Bispectral Index, Entropy, and Quantitative Electroencephalogram during Single-agent Xenon Anesthesia


Background: The aim was to evaluate the performance of anesthesia depth monitors, Bispectral Index (BIS) and Entropy, during single-agent xenon anesthesia in 17 healthy subjects.

Methods: After mask induction with xenon and intubation, anesthesia was continued with xenon only. BIS, State Entropy and Response Entropy, and electroencephalogram were monitored throughout induction, steady-state anesthesia, and emergence. The performance of BIS, State Entropy, and Response Entropy were evaluated with prediction probability, sensitivity, and specificity analyses. The power spectrum of the raw electroencephalogram signal was calculated.

Results: The concentration (SD) xenon concentration during anesthesia was 66.4% (2.4%). BIS, State Entropy, and Response Entropy demonstrated low prediction probability values at loss of response (0.455, 0.656, and 0.619) but 1 min after that the values were high (0.804, 0.941, and 0.929). Thereafter, equally good performance was demonstrated for all indices. At emergence, the prediction probability values to distinguish between steady-state anesthesia and return of response for BIS, State Entropy, and Response Entropy were 0.988, 0.892, and 0.992. No statistical differences between the performances of the monitors were observed. Quantitative electroencephalogram analyses showed generalized increase in total power (P < 0.001), delta (P < 0.001) and theta activity (P < 0.001), and increased alpha activity (P = 0.003) in the frontal brain regions.

Conclusions: Electroencephalogram-derived depth of sedation indices BIS and Entropy showed a delay to detect loss of response during induction of xenon anesthesia. Both monitors performed well in distinguishing between conscious and unconscious states during steady-state anesthesia. Xenon-induced changes in electroencephalogram closely resemble those induced by propofol.

XENON is a noble gas that has anesthetic properties supposedly mediated via antagonism of the N-methyl-D-aspartate (NMDA) receptors.1 Xenon has recently been granted marketing authorization for anesthetic maintenance in Germany.2 Xenon anesthesia is associated with cardiovascular stability,3,4 and recent experimental data also indicate that xenon has both cardioprotective5,6 and neuroprotective effects.7–9 Because of its potential organ protective effects, xenon has been suggested as a putative neuroanesthetic.

Monitoring the state of hypnosis during general anesthesia has become standard in anesthetic care. Electroencephalogram (EEG) results can be mathematically transformed into numeric indices that can be easily interpreted by the tending anesthesiologist. The use of these indices may decrease the consumption of anesthetics and reduce the incidence of awareness during anesthesia.10,11 Nevertheless, these EEG-based indices may not always perform well with all anesthetic agents, particularly with those acting via the NMDA receptor.12,13 Because there are only a few previous reports on the use of xenon alone for induction or maintenance of anesthesia,3,14,15 the role of the anesthesia depth monitors during xenon anesthesia is unclear. Their reliability in measuring xenon-induced hypnosis has even been questioned.16 In addition, there are not much data on the effects of surgical concentrations of xenon on quantitative EEG (qEEG) variables in humans.17

The aim of this study was to assess the performance of anesthesia depth indices, Bispectral Index (BIS) and Entropy, during induction and maintenance of single-agent xenon anesthesia in healthy subjects. The power spectrum of the raw EEG signal was studied to observe the effects of xenon on qEEG and for the detailed evaluation of the performance of the EEG-derived indices.

Materials and Methods

Subjects and Study Design

The study protocol was approved by the local ethical committee (Turku University, Finland) and the National Agency for Medicines and included two separate positron emission tomography studies (results presented separately). In Part I 18 (n = 9), BIS, State Entropy (SE),
and Response Entropy (RE) were recorded during single-agent xenon anesthesia. In Part II (n = 8), we also collected qEEG. Thus, 17 healthy, male, right-handed, nonsmoking volunteers aged 20-27 yr (body mass index 20.7–28.7 kg/m²) were enrolled after giving written informed consent in this open, nonrandomized study. The subjects underwent a thorough physical examination including laboratory testing. All subjects were considered as American Society of Anesthesiologists I class and had no history of drug allergies or drug abuse, and none was receiving ongoing medication. Subjects fasted overnight and refrained from using alcohol or any medication for 48 h before anesthesia.

