Validation of the index of consciousness during sevoflurane and remifentanil anaesthesia: a comparison with the bispectral index and the cerebral state index

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Background. The purpose of this study was to validate a new level of consciousness monitor derived from the EEG, called the index of consciousness (IoC), by comparing it with the bispectral index (BIS) and the cerebral state index (CSI) during general anaesthesia for cardiac surgery using sevoflurane, remifentanil, and atracurium.

Methods. After ethical committee approval and written patient consent, data from 35 patients [31 males, four females, age 55 (10) yr] were recorded during general anaesthesia for elective cardiac bypass surgery. All patients were induced with sevoflurane 8%, until the Observer’s Assessment of Alertness and Sedation (OAAS) scale level 1 was reached, and then was set at a 1% end-tidal sevoflurane concentration. Subsequently, remifentanil and atracurium were administered, the trachea was intubated, and the procedure continued as usual. To assess accuracy, the prediction probability (Pk) was calculated both during induction and during maintenance.

Results. The Pk values [mean (SE)] for IoC, BIS, and CSI during induction were 0.90 (0.01), 0.90 (0.01), and 0.88 (0.01), respectively, whereas the corresponding Pk values during maintenance were 0.95 (0.01), 0.94 (0.01), and 0.60 (0.01).

Conclusions. The three indices performed equally well during the induction phase and were able to predict the level of consciousness of the patients satisfactorily. During maintenance, the IoC and the BIS showed good agreement with the clinical signs. The CSI was significantly influenced by the administration of atracurium; therefore, the agreement with the OAAS scale during the maintenance phase was significantly less for CSI than for IoC and BIS.

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Monitoring the level of consciousness during general anaesthesia can reduce the risk of awareness and may avoid excessively deep anaesthesia.1–5 Reduction in anaesthetics consumption and faster recovery has also been reported.6–7 A too deep anaesthesia might cause longer time until wake up and an increased drug consumption. It has also been reported that the survival rate after general anaesthesia might be affected by a very deep level of anaesthesia; however, this is a hypothesis which needs further research to be confirmed.8 Only when the applied neuromonitor systems are considered reliable, the anaesthetist can gain confidence in

1Declaration of interest. H. L. has been a non-paid consultant for both the CSM (Danmeter) and the IoC-view (Morpheus Medical) devices and he is a shareholder in Morpheus Medical, the manufacturers of the IoC.
monitoring the level of consciousness. In terms of statistics, this can be expressed as high sensitivity and specificity or as a high prediction probability (Pk). This means that the derived index shows a little overlap between values at the awake and the asleep state and ideally between different depth of anaesthesia levels.

The purpose of this study was to validate the index of consciousness (IoC, IoC-view, Morpheus Medical, Spain) by comparing it with the bispectral index (BIS, Aspect Medical, Newton, IL, USA) and the cerebral state index (CSI) (CSM, Danmeter, Odensee, Denmark) during general anaesthesia for cardiac surgery using sevoflurane, remifentanil, and atracurium.

**Methods**

After ethical committee approval and written patient consent, 35 consecutive patients were enrolled. The inclusion criteria were elective cardiac bypass surgery with extracorporeal circulation (ECC) and a left ventricular ejection fraction >35%. The exclusion criteria were dementia, stroke, or psychiatric medication. Anaesthesia was induced in all patients using sevoflurane 8 vol%, until the Observer’s Assessment of Alertness and Sedation (OAAS) scale level 1 was reached (no response to mild prodding and shaking). Then, sevoflurane administration was lowered to a 1 vol% end-tidal concentration. Five minutes after the patient had reached OAAS 1, atracurium 0.6 mg kg\(^{-1}\) and a continuous remifentanil infusion 0.3–0.5 μg kg\(^{-1}\) min\(^{-1}\) (after a bolus of 1 μg kg\(^{-1}\) in 1 min) were administered. Thereafter, the trachea was intubated and the standard surgical procedure was started. One minute after ECC was initiated, sevoflurane was set at 0.7 vol% directly into the cardiopulmonary machine while maintaining the remifentanil infusion at 0.3–0.5 μg kg\(^{-1}\) min\(^{-1}\). After separation from the ECC was completed, sevoflurane was set again at 1 vol% end-tidal in the anaesthesia machine while maintaining the remifentanil infusion at the same dose. The study was ended at the end of the surgery. The patient was transported out of the operating room (OR) before recovery of consciousness; therefore, it was not recorded.

