the minute burst count (BC), frontal electromyographic activity (EMG)—which results from analyzing the EEG signal in the 70–110 Hz frequency interval (assumed to be produced by spontaneous frontal muscles activity) and is between 30 and 55 dB [37].

BIS monitoring can be used in the intensive care wards as well, to monitor patient sedation [38]: in traumatic brain injury, a value under 60 correlates with a negative prognosis [39]. BIS monitoring may also be used to detect cerebral vasospasm in critical patients [40]; it has been proven that it correlates well with the consciousness level of the ICU patients, it aids in adjusting sedative dosage, it has a prognostic value and it is useful in monitoring induced coma for a status epilepticus [41–44].

EMG activity is not greatly influenced by the degree of curare neuromotor block, but the pain stimulus EMG variation during anesthesia depends on the degree of neuromuscular block [45].

3.2.3.1. BIS monitoring limitations

BIS analysis of EEG signal provides information only on the sedation during anesthesia, and not on global anesthetic depth. The BIS score does not accurately predict when the patient will regain consciousness. Recent studies have shown that both loss of consciousness and waking up from anesthesia correlate with gamma cortical activity, as losing consciousness is caused by gamma rhythm cessation [46, 47]. BIS monitors cannot gather gamma rhythm EEG signal, as it can only be optimally recorded through dura mater electrodes.

BIS monitors pick up EEG signal in the prefrontal area, where spontaneous electromyographic activity interferes with gamma rhythm frequency. The BIS score cannot predict pain stimuli hemodynamic reactivity during anesthesia and is influenced by the type of anesthetic used—volatile anesthesia, for the same anesthetic potency, differently alter EEG activity. Furthermore, it is not influenced by cerebral perfusion and hypoglycemia [48].

3.2.4. Narcotrend monitoring

This monitor was marketed in 2000 by the Monitor Technik company. The EEG signal is picked up by three electrodes in the frontal area. It is then filtered and noise is removed. EEG is analyzed in the 0.5–47 Hz frequency domain. The algorithm includes the relative power of alpha, beta, theta and delta frequencies, median frequency, spectral edge frequency and spectral entropy. This monitor displays values between 0 and 100. The depth of anesthesia is divided into five stages [49]. The values provided by this monitor are well correlated with the ones provided by BIS monitoring [50]. The Narcotrend monitor has been proven useful in the postoperative care of the patients who underwent propofol sedation during cardiac surgery [51].

3.2.5. Consciousness index

The monitor for the consciousness index is a wireless, portable monitor as well, with a 10-meters range. It is produced by Morpheus Medical. It provides a score with values between 0 and 100, and, similar to the BIS monitoring during anesthesia, the value of the consciousness index must be maintained between 40 and 60 to prevent waking up during anesthesia. This monitor analyzes EEG, using symbolic dynamic analysis. As EEG is a variation of potential through time, it can be seen as a dynamic system, in which every moment has a state that can be defined through a real number. The dynamic symbol method analyzes a dynamic system as being composed of a discrete sequence of abstract symbols that each correspond to a system state [52].

This monitor was compared with BIS monitoring and similar results were found [53].

There is one other consciousness index that uses Lempel-Ziv complexity analysis. This method was established in 2013 by a team of researchers led by Adenauer Casali and Olivia Gosseries. This index was studied during midazolam sedation and propofol-xenon anesthesia, on a limited number of subjects. It is based on evaluating cortical reactivity and intercortical connectivity, using high-density EEG and transcranial magnetic stimulation on several cortical areas: superior occipital gyrus, superior medial frontal gyrus, superior parietal gyrus and premotor rostral cortex. EEG signals were analyzed using the Lempel-Ziv complexity algorithm, which approximates the amount of nonredundant information in a binary system, thus estimating the minimal amount of patterns required to describe a signal. The less EEG signal nonredundant information there is, the less complex the signal and deep the anesthesia is [54].

