

EOG Elicited by Rhythmic Auditory Predicts the Depth of Sedation During Sevoflurane Anesthesia

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Research Article

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Abstract

Background: Several electroencephalographic (EEG) variables have been used to estimate changes in human brain electrical activity during changing states of consciousness as a clinical monitoring tool to anesthesia and sedation. However, the EEG signal is weak and extremely susceptible to suppression interference. The use of EEG variables as anesthesia monitors is still controversial. Recent studies have shown a new language paradigm that elicited rhythmic brain responses and ocular muscle activity tracking sentence rhythms in speech. Electrooculogram (EOG) driven by rhythmic auditory stimulation has a larger amplitude than EEG variables and a higher temporal resolution than event-related brain potentials, which may be a potential monitor of anesthetic depth.

Methods: Twenty-five patients inhaled sevoflurane via laryngeal mask for induction of anesthesia. The initial concentration of sevoflurane was set to 0.4% and increased by 0.1% every 1 min until loss of consciousness. During the entire operation, rhythmic auditory stimulation was presented binaurally to elicit ocular muscle activity.

Results: When the end-tidal sevoflurane concentration (Et_{sevo}) was low, the EOG had a significant spectral peak at 0.5 Hz, which is the same frequency as the rhythmic auditory stimulation, and then the peak value of EOG decreased with the increase of Et_{sevo} . Peak value of EOG spectrum under the rhythmic auditory stimulation (PERA) showed significant differences in different depth of sedation (wakefulness: 84.0 ± 22.8 , light sedation: 47.0 ± 27.7 , deep sedation: 10.9 ± 16.5 , $P < 0.01$). PERA is correlated well with Et_{sevo} (-0.75 , $P < 0.01$) and was able to predict the sedation depth during the induction period of anesthesia well ($P_K = 0.92 \pm 0.08$).

Conclusion: We found that the ocular muscle activity synchronizes to the rhythmic auditory stimulation structures during induction with sevoflurane. With the increase of Et_{sevo} , the synchronizing ability of the ocular electricity to rhythmic auditory stimulation gradually weakens and eventually disappears. Based on this evidence, the EOG driven by a rhythmic auditory stimulation may be a new and reliable approach to characterize and predict anesthetic depth objectively.

Trial registration: The research project was registered at chictr.org.cn (ChiCTR1900026590, 2019/10/15).

Introduction

Depth of anesthesia (DoA) monitoring during surgery is a critical and challenging task. An accurate assessment of the DoA helps correctly deliver anesthesia agents to patients and prevent anesthesia awareness.[1] Since the sensitive changes of the electroencephalography (EEG) temporal and spectral features during anesthetic-induced, several EEG based monitors have been developed to assess anesthetic depth, for example, BIS and Narcotrend.[2–4] However, the EEG signal is weak and extremely susceptible to suppression interference than the other electrophysiological signal, which has also been found to have some limitations in clinical applications.[5–7]

Recent studies have shown a new language paradigm that elicited rhythmic brain responses and ocular muscle activity tracking sentence rhythms.[8, 9] Some researchers have successfully applied this paradigm to assessing residual consciousness and cognitive abilities in unresponsive patients[10]. Electrooculogram (EOG) driven by rhythmic auditory stimulation has a larger amplitude than EEG variables and a higher temporal resolution than event-related brain potentials, which has the potential to become a new indicator of anesthesia monitoring.

In the present study, we hypothesize the EOG driven by rhythmic auditory stimulation can monitor anesthetic depth. EOG synchronized to the rhythmic auditory stimulation structures, which are potentially driven by temporal attention.[9] So rhythmic auditory stimulation needs to attract the patient's attention as much as possible. In various experiments and clinical studies, it has been shown that auditory calling one's name captures attention and stimulates the cerebral cortex more than other auditory materials.[11–13] At the same time, vertical EOG has a stronger ability to synchronize the linguistic sequence than horizontal EOG.[9] In this study, we used rhythmic auditory stimulation that calls the patient's own name and collected the patient's vertical EOG to analyze his response to the rhythmic auditory stimulation.

In this paper, we administered a rhythmic auditory stimulation to patients under anesthesia induced by sevoflurane. We then studied whether the EOG synchronized to the rhythmic auditory stimulation structures under different end-tidal sevoflurane concentrations (Etsevo) and compared it with the bispectral index (BIS) to assess whether it can help inform diagnosis depth of sedation during the induction of anesthesia.

