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Is your patient sleeping?

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Introduction

The most used means to monitor anaesthesia depth is the analysis of an electroencephalograph (EEG) signal. Although different, two systems are available for clinical practice: the bispectral index (BIS) and the analysis of entropy.

Several studies and cases did report an influence of a muscle relaxant bolus on bispectral values during anaesthesia. Very few report the same problem as regards to entropy.

Entropy is an innovative monitoring modality that is designed to provide information on the electrical activity of the central nervous system during general anaesthesia. Entropy monitoring is based on acquisition and processing of raw EEG and facial electromyograph (FEMG) signals by using the entropy algorithm. This one consists of spectral entropy based on information theory in a Datex-Ohmeda application (Helsinki, Finland) [1,2]. We present two case reports that also show the effect of a muscle relaxant bolus on the Datex-Ohmeda entropy values, which may call in question the reliability of this monitoring mean of anaesthesia depth.

Case description

Case 1

A 70-year-old intensive care patient had been treated for prostate cancer. Radiotherapy had been complicated with recurrent haematurias from 'radic cystitis'. Because of persistent anaemia, despite several limited surgical procedures, the patient had to be operated for an urgent haemostatic cystectomy.

The patient was monitored with standard equipment, including continuous electrocardiography, capnography, pulse oximetry and a neuromuscular monitoring (train of four). He also benefited from an invasive arterial blood pressure measurement, and an analysis of the entropy parameters was provided by the M-ENTROPY analysis module (Datex-Ohmeda), the captor being located frontotemporaly.

The patient's lungs were already mechanically ventilated, and he was continuously sedated with midazolam ($20\,mg\,h^{-1}$) and sufentanil ($20\,\mu g\,h^{-1}$). Along with continuous sedation, ketamine, initially $1\,mg\,kg^{-1}$, then every 20 min, was administered; state and response entropy remained above 90. Forty minutes after the beginning of the procedure, as state entropy and response entropy were still at the same values, myorelaxation was needed and atracurium, $0.4\,mg\,kg^{-1}$, was administered.

A sudden decrease in both state entropy and response entropy to 30 was observed, without any haemodynamic modification. The same phenomenon was observed with subsequent atracurium injections.

Case 2

A 45-year-old woman with liver cirrhosis had to undergo an urgent ligation of gastrooesophageal varices for life-threatening bleeding. Tracheal intubation relayed on a rapid sequence induction with ketamine ($1\,mg\,kg^{-1}$) and succinylcholine ($0.6\,mg\,kg^{-1}$). A target-controlled infusion of propofol was chosen for maintenance of anaesthesia. Because of haemodynamic instability, entropy was monitored, and along with plasma expansion, a perfusion of phenylephrine was started. Entropy, which was initially low (less than 40), rapidly arose to awake values, so that propofol target was progressively increased to $2\,\mu g\,ml^{-1}$, then up to $3\,\mu g\,ml^{-1}$. Despite this maintenance dose, both entropy values remained high (Fig. 1). For facilitation of the procedure, a supplementary dose of celocurine (15 mg) was administered, and surprisingly, entropy values fell to 20. Then, propofol plasma concentration target was kept at $2.5\,\mu g\,ml^{-1}$. After completion of the procedure, the patient was rapidly awaken, and the trachea was extubated. There were no signs of peroperatory memorizing.

Discussion

By adding the measurement of cortical electrical activity, the clinician is meant to assess the effect of anaesthetics more comprehensively. Usually, a sufficient depth of anaesthesia will match a BIS value between 40 and 60, also the same for entropy, but several studies indicate that muscle relaxation may interfere with the BIS. One only relates to entropy.

The most pertinent question finally arising is whether patients are really sleeping or not. In other words, by lowering BIS and entropy values, do muscle relaxants

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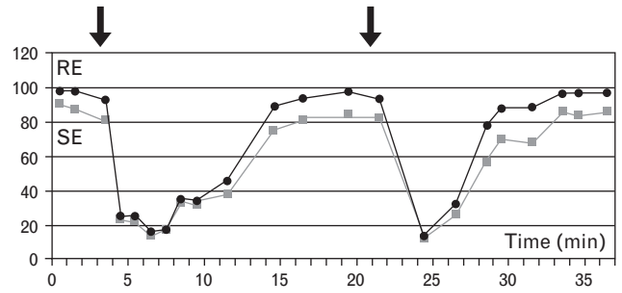
Fig. 1



Response entropy and state entropy trend showing state entropy and response entropy decrease after the injections of succinylcholine (arrows). RE, response entropy; SE, state entropy.

really improve narcosis or, on the contrary, falsify consciousness monitoring? The technical problem is that topographic areas, where the electrical activity of cortical neurones is recorded from, are overlapping that of facial muscles.