3.2.6. Approximate entropy

Entropy is the degree of disorder in a system, thus an extensive measurement of chaos. At the beginning of the twentieth century, the mathematicians Andrey Kolmogorov and Henri Poincare further developed the mathematical analysis of chaos. In 1991, Steven Pincus introduced the notion of approximate entropy. Approximate entropy measures the complexity of a system. As it is little influenced by noise, it has an advantage in the analysis of systems exposed to a strong source of noise. Mathematically, approximate entropy quantifies how constant the distance between two vectors in a series is [55].

The following formula is used to calculate approximate entropy:

$$ApEn(Sn, m, r) = \ln\left(\frac{C_m(r)}{C_{m+1}(r)}\right) \quad (5)$$

where m = length of the pattern,

Cm(r) = prevalence of repetitive patterns, with the length m.

Applied to time series, approximate entropy is a measurement of series predictability. As we know, electroencephalographic signal is a time variation of scalp-recorded potential. Thus, electroencephalographic signal may be described as a time series. Calculating approximate entropy, there results an estimation of EEG signal predictability, and, inherently, an estimation of the signal complexity. The more awake the patient is, the higher values the approximate entropy will have, as the EEG is more complex and less predictable. During deep sedation, EEG complexity lowers and thus will be more predictable, with a lower approximate entropy value.

Approximate value is used to estimate anesthesia depth and correlates well with BIS and SEF indices, during propofol-remifentanil anesthesia [56].

3.2.7. Permutation entropy

Permutation entropy is another method of estimating the chaos, which analyzes the probability of appearance of a motive of amplitude over a certain amount of time. The more motifs there are, the more complex the signal is, therefore the more awake the patient is. When the probability of appearance of all motifs is equal, permutation entropy equals 1. The calculation algorithm for the permutation entropy was published in 2002 by Bandt, and in 2008, Jordan et al. use this algorithm to study electroencephalograms [57, 58].

$$PE = -\frac{\sum P_i \times \ln P_i}{\ln N} \quad (6)$$

where P = probability of appearance of a motif,

N = number of motifs.

An important parameter is the signal acquisition frequency, the algorithm being designed for a frequency of 100 or 128 Hz.

In 2008, Olofsen et al. studied EEG by using permutation entropy during propofol anesthesia and described six types of motifs: peaks, slopes and grooves [59].

Using permutation entropy, the transition between loss of consciousness and consciousness can be detected by analyzing 2-seconds EEG recordings [60].

3.2.8. EEG fractality

Fractal analysis of the EEG signal implies measuring the degree of self-similarity of the signal. EEG fractal analysis was used to study sleep, anesthesia or convulsions [61–63].

Another analysis parameter for complexity, similar with fractal analysis, is detrended fluctuation analysis (DFA). It is an analysis method for signal self-similarity and was used to evaluate EEG and was suggested as a possible quantification parameter of anesthesia depth [64].

3.2.9. Auditory evoked potentials

Changes in the latency and amplitude of auditory evoked potentials of middle latency (early cortical), that appear 20–80 ms after auditory stimulation, can be correlated with anesthetic depth [65–67].

The auditory evoked potential index (AAI) is an algorithm integrating amplitude variations of several consecutive potentials and generating a numerical outcome, between 0 and 99, similar to the bispectral index [68]. Patients lose consciousness under 40, and surgical anesthesia appears under 20. AAI values are well correlated with BIS values [69]. In the ICU, middle latency evoked potentials have a positive prognostic value in the patients who required craniotomy for TBI, and there has been noticed a strong correlation between pupillary responses, intracranial pressure and auditory evoked potentials in patients with supratentorial mass lesions [70, 71].

4. Near-infrared spectroscopy (NIRS)

Jobsis first noticed in 1977 [72] that tissues are transparent for a wavelength of light of 700–950 nm. Based on this, the concentration of oxyhemoglobin, deoxyhemoglobin and cytochrome C oxidase can be measured (only the first two are used in clinical practice).

