# Effects of Neuromuscular Blockages on Entropy Monitoring During Sevoflurane Anesthesia

Authors' Contribution:
Study Design **A**
Data Collection **B**
Statistical Analysis **C**
Data Interpretation **D**
Manuscript Preparation **E**
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**Background:** There are no data available on the effects of different degrees of neuromuscular blockade on spectral entropy during sevoflurane anesthesia. This study aimed to observe the effects of different degrees of neuromuscular blockade on state and response entropy during sevoflurane anesthesia.

**Material/Methods:** Eighty-one female patients were randomized to 9 groups (n=9 per group) according to the concentration of sevoflurane and degree of neuromuscular blockade. Response and state entropy were monitored. The endpoints were: 1) impact of neuromuscular blockade on state entropy and response entropy, and the difference between response entropy and state entropy; and 2) the response of entropy after cutaneous tetanic electrical noxious stimulation to the ulnar nerve under different degrees of neuromuscular blockade and concentrations of sevoflurane.

**Results:** These were no significant differences in response entropy or state entropy, or differences between response entropy and state entropy among the groups in the awake state (P>0.05). Without noxious stimulation, sevoflurane concentrations and neuromuscular blockade had no significant effects on response entropy or state entropy, or on the difference between response entropy and state entropy (all P>0.05), but sevoflurane concentrations showed a significant effect on state entropy (P<0.05). After noxious stimulation, sevoflurane concentrations and neuromuscular blockade had significant effects on response entropy and state entropy, and on the difference between response entropy and state entropy.

**Conclusions:** Response entropy and state entropy decreased with increasing sevoflurane concentration. Neuromuscular blockade did not affect entropy without noxious stimulation. With stimulation, muscle relaxants significantly reduced the changes in entropy, and there were significant effects of neuromuscular blockade and sevoflurane on entropy.

**MeSH Keywords:** **Anesthesia • Entropy • Neuromuscular Blockade**

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## Background

Depth of anesthesia monitoring can measure the levels of patient consciousness during general anesthesia, and it is clinically important to avoid intra-operative awareness and eventual postoperative complications [1]. The bispectral index (BIS) is the most widely used monitoring method; it is a combination of time domain, frequency domain, and high-order spectral subparameters [2]. The entropy module assesses the depth of anesthesia by estimating the Shannon entropy of the power spectrum (called the spectral entropy) [3]. Previous studies showed that spectral entropy is more sensitive to the deepening of anesthesia in comparison with BIS [4,5].

An important electromyographic (EMG) component that originates from the facial muscles is included by an electroencephalography (EEG) signal. The M-Entropy module can separate EEG and EMG signals and produce 2 different numbers: state entropy (SE) and response entropy (RE). SE is calculated over the EEG-dominant part of the spectrum and shows the patient's cortical state. RE includes the EEG and EMG dominant parts of the spectrum [6,7]. Therefore, the SE value is always lower or equal to the RE value. When there is no EMG activity, SE and RE values are the same. Therefore, the RE-SE difference can indicate muscular activity. Motor innervation of the upper facial muscles originates from the brainstem, with links to the vigilance centers. Sudden appearance of an EMG signal usually suggests that the patient is responding to some extraneous stimulus, like pain [5,8]. Although an increase in the RE-SE difference appears to be helpful for assessing nociception, spectral entropy cannot indicate the exact level of stimulation [9]. Spectral entropy, especially RE, provides more information on the depth of anesthesia than does BIS [10]. Hence, spectral entropy can be used for assessing the depth of anesthesia during inhalation and intravenous induction of general anesthesia, monitoring the depth of propofol sedation, and predicting arousal reactions and motor responses [11–14].

The use of muscle relaxants is usually necessary to maintain skeletal muscle paralysis and facilitate mechanical ventilation during general anesthesia. Muscle relaxation affects EEG monitoring by causing the inhibition of frontal muscle activity [15–17]. Lanier et al. suggested that extending or shrinking muscle fibers causes afferent impulses to the waking centers. Then, a depressant effect is provided by the muscle relaxation, possibly by reducing the input [18]. Nevertheless, this remains controversial, since Fahey et al. [19] showed that the application of a muscle relaxant in completely awakened volunteers had no impact on sedation [20].

