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Entropy indices *vs* the bispectral index™ for estimating nociception during sevoflurane anaesthesia

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Background. It is now possible to acquire and process raw EEG and frontal EMG signals to produce two spectral-entropy-based indices (response entropy and state entropy) reflective of analgesic and hypnotic levels during general anaesthesia (with the Datex-Ohmeda S/5 Entropy Module, Datex-Ohmeda, Helsinki, Finland). However, there are no data available on the accuracy of the Entropy Module in estimating nociception during sevoflurane anaesthesia.

Methods. Forty female patients were enrolled in the present study. Each patient was allocated randomly to one of four end-tidal sevoflurane concentration (ET_{sev}) groups (1.3, 1.7, 2.1 or 2.5%). A BIS Sensor™ (Aspect Medical Systems, Newton, MA) and an Entropy Sensor™ (Datex-Ohmeda) were applied side-by-side to the forehead. The bispectral index (A-2000 BIS Monitor, version 3.4, Aspect Medical Systems), response entropy, state entropy and patient movement were observed after electrical stimulation (20, 40, 60 and 80 mA, 100 Hz, 5 s) and after skin incision during sevoflurane anaesthesia (1.3, 1.7, 2.1 or 2.5%). Accuracy of the EEG variables in differentiating the intensity of electrical stimulation was estimated by the prediction probability (P_K) values.

Results. Response entropy and state entropy [median, (range)] before skin incision were significantly lower in patients who did not move [29 (15–41) and 24 (14–41)] than in those that did [38 (24–53) and 37 (24–52)], but there was no significant difference in BIS. All EEG variables increased significantly ($P<0.0001$ for all) with increases in the intensity of electrical stimulation. The difference between response entropy and state entropy increased with increases in the electrical stimulation ($P<0.0001$). However, no EEG variables could differentiate the intensity of the electrical stimulations accurately because of low P_K-values ($P_K<0.8$).

Conclusion. Noxious stimulation increased the difference between response entropy and state entropy. However, an increase in the difference does not always indicate inadequate analgesia and should be interpreted carefully during anaesthesia.

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To measure the depth of anaesthesia, EEG signals are analysed during anaesthesia. Among the EEG-derived indices, the bispectral index (BIS™, Aspect Medical Systems, Newton, MA) is widely used and documented in estimating the hypnotic level during general anaesthesia. This index has proven to be a highly sensitive and specific measure of the anaesthetic effect in comparison with other EEG-derived variables.[1 2] Anaesthetic depth can also be measured by means of spectral entropy with the use of tools such as the Datex-Ohmeda S/5 Entropy™ Module (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland). It is now possible to acquire and process raw EEG and frontal EMG (fEMG) signals to produce two spectral-entropy-based indices (response entropy and state entropy)

reflective of nociceptive and hypnotic levels during general anaesthesia. EEG signals change from fast wave activity to slow wave activity when anaesthesia deepens, and the Entropy Module measures the irregularity of the EEG by means of an entropy algorithm to assess the depth of anaesthesia. State entropy, which is calculated for frequencies ranging from 0.8 to 37 Hz, consists of the entropy of the EEG signal reflecting the patient's cortical activity. Response entropy includes additional higher frequencies up to 47 Hz, reflecting both EEG and fEMG activity. Response entropy becomes equal to state entropy when the EMG power (sum of the spectral power between 32 and 47 Hz) is equal to zero. The difference between response entropy and state entropy serves as an indicator for EMG activation.[3]

The definition of inadequate analgesia is still unclear. Various signs such as patient movement, increase in arterial pressure or heart rate (HR) and increase in the release of catecholamine in response to noxious stimulation have all been defined as signs of inadequate analgesia. Motor response to noxious stimulation has been used as one of the indicators of inadequate analgesia. EMG activity reflects subcortical activity during general anaesthesia. According to previous studies, subcortical structures could be a site of the analgesic effect of anaesthetics.[4–6] Although fEMG has not gained clinical acceptance, it has been reported that fEMG may be of value in assessing adequacy of anaesthesia.[7 8] Therefore, we hypothesized that the difference between response entropy and state entropy, which is the constituent of fEMG, also reflects nociception. Although it has been reported that sensitivity, specificity and prediction probability (P_K) values of the entropy indices for differentiating between consciousness and unconsciousness are high and comparable with corresponding BIS values,[9 10] it is still unclear whether the difference between response entropy and state entropy can be used as an indicator of an inadequate level of analgesia. In the present study, we investigated the accuracy of entropy monitoring to estimate nociception during sevoflurane anaesthesia in comparison with the accuracy of BIS monitoring.

