Electroencephalogram Approximate Entropy Correctly Classifies the Occurrence of Burst Suppression Pattern as Increasing Anesthetic Drug Effect

Jörgen Bruhn, M.D.,* Heiko Röpcke, M.D.,† Benno Rehberg, M.D.,† Thomas Bouillon, M.D.,* Andreas Hoeft, M.D., Ph.D.‡

Background: Approximate entropy, a measure of signal complexity and regularity, quantifies electroencephalogram changes during anesthesia. With increasing doses of anesthetics, burst-suppression patterns occur. Because of the high-frequency bursts, spectrally based parameters such as median electroencephalogram frequency and spectral edge frequency 95 do not decrease, incorrectly suggesting lightening of anesthesia. The authors investigated whether the approximate entropy algorithm correctly classifies the occurrence of burst suppression as deepening of anesthesia.

Methods: Eleven female patients scheduled for elective major surgery were studied. After propofol induction, anesthesia was maintained with isoflurane only. Before surgery, the end-tidal isoflurane concentration was varied between 0.6 and 1.3 minimum alveolar concentration. The raw electroencephalogram was continuously recorded and sampled at 128 Hz. Approximate entropy, electroencephalogram median frequency, spectral edge frequency 95, burst-suppression ratio, and burst-compensated spectral edge frequency 95 were calculated offline from 8-s epochs. The relation between burst-suppression ratio and approximate entropy, electroencephalogram median frequency, spectral edge frequency 95, and burst–compensated spectral edge frequency 95 was analyzed using Pearson correlation coefficient.

Results: Higher isoflurane concentrations were associated with higher burst-suppression ratios. Electroencephalogram median frequency ($r = 0.34$) and spectral edge frequency 95 ($r = 0.29$) increased, approximate entropy ($r = -0.94$) and burst–compensated spectral edge frequency 95 ($r = -0.88$) decreased with increasing burst–suppression ratio.

Conclusion: Electroencephalogram approximate entropy, but not electroencephalogram median frequency or spectral edge frequency 95 without burst compensation, correctly classifies the occurrence of burst–suppression pattern as increasing anesthetic drug effect. (Key words: Monitoring; nonlinear dynamics; pharmacokinetic–pharmacodynamic analysis.)

Approximate entropy has recently been suggested as an electroencephalogram measure of anesthetic drug effect, because increasing anesthetic concentrations are associated with increasing electroencephalogram pattern regularity. As conventionally used electroencephalogram parameters, e.g., spectral edge frequency 95, electroencephalogram approximate entropy decreases (= increase of regularity) with increasing anesthetic concentration. However, at high doses of anesthetics, periods of electroencephalogram silence with intermittent bursts of high frequencies (known as burst–suppression pattern) occur. Burst–suppression is associated with the occurrence of high frequencies in the power spectrum. Because of this phenomena, parameters such as median electroencephalogram frequency and spectral edge frequency do not decrease and therefore fail to characterize increasing anesthetic drug effect at high doses of anesthetics.

We hypothesized that the intermittent periods of relative quiescence, noted as suppression, are interpreted as highly regular by the approximate entropy algorithm and are therefore correctly classified as further increasing anesthetic drug effect. In contrast to the frequency-based electroencephalogram parameters, the electroencephalogram approximate entropy therefore may correctly classify the occurrence of burst–suppression pattern as increasing anesthetic drug effect.

Materials and Methods

Patients and Anesthesia

After obtaining approval from the local ethics committee, written informed consent was obtained from 11 female patients, aged 23–62 yr, scheduled for elective surgery. Not included were patients with apparent neurologic deficit, thyroid dysfunction, or pregnancy. The patients received 7.5 mg midazolam orally 60 min before surgery. Anesthesia was induced with 2.5 mg/kg propofol. Vecuronium (0.1 mg/kg) was administered for neuromuscular block. Once the trachea was intubated, anesthesia was maintained with isoflurane as the sole anesthetic agent. End-tidal isoflurane concentrations were measured using the infrared spectrophotometric analyzer of an anesthesia work station (Cicero, Dräger, Lübeck, Germany). The patients’ lung were ventilated with oxygen and air (fraction of inspired oxygen = 0.4). End-tidal carbon dioxide tension
was measured, and ventilation was adjusted to normocapnia (end-tidal pressure of carbon dioxide $\left[\text{PETCO}_2\right] = 35$ mmHg). The arterial pressure was noninvasively measured and maintained within 15% of the preanesthetic value with crystalloid or colloid infusions. To minimize the influence of propofol on the electroencephalogram, a 30-min waiting period was allowed before data collection. Thereafter, the end-tidal isoflurane concentration was varied between 0.6 and 1.3 minimum alveolar concentration. The electroencephalogram recording time ranged from 30 to 75 min. Surgery commenced immediately after termination of the study.

