

Electroencephalographic Bicoherence Is Sensitive to Noxious Stimuli during Isoflurane or Sevoflurane Anesthesia

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Background: The authors previously reported changes in electroencephalographic bicoherence during isoflurane anesthesia combined with epidural anesthesia. Here, they examined the influence of noxious stimuli on electroencephalographic bicoherence as well as on the Bispectral Index (BIS) and the 95% spectral edge frequency (SEF₉₅).

Methods: The authors enrolled 48 elective abdominal surgery patients (aged 22–77 years; American Society of Anesthesiologists physical status I or II). Raw electroencephalographic signals as well as BIS and SEF₉₅ were recorded on a computer using a BIS[®] monitor (A-1050) and Bispectrum Analyzer (BSA) for BIS (the authors' original software). Using BSA for BIS, the authors evaluated the two peak heights of electroencephalographic bicoherence. Anesthesia was induced with 3 mg/kg thiopental and was maintained with, in air–oxygen, 1.0% isoflurane or 1.5% sevoflurane. After confirming the steady state, the authors recorded baseline values. In experiment 1, they administered 3 μg/kg fentanyl 5 min after incision and investigated the changes in electroencephalographic derivatives at 5 and 10 min after incision. In experiment 2, they administered a similar dose of fentanyl 5 min before incision and investigated the changes in electroencephalographic derivatives immediately before and 5 min after incision.

Results: In experiment 1, after incision, both peak heights of electroencephalographic bicoherence significantly decreased but returned to control values after fentanyl administration. By contrast, after incision, BIS and SEF₉₅ showed individual variability. In experiment 2, although fentanyl itself did not affect all electroencephalographic derivatives before incision, the variables remained unchanged after incision.

Conclusion: Noxious stimuli decreased the peak heights of electroencephalographic bicoherence, an effect that was counteracted by fentanyl analgesia.

WE previously confirmed the methodology of bispectral analysis of electroencephalographic signals¹ and reported changes during isoflurane in electroencephalographic bicoherence, namely the degree of phase coupling.² In the previous study, we used epidural anesthesia to suppress the influence of surgical stimuli on electroencephalographic bicoherence. When surgical stimuli were adequately blocked, electroencephalo-

graphic bicoherence values increased in two restricted regions in bifrequency space with an increase in isoflurane concentration. In other regions, their values were generally low at every anesthetic level. Furthermore, the heights of two peaks of electroencephalographic bicoherence correlated well with isoflurane concentration. We then defined two peak heights of electroencephalographic bicoherence as pBIC-low and pBIC-high (more precise definitions are described in the appendix).

Several other reports have also shown that surgical stimuli and their analgesic suppression also affect electroencephalogram during anesthesia. For example, Röpke *et al.*³ reported that surgical stimuli shift the electroencephalographic signals recorded during desflurane anesthesia. Hodgson and Liu⁴ reported that epidural lidocaine reduced the dose of sevoflurane required to maintain an adequate level of anesthesia as indicated by the Bispectral Index (BIS). Finally, Guignard *et al.*⁵ reported that remifentanyl affected the BIS only when a painful stimulus was applied. If we could pick out noxious stimuli-related changes in the electroencephalogram, we might be able to practically assess the adequacy of analgesia (*i.e.*, antinociceptive effect) during surgery. However, no electroencephalogram-derived parameter has been established to indicate the adequacy of analgesia during surgery. We therefore hypothesized that noxious stimuli would change electroencephalographic bicoherence and that providing analgesia (*via* fentanyl) would ablate this phenomenon. Here, we investigated the influence of surgical stimuli on pBIC-low and pBIC-high as well as electroencephalogram-derived parameters such as the BIS and the 95% spectral edge frequency (SEF₉₅).

Materials and Methods

Patients

After securing institutional approval (Osaka Prefectural Habikino Hospital, Osaka, Japan) and written informed consent from the participants, we enrolled 48 patients (male and female; aged 22–77 yr; American Society of Anesthesiologists physical status I or II) who underwent elective abdominal surgery. Patients with coronary artery disease were not included in this study. None of these participants reported neurologic or psychiatric disorders or were receiving medications for such diseases.

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Received from the Osaka Prefectural Habikino Hospital, Osaka, Japan. Submitted for publication June 25, 2003. Accepted for publication October 16, 2003. Support was provided solely from institutional and/or departmental sources.

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Anesthetic Protocols

Premedication was not applied. Initially, an epidural catheter was placed at the appropriate spinal location. However, no drug was administered epidurally before the completion of the study protocol. Anesthesia was induced with 3 mg/kg thiopental followed by inhalation of isoflurane (groups 1 and 3) or sevoflurane (groups 2 and 4) and administration of 0.12 mg/kg vecuronium. To maintain adequate oxygenation and normocapnia, the trachea was intubated and the lungs were mechanically ventilated with oxygen-air (fraction of inspired oxygen [F_{iO_2}] = 40%). The expired concentration of anesthetics was monitored using CAPNOMAC (DATEX, Helsinki, Finland), and the measurements were recorded and stored on the computer. After this, end-tidal concentration was kept at 1.0% for isoflurane (groups 1 and 3) and at 1.5% for sevoflurane (groups 2 and 4). Nitrous oxide was not used. Throughout the study, we tried to adjust the inspired concentration of anesthetics to keep the expired concentration at the purposed level. Noninvasive blood pressure and heart rate were measured at 1-min intervals during the study period by an anesthesia monitor (BP508; COLIN, Tokyo, Japan).