Methods

Participants

After we obtained the permission of the ethics committee of the First Affiliated Hospital of Zhejiang University and informed written consent from all of the patients (Chairperson: Ming Zheng, date of registration: 2019/10/15, registration number: ChiCTR1900026590, principal investigator's names: Guozheng Wang, Delin Zhang, Fan Hang, Kangli Dong), based on resources available, we enrolled 40 patients (American Society of Anesthesiologists grade 1 or 2, 22 male and 18 female participants between 18–70 years old). All selected patients were scheduled for lower limb surgery and had no hearing impairment or neurological disorders. Pregnant women, people taking opioids or sedatives within 24 h, or people at risk for aspiration were excluded. All of the patients fasted for a minimum of 6 h before surgery.

As shown in Figure 1, based on resources available, forty patients were initially assessed in this study, but 8 patients withdrew before allocation to a study group. Of these patients, 3 met the exclusion criteria, and 5 declined to participate. Thirty-two patients were enrolled in the study. Five patients were excluded because of poor signal quality caused by extreme body movements during the operation. In total, data from 27 patients were analyzed.

Anesthetic technique and task

When the patient arrived in the operating room, an 18-G intravenous (IV) cannula was secured, and a standard electrocardiograph, non-invasive blood pressure, and pulse oximetry (SpO₂) monitoring were acquired. Baseline heart rate (HR), mean blood pressure (MBP), and SpO₂ readings were also obtained. The bispectral index (BIS) value was displayed using an Aspect EEG monitor (Model A-1000; Aspect Medical Systems). We then obtained the patient's EOG signals by the Waveguard EEG Cap from ANT Neuro. The patient put on binaural headphones to hear the rhythmic auditory stimulation. We selected the combined lumbar and epidural anesthesia to induce anesthesia in the patient's lower limbs, specifically using sevoflurane for the induction and maintenance of anesthesia in the laryngeal mask airway. After all of the medical equipment was set up, an 18-G intravenous (IV) cannula was secured, and Lactated Ringer's solution was infused at a rate of 10 ml/kg/h to all of the patients. The patient was placed lying on the lateral recumbent position with the L3-4 gap as the puncture point. After successfully puncture, a dose of 2.5 mg/kg of Ropivacaine hydrochloride was injected into the subarachnoid space, and the epidural tube was fixed into place. For patients whose anesthesia level did not reach the eighth thoracic level 10 min after the drug administration, a total of 5 ml of 0.5% Ropivacaine was also injected from the epidural tube. Anesthesia was then induced using sevoflurane in 100% oxygen. The initial concentration of sevoflurane was set to 0.4% and was then increased by 0.1% every 1 min until loss of consciousness (After the Et_{sevo} is greater than 2%, the anesthesiologist verifies whether the consciousness has disappeared through oral commands.) We subsequently increased the sevoflurane concentrations to 8% for at least 4 min until the LMA was inserted, and then decreased the concentration of sevoflurane to 2% for maintenance. Throughout this procedure, Et_{sevo} and PECO₂ were continuously monitored, and ventilation was supported manually if respiration was inadequate, and spontaneous breathing was maintained. The rhythmic auditory stimulation (calling the patient's name) were circulated throughout the entire procedure, and patients were instructed to concentrate on listening to the rhythmic auditory stimulation.

Auditory stimulation and experimental design

Before the experiment, the neospeech synthesizer synthesized the auditory stimulation (16-bit, 16k sampling rate, Chinese Mandarin, 87–90 dB intensity). The rhythmic auditory stimulation was played by binaural headphones during the experiment and lasted two h. The rhythmic auditory stimulation was a periodic signal with 30 s, with the first 20 s as blank sounds, and calling the patient's name every 2 s in the last 10 s (Figure 2A). We compared the EOG signal during the "blank sound" segment with the signal during the "name-calling" segment to study the effect of rhythmic auditory stimulation on EOG. According to the Et_{sevo} during anesthesia induction, we divided the patient's depth of sedation into wakefulness, light sedation, and deep sedation. The Et_{sevo} in the three states was 0%–0.5%, 0.7%–0.9%, and 1.2%–1.4%, respectively. In comparing the EOG of patients in different depth of sedation, we studied sevoflurane's effect on the EOG driven by the auditory stimulus sequences (Figure 2B).

