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Assessing the depth of dexmedetomidine-induced sedation with electroencephalogram (EEG)-based spectral entropy

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Background: Adequate sedation of critically ill patients improves the outcome of intensive care. Maintaining an optimal level of sedation in the intensive care unit (ICU) is difficult because of a lack of appropriate monitoring methods to guide drug dosing. Dexmedetomidine, a selective α_2 -adrenoceptor agonist, has recently been introduced for the sedation of ICU patients. This study investigated the utility of electroencephalogram (EEG)-based spectral entropy monitoring (with M-ENTROPY™, GE Healthcare, Helsinki, Finland) for the assessment of dexmedetomidine-induced sedation.

Methods: Eleven healthy, non-smoking men, aged 23.9 ± 2.5 years (mean \pm standard deviation), were recruited. Spectral entropy was recorded before and during low (0.5 ng/ml) and high (5 ng/ml) plasma concentrations of dexmedetomidine. At the end of the infusion, subjects were awakened by verbal command and light shaking.

Results: Spectral entropy decreased from 84 ± 5 to 66 ± 16 ($P = 0.029$) during low dexmedetomidine levels and from 84 ± 5 to 20 ± 12 ($P < 0.001$) during high dexmedetomidine levels.

Transitions during loss and regaining of consciousness were analysed separately. Entropy decreased from 76 ± 8 before to 43 ± 10 ($P < 0.001$) after loss of consciousness, and increased from 14 ± 4 to 63 ± 13 ($P < 0.001$) on regaining of consciousness. These changes were consistent across all subjects. Prediction probability and sensitivity values indicated a high predictive performance of the method.

Conclusion: The depth of dexmedetomidine-induced sedation can be monitored with EEG-based spectral entropy. These results should be confirmed in a clinical setting.

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Key words: α_2 -adrenergic agonists; dexmedetomidine; electroencephalogram; electroencephalogram-based spectral entropy; intensive care unit; monitoring; sedation.

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THE administration of sedative drugs is an important part of the treatment of patients in the intensive care unit (ICU), and the optimization of individual dosing of sedatives facilitates the outcome of intensive care (1, 2). An optimal level of sedation in the ICU is defined as a calm and comfortable patient who can be easily aroused, with maintenance of the normal sleep–wake cycle (3). Adequate sedation is also required to reduce anxiety and disorientation and to minimize discomfort during mechanical ventilation. Monitoring the level of sedation of critically ill patients in the ICU is difficult; both over-sedation and agitation as a result of under-sedation should be avoided by frequent assessments (4). The excessive use of sedatives results in the prolongation of

mechanical ventilation and length of ICU stay and increases the complication rates and, ultimately, the costs of ICU treatment (1, 2, 5, 6). The continuous use of sedatives also complicates neurological examination of the patient, and may possibly prevent the early detection of acute delirium or harmful intracranial events (1).

Subjective clinical scoring systems for the estimation of the level of sedation are available, but are not applicable for deeply sedated or relaxed patients. Therefore, a validated and reliable objective method to assess the depth of sedation in the ICU is needed. New electroencephalogram (EEG)-based monitors have been introduced to assess the hypnotic component of general anaesthesia. The recently released

Entropy Monitor (GE Healthcare, Helsinki, Finland) has been shown to be a valid indicator of the hypnotic effects of propofol, thiopental, sevoflurane, isoflurane and desflurane during general anaesthesia (7–10). The Entropy Monitor calculates the time-frequency-balanced spectral entropy of the EEG signal and generates two indices: the state entropy (SE), which reflects the cortical activity of the patient, and the response entropy (RE), which also includes frontal electromyographic (EMG) activity (11).

Dexmedetomidine is a potent, highly selective adrenergic α_2 -receptor agonist. It is used for the short-term sedation of patients undergoing mechanical ventilation in the ICU. Intravenous infusion of dexmedetomidine induces sympatholytic effects, including sedation and decreased blood pressure and heart rate. Dexmedetomidine has no clinically significant adverse effects on respiration (12–14), and has been shown to provide effective post-surgical analgesia (15, 16). Furthermore, patients sedated with dexmedetomidine remain cooperative and can be easily aroused for procedures and clinical testing (13, 17, 18).

As patients receiving dexmedetomidine can be easily aroused also from deeper levels of sedation, conventional sedation scoring systems that are based on clinical observations may not be ideal for monitoring dexmedetomidine-induced sedation. Furthermore, the use of acoustic and tactile stimulation related to conventional scoring systems may cause undesired arousal and agitation in these patients (19). EEG-based monitoring may thus offer a more adequate assessment of sedation when using dexmedetomidine. This study was conducted to determine the performance of the Entropy Monitor in the assessment of sedation during dexmedetomidine infusion, and to investigate dexmedetomidine-induced changes in classical quantitative EEG variables in healthy subjects.