Electroencephalographic Monitoring and Data Acquisition

Electroencephalographic data were monitored with an A-1050 monitor (Aspect Medical Systems, Natick, MA; software version 3.4). After mild abrasion of the skin, four self-sticking frontal surface electrodes (At1 and At2, with Fpz as reference and Fp1 as the ground) were placed on both sides of the outer malar bone. The electrode impedance was kept at 5 k Ω or less throughout the study. All binary data packets, containing raw wave data as well as BIS and other processed parameters, were recorded *via* an RS232 interface on a personal computer (CF-B5R; Panasonic, Osaka, Japan) using Bispectrum Analyzer (BSA) for BIS¹ (our original software). Using BSA for BIS, electroencephalographic bicoherence values were calculated from the Fpz-At1 lead. Details of the electroencephalographic bicoherence calculation are described in the appendix. In summary, for the two peaks of electroencephalographic bicoherence that emerge at the clinical level of anesthesia, the heights are defined as pBIC-low and pBIC-high. In this study, we investigated changes in pBIC-low and pBIC-high as well as in BIS and SEF₉₅. To eliminate the interference caused by the use of electrosurgical cautery and to maintain data quality, we calculated electroencephalographic bicoherence values from 360 artifact-free epochs from the 480 epochs available for electroencephalographic signals in each sampling period. We also filtered BIS and SEF₉₅ values for those that had signal quality index values greater than 0.8, recorded in the latest 30 s from the sampling point. Here, the signal quality index was the value obtained from the BIS[®] monitor. We also requested

Table 1. Demographic Data of Each Group

| Group | Age, yr | Weight, kg | Sex (M/F) |
|-------|-----------------|-----------------|-----------|
| 1 | 48.4 \pm 17.2 | 51.5 \pm 6.5 | 4/8 |
| 2 | 53.0 \pm 18.0 | 57.2 \pm 10.9 | 5/7 |
| 3 | 43.8 \pm 16.7 | 58.7 \pm 15.8 | 5/7 |
| 4 | 51.8 \pm 13.1 | 56.8 \pm 10.6 | 6/6 |

that surgeons minimize the use of electrosurgical cautery. Twenty minutes after intubation, we confirmed the equilibrium of both the electroencephalogram and the expired concentration of anesthetics, and then we started the study protocols.

Experiment 1

First, in group 1 (isoflurane) and in group 2 (sevoflurane), we investigated the influence on the electroencephalogram of noxious stimuli. In this experiment, we administered 3 μ g/kg fentanyl intravenously 5 min after incision. We recorded electroencephalographic derivatives at the following three points: before incision, just before fentanyl administration, and 5 min after fentanyl administration.

Experiment 2

Second, in group 3 (isoflurane) and in group 4 (sevoflurane), we investigated the influence on the electroencephalogram of fentanyl when it was administered before incision. In this experiment, we administered 3 μ g/kg fentanyl after baseline recording. Five minutes after administration of fentanyl, we recorded the second run of electroencephalogram derivatives, after which surgery commenced. Finally, the third run of data was recorded 5 min after incision.

Statistics

We compared pBIC-low, pBIC-high, BIS, and SEF₉₅ in each condition. Data for each group were analyzed by one-way analysis of variance and Scheffé multiple-comparison test. *P* values less than 0.01 were considered significant.

Results

Table 1 shows demographic data. There were no significant differences among the groups. For acquired electroencephalographic data, no electromyographic contamination was observed in any of the measurements. Furthermore, all patients provided reliable electroencephalographic derivatives with signal quality index values of 0.8 or greater.

Figure 1 shows typical changes in electroencephalographic bicoherence (group 1, patient 3). Before incision, two prominent peaks were observed in the bifrequency space (fig. 1A). After incision, the peak of electroencephalographic bicoherence at approximately