Methods

After approval was obtained from the institutional ethics committee of the National West-Saitama Central Hospital (Saitama, Japan), informed consent was obtained from 40 female, ASA class I–II patients, aged 22–54 yr, who were undergoing gynaecological surgery. Exclusion criteria included disease or injury affecting the central nervous system, recent use of psychoactive or analgesic medication, neurological disorder, alcohol or drug abuse and weight less than 70% or more than 130% of ideal body weight.

All patients received i.m. atropine 0.5 mg 30 min before induction of anaesthesia. An epidural catheter was inserted between T12 and L1, but it was not used until completion of the study period. Anaesthesia was induced by inhalation of 5% sevoflurane with a fresh gas flow of 6 litre min^{-1} (100% oxygen) via a face mask. The anaesthetist called the patient's name in a loud voice every 10 s until loss of consciousness was observed. Loss of verbal response, eye opening or movement after the patient's name was called loudly was defined as loss of consciousness. The BIS, state entropy and response entropy values at loss of consciousness were recorded. After loss of consciousness, vecuronium bromide 0.016 mg kg^{-1} was administered to the patient as a 'priming' dose, followed by injection of succinylcholine 1.5 mg kg^{-1}. After muscle relaxation, the ProSeal™ (LMA North America, Inc., San Diego, CA) laryngeal mask airway was inserted, and ventilation was controlled to maintain end-tidal CO_2 at 35–40 mm Hg. Each patient was allocated randomly to one of four end-tidal sevoflurane concentration (ET_{sev}) groups (1.3, 1.7, 2.1 or 2.5%), and the ET_{sev} was fixed until completion of the study period. After a 20 min maintenance period, BIS, response entropy and state entropy values were again recorded as baseline values, and tetanic electrical stimulations (100 Hz, 5 s) were applied to the left volar forearm over the ulnar nerve with a peripheral nerve stimulator (NS252, Fisher & Paykel Healthcare Division, Panmure, Auckland, New Zealand). Electrical stimulations (20, 40, 60 and 80 mA, in this order) were applied to all patients, and the maximum BIS, state entropy and response entropy values, mean arterial pressure and HR after each electrical stimulation were recorded. Electrical stimulations were applied at 15 min intervals. More than 20 min after the last electrical stimulation, surgery was started, and the BIS, response entropy and state entropy values and patient movement immediately after skin incision were observed. A positive response was defined as gross movement of the right arm, legs or head within the first minute after stimulation. Intraoperative awareness or recall was checked after recovery from anaesthesia and also the next day.

To capture the EEG signal, a BIS Sensor™ (Aspect Medical Systems) and an Entropy Sensor™ (Datex-Ohmeda, Helsinki, Finland) were applied side-by-side to the forehead. The BIS was generated by the A-2000 BIS Monitor (version 3.4) with its required software (version 3.12) (Aspect Medical Systems). The smoothing time was set at 15 s. Entropy was measured with an Entropy Module of the AS3™ Monitor (Datex-Ohmeda) and recorded at 1 min intervals with Datex-Ohmeda software S/5 correct (version 4) on to the computer hard disk. The maximum values of the EEG variables after electric stimulation were recorded offline. Inspiratory and expiratory gas concentrations were measured with a Capnomac Ultima (Datex-Ohmeda). Non-invasive blood pressure, HR and oxygen saturation were recorded at 1 min intervals.