**Electroencephalogram Analysis**

The electroencephalogram was recorded continuously at C3 or C4 referenced to Fpz (international 10–20 system of electrode placement), using sterile platinum needle electrodes (Dantec, Copenhagen, Denmark). Electrode impedance was kept below 2 kΩ. Electroencephalogram recordings were performed with a Dantec Neuromatic 2000 system. Analog filters were set to 0.5 and 1,000 Hz. The electroencephalogram signal was digitized at a rate of 4,096 Hz, filtered with a 32-Hz low-pass filter (four-pole Butterworth-type filter) and stored on a computer hard disk for further offline analysis with a sampling rate of 128 Hz. The electroencephalogram signal was divided into epochs of 8-s duration, and the approximate entropy (see below) was determined. In addition, the 50% quantile of the power spectrum (median) and the 95% quantile of the power spectrum (SEF95) were calculated with commercially available software (DASYlab, DATALOG, Moenchengladbach, Germany). The electroencephalogram recordings were visually screened for artifacts. For each 8-s interval, the burst-suppression ratio was calculated according to Rampil et al. The algorithm defined intervals of suppression as periods longer than 240 ms during which the electroencephalogram amplitude did not exceed 5.0 μV, then calculated the percentage of periods in each 8-s epoch that met the criteria for suppression. The burst-compensated spectral edge frequency 95 (BcSEF95) was calculated as a proportional reduction of the spectral edge frequency 95 (SEF95) in the presence of burst suppression: [BcSEF95 = SEF95 · (1 - burst-suppression ratio/100)].

**Approximate Entropy**

The approximate entropy was calculated offline on a personal computer as previously described. A step-by-step procedure with an example, a VisualBasic program, and a Fortran program to calculate approximate entropy have been published. Approximate entropy as a relative (not absolute) measure depends on three parameters: the length of the epoch (N), the length of compared runs of data (m), and a filtering level (r). In this study, N was fixed at 1,024, thus one value of approximate entropy could be calculated for each 8-s electroencephalogram epoch. The noise filter $r$ was defined as relative fraction of the SD of the 1,024 amplitude values. We used the parameter set $m = 2, r = 0.2 · SD$, which was found to exert the best performance for electroencephalogram approximate entropy in a preliminary study. If the SD of the 1,024 amplitude values was below a lower threshold of 7 μV, $r$ was set to 0.2 · (mean of the SDs of the three previous epochs with a standard deviation $> 7$ μV).

**Pharmacodynamic and Statistical Analysis**

The relation between effect compartment concentration and electroencephalogram burst-suppression ratio was modeled with a fractional sigmoid $E_{\text{max}}$ model (Hill equation):

$$E = E_0 \cdot \left[1 - c_{\text{eff}}/(C_{50} + c_{\text{eff}}')\right]$$

where $E_0$ is the baseline effect of each individual (i.e., 0% burst-suppression ratio), $c_{\text{eff}}$ is the apparent effect side concentration, $C_{50}$ is the concentration that causes 50% of the maximum effect (i.e., 50% burst-suppression ratio), and $\lambda$ describes the slope of the concentration-response relation.

Isoflurane effect compartment concentrations were modeled for each 8-s electroencephalogram epoch. The noise filter $r$ was defined as relative fraction of the SD of the 1,024 amplitude values. We used the parameter set $m = 2, r = 0.2 · SD$, which was found to exert the best performance for electroencephalogram approximate entropy in a preliminary study. If the SD of the 1,024 amplitude values was below a lower threshold of 7 μV, $r$ was set to 0.2 · (mean of the SDs of the three previous epochs with a standard deviation $> 7$ μV).
obtained by simultaneous pharmacokinetic–pharmacodynamic modeling. To eliminate the hysteresis between the end-tidal concentrations of isoflurane and the electroencephalogram effect, an effect compartment was introduced into the model:

\[
\frac{dC_{\text{eff}}}{dt} = (C_{\text{et}} - C_{\text{eff}}) \cdot k_{\text{eo}}
\]

where \(C_{\text{et}}\) is end-tidal concentrations of the respective volatile anesthetic, \(C_{\text{eff}}\) is effect compartment concentration of the respective volatile anesthetic, and \(k_{\text{eo}}\) is first-order rate constant determining the efflux from the effect compartment.

The data of each person were fit separately. The parameters of the above models were estimated using nonlinear regression with ordinary least squares. The parameters for the model for all patients (burst-suppression ratio vs. isoflurane effect compartment concentration) were obtained by the two-stage standard approach. The computations were performed on a spreadsheet using the Excel software program (Microsoft, Redmond, WA), and the parameters were optimized with the Solver tool within Excel.

The relation between burst-suppression ratio and approximate entropy, median electroencephalogram frequency, spectral edge frequency 95, and burst-compensated spectral edge frequency 95 was analyzed using the Pearson correlation coefficient.

