Specific Problems in Interpretation of Absolute Values of Spectral Edge Frequency (SEF) in comparison to Bispectral Index (BIS) for Assessing Depth of Anesthesia

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Citation

Abstract
The spectral edge frequency (SEF) is a milestone in the computer-assisted EEG analysis for assessing the depth of anesthesia. The SEF as well as the bispectral index (BIS) are numerical descriptors of the EEG. For both, SEF and BIS, limits have been reported within which recall and hemodynamic or motor responses to surgical stimuli are unlikely. We studied the SEF at four different states of anesthesia based on individual observations. Further, we compared the SEF and BIS values in relation to the proposed limits at different endtidal concentrations of sevoflurane (1.2 and 2.4 Vol%et) and desflurane (3.0 and 6.0 Vol%et).

The SEF and BIS values were assessed according to the proposed limits for SEF (13.65 and 12 Hz) and BIS (60).

We found a high interindividual variability and low intrapersonal stability of the SEF values in the awake state. These findings impair the discrimination of awake and sleep state.

The mean SEF was outside the target range at both endtidal concentrations of sevoflurane and desflurane. In contrast, mean BIS values at all measuring phases during anesthesia met the goal of < 60.

The increased concentrations of anesthetics are not reflected adequately in the phases of excitation and burst suppression activity.

Summarizing, a suitable, statistically calculated approximate target limit of SEF as a tool to guide the depth of anesthesia does not seem to be available at the present time.

INTRODUCTION
The idea of target values to guide the depth of anesthesia is intriguing. In this context the development of the spectral edge frequency (SEF) as an univariate descriptor of the EEG was a milestone. The SEF is derived from the power spectrum of the computer-assisted EEG.

It reflects the frequency below which a defined power of total power spectrum is situated (Figure 1).
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Figure 1
Figure 1: Spectral edge frequency (SEF 90) as a derivate of EEG spectral analysis (MDF: mean dominant frequency; PF: peak frequency; SMF: spectral median frequency; SEF: spectral edge frequency).

The SEF 90 and SEF 95 have been reported to be associated with increasing concentrations of volatile anesthetic agents \(^{3,5,4}\) . On contrary there exist reports that claim limited clinical relevance of SEF for estimating depth of anesthesia \(^{6,7,8}\) .

The aim of this paper is to study the SEF values at different phases of anesthesiological management and to bring this data in relation to the target limits reported in the literature \(^{1,9,10,11,12}\) and to compare the SEF data with the simultaneously registered data of the bispectral index (BIS).

Finally our data and episodic observations were compared to the four EEG-phases of anesthesia as summarized by Bruhn \(^{13}\).

MATERIALS AND METHODS

PATIENTS AND MONITORING

After institutional review board approval and written consent, we enrolled 64 patients (27 female, 37 male; ASA status 1-3; mean age 51.7 ± 13.9 years; range, 22-75 years) undergoing lumbar spine surgery (Table 1). None of the patients had a history or clinical signs of a central nervous system disorder.

Monitoring: EEGs were recorded with Aspect A 1000 Monitor; (Aspect Medical Systems, Natick, MA, USA) via a two-channel referential montage. The surface electrodes (Zipprep; Aspect Medical Systems, Natick, MA, USA) were placed according to the international 10-20 system at F7 and F8 with Fz as the reference and Fp1 as the ground. The impedance was < 5 kOhm. Standard monitoring included ECG, noninvasive blood pressure, peripheral oxygen saturation (SaO\(_2\)), end expiratory carbon dioxide (etCO\(_2\)), inspiratory and expiratory gas concentrations. Postoperative recall was assessed by a standardized 5-question concept \(^{14,9}\).

Measuring phases: The first measuring phase (MP1) took place before inducing anesthesia with the patient's eyes closed. The second measuring phase (MP2) was obtained after equilibration of sevoflurane at 1.2 Vol\%\(\text{et}\) or desflurane at 3.0 Vol\%\(\text{et}\). The third measuring phase (MP3) was 1 minute after the skin incision. The fourth measuring phase (MP4) took place 10 minutes after the endtidal gas concentrations were doubled to 2.4 Vol\%\(\text{et}\) (sevoflurane) and 6 Vol\%\(\text{et}\) (desflurane), respectively.

Table 1: Anthropomorphic data of patients in the sevoflurane and desflurane groups (mean SD).

