

Changes of Electroencephalographic Bicoherence during Isoflurane Anesthesia Combined with Epidural Anesthesia

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Background: The authors previously reported that, during isoflurane anesthesia, electroencephalographic bicoherence values changed in a fairly restricted region of frequency *versus* frequency space. The aim of the current study was to clarify the relation between electroencephalographic bicoherence and the isoflurane concentration.

Methods: Thirty elective abdominal surgery patients (male and female, aged 34–77 yr, American Society of Anesthesiologists physical status I–II) were enrolled. After electroencephalogram recording with patients in an awake state, anesthesia was induced with 3 mg/kg thiopental and maintained with oxygen and isoflurane. Continuous epidural anesthesia with 80–100 mg/kg 1% lidocaine was also administered. Using software they developed, the authors continuously recorded the FP₁–A₁ lead of the electroencephalographic signal and expired isoflurane concentration to an IBM-PC compatible computer. After confirming the steady state of each isoflurane (end-tidal concentration at 0.3, 0.5, 0.7, 0.9, 1.1, 1.3, and 1.5%), electroencephalographic bicoherence values were calculated.

Results: In a light anesthetic state, electroencephalographic bicoherence values were low (generally $\leq 15.0\%$). At increased concentrations of isoflurane, two peaks of electroencephalographic bicoherence emerged along the diagonal line ($f_1 = f_2$). The peak emerged at around 4.0 Hz and grew higher as isoflurane concentration increased until it reached a plateau ($43.8 \pm 3.5\%$, mean \pm SD) at isoflurane 0.9%. The other peak, at about 10.0 Hz, also became significantly higher and reached a plateau ($32.6 \pm 9.2\%$) at isoflurane 0.9%; at isoflurane 1.3%, however, this peak slightly decreased.

Conclusion: Changes in the height of two electroencephalographic bicoherence peaks correlated well with isoflurane concentration.

BISPECTRAL analysis is the core technology of the BIS[®] monitor (Aspect Medical Systems, Natick, MA). Sigl and Chamoun¹ briefly described the changes in electroencephalographic bicoherence in the period between preinduction and preincision isoflurane anesthesia, but there were no precise description of how bispectral analysis of electroencephalographic data can be useful in assessing the depth of anesthesia.

Sigl and Chamoun¹ described the principle of bispectral analysis in detail. Here we briefly explained the essence. Assume that two wave components with frequencies f_1 and f_2 were given to a neural circuit, and output signal with frequency $f_1 + f_2$ was generated. If phase angles of the original components θ_1 and θ_2 were inherited to the generated signal in form as $\theta_1 + \theta_2$, then these components are called as “phase coupled.” Such phase coupling is typical of nonlinear systems. Here, “nonlinear” means the functions other than addition or subtraction. Bispectral analysis quantifies the degree of “phase coupling” among the components with frequencies of f_1 , f_2 , and $f_1 + f_2$ in the signals. Such relation could not be analyzed by power spectral analysis. Practically, increase of electroencephalographic bicoherence would indicate that nonlinear modulation occurred in specific neural circuit.

The direct indicator of the degree of phase coupling is bicoherence, which is the normalized parameter of bispectrum. As the bispectrum value itself is influenced by the magnitude of the original components as well as by the degree of phase coupling, we cannot directly assess the degree of phase coupling by bispectrum. That is why bicoherence is the most important element of bispectral analysis. Bullock *et al.*² also emphasized the importance of bicoherence in bispectral analysis.

To investigate the relation between electroencephalographic bicoherence and the depth of anesthesia, we developed the software Bispectrum Analyzer (made by S.H.) for real-time bispectral analysis of electroencephalographic data.³ Developed with C++ Builder Version .5[®] (Borland Japan Co., Tokyo, Japan), Bispectrum Analyzer runs with Microsoft Windows 95/98[®]. At the same time we had also confirmed the most reasonable method for calculating electroencephalographic bicoherence.³

Because bicoherence is derived from two frequencies of electroencephalographic components, tens of thousands of bicoherence values result from every calculation, and the challenge is thus to determine which values are relevant and how to quantify these to yield readily understood parameters. Fortunately, as we previously reported, electroencephalographic bicoherence values changed in fairly restricted region of frequency *versus* frequency space,³ and, within this region, the values vary in a simple way. From those earlier observation, we defined two parameters derived from electroencephalographic bicoherence. In this study we tried these newly developed parameters.