**Results**

In 11 patients, a total of 504 min of artifact-free electroencephalogram (3,778 8-s epochs) were recorded and analyzed. A total of 1,833 epochs (48.5%) included burst-suppression patterns, whereas 1,945 epochs (51.5%) did not include burst-suppression patterns.

The burst-suppression ratio increased with increasing isoflurane concentrations (fig. 1). Figure 2 shows the relation between isoflurane effect compartment concentrations and burst-suppression ratio for every individual patient and the model for all patients. Table 1 shows the pharmacodynamic parameters estimated with burst-suppression ratio.

**Table 1. The Pharmacodynamic Parameters Estimated with Burst-suppression Ratio**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(k_{\text{eo}})</td>
<td>0.28</td>
<td>0.15</td>
</tr>
<tr>
<td>(E_0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(E_{\text{max}})</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>(E_{C50})</td>
<td>1.51</td>
<td>0.15</td>
</tr>
<tr>
<td>(\lambda)</td>
<td>18.53</td>
<td>14.13</td>
</tr>
</tbody>
</table>

\(E_{C50}\) = concentration that causes 50% of the maximum effect; \(E_{\text{max}}\) = maximum effect; \(E_0\) = baseline effect; \(k_{\text{eo}}\) = first-order rate constant determining the efflux from the effect compartment; \(\lambda\) = slope of the concentration–response relation.
mean and SD of the pharmacokinetic and pharmacodynamic parameters.

As expected, there was no uniform relation between burst-suppression ratio and median electroencephalogram frequency and spectral edge frequency 95. A moderate trend for median electroencephalogram frequency \( r = 0.34 \) and spectral edge frequency 95 \( r = 0.29 \) to increase with increasing burst-suppression ratio (fig. 3) could be observed.

In contrast, with increasing burst-suppression ratio, approximate entropy continuously decreased. The electroencephalogram approximate entropy was closely inversely related \( r = -0.94 \) to burst-suppression ratio during isoflurane anesthesia could be demonstrated in this study.

The electroencephalogram silence during suppression is not truly a zero line. There are always low-voltage differences between the data points during suppression. The interpretation as high regular of the suppression by the approximate entropy algorithm is ensured as long as the “noise” filter level \( r \) is higher than the voltage differences between the data points during suppression. The filter level \( r \) was defined as a relative fraction of the SD of the 1,024 amplitude values. The amplitudes of the electroencephalogram waves, and especially of the burst waves, lead to a high enough filter level \( r \) as a percentage of the SD. Only if the suppression exceeds approximately 70% of the length of the epoch is it no longer guaranteed that the filter level \( r \) is high enough to determine different data points during suppression as “equal.”

This increasing danger of a misinterpretation of the “noise” during complete or almost-complete suppression by the approximate entropy algorithm was solved by the introduction of a lower threshold for the filter level \( r \). However, the adjustment for the filter level \( r \) was developed using the same data set, which represents a limitation.

The occurrence of high-frequency waves during the bursts let the frequency-based electroencephalogram parameters, such as median electroencephalogram frequency and spectral edge frequency 95, tend to increase with increasing appearance of burst-suppression. In
principle, the result is a biphasic shape of the dose-response curve of the frequency-based electroencephalogram parameters. A biphasic shape could lead to the danger of misclassification and the danger of a deleterious overdosing or underdosing of the anesthetics in an processed electroencephalogram-leaded anesthesia. Therefore, an anesthetic dosing regimen driven by frequency-based electroencephalogram parameters such as median electroencephalogram frequency and spectral edge frequency must not be used without an additional burst-suppression algorithm,9 as realized in the burst-compensated spectral edge frequency algorithm.6

In fact, an algorithm to identify burst-suppression pattern is also implemented in the so-called bispectral index, which is partially a frequency-based parameter, too, to avoid the trend to increase with increasing appearance of burst suppression.10,11 Still, Detsch et al.12 reported in the presence of few burst-suppression patterns that increasing isoflurane may induce paradoxical increases of the electroencephalogram bispectral index. Obviously, detection of burst-suppression has its own limitations with less than 100% correct automatic classification of burst-suppression patterns.13,14 Our data suggest that these problems can be avoided using electroencephalogram approximate entropy when burst-suppression pattern may occur.

We conclude that the electroencephalogram approximate entropy, but not electroencephalogram median frequency or spectral edge frequency 95 without burst compensation, correctly classifies the occurrence of burst suppression as an increasing anesthetic drug effect.

References

5. Rampil IJ: No correlation between quantitative electroencephalographic measurements and movement responses to noxious stimuli during isoflurane anesthesia in rats. ANESTHESIOLOGY 1992; 77:920–5

Anesthesiology, V 93, No 4, Oct 2000