Therefore, the aims of this research were: 1) to investigate the effects of different degrees of neuromuscular blockade on differences in SE, RE, and RE-SE provided by the spectral entropy monitor during sevoflurane anesthesia; and 2) how spectral entropy responds after a noxious stimulation under different degrees of neuromuscular blockade and concentrations of sevoflurane inhalation.

## Material and Methods

### Ethics statement

This study was approved by the Institutional Ethics Committee of Shanghai General Hospital (Shanghai, China) on April 6, 2016 and registered in April 2016 at www.chictr.org.cn (#ChiCTR-OOC-16008293). The trial was carried out from May 2016 to December 2016 at the Department of Anesthesiology, Shanghai General Hospital of Nanjing Medical University.

### Study design and patients

This was a factorial prospective study of 3 concentrations of sevoflurane inhalation and 3 degrees of neuromuscular blockade. Eighty-one female patients scheduled for gynecological surgery were recruited. To reduce the confounding factors and avoid sex-related EEG differences [19], only women were recruited. The inclusion criteria were: 1) ASA class I–II; 2) aged 20–60 years; and 3) scheduled to undergo gynecological surgery. The exclusion criteria were: 1) disease or injury affecting the central nervous system; 2) recent use of psychoactive or analgesic medication; 3) neurological disorder or alcohol or drug abuse; or 4) weight <70% or >130% the ideal body weight.

### Grouping

The randomization sequence was prepared by an independent statistician in sealed envelopes, using a computer-generated table. The envelopes were opened sequentially 1 h before surgery. All patients were randomized to 9 groups (n=9 per group) based on different concentrations of sevoflurane inhalation (MAC, minimum alveolar concentration) and degrees of neuromuscular blockade (NMB=1-T1, depression of the first twitch using the acceleromyography device): group 1A (0.6 MAC, NMB 50%); group 1B (0.6 MAC, NMB 75%); group 1C (0.6 MAC, NMB 100%); group 2A (0.8 MAC, NMB 50%); group 2B (0.8 MAC, NMB 75%); group 2C (0.8 MAC, NMB 100%); group 3A (1.0 MAC, NMB 50%); group 3B (1.0 MAC, NMB 75%); and group 3C (1.0 MAC, NMB 100%).

### Anesthesia and study protocol

No premedication was given. After the patients entered the operating room, a venous channel was inserted into a large peripheral vein. Data from routine monitoring, including non-invasive arterial blood pressure, pulse blood oxygen saturation, and

end-tidal oxygen concentration (ETO2), end-tidal carbon dioxide concentration (ETCO2), and end-tidal sevoflurane concentration (ETSEV), were collected using a Datex Ohmeda S/5TM anesthesia monitor (Datex Ohmeda, Helsinki, Finland) [21]. Neuromuscular blockade (2 Hz for 1.5 s every 11.5 s) was continuously assessed by acceleromyography using the TOF-watch SX system (Organon, Dublin, Ireland), starting when the patients were unconscious. RE and SE were monitored using a Datex Ohmeda S/5TM Entropy Module (M-Entropy) and the Entropy Sensor system (Datex Ohmeda, Helsinki, Finland). Baseline RE, SE, and T1 (first twitch by acceleromyography) were recorded. Anesthesia was induced by inhalation of 8% sevoflurane for 2 min using a fresh gas flow of 8 L·min$^{-1}$ followed by 4% for 3 min [21]. Tracheal intubation was facilitated with rocuronium 0.6 mg kg$^{-1}$ after an acceleromyography count of 0. Anesthesia was maintained with sevoflurane in an air–O$_2$ mixture (FiO2 0.6, 1 L·min$^{-1}$). Mechanical ventilation was maintained at a tidal volume of 8–10 ml·kg$^{-1}$. Ventilator frequency was adjusted for maintenance of an ETCO2 of 4.00–4.67 kPa. Ephedrine was administered when mean arterial pressure was <70 mmHg. Atropine was administered when heart rate was <50 beats min$^{-1}$ during induction. After equilibration for 30 min at sevoflurane concentrations of 0.6 MAC, 0.8 MAC, and 1.0 MAC, according to grouping, rocuronium was administered as a continuous IV infusion adjusted until 50%, 75%, or 100% depression of T1 was observed, again according to grouping. A cutaneous tetanic electrical stimulation of 80 mA at 100 Hz for 5 s was applied to the ulnar nerve as a noxious stimulation. The entire experiment ended before the start of surgery. All procedures were carried out by the same anesthesiologist with 4 years of clinical experience.

