

Effect of depth of anesthesia on the phase lag entropy in patients undergoing general anesthesia by propofol

A STROBE-compliant study

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Abstract

The PLEM100 (Inbody Co., Ltd., Seoul, Korea) is a device for measuring phase lag entropy (PLE), a recently developed index for the quantification of consciousness during sedation and general anesthesia. In the present study, we assessed changes in PLE along with the level of consciousness during the induction of general anesthesia using propofol. PLE was compared with the bispectral index (BIS), which is currently the most commonly used index of consciousness.

After obtaining Institutional Review Board approval and written informed consent, we enrolled 15 patients (8 men, 7 women; mean age: 37 ± 9 years; mean height: 168 ± 8 cm; mean weight: 68 ± 11 kg) undergoing nasal bone reduction. PLE and BIS sensors were attached simultaneously, and general anesthesia was induced via target-controlled infusion (TCI) of propofol. PLE and BIS scores were recorded when the calculated effect site concentration shown on the TCI pump was equal to the target concentrations of 1.5, 2.0, 2.5, 2.8, 3.0, 3.2, 3.4, and $3.5 \mu\text{g/mL}$ (and at each $0.1 \mu\text{g/mL}$ increase, thereafter). Observer's Assessment of Alertness/Sedation (OAA/S) scores were also recorded until unconsciousness was achieved. Throughout the anesthesia period, all pairs of PLE and BIS data were collected using data acquisition software.

The partial correlation coefficients between OAA/S scores and PLE, and between OAA/S scores and BIS were 0.778 ($P < .001$) and 0.846 ($P < .001$), respectively. Throughout the period of anesthesia, PLE and BIS exhibited a significant positive correlation. The partial correlation coefficient prior to the loss of consciousness was 0.838 ($P < .001$), and 0.669 ($P < .001$) following the loss of consciousness. Intra-class correlation between the 2 indices was 0.889 ($P < .001$) and 0.791 ($P < .001$) prior and following the loss of consciousness, respectively.

PLE exhibited a strong and predictable correlation with both BIS and OAA/S scores. These results suggest that PLE is reliable for assessing the level of consciousness during sedation and general anesthesia.

Abbreviations: ASA = American Society of Anesthesiologists, BIS = bispectral index, EEG = Electroencephalography, EMG = Electromyography, OAA/S = Observer's Assessment of Alertness/Sedation, PLE = phase lag entropy, TCI = target-controlled infusion pump.

Keywords: bispectral index, general anesthesia, phase lag entropy

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1. Introduction

The bispectral index (BIS), a quantitative index obtained from processed electroencephalography (EEG) data, is the most commonly used indicator of consciousness in patients under general anesthesia. The BIS is determined based on scalp EEG signals acquired from frontal electrode arrays using multiple regression analysis techniques.^[1,2] The use of BIS during surgery has been reported to reduce the use of anesthetics, shorten recovery time, and reduce the incidence of side effects.^[3,4] Ibrahim et al^[5] reported that the BIS has drug-specific properties and predicts sedation with propofol slightly better than sevoflurane or midazolam. The BIS has a unitless value between 0 and 100. The value of 100 represents a fully awake state and 0 corresponds to electroencephalographic silence; values between 40 and 60 are suggested for general anesthesia.^[6] Recently, new indicators have been developed in an attempt to more accurately evaluate the level of consciousness of patients under anesthesia. One such indicator is phase lag entropy (PLE).^[7]

Neural communication exhibits a non-stationary and transient nature, and the functional connectivity of the brain in mammals continues to fluctuate even at rest.^[8,9] Modern theories of consciousness support the notion that the brain exhibits various functional patterns during the waking state, while a lack of such patterns is observed in the unconscious state.^[10] Previous EEG and functional magnetic resonance imaging (fMRI) studies have reported fluctuating patterns of functional connectivity in the resting state.^[9,11–14]

In order to quantify the diversity of brain functional patterns, PLE extracts the temporal characteristics of the phase relationship between 2 EEG signals.^[7] Like BIS, PLE has a value from 0 to 100. The range of values suitable for anesthesia is expected to be from 40 to 60, but this is likely to change as its utility continues to be studied. Ki et al^[15] reported that PLE was useful in predicting hypnotic depth in propofol sedation, while Seo et al^[16] reported that PLE may represent an alternative to BIS in monitoring the depth of anesthesia.