BIS pretends to give an estimation of the reliability of the cortical signal by taking the EMG signal into account. As far as long entropy (a measure of disorder) is concerned, this problem seems to be solved with the calculation of two different parameters: the response entropy and the state entropy. Electrical activity of the brain (EEG) changes from irregular to more regular patterns when anaesthesia deepens. Deepening anaesthesia is thus indicated with decreasing entropy values. But similarly, the activity on facial muscles (FEMG) quiets down as the deeper parts of the brain (i.e. brain stem) are increasingly saturated with anaesthetics. Entropy measures the irregularity of EEG and FEMG signals separately [1,2]. Response entropy is a continuous processed variable (range 0–100) for fast detection of activation of facial muscles, that is, FEMG, and state entropy, a continuous processed variable (range 0–91), calculated from the EEG. State entropy has been designed to be sensitive to the hypnotic effect of anaesthetic drugs in the brain [1,2]. EEG and EMG signals are conventionally considered to be situated in the 0.5–30 and 30–300 Hz bands, respectively. In fact, response entropy is computed over a frequency range of 0.8–47 Hz and contains even the higher EMG-dominated frequencies [1]. State entropy is computed over the frequency range of 0.8–32 Hz, which corresponds to the EEG-dominated part of the spectrum, thus primarily reflecting cortical activity. The main difference between response entropy and state entropy indices thus corresponds to the contribution of frequencies between 32 and 47 Hz [2]. In fact, it is clear that contrary to the manufacturer claim, state entropy cannot be considered an entirely specific measure of EEG. Especially, the state entropy frequency range (0.8–32 Hz) overlaps, although partly, the EMG frequency range (30–300 Hz). From our point of view, despite the attempt to differentiate the origin of the two signals, state entropy and response entropy clearly point towards the same activity. Indeed, the calculation of the correlation coefficient for state entropy vs. response entropy from Fig. 1 data gives $r = 0.99$ and $t = 36.7$ ($P < 0.0001$). This definitely confirms that the two values are not independent ones.

Because the frequency composition of EEG and EMG artifact overlap in the 30–50 Hz range, simple filtering will not completely remove EMG artifact from single-channel EEG recordings. Consequently, when the strength of the EMG component becomes significant, relative to the EEG component within the measured signal, EMG signal from the facial muscles may interfere with spectral and bispectral features used to calculate the BIS. EMG contamination in deeply unconscious patients may falsely mimic the EEG of awake patients, and thus falsely increase BIS [3]. Muscle relaxant administration, when paralysing the above mentioned muscles, would then abolish these EMG artefacts, and thus reveal the true level of BIS. This theory may indistinctly apply to entropy, especially response entropy.

It is necessary not to evade an alternative explanation, the so-called 'afferent muscle spindle theory', developed in the 1960s [3], then expanded by Lanier *et al.* [4] to explain their observations that paralysis diminishes EEG activity in dogs. This theory states that stretching or contracting muscle fibres provides significant inputs to arousal centres in the brain. Muscle relaxation would hypothetically decrease arousal stimulation and potentially provide a sedative effect. This theory was consistent with reports of reductions in minimum alveolar concentration in humans [5,6] and dogs [7] related to neuromuscular blockade. However, subsequent studies failed to confirm these findings [8].

What kind of clinical information would be available to confirm our hypothesis? Concerning entropy, very few, and it remains unavoidable to question the case reports that mention unexpected interferences between muscle relaxants and the other EEG-derived signal, namely the BIS. Indeed, several studies mentioned muscle relaxant-related effects on BIS values.

Inoue *et al.* [9] demonstrated that the level of consciousness could be decreased by neuromuscular blockade during moderate sedation, but surprisingly, was not affected during deep sedation. Another study on fully awake volunteers showed that BIS decreased in response to muscle relaxation and paralleled spontaneous EMG activity of facial muscles. In turn, recovery of BIS coincided with the reappearance of spontaneous electromyographic activity [10]. During the entire experiment, the test person had full consciousness and detailed recall

and felt comfortable with mask ventilation. Accordingly, two cases were reported in which the BIS failed to measure depth of anaesthesia but instead was a measure of EMG activity [11]. In the first case, BIS paradoxically increased after the increase in propofol concentration, correlating with increasing EMG activity. In the second case, the administration of a nondepolarizing muscle relaxant decreased the BIS value at constant anaesthetic drug concentrations. In contradiction to these different studies, Greif *et al*. [3] demonstrated that the BIS level and EMG tone were unaltered by mivacurium administration during propofol anaesthesia.

On the contrary, considering the relationships between entropy and muscle relaxation, only one case reported that, in lightly anaesthetized patients, muscle relaxant administration decreases BIS and response entropy but not state entropy values [2]. Contrary to the study by Liu *et al*. [2], both state entropy and response entropy decreased after neuromuscular blockade in the two present case reports. Although the decrease in state entropy, a parameter not meant to be artefacted by EMG activity, could apparently agree with the 'afferent muscle spindle theory', we show that response entropy is clearly correlated with state entropy, and as described above, the experience of awake volunteers demonstrated that a sedative side effect associated with muscle relaxant injection may be excluded [10].

With our case reports relating the sensitivity of state entropy to muscle relaxants, in the last analysis, how strong should our confidence in entropy or BIS data be?

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