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Diagnostic and prognostic use of bispectral index in coma, vegetative state and related disorders

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Abstract

Primary objective: This study investigates (1) the utility of the bispectral index (BIS) to distinguish levels of consciousness in severely brain damaged patients and, particularly, disentangle vegetative state (VS) from minimally conscious state (MCS), as compared to other EEG parameters; (2) the prognostic value of BIS with regards to recovery after 1 year.

Research design: Multi-centric prospective study.

Method and procedures: Unsedated patients recovering from coma were followed until death or transferal. Automated electrophysiological and standardized behavioural assessments were carried out twice a week. EEG recordings were categorized according to level of consciousness (coma, VS, MCS and Exit MCS). Outcome was assessed at 1 year post-insult.

Main outcomes and results: One hundred and fifty-six EEG epochs obtained in 43 patients were included in the analyses. BIS showed a higher correlation with behavioural scales as compared to other EEG parameters. Moreover, BIS values differentiated levels of consciousness and distinguished VS from MCS while other EEG parameters did not. Finally, higher BIS values were found in patients who recovered at 1 year post-insult as compared to patients who did not recover.

Conclusion: EEG-BIS recording is an interesting additional method to help in the diagnosis as well as in the prognosis of severely brain injured patients recovering from coma.

Keywords: *Bispectral Index, electroencephalography, coma, vegetative state, minimally conscious state, brain injury*

Introduction

The assessment of consciousness level in severely brain damaged patients represents a real challenge. As opposed to coma, patients in a vegetative state (VS) open their eyes, indicating restoration of sleep–wake cycles, and recover other autonomous functions such as spontaneous breathing. However, these patients fail to show any voluntary motor activity [1], which is not the case of minimally conscious patients (MCS). Patients in a MCS show limited but reproducible signs of voluntary movements such as orientated responses to noxious stimulation, visual fixation or pursuit, response to verbal command or context-specific emotional behaviour [2]. Finally, emergence from MCS (EMCS) is defined by the return of functional communication or object use [2]. The distinction between conscious and unconscious state and, hence, between vegetative and minimally conscious state is mainly based on

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bedside behavioural examination. However, tracheotomy and artificial ventilation, severe motor disability, fluctuations in level of arousal and reduced attentional capacities make the assessment for identifying voluntary movements often very difficult. A high percentage of misdiagnoses has been reported in several studies (~30% of patients diagnosed as VS actually are MCS) [3, 4] and may have major consequences on patient management and therapeutic decisions [5].

For this reason, additional objective measurement tools are needed for achieving more accurate diagnoses. Electrophysiological measures which permit bedside assessment could be particularly helpful since they present the advantage of directly and objectively recording spontaneous brain activity at each level of consciousness without requiring any behavioural response by the patient. Traditional electroencephalographic (EEG) measures have shown their efficiency in predicting outcome after anoxic or traumatic brain damage [6–10]. However, disentangling the altered states of consciousness solely based on EEG recording is currently not possible [11] and analyses require expertise and time. The EEG bispectral index (BIS) could be an interesting alternative [12]. The BIS is a variable statistically and automatically derived from the EEG, originally designed and validated as a measure of depth of anaesthesia and sedation. The set of algorithms used to calculate the BIS is empirically derived from three main EEG parameters: (1) the ratio of the power in the beta ranges provided by frequency analysis, (2) the ratio of the bicoherence in fast and slower frequencies provided by bispectral analysis [13] and (3) the burst suppression ratio—the proportion of isoelectric signal provided by time domain analysis. The BIS is normalized on a scale of 0 (isoelectric signal) to 100 (patient fully aroused). The values range from 40–55 when the patient is considered as unconscious during general anaesthesia [14]. Low BIS values have also been observed during other diminished states of consciousness such as natural sleep [15, 16]. Recently, attempts have been made to assess the usefulness of BIS monitoring [17, 18] in the case of severe brain injury. However, these studies did not directly investigate the ability of the BIS to determine the level of consciousness and, more precisely, to disentangle VS from MCS. The first aim of the present study will be, hence, to investigate the capacity of the BIS to disentangle the altered states of consciousness with a special focus on the differentiation between VS and MCS as compared to other EEG parameters. This study was also interested in the prognostic value of BIS and, particularly, the prognostic value of BIS as regards to recovery at 1 year post-insult.