In the present study, we investigated the effect of propofol-induced changes in the level of consciousness on PLE in patients undergoing general anesthesia. To confirm the clinical usefulness of this index, we also compared PLE values with BIS values.

2. Methods

2.1. Participants

This prospective clinical trial was conducted between July 25, 2017 and June 30, 2018, at Haeundae Paik Hospital (Busan, Korea). The study was approved by the Institutional Review Board of Haeundae Paik Hospital (HPIRB 2017-06-006-002) and the National Research Institute of Health (KCT0002727, <https://cris.nih.go.kr/cris/en/>). Written informed consent was obtained from all participants in this study. Inclusion criteria were as follows: age over 20 years; American Society of Anesthesiologists (ASA) physical status I–II; scheduled to undergo reduction surgery for nasal bone fractures. Exclusion criteria were as follows: patient refusal; ASA physical status III or higher; previous hypersensitivity to propofol; history of neurologic disease including epilepsy; history of psychiatric disorders or psychiatric drug use; history of cardiovascular disease, respiratory disease, renal impairment, or hepatic dysfunction.

The sample size was calculated based on a previous study by Yu et al,^[17] which reported a correlation coefficient of 0.66 between BIS and Observer's Assessment of Alertness/Sedation (OAA/S)

scores (5 = responds readily to name spoken in normal tone; 4 = lethargic response to name spoken in normal tone, 3 = responds only after name is called loudly or repeatedly, 2 = responds only after mild prodding or shaking, 1 = does not respond to mild prodding or shaking). Using an alpha error of 0.05 and a statistical power of 80%, a sample size of 15 patients was calculated.

3. Methods

This study was conducted by an anesthesiologist (JHP, corresponding author). Unilateral sensors of BIS VISTA (BISx Revision 1.05, Aspect Medical System, Inc., Norwood, MA, USA) were attached to the left temporo-frontal area. PLE (PLEM100 Version 1.0; Inbody Co., Ltd.) sensors were placed on bilateral temporo-frontal area simultaneously with the BIS sensor. Vital signs were monitored, and data were collected automatically using data acquisition software (Vital Recorder version 1.8.1.2, Seoul National University College of Medicine, Seoul, Korea). Data collected included noninvasive blood pressure, heart rate, peripheral pulse oximetry (SpO₂), end-tidal carbon dioxide, body temperature, infused dose, and effect site concentration of propofol delivered via a target-controlled infusion (TCI) pump (Orchestra Base Primea, Fresenius Kabi, Brezins, France), and BIS scores. PLE values were collected simultaneously by the PLE device. Data collected by the data acquisition program and the PLE device were synchronized by recording time later.

Patients were requested to close their eyes and remain calm during preparation. They were told to open their eyes and answer only if the experimenter called their names or gave a gentle shake. Ketorolac (30 mg) was intravenously injected prior to the induction of anesthesia for perioperative pain control. General anesthesia was induced via TCI of propofol. The first target effect site concentration of propofol was set to 1.5 µg/mL using the Schnider model.^[18] When the calculated effect site concentration shown on the TCI pump was equal to the target concentration, mental status was assessed using OAA/S scores, and BIS and PLE scores were recorded. The target effect site concentration was increased to 2.0, 2.5, 2.8, 3.0, 3.2, 3.4, and 3.5 µg/mL (0.1 µg/mL increases thereafter), and the OAA/S, BIS, and PLE scores were recorded for each concentration until loss of consciousness had occurred (i.e., OAA/S score of 1).