To analyse the differences in each indicator (BIS, response entropy and state entropy) with increases in ET_{sev}, one-way ANOVA was used. When P was <0.05, *post-hoc* testing was performed with Dunn's multiple comparisons test. The differences in BIS, response entropy, state entropy and ET_{sev} values before skin incision between

patients who moved after skin incision (movers) and those who did not (non-movers) were analysed using Student's *t*-test. The relation between the entropy indices and ET_{sev} and probability of a positive response to skin incision was determined by means of logistic regression analysis. EEG variables after each electrical stimulation under each sevoflurane concentration were analysed by two-way ANOVA followed by Bonferroni *post-hoc* test. The difference between response entropy and state entropy after each electrical stimulation under each sevoflurane concentration was analysed by two-way ANOVA followed by Bonferroni *post-hoc* test. In addition, the linear correlation coefficient between BIS and each of the two entropy indices (response entropy and state entropy) was calculated.

We further investigated the ability of the indicators (BIS, response entropy and state entropy) to detect the level of analgesia using P_K, which was calculated with a Microsoft Excel Macro (PKMACRO) provided by Smith and colleagues.[11 12] To compute the P_K, BIS, state entropy, response entropy and the difference between response entropy and state entropy were analysed as the predicting variables, and the intensity of the electrical stimulations (20, 40, 60 and 80 mA) as the strength of noxious stimulation was the value of the variable to be predicted. In the present study, a P_K-value of 1.0 was taken to mean that the variable correctly predicts the strength of noxious stimulation. A P_K-value of 0.5 was taken to mean there is a 50% chance that the indicator correctly predicts the strength of noxious stimulation. $P<0.05$ was considered statistically significant.

Table 1 Patient characteristics. Mean (range or SD) values are shown

	Sevoflurane concentration			
	1.3% (*n*=10)	**1.7% (*n*=10)**	**2.1% (*n*=10)**	**2.5% (*n*=10)**
Age (yr)	40.5 (26–53)	40.0 (32–46)	40.8 (25–51)	41.0 (22–54)
Height (cm)	154.6 (4.2)	158.5 (4.7)	158.2 (4.9)	158.2 (4.7)
Weight (kg)	53.7 (5.3)	52.5 (7.4)	57.2 (10.1)	49.5 (4.2)

Results

Patient characteristics are shown in Table 1. No intraoperative awareness or recall was reported by any patient in the study.

The median values (range) of BIS, response entropy and state entropy at loss of consciousness were 88 (53–98), 92 (38–99) and 85 (25–96), respectively. The P_K-values (SE) of BIS, response entropy and state entropy for loss of consciousness were 0.841 (0.030), 0.841 (0.024) and 0.825 (0.029), respectively.

Individual BIS, response entropy and state entropy values at each sevoflurane concentration (1.3, 1.7, 2.1 and 2.5%) before electrical stimulation are plotted in Figure 1. The response entropy and state entropy values decreased significantly ($P<0.01$) with increases in sevoflurane