<table>
<thead>
<tr>
<th></th>
<th>sevoflurane</th>
<th>desflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>male</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>female</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>age (years)</td>
<td>50.4 ± 13.8</td>
<td>52.9 ± 13.9</td>
</tr>
<tr>
<td>body weight (kg)</td>
<td>73.6 ± 14.5</td>
<td>77.8 ± 13.5</td>
</tr>
</tbody>
</table>

Patients were premedicated with 7.5 mg midazolam 1 hour before anesthesia. Induction and maintenance of anesthesia were standardized. Anesthesia was induced with fentanyl (1.5 µg/kg) and thiopental (1-3 mg/kg i.v.). Paralysis was achieved with vecuronium (0.1 mg/kg). Patients were randomized to receive sevoflurane (n = 32) or isoflurane (n = 32). In patients receiving sevoflurane, the endtidal gas concentrations at measuring points were 1.2 and 2.4 Vol\%.

In patients receiving desflurane measurements were obtained at equivalent concentrations (3 and 6 Vol\%\(\text{et}\)). Both volatile anesthetics were administered via a 70 % N\(_2\)O/O\(_2\) mixture (3L/min). Ventilation was regulated to keep et CO\(_2\) between 32 and 36 mmHg.
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STATISTICS
The value obtained at each measuring phase were calculated for each group. We analysed the differences between the consecutive measuring phases in both groups. Also, the results between the groups were compared for each measuring phase.

The data were tested with analysis of variance (Kruskal Wallis One Way ANOVA on Ranks) using SigmaStat (Jandel Scientifics Corp. Erkrath, Germany). As post hoc analyses Dunn’s method and Tukey test were used. Changes were considered significant at a p-value < 0.05.

Both SEF and BIS results were analysed according to target values gleaned from other reports. For SEF, we analysed the results according to two target frequencies, 13.6 Hz $[10]$ and 12 Hz $[11]$.

The upper target level of BIS was set at 60 $[14,15,16,17]$.

RESULTS
Tables 2 a and 2 b show the mean SEF and BIS values and hemodynamic data of the 4 measuring phases with sevoflurane and desflurane respectively.

**Figure 3**
Table 2 a: Mean SD SEF (l = left; r = right), BIS, mean arterial pressure (MAP), and heart rate (HR) at the 4 measuring phases (MP1 – MP4) with sevoflurane.

<table>
<thead>
<tr>
<th>Sevoflurane</th>
<th>MP 1</th>
<th>MP 2</th>
<th>MP 3</th>
<th>MP 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEF (Hz) I</td>
<td>19.4±8.8</td>
<td>19.3±3.2</td>
<td>10.4±3.5</td>
<td>15.8±3.7</td>
</tr>
<tr>
<td>SEF (Hz) r</td>
<td>17.9±8.9</td>
<td>17.9±3.1</td>
<td>18.0±3.4</td>
<td>15.8±3.4</td>
</tr>
<tr>
<td>BIS</td>
<td>94.5±4.7</td>
<td>52.1±11.6</td>
<td>50.6±11.3</td>
<td>41.9±11.1</td>
</tr>
<tr>
<td>MAP(mmHg)</td>
<td>79.7±14.8</td>
<td>70.2±14.9</td>
<td>77.6±14.6</td>
<td>71.5±15.8</td>
</tr>
<tr>
<td>HR(beats/min)</td>
<td>75.6±12.3</td>
<td>70.2±15.6</td>
<td>76.6±15.1</td>
<td>70.5±15.1</td>
</tr>
</tbody>
</table>

**Figure 4**
Table 2 b: Mean SD SEF (l = left; r = right), BIS, mean arterial pressure (MAP), and heart rate (HR) at the 4 measuring phases (MP1 – MP4) with desflurane.

<table>
<thead>
<tr>
<th>Desflurane</th>
<th>MP 1</th>
<th>MP 2</th>
<th>MP 3</th>
<th>MP 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEF (Hz) I</td>
<td>20.0±6.4</td>
<td>17.4±3.0</td>
<td>18.8±5.2</td>
<td>12.2±4.3</td>
</tr>
<tr>
<td>SEF (Hz) r</td>
<td>18.6±6.6</td>
<td>17.5±3.2</td>
<td>16.9±5.0</td>
<td>12.2±4.5</td>
</tr>
<tr>
<td>BIS</td>
<td>94.9±8.8</td>
<td>52.1±14.1</td>
<td>51.2±17.4</td>
<td>39.9±16.1</td>
</tr>
<tr>
<td>MAP(mmHg)</td>
<td>79.7±16.5</td>
<td>75.6±15.2</td>
<td>97.6±15.6</td>
<td>91.4±15.1</td>
</tr>
<tr>
<td>HR(beats/min)</td>
<td>75.1±12.5</td>
<td>74.8±15.6</td>
<td>81.1±15.9</td>
<td>81.5±17.3</td>
</tr>
</tbody>
</table>

Major standard deviations of SEF were found in the premedicated patients at awake state (MP1, Figure 2) before induction of anesthesia. These results were in contrast to BIS, which showed the lowest standard deviation of all measurement parameters at this measuring phase (Tabs. 2 a, b).