Data Processing

We used MATLAB (MathWorks, Natick, MA) for data analysis. The EOG recordings were bandpass (0.2–20 Hz) filtered and separated by a 30s analysis window (the period length of the auditory stimulation). According to the rhythmic auditory stimulation structure, we then divided every 30 s EOG signal into a 20 s "blank sound" segment and a 10 s "name-calling" segment. Each segment was converted to the frequency domain using a discrete Fourier transform (DFT) without any additional smoothing window. We normalized each segment of the EOG spectrum at 0.5 Hz and multiplied it by 100. In the case of a patient in the same end-tidal concentration receiving multiple auditory stimuli, we used the multiple spectrum values' arithmetic mean as the patient's spectrum value at this end-tidal concentration.

Statistical analysis

The statistical significance of a spectral peak at the frequency of 0.5 Hz was tested by comparing the power at 0.5 Hz with the power of two neighboring frequencies using a bootstrap method by resampling 10,000 times. If the response was stronger at the 0.5 Hz frequency than the neighboring frequencies in $A\%$ of the resampled data, the significance level was $(100A+1)/10001$. Bootstrap was also used to estimate the standard error of mean (SE) across participants, and for this purpose, participants were resampled with replacement 100 times.

One-way analysis of variance (ANOVA) was used to examine the significance of differences of patients' Peak value of EOG spectrum under the rhythmic auditory stimulation (PERA) or the BIS value in the three different Et_{sevo} levels. We applied Bonferroni corrections to the post hoc analyses, and P values < 0.05 were considered to be significant. Results are designated as mean (SD) or 95% confidence interval (95% CI).

The prediction probability (P_K) was used to evaluate the PERA or BIS value's predictive ability for sedation depth. The mathematical basis of P_K was proposed and explained by Smith et al. in 1996.[14] In the process of calculating P_K , we used the BIS value or the PERA as the predicting variable and the actual depth of sedation (determined by the Et_{sevo}) as the value of the variable to be predicted. The closer the value of P_K is to 1, the better the prediction effect. The P_K values were subsequently calculated for BIS and PERA. Two methods calculated each type of P_K value described above. First, P_{Ksev} indicates the probability of correctly predicting the ET_{sevo} . Second, P_{KDS} represents the probability of correctly predicting the depth of sedation.

Results

EOG spectrogram at a different end-tidal concentration of sevoflurane

The patient's Et_{sevo} increased slowly during anesthesia induction. Meanwhile, we recorded the vertical EOG spectrum of the patient (Fig. 3). Bootstrap was used to evaluate the significance of the patient's EOG at the peak of 0.5 Hz. We calculated the 95% CI of the spectral value at 0.5 Hz during induction of anesthesia (Table 1). The results show that when the Et_{sevo} is low, the EOG had a significant spectral peak at 0.5 Hz, which is the same frequency as auditory stimulation calling one's name. Moreover, the 0.5 Hz energy peak value of EOG decreased with the increase of Et_{sevo} (Fig. 3A), suggesting that one's ocular muscle activity synchronized with the auditory stimulation calling one's name, and this ability decreased as the Et_{sevo} increased during induction of anesthesia. At the same time, we also calculated the EOG spectrum without rhythmic auditory stimulation at different Et_{sevo} (Fig. 3B) and found no energy peak of 0.5 Hz at any Et_{sevo} . This further illustrates that the 0.5 Hz EOG energy peak of Fig. 3A was elicited by rhythmic auditory stimulation.

Table 1
Spectral value at 0.5 Hz under calling one's name or blank sound

ETsevo	Under sound calling one's name			Under blank sound		
	Mean	SE	95% CI	Mean	SE	95% CI
0.0%	86.7**	3.5	79.8–93.6	14.3	3.2	7.7–20.9
0.4%	79.8**	3.7	72.5–87.1	20.5	4.0	12.3–26.5
0.5%	70.8**	5.4	60.2–81.4	17.3	4.5	8.2–26.5
0.6%	50.8**	5.6	39.8–61.9	11.8	2.1	7.5–16.1
0.7%	44.6**	5.3	34.0–55.1	12.6	3.2	6.0–19.2
0.8%	31.2**	5.4	20.6–41.8	12.2	3.1	5.7–18.7
0.9%	35.9**	4.9	26.3–45.5	8.9	1.5	5.9–11.9
1.0%	16.7**	3.0	10.9–22.6	10.3	2.4	5.4–15.2
1.1%	9.4*	3.9	1.9–17.0	8.3	1.8	4.5–11.9
1.2%	6.9	3.5	0.1–13.6	5.7	1.3	3.0–8.3
1.3%	3.1	3.7	0–10.3	5.8	0.9	3.9–7.7
1.4%	1.5	1.5	0–5.4	4.3	0.7	2.8–5.8