As said, evaluation of the hypnotic component of anaesthesia was done using the responsiveness component of the OAAS scale. This is an assessment procedure involving a presentation of progressively more intense stimulation, ranging from a moderate speaking voice to physical shaking or moderate noxious stimulus (trapezius squeeze) until response is observed (5, responds readily to name spoken in normal tone; 4, lethargic response to name spoken in normal tone; 3, responds only after name is called loudly, repeatedly, or both; 2, responds only after mild prodding or shaking; 1, responds only after painful trapezius squeeze; and 0, no response after painful trapezius squeeze).

The IoC-view monitor recorded the EEG from three surface electrodes [middle forehead (+), left forehead (ref), and over left zygomatic bone (−)]. From the raw EEG, linear parameters (spectral analysis) and non-linear parameters (symbolic dynamics) were extracted and merged together with a logistic regression function combined with fuzzy rules to define the IoC. The IoC is a unitless scale from 99 (awake) to 0 (isoelectric EEG, coma) while adequate range for surgical anaesthesia is 60–40 as recommended by the manufacturer. The algorithm is described in more detail in the Appendix.

The CSI was recorded with the Cerebral State Monitor (CSI ver. 1.1). A more detailed description of the CSI can be found in the article by Jensen and colleagues.

The BIS was recorded with the A-2000 BIS monitor version XP. The three monitors have an EMG indicator, which indicates the electrical activity of the facial muscles on a scale from 0 to 100, when the patient is paralysed then the EMG indicator should decrease. The frequency ranges used for the estimation of the EMG is the following: $EMG_{BIS} = 70–110$ Hz, $EMG_{IoC} = 30–42$ Hz, and $EMG_{CSI} = 75–85$ Hz.

The skin was carefully prepared before attaching the electrodes. The electrodes were always positioned as recommended by the manufacturers. It was also ensured that the electrodes did not have any contact between each other in order to avoid interferences during the automatic measure of the impedance.

Vital signs [heart rate, pulse oximetry ($\text{SpO}_2$), and invasive arterial pressure] were recorded using an S/5 monitor (GE Healthcare, Helsinki, Finland). The data from the three neuromonitors and the S/5 monitor were recorded and stored in a PC using Rugloop II software (Demed, Temse, Belgium).

The level of consciousness was assessed by the OAAS every minute during the anaesthetic induction until the atracurium was administered by the same observer in all patients and who was blinded to the monitors. During ECC, when the effect of the neuromuscular blocking agents (NMBA) had ceased, the OAAS level of the patient was assessed again.

Just before each OAAS observation, measures of the IoC, BIS, and CSI were recorded. The OAAS observation was always carried out after the recording of the electroencephalographic indices in order not to bias the observations due to arousal.

The ability of the IoC, BIS, and CSI to describe loss of consciousness and anaesthetic depth was evaluated using prediction probability (Pk), which compares the performance of indicators having different units of measurements, as developed by Smith and colleagues. Pk was calculated using Somer’s $d$ test with linear transformation to the range of 0–1, where 1 corresponds to an exact prediction of the clinical scale, whereas 0.5 is not better than tossing a fair coin. After administration of atracurium, the OAAS cannot be assessed, hence during maintenance, the effect of the atracurium was allowed to wear off. Then, the OAAS was...
assessed twice in every patient, shortly before a new bolus of atracurium was administered. Separate Pk values were calculated for these measurements including a reference value at the awake state at OAAS 5, this value was termed Pk during maintenance. Therefore, this Pk calculation has the full range from anaesthetized to awake including OAAS levels 5, 1, and 0. The mean (sd) effect of atracurium on the three indices was defined as the difference in IoC/BIS/CSI value immediately before and 180 s after administration of atracurium. The average change in the EMG index after the atracurium administration in each of the three monitors was also assessed.

**Results**

All 35 patients completed the study and were compliant with the inclusion criteria [31 males, four females, age 55 (10) yr, ASA III, and left ventricular ejection fraction >35%]. Table 1 shows the results of the indices [mean (sd)] while awake and after anaesthetic induction. During induction, 5 or 6 OAAS evaluations were done. During maintenance, two OAAS evaluations were performed. Figure 1 shows the raw data used for the Pk calculations, including values registered both during induction and during maintenance.

There was no significant difference in performance among the three devices during the induction of anaesthesia according to the Pk values [0.90 (0.01); 0.88 (0.01); 0.90 (0.01) for IoC, CSI, and BIS, respectively].