The unpremedicated subjects were anesthetized using mask induction with 63% target end-tidal concentration of xenon, considered as approximately 1 minimum alveolar concentration (MAC). Anesthesia was continued with closed-system mechanical ventilation with xenon as the single anesthetic. After a 2-h period, xenon was discontinued and the subjects were allowed to recover. During anesthesia, the volunteers were not subjected to any noxious interventions as they only underwent repeated noninvasive positron emission tomography scans.

**Monitoring**

On arrival at the study premises, a forearm vein was cannulated for drug administration, and the radial artery was cannulated for blood sampling and invasive blood pressure monitoring. Physiologic saline was given intravenously at a rate of 100 ml/h throughout anesthesia, after which time the fluid infusion was changed to 5% glucose. Monitoring included invasive blood pressure, pulse oximetry, five-lead electrocardiogram, muscle relaxation (train-of-four), and nasopharyngeal temperature (GE Datex-Ohmeda S/5 anesthesia monitor; GE Healthcare, Helsinki, Finland). All data were automatically recorded throughout the study: vital parameters at 10-s intervals and waveforms at their corresponding sample frequencies (S/5 Collect Software, GE Healthcare). In addition, airway pressure, and concentrations of oxygen, carbon dioxide, and xenon in the ventilation circuit were recorded during anesthesia. Repeated blood gas analyses were performed during anesthesia using a portable device (i-STAT; Abbott Laboratories, Birmingham, UK) to adjust and maintain normoventilation.

Depth of sedation was monitored with BIS® (BIS XP, algorithm version 4.0, smoothing rate 15 s) and Entropy (Entropy module; GE Healthcare) indices throughout anesthesia as recommended by the manufacturers. The skin of the forehead was prepared with alcohol, and disposable BIS (Aspect Medical Systems, Natick, MA) and Entropy sensors (GE Healthcare) were placed on the forehead in close proximity. The sides of temporal electrodes were randomized. The active temporal electrode was placed to the right for BIS in nine subjects and for Entropy in eight subjects.

BIS is a weighted sum of three variables derived from bispectral (0.5–47 Hz), spectral (11–47 Hz), and time domain contents of EEG. For easier interpretation, these variables were transformed into BIS scale from 0 to 100. Values close to the maximum of 100 indicate state of awareness and values less than 40 indicate deep hypnotic state. Entropy module computes the time frequency-balanced spectral entropy using a combination of time and frequency domain EEG measures. As a result, the monitor generates two indices, SE and RE, which are calculated from different frequency ranges of the raw EEG signal. SE is derived from the frequency range of 0.8–32 Hz consisting of mainly EEG activity, whereas RE is derived from the range of 0.8–47 Hz and includes muscle activity from the muscles of the forehead. SE and RE are scaled in ranges of 0–91 and 0–100, respectively.