After loss of consciousness, rocuronium bromide (0.6 mg/kg) was administered intravenously, and patients were intubated after 2 minutes. The target effect site concentration of propofol was controlled during the operation to maintain adequate depth of anesthesia. BIS and PLE values were observed during anesthetic management but were not used as guidelines for anesthetic management.^[19] Anesthesia was maintained based on vital signs and clinical signs. Baseline systolic arterial pressure was defined as the measurement obtained just before induction of anesthesia. Signs of inadequate anesthesia were defined as hypertension (systolic arterial pressure >40 mmHg), tachycardia (heart rate >100 beats/min), facial grimacing, lacrimation, and sweating.^[20] In addition, we monitored for hypotension (systolic arterial pressure <40 mmHg) and bradycardia (heart rate <45 beats/min) during maintenance anesthesia. Using these signs and the signs for inadequate anesthesia, the effect site concentration of propofol was increased or decreased according to the anesthesiologist's judgment. Persistent hypotension was corrected with intravenous fluid replacement and a bolus of intravenous vasopressor (phenylephrine 100 mcg).

Once the nasal bone reduction had been completed, TOF-watch SX (Organon, Ireland) was used to determine the adequacy

Table 1
Baseline characteristics of the patients who met the inclusion criteria.

Variable	n (%) or mean ± SD
Age, y	37.07 ± 9.39
Height, cm	167.53 ± 7.55
Weight, kg	67.73 ± 11.14
Sex	
Male	8 (53.3)
Female	7 (46.7)
ASA class	
1	10 (66.7)
2	5 (33.3)

Data are presented as number (n, proportion, %) or mean ± standard deviation. ASA=American Society of Anesthesiologists, SD=standard deviation.

of recovery from rocuronium. Intravenous sugammadex (4 mg/kg) was administered to patients with post-tetanic counts of 1 to 2, while 2 mg/kg of sugammadex was injected following the appearance of T2. Following sugammadex administration, the target concentration of propofol was set to the concentration at which the patient had lost consciousness. The effect site concentration was decreased to the minimum required to maintain anesthesia, and infusion was discontinued when the dressing was completed. Following adequate recovery from rocuronium, BIS and PLE values were recorded. Patients were extubated when OAA/S scores reached 3. Apart from assessing consciousness levels using the OAA/S score, BIS, and PLE, data pairs of BIS and PLE were acquired over the entire period of anesthesia. Since PLE and BIS values are updated every 4 and 1 second, respectively, every 4th value of BIS was taken and data pairs were extracted at intervals of 4 seconds.

3.1. Electroencephalographic analysis

EEG data were recorded continuously with a preamplifier bandwidth of 0.5 to 45 Hz and a sampling frequency (f_s) of 128 Hz at frontal (AF3, AF4) and prefrontal (FP1, FP2) montages (PLEM100). PLE was calculated between 2 EEG signals from frontal and prefrontal montages (AF3–FP1, AF3–FP2, AF4–FP1, AF4–FP2).^[17] Direct current offset was performed by subtracting the average amplitude of data from every 4-second epoch. High-amplitude (>75 μ V) eye blink artifacts were removed from the EEG signals, as previously described.^[21] In the pre-processed data, the temporal phase difference between 2 EEG signals ($\Delta_t, t = 1, 2, \dots, N$) was binarized, where N represents the number of data points acquired from 4- or 8-second epochs.

The vector, Φ_t , which denotes the temporal pattern of the phase relationship between 2 EEG signals, was given as follows:

$$\Phi_t = \{ \Delta_t, \Delta_{t+r} \dots, \Delta_{t+(m-1) \cdot \tau} \}, t = 1, 2, \dots, N - (m - 1) \cdot \tau$$

In the above equation, τ represents time lag with a resolution of $1/f_s$, while m represents the number of dimensions for extracting the temporal pattern of the phase relationship. If the phase of the first signal precedes the second signal, the temporal phase difference is positive, and $\Delta_t = 1$. If the phase of the first signal lags behind the second signal, the temporal difference becomes negative, and $\Delta_t = 0$. For example, when $m = 3$, 2^m patterns of Φ_t can be generated: {0, 0, 0}, {0, 0, 1}, {0, 1, 0}, {1, 0, 0}, {0, 1, 1}, {1, 0, 1}, {1, 1, 0}, and {1, 1, 1}. PLE was calculated by applying the standard Shannon entropy formula to the distribution of the phase patterns.