N = 27. **p* < 0.05; ***p* < 0.01. SE: standard error, Et_{sevo} : end-tidal sevoflurane

PERA and BIS during the different depth of sedation

We calculated the 0.5 Hz Peak value of EOG spectrum under the rhythmic auditory stimulation (PERA). To study whether the changes in PERA or BIS showed consistent changes with the depth of sedation, we recorded the changes in patients' PERA and BIS values while the Et_{sevo} increased (Fig. 4A and Fig. 4B). As

the Et_{sevo} increases, PERA and BIS both decreased significantly. During the induction of anesthesia, PERA or BIS were significantly correlated with the end-tidal sevoflurane ($P < 0.01$), and PERA (-0.75) showed a stronger correlation with the end-tidal concentration of sevoflurane than did BIS (-0.64).

According to patients' Et_{sevo} , the depth of sedation of patients was divided into the following three conditions: wakefulness (0–0.5%), light sedation (0.7–0.9%), and deep sedation (1.2–1.4%). We used an ANOVA to examine the differences between patients' PERA in different depth of sedation. We found a significant difference in PERA between the three sedation depths (Fig. 4C). PERA under the wakefulness condition was significantly higher than that under light sedation, and PERA under light sedation was also significantly higher than that under deep sedation (wakefulness: 78.8; 95% CI, 73.9 to 83.7; light sedation: 36.8; 95% CI, 30.8 to 42.8; deep sedation: 3.8; 95% CI, 0.2 to 7.4; $P < 0.01$).

To further evaluate PERA's prediction ability on the depth of sedation and compare it to the BIS value, we calculated the prediction probabilities (P_K) of PERA and BIS for the Et_{sevo} and depths of sedation, respectively (Fig. 4B). $P_{K_{sev}}$ indicates the probability of correctly predicting the end-tidal concentration of sevoflurane, and $P_{K_{DS}}$ indicates the probability of correctly predicting the depth of sedation. We found that the $P_{K_{sev}}$ of PERA (0.84; 95% CI, 0.81 to 0.87; $P < 0.01$) was slightly lower than $P_{K_{sev}}$ of BIS (0.85; 95% CI, 0.82 to 0.88; $P < 0.01$) and that the $P_{K_{DS}}$ of PERA (0.92; 95% CI, 0.90 to 0.94; $P < 0.01$) was slightly higher than the $P_{K_{DS}}$ of BIS (0.90; 95% CI, 0.87 to 0.93; $P < 0.01$). Overall, PERA showed a similar ability to predict sedation depth as BIS, and both were able to predict the sedation depth during the induction period of anesthesia well

Discussion

Our results show that when people are conscious, EOG accurately tracks the rhythmic auditory stimulation calling one's name. As the anesthesia deepens, the tracking effect of EOG on auditory stimulation gradually weakens and eventually disappears. We showed that this tracking effect is manifested in the patient's EOG signal showing the same spectral peak with the rhythmic auditory stimulation of calling one's name and that the peak of the spectrum gradually weakens as the Et_{sevo} increases. Based on this effect, EOG elicited by rhythmic auditory stimulation has the potential to be a new and reliable approach to characterize and predict the depth of anesthesia objectively.

It is known that cortical activity can track phrases and sentences in speech[8, 15, 16] and meters in music.[17] According to recent research, we also know that ocular muscle activity tracking the rhythms in speech, which is potentially driven by temporal attention.[9] Moreover, they by show that the phase of low-frequency neural activity tracks attended syllables in a sentence and by showing ocular synchronization to the attentional focus.[9] And some research shows that part of the attention network,[18, 19] including the frontal eye fields and posterior parietal cortex, is also involved in controlling eye movements and blinking.[9, 20, 21] This means that the attention network is related to the eye movement network and that attention transfer and concentration will also affect the eye movement. When patients heard their name

being relayed, attention was shifted to the reception and processing of the voice, which drove eye movements. Some studies have additionally shown that the cognitive attention network can be damaged under general anesthesia.[22, 23] Therefore, during the induction of anesthesia, anesthetics reduced the patients' ability to concentrate and minimizing the ability of EOG to track the rhythmic auditory stimulation.