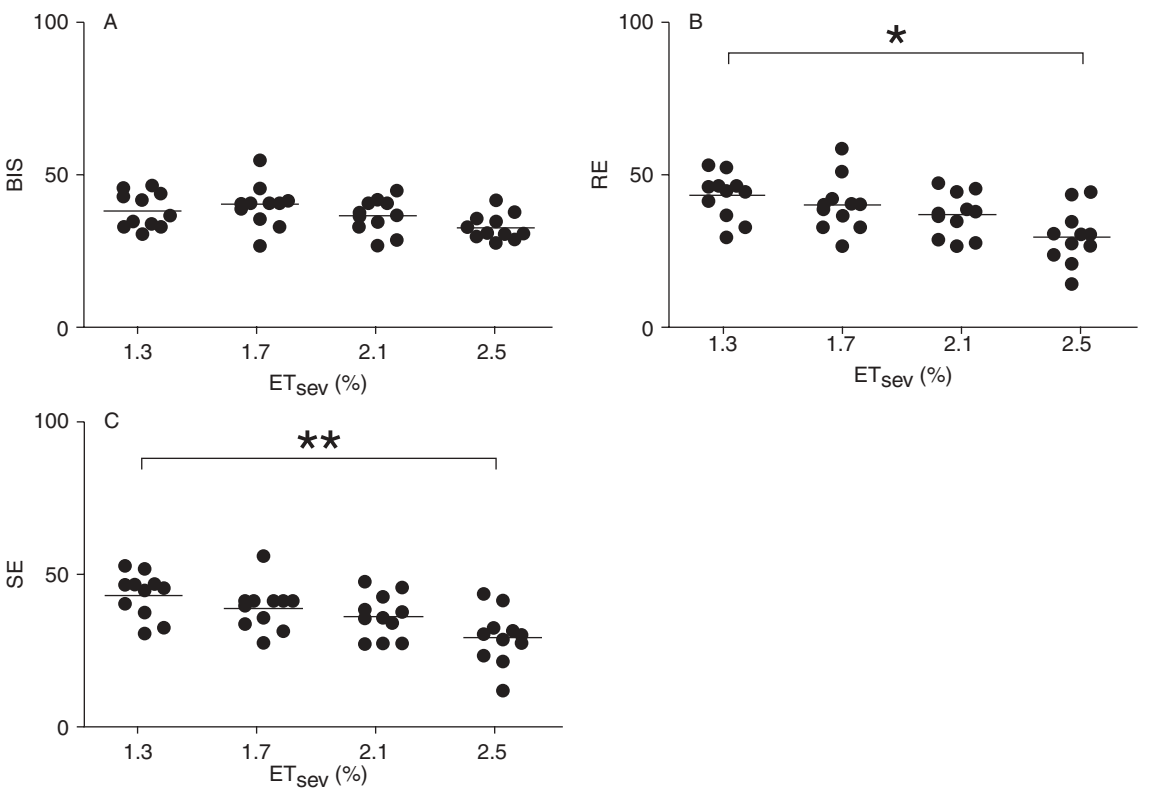

Fig 1 Individual (A) BIS, (B) response entropy (RE) and (C) state entropy (SE) values with increases in end-tidal sevoflurane concentration (ET_{sev}). * and ** indicate significant differences ($P<0.05$ and 0.01, respectively).

