Clinical Validation of the Cerebral State Monitor CSM

Updated February 13, 2005

CSM monitor is a non-invasive medical device approved/registered in Europe[1] and in the U.S.[2] for the monitoring of the level of consciousness in the brain through data acquisition from the EEG signals of the anaesthetized or sedated patient in all areas of the hospital. Further clinical validation takes place by professionals using the device in scientific and clinical studies. In this document we have compiled the current published abstracts, posters and papers. Several clinical studies are defined and/or initiated for the CSM. These will be included in an updated version of this document when available.

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[1] CE mark following the provisions of 93/42/EEC

[2] Food and Drug Administration (FDA) 510 K042315 Premarket Notification Clearance

Validation of the Cerebral State Monitor for assessing anaesthetic depth

Presentation Time: Tuesday, 9:15 a.m. - 10:45 a.m.

AUTHORS: **E. W. Jensen**[1], H. Litvan[2];
AFFILIATION: [1]CREB, Sant Pol de Mar, Spain, [2]Hospital Santa Creu y Sant Pablo, Barcelona, Spain.

Presentation Number: S-229

Introduction: The objective of this study was the validation of a new index, called Cerebral State Index (CSI) during cardiac anaesthesia. The CSI was defined using sub-parameters from the EEG as inputs of an adaptive neuro-fuzzy inference system (ANFIS). The advantage of ANFIS is that it does not assume an underlying mathematical function governing the causal relationship between the EEG values and the clinical state of the patient.

Methods: The study was approved by the local ethics committee. Fifteen patients, (12 male, 3 female, age 60-79 years) scheduled elective cardiac surgery were included in the study. Propofol was the only anaesthetic, administered using a TCI- pump (target 5 ug/ml plasma concentration during 5 min). CSI and BIS was monitored simultaneously and LOC defined as loss of response to a verbal command was assessed. After LOC, surgery was carried out according to the protocol of the department.

Results: Both CSI and BIS showed significant differences between awake and anaesthetised values as shown in the table (mean(SD)). During surgery, both BIS and CSI remained below 60 and in an interview 24 h after surgery none of the patients reported intra operative awareness

	CSI	BIS
Awake	92(5)	94(6)
LOC	55(4)	56(4)

Discussion: The results show that in this population depth of anaesthesia can be measured reliably by using a combination of parameters calculated from the frequency content of the EEG.

Cerebral State Index to Predict Patient Responsiveness During Sevoflurane Anesthesia. A Comparison With Bispectral Index

Presentation Time: Saturday, 11:30 a.m. - 1:00 p.m.

AUTHORS: **S. S. HO**, M. T. Chan, T. Gin;

AFFILIATION: The Chinese University of Hong Kong, Shatin, NT, Hong Kong Special Administrative Region of China.

Presentation Number: S-184

Introduction: The cerebral state index (CSI) is a novel indicator of anesthetic drug effect. It combines several electroencephalographic (EEG) parameters using the adaptive neuro-fuzzy inference system.[1] The purpose of this study is to compare the accuracy of CSI with bispectral index (BIS) to predict patient response during sevoflurane anesthesia.

Methods: This study was approved by ethics committee. Twenty patients (12 F: 8 M), ASA 1-2, aged 20-47 years, scheduled for general surgery gave written informed consents. Patients received increasing concentrations of sevoflurane via a tight fitting face mask, until they lost response to verbal command. CSI was measured by a cerebral state monitor (Danmeter, Odense A/S, Denmark), using Fpz-A1 montage. BIS (version 3.4) was recorded by a right frontal BIS-XP sensor, and was computed online by an A-2000 monitor (Aspect Medical, Newtown, MA). Ten minutes was allowed for equilibration before each step change (0.1%) in sevoflurane concentration. End-tidal CO_2 concentration was maintained at 3.5-4.0 vol%. Patient response was assessed by an blinded observer using the modified Observer's Assessment of Alertness/Sedation (OAA/S) scale.[2] Loss of response was defined as OAA/S score ≤ 2. Patient responses *vs* CSI or BIS were analyzed by logistic regression and sevoflurane concentration *vs* CSI or BIS was tested by nonlinear regression. The ability of CSI or BIS to detect OAA/S level was evaluated by prediction probability (P_K, ranging from 0-1), P_K of 1 indicates perfect prediction. Differences between indices were tested by Mann-Whitney test.