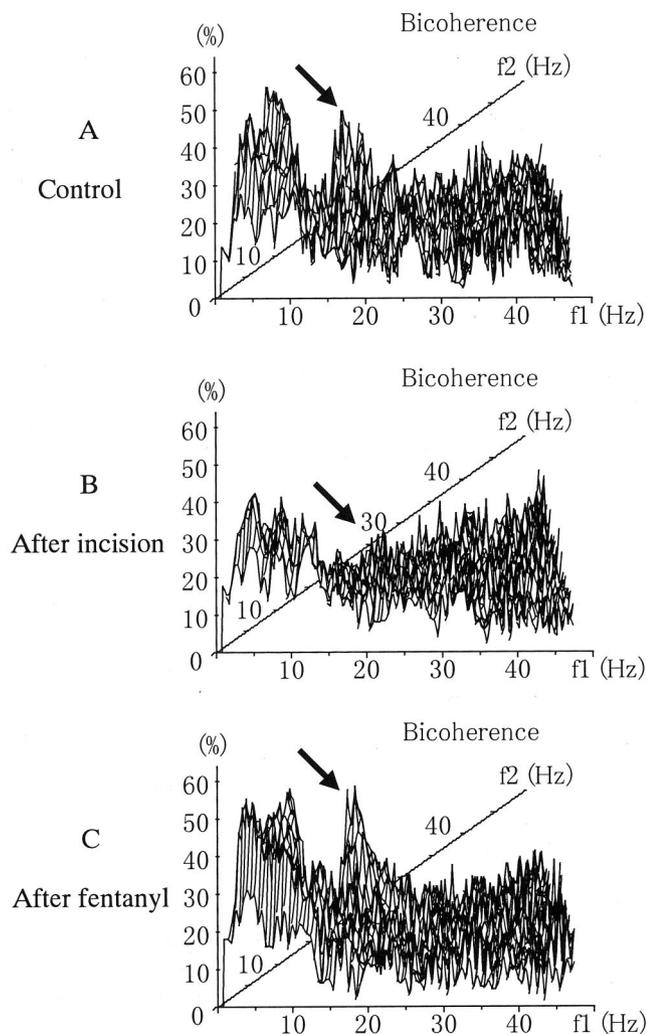


Fig. 1. Electroencephalographic bicoherence patterns of patient 3 during isoflurane anesthesia before incision (A), 5 min after incision (B), and 5 min after fentanyl administration. *Thick arrows indicate the peaks of electroencephalographic bicoherence in the higher frequency region.*

10 Hz was diminished (indicated by arrows), and another peak also became small (fig. 1B). After fentanyl administration, these two peaks became as high as those observed before incision (fig. 1C). Changes in electroencephalographic bicoherence observed in group 2 were the same as described above.

Figure 2 shows the influence of surgical stimuli on pBIC-low and pBIC-high in group 1 (fig. 2A) and in group 2 (fig. 2B). Both pBIC values significantly decreased after incision, and they returned to control values after fentanyl administration. In both groups, after incision, pBIC-high decreased to close to the background level ($\leq 15\%$). Although pBIC-low also significantly decreased, the relative decline was less, and the peaks were still distinctly higher than the background level.

Figure 3 shows the changes in BIS values for group 1 (fig. 3A) and group 2 (fig. 3B). In both groups, BIS was individually variable. For example, although BIS in-

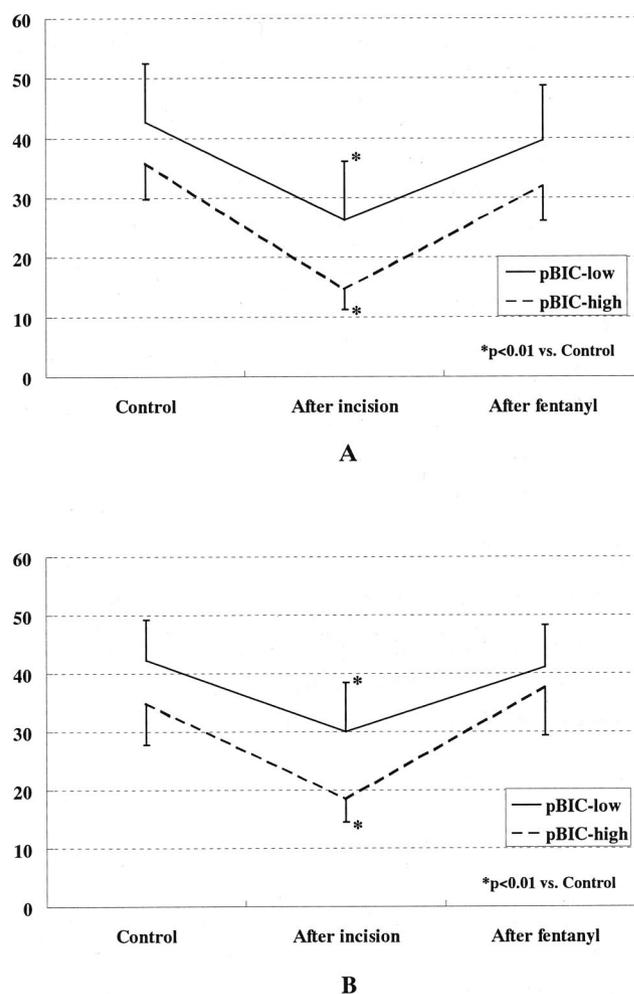


Fig. 2. Changes of peak bicoherence (pBIC)-high and pBIC-low during isoflurane anesthesia (A) and during sevoflurane anesthesia (B) in experiment 1. * Significant difference from the control values.

creased ($\Delta\text{BIS} \geq 5$) in four patients in group 1 and two patients in group 2, it decreased in three patients in group 1 and seven patients in group 2. In the other patients, BIS was unchanged. Although BIS did not change in five patients in experiment 1, in each patient, waveforms of the electroencephalogram were changed. Figure 4A shows the waveform of patient 8 before incision. This spindle wave-dominant pattern was the typical waveform of the electroencephalogram in the non-surgical state. Figure 4B shows the waveform of electroencephalogram of patient 8 after incision. The electroencephalographic pattern changed to fast wave with lower amplitude dominant, which indicates electroencephalographic desynchronization. In this patient, the BIS value increased from 43 to 50. Figure 4C shows the electroencephalogram of patient 1 after incision: The electroencephalographic pattern changed to a large (amplitude $\geq 50 \mu\text{V}$) delta wave-dominant pattern, and the BIS value decreased from 44 to 28. In patients who did not show changes in BIS, the electroencephalo-