Methods

Subjects

The data were collected in a study assessing the effects of dexmedetomidine on myocardial perfusion using positron emission tomography (20). The study protocol was approved by the Ethical Committee of the Hospital District of South-west Finland (Turku, Finland). After giving written informed consent, 12 healthy (American Society of Anesthesiologists physical status class I), non-smoking, male volunteers, aged 23.9 ± 2.5 years [mean \pm standard deviation (SD)] (range, 20–28 years), with a body mass index of 23.7 ± 2.3 kg/m², were recruited. The EEG recording from one subject failed because of technical problems, and

therefore the present study is based on 11 subjects. All subjects underwent a detailed health examination, including an interview, physical examination, laboratory screening, bicycle maximal exercise test and a 12-lead electrocardiogram. None of the subjects had a history of cardiac arrhythmia, drug allergies, allergic reactions or ongoing medications. The subjects refrained from consuming alcohol or any medication for 48 h, and fasted from midnight prior to the study.

Study design

This open-label, non-randomized, dose-escalation study consisted of three phases: without drug (BASELINE), targeted plasma dexmedetomidine concentration of 0.5 ng/ml (LOW DEX) and targeted plasma dexmedetomidine concentration of 3.2 ng/ml (HIGH DEX). The study design is presented in Fig. 1. A Harvard 22 syringe pump (Harvard Apparatus, South Natick, MA), connected to a portable computer running Stanpump software (available at <http://anesthesia.stanford.edu/pkpd>), was used to administer dexmedetomidine (Precedex[®] 200 μ g/2 ml, Abbott Laboratories, Abbott Park, IL) as a continuous intravenous target-controlled infusion. We used the same pharmacokinetic parameters of dexmedetomidine as employed by Talke et al. (21). A moderate overshooting of dexmedetomidine concentration in plasma was expected during HIGH DEX (12, 22). During LOW DEX, the measured (mean \pm SD) plasma concentration of dexmedetomidine was

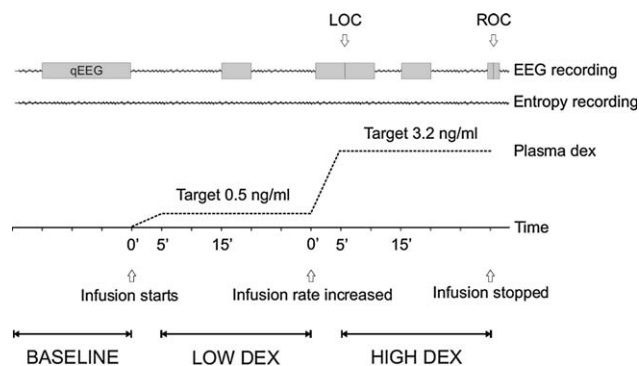


Fig. 1. Outline of the study design and set-up. After the baseline measurements had been completed, the LOW DEX phase was started with a dexmedetomidine infusion targeted to a plasma drug concentration of 0.5 ng/ml. HIGH DEX was started by increasing the rate of dexmedetomidine infusion to target a plasma concentration of 3.2 ng/ml. Entropy and electroencephalogram (EEG) were recorded continuously throughout the study. Quantitative EEG (qEEG) analysis was performed at baseline, during LOW DEX and HIGH DEX, and before and after loss and regaining of consciousness (LOC and ROC) at the time periods illustrated by the grey squares on top of the EEG recording line. See text for details. DEX/dex, dexmedetomidine.

0.5 ± 0.1 ng/ml and during HIGH DEX 5.1 ± 1.0 ng/ml. During LOW DEX the subjects were allowed to lie quietly. When the infusion of the higher targeted concentration was initiated, the subjects were asked to squeeze the investigator's hand twice at approximately 10-s intervals. Failure to comply was interpreted as a loss of consciousness (LOC). At the end of the HIGH DEX infusion, regaining of consciousness (ROC) was defined as the moment at which the subject could be aroused by calling his name and shaking slightly, if needed. A meaningful response was considered to indicate arousal.