The aim of this study was to test the effectiveness of the parameters that we discovered and then to clarify

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the relation between electroencephalographic bicoherence and isoflurane concentration.

Materials and Methods

After obtaining institutional approval and written informed consent from the participants, we enrolled 32 elective abdominal surgery patients (age 34–77 yr, American Society of Anesthesiologist physical status I–II) whose estimated duration of surgery was likely to be longer than 3 h. None of these participants had any neurologic or psychiatric disorders, nor were they receiving medication with any drugs known to influence anesthetic or analgesic effects. Two of 32 patients were excluded because surgery finished too early for data collection.

Thirty minutes before the admission to the operating room, each patient received intramuscular premedication with 0.5 mg atropine. Initially, an epidural catheter was placed at the appropriate spinal location. After confirming the effect of epidural analgesia, anesthesia was induced with 3 mg/kg thiopental. After tracheal intubation, anesthesia was maintained with isoflurane, oxygen, and nitrogen. Nitrous oxide was not used. Vecuronium was given as required. Lidocaine 1% (80–110 mg/h; initial dose, 90–100 mg) was administered epidurally. Patients received controlled ventilation to maintain adequate oxygenation and normocapnia. To keep mean blood pressure at 60 mmHg, as required, we administered $2\text{--}5\ \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ dopamine.

Electroencephalographic data was measured as previously described.³ Briefly, before induction of anesthesia, five electroencephalographic electrodes (A_1 , A_2 , FP_1 , FP_2 , and FP_z ; according to the International 10–20 System) were attached to the patients. FP_z is used as body ground. We continuously sampled the output from a single electroencephalographic lead ($FP_1\text{--}A_1$) using a 514X-2 electroencephalographic telemetry system (GE Marquette, Tokyo, Japan) and used the Bispectrum Analyzer software to analyze the data in real time. Data from other channels were not used in the current study. We sampled electroencephalographic data at 512 Hz. After artifact detection, wave data were down-sampled at 128 Hz by averaging every four samples to improve the accuracy of data sampling. The electroencephalographic low-pass filter was set at 60 Hz, and time constant of the amplifier was set to 0.3 s. We used 2-s epochs, and each epoch was overlapped the previous one by 75%. After applying a Blackman window function, the Fourier transform of each epoch was computed. We then calculated electroencephalographic bispectrum and bicoherence values from 3 min of electroencephalographic sample (360 epochs) according to previously described equations.³ For more detailed data analysis, we also analyzed the recorded electroencephalographic data immediately after the surgery.

The expired concentration of isoflurane was continuously monitored using Capnomac (Datex, Helsinki, Finland), and we used the Bispectrum Analyzer software to record these data simultaneously along with electroencephalographic data.

Data Collection

To minimize the influence of thiopental, all data, except those gathered with patients in the awake state, were obtained at least 1 h after the induction of anesthesia. Epidural anesthesia was administered to minimize the influence of surgical stress on electroencephalogram during surgery.

In data correction periods, to archive a steady state, the end-tidal concentration of isoflurane was purposely maintained at set levels for 30 min and then changed to another concentration. If the effect of epidural anesthesia would not be sufficient, electroencephalographic pattern would be varied irregularly by surgical stimuli. Therefore, we examined the stability of electroencephalographic pattern by monitoring the stability of spectral edge frequency 90% (SEF90) to try to confirm the effectiveness of epidural anesthesia.

Our previous study revealed that bicoherence values showed two peaks in a fairly low-frequency (≤ 15.0 Hz) 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 (fig. 1). 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 percentage (0–100%).