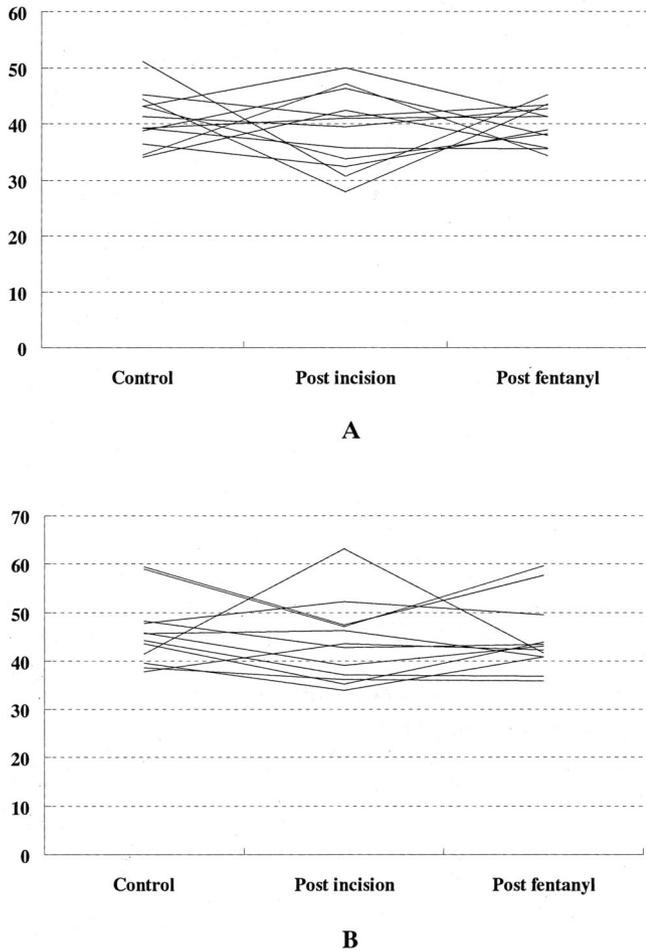


Fig. 3. Changes of Bispectral Index values in each case during isoflurane anesthesia (A) and during sevoflurane anesthesia (B) in experiment 1.

graphic waveform changed to a mixed pattern with fast wave and delta wave. Trends in SEF_{95} were paralleled by BIS values. Finally, administration of fentanyl restored electroencephalographic waveforms, along with BIS and SEF_{95} readings, to similarity with those observed before incision. Although BIS values and SEF_{95} showed individual variability for each patient, in each instance, the relation of the two values correlated well: When BIS increased, SEF_{95} also increased.

Table 2 shows the average changes of BIS and SEF_{95} in experiment 1. No significant differences emerged from comparing data from the three sampling periods. Consequently, BIS and SEF_{95} did not indicate changes in the electroencephalogram after incision.

Table 3 shows the changes in electroencephalographic derivatives in experiment 2. In both groups (groups 3 and 4), fentanyl administration alone did not cause significant changes in all electroencephalographic derivatives. Although the waveform of the electroencephalogram transiently changed just after incision, it returned to the preincisional pattern soon after. Finally, 5 min

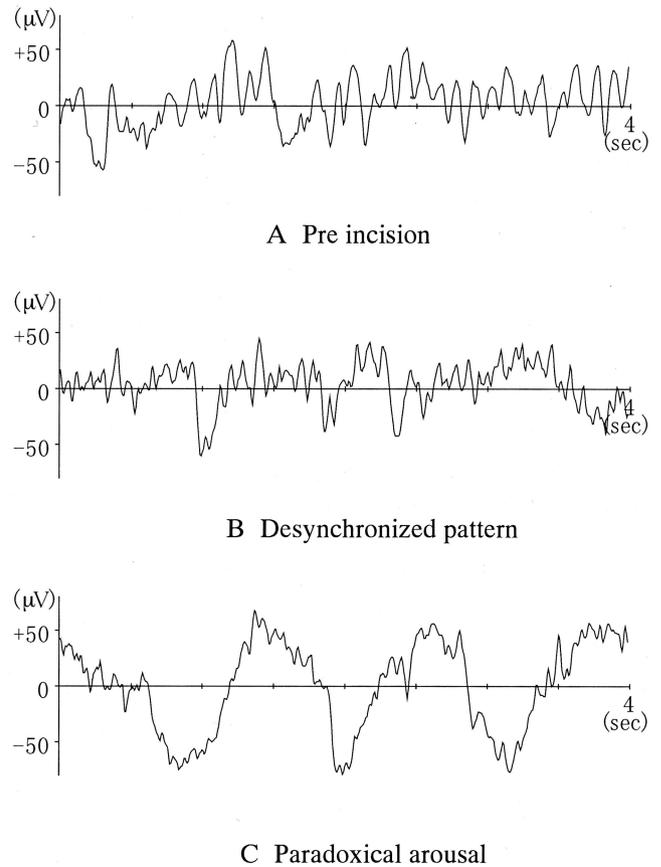


Fig. 4. Typical electroencephalographic waveform observed before incision (A), desynchronized pattern after incision (B), and so-called paradoxical arousal pattern after incision (C).

after incision, none of the electroencephalographic derivatives showed any significant changes.