### Data collection

Blood pressure, heart rate, RE, SE, and T1 were recorded before induction (awake state, Ta), after equilibration of sevoflurane concentration and NMB for 30 min (Tb), and 1 min after noxious stimulation (Tc). RE and SE values were recorded as a mean of 10 s (3 consecutive readings) at Ta, Tb, and Tc. The RE–SE difference was calculated by subtracting the SE value from the concurrent RE value.

### Endpoints

The primary endpoint was the impact of different degrees of neuromuscular blockade on SE, RE, and RE-SE difference. The secondary endpoint was the response of spectral entropy after noxious stimulation under different degrees of neuromuscular blockade and different concentrations of sevoflurane inhalation.

### Statistical methods

Based on a previous study [9], the mean post-stimulation RE values were estimated at 58 (30–68) for 1.7% of ETsev, 45 (36–59) for 2.1% ETsev, and 39 (25–54) for 2.5% ETsev. Assuming a type I error of 0.05 and a power of 0.80, 9 patients were required in each group.

Continuous data were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed data are presented as means (standard deviation) and were analyzed using one-way analysis of variance (ANOVA) with the post hoc LSD test. Pre-post anesthesia analyses were carried out using repeated-measures ANOVA. Non-normally distributed data are presented as median (range). Categorical data are presented as n and proportions, and were analyzed using the Fisher's exact test. Correlation analysis of spectral entropy with 0.6–1.0 MAC sevoflurane was performed using Pearson's rank correlation test. Spectral entropy values among groups were analyzed and compared with a linear mixed-model analysis, whereas the differences between any 2 groups were assessed by the least significant difference (LSD) test. All statistical analyses were performed using SPSS 22.0 for Windows (IBM, Armonk, NY, USA). Two-sided P-values <0.05 were considered statistically significant.

## Results

### Characteristics of the patients

Figure 1 presents the study flowchart. All randomized patients completed the study. Table 1 presents the characteristics of the subjects. No awareness during the surgeries or recall was reported by any patient in the study.

### Correlation between spectral entropy and sevoflurane concentrations

RE and SE at Ta and Tb, and RE-SE at Tb were inversely correlated with sevoflurane concentrations (all P<0.01) (Table 2).

### Effect of neuromuscular blockade on spectral entropy in the awake state (Ta)

These was no significant difference in RE, SE, or RE-SE among the groups in the awake state (at Ta) (all P>0.05). With NMB 50% and NMB 75%, RE and SE were significantly different under each sevoflurane concentration (all P<0.05), while RE-SE was not (all P>0.05). With NMB 100%, RE and SE under 1.0 MAC sevoflurane were significantly lower than under 0.6 MAC and 0.8 MAC (all P<0.05). Under 0.6 MAC, 0.8 MAC, and 1.0 MAC sevoflurane, RE, SE, and RE-SE did not show significant differences with each NMB (all P>0.05) (Table 3).
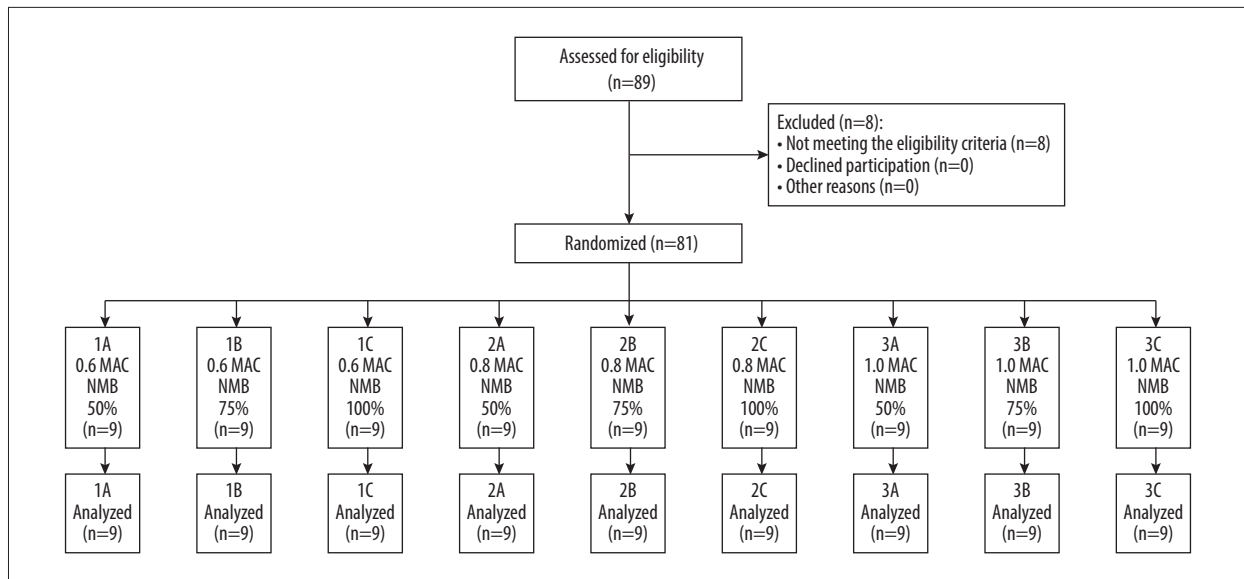
**Figure 1.** Study flowchart.