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

In each analysis, $aBIC(f)$ values ($2.0 \leq f \leq 15.0$ Hz at each 0.5-Hz step) were calculated from 3 consecutive min of artifact-free electroencephalographic waveforms. Then we defined the maximum value among $aBIC(f)$ $2.0 \leq f \leq 6.0$ Hz as pBIC-low and the maximum value among $aBIC(f)$ $7.0 \leq f \leq 13.0$ Hz as pBIC-high. Finally, we investigated the changes in both pBICs and peak frequencies at 0% isoflurane concentration (awake) and 0.3, 0.5, 0.7, 0.9, 1.1, 1.3, and 1.5%. Bicoherence values in the awake state were obtained before induction of anesthesia. Bicoherence values for isoflurane at 0.7–1.5% were obtained during surgery; isoflurane was initially increased to 1.5% and then stepped down to 0.7%. When a “burst and suppression” pattern was apparent on the electroencephalograph, we did not further increase the

Defined area for aBIC(f)

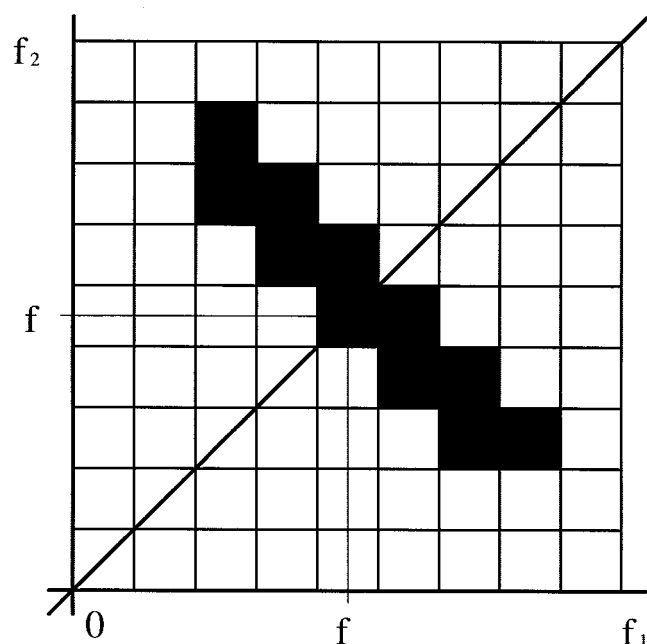


Fig. 1. Defined area for calculating the average of bicoherence values in the area across the diagonal plot [aBIC(f)] along the plot of frequency *versus* frequency space.

isoflurane concentration; such a pattern was unlikely to yield useful data for our spectral electroencephalographic analysis. Indeed, preliminary study (data not shown) revealed irregularity in bicoherence patterns when electroencephalographic waveforms show “burst and suppression” patterns. Finally, immediately after the operation, data to calculate bicoherence values at 0.3 and 0.5% isoflurane were obtained.

Statistics

We compared pBIC-low and pBIC-high values at each isoflurane concentration. We also compared the frequencies of pBIC-low and pBIC-high. Data were analyzed by one-way analysis of variance and Scheffé multiple comparison test. $P < 0.01$ was considered significant.

Results

Demographic data is shown in table 1. When patients were awake, we could not obtain electroencephalographic signals that were clean enough for bicoherence

Table 1. Demographic Data

	Mean \pm SD	Range
Age (yr)	59 \pm 11	(34–77)
Weight (kg)	53.8 \pm 8.7	(39.4–71.0)
Height (cm)	155.1 \pm 7.4	(143.0–175.0)
Male (n)	8	
Female (n)	22	

Table 2. Ranges of pBIC_low and pBIC_high, and Number of Samples in Each Isoflurane Concentration

