Comparative evaluation of the cerebral state index and the bispectral index during target-controlled infusion of propofol

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Background. Cerebral state index (CSI) has recently been introduced as an intra-operative monitor of anaesthetic depth. We compared the performance of the CSI to the bispectral index (BIS) in measuring depth of anaesthesia during target-controlled infusion (TCI) of propofol.

Methods. Twenty Chinese patients undergoing general anaesthesia were recruited. CSI and BIS, and predicted effect-site concentration of propofol were recorded. The level of sedation was tested by Modified Observer’s Assessment of Alertness/Sedation Scale (MOAAS) every 20 s during stepwise increase (TCI, $0.5 \, \mu g \, ml^{-1}$) of propofol. The loss of verbal contact (LVC) and loss of response (LOR) were defined by MOAAS values of 2–3 and less than 2, respectively. Baseline variability and the prediction probability (PK) were calculated for the BIS and CSI. The values of BIS05 and CSI05, BIS50 and CSI50, BIS95 and CSI95 were calculated at each end-point (LVC and LOR).

Results. Baseline variability of CSI was more than that of BIS. Both CSI and BIS showed a high prediction probability for the steps awake vs LVC, awake vs LOR, and LVC vs LOR, and good correlations with MOAAS values.

Conclusion. Despite larger baseline variation, CSI performed as well as BIS in terms of PK values and correlations with step changes in sedation.


Keywords: anaesthesia, depth; anaesthetics i.v., propofol; monitoring, cerebral state index; monitoring, bispectral index

Accepted for publication: August 24, 2005

Electroencephalography has been introduced in anaesthesia to monitor the hypnotic state of patients. Different analytical concepts have been presented to quantify the changes in the electroencephalogram during anaesthesia. In 1992, the bispectral index monitor (BIS; Aspect Medical Systems, Newton, MA), became available; this monitor is based on the bispectral analysis that relies on the correlation of the phase between different frequency components of the electroencephalogram. The effects of anaesthetic drugs and the anaesthetized state on BIS monitoring have been well characterized. More recently, the cerebral state index (CSI) monitoring (CIF, Danmeter, Odense, Denmark) has been certified for clinical use in China. The value of CSI, like BIS, ranges from 0 to 100 (awake).

The aim of the current study was to give a first impression of the new CSI during target-controlled infusion (TCI) of propofol. In particular, we were interested in whether the CSI monitor is as reliable or better or worse than BIS monitor in reflecting changes during increasing propofol infusions and sedation levels, and whether CSI or BIS better predicted loss of verbal contact (LVC) and loss of response (LOR) during blood propofol concentrations held constant for 5 min.

Methods

Twenty patients, aged between 18 and 65 yr, ASA I or II, undergoing general anaesthesia were entered into the study. Approval was granted by the local institutional ethics committee and written informed consent was obtained from all the participants. Exclusion criteria were recent administration of sedative or opioid drugs, impairment of renal, hepatic, cardiac or respiratory function, and body weight less than 80% or greater than 120% of ideal weight.

All patients were pre-medicated with atropine 0.5 mg i.m. 30 min before induction of anaesthesia. After arrival in the induction room, standard monitoring was started. The skin of the forehead was prepared with isopropanol 70%, and BIS and CSI monitoring electrodes were positioned as recommended by the manufacturers. The electroencephalogram was recorded continuously using a BIS monitor (Aspect...
A-2000, Aspect Medical Systems, Newton, MA; version XP) and the CSI monitor (CSI™ Dannmeter, Odense, Denmark). The data were automatically recorded in intervals of 1–5 s. BIS values were recorded and transferred to computer hard disk for off-line analysis. The smoothing time period for the BIS monitor was set at 15 s. The values of CSI were recorded using the Dannmeter A/S CSM capture V2.02 onto the computer hard disk.

The anaesthesia was induced with a TCI of propofol starting at the target of 0.5 μg ml⁻¹; this was followed by a stepwise increase in TCI with each step increase amounting to 0.5 μg ml⁻¹ and maintained over 5 min. We used Diprifusor (software version 2; AstraZeneca), which contains the pharmacokinetic model described by Marsh and colleagues,6 for administering propofol. This system displays both the predicted blood propofol concentration and the effect-site propofol concentration. The model uses an equilibration rate constant, \( k_{eo} \), of 0.2 min⁻¹, which was defined as MOAAS values less than 2. Fentanyl and muscle relaxants were given 5 min after MOAAS values of 1–5 s. BIS values were recorded and transferred to the computer hard disk.

Heart rate (HR), non-invasive mean arterial pressure (MAP), and oxygen saturation were measured and registered at every point of measurement by Agilent A3 patient monitor (Agilent A3®, Agilent Technologies, Palo Alto, CA, USA). The predicted effect-site concentrations of propofol in TCI system were recorded when they increased by more than 0.1 μg ml⁻¹.