These findings shed light on the brain's ability to process information as anesthesia deepens. Human cognitive processing occurs in hierarchically organized neural organizations in the brain,[24] where external stimuli are received and recorded by the primary sensory cortex. As sensory information is transferred to a higher-level cortex for processing, it finally generates cognition, such as perception, memory, and judgment. The process of the lower-order neural representation of sensory stimuli becoming synthesized in the higher-order brain regions is also described by the notion of cognitive binding.[25–28] Studies have shown that anesthesia can lead to disrupted functional connections between sensory processing and higher-order processing cortical regions in the temporal, frontal, and parietal lobes, which causes the cerebral cortex to lose the ability to process phrases and sentences.[8, 29–33] In our study, the tracking effect of EOG in rhythmic auditory stimulation gradually weakened and eventually disappeared during the induction of anesthesia, which may reflect the brain's ability to process information that was negatively affected by sevoflurane-induced anesthesia. During anesthesia, this breakdown left the patients unable to process the rhythmic auditory stimulation they heard, which further caused the eye movements driven by the rhythmic auditory stimulation to disappear.

As we demonstrated, PERA decreased as the depth of sedation deepened. PERA, therefore, has the potential to become a new indicator of the depth of anesthesia. Moreover, PERA has a similar PK value and a higher degree of linear correlation than BIS, and therefore has a good predictive ability for Etsevo in anesthesia. However, the relationship between PERA and end-tidal sevoflurane concentration also showed significant inter-individual and intra-individual variability. Some patients did not significantly respond to their names throughout the process, potentially due to not focusing on the rhythmic auditory stimulation. If PERA is to be used as an indicator of the depth of anesthesia, how to make patients focus on the rhythmic auditory stimulation as much as possible may be a problem that needs to be further solved.

In conclusion, we found that the ocular muscle activity synchronizes to the rhythmic auditory stimulation structures during different Et_{sevo} levels, and the tracking effect gradually weakens and eventually disappears through the induction of anesthesia. Based on this phenomenon, we proposed a new method that has the potential to be a new and reliable approach to characterize and predict the depth of anesthesia objectively.

Abbreviations

EEG: Electroencephalographic; EOG: Electrooculogram; Etsevo: End-tidal sevoflurane concentration; PERA: Peak value of EOG spectrum under the rhythmic auditory stimulation; DoA: Depth of anesthesia; BIS:

Bispectral index; SpO₂: Oxygen saturation; HR: Heart rate; MBP: Mean blood pressure; DFT: Discrete Fourier transform; SE: Standard error of mean; ANOVA: One-way analysis of variance; PK: Prediction probabilities;

Declarations

relevant guidelines and regulations

This study was performed in accordance with the Declaration of Helsinki. We also obtained written informed consent from all patients participating in the trial.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of First Affiliated Hospital of Zhejiang University (20191362). Written informed consent of patients was obtained according to the Declaration of Helsinki. We also registered in chictr.org.cn (ChiCTR1900026590).

Consent for publication

Not applicable.

Availability of data and materials

The dataset generated and analyzed during the current study is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Delin Zhang: This author designed the experiments and provided experimental equipment, site and funding support.

Guozheng Wang and Jun Liu: This author wrote the body of the article and carried out the experimental work and the data collection and interpretation.

Fan Hang and Kangli Dong: This author participated in data collection.