**Table 1.** Patient characteristics.

| Group | n | Age | Height | Weight |
|-------|---|-----|--------|--------|
| 1A | 9 | 43.56±9.59 | 159.56±4.83 | 57.78±6.48 |
| 1B | 9 | 40.44±11.49 | 161.67±5.32 | 58.33±5.34 |
| 1C | 9 | 40.33±11.27 | 160.44±7.12 | 57.11±6.09 |
| 2A | 9 | 45.22±9.04 | 159.67±7.09 | 52.44±5.62 |
| 2B | 9 | 40.11±11.40 | 160.22±3.64 | 55.44±5.18 |
| 2C | 9 | 45.56±9.68 | 159.44±5.55 | 56.56±4.69 |
| 3A | 9 | 39.56±10.83 | 159.22±6.12 | 57.11±4.70 |
| 3B | 9 | 43.67±10.65 | 159.67±3.81 | 59.56±5.34 |
| 3C | 9 | 41.33±13.41 | 159.33±4.80 | 55.44±5.64 |

**Table 2.** Correlation of entropy and sevoflurane concentrations.

| | Sevoflurane concentrations | |
|---|---|---|
| | r | P |
| Pre RE | −0.805 | 0.000 |
| Pre SE | −0.811 | 0.000 |
| Post RE | −0.827 | 0.000 |
| Post SE | −0.796 | 0.000 |
| Pre RE-SE | −0.216 | 0.053 |
| Post RE-SE | −0.762 | 0.000 |

## Effect of neuromuscular blockade on spectral entropy after 30 min of anesthesia but before noxious stimulation (Tb) and after noxious stimulation (Tc)

Without noxious stimulation, we found a significant effect of sevoflurane concentrations on RE, SE, and RE-SE, but without significant interactions between sevoflurane concentrations and NMB (Table 4).

RE was significantly higher after noxious stimulation than before in groups 1A, 1B, 1C, 2A, 2B, 2C, and 3A (all P<0.05). SE was significantly higher after noxious stimulation than before in groups 1A, 1B, 1C, 2A, 2B, and 2C (all P<0.05). RE-SE was significantly higher after noxious stimulation than before in groups 1A, 1B, 1C, 2A, 2B, and 2C (P<0.05) (Figure 2).