3.2. Statistical analysis

Since the data contained ordinal scales or did not meet the normality test, correlation analysis was performed using Spearman test. In order to evaluate whether the 2 indices reflect the level of consciousness properly during the induction period, the partial correlation coefficients controlling for study participants between OAA/S scores, BIS, and PLE were used. In addition, Steiger Z-test was performed to examine the difference between 2 dependent correlation coefficients: those between OAA/S scores and PLE, and those between OAA/S scores and BIS.^[22] During the entire period of anesthesia, partial correlation coefficient and intraclass correlation coefficient (ICC) were calculated to evaluate the correlation and agreement between BIS and PLE. The lowest acceptable ICC was set to ≥ 0.70 . Scatter and box plots were also generated to display the data.

All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY), Excel (Microsoft Office 365, Microsoft, WA), and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). P values (P) < .05 were considered statistically significant.

4. Results

A total of 15 patients participated in the present study. The demographic and clinical characteristics of the included patients are shown in Table 1.

A total of 7757 data pairs were obtained after removing samples with a signal quality index <40, from the extracted data. Prior to the loss of consciousness, we obtained 2154 data pairs, while 5603 pairs were obtained following the loss of consciousness. A total of 108 OAA/S scores were obtained during the induction period, matching the data pairs obtained during that time.

The median [25%–75%] BIS values were 90.5 [83.0; 93.0] in the awake state, with an OAA/S score of 5, and 59.0 [56.0; 61.0] at the exact point of unconsciousness, with an OAA/S score of 1. Likewise, the median PLE values were 85.0 [82.0; 89.0] in the awake state and 55.0 [47.5; 61.5] at the exact point of unconsciousness (Table 2).

Table 2
Descriptive statistics of BIS and PLE by OAA/S score.

OAA/S score	5 (n=26)	4 (n=35)	3 (n=13)	2 (n=19)	1 (n=15)
PLE	86.0 [82.0; 89.0]	80.0 [74.0; 85.5]	69.0 [63.0; 76.0]	66.0 [58.0; 70.0]	54.0 [47.0; 61.5]
BIS	90.5 [83.0; 93.0]	81.0 [79.0; 88.0]	72.0 [65.0; 77.0]	64.0 [61.0; 68.5]	59.0 [56.0; 61.0]

Data are presented as median [25%–75%]. BIS=bispectral index, n=the number of corresponding OAA/S scores obtained during induction period in all patients, OAA/S score=Observer’s Assessment of Alertness/Sedation score, PLE=phase lag entropy.

Table 3
The partial correlation coefficients controlling for study subjects.

	OAA/S score (n=108)	PLE (n=108)	BIS (n=108)
OAA/S score	1.0		
PLE	0.778*	1.0	
BIS	0.846*	0.882*	1.0

BIS=bispectral index, n=the number of total OAA/S scores obtained during induction period in all patients, OAA/S score=Observer's Assessment of Alertness/Sedation score, PLE=phase lag entropy.

* $P < .001$. No adjustment for multiple testing was applied since it is explorative testing.

The partial correlation coefficients between OAA/S scores and PLE, and between OAA/S scores and BIS were 0.778 ($P < .001$) and 0.846 ($P < .001$), respectively (Table 3). The P value calculated by Steiger Z-test was .360, indicating that there was no significant difference between the 2 correlation coefficients.

For PLE/BIS pairs measured throughout the period of anesthesia, median PLE values corresponding to BIS values of 40, 50, and 60 were 41.0 [38.5; 48.0], 48.0 [46.0; 53.0], and 57.0 [53.0; 61.0], respectively. Median BIS values corresponding to PLE values of 40, 50, and 60 were 45.0 [40.0; 49.0], 50.5 [47.0; 56.0], and 61.0 [57.0; 65.0], respectively (Fig. 1).

Throughout the period of anesthesia, PLE and BIS exhibited a significant positive correlation (Table 4). The partial correlation coefficient prior to the loss of consciousness was 0.838 ($P < .001$), and 0.669 ($P < .001$) following the loss of consciousness (Fig. 2).