Isoflurane (%)	pBIC_low (%)	pBIC_high (%)	N
0.3	9.4–19.0	9.9–21.0	30
0.5	11.1–38.1	9.7–38.4	23
0.7	9.5–58.9	10.8–43.5	27
0.9	27.0–61.5	11.3–56.9	30
1.1	34.2–56.4	17.7–54.6	29
1.3	29.5–62.4	15.5–56.0	25
1.5	32.3–60.3	13.4–43.4	10

calculation without contaminated electromyogram or other types of artifacts; consequently, we excluded the data recorded in the awake state from the statistical results. For 11 patients, however, we calculated bicoherence values from 200 to 250 epochs of electroencephalograph by manually eliminating the artifact-contaminated epochs. In eight cases, bicoherence values were generally small ($\leq 15.0\%$) along the entire plot of frequency *versus* frequency space. But a peak in α range in bicoherence was apparent in data from three patients who exhibited high power in the α range of the power spectrum.

In seven cases, scheduling in the surgical center did not allow us to obtain electroencephalographic signals at isoflurane 0.5%. We also observed a “burst and suppression” pattern in one case at 1.1% isoflurane concentration, in seven cases at 1.3%, and in 20 cases at 1.5%. Those data were excluded from statistical analysis. The numbers of pBIC values used for statistical analysis are shown in the right column of table 2.

Figure 2 shows typical bicoherence patterns at each isoflurane concentration in a 49-yr-old man who, for treatment of metastatic stomach leiomyosarcoma, underwent resection of the spleen, tail of pancreas, and segment 4 of the liver. At 0.3% isoflurane, all bicoherence values were small. At increasing isoflurane concentrations, two gradually growing peaks emerged. Furthermore, the peak in the α range moved to a lower region when isoflurane concentration increased. This was the one of the cases in which the electroencephalograph showed a “burst and suppression” pattern at 1.5% isoflurane.

Figure 3 shows the relation between pBICs (pBIC-low and pBIC-high) and isoflurane concentration. At 0.3% isoflurane, both pBICs were low ($\leq 15\%$). As isoflurane concentration increased, pBIC-low became significantly higher until it reached at plateau ($43.8 \pm 3.5\%$, mean \pm SD) at 0.9% isoflurane. Similarly, pBIC-high heightened significantly as isoflurane concentration increased, reaching a plateau ($32.6 \pm 9.2\%$) at 0.9% isoflurane. After this, at a higher isoflurane concentration ($\geq 1.3\%$), the plateau dipped slightly, although not significantly. At 0.9% isoflurane, SEF90 decreased to 12.0 ± 1.9 Hz.

Average values of pBICs changed rather gradually, as shown in figure 3. Observing these changes in each case we could see that, accompanied by an increase in SEF90