**Table 3.** RE, SE, and RE-SE in awake state and before noxious stimulation ($n=9$, $\overline{\chi}\pm s$).

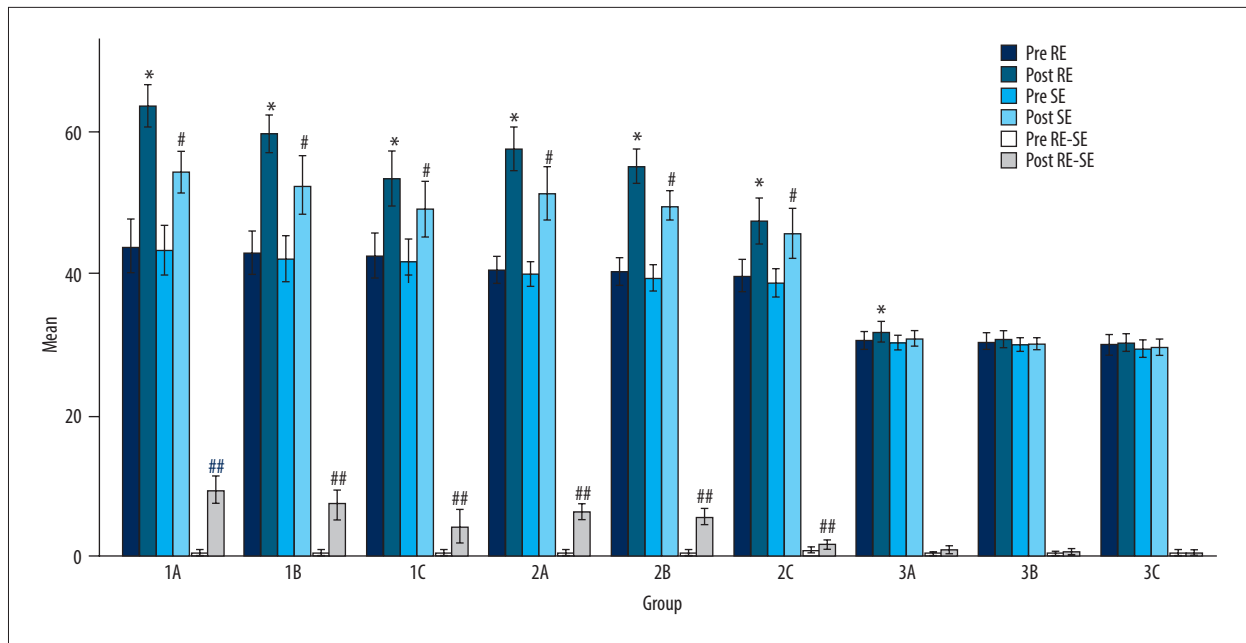| | Sevoflurane concentration | Awake | NMB | | |
|---|---|---|---|---|---|
| | | | 50% | 75% | 100% |
| RE | 0 | 96.81±1.64 | | | |
| | 0.6MAC | | 44.00±4.90# | 43.00±3.97# | 42.67±4.21 |
| | 0.8MAC | | 40.67±2.50## | 40.33±2.50## | 39.78±2.99## |
| | 1.0MAC | | 30.67±1.58* | 30.44±1.51* | 30.00±1.94* |
| SE | 0 | 86.63±1.56 | | | |
| | 0.6MAC | | 43.44±4.69# | 42.22±4.18# | 41.89±4.08 |
| | 0.8MAC | | 40.00±2.29## | 39.56±2.46## | 38.78±2.59## |
| | 1.0MAC | | 30.33±1.32* | 30.00±1.23* | 29.44±1.67* |
| RE-SE | 0 | 10.19±1.24 | | | |
| | 0.6MAC | | 0.56±0.53 | 0.78±0.44 | 0.78±0.44 |
| | 0.8MAC | | 0.67±0.50 | 0.78±0.44 | 1.00±0.50 |
| | 1.0MAC | | 0.33±0.50 | 0.44±0.53 | 0.56±0.53 |

With settled degree of NMB, #, ## and * indicate in comparison between 0.6MAC *vs.* 0.8MAC, 0.8MAC *vs.* 1.0MAC, and 0.6MAC *vs.* 1.0MAC.