**Figure 5**
Figure 2: SEF 95 in awake state before anesthesia with sevoflurane and desflurane (box plots: the ends of the boxes define the 25 th and 75 th percentiles, a line shows the median, and error bars show the 10 th and 90 th percentiles).

The decreases in SEF between the awake state (MP1) and anesthesia at MP2 were not significant with either sevoflurane or desflurane. In contrast, mean BIS decreased significantly (p < 0.05) with both gasses (MP1 to MP2). After skin incision (MP3), SEF showed no significant increase with sevoflurane in relation to MP2; BIS remained nearly unchanged.

At the fourth measuring phase (MP4) the mean SEF values were significantly (p < 0.05) lower compared to MP2. A similar significant decrease occurred with desflurane.

The BIS also decreased at the same MP4. At MP2, mean SEF values did not meet the respective targets of 13.6 Hz and 12 Hz with sevoflurane 1.2 Vol% and desflurane 3 Vol%. With sevoflurane, the mean SEF values did not decrease under the target levels even when the concentration of the anesthetic gas was doubled (MP4) (Figure 3). With desflurane, the limit of 13.6 Hz was met, but not the limit of 12 Hz. In contrast, the mean BIS values met the target of 60 with both anesthetics at both concentrations.
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**Figure 6**
Figure 6: Box plots of SEF 95 and BIS at MP2 and MP4. Compare the boxes of SEF 95 with the target lines at 12 Hz and 13.6 Hz and the boxes of BIS with the target line at 60.

The hemodynamic values were mostly stable. With desflurane there was a marked increase of heart rate and a significant increase of mean arterial pressure at MP3 (Tab. 2 b).

No patient described recall.

The results of the statistical analyses are summarized in the appendix.

**DISCUSSION**

Considering the different concentrations of anesthetics and corresponding EEG-patterns, 4 phases of anesthesia were differentiated as follows by some authors [13]:

1. “Awake–EEG” phase
2. “Excitation” phase
3. “Surgical anesthetic depth” phase
4. “Burst-suppression pattern” phase

In correlation with the increasing concentrations of anesthetics, continuous alterations in SEF values to lower frequencies are to be expected after running through the 4 phases.

However, low concentration of anesthetics can convey the so-called awake EEG into an EEG pattern dominated by high frequencies.

After increasing anesthetic concentrations further, a decrease to lower EEG frequencies occurs. Very high concentrations of anesthetics lead to burst-suppression-patterns which finally result in the loss of cerebral bioelectric activity as seen in the “isoelectrical EEG”.

**1. AWAKE PHASE**

Goals of EEG measurement parameters in this phase are:

a) high intrapersonal stability and
b) low interpersonal deviation.

Thus, the best probability for determining between awake and sleep phases should be achieved.

The results of this study show a very high deviation of SEF values during the awake phase. Latter reaches the SEF target limits necessary for “adequate depth of anesthesia during surgery”.

In comparison, the deviation of BIS values is so narrow, that there is no overlapping with BIS target limit (60) indicating “surgical tolerance”.

A high intrapersonal instability of SEF-values is reported in awake subjects [18]. For comparison, the bi-hemispherical instability of SEF values in an awake, healthy female volunteer (Figure 4).

**Figure 7**
Figure 7: Bi-hemispherical instability of SEF values in an awake healthy volunteer (female, 22 years) with eyes closed (with permission of the volunteer).

Reports regarding Approximate Entropy (ApEn) refer to a higher stability of measurement values [18] in the phase before inducing anesthesia in comparison to SEF.

