Explaining Entropy responses after a noxious stimulus, with or without neuromuscular blocking agents, by means of the raw electroencephalographic and electromyographic characteristics

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Key points

- Skin incision may cause simultaneous EMG and EEG arousals, sometimes only EEG arousal is detected.
- The respective power spectra of EEG and EMG overlap significantly at frequencies of 20–50 Hz.
- Response Entropy is susceptible to the use of rocuronium, limiting its usefulness in detecting noiception.
- In cases of misleading numerical values, the correct interpretation of the raw signal is necessary.

Background. Entropy™, an anaesthetic EEG monitoring method, yields two parameters: State Entropy (SE) and Response Entropy (RE). SE reflects the hypnotic level of the patient. RE covers also the EMG-dominant part of the frequency spectrum, reflecting the upper facial EMG response to noxious stimulation. We studied the EEG, EMG, and Entropy values before and after skin incision, and the effect of rocuronium on Entropy and EMG at skin incision during sevoflurane–nitrous oxide (N₂O) anaesthesia.

Methods. Thirty-eight patients were anaesthetized with sevoflurane–N₂O or sevoflurane–N₂O–rocuronium. The biosignal was stored and analysed off-line to detect EEG patterns, EMG, and artifacts. The signal, its power spectrum, SE, RE, and RE–SE values were analysed before and after skin incision. The EEG arousal was classified as β (increase in over 8 Hz activity and decrease in under 4 Hz activity with a typical β pattern) or δ (increase in under 4 Hz activity with the characteristic rhythmic δ pattern and a decrease in over 8 Hz activity).

Results. The EEG arousal appeared in 17 of 19 and 15 of 19 patients (NS), and the EMG arousal in 0 of 19 and 13 of 19 patients (P < 0.01) with and without rocuronium, respectively. Both β (n = 30) and EMG arousals increased SE and RE. The δ arousal (n = 2) decreased both SE and RE. A significant increase in RE–SE values was only seen in patients without rocuronium.

Conclusions. During sevoflurane–N₂O anaesthesia, both EEG and EMG arousals were seen. β and δ arousals had opposite effects on the Entropy values. The EMG arousal was abolished by rocuronium at the train of four level 0/4.

Keywords: anaesthetics volatile, sevoflurane; depth of anaesthesia; measurement techniques, electromyography; monitoring, electroencephalography; neuromuscular block, rocuronium

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One of the commercially available depth of anaesthesia monitors based on EEG is M-Entropy™ module (GE Healthcare, Helsinki, Finland), which calculates the characteristics of upper facial biosignal with an analysis of time–frequency balanced spectral entropy, taking into account the amount of suppressed EEG signal. The resulting index of EEG and EMG activities, Entropy, has been shown to be a valid indicator of the hypnotic effect of propofol, thiopental, isoflurane, sevoflurane, and desflurane.

Entropy yields two parameters: State Entropy (SE) and Response Entropy (RE). SE, computed over the EEG-dominant (0.8–32 Hz) frequency range, reflects the cortical state of the patient. RE, computed over the EEG- and EMG-dominant frequency ranges (0.8–47 Hz), serves at least partly as an indicator of upper facial EMG activation, which has been shown to represent nociception or impending awakening.

The studies about the effect of neuromuscular blocking agents (NMBAs) on the depth of anaesthesia monitors have been conducted under many different study regimens and in different surgical settings, so they have yielded different results. First, EMG has been reported to influence the reliability of the depth of anaesthesia monitors. The
Bispectral Index\textsuperscript{TM} (BIS) values have been falsely elevated by EMG activity in anaesthetized and sedated patients.\textsuperscript{3, 6} However, during deep propofol anaesthesia (BIS<50) without nociceptive stimuli, NMBAs did not have an effect on the BIS values.\textsuperscript{7} Low-frequency (\textless{}32 Hz) EMG activity has led to misleading Entropy values during propofol anaesthesia without NMBAs.\textsuperscript{3} It has been reported that rocuronium alters the RE and RE–SE responses to laryngoscopy\textsuperscript{10} and that the rocuronium-induced alteration in the RE–SE response to intubation is dose-dependent.\textsuperscript{11}