The baseline variability of BIS and CSI values was calculated by computing the coefficient of variation (CV) on the values that were obtained during the last 1 min before starting propofol infusion. Correlations were made between MOAAS and CSI, BIS, MAP and HR, and Spearman correlation coefficients were calculated. For BIS and CSI, we calculated the prediction probability (\( P_K \)) as described by Smith and colleagues.10,11 \( P_K \) was calculated as the Somers \( d \) statistic using SPSS version 12. The Somers \( d \) statistic was then rescaled from the −1 to +1 range of the Somers \( d \) statistic to the 0 to 1 range of \( P_K \) so that

\[
P_K = \frac{1 - (\text{Somers } d)}{2}.
\]

Assessment of the linear association between BIS, CSI or predicted effect-site concentrations and the probability of LVC and LOR were performed using logistic regression. A quantal response model (Probit analysis) was used to calculate \( E_{C05} \) (BIS05 or CSI05), \( E_{C50} \) (BIS50 or CSI50) and \( E_{C95} \) (BIS95 or CSI95) at each end-point (LVC and LOR) based on recordings of predicted effect site concentrations, CSI and BIS values. Statistical analyses were performed using the SPSS package (version 12.0; SPSS, Chicago, IL) and SigmaPlot (version 9.0). A \( P \)-value less than 0.05 was considered statistically significant.

### Results

We studied eight men and 12 women. The mean (sd) value of their age, weight and height were 37.7 (16.2) yr, 62.0 (3.8) kg, and 165 (6.5) cm, respectively. Induction of anaesthesia was smooth in all patients, although seven patients reported pain on injection of propofol. All measured data were included in the analysis.

The baseline (awake) values [mean (sd)] of CSI and BIS were 93.9 (5.0) and 95.3 (2.9), respectively. Compared with BIS, CSI had larger baseline variability as defined by the coefficient of variation (5.4 vs 3.3).

CSI and BIS decreased after induction of anaesthesia (Fig. 1). The increase in sedation (MOAAS decreasing from 5 to 0) was associated with decreases in the median values of CSI (from 90.2 to 40.1) as well as BIS (from 94.1 to 34.1). CSI correlated best with MOAAS \( (r=0.929) \), but the difference from BIS was not statistically significant (Table 2). The coefficients of correlation between MOAAS, and CSI and BIS, were higher than those between MOAAS, and MAP and HR (Table 2). CSI and BIS showed a high prediction probability \( (P_K>0.9) \) for the steps awake vs LVC, awake vs LOR, and LVC vs LOR. \( P_K \) was higher for CSI and BIS than for MAP and HR, and there were no significant differences in \( P_K \) values between CSI and BIS.

The probabilities of LVC and LOR vs predicted effect-site propofol concentrations are shown in Figure 2. The probabilities of LOV and LOR vs BIS and CSI are respectively shown in Figures 3 and 4. Good correlations between BIS and the predicted effect-site concentration of propofol \( (r^2=0.787, P<0.001) \) and between CSI and the predicted effect-site concentration of propofol \( (r^2=0.792, P<0.001) \) were noted. Predicted effect-site propofol concentrations, and the values of BIS and CSI at LVC and LOR for 5, 50 and 95% of the patients are shown in Tables 3 and 4, respectively.

### Discussion

This study was designed to compare the effect of induction of anaesthesia using propofol on the derived EEG variable CSI. The study demonstrates that induction with propofol alone resulted in a progressive decrease in CSI values, similar to a progressive decrease in BIS values, during decreasing values of MOAAS.
In this study, we compared CSI and BIS, as two measures of depth of anaesthesia, during increasing predicted effect-site concentration of propofol. Baseline variability can profoundly affect EEG-based pharmacodynamic estimation of parameters assessing depth of anaesthesia. Therefore, we calculated CV on the data before administering the anaesthetic. BIS showed the higher baseline stability between the two measures. Baseline variation might decrease the predictive ability of the univariate parameter, as stated by Bruhn and colleagues. Baseline variation was considered to be related to the smoothing times. Smoothing time of BIS monitor was 15 s and that for CSI monitor was around 10 s, the shorter smoothing time of CSI could have resulted in relatively increased variability.

Table 2 Spearman correlation coefficient (r) for the MOAAS and \( P_k \) for distinguishing different investigated states. SEE, standard error of the estimate; BIS, bispectral index; CSI, cerebral state index; HR, heart rate

<table>
<thead>
<tr>
<th>Spearman correlation</th>
<th>( P_k ) (SEE)</th>
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<tbody>
<tr>
<td>( R )</td>
<td>( P )-value</td>
</tr>
<tr>
<td></td>
<td>Awake vs LVC</td>
</tr>
<tr>
<td>BIS</td>
<td>0.915</td>
</tr>
<tr>
<td>CSI</td>
<td>0.929</td>
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<tr>
<td>HR</td>
<td>0.085</td>
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<tr>
<td>MAP</td>
<td>0.421</td>
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Fig 1 (A) BIS, (B) CSI, (C) HR and (D) MAP, during different sedation levels (MOAAS 5 to 0). To demonstrate the scatter of the data 95th, 90th, 75th, 50th, 25th, 10th, and 5th centiles are represented.