Starting from the oxyHb and deoxyHb concentrations, one can estimate regional saturation of oxygen (rSO_2) in a tissue. Furthermore, the regional changes of blood flow can be assessed, by evaluating the changes of total hemoglobin (HbT). Monitors for cerebral oxygenation, that are based on the NIRS technology, use a sensor placed above the tissue, whose oxygenation is to be measured. The sensor is made of emitting and detecting diodes, placed within 4–8 cm of each other. Detecting diodes will detect the infrared light reflected by the tissue. In the case of cerebral tissue, the infrared light can penetrate up to a depth of 0.6–1 centimeters [73]. Thus, cerebral oxygenation through this method is underestimated, compared with jugular vein saturation ($SjVO_2$) [74]. Among the benefits of this method are the noninvasive character and the ease of use at the bedside.

In the case of the brain, rSO_2 values are closer to the venous saturation than to arterial saturation because 70% of cerebral blood is in the veins and capillaries, and thus, normal cerebral rSO_2 values are between 60 and 80%. Using NIRS in the current clinical practice began in the 1980s, with the first studies on monitoring cerebral function in the adult and neonate. More recent studies are focused upon evaluating prehospital coma gravity. For example, Peters et al. [75] observed in a study including 25 patients that NIRS has a sensitivity of 93.3% and a specificity of 78.6% over CT scans in detecting intracranial hematoma.

Additionally, NIRS values have prognostic value in TBI patients. The values of rSO_2 at hospital admission were 74.7 ± 1.5% in the case of surviving patients and 61.9 ± 19.4%

in nonsurvivors [76]; therefore, rSO_2 under 60% are associated with increased mortality. In the case of resuscitated SCR patients, rSO_2 in the first 24 hours was 68.2% for survivors and 62.9% for nonsurvivors [77]. As for blood flow variation monitoring, it was noticed that the cerebral oximetry index (Cox), determined through NIRS, is a good substitute of the mean velocity index (Mx)—determined through transcranial Doppler echography (TCD) [78]. NIRS is also useful in detecting vasospasm in subarachnoid hemorrhage (SAH) patients as well [79].

5. Cortical connectivity and coma

During coma states as during the anesthesia, there is a decrease in connectivity ("communication") between different cortical regions, or between cortical and subcortical regions, caused by a reduction of cerebral activity. The basis of cortical connectivity is made of structural links, such as synapses and neural fibers.

In clinical practice, the evaluation of connectivity is performed by analyzing the coherence/correlation between biological signals (EEG, ECoG and local-field potentials) from different regions of the brain.

Functional connectivity is based on biological signals analysis, which can be described as time series (such as the EEG) and can quantify cortical connectivity using statistical analysis (correlation) of the EEG signals from different cortical areas. The better the EEG signals are correlated (estimated by the correlation coefficient, XAppEn, mscohere), the more they are alike; therefore, there is a good connectivity between the cortical areas. Importantly, good statistical correlation of biological signals does not necessarily involve causality, and does not point out the direction the information moves [80]. Unlike structural connectivity, functional connectivity is time-dependent [81].

Effective connectivity may be regarded as a unit of structural and functional connectivity. It is the latest instrument trying to establish causal relations between neural network components [81]. Effective connectivity is calculated using complex mathematical algorithms (such as Granger causality or transfer entropy), applied to time series.

The state of consciousness, according to Buzsaki (2007), is the consequence of the functional transformation of information contained by a neural network. Both posterior parietal and prefrontal association areas and frontoparietal network information integration were considered involved in the generation and maintenance of the state of consciousness [82, 83]. During sleep, which is a reversible modification of consciousness as well, there is a modification of cortical connectivity; therefore, during NREM sleep, it lowers and during REM sleep, it increases [84].