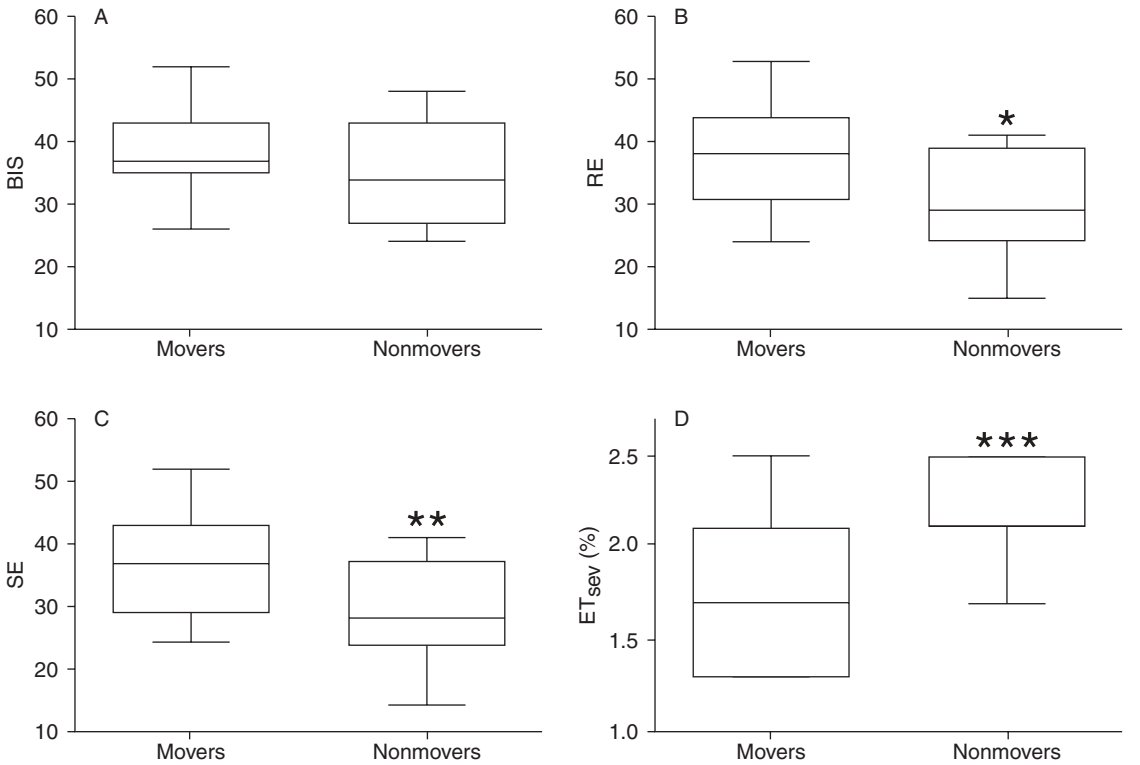

Fig 2 Box plots of (A) BIS, (B) response entropy (RE), (C) state entropy (SE) and (D) end-tidal sevoflurane concentration (ET_{sev}) values before skin incision. Box indicates mean and 25% (box top) and 75% (box bottom), whiskers indicate the 5th and 95th percentiles. 'Movers' indicates patients who moved after skin incision; 'nonmovers' indicates patients who did not. *, **, and *** indicate significant differences (P<0.05, 0.01, and 0.001, respectively).

concentration, whereas the BIS value did not. The difference between response entropy and state entropy did not change significantly with increases in sevoflurane concentration.

BIS, response entropy, state entropy and ET_{sev} values before the skin incision are shown in Figure 2. In movers and non-movers, median values (range) of BIS were 37 (26–52) and 34 (24–42), respectively; response entropy was 38 (24–53) and 29 (15–41), respectively; state entropy was 37 (24–52) and 24 (14–41); ET_{sev} was 1.7 (1.3–2.5) and 2.1 (1.7–2.5). The response entropy and state entropy before skin incision were significantly higher in the movers (P<0.05 and <0.01, respectively), and ET_{sev} was significantly higher in the non-movers (P<0.001). There was no significant difference in the BIS between movers and non-movers.

The probability curves of the response to skin incision in terms of response entropy and state entropy are shown in Figure 3. The response entropy and state entropy values at which 50% of the patients lost the response to skin incision were 26.4 and 26.0, respectively. The ET_{sev} that prevented movement in response to skin incision in 50% of patients (minimum alveolar concentration) was 2.31%.

The maximum response entropy, state entropy and BIS values after electrical stimulation are shown in Table 2. Under the same sevoflurane concentration, all indices increased significantly with increases in the intensity of the electrical stimulus. However, the maximum values of all indices after electrical stimulation decreased significantly with increases in the concentration of sevoflurane.

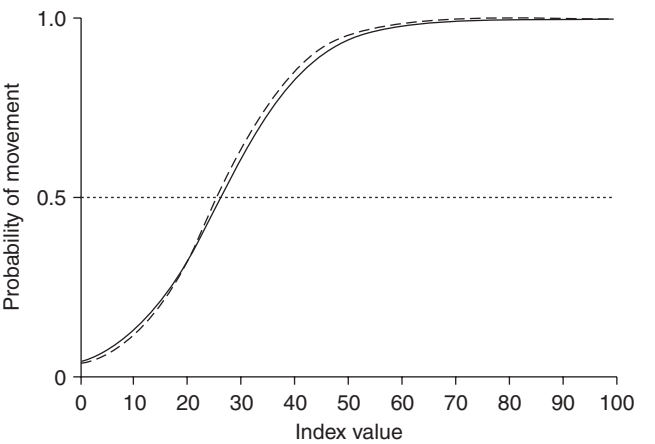

Fig 3 Probability of movement as a function of entropy before skin incision. Solid line is the curve calculated by means of response entropy. Dashed line is the curve calculated by means of state entropy. Probability of 1.0 means all patients move after skin incision, whereas probability of 0 means no patient moves.

The difference between response entropy and state entropy after electrical stimulation is shown in Figure 4.