Materials and methods

Patients recovering from coma were followed by an experienced neuropsychologist (CS) by means of EEG-BIS measurements in addition to repeated behavioural assessments (including the Glasgow Coma Scale and the Coma Recovery Scale–Revised; see below). Inclusion criteria were: aged >18 years; no significant neurological or neurosurgical history; absence of centrally acting drugs or neuromuscular function blockers 24 hours prior to study; diagnosed as comatose [19] or in a VS [1] or MCS [2] as defined by international criteria and caused by any aetiology (i.e. traumatic and non-traumatic injury). Behavioural assessment started at the intensive care unit 24 hours after the sedation was interrupted. Patients were evaluated twice a week (interval between assessments was 3 days) and were followed until transferral, EMCS [2] or death. Participating centres were intensive care, neurology and neurorehabilitation units of the 'Sart Tilman' university hospital and the 'Citadelle' regional hospital of Liège. Information on each patient's outcome was collected by phone at 1 year post-insult using the Glasgow Outcome Scale (GOS) [20]. The study was approved by the Ethics Committee of the Medicine Faculty of the University of Liege and written informed consent was obtained by the patients' legal surrogates.

EEG measurements

After skin preparation with isopropyl alcohol, EEG-BIS pads were placed in a standard frontal bipolar montage with a ground electrode placed on the temple and two electrodes placed on the centre of the forehead and connected to the A-2000 BIS monitor (Aspect Medical Systems, Newton, USA). Data were sampled at 256 Hz and filtered with an analogue bandpass filtering of 0.3–70 Hz. The A-2000 monitor provides a continuous output of the raw EEG pattern and divides the raw EEG data into 2 second epochs. At least eight epochs of 'clean' EEG data are required to calculate the BIS (the minimum 'smoothing period' is 15 seconds). Given that drowsiness is associated with reduced BIS values [15, 16], recordings began 5 minutes after sustained auditory and noxious stimulation (as employed in the GCS) [21]. Each measurement lasted 28 ± 10 minutes. The following EEG parameters were automatically derived by the A-2000 BIS monitor (Aspect Medical Systems, Newton, USA) and collected on a laptop computer for subsequent offline analyses: BIS; spectral edge frequency (SEF95; the frequency below which 95% of the total EEG power resides); total EEG power (TOTPOW; the sum of the different frequency ranges obtained during the EEG recording); frontal spontaneous electromyography

(F-EMG; the percentage of changes in frontal muscle activity). Data were excluded if (1) electrode impedances were superior to 10 kΩ; (2) contaminated by gross artifact, such as eye movements; (3) contaminated by major EMG activity (i.e. F-EMG ≥70 Hz); (4) signal quality index was <80% (SQI; quantified as the percentage of the prior 60 seconds of data usable for calculation of EEG spectral variables); (5) low sedation was administered to the patient in order to decrease pain, less than 24 hours prior to the recording.

Clinical measurements

In parallel to EEG measurement, a behavioural assessment was performed in order to determine patients' consciousness level using standardized coma scales such as the Glasgow Coma Scale (GCS) [21] and the Coma Recovery Scale–Revised (CRS-R) [22]. The GCS score represents the sum of three sub-scores (eye opening sub-scale, motor sub-scale and verbal response sub-scale) and is scored from 3 (worst) to 15 (best). The CRS-R had been specifically developed to differentiate VS from MCS patients but also MCS from patients who emerged from this state. It consists of 23 hierarchically arranged items that comprise six sub-scales addressing arousal, auditory, visual, motor, oromotor/verbal and communication functions. The lowest item on each sub-scale represents reflexive activity while the highest item represents cognitively-mediated behaviours. The French adaptation of the CRS-R [23] was employed here.