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Figures

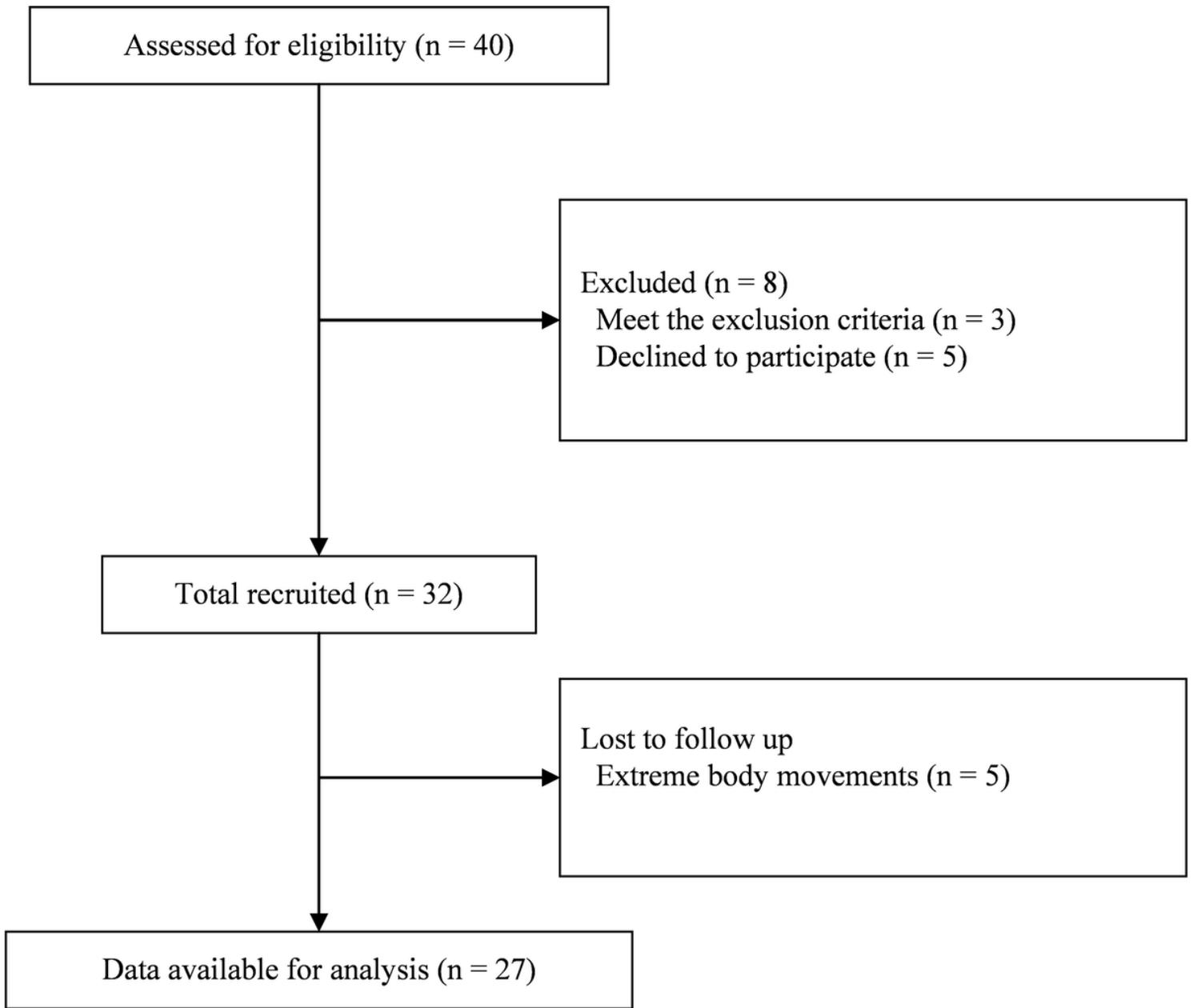


Figure 1

Study flowchart showing the study procedures.