Table 2 BIS, response entropy and state entropy values after electrical stimulation. ET_{sev}, end-tidal sevoflurane; BIS, bispectral index; RE, response entropy; SE, state entropy. Data are shown as median (inter-quartile range, range). *, **, and *** indicate $P<0.05$, 0.01, and 0.001 in comparison to baseline

	ET_{sev} (%)	Stimulation intensity				
		Baseline	20 mA	40 mA	60 mA	80 mA
BIS	1.3	36 (11, 31–46)	47 (15, 32–56)*	50 (13, 38–64)*	53 (18, 36–61)***	57 (14, 39–68)***
	1.7	41 (9, 27–55)	43 (14, 30–62)	48 (20, 31–64)**	45 (19, 35–64)*	44 (21, 28–70)**
	2.1	37 (10, 27–42)	41 (10, 31–51)	46 (15, 32–52)**	43 (13, 38–58)**	45 (11, 41–57)**
	2.5	31 (7, 28–42)	37 (9, 30–63)	40 (13, 29–55)	41 (18, 29–58)**	40 (14, 25–52)
RE	1.3	45 (12, 30–53)	46 (19, 39–65)	61 (26, 46–82)***	59 (20, 44–73)*	64 (35, 45–86)***
	1.7	40 (9, 27–59)	47 (17, 28–59)	50 (16, 35–69)	57 (15, 30–68)*	58 (14, 30–68)**
	2.1	38 (13, 27–46)	45 (28, 27–67)	43 (20, 24–61)*	43 (24, 30–58)*	45 (21, 36–59)***
	2.5	30 (10, 14–45)	34 (16, 22–51)	33 (11, 18–51)	33 (16, 22–52)**	39 (19, 25–54)***
SE	1.3	45 (11, 30–52)	45 (18, 34–62)	55 (21, 39–78)***	57 (22, 37–66)**	62 (27, 38–75)***
	1.7	40 (9, 27–55)	45 (9, 27–56)	46 (12, 34–56)	45 (12, 36–54)	51 (22, 30–62)*
	2.1	35 (13, 27–45)	42 (24, 26–62)	41 (15, 23–51)	41 (18, 26–54)	41 (18, 29–51)
	2.5	29 (10, 12–43)	33 (14, 20–46)*	31 (11, 17–42)	31 (15, 20–45)	36 (17, 24–52)***

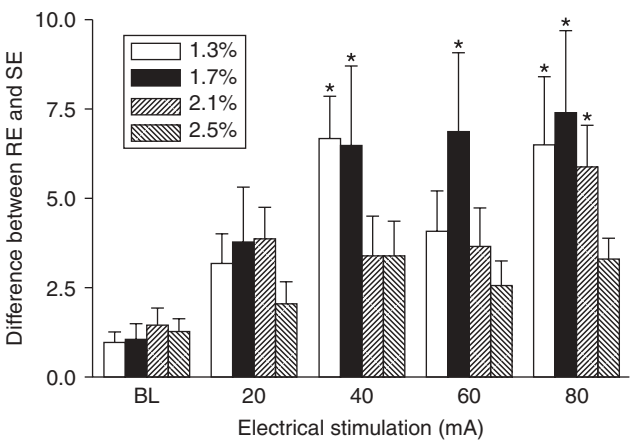

Fig 4 Difference between response entropy (RE) and state entropy (SE) after electrical stimulation. The differences increased significantly, except with sevoflurane 2.5%. Data are presented as mean (SEM). *indicates significant differences ($P<0.05$) compared with baseline (BL).

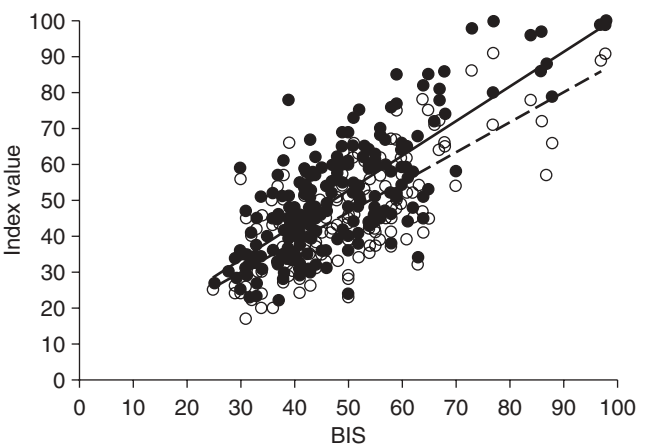

Fig 5 Relation between response entropy (open circles) or state entropy (closed circles) and BIS. The regression lines are superimposed as a bold (response entropy) or dashed (state entropy) line.