Results: Both CSI and BIS decreased with increasing concentration of sevoflurane (Figure A). The correlation coefficients were -0.83 and -0.79 for CSI and BIS, respectively. The values at which 50% (95% CI) of patients failed to respond to verbal command were 72 (69-75) for CSI and 69 (66-73) for BIS (Figure B). The P_K ($\pm$SE) values indicates similar accuracy of CSI (0.89 ± 0.04) and BIS (0.87 ± 0.03) to predict OAA/S scale.

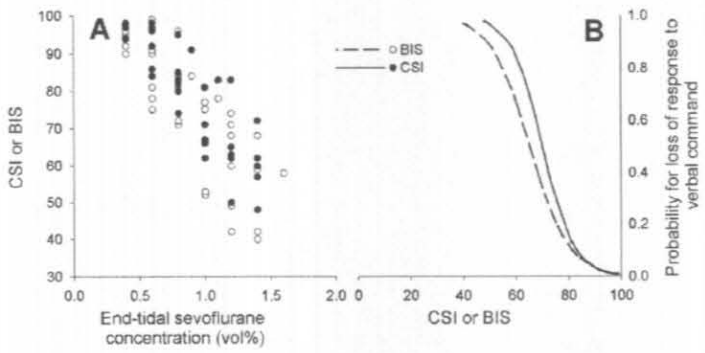
Discussion: During steady state conditions, we found that both CSI and BIS accurately detect the level of consciousness after sevoflurane anesthesia.

Reference:

1. IEEE Trans Syst Man Cybern 1993,23:665-685.

2. J Clin Psychopharmacol 1990;10:244-51.

Figure. Changes of CSI and BIS at different sevoflurane concentration (A). Probability of loss of response to verbal command as a function of CSI and BIS (B).



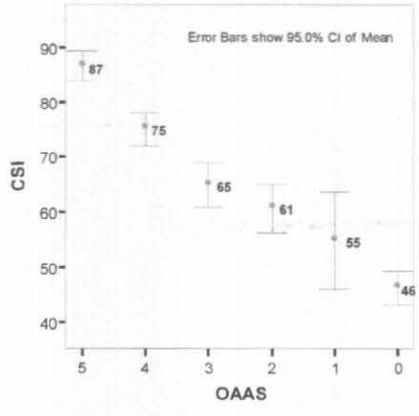
Abstract Title: **Definition of a new index for depth of anesthesia using EEG sub-parameters combined by fuzzy logic.**

Authors: **BE Rodriguez, MSc[1], EW Jensen, PhD[1], P Martinez, MSc[1], H Litvan, MD, PhD[1], MMRF Struys, MD, PhD[2]**
[1]Cardiac Anesthesia Research Unit, Hospital Santa Creu I Sant Pau, Barcelona, Spain
[2]Gent University Hospital, Gent, Belgium

Background and Goal of Study. The objective of this study was to show that a reliable index for assessing consciousness in anaesthetised patients could be defined using sub-parameters from the EEG as inputs of an adaptive neuro-fuzzy inference system (ANFIS). The advantage of ANFIS is that it does not assume an underlying mathematical function governing the causal relationship between the EEG values and the clinical state of the patient. The performance of the new index, called Cerebral State Index (CSI), was evaluated in a retrospective study.

Materials and Methods. After Gent Hospital Ethics Committee approval, informed consent was obtained from 20 ASA I female patients (18-60 years), scheduled for ambulatory gynecologic surgery. The data has recently been published in another study[1]. Propofol infusion was initiated until the patient had no response to noxious stimuli (Observer's Assessment of Alertness and Sedation scale (OAAS) 0). OAAS level was estimated every 4min. and the effect-site concentration for propofol was calculated using the Schnider model. Four EEG sub-parameters (beta ratio=$\log(E_{30\text{-}42.5Hz}/E_{11\text{-}21Hz})$, alpha ratio=$\log(E_{30\text{-}42.5Hz}/E_{6\text{-}12Hz})$, beta – alpha ratio=$\log(E_{6\text{-}12.5Hz}/E_{11\text{-}21Hz})$ and Burst Suppression) were used to define the inputs to the fuzzy system. The output of the fuzzy system is the CSI.

Results and Discussions. The prediction probability (Pk) between the CSI and OAAS was 0.92. The figure shows the box plot of the CSI versus the OAAS for the data set.



Conclusion. The results show that in this population depth of anaesthesia can be measured reliably by using a combination of parameters calculated from the frequency content of the EEG.