During the maintenance phase, there was no significant difference between the IoC [0.95 (0.01)] and the BIS [0.94 (0.01)], whereas the CSI had a significantly (t-test \( P<0.05 \)) lower Pk [0.60 (0.01)]. The lower Pk for the CSI was due to high CSI values during maintenance, although all patients were deemed to be well anaesthetized with an OAAS \( \leq 1 \). During maintenance, at the time of assessment of OAAS (shortly before the administration of NMBA), none of the patients had an OAAS larger than 1. The administration of atracurium caused the EMG indicators to decrease on average 42, 48, and 47 in the EMG BIS, EMG IoC, and EMG CSI, respectively. Simultaneously, the CSI decreased more than 25 points in nine patients immediately after administration of NMBA, whereas BIS and IoC decreased <25 for all patients. The mean (sd) effect on BIS, IoC, and CSI due to administration of NMBA during maintenance was 10 (8), 12 (7), and 35 (20). Figure 2A shows an example of the effect of the facial muscle EMG on the three monitors. The IoC and the BIS were not significantly affected by the EMG whereas the CSI increased from values around 40 up to 95, while after administration of the NMBA, the CSI dropped down to values around 40 as before the EMG started to increase.

**Discussion**

This is a first study in the validation process of the IoC. The IoC was compared with the BIS and the CSI during
induction and maintenance of anaesthesia with sevoflurane and remifentanil. The BIS has been validated in a high number of articles whereas the CSI is a relatively new device as well.

The three monitors performed similar during the induction of anaesthesia clearly identifying when the patients scored an OAAS of 5 (awake) vs an OAAS of 1 (anaesthetized). During maintenance, the BIS and the IoC agreed with the clinical signs as assessed by the OAAS scale as proved by Pk values above 0.9. It has to be stated that the Pk value depends on the coarseness of the observer scale. If only two levels are used (awake/anaesthetized), the Pk tends to be high, often 0.99. If all levels from the OAAS scale are observed, then the Pk is unlikely to be larger than 0.96. Even lower values (around 0.7) can be observed if a very fine scale is used. Therefore, it is impossible to compare Pk values between studies. Although this is a shortfall of the Pk analysis, it remains a useful tool to compare the accuracy of several indices with different units to detect an independent variable within one study setting.

The CSI was in several cases significantly higher than what was expected according to the OAAS scale, as shown in Figure 2A. A bolus of 0.3 mg kg\(^{-1}\) of atracurium caused the CSI to decrease down to values in the range on general anaesthesia, i.e. 60 to 40. It has been reported in an article by Messner and colleagues\(^{15}\) that the BIS can also be influenced by NMBA, although the design of that study was different from good clinical practice, as the volunteers in the study were given NMBA while being awake. The NMBA might have some interaction with sevoflurane,\(^ {16}\) this has been reported before; therefore, a deepening in the anaesthetic level after the administration of NMBA cannot be excluded. The BIS and the IoC decreased 10 and 12 points on average, respectively, whereas the CSI decreased 35 on average. Moderate changes in the indices after NMBA administration could be explained by an NMBA–sevoflurane interaction affecting the level of consciousness of the patient, although this needs further studies to be confirmed. Major changes in the index, as observed in the CSI, cause ambiguity in the interpretation of the index, hence a low Pk value, because some index values while anaesthetized raise above those recorded while awake, as shown in Figure 2B.

None of the patients was awake before administration of atracurium, they were at these measurements without consciousness, with an OAAS level \(\leq 1\). Although a decrease was observed in all three EMG indices, care should be taken in the interpretation, as the definition and the frequency bands used for each EMG indicator are not the same. Therefore, a direct comparison of changes in EMG range for each monitor cannot be done.

Both the BIS and the IoC use measures of the complexity of the EEG. In the case of the BIS, the bispectral analysis of the EEG is used, which is a measure of the coupling among the frequencies in the EEG. The IoC applies the symbolic dynamics method, which establishes the complexity of the EEG, by converting the EEG samples into series of symbols. This is important for separating non-linear and linear components of the EEG, and probably also for separating the EEG from the EMG.