**qEEG Recording**

EEG was continuously recorded throughout the study with four-channel digital EEG equipment (GE Datex-Ohmeda S/5™ EEG Module; GE Healthcare) and stored online (S/5 Collect software; GE Healthcare). EEG signal sample rate was 100 Hz and pass-band was 0.5–30 Hz. Ag-AgCl electrodes and the International 10–20 Electrode Placement System were used. Bipolar montage included the F4–C4, F3–C3, T8–O2, and T7–O1 derivations covering the midfrontal-central and posterior temporal-occipital regions of both hemispheres. The skin was prepared to keep the electrode impedance under 5 kΩ, and the electrodes were fixed with electrode paste (Grass-paste; Astro-Medical; Grass Instrument Division, W. Warwick, RI). The EEG signal was further processed using commercial software (Matlab 6.5, The Mathworks Inc., Natick, MA). Raw EEG data were visually analyzed offline, and artifact-contaminated EEG segments were excluded. Only epochs without high-amplitude artifacts, caused by limb or eye movements, were included in power spectral analyses with an epoch length of 4 s. Absolute power spectra (μV²/Hz) of each epoch were obtained with the psd-function of the software. The psd-function uses fast Fourier transform with Hanning windowing. Power spectra from individual epochs were averaged to obtain final power spectra for each analysis period. Power spectrum analysis was performed during two time periods: awake baseline data before xenon administration (6-184 epochs depending on the amount of artifact-free EEG) and a 5-min period during steady-state anesthesia at least 30 min after intubation (73–75 epochs). Artifacts during loss of response (LOR) and return of response (ROR) did not allow qEEG analysis at those time points. Absolute band powers (μV²) were calculated from the following bands: total power (1.0-30.0 Hz), delta (1.0–3.25 Hz), theta (3.5–8.0 Hz), alpha (8.25–13.0 Hz), and beta (13.25–30.0 Hz). In addition, 95% spectral edge frequency and relative power for each band were calculated.
Anesthesia

Denitrogenation of the subjects was performed by having them breathe 100% oxygen through a tight 5-cm H\textsubscript{2}O continuous positive airway pressure mask for 1 h. After the denitrogenation period, the subjects were told to hold their breath to avoid any breathing of room air while the pressure mask was changed to a tightly fitting regular face mask connected to the closed loop anesthesia ventilator (PhysioFlex, Dräger, Lübeck, Germany). Thereafter, anesthesia was induced by changing the inhaled oxygen concentration from 100% to 21%, thus increasing the xenon concentration in the gas mixture. The subjects continued breathing spontaneously via the face mask. Xenon concentration increase was facilitated by flushing the breathing system with a mixture of xenon only in oxygen. Additional 10- to 20-mg bolus doses of rocuronium were given to maintain muscle relaxation at one twitch of train-of-four. In case of obvious pain reaction because of intubation (rapid elevation in blood pressure or heart rate or other clinical signs of insufficient anesthesia), subjects were given a single 25-μg intravenous dose of remifentanil (Ultiva; GlaxoSmithKline, Helsinki, Finland), and tracheal intubation was performed when complete muscle relaxation was achieved. Anesthesia was continued with xenon only in oxygen. Additional 10- to 20-mg bolus doses of rocuronium were given to maintain muscle relaxation at one twitch of train-of-four. In case of obvious pain reaction because of intubation (rapid elevation in blood pressure or heart rate or other clinical signs of insufficient anesthesia), subjects were given a single 25-μg intravenous dose of remifentanil (Ultiva; GlaxoSmithKline, Helsinki, Finland). The time interval between opioid administration and the period of steady-state anesthesia was longer than 30 min. A warming blanket (BairHugger, Arizant Healthcare Inc, Eden Prairie, MN) was used to stabilize body temperature. After approximately 2 h, xenon was discontinued and muscle relaxation was reversed with a combination of neostigmine and glycopyrrolate (Robinul-Neostigmine; Wyeth Lederle, Helsinki, Finland). Subjects were extubated as they recovered spontaneous breathing and regained responsiveness. The first two subjects were given antiemetics when nausea occurred. Thereafter, antiemetics were given prophylactically before emergence to all other subjects. The antiemetics included dehydrobenzperidol (DHPBP 1.25 mg/ml; OTL Pharma, Paris, France), dexametasone (Oradexon 5 mg/ml; Organon), and ondansetron (Zofran 2 mg/ml; GlaxoSmithKline). The subjects were monitored for stable vital signs for at least 1 h, and they were discharged according to our hospital’s criteria for ambulatory surgery patients. Subjects completed a modified structured questionnaire by Brice et al. on possible awareness during anesthesia and possible hallucinations immediately after ROR and 1 d and 6 wk after anesthesia.

Predicted clinical events during anesthesia were LOR, intubation, steady-state anesthesia, and ROR. Reaction was assessed at 10-s intervals by requesting the subject to squeeze the investigator’s hand twice. LOR was interpreted as a failure to execute this task. ROR was defined as an adequate response to verbal command after termination of xenon administration. The hemodynamic response to tracheal intubation was determined as the maximal value of heart rate and arterial blood pressures within a 10-min period after intubation compared with the value 1 min before intubation.