Table 4 shows the hemodynamic changes in each group. In experiment 1, after incision, mean blood pressure and heart rate both increased significantly but returned to control levels after fentanyl administration. In some patients, blood pressure remained high even after fentanyl administration. In experiment 2, after fentanyl administration, mean blood pressure and heart rate significantly decreased. After incision, although mean blood pressure subsequently increased to control level, heart rate stayed low.

When they were interviewed on the first postoperative day, none of the participants recalled any events that occurred during surgery.

Table 2. BIS and SEF_{95} Values in Experiment 1

| | Control | After Incision | After Fentanyl |
|------------|------------|----------------|----------------|
| Group 1 | | | |
| BIS | 41.3 ± 4.5 | 37.6 ± 6.9 | 40.2 ± 3.2 |
| SEF_{95} | 13.5 ± 1.8 | 11.9 ± 2.8 | 13.3 ± 1.5 |
| Group 2 | | | |
| BIS | 45.9 ± 7.1 | 44.1 ± 9.6 | 44.6 ± 7.4 |
| SEF_{95} | 14.3 ± 1.8 | 14.5 ± 3.4 | 14.2 ± 1.8 |

BIS = Bispectral Index; SEF_{95} = 95% spectral edge frequency.

Table 3. BIS, SEF₉₅, and pBIC Values in Experiment 2

| | Control | After Fentanyl | After Incision |
|-------------------|-------------|----------------|----------------|
| Group 3 | | | |
| BIS | 41.4 ± 3.1 | 41.7 ± 2.9 | 42.2 ± 2.8 |
| SEF ₉₅ | 13.1 ± 1.5 | 13.0 ± 1.3 | 13.5 ± 1.3 |
| pBIC-low | 45.1 ± 9.9 | 47.5 ± 9.4 | 44.6 ± 9.3 |
| pBIC-high | 35.1 ± 7.5 | 39.1 ± 7.8 | 37.7 ± 9.5 |
| Group 4 | | | |
| BIS | 42.1 ± 4.8 | 42.5 ± 5.7 | 43.1 ± 5.6 |
| SEF ₉₅ | 13.4 ± 1.2 | 13.3 ± 1.2 | 13.4 ± 1.3 |
| pBIC-low | 40.9 ± 5.6 | 39.0 ± 6.6 | 38.6 ± 7.0 |
| pBIC-high | 32.5 ± 12.6 | 34.9 ± 11.7 | 34.0 ± 10.9 |

BIS = Bispectral Index; pBIC = peak bio coherence; SEF₉₅ = 95% spectral edge frequency.

Discussion

Our data show significant decreases in both pBIC-low and pBIC-high after incision and a return to preincisional values after 3 μg/kg fentanyl administration. As shown in the experiment 2, fentanyl itself did not influence electroencephalogram before or after incision. These results indicate that the decreases in pBIC-low and pBIC-high after incision were related to surgical stimuli and that these stimuli were blocked by the analgesic effect of fentanyl.

In our previous study,² we observed no changes in electroencephalographic bio coherence after incision when epidural anesthesia was applied before surgery, which indicated that adequate analgesia could block the influence of surgical stimuli on electroencephalographic bio coherence. Our previous findings also suggested that increases in pBIC-low indicate increased activity of delta waves and a similar association of pBIC-high with spindle waves. That is, we speculated that increased pBIC-low and pBIC-high would indicate greater electroencephalographic synchronization driven by the thalamic reticular nucleus. Subsequent decreases in pBIC-low and pBIC-high by surgical stimuli would also indicate distur-

bance of thalamic drive by sensory inputs to the thalamus or the cortex. From this point of view, pBIC data seem to be useful for evaluating, during anesthesia, the effectiveness of analgesics in counteracting noxious stimuli.

On the other hand, BIS values and SEF₉₅ showed individual variability after incision. In some patients, the values increased; in others, they decreased; and in some, they stayed the same. Consequently, after incision, we found no general statistically significant changes in either BIS values or SEF₉₅. What was the cause of this variability? Generally, noxious stimuli change the electroencephalogram into a pattern with low-voltage and high-frequency components dominating (as shown in fig. 4B), which results in the increased SEF₉₅. In some specific situations, however, large delta waves became dominant in the electroencephalogram (as shown in fig. 4C), a pattern known as “paradoxical arousal.”⁶ Here, the increase of the δ-range power spectrum reduced SEF₉₅. Kiyama and Takeda⁷ reported that, during administration of 1.0% isoflurane and 66% nitrous oxide anesthesia, when epidural anesthesia was not applied, SEF₉₀ significantly decreased and blood pressure increased after incision. In their study, after incision, all patients without epidural anesthesia showed paradoxical arousal accompanied by significantly lower SEF₉₀. Kochs *et al.*⁸ have reported that, during 1.2% isoflurane with 66% nitrous oxide, noxious stimuli prompted decreased α activity in 53% and increased δ activity in 44% of patients. These power-spectrum changes also seem to be paradoxical arousal. Röpke *et al.*³ have investigated the influence of surgical stimulation on BIS values during desflurane anesthesia but did not report any evidence of paradoxical arousal. Using a feline model, Kaada *et al.*⁹ have reported the effect of high-frequency midbrain reticular stimulation on the electroencephalogram. They reported that even when stimulation is added on the same neuron, the changing electroencephalographic pattern depends on the dose of anesthetics and the intensity of the stimuli. These reports suggest that paradoxical arousal occurs only when some specific conditions are satisfied. It seems that paradoxical arousal is more likely to be observed when intense noxious stimuli are added during moderate anesthesia. In the protocol, we used a uniform anesthetic concentration, but individual sensitivity to anesthetics varies, as does the intensity of response to surgical stimuli. These facts could account for postincisional SEF₉₅ inconsistency.