Electrophysiological recordings

After cleaning the skin of the forehead with an alcohol swab, the self-adhesive electrode strip (Entropy Sensor, GE Healthcare) was positioned on the forehead as recommended by the manufacturer. The Entropy Sensor records electroencephalographic and EMG activity with a fixed electrode set recording the EEG of the frontopolar–anterior temporal region. The algorithm used in the GE Datex-Ohmeda S/5™ Entropy Module is based on time–frequency-balanced spectral entropy (7). In this device, SE is calculated over the frequency range 0.8–32 Hz, and is dominated by the EEG reflecting primarily the activity level of the cortical neurons. RE is computed over the frequency range 0.8–47 Hz, and includes more frontal EMG activity than SE. RE therefore reacts rapidly to the restoration of muscle tone indicating lightening of anaesthesia. These two values are displayed on the monitor screen, and vary between 0 and 91 (SE) and 0 and 100 (RE), high values indicating a conscious and alert state and low values indicating deeper levels of hypnosis (11).

After a sufficient stabilization period, baseline EEG and entropy data recording was started using a GE Datex-Ohmeda S/5 Anaesthesia Monitor (GE Healthcare). A portable computer running S/5 Collect software (GE Datex-Ohmeda S/5 Collect Version 4.0, GE Healthcare) was used to record the individual values of SE and RE at intervals of 10 s and the digital EEG (sampling rate, 400 Hz) throughout the study. SE and RE were continuously recorded on line with the Entropy Module. Raw EEG data were analysed visually off line, and artefact-contaminated EEG segments were excluded. Only epochs without high-amplitude artefacts, such as eye movements, and with stable baseline were included in power spectral analysis. The epoch length was 5 s.

All EEG variables were calculated for the following periods: BASELINE, 20-min period starting after

a stabilization period of approximately 30 min at the baseline (60 ± 64 epochs in spectral analysis); LOW DEX, 5-min period starting 15 min after the start of the dexmedetomidine infusion aiming at a pseudo-steady-state plasma drug concentration of 0.5 ng/ml (51 ± 13 epochs); HIGH DEX, 5-min period starting 15 min after the start of the dexmedetomidine infusion aiming at a pseudo-steady-state plasma drug concentration of 3.2 ng/ml (54 ± 10 epochs); before LOC, 5-min period before LOC (31 ± 16 epochs); after LOC, 5-min period after LOC (56 ± 6 epochs); before ROC, 1-min period before ROC (10 ± 2 epochs); after ROC, 1-min period after ROC (9 ± 3 epochs) (Fig. 1). The first analysis period (BASELINE) was longer than the subsequent sampling times (5 and 1 min) because of excessive eye movements and other artefacts contaminating the EEG signal at the baseline. SE and RE values decreased smoothly at LOC, and therefore the 5-min period was considered to be sufficient. Changes in the SE and RE values were more rapid at ROC (Fig. 3, see later), and therefore a 1-min sampling time was chosen to provide precise information about the transition phase.

EEG data were processed with Matlab 6.5 (The Mathworks Inc., Natick, MA). Absolute power spectra ($\mu\text{V}^2/\text{Hz}$) of each 5-s epoch were obtained with the psd function of Matlab. The psd function utilizes fast Fourier transformation with Hanning windowing. Power spectra from individual epochs were averaged to obtain final power spectra for each analysis period. Absolute band powers (μV^2) were calculated from the power spectra in the following frequency bands: delta (1.0–3.2 Hz), theta (3.4–8.0 Hz), alpha (8.2–13.0 Hz), beta (13.2–30.0 Hz), total power (1.0–30.0 Hz), EMG (55.0–145.0 Hz) and the following additional narrow bands: slow theta (3.2–5.0 Hz), fast theta (5.2–8.0 Hz), slow beta (13.2–20.0 Hz) and fast beta (20.2–30.0 Hz). The relative power (%) for each band was calculated by dividing the power in each frequency band by the total power. In addition, the 95% spectral edge frequency (SEF95) from the frequency range of 1.0–30.0 Hz was calculated (the frequency below which 95% of the total EEG power is found). The frequency range 1.0–30.0 Hz was chosen because of the abundant EMG activity during light sedation and because this range has been used commonly in anaesthesiologic EEG studies.

Statistical analyses

Entropy and EEG variables were analysed using repeated measures analysis of variance (RM ANOVA), with dexmedetomidine concentration as

a within-factor. Logarithmic transformation was applied when necessary to meet the assumption of normality prior to statistical analyses. Linear contrasts within the same RM ANOVA model were used to estimate differences between the levels. Tukey–Kramer correction was applied for multiple comparisons. A two-sample *t*-test was used to test for differences between the EEG variables before and after LOC and ROC. A two-sided *P*-value of less than 0.05 was considered to be statistically significant. Statistical analyses were conducted using SAS (version 8.2, SAS Institute Inc., Cary, NC). Data are presented as the mean \pm SD unless stated otherwise.