Statistical Analysis

Prediction probability (P\textsubscript{K}) was calculated to evaluate how accurately BIS, RE, or SE distinguishes among different time points of anesthesia. A value of P\textsubscript{K} = 0.5 means that the indicator predicts the observed anesthetic depths no better than a 50/50 chance, and a value of P\textsubscript{K} = 1.0 means that the indicator always predicts the observed anesthetic depths correctly. P\textsubscript{K} and its SE, which was estimated with the jackknife method, were based on the assumption that all assessments were independent. A Student’s t test with Bonferroni correction was used to evaluate whether the P\textsubscript{K} for one variable was different from another one. A custom spreadsheet macro P\textsubscript{K}MACRO was used in P\textsubscript{K} analysis.

P\textsubscript{K} analysis was performed for awake versus LOR, LOR versus intubation, and steady-state anesthesia versus ROR. To determine the delay of the indices to indicate LOR, P\textsubscript{K} analyses 1, 2, 3, and 4 min after LOR were performed. BIS and Entropy data for the P\textsubscript{K} analysis were single values just before start of xenon induction (awake), immediately after LOR, just before intubation, during steady-state anesthesia, and immediately after ROR.

Sensitivity and specificity were calculated to evaluate whether BIS, RE, or SE correctly classify the responsiveness and unresponsiveness states. Sensitivity and specificity were calculated from pooled data of all subjects over two 10-min periods, first 5 min before and after the LOR and similarly before and after the ROR. Sensitivity was defined as the proportion of data points taken during the responsiveness state and indicating responsiveness. Specificity was defined as the proportion of data points taken during the unresponsiveness state and indicating unresponsiveness. Cutoff values for sensitivity and specificity for the indices were obtained from receiver operating characteristics curve. Optimal cutoff values for each variable were defined by maximizing the sum of sensitivity and specificity. In addition, specificity was derived with the cutoff value resulting in 100% sensitivity, which has been stated as an essential feature of the anesthetic depth monitor. Sensitivity and specificity were calculated with commercial software (Matlab 6.5, The Mathworks Inc.).

Statistical Analysis of the Vital Parameters and qEEG

There were no statistically significant hemisphere-by-derivation interactions in qEEG; therefore, the right
hemisphere was selected for further analysis. The repeated-measures analysis of variance model, including the condition (baseline/anesthesia) and derivation (frontal/occipital) as the within factors, was fitted to the qEEG variables. All main effects and interaction effects were analyzed. Absolute qEEG variables were log-transformed before fitting the model.

Vital monitoring variables were analyzed with a repeated-measures analysis of variance model using the hypnotic state as a within factor. The pair-wise comparisons, including estimates and statistical tests among different conditions (baseline/induction/anesthesia) were performed using the linear contrasts of the same model. The 95% confidence intervals were calculated for the estimates. To estimate the effect of remifentanil on studied variables, another repeated-measures analysis of variance model was fitted, including the condition as a within factor and the use of remifentanil (no/yes) as a between factor. A two-sided $P$ value of less than 0.05 was considered statistically significant. Statistical analysis was conducted with SAS (version 8.2; SAS Institute Inc., Cary, NC).

## Results

All subjects were successfully anesthetized, and the mean (SD) xenon concentration during anesthesia was 66.4% (2.4%). The mean length of anesthesia was 1.9 (0.4) hours. Six subjects (35.3%; five in Part I and one in Part II) were given a 25-μg bolus dose of remifentanil because of pain reaction to intubation. Use of remifentanil did not have statistically significant effects on the BIS, SE, RE, or hemodynamic results. LOR was achieved 216 (91) s after xenon was started. After xenon administration was terminated, the mean time for ROR was 219 (91) s. ROR could not be determined for two subjects because of residual muscle relaxation.