The difference increased with increases in the intensity of electrical stimulus. However, there was no significant change in the difference between response entropy and state entropy with increases in the sevoflurane concentrations.

Linear correlation between BIS and each of the two entropy indices was calculated as follows (Fig. 5): response entropy=0.97×BIS+4.12 resulting in a correlation coefficient of 0.77, and state entropy=0.84×BIS−5.89 resulting in a correlation coefficient of 0.75. All data pairs were included in this analysis.

P_K-values for the intensity of the stimulus are shown in Table 3. No variables showed much ability to predict the intensity of the stimulus because of low P_K-values.

Discussion

In the present study, we investigated the accuracy of response entropy, state entropy and BIS as indicators of nociception during sevoflurane anaesthesia to determine whether the difference between response entropy and state entropy can indicate inadequate analgesia. Noxious stimulation was shown to increase response entropy more than state entropy. However, all indices did not always increase (decrease) when the intensity of noxious stimulus increased (decreased). Therefore, neither response entropy and state entropy nor BIS was sufficiently accurate to determine the strength of noxious stimulation because of low P_K-values.

The response entropy, state entropy and BIS values at loss of consciousness in the present study were higher than those in a previous study.[13] This may be attributed to our protocol. In the present study, sevoflurane 5% was used to induce anaesthesia. Induction by sevoflurane 5% inhalation might be too rapid for accurate assessment of values at loss of consciousness because response entropy, state entropy and BIS are each computed during a particular time window (1.92, 15 and 15 s, respectively).

Table 3 Prediction probability of each variable for differentiating the intensities of electrical stimulations at each end-tidal sevoflurane concentration. ET_{sev}, end-tidal sevoflurane; BIS, bispectral index; RE, response entropy; SE, state entropy, RE−SE, the difference between response entropy and state entropy; MAP, mean arterial pressure, HR, heart rate. Mean (SE) values are shown

	ET_{sev} (%)			
	1.3	**1.7**	**2.1**	**2.5**
BIS	0.732 (0.036)	0.591 (0.047)	0.665 (0.035)	0.585 (0.049)
RE	0.689 (0.041)	0.679 (0.047)	0.577 (0.040)	0.569 (0.048)
SE	0.655 (0.045)	0.643 (0.051)	0.557 (0.043)	0.583 (0.049)
RE−SE	0.686 (0.046)	0.659 (0.058)	0.641 (0.048)	0.528 (0.057)
MAP	0.570 (0.047)	0.600 (0.047)	0.654 (0.044)	0.585 (0.049)
HR	0.638 (0.043)	0.634 (0.042)	0.655 (0.037)	0.614 (0.044)

Entropy indices and BIS correlated linearly for the range of sevoflurane concentrations used in the present study. In another study, there was no linear correlation between BIS and entropy indices above a BIS value of 60 with sevoflurane anaesthesia.[9] This was because the BIS values for different levels of anaesthesia are calculated with different algorithms.[14] In the present study, 1.3–2.5% sevoflurane was used, and most BIS values were between 30 and 70 at these concentrations. This suggests that linear correlation between BIS and entropy indices was observed in our study because most of the BIS values were calculated with the same algorithm for our range of sevoflurane concentrations.

In the present study, although the sample size was not adequate to evaluate the changes in BIS, BIS did not decrease significantly with an increase in the sevoflurane concentration from 1.3 to 2.5%, whereas both entropy indices decreased significantly. In a previous study, similar results in BIS were reported for sevoflurane concentrations greater than 1.4%.[2] Because sevoflurane concentrations greater than 1.4% are often used in clinical settings, its inaccuracy as an indicator of anaesthetic depth makes BIS disadvantageous in comparison with entropy indices. However, BIS values were clinically low in the sevoflurane concentrations used in the present study. For titration of the amount of agent given to achieve a BIS that guarantees unconsciousness, a lack of sensitivity to sevoflurane concentration at low index values is not limiting.