Statistical analysis

Using the mixed model approach of SAS (SAS Institute Inc., Cary, NC) [24], the behavioral scores obtained using the GCS and the CRS-R were first correlated with the EEG parameters that were collected (BIS, SEF95, TOTPOW, F-EMG), in order to determine the relationship between behavioural scales which assess the consciousness level and EEG parameters.

To detect which parameter differentiates the altered states of consciousness, the EEG parameters obtained in this study (BIS, SEF95, TOTPOW, F-EMG) were tested with mixed repeated measures ANOVAs with consciousness status (coma, VS, MCS, EMCS) as between-subject factor. Significant results were further explored using Tukey post-hoc analyses in order to identify, more specifically, which parameter disentangles VS from MCS patients.

Simple ANOVA were also used to test whether the BIS recorded during the first assessment was different between patients with a good recovery (GOS 3–5) and patients with a bad recovery (GOS 1–2) after 1 year.

Results

Forty-three patients (mean age of 58 ± 19) were enrolled in this study. The aetiology was traumatic in 16 patients; non-traumatic cases included post-anoxic-ischemic encephalopathy ($n = 10$), ischemic or haemorrhagic stroke ($n = 8$), aneurismal subarachnoid haemorrhage ($n = 2$), metabolic encephalopathies ($n = 2$), status epilepticus ($n = 2$) and encephalitis ($n = 3$). Among all the patients, 23 died (GOS 1), two stayed in a VS (GOS 2), three showed a severe disability (GOS 3), nine showed a moderate disability (GOS4) and five had a good recovery (GOS 5). Patients were followed from 1–11 weeks (i.e. 6 ± 5 evaluations per patient) and assessments were carried out 9 ± 10 days after onset]. A total of 274 observations comprising EEG measurements and behavioural evaluations were made in 43 patients. The statistical analysis was, however, restricted to the first 6 consecutive weeks post-insult in order to limit variability in the total observation periods. Additionally, 44 recordings were excluded because EEG data were of sub-optimal quality (SQI < 80%) and 38 were excluded because patients received low sedation in order to decrease pain within the prior 24 hours. Hence, 156 observations were used for further analysis. Table I summarizes behavioural and EEG measures in the four groups (i.e. coma, VS, MCS, EMCS). The correlation analysis showed that the BIS parameter had the highest correlation with both behavioural scales (Table II).

The mixed model ANOVA revealed significant differences for BIS ($F = 15.9$; $p < 0.001$), SEF95 ($F = 6.6$; $p < 0.001$) and F-EMG ($F = 9.0$; $p < 0.001$) as a function of level of consciousness state (Coma, VS, MCS and EMCS). Post-hoc analysis revealed that the BIS differentiates VS from MCS groups ($t = 3.6$; $p < 0.001$) (Figure 1), whereas SEF95 and F-EMG failed to do so. Additionally, a simple ANOVA was performed to test whether the BIS could be different according to aetiologies such as traumatic ($n = 16$), anoxic ($n = 10$) or others ($n = 17$). No significant results were obtained.

Finally, significantly higher BIS values were observed during the first recording for patients who had a good recovery (78 ± 16) as compared to patients who had a bad recovery after 1 year (62 ± 25) ($F = 5.64$; $p = 0.02$).

Conclusion

The objectives of this study were to investigate (1) the capacity of the BIS to disentangle altered states of consciousness and, particularly, VS from MCS,

Table I. EEG and behavioural measurements in the different clinical entities (mean ± SD).