High concentrations of remifentanil were used in this study as the patients were undergoing cardiac anaesthesia. Remifentanil can cause muscle rigidity and could also increase the presence of EMG; therefore, it is possible that in this particular kind of anaesthesia, the EMG affects to a higher extent the CSI than in other anaesthetic techniques. Artifactual increase of the CSI due to EMG was also described by Hoymork and colleagues.\(^ {17}\)

This study is not an exhaustive validation of the IoC, for example, we did not study the performance of the monitors during recovery. A full validation is a multi-study process with progressive steps. Several more studies should be carried out validating the performance under different clinical conditions. Pharmacodynamic validation should be done both with inhalatory agents and i.v. anaesthesia. Resistance to artifacts from electrosurgery should
be tested, outcome studies validating if reduced recovery time, morbidities, or other factors are improved. The effect on the IoC of co-administration of other drugs such as N₂O or ketamine should also be explored. Finally, cost-effectiveness of the IoC should also be explored.

In conclusion, the IoC correlated well to the OAAS scale and to the BIS and showed acceptable resistance to the interference from the facial muscle EMG during general anaesthesia with sevoflurane and remifentanil for cardiac surgery.

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Appendix

Definition of IoC

The principal parameter of the IoC is the symbolic dynamics method. This method divides the EEG signals in a finite number of partitions and labels each partition with a symbol. The alternation of the symbols is what defines the symbolic dynamics. The symbolic dynamics is transforming a time series into a symbol sequence which provide a model for the orbits of the dynamical system via a space of sequences. For example, positive numbers use the symbol 1 and negative numbers use the symbol 0. Calculating attributes of the symbol sequence can reveal non-linear characteristics of the EEG. Symbolic Dynamics using two symbols can be represented by the formula below:

\[ S_j = \sum_{i=1}^{M-1} \left\{ \begin{array}{ll} 0 & \text{if} \left| u'_i - u'_{i+M-1} \right| \geq a + SD \\ 1 & \text{if} \left| u'_i - u'_{i+M-1} \right| < a + SD \end{array} \right. \quad J = 1, \ldots, N-M+1 \]

where \( u_i \) and \( u_{i+1} \) are subsequent samples, \( a \) is the standard deviation which is multiplied with the factor \( a \). Hence, if the difference between subsequent samples is larger than a factor multiplied on the \( SD \), then the symbol is defined as 0, on the contrary the symbol is defined as 1.

The symbolic dynamics detect the complexity of the EEG which makes it a correlate to the depth of anaesthesia. An analogy can be drawn to methods using entropy as this method also expresses the complexity of the EEG.

Apart from the symbolic dynamics, the IoC-view also integrates the beta-ratio during the superficial anaesthesia and the amount of suppression of the EEG (ESR, EEG suppression rate) in deep anaesthesia. These three parameters are combined through a discriminatory function in order to define the IoC-view index (Fig. A1A and B).

IoC-view scale

The IoC-view is a continuous processed EEG parameter that correlates to the patient’s level of hypnosis where decreasing IoC-view values correspond to gradually loss of consciousness and a deepening of the level of anaesthesia. In a unitless scale from 99 to 0, an index of 99 indicates an awake patient and an index of 0 indicates a flat EEG (Table A1). As with the other depth of anaesthesia monitors, the number of the index in this case IoC should not be used as the sole parameter for adjusting the anaesthetic dose.

<table>
<thead>
<tr>
<th>IoC</th>
<th>Clinical state</th>
</tr>
</thead>
<tbody>
<tr>
<td>99</td>
<td>Awake</td>
</tr>
<tr>
<td>80</td>
<td>Sedation</td>
</tr>
<tr>
<td>60</td>
<td>General anaesthesia</td>
</tr>
<tr>
<td>40</td>
<td>Deep anaesthesia</td>
</tr>
<tr>
<td>39</td>
<td>Isoelectric EEG</td>
</tr>
</tbody>
</table>

The IoC-view monitor

Figure A2 shows a representation of the IoC-view monitor. All the data obtained with the IoC-view monitor could be sent via Bluetooth to a handheld or a PC where they could be presented and recorded.

Electrode position

The IoC-view monitor requires three silver–silver chloride surface electrodes on the face of the patient. The positive
Electromyography

The monitor includes an EMG filter that eliminates most of the potential interfering EMG activity. The EMG bar shows the energy of the EMG level in the 30–45 Hz frequency band. The bar is situated on the left side of the display in blue colour. EMG activity can increase due to:

(i) reflex reactions to painful stimuli during the procedure;
(ii) need of muscular relaxation;
(iii) muscular rigidity.

The EMG bar should be checked frequently, especially in the case of a sudden increase in the IoC index. If the increase in the IoC is accompanied by an increase in muscular activity, there is a risk that EMG is causing interference. When this happens, special attention must be paid to the clinical signs of the patient during surgery.

References