### BIS and Entropy

The median values and interquartile ranges for BIS, SE, and RE at awake, LOR, steady-state anesthesia, and ROR are presented in table 1. At LOR, the median values for BIS, SE, and RE were 98, 88, and 98; at ROR, respective values were 70, 41, and 61. The corresponding values throughout anesthesia are presented in figure 1.

<table>
<thead>
<tr>
<th>Awake</th>
<th>LOR</th>
<th>Steady-state Anesthesia</th>
<th>ROR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIS</td>
<td>98 (97–98)</td>
<td>98 (97–98)</td>
<td>26 (24–31)</td>
</tr>
<tr>
<td>SE</td>
<td>89 (87–90)</td>
<td>88 (87–89)</td>
<td>18 (12–24)</td>
</tr>
<tr>
<td>RE</td>
<td>99 (98–99)</td>
<td>98 (96–99)</td>
<td>18 (12–24)</td>
</tr>
</tbody>
</table>

Values are presented as median values (lower and upper quartiles). Use of remifentanil did not affect the results.

BIS = bispectral index; LOR = loss of response; RE = response entropy; ROR = return of response; SE = spectral entropy.
response; RE
entropy; SS
posterior derivation. A slight increase in beta band in
during xenon anesthesia compared with awake base-
slight increase in the total amount of alpha activity
bands increased during xenon anesthesia. There was a
the frontal derivation. Slow activity in delta and theta
total absolute power was detected predominantly in
right hemisphere was se-
lected for further analyses. Results of
PK analyses 1, 2, 3, and 4 min after LOR are presented
in table 3.
Sensitivity, specificity, and cutoff values during LOR
and ROR are presented in table 4. During LOR, all indices
were equally sensitive, with optimal cutoff points, and
were approximately equally specific at the cutoff point of 100% sensitivity.

qEEG
The results of qEEG analysis are presented in table 5. There were no significant differences between the
two hemispheres, except for a physiologic slight am-
plitude difference in alpha band at awake in the oc-
cipital derivation, and the right hemisphere was se-
lected for further analyses. Generally, an increase in
total absolute power was detected predominantly in
the frontal derivation. Slow activity in delta and theta
bands increased during xenon anesthesia. There was a
slight increase in the total amount of alpha activity
during xenon anesthesia compared with awake base-
line in the frontal region, whereas it decreased in the
posterior derivation. A slight increase in beta band in

<table>
<thead>
<tr>
<th>Table 3. Serial PK Analysis after LOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>P_k AW vs LOR</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>BIS 0.804 (0.081)</td>
</tr>
<tr>
<td>RE 0.829 (0.059)</td>
</tr>
<tr>
<td>SE 0.941 (0.040)</td>
</tr>
</tbody>
</table>

To demonstrate the delay in bispectral index (BIS), response entropy (RE),
and state entropy (SE), serial prediction probability (P_k) analysis was per-
formed 1, 2, 3, and 4 min after loss of response (LOR). No significant
differences were observed among the indices.

AW = awake.

Hemodynamics
The mean vital and hemodynamic variables at awake,
during induction, and steady-state anesthesia are pre-
seated in table 6. Generally, both blood pressure and
heart rate increased during induction and, later, in re-
sponse to intubation. On average, intubation increased
the mean arterial pressure by 12.0 mmHg (95% CI 5.3–
18.8) and heart rate by 18.9 beats/min (CI 9.3–28.5)
table 7). After steady-state anesthesia was achieved,
blood pressure and heart rate returned to slightly below
their respective baseline values and thereafter remained
unchanged throughout anesthesia. Hypotension (de-
defined as a decrease of more than 30% of baseline values
in systolic or mean arterial pressure) was not observed in
any of the subjects.

Adverse Events
No serious adverse events were observed. Five sub-
jects (27.8%) became agitated (muscle rigidity or an
attempt to move vigorously) immediately before LOR
during the induction. Muscle rigidity was severe enough
to make manual ventilation difficult. Eight subjects
(47.0%) suffered from nausea during recovery. Despite
antiemetic therapy, three subjects (17.6%) vomited. Two
subjects (11.8%) experienced hallucinations. None of
the subjects reported any memories or recalls that could
be considered indicative of awareness during anesthesia on the structured questionnaire.