Clinical entity	Number of evaluations	Number of patients	GCS	CRS-R	BIS	SEF95	TOTPOW	F-EMG
COMA	22	16	4 ± 1	2 ± 1	54 ± 23	10 ± 6	60 ± 5	39 ± 7
VS	32	13	6 ± 1	6 ± 2	63 ± 15	10 ± 4	60 ± 5	42 ± 6
MCS	81	30	10 ± 2	12 ± 4	80 ± 16	13 ± 6	60 ± 4	45 ± 6
EMCS	21	13	14 ± 1	21 ± 2	90 ± 11	21 ± 17	48 ± 3	50 ± 10

VS = vegetative state; MCS = minimally conscious state; EMCS = exit from MCS; GCS = Glasgow Coma Scale; CRS-R = Coma Recovery Scale-Revised; BIS = bispectral index (arbitrary values); SEF95 = 95% spectral edge frequency (in decibels); TOTPOW = total EEG power; F-EMG = frontal spontaneous electromyography (70–110 Hz).

Table II. Correlation coefficients between behavioural and EEG measurements.

	BIS	SEF95	TOTPOW	F-EMG
GCS score	0.60	0.41	−0.05	0.49
CRS-R score	0.57	0.45	−0.12	0.46

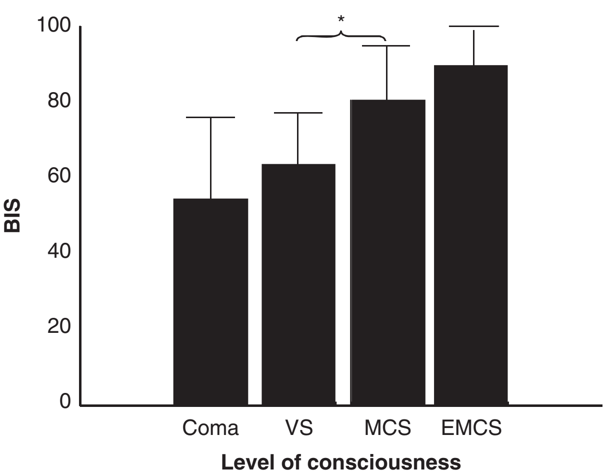

Figure 1. Mean (SD) of BIS values in comatose, vegetative (VS), minimally conscious (MCS) and exit from MCS (EMCS) patients. Asterisk marks significant difference between VS and MCS groups ($p < 0.05$).

compared to other EEG parameters; and (2) the prognostic value of BIS as regards recovery at 1 year.

As regards the first objective and according to the results, the BIS permits to differentiate VS from MCS patients. Indeed, BIS values were significantly lower in VS patients as compared to MCS patients. This finding is consistent with previous case reports which showed a decrease in BIS values after loss of consciousness due to transitory cerebral ischemia [25], hypoglycemia [26, 27] or epilepsy [28, 29]. This result is also in line with the positive correlation that was found between the BIS and the scores at the behavioural scales, suggesting that the higher the BIS, the higher the consciousness level assessed by the behavioural scales. Additionally, it was noticed that BIS values, relative to other EEG parameters, were most strongly correlated with the CRS-R scores. The CRS-R is a sensitive behavioural scale which was developed to differentiate VS from MCS [22]. Previous studies having mainly shown a correlation between the BIS and the GCS [17, 18], this study is therefore the first to show a correlation between the BIS and a sensitive diagnostic scale such as the CRS-R. Moreover, it was found that other parameters such as variables provided by frequency analyses (i.e. SEF95, TOTPOW) or frontal muscle activity (i.e. F-EMG) were not found to be helpful in the distinction between VS and MCS. The BIS is therefore the only parameter which permits this distinction. A potential explanation of this apparent higher efficacy of the BIS score is that information given by the decomposed EEG parameters considered in this study is not sufficient in itself for differentiating MCS and VS (although one should note that SEF-95 and F-EMG were more generally associated with levels of consciousness, as shown by the mixed repeated measures ANOVA analyses). On the contrary, the BIS integrates information coming from different analyses and parameters and reflects therefore a more complete EEG analysis, enabling one to differentiate the two groups (here, VS and MCS).