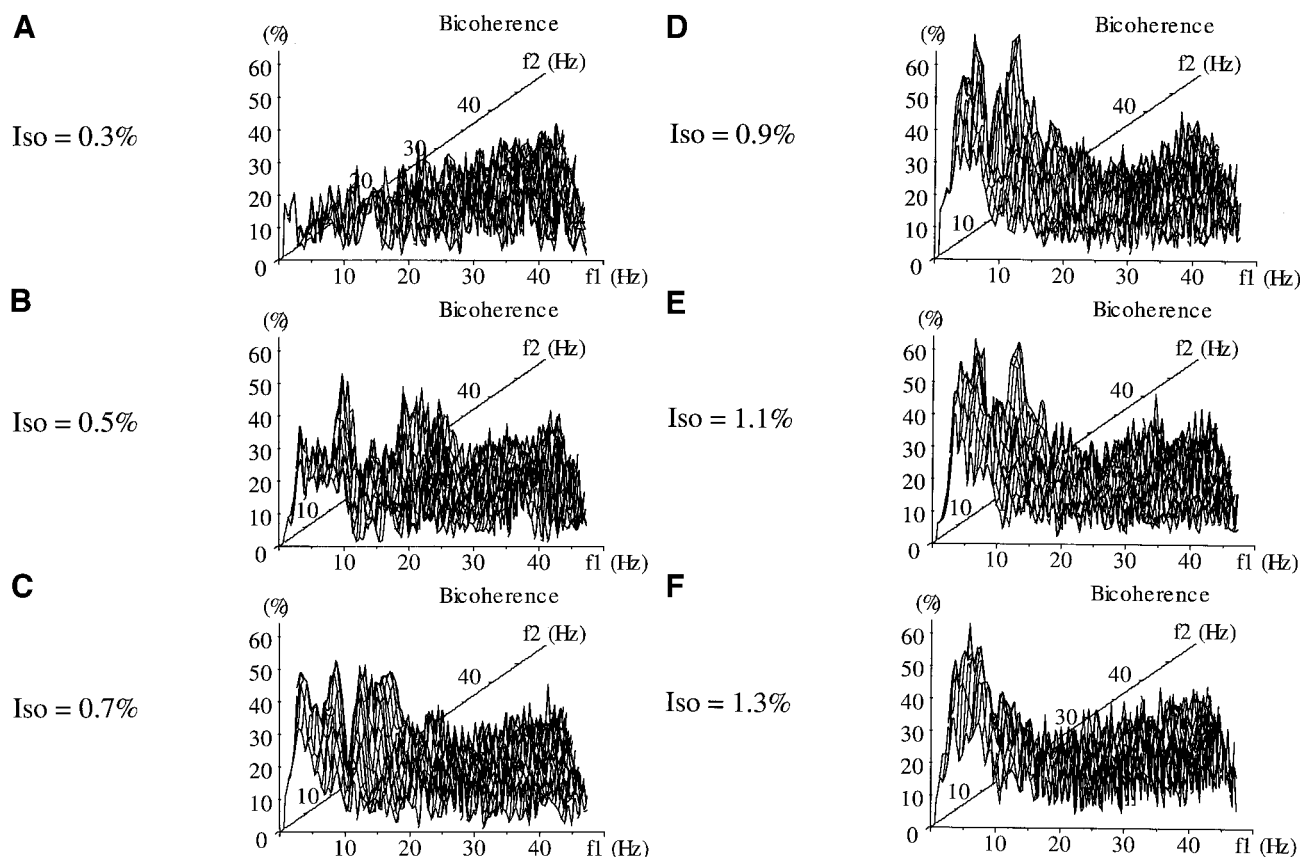


Fig. 2. Typical patterns of electroencephalographic bicoherence in 49-yr-old man who, for treatment of metastatic stomach leiomyosarcoma, underwent resection of the spleen, tail of pancreas, and liver segment 4. Bicoherence values are plotted topographically. Expired isoflurane concentration was 0.3% (A), 0.5% (B), 0.7% (C), 0.9% (D), 1.1% (E), and 1.3% (F).

(≥ 14 Hz) and decrease in electroencephalographic amplitude, pBICs sometimes changed more steeply at certain isoflurane concentrations, which indicates that the level of anesthesia was inadequate. For example, in patient no. 1, pBIC-high decreased 38.3% to 14.0% when isoflurane decreased from 0.5% to 0.3%. And in patient

no. 5, pBIC-high decreased from 42.9% to 19.9% when isoflurane decreased from 0.9% to 0.7%.

Table 2 shows the ranges for pBIC-low and pBIC-high. Minimum pBIC-low values were less than 20% when isoflurane concentration was less than 0.9%. When isoflurane concentration was 0.9% or higher, however, all pBIC-low values were greater than 25%, whereas pBIC-high values in some cases remained below 20%.

Figure 4 shows the relation between pBIC frequencies and isoflurane concentration. Although the frequency of pBIC-low was about 4.0 Hz and was not significantly changed, the frequency of pBIC-high gradually became lower. At 0.9% isoflurane or greater, the frequency of pBIC-high was significantly lower than that at 0.3% isoflurane.