**Discussion**

The present study shows some limitations of BIS and Entropy to monitor the depth of sedation during xenon anesthesia. Both EEG-derived indices showed a delay to detect LOR during induction of xenon anesthesia. Moreover, the values of ROR were lower than the values of LOR. However, both monitors performed well in distinguishing between conscious and unconscious states during steady-state anesthesia. Xenon anesthesia induced changes in raw EEG, which surprisingly closely resemble those induced by propofol.\(^{26}\) These changes included increased amplitude and slowing of the signal with frontal area dominance.

Although the exact mechanism of the anesthetic action of xenon is still to be determined, it is thought that xenon exerts its effects by antagonism of glutamatergic transmission.\(^{27}\) Most of the anesthetics act by enhancing the inhibitory γ-aminobutyric acid type A transmission, and anesthesia depth indices have been validated for several hypnotics of this type. However, these indices may perform worse or even fail with NMDA antagonists such as ketamine.\(^{29}\)

The utility of anesthesia depth monitors during xenon anesthesia has been questioned as low BIS values did not necessarily indicate adequate hypnosis in a study by Goto et al.\(^{16}\) However, the performance analysis for BIS was executed only at emergence from anesthesia. In addition, the observed discrepancy between BIS and clinically determined consciousness could have been a consequence from the remaining slow EEG because of the residual anesthetic effect indicated by low 95% spectral edge frequency in that study. Accordingly, our data demonstrated lower values for BIS and Entropy at ROR than at awake. Other means of anesthetic depth assessments, such as the middle latency auditory-evoked potentials, have been shown to possibly be useful in monitoring hypnosis during xenon anesthesia.\(^{30}\)

**Table 5. Quantitative EEG Variables at Awake and during Xenon Anesthesia**

<table>
<thead>
<tr>
<th>EEG Variable</th>
<th>F4–C4 Awake</th>
<th>F6–O2 Awake</th>
<th>F4–C4 Xenon</th>
<th>F6–O2 Xenon</th>
<th>Significance of Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total power, μV^2</td>
<td>93.1 (32.0)</td>
<td>90.5 (59.6)</td>
<td>1287.6 (826.4)</td>
<td>742.9 (518.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delta, μV^2</td>
<td>45.9 (12.0)</td>
<td>25.7 (8.6)</td>
<td>1008.0 (855.1)</td>
<td>567.7 (518.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Theta, μV^2</td>
<td>18.3 (8.1)</td>
<td>14.4 (8.6)</td>
<td>212.3 (121.3)</td>
<td>131.1 (59.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alpha, μV^2</td>
<td>16.3 (12.2)</td>
<td>37.8 (43.7)</td>
<td>49.5 (27.5)</td>
<td>32.6 (11.5)</td>
<td>0.030 NS</td>
</tr>
<tr>
<td>Beta, μV^2</td>
<td>12.6 (8.5)</td>
<td>12.6 (8.3)</td>
<td>17.4 (11.0)</td>
<td>11.6 (7.2)</td>
<td>NS 0.022 0.005</td>
</tr>
<tr>
<td>Delta, %</td>
<td>52.4 (13.4)</td>
<td>36.3 (16.5)</td>
<td>70.0 (23.2)</td>
<td>68.1 (21.1)</td>
<td>0.045 0.002 &lt;0.001</td>
</tr>
<tr>
<td>Theta, %</td>
<td>19.3 (2.4)</td>
<td>16.7 (3.2)</td>
<td>22.9 (20.0)</td>
<td>23.8 (17.5)</td>
<td>NS NS NS</td>
</tr>
<tr>
<td>Alpha, %</td>
<td>15.6 (8.2)</td>
<td>33.0 (18.6)</td>
<td>5.2 (3.6)</td>
<td>5.9 (3.4)</td>
<td>0.003 0.002 0.004</td>
</tr>
<tr>
<td>Beta, %</td>
<td>12.7 (6.3)</td>
<td>14.0 (3.9)</td>
<td>1.9 (1.5)</td>
<td>2.2 (2.0)</td>
<td>&lt;0.001 NS NS</td>
</tr>
<tr>
<td>SEF95, Hz</td>
<td>19.3 (3.7)</td>
<td>20.1 (2.5)</td>
<td>8.3 (3.0)</td>
<td>9.3 (2.6)</td>
<td>&lt;0.001 NS NS</td>
</tr>
</tbody>
</table>