The reliability between BIS and PLE values, calculated using the ICC before and after the loss of consciousness, was 0.889 ($P < .001$) and 0.791 ($P < .001$), respectively (Table 5).

5. Discussion

In the present study, we assessed changes in PLE along with the level of consciousness during the induction of general anesthesia using propofol in patients undergoing nasal bone reduction. Participants were patients undergoing nasal bone reduction.

Table 4
The partial correlation coefficients between PLE and BIS controlling for study subjects according to the periods of general anesthesia.

Period of sampling	n	Partial correlation coefficient (P)
Before consciousness loss	2154	0.838 (<.001*)
After consciousness loss	5603	0.669 (<.001*)

After consciousness loss=period that patients' OAA/S score change from 1 to 3, before consciousness loss=period that patients' OAA/S score change from 5 to 1, n=the number of data pairs of PLE and BIS obtained during corresponding period in all patients.

* $P < .001$. No adjustment for multiple testing was applied since it is explorative testing.

Because this procedure is non-invasive and does not require electrocautery, the possibility of EEG contamination is expected to be minimal. Ketorolac (30mg) was administered prior to the induction of anesthesia to control perioperative pain, following which anesthesia was induced by propofol alone. Therefore, nasal bone reduction surgery was thought to be a good option for monitoring the change of consciousness following propofol administration while minimizing the influence of external factors such as opioid and electrocautery.

PLE and BIS decreased proportionally and predictably with decreasing OAA/S scores, which reflect the level of consciousness during general anesthesia. Furthermore, Steiger Z-test revealed no significant differences in the correlation between OAA/S scores and PLE, and the correlation between OAA/S scores and BIS.^[18] When OAA/S scores reached 1, the criterion for endotracheal intubation with muscle relaxants, PLE and BIS values were 54.0 [47.0; 61.5] and 59.0 [56.0; 61.0], respectively. These values were within the range commonly used for each device (i.e., 40 to 60). PLE and BIS values at 40, 50, and 60, which correspond to both extremes, and the median value of the range considered appropriate for general anesthesia, were largely similar to each other. In addition, we observed a significant correlation between PLE and BIS. These results suggest that, both indices should be in close range with each other; for example, when one index is within the range of 40 to 60, the other should be within a similar range.

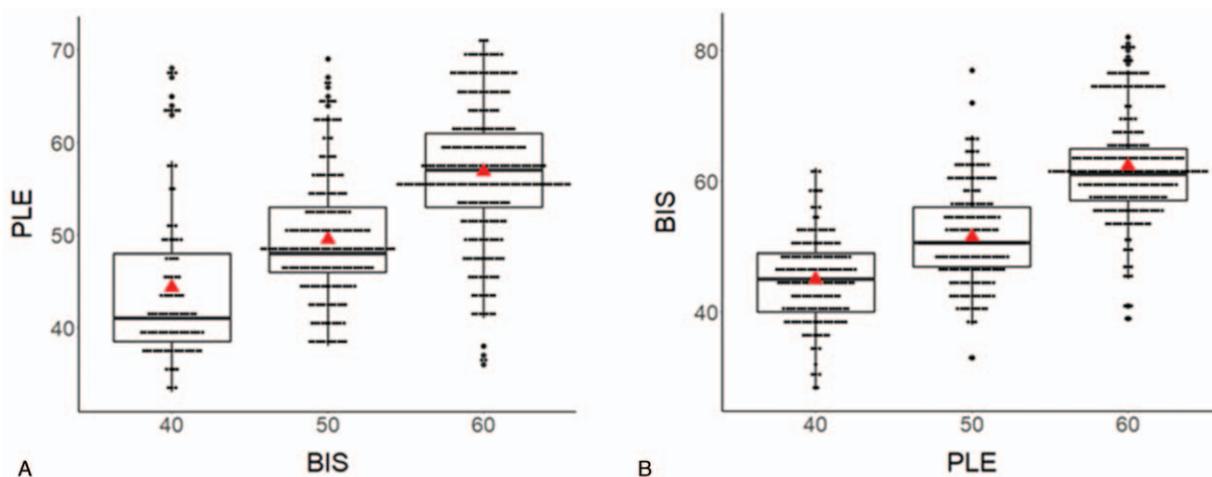


Figure 1. Box plots showing distributions of BIS and PLE during general anesthesia. (A) PLE distribution across BIS group, (B) BIS distribution across PLE group. Triangles represent means of the data. BIS=bispectral index; PLE=phase lag entropy.