Performance analyses were carried out with both RE and SE values against clinical observation (conscious or unconscious). Data from the 20-min time window starting at the beginning of HIGH DEX were used in the analysis. Thus, this time period includes data before and after LOC. Subjects were allowed to fall asleep during LOW DEX, which caused low entropy values during that period. However, at the beginning of HIGH DEX, all subjects were awakened. The prediction probability (P_K) describes the ability of SE and RE to discriminate between conscious and unconscious states. P_K and its standard error were calculated with the jackknife method from pooled data over all subjects (23). In general, P_K estimates the performance of the anaesthetic depth indicator independently of the choice of cut-off point. It gives the probability that the indicator values of two randomly selected data points predict correctly the clinical states (conscious or unconscious). A value of $P_K = 0.5$ indicates that the indicator predicts the observed anaesthetic depth with no better than a 50 : 50 chance, and a value of $P_K = 1$ indicates that the indicator always correctly predicts the observed anaesthetic depth. The performance was further evaluated using sensitivity, specificity and positive and negative predictive values. Cut-off points were optimized from receiver operating characteristic curves to maximize the sum of sensitivity and specificity. The sensitivity was defined as the proportion of entropy values indicating consciousness during the conscious state. The specificity was defined as the proportion of entropy values indicating unconsciousness during the unconscious state. The positive predictive value was defined to indicate consciousness above the cut-off values and the negative predictive value to indicate unconsciousness below the cut-off values. Performance analysis was carried out using Matlab 6.5.

Results

LOW DEX caused drowsiness, but all subjects remained responsive. During HIGH DEX, subjects were under moderate sedation; there was no response to normal speech, but subjects could be awakened with loud verbal commands and physical stimulation.

Spectral entropy decreased in a concentration-dependent manner. The baseline SE value was 84 ± 5 and decreased to 66 ± 16 ($P = 0.029$) and 20 ± 12 ($P < 0.001$) during the LOW DEX and HIGH DEX phases, respectively (Fig. 2A). RE decreased from a baseline value of 95 ± 3 to 75 ± 18 ($P = 0.025$) during LOW DEX and 22 ± 15 ($P < 0.001$) during HIGH DEX. Both the SE and RE values also clearly indicated LOC; SE values abruptly decreased from 76 ± 8 (before LOC) to 43 ± 10 (after LOC) ($P < 0.001$), and RE decreased from 87 ± 8 (before LOC) to 49 ± 12 after LOC ($P < 0.001$). At the end of the HIGH DEX phase, the 1 min mean SE value increased from 14 ± 4 before ROC to 63 ± 13 after ROC ($P < 0.001$), and the RE value increased from 16 ± 5 before ROC to 74 ± 14 after ROC ($P < 0.001$). Individual SE values immediately before and after LOC and ROC are presented in Fig. 2(B, C). After the subjects had been aroused and ROC detected, they were allowed to fall asleep again, and SE and RE values showed a simultaneous rapid decrease (Fig. 3).

The P_K (mean \pm standard error) values were 0.983 ± 0.003 for SE and 0.984 ± 0.003 for RE. Cut-off values of 56 for SE and 65 for RE were obtained from the receiver operating characteristic curve (Fig. 4). Mean \pm SD sensitivity values were $98.1 \pm 3.3\%$ for SE and $96.9 \pm 6.2\%$ for RE, and the specificity values were $89.9 \pm 12.3\%$ for SE and $89.6 \pm 12.9\%$ for RE. The positive predictive values were $84.0 \pm 12.2\%$ for SE and $84.5 \pm 11.3\%$ for RE. The negative predictive values were $99.4 \pm 1.1\%$ for SE and $99.0 \pm 2.0\%$ for RE.

Table 1 presents all processed EEG variables in the three phases of the study. When comparing the awake state with LOW DEX, there were no significant changes in the EEG power spectral variables. Differences between the awake state and HIGH DEX included increases in the absolute powers of delta, theta, slow theta and fast theta frequency bands and decreases in beta and fast beta powers, and a clear increase in total power. Comparing LOW DEX and HIGH DEX, there were increases in the absolute powers of the delta, theta, slow theta and fast theta bands, and an increase in total power. Fast beta power was lower at HIGH DEX than at LOW DEX. There were significant differences in all EEG power