Electroencephalogram (EEG) was recorded from the right side midfrontal central (F4–C4) and temporo-occipital (T6–O2) derivations. Values are presented as mean (SD) for absolute and relative (%) powers for delta, theta, alpha, and beta band activity and 95% spectral edge frequency (SEF95). The use of remifentanil could not be statistically tested because there was only one subject who received the drug.

NS = not significant.

Table 6. Vital Parameters during Xenon Induction and Anesthesia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Awake Value</th>
<th>Induction Value</th>
<th>Steady-state Anesthesia Value</th>
<th>Awake vs Induction P Value</th>
<th>Awake vs Steady State P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>56.0 (7.7)</td>
<td>73.1 (16.6)</td>
<td>62.4 (13.7)</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic arterial pressure, mm Hg</td>
<td>142.2 (9.9)</td>
<td>159.6 (15.2)</td>
<td>133.8 (12.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic arterial pressure, mm Hg</td>
<td>69.3 (8.0)</td>
<td>76.9 (8.3)</td>
<td>72.6 (7.8)</td>
<td>0.003</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>89.8 (4.8)</td>
<td>103.5 (7.0)</td>
<td>94.9 (8.8)</td>
<td>&lt;0.001</td>
<td>0.045</td>
</tr>
<tr>
<td>Peripheral oxygen saturation, %</td>
<td>98.6 (0.7)</td>
<td>99.8 (8.0)</td>
<td>96.9 (1.2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End-tidal CO₂, mm Hg</td>
<td>41.3 (3.8)</td>
<td>36.8 (4.3)</td>
<td>39.8 (2.3)</td>
<td>0.010</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial pCO₂, mm Hg</td>
<td>41.9 (1.99)</td>
<td>—</td>
<td>40.9 (2.6)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Arterial pO₂, mm Hg</td>
<td>95.2 (8.5)</td>
<td>—</td>
<td>93.1 (13.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>14.2 (3.2)</td>
<td>13.7 (2.9)</td>
<td>9.7 (1.4)</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>36.1 (0.5)</td>
<td>—</td>
<td>36.0 (0.4)</td>
<td>NA</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are shown as group mean values (SD). The use of remifentanil did not affect the results. Induction begins from start of xenon administration and ends to loss of response.

NA = not applicable; NS = not significant.

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BIS and Entropy use different mathematical principles to transform the changes in EEG signals into a practical scoring system. Comparative studies between the usefulness of BIS and Entropy have been performed with sevoflurane and propofol.51,52 Both indices have been similarly reliable in the models tested. Accordingly, in the present study, there were no differences in the performance of these monitors at any time points in the Pk analysis. BIS, SE, and RE demonstrated low Pk values at LOR, but by 1 min after LOR, the values were already high, which demonstrates the delay observed in detecting LOR. An increase in all three indices was detected after the initial decrease, which may be related to painful stimulus caused by intubation. After steady state was achieved, all indices remained below their corresponding cutoff values, and importantly, the clinical status correlated uniformly with the information obtained from both monitors in our study. None of the subjects reported possible awareness during anesthesia. At emergence, the performance of these monitors was good in the analyses, although lower absolute values for these indices were observed at ROR than at LOR. Interestingly, the median value for SE at ROR was as low as 41, a value that is in the range for surgical anesthesia. Good performance in the analyses might be explained by the very low values during steady state, indicative of deep sedation. However, the performance in our study was tested only at few time points, and our healthy volunteers were not subjected to painful interventions, which resulted in quite low values in the indices during steady-state anesthesia.