Even so, the question as to why BIS values showed similar variability must be answered. Rampil¹⁰ has asserted that in BIS calculation, SynchFastSlow, derived from the amplitude of the bispectrum, predominates during surgical levels of hypnosis. The amplitude of the bispectrum, however, contains phase information from the original signal and is more likely to be influenced by the power spectrum. If so, major changes in the ampli-

Table 4. Hemodynamic Parameters in Both Experiments

| Experiment 1 | Control | After Incision | After Fentanyl |
|--------------|-------------|----------------|----------------|
| Group 1 | | | |
| MBP | 71.5 ± 11.8 | 112.8 ± 10.5* | 83.0 ± 12.3 |
| HR | 71.0 ± 11.5 | 99.6 ± 19.0* | 68.3 ± 9.7 |
| Group 2 | | | |
| MBP | 79.8 ± 8.6 | 108.4 ± 15.0* | 86.3 ± 15.3 |
| HR | 67.3 ± 10.0 | 76.3 ± 10.1* | 62.6 ± 9.3 |
| Experiment 2 | Control | After Fentanyl | After Incision |
| Group 3 | | | |
| MBP | 78.4 ± 11.8 | 67.5 ± 8.8* | 84.8 ± 13.8 |
| HR | 71.5 ± 11.9 | 61.3 ± 12.9* | 59.4 ± 12.6* |
| Group 4 | | | |
| MBP | 81.8 ± 18.0 | 69.8 ± 15.3* | 81.2 ± 23.6 |
| HR | 63.5 ± 9.6 | 56.8 ± 10.9* | 56.4 ± 10.3* |

* Significant difference from the control values.

HR = heart rate; MBP = mean blood pressure.

tude of bispectra result from changes in power spectra. Elsewhere, Goto¹¹ has reported that, at BIS values of 40–60, changes in BIS correlate well with SEF₉₅ variation. Our data show similar concomitant variation in BIS values and SEF₉₅. Because BIS calculation methods are not in the public domain, we are unable to precisely account for allied phenomena. It is prudent to pay attention to paradoxical arousal when BIS values or SEF₉₅ values are used to evaluate depth of anesthesia.

After investigating the effect of fentanyl on the electroencephalogram, Scott *et al.*¹² reported that, in combination with pharmacokinetic simulation, fentanyl had little effect on the electroencephalogram when the effect site concentration was below 5.0 ng/ml. Pharmacokinetic simulation also revealed that the effect site concentration of fentanyl increases to more than 2.0 ng/ml within 3 min and peaks (4.5 ng/ml) at 7 min after bolus administration of 3 μ g/kg fentanyl, after which the effect site concentration of fentanyl remains greater than 2.0 ng/ml for about 20 min. Although there was wide individual variation in sensitivity to the opioid, 2.0 ng/ml fentanyl or more would produce adequate analgesia in most patients.¹³ Therefore, we decided that 3 μ g/kg fentanyl would be adequate to investigate its analgesic effect on the electroencephalogram.

Although in experiment 1 all electroencephalogram-derived parameters returned to preincisional values after 3 μ g/kg fentanyl administration, blood pressure did not always return to the previous values. Before surgery, fentanyl decreased mean blood pressure and heart rate without having an effect on electroencephalographic patterns. Electroencephalographic activities are derived from cortical activity, whereas hemodynamics are controlled by structures in the lower brain. A discrepancy between the electroencephalographic responses and changing hemodynamic parameters is not surprising.

In both experiments, we calculated pBIC values at three different sampling points with 5-min intervals. Strictly speaking, electroencephalographic derivatives do not indicate the electrical activity of the brain immediately before and 5 min after incision. However, because electric activity rapidly changes within 1 min after incision or fentanyl administration, these values can properly reflect the electrical status of the brain before incision, after incision, or after fentanyl administration.

Here, we used uniform concentrations of isoflurane (1.0%) and sevoflurane (1.5%) that were slightly higher than those we apply in our routine clinical practice. When adequate analgesia was obtained, 0.8–0.9% isoflurane or 1.2–1.4% sevoflurane is normally sufficient to maintain an adequate level of hypnosis. We used this higher concentration because at lower concentrations, surgical stimuli might cause arousal during surgery, which is ethically irresponsible. At higher concentrations, there is a risk of electroencephalographic patterns changing into “burst and suppression” mode. As dis-

cussed in the previous report,² it is inappropriate to apply bispectral analysis to burst and suppression patterns of the electroencephalogram. We now routinely use our software with the A-1050 in clinical practice, and we often have observed the same phenomenon described in the current study: When the pBIC values have diminished, a small dose of fentanyl can restore them. Consequently, we now consider that decreased pBIC values during surgery are a sign that analgesia is inadequate. The desynchronization of the electroencephalogram that results in the decrease of pBIC values is not likely to be caused by other than noxious stimuli: If administration of fentanyl did not show any effect on the electroencephalogram, the decrease of pBIC values would not be caused by noxious stimuli.