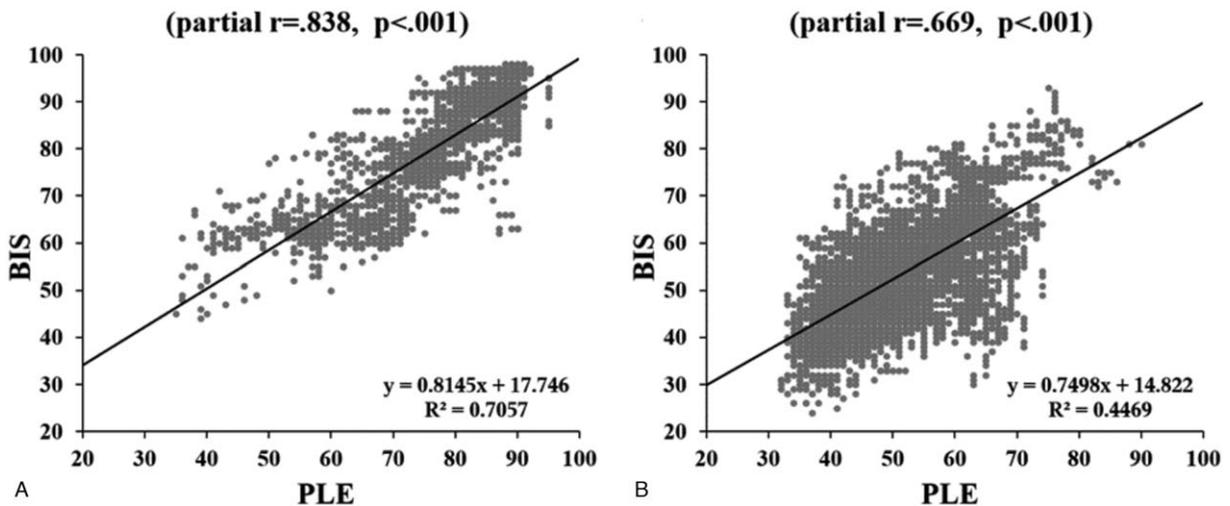


Figure 2. Simple linear regression analysis showing the relationship between PLE and BIS according to the periods of general anesthesia. (A) Before consciousness loss, (B) after loss of consciousness. The correlation coefficient shows a significant decrease following loss of consciousness. BIS = bispectral index; PLE = phase lag entropy.

Here, the partial correlation coefficient between the 2 indices was strong (0.838; $P < .001$) prior to the loss of consciousness, yet somewhat weaker (0.669; $P < .001$) following the loss of consciousness. In addition, the ICCs between the 2 indices were 0.889 ($P < .001$) and 0.791 ($P < .001$) before and after the loss of consciousness, respectively. These changes may have been caused by differences in the algorithms used for each device. The BIS is calculated via a combination of sub-parameters, including burst-suppression ratio, QUAZI suppression, relative β ratio, and SynchFastSlow.^[1,23] Among these, relative β ratio is regarded as a good indicator for detecting the transition between consciousness and unconsciousness in patients who have not been given muscle relaxants.^[24,25] Generally, within the frequency band in which the BIS subparameter is calculated, EMG signals are much stronger than EEG signals, although they gradually decrease as the level of consciousness decreases.^[26–29] Previous studies have indicated that sole administration of muscle relaxants eliminates EMG activity without altering consciousness.^[30–32] Schuller et al^[26] reported that the BIS decreases to the level of deep sedation or general anesthesia when muscle relaxants are administered without anesthetic agents. Therefore, decreases in EMG signals due to the use of muscle relaxants may have caused changes in BIS by altering the weights of the subparameters. In contrast, PLE is calculated from the phase difference between the 2 channels. If a noise signal such as EMG flows into 2 channels at the same time, it does not significantly affect the positive or negative directionality of the phase relationship. Therefore, it is

ignored in calculating and patterning the phase difference. Thus, in theory, changes in EMG following muscle relaxants do not affect the level of PLE.