Although the prediction of movement in response to skin incision by means of EEG-derived variables[2 13 15–18] has been well described, the accuracy of such a prediction has not been established. In the present study with sevoflurane anaesthesia, response entropy and state entropy before skin incision were significantly lower and ET_{sev} was significantly higher in non-movers than in movers, but there was no significant difference in BIS. In the range of sevoflurane concentrations used in the present study, response entropy and state entropy decreased with increases in the sevoflurane concentration, whereas BIS did not. This difference between BIS and entropy indices may explain why a significant difference was observed between movers and non-movers in entropy indices but not in BIS.

In the present study, no EEG variable could differentiate the intensity of electrical stimulation accurately because of low P_K-values. The P_K-values of EEG variables were almost the same as the P_K-values of MAP or HR. Although it is uncertain whether the intensity of the electrical stimulus is equal to the strength of noxious stimulation, both BIS and entropy indices seem to be inadequate for quantifying noxious stimulation.

In the present study, BIS increased significantly with electrical stimulation. It has been reported that the action of isoflurane in the spinal cord indirectly alters brain cortical activity as measured by EEG changes induced by electrical stimulation of the reticular formation.[19] Therefore, the increase in BIS was thought to be because of a decrease in the level of hypnosis caused by noxious stimulation. However, BIS also increases under light hypnosis because of insufficient administration of hypnotic agents. Ultimately, an increase in BIS during general anaesthesia, possibly similar to a change in other EEG derivatives, indicates one of two different anaesthetic states: light hypnosis or inadequate analgesia.

In a previous study of a goat brain model,[4] subcortical structures were suggested to be the site of the analgesic effect of anaesthetics. In other studies,[5 6] depression of the motor response to noxious stimulation by general anaesthetics was suggested to be caused by immobilization and antinociceptive effects in the spinal cord. Therefore, excitability of subcortical structures evoked by noxious stimulation, with EMG activation taken as the motor response, which increases the difference between response entropy and state entropy, may indicate inadequate analgesia. Thus, we hypothesized that an increase in the difference between response entropy and state entropy, that is, the fEMG activity, could indicate nociception during general anaesthesia. Certainly, in our study, the difference increased significantly after electrical stimulation. However, we concluded that the increase in the difference between response entropy and state entropy merely indicates the motor response to noxious stimulation and is not a direct indication of analgesia *per se*.

In a previous study measuring the plasma norepinephrine concentration as the stress response during sevoflurane anaesthesia, it was found that a high concentration of sevoflurane could not suppress the adrenergic nervous system responses to surgical noxious stimulation,[20] but it could suppress the motor response to noxious stimulation. This probably indicates that fEMG is not activated even under inadequate analgesia during high-concentration sevoflurane anaesthesia because of the suppressive effect of sevoflurane on motor response to noxious stimulation. Furthermore, in a previous study, fEMG activity was found to indicate pending arousal during anaesthesia,[21] and recovery from paralysis produces an increase in fEMG.[22] Thus, the absence of fEMG activation after noxious stimulation does not always indicate adequate analgesia, especially during sevoflurane anaesthesia, and fEMG activation does not always indicate

inadequate analgesia. Therefore, the difference between the two entropy indices should be interpreted carefully during anaesthesia.

We did not use neuromuscular blocking agents during the study period so that we could observe patient movements after noxious stimulation. Therefore, it is possible that EMG activity after noxious stimulation contaminated our results. Facial muscles have been found to be more resistant than other skeletal muscles to neuromuscular blocking agents,[23 24] and noxious stimulation has been found to increase the difference between response entropy and state entropy before recovery from paralysis.[22] Furthermore, neuromuscular blocking agents are usually used in clinical anaesthesia. Therefore, in evaluating nociception, further studies that incorporate a neuromuscular blocking agent are needed to clarify the role of fEMG activity.

In conclusion, noxious stimulation increased both BIS and entropy, but neither BIS nor entropy indices could quantify the intensity of the stimulation. Furthermore, although response entropy increased more than state entropy after noxious stimulation, it is possible that the increase in the difference between these two indices did not always indicate inadequate blockade of noxious stimulation. Therefore, although the increase in the difference seems to be useful in estimating the nociception, the difference should be interpreted carefully during anaesthesia.

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