In the current study, we were careful to maintain the expired concentration of anesthetics during the study period. Because noxious stimuli increase cardiac output, which in turn increases the uptake of anesthetics in the lung, the expired concentration of anesthetics tended to decrease after incision. By contrast, blockade of noxious stimuli restores cardiac output, which results in increasing the expired concentration of anesthetics. Because only 0.05% of the changes in isoflurane concentration can influence the electroencephalogram, this point was important to our current study.

After incision, in all patients in groups 1 and 2, we found lower peaks in pBIC-low and pBIC-high. For two patients in group 2, however, the control values for pBIC-high were relatively low. Consequently, for those patients, the changes of pBIC-high were rather small. In our previous study, we also noted similar individual variation in pBIC-high values. For such patients, pBIC-high would have limited merit as an indicator of analgesia. Despite this limitation, pBIC values are useful indicators for most patients.

When the influence of noxious stimuli on the electroencephalogram was prevented by sufficient analgesia, changes in electroencephalographic pattern corresponded well with the dose of hypnotic agent. Therefore, the level of hypnosis during surgery, *i.e.*, electroencephalographic status, is determined by the interaction of three factors: dose of hypnotic agent, effectiveness of analgesia, and intensity of surgical stimuli. Because changes in electroencephalographic coherence also depend on concentration of anesthetics,² to use pBIC values as an indicator of analgesia, it would be better to maintain a uniform concentration of anesthetics. Bearing in mind that Antognini and Carstens¹⁴ concluded that analgesia is not an essential component of anesthesia because, although analgesics reduce or eliminate pain, pain is the conscious awareness of a noxious stimulus, we define *analgesia* as antinociception, which remains effective even in anesthetic states. That is why we consider analgesia an essential element of anesthesia. Without analgesia, the high concentra-

tions of volatile anesthetics required to prevent patient awareness during surgery would delay postoperative recovery from anesthesia, which is undesirable in clinical practice. Furthermore, many studies have confirmed that volatile anesthetics are unable to suppress brain responses to noxious stimuli.^{15,16} For example, Segawa *et al.*¹⁵ have shown that even high concentrations of isoflurane or sevoflurane do not suppress hemodynamic center responses. That is, volatile anesthetics are unable to suppress noxious stimuli. To block nociception, neural blockade or narcotics are required to adequately suppress noxious input. The suppression of noxious input makes it unnecessary to alter the concentration of anesthetics to maintain unconsciousness during surgery. Finally, after determining the adequate concentration of anesthetics by electroencephalogram before incision, the dose of analgesic agent can be guided by pBIC values. Intraoperatively, the dose of analgesics, rather than the concentration of anesthetic agents, should be adjusted. With our strategy of anesthetic management, we could adequately manage both hypnosis and analgesia by referencing electroencephalographic bicoherence and other derivatives during surgery.

Appendix

Bispectral Analysis and Phase Information

The most popular method of analyzing the electroencephalogram is power spectral analysis. Fourier transform is often used for the analysis. Fourier transform converts a signal from time domain representation to a frequency domain representation. Although frequency components calculated by Fourier transform contain phase information, only their magnitudes are used in power spectral analysis. On the other hand, bispectral analysis uses the phase information.

Quadratic Phase Coupling

Here, we assumed that a neural circuit received two waves with frequencies f_1 , f_2 and phase angles θ_1 , θ_2 , respectively, and then generated a wave with frequency $f_1 + f_2$ and phase angle θ_3 . If phase angles of original waves (θ_1 , θ_2) were inherited to the phase angle of the output wave in manner of $\theta_1 + \theta_2$, those signal components were called *phase coupled*. Strictly speaking, considering the processing delay in the circuit, the phase angle of the output signal would become $\theta_1 + \theta_2 - \alpha$. Such a phenomenon is often observed in nonlinear systems. Bispectral analysis quantifies the quadratic phase coupling between the components of a signal.

Bispectral Calculation

To compute the bispectrum, signals are first divided into a series of epochs. Then Fourier transform of each epoch is computed. As described by Sigl and Chamoun,¹⁷ bispectrum $B(f_1, f_2)$ is calculated from the following equations.

$$TP_j(f_1, f_2) = X_j(f_1) \cdot X_j(f_2) \cdot X_j^*(f_1 + f_2) \quad (1)$$

$$B(f_1, f_2) = \left| \sum_j TP_j(f_1, f_2) \right| \quad (2)$$

$X(f_1)$, $X(f_2)$ and $X(f_1 + f_2)$ are complex values calculated from Fourier transform. $X^*(f)$ is the conjugate of $X(f)$. TP_j is called the *triple product*.