Contrary to what might be expected, PLE levels in the induction period tended to be generally lower than in BIS. BIS and PLE have completely different algorithms for numerical computation, and the range of values that appear for the same level of consciousness can be partially different. More important point to note than the relatively high or low level is, as with the BIS study by Schuller et al,^[26] whether there is a change in PLE levels following administration of muscle relaxants in awake state. Since this study is an observational study conducted under common general anesthesia, this issue was not directly addressed. Further well-designed studies are needed.

As muscle relaxants were administered immediately after the loss of consciousness, a sharp change in EMG signals may also have occurred during this time. In addition, changes in EEG signals due to noxious stimuli may have influenced the correlation between the 2 indicators, since the period after the loss of consciousness includes intubation, surgical procedures, and extubation.

Both the sources and algorithms used for EEG signals differ. Prior to the loss of consciousness, the fit of the algorithm may have been optimized for detecting changes in the level of consciousness, resulting in high correlation/agreement between the 2 indices. However, since it was not possible to receive feedback from patients after the loss of consciousness, algorithms

Table 5
Inter-rater reliability between bispectral index and phase lag entropy.

Period of sampling	Inter-rater reliability between PLE and BIS	
	ICC (95% CI)	P
Before consciousness loss (n = 2154)	0.889 (0.782–0.933)	<.001
After consciousness loss (n = 5603)	0.791 (0.767–0.812)	<.001

After consciousness loss = period that patients' OAA/S score change from 1 to 3, Before consciousness loss = period that patients' OAA/S score change from 5 to 1, BIS = bispectral index, ICC = intraclass correlation, n = the number of data pairs of PLE and BIS obtained during corresponding period in all patients, PLE = phase lag entropy.

that quantify various types of stimuli and cerebral activity during this period may have yielded different results. Our results indicated that the correlation coefficients and ICCs between the 2 indices decreased following the loss of consciousness. However, since patients are unconscious during anesthesia, it is difficult to define which index better reflects the “real” depth of anesthesia. Therefore, these results indicate that the output values of the 2 indices differ slightly more depending on the algorithms used in the anesthetic state, not that 1 index is superior to the other. Nonetheless, the ICCs between the 2 indices suggested high reliability (>0.7), both before and after the loss of consciousness. The ICC is considered superior to the correlation coefficient for evaluating reliability because it includes information regarding both the correlation and the bias between the measured values.^[33] These results suggest that the 2 indices are interchangeable, in accordance with the findings of the recent studies.^[15,16]

Although we observed a positive correlation between the 2 indices, further research is required to address the limitations of the present study. First, as mentioned above, the present study could not confirm the pure effect of EMG on PLE. It is necessary to observe the changes in PLE following muscle relaxant administration in the absence of anesthetics. Second, we did not determine the time at which strong noxious stimulation (e.g., tracheal intubation or surgical stimulation) occurred after the loss of consciousness. The correlation between the 2 indices may vary depending on the intensity of the stimulus. More detailed studies are required to determine whether the correlation differs based on the presence or absence of harmful stimuli. Third, the anesthetics used in PLE studies are still limited to propofol. Because different anesthetics may cause different responses, it is necessary to confirm that the PLE reliably reflects the level of consciousness following administration of other intravenous or inhalation anesthetics.

In conclusion, our findings demonstrated that PLE exhibited a strong correlation with the level of consciousness and high agreement with the BIS, which is currently used as the gold standard for monitoring the level of consciousness during surgery. These results suggest that PLE is a reliable indicator of sedation during the propofol-induced anesthesia.

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