Since the introduction of Entropy in 2004, its behaviour during anaesthesia and nociceptive stimuli has been studied extensively. In these studies, the focus has been on the numerical values, and the analysis of the signal per se has been neglected. The original biosignal, or even the spectral analysis of the biosignal, has only rarely been compared with the index values.\textsuperscript{3}

The primary endpoint of this study was the behaviour of original biosignal, both its visual appearance and spectral content for EEG and EMG signs of arousal, before and after skin incision during sevoflurane–nitrous oxide (N\textsubscript{2}O) anaesthesia, in patients with or without rocuronium. The secondary endpoints were the effects of EMG and EEG arousals on the Entropy parameters, and the effect of rocuronium on the Entropy’s numerical values.

\section*{Methods}

This study followed the design of a prospective clinical study. After the approval of the local Ethics Committee and Finnish National Agency for Medicines and after written informed consent, 39 female patients undergoing laparoscopic gynecological surgery were studied. Inclusion criteria were: expected duration of operation \textgreater{}30 min, age 18–60 yr, and ASA physical status 1 or II. Patients were excluded if they had a disease or an injury affecting the central nervous system, alcohol or drug abuse, or BMI \textgreater{}28. All patients fasted overnight before surgery.

\section*{Anaesthesia and study protocol}

The original biosignal, Entropy parameters calculated from the biosignal, and vital signs were collected on a laptop computer under two anaesthetic regimens, both of which included premedication with diazepam 10 mg p.o. Premedication was given to all patients 60 min before induction of anaesthesia. An i.v. route was established for all patients and an infusion of isotonic saline was started. Intermittent non-invasive arterial pressure was recorded every 5 min. Electrocardiogram, inspired fractions (F\textsubscript{I}), end-tidal concentrations of anaesthetic gases and CO\textsubscript{2}, and peripheral oxygen saturation were continuously monitored with the Datex-Ohmeda S\textsuperscript{5}\textsuperscript{TM} Anaesthesia Monitor.

Twenty patients were administered propofol 1 mg kg\textsuperscript{-1} i.v., followed by manually controlled ventilation with 8% sevoflurane in a 67% N\textsubscript{2}O–oxygen mixture via a face mask. Tracheal intubation was performed, as gently as possible, 150 s later. If intubation difficulties were met, mask ventilation was restarted and another intubation attempt was made 1–3 min later. If the second attempt was unsuccessful, rocuronium was given and the patient was discarded from the study. After securing the airway, controlled mechanical ventilation was started with a fresh flow of 6 litre min\textsuperscript{-1} (67% N\textsubscript{2}O in oxygen). To facilitate the intubation conditions, relatively high sevoflurane concentrations (up to 8\%) were used before laryngoscopy. After successful intubation, the sevoflurane concentration was adjusted to keep SE between 40 and 60, the target value being 50. In the case of an increase in SE above 65, as a rescue medication, the sevoflurane vaporizer was adjusted according to the anaesthesiologist’s judgement, up to maximum (F\textsubscript{I} 8\%), in order to prevent awareness. After a rescue bolus of sevoflurane, the sevoflurane vaporizer was readjusted once the SE values decreased below 60.

Nineteen patients were anaesthetized the same way as described above, but once the entropy values decreased below 50, patients received rocuronium 0.6 mg kg\textsuperscript{-1}. Tracheal intubation was performed after neuromuscular transmission was 0/4. Neuromuscular transmission was monitored with the M-NMT Mechnosensor\textsuperscript{TM} (Datex-Ohmeda, Helsinki, Finland) and assessed using the train of four (TOF) stimulation mode. The calibration of the Mechnosensor was performed in all patients according to the manufacturer’s guidelines before NMBA administration.