Discussion

Our data show that both of the pBICs significantly increase with increasing isoflurane concentration, which suggests that the distribution pattern of bicoherence values is likely to be a good indicator for assessing the effect of isoflurane during surgery. We showed that pBIC-low flattened out at isoflurane 0.9% and that at this level, minimum pBIC-low values were more than 25%

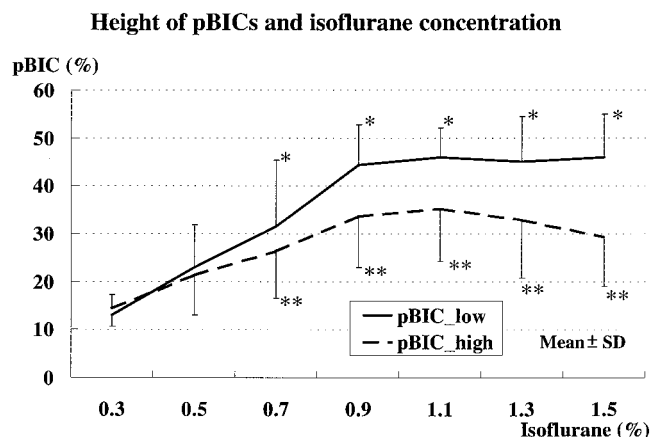


Fig. 3. Relation between the peak heights of bicoherence (pBIC-low and pBIC-high) and isoflurane concentration. *Significant difference in height of pBIC-low values compared with height at 0.3% of isoflurane concentration. **Significant difference in height of pBIC-high values compared with height at 0.3% of isoflurane concentration.

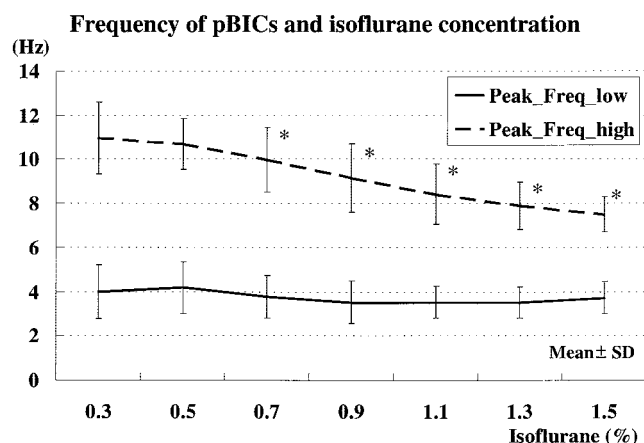


Fig. 4. Relation between the frequencies of peak heights of bicoherence (pBICs) and isoflurane concentration. *Significant difference in the frequency of pBIC-high compared with frequency at 0.3% of isoflurane concentration.

accompanied by enough low SEF90 (12.0 ± 1.9 Hz). These results indicate that high pBIC-low values are reliable indicators of adequate hypnotic level, because it is generally considered that SEF90 of lower than 14 Hz is sufficient during surgery.^{4,5} On the other hand, at all isoflurane concentrations the minimum values for pBIC-high were less than 20%; low pBIC-high may not be a reliable indicator for adequate hypnotic level.

We were able to calculate electroencephalographic bicoherence values in the awake state for only a small number of patients, and each analysis was further restricted to a small number of electroencephalographic epochs. Consequently, we could not draw any decisive conclusions about the pattern of electroencephalographic bicoherence in the awake state. Generally speaking, however, patients who showed high power in α range in the power spectrum also showed a peak at the α range along the diagonal plot of frequency *versus* frequency space; other patients did not show any peaks of electroencephalographic bicoherence. Barnett *et al.*⁶ reported that significantly high values of bicoherence were found in the α region in awake subjects with high α activity. Although their way of calculating bicoherence and placement of electroencephalographic leads differed from ours, our results accord fairly well with theirs. Thus, electroencephalographic bicoherence in the awake state seems to depend on the physiologic status of the subject.