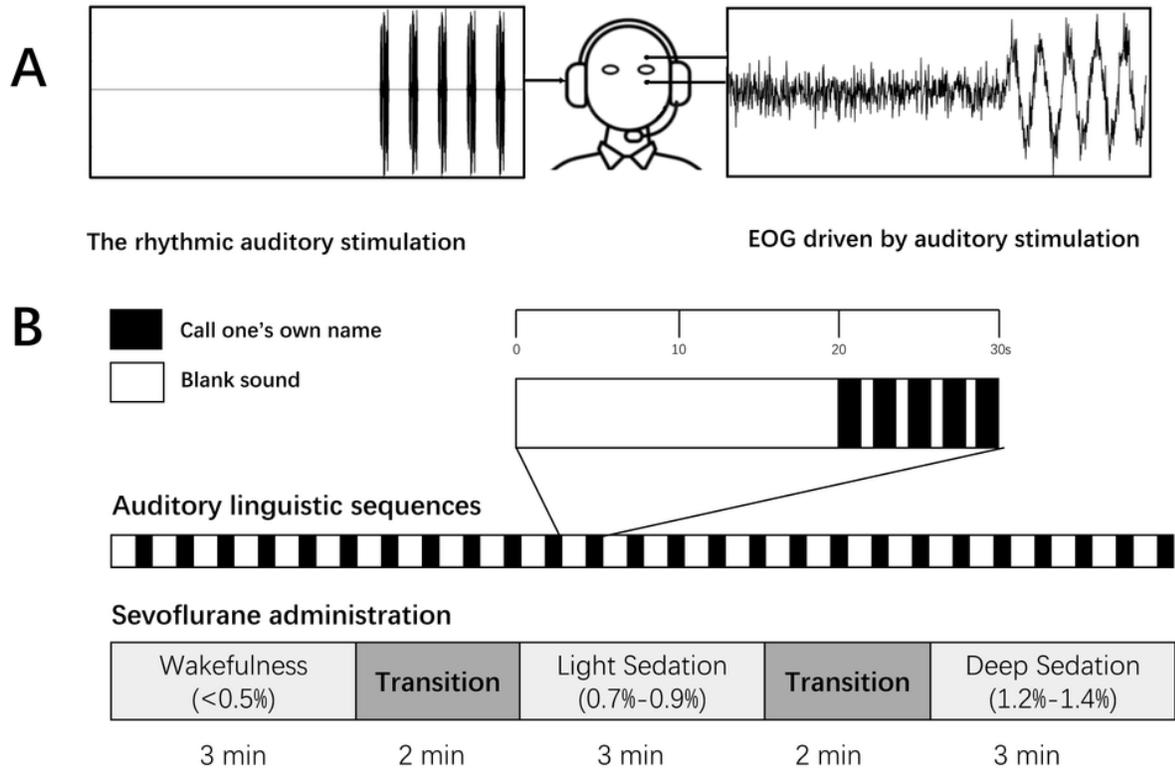


Figure 2

Scheme of the experimental protocol. A. The patient receives rhythmic auditory stimulation during the induction of anesthesia, and we recorded its vertical EOG. B. The patient receives rhythmic auditory stimulation into wakefulness, light sedation, and deep sedation (the Etsevo in patients in the three states was 0% –0.5%, 0.7%–0.9%, and 1.2%–1.4%, respectively).

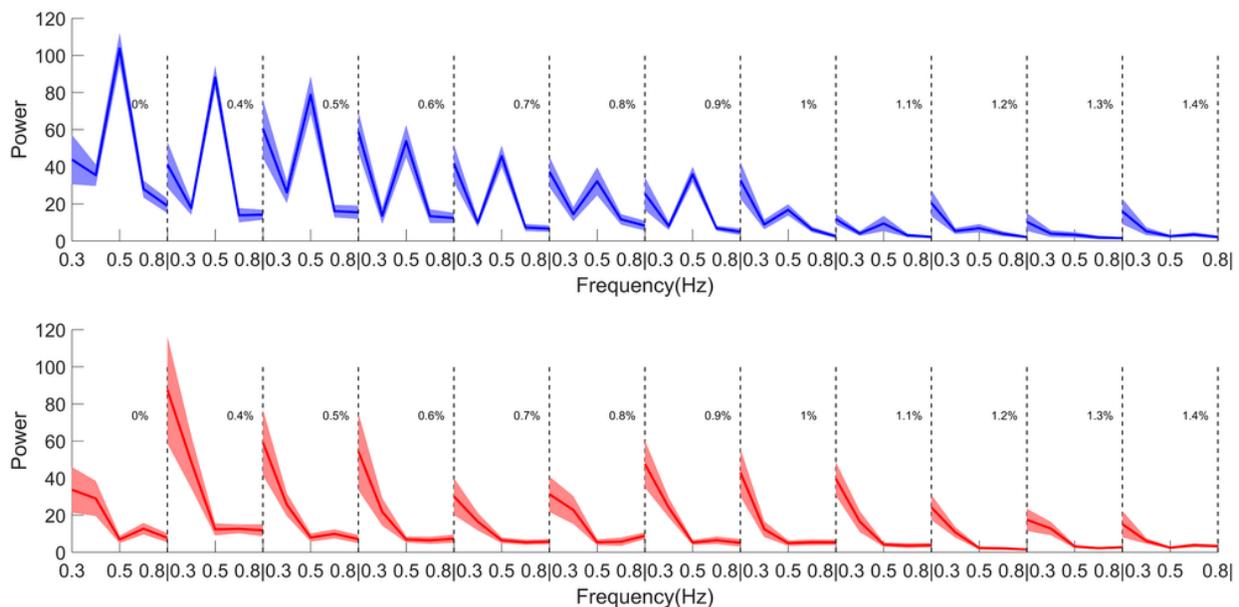


Figure 3

Spectrogram of patients' EOG at different Etsevo. Vertical dashed lines separate the EOG spectrograms at different end-tidal concentrations, and the concentration of Etsevo is indicated in the upper right corner of each Figure. Each spectrogram is the 0.3–0.8 Hz portion of the complete spectrogram. A. The EOG spectrum of the patients when they heard the headset calling their name at different Etsevo. B. The EOG spectrum of the patients when they heard the blank sound.