**2. EXCITATION PHASE**

As described above, low concentrations of anesthetics can induce transient high frequencies in the EEG. As a result,
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higher SEF 95 values can be registered in both awake, as well as unconscious individuals. Its cause lies in the frequency dependency of the SEF. In other words, SEF can increase with superficial anesthesia during induction and then decrease with deepening anesthesia [8]. Therefore, both awake and asleep patients can show similar SEF values. Further, ketamine and N\textsubscript{2}O do not decrease SEF 95 even with increasing sedation, when applying propofol-fentanyl anesthesia [19]. Using suitable algorithms, BIS and ApEn numerically reflect the concentration-related decrease in unconsciousness during the excitation phase with higher plausibility.

3. SURGICAL ANESTHETIC DEPTH PHASE

In a simultaneous pharmacokinetic-pharmacodynamic model based on different end-tidal desflurane concentrations, a higher correlation between the desflurane effect compartment concentration of SEF could be determined as for ApEn and BIS [20].

Our results deny the SEF 95 to be a suitable control parameter for the adequate depth of anesthesia. The mean values of SEF lie under the SEF target limit of 12 Hz for the adequate depth of anesthesia either at 3.0 or at 6.0 Vol\%et. The same holds true for the sevoflurane concentrations of 1.2 and 2.4 Vol\%et. Only at 6 Vol\%et desflurane the target limit of 13.6 Hz is slightly underwent by the SEF readings.

Our results appear to confirm the results by Drummond et al [10]. This group demonstrated consistent trends in SEF during emergence from anesthesia, but the absolute values in their study varied sufficiently so that even a post hoc approach could not identify critical thresholds. Further reports note that SEF is of limited clinical relevance [7]. Using isoflurane, a surgical stimulus can cause paradoxical arousal and an unexpected decrease in SEF values [5]. It is unclear to what extent system algorithms contribute to such findings [2].

Compared with SEF, this study shows that mean values of BIS lie under the target value of BIS (60) at all gas concentrations of sevoflurane and desflurane (Figure 3). However, we must critically note, that a great deviation of measurement values regarding BIS occurs during the phase of “surgical anesthetic depth”. In addition, several reports about paradoxical BIS phenomena under different circumstances exist [23,24,25,26,27,28,29,30]. Because of these facts, individual BIS results require careful interpretation. Trend monitoring of BIS is useful but requires analysing the plausibility of the numerical values with online integrated control of the native EEG [33].

4. BURST SUPPRESSION-PATTERN PHASE

In high anesthetic concentrations, the EEG shows patterns characterized by changing episodes without essential bioelectric activity (suppression) and episodes of intermitting high frequency activity (bursts). Based on the frequency dependency of SEF, high frequency EEG periods (bursts) lead to paradoxical elevated SEF values after administrating higher concentrations of anesthetics during this phase (Figure 5).

Figure 8
Figure 5: Paradoxically elevated SEF values during burst suppression activity after propofol administration. Note the paradoxical elevated SEF values during isoelectric periods that can be caused by contamination of the EEG by biological artefacts such as ventricular complexes in ECG [33] (Figure 6).
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Figure 9
Figure 6: Paradoxically increased SEF values during isoelectric silence caused by propofol. By the implementation of a “burst supression ratio” and “quazi supression” as sub-parameters [2], BIS values are more plausible during the burst suppression phase than SEF values (Figure 7 - 9).

Figure 11
Figure 8: Burst suppression ratio versus BIS (modified from J. Bruhn: F.M.I. Update, no. 3, 2002, http://www.anaesthconsult.de).

The ApEn is a measure for the regularity of the EEG-waves and correctly reflects the isoelectric line in this phase of deep anesthesia.

Figure 12

CONCLUSION
Under ideal circumstances (no artefacts, no excitation, no burst suppression activity), a promising correlation of SEF to the corresponding anesthetic concentrations is described in the simulation model for the “surgical tolerance phase”.

However, the hypothetical premises deviate from the real biological processes. The increasing gas concentrations are not reflected mono-phasicly for the frequency dependent SEF. This is primarily recorded in the phases of excitation and burst suppression activity. During the awake phase, SEF indicates a high interpersonal variability and a low intrapersonal stability, which makes the differentiation between the awake and asleep phase difficult. A suitable, statistically calculated approximate target limit of SEF as a
tool to guide the depth of anesthesia does not seem to be available at the present time.

APPENDIX - RESULTS OF THE STATISTICAL ANALYSES

Figure 13

Figure 14

Figure 15

Figure 16
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Figure 17

**HR - sevoflurane**

Figure 19

**SEF right - desflurane**

Figure 18

**SEF left - desflurane**

Figure 20

**BIS - desflurane**
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Figure 21

Figure 22

References

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