After tracheal intubation, commencement of ventilation, and preparing the patient for surgery, the permission to start laparoscopy was granted. Before surgical manipulation, the patient was not touched or otherwise disturbed for 5 min to ensure artifact-free data collection. The setting of the patient to the gynaecological position, washing of the abdomen, application of the sterile drapes, and the 5 min equilibrium period amounted to a mean of 21 and 29 min between intubation and skin incision in groups with and without NMBA, respectively. An additional 10 mg bolus of rocuronium was given for eight patients, whose TOF exceeded 0/4. The study was completed 1 min after setting of the first laparoscopy trochar. Thereafter, the administration of N\textsubscript{2}O was discontinued and the patient’s lungs were ventilated with air/O\textsubscript{2} (F\textsubscript{I}O\textsubscript{2} 0.33). After completion of the study period, fentanyl and rocuronium were given according to clinical needs. All patients were interviewed during the first postoperative day, regarding their possible anaesthesia- and surgery-related memories and intubation-associated sequelae. Furthermore, the patients were encouraged to report their possible operation-related memories later on to the researchers by phone.

\section*{EEG acquisition}

Entropy monitoring started before induction of anaesthesia and continued uninterrupted until the end of the study. The forehead biosignal was collected with a disposable electrode strip (Entropy Sensor, GE Healthcare) for Entropy measurement. After de-greasing of the forehead skin using 70% isopropanol, the strip was positioned as recommended...
by the manufacturer. The signal was acquired from two electrodes of the strip: one frontally in the midline, 2 cm above the eyebrows, and the other 2 cm laterally from the outer canthus of the left eye. The first electrode was on the frontalis muscle, recording the EEG from the frontalis poles, and the second electrode was on the orbicularis oculi and temporal muscles, recording the EEG from the frontalis and temporal lobes, including the basal forebrain and the medial temporal cortex. The EEG was collected with an Entropy Module of the S/5SM Anaesthesia Monitor (GE Healthcare), with a sampling rate of 400 Hz. High- and low-pass filters of 0.5 and 118 Hz (–3 dB; 60 dB/decade), respectively, were applied. A power-line artifact at 50 Hz was not filtered. The EEG was downloaded and stored on a laptop computer with S5 Collect software (GE Healthcare).

Analyses of the biosignal

The raw signal was analyzed with high resolution, and with the power spectrum. The typical EMG pattern in the original signal, with a considerable power increase of above 40 Hz, was classified as EMG arousal. The depression of δ (<4 Hz) activity, increase in over 8 Hz activity, and minimal increase of above 40 Hz, together with the characteristic β pattern, were classified as β arousal. Skin incision-associated increase in δ activity and a simultaneous decrease in over 8 Hz activity were classified as δ arousal.

Spectrogram, that is, a presentation of the spectral content of a biosignal, was produced with SomnologicaTM sleep analysis program (Medcare Flaga, Reykjavík, Iceland). In such a presentation, power spectra of consecutive 1.0 s samples of the signal are calculated and presented vertically in the direction of the y-axis and plotted against time in the x-axis. The density (i.e. ‘darkness’) of the spectrogram reveals the amount of activity at the respective frequency. Thus, the spectrogram presents the same information as successive power spectra, but in a compressed form. A power-line artifact is seen in the spectrogram as a sharp activity band at 50 Hz, and an ECG or electro-oculogram artifact is typically located at a rather low-frequency range. Therefore, an EMG is virtually the only artifact that is displayed over a wide frequency range.

In statistical analyses, RE and SE values were analyzed off-line as a mean of 15 s (three consecutive readings collected by the S5 Collect software) 1 min before and 1 min after commencement of surgery. The RE–SE difference was calculated by subtracting the SE value from the simultaneous RE value.

Both the raw biosignal and the spectrogram at the time point of skin incision were inspected visually off-line, without knowledge of the behaviour of Entropy indices, by an experienced clinical neurophysiologist (V.J.), to judge the presence or absence of an EMG. Later on, all authors, to ensure the agreement of the detections, analyzed the traces and classifications jointly. To analyze the effect of EMG on the EEG spectrum, power spectra before and after commencement of surgery were drawn in all patients. In the calculation of the power spectrum, a window of 10 s was used.