As previously mentioned, there were variations of electroencephalographic bicoherence pattern in awake state. On the other hand, once the patients were anesthetized, despite interindividual variations among the absolute heights of the peaks, the changing patterns of electroencephalographic bicoherence were similar for different individuals. During light anesthesia, when isoflurane concentration was 0.3%, all electroencephalographic bicoherence values were small. With increasing

isoflurane concentrations, two gradually increasing peaks appeared along diagonal plot shown in figure 3. For some patients, pBICs changed more steeply (see Results) when isoflurane concentration was reduced to the next level. These decreases were accompanied by the increase of SEF90. Thus, in each instance, the changing pattern of pBICs provided useful information in estimating the effect of isoflurane.

In this study we calculated electroencephalographic bicoherence from artifact-free epochs. In contemplating the practical use of pBIC information in clinical settings, however, it is necessary to pay attention to the influence of artifacts on electroencephalographic bicoherence. Electroencephalographic bicoherence readings are especially susceptible to the influence of large-amplitude artifacts. During light anesthesia, when electroencephalographic amplitudes became rather small, caused by those artifacts, we sometimes observed pseudopeaks of electroencephalographic bicoherence at about 2–3 Hz. Such pseudopeak would make pBIC-low unusually high. Rather than being a problem for electroencephalographic bicoherence calculation *per se*, this issue can be resolved by the development of better artifact detection algorithms.

As shown in figure 4, frequency of pBIC-high decreased as isoflurane concentration increased. This frequency shift seemed to be coincident with the peak frequency shift in the power spectrum. We were unable to analyze this point in detail because we calculated the power spectrum in steps (0.5 Hz) too wide for precise analysis. Further research is required to clarify this point. More detailed knowledge of the frequency of pBIC-high is likely to provide additional information to assess the effect of isoflurane.

Then why did two pBICs increase and why did such a peak shift occur when isoflurane concentration increased? We tried to explain this phenomenon based on the electroencephalographic generation mechanism. As shown in Results, pBIC-high emerged in 7–14 Hz of frequency, which was the frequency of spindle wave, and pBIC-low emerged around 4 Hz, which was the frequency of δ wave. Spindle wave becomes predominant in the light anesthetic state; however, in a deeper anesthetic level, spindle wave becomes smaller and the δ wave becomes predominant. Steriade *et al.*^{7,8} investigated the pacemakers of these two electroencephalographic waves by electroencephalographic combined with simultaneous intracellular recordings. They concluded that the pacemaker of the spindle wave was thalamo-cortico-thalamic circuits and the rhythm of the δ wave was the intrinsic rhythm of thalamocortical neurons. If we assume that nonlinear modulation among those waves would occur in the thalamus, our observation would be explained. With this assumption, predominance of spindle wave and δ wave would result in high electroencephalographic bicoherence in those frequen-

cies. As shown in Results, pBIC-high first increased and then decreased, which seemed to be related to the changes of spindle wave activity, but pBIC-low reached a plateau phase at 0.9% of isoflurane, which would not be compatible with the activity of the δ wave. Steriade *et al.*⁸ reported that the rhythm of the δ wave was also generated other than in the thalamus. Some activity of δ rhythm in a deeper anesthetic state would be generated by another mechanism. That would be why pBIC-low did not increase at a deeper anesthetic level. Furthermore, thalamo-cortico-thalamic circuits would contain more neuronal connections than intrinsic circuit in the thalamus, and the pacemaker of the spindle wave would be more likely to be affected by isoflurane than that of the δ wave. As a result, only the frequency of pBIC-high decreased when isoflurane concentration was increased. Thus, the changes in electroencephalographic bicoherence would indicate the activities of the spindle and δ waves among total electroencephalographic activities indirectly. These are only hypotheses, but we believed that these are near the mark.