It has been reported that instant change in an artificial EEG signal causes a 14-s lag in BIS to change from values indicating awareness to values indicating surgical hypnosis.54 It can therefore be assumed that, in addition to the computational delay, other causes for delay may exist. In our study, there was a rather wide interindividual variability in the time between the LOR and the index number indicating unconscious state. Agitation with ensuing muscle tone for some subjects may have caused this variability.

The actual changes in the raw EEG signal should always be considered when evaluating the usefulness of EEG-derived indices. For instance, the poor performance of these monitors with ketamine29 has been associated with a different profile of ketamine-induced EEG power spectral changes compared with anesthetics acting via γ-aminobutyric acid type A receptors.26 In earlier EEG studies, subanesthetic xenon has been shown to induce a decrease in alpha and beta activity and an increase in theta activity with unchanged delta band.35,36 However, there are much less data about the effects of surgical concentrations of single-agent xenon on the EEG spectrum. It has been shown in three healthy subjects that xenon inhalation, at concentrations sufficient to cause unconsciousness, increased theta and gamma activity with no change in the delta band.17 In that study, the subjects were allowed to recover immediately after LOR; therefore, a steady anesthetic state was likely not achieved. This may have caused the difference in the delta band between those previous observations and our findings. In fact, qEEG in the present study showed changes that resemble those induced by propofol.26 An increase in total power with frontal predominance was also observed in our study. In addition to increased power in the slow frequency bands, a relative increase in the alpha band was seen in the frontal areas. This finding is in strict contradiction to those observed during ketamine anesthesia.29 Recently, it has been suggested that the anesthetic mechanism of xenon might in fact differ from that of ketamine.37 It has been shown that xenon anesthesia induces a reduction in both regional cerebral glucose metabolism and blood flow.18,37 Ketamine induces quite different effects on cerebral metabolism and blood flow.38 Because the profile of EEG changes during xenon anesthesia are closer to those induced by propofol than those induced by NMDA-antagonistic regimens, the assumptions of different mechanism of action compared with other NMDA-antagonists are indirectly supported.

Xenon anesthesia has been shown to be associated with better preserved blood pressure and heart rate than, e.g., isoflurane-nitrous oxide or propofol anesthesia,5,59 even in patients with compromised myocardium.4 Similarly, in the present study, the induction and maintenance of anesthesia with xenon were associated with minor hemodynamic changes. In our subjects, 1.0 MAC anesthesia was not quite sufficient to blunt all hemodynamic responses to laryngoscopy and tracheal intubation. Indeed, it has been suggested that the 1.0 MAC value for xenon in young men might be closer to 70%.14 Six of our 17 subjects received a single bolus of the short-acting opioid remifentanil to attenuate the pain reaction induced by intubation. Considering the mean time interval between the opioid bolus and the extremely short half-life of remifentanil (approximately 3 min in healthy young men)50, it is unlikely that it would have affected the results. However, this possibility was taken into consideration in the statistical analysis of BIS,
Entropy, and hemodynamic data; importantly, remifentanil did not affect the results.

In an earlier study, the mean induction time with xenon was 71 s. The significantly longer time to LOR in patients emerging from xenon anesthesia is a logical result from the low blood/gas partition coefficient, and it has also been observed earlier.\(^4\)\(^5\) Induction with xenon caused agitation in five subjects, again an effect observed previously, predominantly in men.\(^6\) In our study, the frequency of nausea and vomiting was high, which has also been reported in other studies.\(^7\)\(^8\) Agitation and nausea may be related to NMDA antagonism, similar to ketamine.\(^9\)

In conclusion, BIS and SE performed well after steady state was achieved, but during induction and emergence, there were delays in detecting the clinical state. These results should be extrapolated with caution to a clinical setting as the volunteers were not subjected to noxious stimuli in our study. Surprisingly, xenon-induced changes in EEG closely resembled those induced by propofol.

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