Statistical methods

Owing to the fact that the actual biosignal has not been previously studied in the present setting, the power calculation was based on the behaviour of RE–SE difference, a phenomenon thought to reflect EMG activation. In the power calculation, the results of Hans and colleagues10 (RE–SE difference of 4 units with rocuronium and 11 units without rocuronium, SD 6 units) were utilized. Because sevoflurane and N2O possess anti-nociceptive properties (in the study by Hans and colleagues, propofol was used as an anaesthetic agent), a 50% reduction in the RE–SE difference and the SD was assumed. To test whether the RE–SE difference is lower when NMBAs are used, the study was designed to have a power of 80% to detect a statistical significance in the RE–SE difference between groups with and without rocuronium, assuming a two-sided α level of 0.05, with nociception-associated mean RE–SE differences of 2 and 5.5 units (SD 3 units) between groups, respectively. To meet the criteria of power calculation, 12.5 patients per group would be needed. All statistical analyses were performed using SPSS for Windows software (version 16.0, SPSS, Chicago, IL, USA). One-way analysis of variance (ANOVA), followed by t-tests were performed for parametric data, or by χ² tests for non-parametric comparisons, where appropriate. A value P<0.05 was considered statistically significant.

Results

One enrolled patient without rocuronium was excluded because of problems in laryngoscopy and intubation. All others were successfully intubated with one or two attempts. Therefore, 19 patients receiving sevoflurane–N2O and 19 patients receiving sevoflurane–N2O–rocuronium were studied. Patient characteristics did not differ between groups. The mean ages of patients in the sevoflurane–N2O group and those in the sevoflurane–N2O–rocuronium group were 33 and 31 yr, mean weights were 66 and 63 kg, and mean heights were 167 and 167 cm, respectively.

Before skin incision, rescue medication, that is, a rapid increase in inspired sevoflurane concentration, was given to five patients (three with and two without rocuronium). These boluses were given 5, 5, 6, 12, and 13 min before skin incision, respectively.

Skin incision caused a decrease in EEG δ activity and an increase in over 8 Hz activity in 15 patients with rocuronium and in 15 patients without rocuronium. Simultaneous EMG occurred in 13 of the subjects not receiving rocuronium. No EMG was seen in patients with rocuronium (P<0.001). After skin incision, rescue medication was given to 24 patients (9 and 15 patients with and without rocuronium, respectively). The rescue medication was followed by a decrease in over 8 Hz activity and by an increase in δ activity. However, EMG activity continued. In this study, the EMG never appeared without the β arousal. In two patients not receiving rocuronium, the β arousal appeared without the EMG. The incidence of detected EMG in both groups, and the association
between the EMG and the RE–SE difference, RE, and SE, is given in Table 1.

The spectrogram, RE and SE values, end-tidal sevoflurane concentration, and heart rate from the awake state until the end of the study period in an example patient are depicted in Figure 1.

In two patients with rocuronium, the EEG arousal was classified as δ arousal. The δ arousal consisted of an increase in high-amplitude δ activity and a decrease in over 8 Hz activity. Figure 2 shows an example of a δ arousal and its effects on Entropy’s numerical values, 8–13 and 0.5–4 Hz frequency bands, the original biosignal, and the power spectra before and after the arousal.

Rocuronium altered the entropy RE–SE response to skin incision. The skin incision produced a significant increase in RE and SE in both groups, whereas RE–SE increased only in patients without rocuronium. After skin incision, there were significant between-group differences in RE and RE–SE (Fig. 3). Heart rate before skin incision was higher in patients with rocuronium than in those without rocuronium. Skin incision caused an increase in heart rate in both groups.

**Discussion**

The first finding in our study was that skin incision caused both EMG and EEG arousals. The two arousals often occurred simultaneously, but in some patients, only the EEG arousal was detected. In patients receiving rocuronium, the EMG arousal was abolished and only the EEG arousal was seen. Most EEG arousals consisted of mixed high-amplitude slow activity turning into higher frequency low-amplitude activity, that is, β arousal. In two patients, skin incision caused a mixed frequency EEG to turn into high-amplitude δ activity and the vanishing of the high-frequency activity, that is, δ arousal. The δ arousal is also called ‘paradoxical’ or ‘reverse’ arousal.12

Spectral entropy yields high values when the power spectrum is flat and low values when the power spectrum is more uneven.2 During deepening anaesthesia, the slow activity in the EEG gradually increases, producing an increasing spectral peak at the lower frequency edge of the power spectrum, and this causes a decrease in spectral entropy, and correspondingly, a decrease in RE and SE.