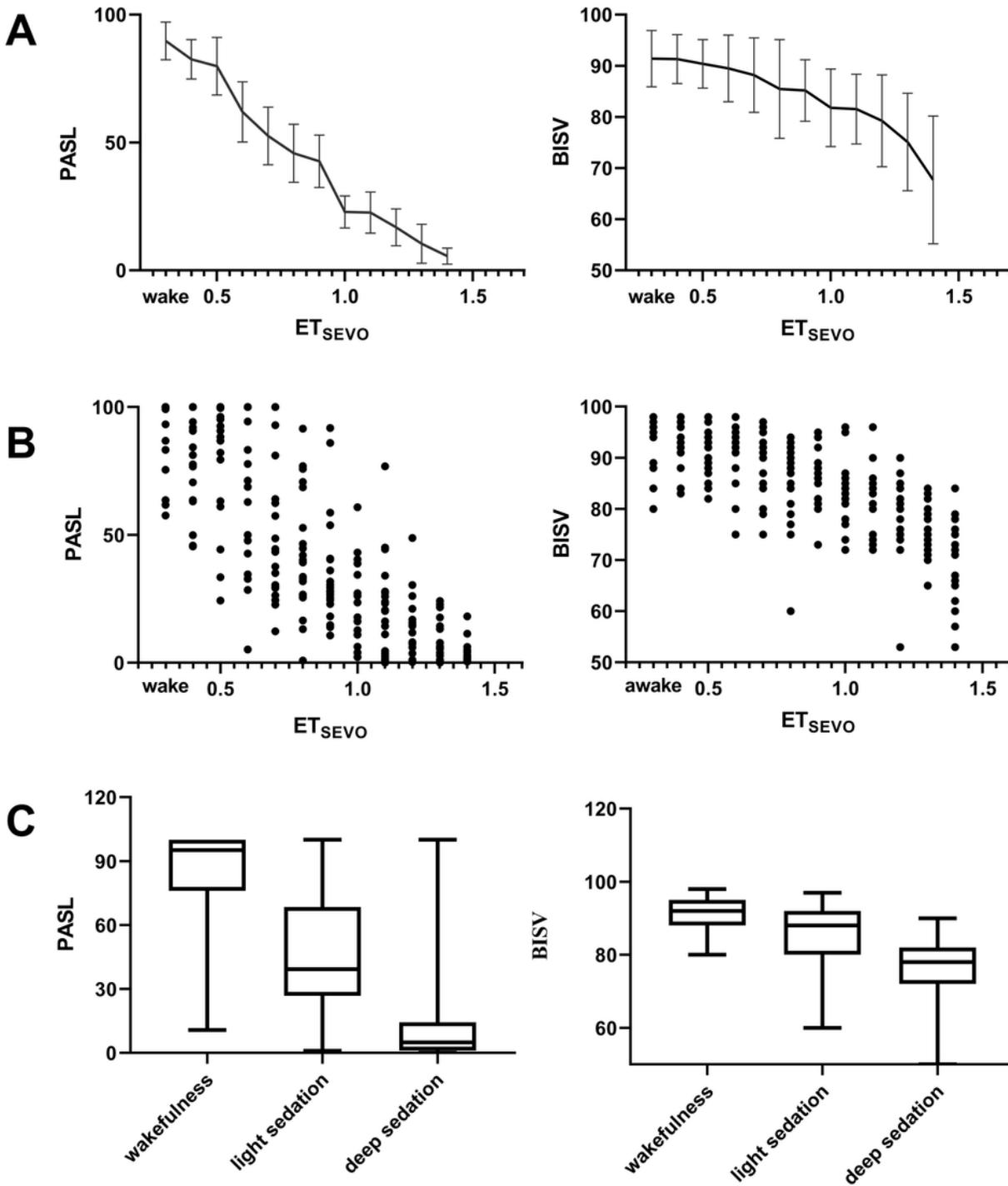


Figure 4

Changes in patients' PERA and BIS with the deepening of sedation. N=25. A. Line graph showing the changes in the patient's PERA and BIS with increasing Etsevo. The error bars indicate the 95% CI range. B. Scatter plots of PERA and BIS for Etsevo. C. Histogram of PERA and BIS in the three different states of consciousness. Error bars indicate the standard deviation.