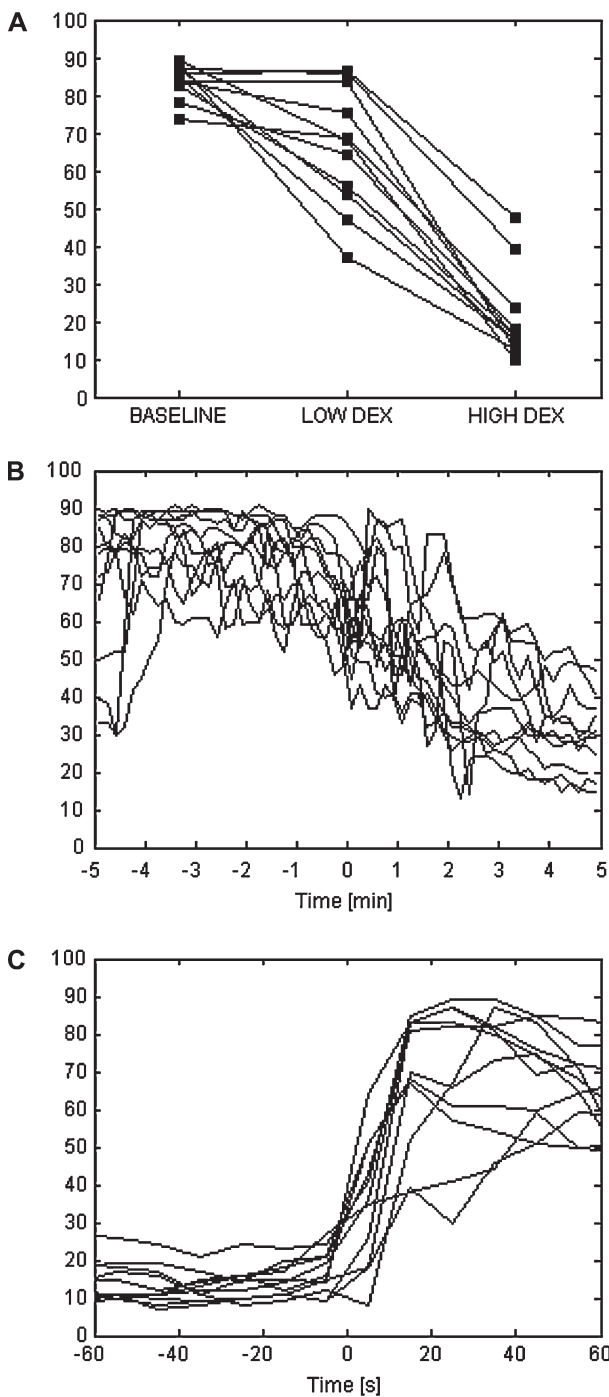


Fig. 2. Individual state entropy (SE) values at different stages of the study (A), before and after loss of consciousness (LOC) (B), and before and after regaining of consciousness (ROC) (C). Individual mean values are shown in (A). Individual curves of SE from 5 min before to 5 min after LOC are shown in (B). Time point 0 indicates LOC. Individual curves of SE from 1 min before to 1 min after ROC are shown in (C). Time point 0 indicates ROC. LOW DEX indicates a measured plasma dexmedetomidine concentration of 0.5 ng/ml and HIGH DEX indicates a measured plasma dexmedetomidine concentration of 5.1 ng/ml.

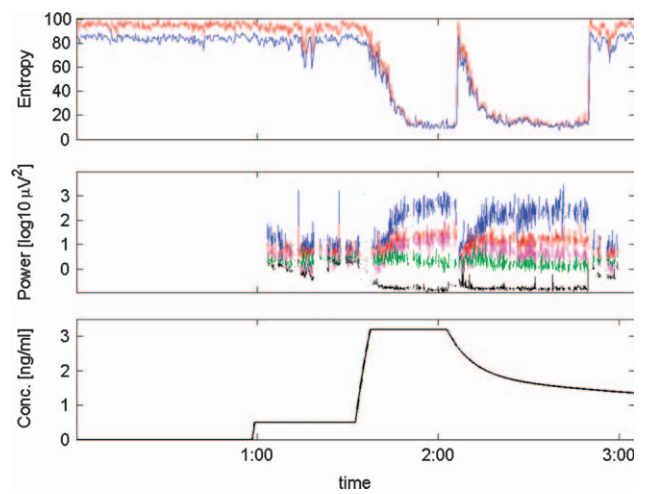


Fig. 3. Top: an example of response entropy (red) and state entropy (blue) from the whole recording period of one subject. At the end of HIGH DEX infusion, the subject was awakened, and then allowed to fall asleep again. (At the end of data collection the subject fell asleep again.) Middle: electroencephalogram (EEG) band powers from the delta (blue), theta (red), alpha (pink) and beta (green) frequency bands and electromyography (black) from the same period. Bottom: targeted plasma dexmedetomidine concentration levels based on Stanpump simulation. The measured plasma concentrations of this subject were 0.48 ng/ml at LOW DEX (targeted, 0.5 ng/ml) and 4.1 ng/ml at HIGH DEX (targeted, 3.2 ng/ml). x-axis presents the time in hours.

bands, except the slow beta and relative slow theta power, when comparing the before and after LOC values. Total power increased and SEF95 decreased at LOC. All of these changes were reversed on awakening (Table 2).