Fig 2 Predicted effect-site concentrations of propofol vs probability of loss of verbal contact and probability of loss of response.
One strategy to test a depth-of-anaesthesia monitor is to compare its performance with the clinically observed level of sedation in the patient. Using this approach, we studied CSI, BIS, MAP and HR during different sedation levels. We used the MOAAS because it provides a good correlation with different degrees of sedation and has been tested in many other studies. In this study, decreases in sedation level were associated with decreases in CSI and BIS. In contrast, changes in MAP and HR did not correlate well with the changes in MOAAS.

A depth-of-anaesthesia monitor should distinguish accurately between different steps of anaesthesia such as awake, LVC or LOR. Thus, for an index to be accurate, the values indicating different steps should not overlap. In this study, we used the $P_k$ to detect the accuracy of the two indices in distinguishing between the investigated steps of anaesthesia. A $P_k$ value of 0.5 would indicate that the index distinguishes between the two steps by 50:50 chance; a $P_k$ value of 1.0 would indicate a correct distinction with no overlap. Our study has shown that CSI and BSI have high prediction probability ($P_k>0.9$) for the steps awake vs LVC, awake vs LOR, and LVC vs LOR. But the $P_k$ values of CSI were not significantly different from BIS. Thus CSI, as an index of depth of anaesthesia, was able to distinguish all investigated states of anaesthesia as accurately as BIS.

We chose to study the Diprifusor system for TCI administration of propofol because it is widely available. It should be mentioned that we did not measure propofol blood/plasma concentrations but used calculated effect-site concentrations. We increased the target concentration of propofol by small increments every 5 min. There was insufficient time for the propofol to equilibrate with the brain. Equilibration of the effect-site with the blood concentration takes four to five times the $T_1/2 (ke)$, where $T_1/2 (ke)$=0.693/$ke$. The Diprifusor uses a $ke$ of 0.2 min$^{-1}$. Therefore, it will take approximately 15 min for blood and effect-site concentrations to equilibrate. Because of this there was considerable discrepancy between the predicted blood and effect-site concentrations, emphasizing that during induction and recovery the effect-site concentration is a more useful clinical correlate than the predicted blood concentration.

Several previous studies have evaluated the relationship of predicted effect-site propofol concentrations to investigated state of consciousness. These studies, unlike our study, showed large differences in $EC_{50}$ for effect-site propofol concentration at LOR. We believe that the differences in $EC_{50}$ can be caused by different criteria used for the clinical state of consciousness, and the different ethnic groups of patients. In this study, we found good correlations between BIS and the predicted effect-site concentration of propofol ($r^2=0.787$) and between CSI and the predicted effect-site concentration of propofol ($r^2=0.792$).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Predicted effect-site propofol concentrations and values of BIS and CSI at LVC for 5, 50 and 95% of patients. Values in parentheses are 95% CI. BIS, bispectral index; CSI, cerebral state index</th>
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<tbody>
<tr>
<td></td>
<td>EC_{0.05} (BIS_{0.05} or CSI_{0.05})</td>
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<tr>
<td>Predicted effect-site concentrations ($\mu$g ml$^{-1}$)</td>
<td>1.1 (0.7–1.3)</td>
</tr>
<tr>
<td>BIS</td>
<td>79.7 (77.0–84.0)</td>
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<tr>
<td>CSI</td>
<td>72.9 (71.1–75.5)</td>
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<tr>
<th>Table 4</th>
<th>Predicted effect-site propofol concentrations and values of BIS and CSI at LOR for 5, 50 and 95% of patients. Values in parentheses are 95% CI. BIS, bispectral index; CSI, cerebral state index</th>
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<td>EC_{0.05} (BIS_{0.05} or CSI_{0.05})</td>
</tr>
<tr>
<td>Predicted effect-site concentrations ($\mu$g ml$^{-1}$)</td>
<td>1.5 (1.1–1.7)</td>
</tr>
<tr>
<td>BIS</td>
<td>78.0 (73.3–85.2)</td>
</tr>
<tr>
<td>CSI</td>
<td>71.3 (67.9–76.3)</td>
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Ninety per cent of patients will have no response to verbal commands and will lose response at CSI between the CSI95 and the CSILO5 for these responses. For LVC, this range was 58.3–72.9 and for LOR it was 38.2–71.3; the corresponding ranges for BIS values were 55.8–79.7 and 35.6–78.0, respectively (Tables 3 and 4). The ranges for CSI are somewhat smaller than that of BIS. It is possible that CSI is slightly better than BIS in detecting LVC and LOR.

In this study, using a specific anaesthetic technique and a single anaesthetic agent, CSI and BIS show nearly similar variation, CSI performed as well as BIS in terms of PK and correlation with level of sedation. However, one study has shown CSI to be not sensitive in detecting LOR achieved with nitrous oxide. Therefore, further studies using other anaesthetic agents and other anaesthetic techniques are necessary to determine the future role of the CSI monitor.

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