Here, we expressed the phase angles of $X(f_1)$, $X(f_2)$, and $X(f_1 + f_2)$

as θ_1 , θ_2 and θ_3 . Then, the phase angle of TP became $(\theta_1 + \theta_2 - \theta_3)$. This can easily be proven when polar coordinates are introduced. Then, we should be aware that the form $(\theta_1 + \theta_2 - \theta_3)$ is suitable to investigate the relation between $(\theta_1 + \theta_2)$ and θ_3 . If those three components are phase coupled, the phase angle of each TP becomes constant. On the contrary, if there were no relation among three components, the phase angle of each TP would become variable. (The bispectrum is the size of sum of triple products as shown in the equation 1.) Then, the bispectrum value tends toward zero, if phase coupling does not exist, whereas the bispectrum value becomes a nonzero value if phase coupling exists. Strictly speaking, if phase coupling exists, the bispectrum value becomes larger and larger with increases in the number of epochs used for calculation. Furthermore, the magnitude of the bispectrum is influenced by the magnitude of the signal as well as the degree of phase coupling; it does not directly indicate the degree of phase coupling. We should then normalize the bispectrum values to estimate the degree of phase coupling. The normalized value of the bispectrum is called *bicoherence*. Bicoherence $BIC(f_1, f_2)$ is calculated from the following equations.

$$BIC(f_1, f_2) = \frac{B(f_1, f_2)}{\sum_j |TP_j(f_1, f_2)|} \cdot 100 \quad (3)$$

$$= \frac{B(f_1, f_2)}{\sum_j \sqrt{P_j(f_1) \cdot P_j(f_2) \cdot P_j(f_1 + f_2)}} \cdot 100 \quad (4)$$

Although several normalizing methods have been described previously, we proved this method is adequate.¹

Meaning of Statistical Analysis

Bispectral analysis is a statistical analysis. To help in understanding the principle of bispectral analysis, here, we use a simple example. Suppose you throw a die and investigate the probability that the die shows 1. Of course, the probability is theoretically 1/6. Even if the die does not show 1 in a single trial, the probability is not zero. We should repeat a large number of trials to obtain a reliable value of the probability. In this example, approximately 100 trials are required to obtain reliable probability. Bispectral analysis is something like this. This example is one dimensional, but bispectral analysis is two dimensional. We previously reported that more than 360 epochs are required to obtain reliable and reproducible values of electroencephalographic bicoherence.¹ When each epoch overlaps by 75% of the previous one, 3 min of electroencephalographic signal is required. Although one might think that 3 min is too long to detect rapid changes in brain status, a smaller deviation enables us to detect even small changes in electroencephalographic bicoherence. When calculated triple products are buffered and bicoherence is updated in a short period, the sampling time for 3 min has an advantage over a shorter one.

Practical Meaning of Electroencephalographic Bicoherence

Our previous study² showed that electroencephalographic bicoherence increased in rather restricted regions of bifrequency space. Those regions seem to be related to spindle waves and delta waves, whose rhythms are generated in the thalamic reticular nucleus. This is only a speculation, but changes in electroencephalographic bicoherence would indicate the activities of spindle waves and delta waves among total electroencephalographic activities.

Peak of Electroencephalographic Bicoherence

Our previous study^{1,2} revealed that bicoherence values showed two peaks in a fairly low-frequency (15.0 Hz or lower) region along the diagonal plot ($f_1 = f_2$) of frequency *versus* frequency space. Because these changes were related in this way, we defined aBIC(f) as an

average of bicoherence values (total, 11 points) in the area across the diagonal plot.² Consequently, considering $BIC(f_1, f_2) = BIC(f_2, f_1)$, we calculated aBIC(f) using the following equation. Here, $BIC(f_1, f_2)$ is a raw bicoherence value calculated by our software, which is expressed by a percentage (0–100%).

$$aBIC(f) = \frac{1}{11} [\text{bic}(f, f) + 2\{\text{bic}(f, f - 0.5) + \text{bic}(f + 0.5, f - 0.5) + \text{bic}(f + 0.5, f - 1.0) + \text{bic}(f + 1.0, f - 1.0) + \text{bic}(f + 1.0, f - 1.5)\}] \quad (5)$$

Then, we defined the maximum value among aBIC(f); from 2.0 to 6.0 Hz as pBIC-low and the maximum value among aBIC(f); from 7.0 to 13.0 Hz as pBIC-high. The frequency of pBIC-low was approximately 4.0 Hz regardless of anesthetic concentration. On the other hand, the frequency of pBIC-high was decreased from 11.0 Hz to 8.0 Hz when the concentration of anesthetics was increased.

BSA Application

In the current study, we used our original software, Bispectrum Analyzer (BSA) for BIS, to calculate electroencephalographic bicoherence. This software runs on Windows 95, 98, 98SE, and ME systems (Microsoft Corp., Redmond, WA) and can gather raw electroencephalographic signal as well as its derivatives calculated by the BIS[®] monitor. Currently, our software supports model A-1050 or A-2000. Because the structure of the data packet and physical parameters for data communication are different in these two monitors, we developed two types of software, namely BSA for A-1050 and BSA for A-2000. Our software calculates the power spectrum and bispectrum/bicoherence and displays them in real time. The method of bispectral calculation is almost identical to that used by BIS[®] monitor. Epoch length is 2 s in duration, and each epoch overlaps by 75% of the previous one. To eliminate artifacts containing epochs, we used artifacts information transmitted from the BIS[®] monitor. Before the Fourier transform is applied, the Blackman window function is applied. Although the BIS[®] monitor seems to calculate bispectrum values from 61.5 s (120 epochs) of the electroencephalographic signal,¹⁸ the BSA calculates bispectrum values from 181.5 s (360 epochs) in the default setting, and the graphical plot of bispectrum/bicoherence is updated every 10 s.

To encourage scientific investigation and analysis of the electroencephalogram as well as clinical monitoring during anesthesia, we are

distributing the BSA software. We believe the BSA can enhance BIS monitoring. Downloads are available *via* the Internet.#

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