Discussion

Our results suggest that, even though dexmedetomidine produces sedation similar to physiological sleep, the Entropy Monitor is capable of reliably indicating the level of dexmedetomidine-induced hypnosis. It also very rapidly and accurately distinguishes transition phases from consciousness to unconsciousness and indicates LOC with high predictive performance. The good positive and negative predictive values of the entropy indices to accurately detect consciousness and unconsciousness also indicate reliable performance of the Entropy Monitor during dexmedetomidine sedation. This is in keeping with a previous report suggesting that a combination of spectral entropy and other EEG variables might work well in assessing the level of propofol sedation (24).

The effects of dexmedetomidine on the human EEG have not been described previously. In experimental animals, dexmedetomidine has been shown

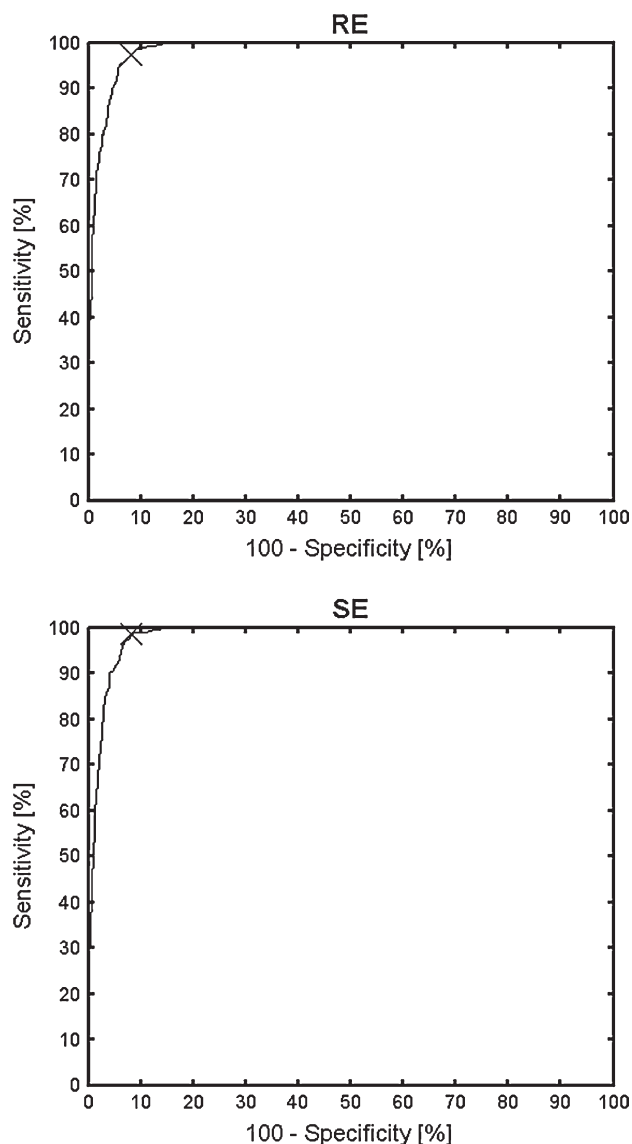


Fig. 4. Receiver operating characteristic curves for response entropy (RE) (top) and state entropy (SE) (bottom). Crosses indicate cut-off values of 65 for RE and 56 for SE.

to produce EEG synchronization (25) and progressive slowing of the EEG, with an increase in amplitude in rats (26) and an increase in delta activity in mice (27). In cats, dexmedetomidine similarly increases the total power and the delta band power of the EEG (28). In line with these experimental data, in the present study, we found an increase in delta and theta band powers during HIGH DEX in humans compared with baseline.

The interpretation of the EEG signal during increasing depths of sedation is complicated by the often biphasic concentration–EEG response relationship (29). Many of the derived EEG variables show biphasic effects in response to increasing concen-

trations of anaesthetic drug. There may be an initial increase in some effects, such as an increase in high-frequency band powers, and a subsequent decrease at higher concentrations or at the time of LOC. This may be related to the initial excitation and desynchronization caused by some agents, such as sevoflurane and propofol (30, 31). Unlike these anaesthetics, dexmedetomidine did not seem to show this property, but it should be acknowledged that we only studied two dose levels of dexmedetomidine.