The EMG and β arousals cause an increase in Entropy values and lead the anaesthesiologist to deepen the level of anaesthesia. The EMG contamination of EEG can lead to overdosing of anaesthetic agents. The δ arousal and the following decrease in SE values, if interpreted incorrectly, can lead to decreasing of the anaesthetic concentration, therefore increasing the risk of intraoperative awareness. It has been suggested that the δ arousal occurs when a patient is exposed to surgical stimuli during inadequate analgesia.13 14

The neurophysiological mechanisms of arousal during anaesthesia are poorly known. They are probably closely related to arousal mechanisms of sleep, which can also produce both β and δ arousals, especially in children.15 Studies done with cats indicate that slow EEG δ activity may
be related to the activation of the reticular formation of the brainstem.\textsuperscript{16}

An example of the δ arousal after skin incision, that is, an increase in δ activity and a decrease in over 8 Hz activity, is shown in Figure 2. In the logarithmic power spectrum, the peak on the left increases, while activity around 20 Hz decreases. This produces a more peaked and uneven power spectrum with a corresponding decrease in spectral entropy. The RE and SE values decrease to levels of deep anaesthesia, usually seen during almost continuous EEG suppression. In the recording displayed in Figure 2, however, no EEG suppressions appeared.

Fig 1 The whole study period in one patient anaesthetized without rocuronium. (a) The numerical values of SE and RE. (b) The end-tidal sevoflurane concentration. (c) Heart rate. The artifacts at \textasciitilde 16 min caused by patient positioning have been dimmed. (d) The spectrogram of the signal recorded with Entropy sensor. The Roman numeral ‘I’ refers to the time point of the power spectrum before intubation, shown as dimmed line in (f). The Roman numerals II, III, and IV refer to the 10 s samples of the original biosignal and to the corresponding power spectra, presented in (e–j). (e) A 10 s sample of the original biosignal at the time of intubation. EMG causes an increase in SE and RE values to maximum. The EEG, however, shows high voltage slow activity which together with high end-tidal sevoflurane concentration, suggests that the patient was deeply unconscious. (f) The respective power spectrum from the same time period. EMG causes a typical increase in the high frequencies of the spectrum. (g) A 10 s sample of the original biosignal \textasciitilde 1 min before skin incision, showing mixed activity. (h) The respective power spectrum from the same period, showing δ activity and a peak around 10 Hz (α activity). (i) A 10 s sample of the original biosignal shortly after the beginning of the operation, showing β activity. (j) The respective power spectrum of (i). A decrease in low frequencies and increased β activity at \textasciitilde 20 Hz indicate EEG arousal. The β activity causes the power spectrum to be more even and flat, increasing the SE and RE to almost awake values, although the patient is in surgical anaesthesia. The raw signal is distinctly different from a typical awake signal. The power at 30–50 Hz also increases during β arousal, which is visible in the spectrogram.
Our second observation was the considerable EMG activity already at frequencies <20 Hz and EEG β activity exceeding 20 Hz, demonstrating that the respective power spectra of EEG and EMG overlap significantly (Fig. 1). Owing to their overlapping power spectra, the contribution of the EEG and the EMG cannot be accurately separated by Entropy. Visually, it is sometimes impossible to distinguish between β activity and the EMG in sleep or anaesthesia recordings, as the EMG generated at a distance from the recording electrodes loses its sharp, spiky appearance. In our opinion, this finding explains the numerous reports where NMBAs have been shown to have an effect on numerical values of the depth of anaesthesia monitors. It also helps us understand why the effect of NMBAs on the depth of anaesthesia monitors varies from one setting to another. The level of anaesthesia, the presence or absence of nociceptive stimuli, the use of anti-nociceptive medication, patient anxiety, and possibly many other confounding factors have contributed to different findings in previous studies. Therefore, in future studies, one should focus both on the original biosignal in the time and frequency domain and on the numerical values of the depth of anaesthesia monitors.