Cortical connectivity changes during anesthesia were first observed in lab animals, and then in humans. Thus, in 2005, the cortical connectivity changes, especially in the prefrontal cortex, during sevoflurane anesthesia of different concentrations, were described. Bouveroux et al. described the effects of propofol on cortical connectivity: during propofol anesthesia, corticocortical and thalamocortical connectivity decreases in frontal-parietal networks, while it is

maintained in the visual and auditory cortex [85]. Mhuircheartaigh et al. regard the lack of response to auditory and pain stimuli during propofol anesthesia as a consequence of putamen-cortex connectivity decreases, while thalamocortical connectivity remains unchanged [86]. Ferrarelli et al. notice as well the frontal intracortical connectivity decreases, during transcranial magnetic stimulation, under midazolam sedation [87]. Cortical connectivity is disrupted in several pathological states, such as brain trauma, vegetative state and memory or attention loss.

During mild brain trauma, there have been described frontal and occipital cortical connectivity changes, a decrease of intercortical connectivity over longer distances and an increase of cortical connectivity over shorter distances [88]. The vegetative state is defined as the abolishing of consciousness, while excitatory external factors are present. While in vegetative state, there is a decrease of cortical connectivity in several areas: prefrontal and premotor cortex, temporal-parietal association areas and posterior cingulate cortex. Furthermore, there is an altered connectivity between prefrontal and premotor cortical areas and posterior cingulate cortex [89]. Subcortical cerebrovascular accidents alter cortical connectivity between the two hemispheres: between supplementary motor areas and between ipsilateral supplementary motor area and lateral premotor area. These neural connectivity modifications, both under physiological and under pathological conditions, make cortical connectivity, if not the most sensitive, among the most sensitive parameters of nervous function.

5.1. Evaluating cortical connectivity

5.1.1. Mathematical algorithms to estimate cortical connectivity

Functional cortical connectivity may be estimated by calculating the correlation coefficient between signals of different regions, the covariance or the coherence of two or several signals. The disadvantage of these algorithms is the inability to determine the direction of data exchange between cortical and subcortical areas.

Effective cortical connectivity is estimated with the direct transfer function (DTF), based on Granger causality. Named after Clive Granger, econometrician awarded the Nobel Memorial Prize in Economic Sciences in 2003, the Granger linear systems causality states that for two time series (such as two EEG channels) with a unidirectional data exchange from the Y series to the X series, the modifications from the Y series will be found after a certain amount of time in the X series, or that analyzing Y series data can better predict X series modifications. By evaluating effective connectivity through DTF, we may analyze several time series/ EEG channels. This algorithm was developed by Polish mathematicians Kaminski and Blinowska in 1991 [90].

BSMART is a cortical connectivity analysis software package that can run on the MATLAB program.

Cortical connectivity can also be evaluated through imagistic methods (such as MRI) or electrophysiological methods (EEG).

High-density electroencephalography (64–256 electrodes) can provide information on intercortical connectivity, and is based on EEG signal analysis of different cortical regions. It has the advantage of being usable bedside, and data analysis can be performed more quickly than in the case of imagistic methods [91, 92].

6. Cortical reactivity and coma state

Evaluating cortical reactivity in coma patients seems to be a useful prognostic tool. In 1995, Gütling noticed that cortical reactivity to external stimuli at 48 and 72 hours correlates well with the neurological outcome at 1.5 years after the incident, in the case of severe head injury [93]. More recent studies, performed by Logi and Rossetti, have shown that the presence of EEG reactivity in coma caused by a traumatic brain injury, a cerebrovascular disease or post-anoxic coma after a cardiac arrest associates a good outcome [94, 95]. Although these studies on using cortical reactivity in the evaluation of coma patients prognostic were published in the 1990s, there is no standardization in this matter, neither of evoked potential type, nor of reactivity-evaluating algorithm one should use.

Particularly useful is the BS state, usually correlated with a negative prognostic. Although regarded as a deep coma state, applying visual, auditory **or** somatosensory stimuli under the BS state gives rise to evoked bursts under isoflurane anesthesia, as proven by Hartikainen [96]. During burst suppression states, cortical reactivity seems to rise proportionally with the suppression, with maximal cortical reactivity at a BS ratio of 40–80%. Additional studies are required to validate a parameter for the cortical reactivity of coma patients.

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