New EEG-based monitoring devices and mathematical algorithms have been developed to maintain an adequate level of hypnosis. Bispectral index (BIS; Aspect Medical Systems, Newton, MA) and entropy monitors have been initially introduced to monitor the level of hypnosis during surgical anaesthesia, not to assess the level of consciousness of critically ill patients during ICU sedation. Spectral entropy as a concept describes the irregularity and complexity characteristics of a signal. In the Entropy Monitor, the spectral entropy describes the irregularity of the EEG signal (11), which decreases with increasing concentrations of commonly used anaesthetic agents. Non-intrusive EEG-based monitoring of ICU sedation may prove to be beneficial, especially when using a sedative agent such as dexmedetomidine. Monitoring can thus be continuous without a need to interfere with the patient with repeated, potentially noxious, manipulations.

In previous studies, dexmedetomidine has been shown to be useful and efficacious in post-operative analgesia and sedation (15, 32–34). Furthermore, the use of dexmedetomidine may also reduce exposure to benzodiazepines, which may help to improve outcome measures, such as the duration of mechanical ventilation and length of ICU stay (35). Because of these beneficial properties, the use of dexmedetomidine is increasing rapidly. It has been shown that daily interruption of the commonly used sedative drug administration enables neurological examination and reduces the need for other diagnostic studies to assess alterations in the neurological status (1). As patients sedated with dexmedetomidine can be easily aroused for immediate clinical evaluation, even when they are deeply sedated, the use of dexmedetomidine for ICU sedation may facilitate early detection of intracerebral catastrophes. Thus, the validation of a reliable and objective method to assess the depth of dexmedetomidine-induced sedation has direct clinical implications.

Our study set-up can be criticized because we did not use any clinical scoring system, such as the Ramsay Score (36) or the Richmond Agitation–Sedation Scale

Table 1

Summary of steady-state absolute and relative electroencephalogram (EEG) band powers and 95% spectral edge frequencies (SEF95) at different stages of dexmedetomidine sedation.

Processed EEG variable	No drug	LOW DEX	HIGH DEX	Overall ANOVA, <i>P</i>
Total power (μV^2)	37.52 ± 18.58	29.27 ± 14.79	244.92 ± 126.00‡¶	< 0.001
Delta (μV^2)	22.42 ± 14.55	17.93 ± 12.64	218.09 ± 119.94‡¶	< 0.001
Theta (μV^2)	5.99 ± 3.78	5.44 ± 1.77	18.33 ± 7.77‡¶	< 0.001
Alpha (μV^2)	5.89 ± 5.04	3.61 ± 1.94	6.98 ± 3.26	NS
Beta (μV^2)	3.22 ± 1.06	2.28 ± 0.66	1.52 ± 0.95*	0.02
Slow theta (μV^2)	3.20 ± 2.28	3.19 ± 1.35	12.60 ± 5.79‡¶	< 0.001
Fast theta (μV^2)	3.29 ± 2.06	2.77 ± 1.02	7.86 ± 3.08‡§	< 0.001
Slow beta (μV^2)	1.53 ± 0.48	1.52 ± 0.56	1.23 ± 0.87	NS
Fast beta (μV^2)	1.69 ± 0.88	0.76 ± 0.26	0.29 ± 0.09‡¶	< 0.001
Delta (%)	57.46 ± 12.32	56.43 ± 13.80	84.77 ± 10.50‡¶	< 0.001
Theta (%)	16.06 ± 5.95	20.83 ± 7.10	9.29 ± 4.48‡¶	< 0.001
Alpha (%)	16.03 ± 10.41	13.29 ± 5.27	4.78 ± 4.93*§	0.016
Beta (%)	10.45 ± 6.01	9.45 ± 4.29	1.16 ± 1.42‡¶	< 0.001
Slow theta (%)	8.43 ± 3.08	11.49 ± 2.75	6.11 ± 2.61§	0.006
Fast theta (%)	8.94 ± 4.20	11.14 ± 6.63	4.20 ± 2.39*§	0.004
Slow beta (%)	4.76 ± 2.16	6.08 ± 2.73	0.88 ± 0.98‡¶	< 0.001
Fast beta (%)	5.70 ± 4.20	3.37 ± 2.16	0.28 ± 0.46‡¶	< 0.001
SEF95 (Hz)	19.38 ± 4.67	16.85 ± 3.93	16.64 ± 4.20	NS

LOW DEX, targeted plasma dexmedetomidine concentration of 0.5 ng/ml; HIGH DEX, targeted plasma dexmedetomidine concentration of 3.2 ng/ml; NS, not significant.