A limitation of this study could be the absence of consideration for the patients' aetiology. However, these results did not show any difference in BIS values according to the aetiology, suggesting that this technique can be used in traumatic or non-traumatic patients without distinction. Given the frontal BIS montage, one could nevertheless expect differences between traumatic and non-traumatic aetiologies. In the case of traumatic aetiology, frontal lesions are very common, whereas diffuse brain lesion is more typically observed with non-traumatic aetiologies such as anoxia or metabolic encephalopathies. Observing a lower BIS in traumatic patients (note that 13 out of our 16 post-traumatic patients showed a frontal lesion) would therefore not be surprising. The observed absence of differences in BIS values between aetiologies might be related to the fact that frontal EEG electrodes not only record the signal coming from the fronto-polar area but also are influenced by the functional neuronal integrity form other—long-distance—brain areas [30]. Furthermore, studies in VS and MCS have shown that even in the absence of structural frontal lobe damage as evidenced by CT or MRI scanning, PET imaging classically shows metabolic dysfunction in frontal associative cortices [31]. Further studies would have nevertheless to be performed in order to comfort the absence of differences in BIS values according to the aetiology.

As regards the second objective, higher BIS values were found during the first assessment for patients who showed bad outcome (i.e. GOS 1 or 2) at 1 year post-insult compared to patients who recovered (i.e. GOS > 2). This suggests that the BIS recorded during the first 2 weeks following the brain lesion provide potentially useful information on the patient's outcome 1 year later. This is in line with recent studies which showed a relation between BIS values recorded in severely brain injured patients and the outcome at, respectively, 3 and 6 months [32, 33]. It should be noted that most of these patients with bad outcome died. Future studies including a larger group of patients are hence warranted to confirm these results.

In conclusion, to the best of the authors' knowledge, the present study is the first to demonstrate (1) the usefulness of automated EEG analysis such as bispectral index measures for disentangling levels of consciousness, such as VS and MCS and (2) the prognostic interest of this technique as regards the recovery of consciousness 1 year post-insult. The results show that the EEG-BIS recording is an interesting additional method for helping clinicians as regards diagnosis as well as prognosis of severely brain injured patients recovering from coma. Nevertheless, the commercially available BIS monitoring was used here, which may employ different mathematical algorithms at any given time and does not permit the user to know the exact EEG parameters which were taken into account in its calculations. Future studies employing open-source techniques such as EEG-entropy measurements [34, 35] as an alternative to disentangle levels of consciousness and, more exactly, the VS from the MCS patients are hence warranted.

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References

1. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (1). New England Journal of Medicine 1994;330:1499–1508.
2. Giacino J, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD, Zasler ND. The minimally conscious state: definition and diagnostic criteria. Neurology 2002;58:349–353.
3. Childs NL, Mercer WN, Childs HW. Accuracy of diagnosis of persistent vegetative state. Neurology 1993;43: 1465–1467.
4. Andrews K, Murphy L, Munday R, Littlewood C. Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. British Medical Journal 1996;313: 13–16.
5. Gill-Thwaites H. Lotteries, loopholes and luck: Misdiagnosis in the vegetative state patient. Brain Injury 2006;20: 1321–1328.
6. Zandbergen EG, de Haan RJ, Stoutenbeek CP, Koelman JH, Hijdra A. Systematic review of early prediction of poor outcome in anoxic-ischaemic coma. Lancet 1998;352: 1808–1812.
7. Young GB. The EEG in coma. Journal of Clinical Neurophysiology 2000;17:473–485.
8. Brenner RP. The interpretation of the EEG in stupor and coma. Neurologist 2005;11:271–284.
9. Husain AM. Electroencephalographic assessment of coma. Journal of Clinical Neurophysiology 2006;23: 208–220.
10. Koenig MA, Kaplan PW, Thakor NV. Clinical neurophysiologic monitoring and brain injury from cardiac arrest. Neurology Clinics 2006;24:89–106.
11. Kulkarni VP, Lin K, Benbadis SR. EEG findings in the persistent vegetative state. Journal of Clinical Neurophysiology 2007;24:433–437.
12. Johansen JW, Sebel PS. Development and clinical application of electroencephalographic bispectrum monitoring. Anesthesiology 2000;93:1336–1344.
13. Barnett TP, Johnson LC, Naitoh P, Hicks N, Nute C. Bispectrum analysis of electroencephalogram signals during waking and sleeping. Science 1971;172:401–402.
14. Rampil IJ. A primer for EEG signal processing in anesthesia. Anesthesiology 1998;89:980–1002.
15. Sleigh JW, Andrzejowski J, Steyn-Ross A, Steyn-Ross M. The bispectral index: A measure of depth of sleep? Anesthesia and Analgesia 1999;88:659–661.