Finally, the third finding in our study was the change in the numerical values of RE, SE, and RE–SE during skin incision. In patients without rocuronium, skin incision caused a significant increase in RE, SE, and RE–SE. In patients receiving rocuronium, skin incision caused a significant increase in RE and SE, whereas no change was detected in RE–SE.

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| Fig 2 | The whole study period in one patient anaesthetized with sevoflurane–N₂O–rocuronium. (A) The numerical values of SE and RE. (B) The end-tidal sevoflurane concentration. (C) Heart rate. (D) Band-pass-filtered EEG 8–13 Hz (α activity); plotted strongly compressed to demonstrate amplitude changes. (E) Band-pass-filtered EEG 0.5–4 Hz, i.e. δ activity. (F and G) A 10 s sample of the original biosignal and the respective power spectrum; plotted from a time point I (before skin incision). (H and I) A 10 s sample of the original biosignal and power spectrum from the time point II (after skin incision). |
skin incision, RE and RE–SE were lower in patients with rocuronium. The behaviour of RE, SE, and RE–SE during commencement of surgery leads us to suggest that Entropy monitoring is susceptible to the use of rocuronium, limiting the usefulness of RE and RE–SE in detecting nociception with a strong neuromuscular block.

A direct effect of NMBAs on the depth of anaesthesia has also been suggested. A controversial ‘afferent muscle spindle’ theory postulates that NMBAs would reduce the muscle tone and the amount of proprioceptive inputs to the reticulo-thalamic activating system, thus reducing the level of arousal, but also disputed by some more recent studies. Before skin incision, end-tidal sevoflurane concentrations in groups with and without rocuronium were 1.11 (0.23) and 1.01 (0.32), respectively (NS). However, since our study design and power analysis were not intended to address the afferent muscle spindle theory, we cannot comment on it.

The behaviour of heart rate during commencement of surgery was not very surprising, as heart rate is often regarded as a standard indicator of nociception. As to why the heart rate before commencement of surgery was higher in patients receiving rocuronium, we have two possible explanations. First, rocuronium may release histamine, thus raising heart rate, although the histamine-releasing effect has been described only after rocuronium doses of >1.2 mg kg$^{-1}$1,2. Secondly, rocuronium is a potentially vagolytic drug, therefore increasing heart rate. Both of these explanations are not totally satisfying and the true nature of the increased heart rate in patients receiving rocuronium may remain unrevealed. Interestingly, also Hans and colleagues reported a higher heart rate in patients receiving rocuronium, but they concluded that a higher heart rate was not clinically significant and that the difference in heart rate did not change during intubation.

The characteristic patterns of signal and its power spectrum allowed us to classify β and EMG arousals. However, they often occur simultaneously, and to more accurately detect them, more than one channel should be recorded. In this study, we were restricted to the single-channel recording of the Entropy monitor.

In conclusion, skin incision can cause both EEG and EMG arousals. EEG arousal can be either β or δ arousal. The β and EMG arousals increase the Entropy values, leading the anaesthesiologist to increase the concentration of anaesthetic agents. The δ arousal decreases the Entropy values and may lead the anaesthesiologist to falsely decrease the concentration of the anaesthetic agent. To avoid misinterpretation of the depth of anaesthesia indices, the display and correct interpretation of the raw signal is necessary. All anaesthesiologists using these monitors should be familiar with the effects of EMG and EEG arousal patterns and understand why they may cause misleading index values.

Conflict of interest
A.Y.-H. is a paid consultant for GE Healthcare Finland.

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Fig 3 The behaviour of RE, SE, RE–SE, and HR (mean±sd) 1 min before and 1 min after skin incision in patients anaesthetized with sevoflurane–N₂O or sevoflurane–N₂O–rocuronium. *P<0.05 and **P<0.01 between the groups; *P<0.05 and **P<0.01 within the groups.
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