Values are given as group means ± standard deviation.

Statistically significant differences: HIGH DEX vs. baseline: **P* < 0.05, †*P* < 0.01, ‡*P* < 0.001; HIGH DEX vs. LOW DEX: §*P* < 0.01, ¶*P* < 0.001.

(RASS) (37), to measure the depth of sedation. Such scales, involving repetitive verbal or noxious stimuli, were not applied in the present study because we wanted to provide undisturbed conditions to assess the effects of dexmedetomidine on the EEG.

The Entropy Monitor performed well in assessing the level of dexmedetomidine-induced sedation in healthy subjects. As our study population consisted of healthy male volunteers, clinical studies with ICU patients are warranted before these results can be

Table 2

Summary of absolute and relative electroencephalogram (EEG) band powers and 95% spectral edge frequencies (SEF95) before and after loss of consciousness (LOC) and before and after regaining of consciousness (ROC).

Processed EEG variable	Before LOC	After LOC	t-test, <i>P</i>	Before ROC	After ROC	t-test, <i>P</i>
Total power (μV^2)	24.47 ± 8.27	68.65 ± 44.05	0.006	356.39 ± 244.46	38.01 ± 29.33	0.002
Delta (μV^2)	12.37 ± 4.84	50.13 ± 39.47	< 0.001	329.56 ± 239.81	28.22 ± 26.08	0.002
Theta (μV^2)	5.00 ± 1.79	9.93 ± 4.27	0.003	18.83 ± 8.65	4.20 ± 2.19	< 0.001
Alpha (μV^2)	4.58 ± 2.87	6.62 ± 3.51	0.034	6.74 ± 3.61	3.36 ± 1.41	0.010
Beta (μV^2)	2.53 ± 0.78	1.97 ± 0.72	0.036	1.26 ± 0.46	2.24 ± 1.10	0.015
Slow theta (μV^2)	2.16 ± 0.50	5.66 ± 2.92	0.002	13.90 ± 8.47	2.43 ± 1.31	< 0.001
Fast theta (μV^2)	3.14 ± 1.48	5.07 ± 2.37	0.009	7.07 ± 1.87	2.16 ± 1.13	< 0.001
Slow beta (μV^2)	1.72 ± 0.77	1.56 ± 0.64	NS	0.96 ± 0.38	1.41 ± 0.68	NS
Fast beta (μV^2)	0.81 ± 0.15	0.41 ± 0.10	< 0.001	0.30 ± 0.10	0.82 ± 0.48	0.005
Delta (%)	50.42 ± 8.89	67.01 ± 11.67	< 0.001	89.12 ± 7.61	66.63 ± 14.08	< 0.001
Theta (%)	20.43 ± 3.44	16.47 ± 4.46	0.021	7.49 ± 5.25	13.04 ± 3.96	0.012
Alpha (%)	18.49 ± 9.39	12.52 ± 6.24	0.034	2.83 ± 2.14	12.27 ± 7.83	0.001
Beta (%)	10.66 ± 2.34	4.00 ± 2.32	< 0.001	0.56 ± 0.44	8.07 ± 4.49	< 0.001
Slow theta (%)	9.23 ± 1.87	9.14 ± 2.35	NS	5.03 ± 2.99	7.64 ± 2.83	NS
Fast theta (%)	12.50 ± 3.59	8.62 ± 3.14	0.015	3.13 ± 2.59	6.68 ± 2.03	0.003
Slow beta (%)	7.04 ± 2.08	3.12 ± 1.87	< 0.001	0.42 ± 0.32	5.22 ± 3.20	< 0.001
Fast beta (%)	3.62 ± 1.34	0.88 ± 0.54	< 0.001	0.15 ± 0.12	2.84 ± 1.49	< 0.001
SEF95 (Hz)	18.00 ± 2.27	11.89 ± 2.23	< 0.001	5.76 ± 2.83	15.40 ± 3.82	< 0.001

NS, not significant. Values are given as group means ± standard deviation from 5-min period before and after LOC and from 1-min period before and after ROC.

applied to clinical practice. ICU patients often present metabolic disturbances, encephalopathies and brain injuries, which all have effects on the EEG. Moreover, many centrally acting medications that may confound the EEG signal are routinely administered during ICU sedation. All of these issues must be taken into consideration when evaluating the EEG-based depth-of-anaesthesia monitors for ICU monitoring, with simultaneous clinical scoring as a reference.

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