**Table 4.** Tests of between-subjects effects of Pre RE, Pre SE, Pre RE-SE, ΔRE, ΔSE, and Δ(RE-SE).

| | Factor | F | Sig. |
|---|---|---|---|
| Pre RE | SEV | 125.816 | .000 |
| | NMB | .645 | .528 |
| | SEV×NMB | .047 | .996 |
| Pre SE | SEV | 130.793 | .000 |
| | NMB | 1.136 | .327 |
| | SEV×NMB | .067 | .992 |
| Pre RE-SE | SEV | 4.051 | .022 |
| | NMB | 1.897 | .157 |
| | SEV×NMB | .128 | .972 |
| ΔRE | SEV | 455.152 | .000 |
| | NMB | 73.901 | .000 |
| | SEV×NMB | 14.278 | .000 |
| ΔSE | SEV | 161.901 | .000 |
| | NMB | 11.932 | .000 |
| | SEV×NMB | 2.632 | .041 |
| Δ(RE-SE) | SEV | 78.526 | .000 |
| | NMB | 29.294 | .000 |
| | SEV×NMB | 5.541 | .001 |

Under sevoflurane at 0.6 MAC and 0.8 MAC, RE with NMB 100% was significantly lower than with NMB 50% and NMB 75% (all P<0.05). Under sevoflurane at 1.0 MAC, RE did not show any significant difference with each degree of NMB (all P>0.05). Under sevoflurane at 0.6 MAC and 0.8 MAC, SE with NMB 100% was significantly lower than with NMB 50% (P<0.05). Under sevoflurane at 1.0 MAC, SE did not show any significant difference with each degree of NMB (all P>0.05). Under sevoflurane at

**Figure 2.** Changes in RE, SE, and RE-SE at Tb (pre-stimulation) and Tc (post-stimulation). * P<0.05 RE Tb *vs*. RE Tc. # P<0.05 SE Tb *vs*. SE Tc. ## P<0.05 RE-SE Tb *vs*. RE-SE Tc.

**Table 5.** RE, SE, and RE-SE after noxious stimulation ($n$=9, $\overline{\chi}$±s).

| | Sevoflurane concentration | NMB | | |
| --- | --- | --- | --- | --- |
| | | 50% | 75% | 100% |
| Post RE | 0.6MAC | 63.44±3.75 | 59.56±3.47 | 53.56±5.15*,## |
| | 0.8MAC | 57.78±4.09 | 52.67±4.15 | 44.11±3.48*,## |
| | 1.0MAC | 34.56±1.94 | 30.78±1.56 | 30.22±1.72 |
| Post SE | 0.6MAC | 53.00±4.00 | 52.56±5.34 | 49.22±5.17* |
| | 0.8MAC | 51.44±4.90 | 47.11±4.68 | 40.78±3.15* |
| | 1.0MAC | 30.56±1.24 | 30.11±1.17 | 29.67±1.50 |
| Post RE-SE | 0.6MAC | 10.44±1.13 | 7.00±3.12 | 4.33±3.08*,## |
| | 0.8MAC | 6.33±1.50 | 5.56±2.24 | 3.33±1.00*,## |
| | 1.0MAC | 4.00±1.00 | 0.67±0.71 | 0.44±0.53 |

During settled sevoflurane concentration, * and ## indicate in comparison between NMB50% *vs*. NMB100% and NMB75% *vs*. NMB100%.

0.6 MAC and 0.8 MAC, RE-SE with NMB 100% was significantly lower than with NMB 50% (all P<0.05). Under sevoflurane at 1.0 MAC, RE-SE did not show significant difference with each degree of NMB (all P>0.05) (Table 5).

After noxious stimulation, we found significant interactions between sevoflurane concentration and NMB on the changes of RE (∆RE), changes of SE (∆SE), and changes of RE-SE (∆RE-SE).

## Discussion

Many studies have explored the effects of inhalation anesthetics, intravenous anesthetics, and muscle relaxants on spectral entropy [3,4,9–11,13,15,20–25], but most did not monitor the degree of neuromuscular blockade, which can be affected by individual variations. In addition, they do not explore the effects of different degrees of neuromuscular blockade on spectral entropy under different concentrations of sevoflurane inhalation. Therefore, the present study used different levels of MAC to quantify the sevoflurane concentration, as well as

different degrees of neuromuscular blockade, controlled by the non-depolarizing muscle relaxant rocuronium.

Correlations between sevoflurane concentration and SE and RE have been demonstrated [25]. In a study by Takamatsu et al., patients were randomly assigned to 4 end-tidal sevoflurane concentration (1.3%, 1.7%, 2.1%, or 2.5%), showing that SE and RE declined significantly with rises in sevoflurane [9]. In the present study, we observed inverse correlations between sevoflurane MAC and RE and SE, but RE-SE without noxious stimulation was not correlated to the concentration of sevoflurane inhalation.