References. 1.Struys MMRF et al. *Anesthesiology* 2002; 96:803-16

Definition of a new Index for Depth of Anaesthesia using
EEG sub-parameters combined by Fuzzy Logics. Poster presented at EuroSIVA 2004.

Please find the poster as a separate page.

Definition of a new Index for Depth of Anaesthesia using EEG sub-parameters combined by Fuzzy Logics

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Introduction

The objective of this study was to show that a reliable index for assessing consciousness in anaesthetised patients could be defined using sub-parameters from the EEG as inputs of an adaptive neuro-fuzzy inference system (ANFIS).

The advantage of ANFIS is that it does not assume an underlying mathematical function governing the causal relationship between the EEG values and the clinical state of the patient.

The performance of the new index, called Cerebral State Index (CSI), was evaluated in a retrospective study.

Methods I[1]

- 20 ASA I female patients aged 18-60yrs scheduled for gynaecological surgery (Gent Hospital Ethics Committee approval and informed consent).
- The patients were anaesthetised with a continuous infusion of propofol (Fresenius Modular DPS Infusion Pump connected to a Fresenius Base A, Fresenius Vial Infusion Systems, Brézins, France) controlled via RUGLOOP software (Demed, Belgium).
- The initial propofol target effect-site concentration was set at 1.5µg/ml and was increased every 4 minutes by 0.5µg/ml until loss of all relevant clinical signs.
- The level of consciousness was assessed before each increase in target concentration using the modified Observers Assessment of Alertness and Sedation (OAAS) scale.

Position of the A-line and BIS electrodes

- Raw EEG was recorded throughout the procedure with an A-line® monitor (Scientific Version 1.4, Danmeter A/S, Odense, Denmark). The A2000 BIS® Monitor (Aspect Medical Systems Inc., Newton, MA) was also attached to the patient.

Methods II

EEG sub-parameters

Four sub-parameters were calculated from the EEG signals:

$$\beta_{ratio} = \log \frac{E_{30\text{-}47.5Hz}}{E_{11\text{-}21Hz}}$$

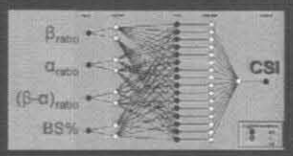
$$\alpha_{ratio} = \log \frac{E_{30\text{-}47.5Hz}}{E_{8\text{-}12Hz}}$$

$$(\beta-\alpha)_{ratio}$$

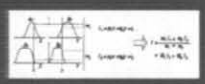
Burst Suppression Rate

ANFIS Model structure

The sub-parameters define the inputs to the ANFIS (Adaptive Neuro Fuzzy Inference System) structure[2].



ANFIS network scheme



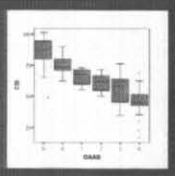
Sugeno-type fuzzy logic

The ANFIS system was trained with the *leave-one-out* method: 19 patients (training), 1 patient (validation)[3].

Results

The prediction probability (Pk) between the CSI and OAAS was 0.92.

The figures show the box and error plots for the CSI versus the OAAS for the data set.



CSI vs OAAS boxplot

CSI vs OAAS error plot

P_K for OAAS Scale	
Bispectral Index	0.93 (0.01)
Cerebral State Index	0.92 (0.01)
AAI version 1.4	0.89 (0.02)

Conclusions

The results show that in this population depth of anaesthesia can be measured reliably by using a combination of parameters calculated from the frequency content of the EEG.

The Pk of the ANFIS combination of β_{ratio}, α_{ratio}, $(\beta-\alpha)_{ratio}$ and BS% was comparable to the Pk of other indexes for measurement of the level of consciousness like the AAI and BIS.

The CSI showed a significant difference between the OAAS levels 0 and 1 ($p<0.05$).

The advantage of the ANFIS method is that it does not assume any underlying physical laws governing the causal relation between the sub-parameters and the clinical state, rather it defines the fuzzy-rules based on the training data.

References

1. MMRF Struys et al. *Performance of the ARX-derived Auditory Evoked Potential Index as an Indicator of Anesthetic Depth.* Anesthesiology 2002;96:803-16
2. Jang JSR, *ANFIS.* IEEE Trans Systems, Man and Cybernetics, 1993;23:665-85
3. EW Jensen et al. *OAAS Surface Model for Anesthetic Drug Interaction using a Fuzzy Inference System.* ISAP 2003 Conference.