16. Nieuwenhuijs D, Coleman EL, Douglas NJ, Drummond GB, Dahan A. Bispectral index values and spectral edge frequency at different stages of physiologic sleep. Anesthesia and Analgesia 2002;94:125–129, table of contents.
17. Gill M, Green SM, Krauss B. Can the bispectral index monitor quantify altered level of consciousness in emergency department patients? Academic Emergency Medicine 2003; 10:175–179.
18. Gilbert TT, Wagner MR, Halukurike V, Paz HL, Garland A. Use of bispectral electroencephalogram monitoring to assess neurologic status in unsedated, critically ill patients. Critical Care Medicine 2001;29:1996–2000.
19. Plum F, Posner JB. The diagnosis of stupor and coma. 1st ed. Philadelphia: Davis, F.A.; 1966.
20. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480–484.
21. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2: 81–84.
22. Giacino J, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: Measurement characteristics and diagnostic utility. Archives of Physical Medicine and Rehabilitation 2004;85:2020–2029.
23. Schnakers C, Majerus S, Laureys S. Diagnosis and investigation of altered states of consciousness. Reanimation 2004;13: 368–375.
24. Hamlett A, Ryan L, Wolfinger R. On the use of PROC MIXED to estimate correlation in the presence of repeated measures. Proceedings of the Twenty-Ninth Annual SAS® Users Group International Conference. SAS Institute Inc.; 2004. p 198.
25. Myles PS, Cairo S. Artifact in the bispectral index in a patient with severe ischemic brain injury. Anesthesia and Analgesia 2004;98:706–707, table of contents.
26. Wu CC, Lin CS, Mok MS. Bispectral index monitoring during hypoglycemic coma. Journal of Clinical Anesthesia 2002;14:305–306.
27. Vivien B, Langeron O, Riou B. Increase in bispectral index (BIS) while correcting a severe hypoglycemia. Anesthesia and Analgesia 2002;95:1824–1825.
28. Tallach RE, Ball DR, Jefferson P. Monitoring seizures with the Bispectral index. Anaesthesia 2004;59:1033–1034.
29. Chinzei M, Sawamura S, Hayashida M, Kitamura T, Tamai H, Hanaoka K. Change in bispectral index during epileptiform electrical activity under sevoflurane anesthesia in a patient with epilepsy. Anesthesia and Analgesia 2004;98: 1734–1736, table of contents.
30. Nuwer MR, Comi G, Emerson R, Fuglsang-Frederiksen A, Guérit JM, Hinrichs H, Ikeda A, Luccas FJ, Rappelsberger P. IFCN standards for digital recording of clinical EEG. The International Federation of Clinical Neurophysiology. Electroencephalograpy and Clinical Neurophysiology Supplement 1999;52:11–14.
31. Laureys S, Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. Lancet Neurology 2004;3:537–546.
32. Shibata S, Imota T, Shigeomi S, Sato W, Enzan K. Use of the bispectral index during the early postresuscitative phase after out-of-hospital cardiac arrest. Journal of Anesthesiology 2005;19:243–246.
33. Fabregas N, Gambus PL, Valero R, Carrero EJ, Salvador L, Zavala E, Ferrer E. Can bispectral index monitoring predict recovery of consciousness in patients with severe brain injury? Anesthesiology 2004;101:43–51.
34. Rosso OA. Entropy changes in brain function. International Journal of Psychophysiology 2007;64:75–80.
35. Bein B. Entropy. Best Practice Research in Clinical Anaesthesiology 2006;20:101–109.