The effects of muscle relaxants on EEG remain controversial. Messner et al. [26] showed that the BIS declines during neuromuscular blockade in completely conscious persons. We found that under the determined sevoflurane concentrations, RE, SE, and RE-SE were not affected by the different degrees of NMB. That might be explained by the reduction of EMG activity of the frontal muscles in anesthetized patients without noxious stimulation, as supported by Ekman et al. [21], but not by Inoue et al. [27], who suggested that BIS is altered by muscle relaxant in moderately sedated patients but not in deeply sedated patients, although muscle relaxant did not influence brain hemodynamics during either moderate or deep sedation. This disagreement might be partly caused by the absence of a control group without neuromuscular blockade or by the limited effects of muscle relaxant on EEG when neuromuscular blockade was >50%. Greif et al. [28] used mivacurium in anesthetized patients with propofol through IV infusion until the first twitch (T1) under 80%, 30%, 20%, 15%, 10%, 5%, or 2% of pre-blockade intensity, but there were no significant differences at the designated blockade levels, and they attributed this lack of effect to the high sedation. As a result, EMG activity might be more significant under lighter anesthesia, in which of the situation of paralysis may have a more significant influence on EMG activity. This might explain, at least in part, the results of the present study.

A number of studies shown that the application of muscle relaxants attenuates the effect of noxious stimulation on EEG during general anesthesia [29–31]. The anesthetic demand might therefore be under-rated if assessed only according to EEG monitoring. Our results showed that spectral entropy values were significantly higher under 0.6–0.8 MAC sevoflurane after noxious stimulation than before. RE and RE-SE decreased significantly, while SE decreased slightly, with increases in the degrees of neuromuscular blockade, as supported by Kawaguchi et al., who showed that the change in entropy due to endotracheal intubation is suppressed by rocuronium in a dose-dependent manner [23]. We found that spectral entropy values increased significantly after noxious simulation at 100% neuromuscular blockade, which might be caused by the

different sensitivities to muscle relaxants between the frontal and limb muscles [32]. We also found that the changes in spectral entropy were significantly reduced under sevoflurane at 1.0 MAC, which was not significantly related to the degrees of neuromuscular blockade. At each degree of neuromuscular blockade, SE decreased significantly with increases in sevoflurane concentrations. RE was affected by the degree of neuromuscular blockade. In addition, in the study of Morgaz et al., beagle dogs were anesthetized with sevoflurane with 5 levels (MAC; 0.75, 1, 1.25, 1.5, and 1.75 MAC), showing no significant changes in the RE, SE, and RE-SE difference before or after the noxious stimulations [24], and there were no significant correlations between MAC and spectral entropy. When the data under 1.75 MAC were eliminated, these correlations were enhanced. A species difference might also be possible.

There are certain limitations to our study. The sample size was small, with only 9 subjects per group, but the power analysis suggested that this number was sufficient. Nevertheless, the number of subjects could be increased in our future studies to improve the validation of the results. The validity of our study may have been limited by the single-center study design. The statistical analysis may have been influenced and we may have neglected some clinically relevant differences. We only focused on the spectral entropy changes under anesthesia, but not during anesthesia recovery. It was reported that spectral entropy values were more delicate and a faster increase was demonstrated by them than the BIS [4]. We did not explore the effect of opioids on spectral entropy. Depth of anesthesia monitors may push forward an immense influence on both anesthetic technology and pharmacology, and how to distinguish and gauge the diverse anesthetic drug effects by precise monitors remains to be explored [33]. Depth of anesthesia monitors might help individualize anesthesia and develop a technique for automatically controlling anesthesia in the future [34].

## Conclusions

RE and SE values decreased with increases in sevoflurane concentration. Neuromuscular blockade did not affect spectral entropy without noxious stimulation. With noxious stimulation, muscle relaxants significantly reduced the changes in spectral entropy and there were significant interactions in spectral entropy between NMB and sevoflurane. These results of entropy monitoring during sevoflurane anesthesia should be interpreted cautiously in consideration of the effects of the muscle relaxants so as not to misjudge the depth of anesthesia.

### Conflicts of interest

None.

**CLINICAL RESEARCH**

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