In the current study, we used epidural anesthesia to suppress surgical stimuli. At the same time, it also blocks the proprioceptive neuronal inputs, which would shift the electroencephalographic pattern. Tverskoy *et al.*⁹ reported that subarachnoid bupivacaine decreases the hypnotic requirement of midazolam and thiopental, a phenomenon confirmed by electroencephalographic data. Pollock *et al.*¹⁰ reported that, correlated with the extent of sensory blockade, spinal anesthesia by itself decreased BIS values. Furthermore, Hodgson *et al.*¹¹ reported that 34% less sevoflurane is required for adequate depth of anesthesia, defined as BIS = 50, when lidocaine epidural anesthesia is also used. These facts suggest why a “burst and suppression” pattern emerged at rather lower concentration of isoflurane than generally reported. On the other hand, because surgical stimuli alters electroencephalographic waveforms, sufficient analgesia is necessary to maintain stationarity during surgery. Because bispectral analysis depends on pseudostationary waveform state, sufficient analgesia is a prerequisite to obtaining reliable bicoherence values. The method we used is feasible in clinical settings, but the effect of epidural anesthesia has to be taken into account when considering the relation between electroencephalographic bicoherence and isoflurane concentration.

Incidentally, during induction of anesthesia or recovery from anesthesia, level of consciousness changes minute by minute. Under these conditions, electroencephalographic signal also changes rapidly, which, strictly speaking, means that the results of bispectral analysis of the electroencephalograph become theoretically invalid. Even so, if some conditions are satisfied, bispectral analysis in the transient state could have some practical significance. Indeed, results in our previous report³ showed that, minute by minute, both pBICs became progressively lower in transient periods of

isoflurane anesthesia. Consequently, at each stage, electroencephalographic bicoherence can provide a practical indication of the effect of isoflurane.

Although Muthuswamy *et al.*¹² have reported on bicoherence when the electroencephalograph showed “burst and suppression” patterns, the study concerned electroencephalographic burst patterns during recovery from hypoxic-asphyxial arrest, and the method of calculating bicoherence differed from ours; consequently, the results are not relevant to the current study. Our preliminary study (data not shown) revealed that electroencephalographic bicoherence pattern in such states was too irregular to provide well-defined peaks. This was due to a decrease in the number of waves with sufficient amplitude for spectral analysis, which in turn means the fewer epochs are available for bicoherence calculation. Furthermore, Fourier transform of restricted-length signals is performed assuming that the observed waveforms are eternally repeated, but this assumption is impossible when “burst and suppression” patterns appeared irregularly in electroencephalographic waveforms. As a result it would not be adequate to apply bispectral analysis, which is based on power spectral analysis, to a “burst and suppression” pattern of an electroencephalograph. Consequently, we excluded data gathered during “burst and suppression” episodes. Other time-variant analytic methods should be applied to analyze such specific electroencephalographic pattern as reported by Schack *et al.*¹³

In the current study, there were wide interindividual variations. For example, in four cases, all electroencephalographic bicoherence values decreased at 0.7% isoflurane, while in the other cases they showed distinct peaks. Furthermore, whereas the electroencephalographic of one patient showed the “burst and suppression” pattern at 1.1% isoflurane, in 10 cases no such pattern was discernible even at 1.5%. These variations could be caused by the extent of analgesic effectiveness of epidural anesthesia or differences in sensitivity to isoflurane; because we confirmed the effectiveness of epidural anesthesia before induction, we considered such interindividual variation are more likely due to differing sensitivity to isoflurane.

Electroencephalogram during surgery would be determined by the balance of the following three factors: effects of hypnotic agents, surgical stimuli, and effect of analgesic agents. In the current study, we used epidural anesthesia to exclude the effect of surgical stimuli. Thus, our results directly showed the effect of isoflurane on electroencephalographic bicoherence. It still remains necessary, however, to examine the effect of noxious stimuli on electroencephalographic bicoherence. This is the future problem.

Here we showed how electroencephalographic bicoherence values change during isoflurane anesthesia combined with epidural anesthesia. Two peaks of bicoherence changed and were well correlated with isoflurane concentration. Results indicate that both pBICs are useful in assessing the effect of isoflurane.

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