A comparison of EEG spectral entropy with conventional quantitative EEG at varying depths of sevoflurane anaesthesia

PR Bartel, *Department of Neurology, University of Pretoria and Pretoria Academic Hospital, South Africa*
FJ Smith, *Department of Anaesthesiology, University of Pretoria and Pretoria Academic Hospital, South Africa*
PJ Becker, *Biostatistics Unit, South African Medical Research Council, and Faculty of Health Sciences, University of Pretoria, South Africa*

Abstract

Background and Aim: *Recently an electroencephalographic (EEG) spectral entropy module (M-ENTROPY) for an anaesthetic monitor has become commercially available. We compared its performance as an indicator of the state of anaesthesia with that of an older conventional quantitative EEG (QEEG) module (M-EEG) by the same manufacturer (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland).* **Methods:** *There were 40 ASA class I or II subjects, aged between 16-60 years, who underwent elective abdominal surgery. EEG data were collected from the printouts of the respective modules. The data presented here were related to four levels of anaesthesia: Pre-anaesthetic wakefulness (state A), 2% sevoflurane end-tidal (ET) concentration after completion of surgery (state B), low ET sevoflurane concentrations (~ 0.5%) just prior to regaining responsiveness (state C), and post-anaesthetic responsiveness (state D).* **Results:** *In terms of the prediction probability (Pk statistic), response entropy (RE) and state entropy (SE) produced higher values (0.95-1.0) than the best performing QEEG variable, frontal amplitude (0.86-0.95). Only RE scores did not overlap between states A and B or between B and D. The misclassification of subjects between states C and D was far lower for RE (28%) than for any of the conventional QEEG measures (>90%).* **Conclusion:** *In on-line monitoring spectral entropy is superior in distinguishing states of anaesthesia and is also easier to use than conventional QEEG. It is speculated that the artefact rejection strategies accorded spectral entropy might significantly benefit conventional QEEG analysis.*

Key Words: *EEG spectral entropy, conventional QEEG, sevoflurane anaesthesia.*

The anaesthetist with an interest in monitoring the brain's electrical activity is confronted with an expanding range of commercially available instruments. These include the Narcotrend (NT; Monitor Technik, Germany), the A-Line® ARX index (AAI) derived from the midlatency auditory evoked potential (Danmeter A/S, Odense, Denmark), and the bispectral index obtained from the BIS® monitor (Aspect Medical Systems, Newton, MA, USA). The most recent system involves time-frequency balanced spectral entropy of the electroencephalographic (EEG) signal via an Entropy Module of the S/5‰ Monitor (M-ENTROPY, Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland). All these approaches share the goal of reducing the complexity of the EEG signal to no more than a few numerical values. These values are proposed to reflect the "depth of anaesthesia"[1] or, as preferred by some authors, the "depth of hypnosis"[2] by utilizing different computerized analysis strategies. One intended consequence is to circumvent the need to have the EEG visually analyzed by an attending experienced clinical neurophysiologist.[3]

Correspondence:
Prof PR Bartel
e-mail: peter.bartel@up.ac.za

Spectral entropy determines the degree of disorder or irregularity of the EEG signal. Values are high in subjects who are awake and decrease with increasing depth of anaesthesia. Spectral entropy yields two scales: Response Entropy (RE), ranging between 0 to100, is an amalgam of EEG and frontal muscle activity while State Entropy (SE), consisting mainly of EEG activity in a lower frequency band, ranges from 0 to 91.[2] Initial reports have produced largely promising results.[2,4,5] However, spectral entropy appears to be insensitive to N_2O anaesthesia.[4] In certain circumstances spectral entropy may be a viable alternative to BIS.[2]

EEG modules based on conventional quantitative EEG (QEEG) or Fourier analysis are still available, for instance the M-EEG module of the S/5™ Monitor (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland). M-EEG™ provides digital readouts of the relative amplitude of four frequency bands for up to four different derivations in addition to other spectral parameters such as the spectral edge frequency (SEF) and the burst-suppression ratio that have a particular application in anaesthetic monitoring.

In the state of wakefulness rhythmical EEG activity is maximal in the posterior regions of the brain. The anaesthetized state is associated with complex topographical changes of EEG activity that include the occurrence of "frontal predominance". The

recent consideration of these changes has produced promising markers of the loss and return of consciousness in relation to anaesthesia.[6]

The aim of the current study was to compare spectral entropy with the performance of conventional QEEG to distinguish between the awake and sevoflurane-anaesthetised states at end tidal concentrations of 2% and approximately 0.5% as well as between the unresponsive and responsive states in the phase of recovery from anaesthesia.

Subjects and Methods

An institutional ethics committee approved this study. Subjects were included after giving informed written consent. The cohort consisted of 40 subjects, 22 males and 18 females ranging in age from 16 to 60 years (mean 38.5 years), scheduled for elective abdominal, excluding vascular, surgery. All subjects were in ASA class I or II. Exclusion criteria included a known pre-existing or current neurological deficit, pregnancy, use of beta-blockers or psychotropic drugs or allergy to anaesthetic drugs.

Anaesthetic Technique

Patients were premedicated with oral midazolam approximately 0.1 mg/kg, roughly 1 hr preoperatively. A Datex-Ohmeda ADU anaesthetic machine was used (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland). After a baseline, awake EEG recording the patients were pre-oxygenated with 100% O_2. Induction of anaesthesia was achieved with the following sequence of drugs: alfentanil 15 mg/kg, vecuronium 0.1 mg/kg, lignocaine 1.5 mg/kg and propofol 2 mg/kg. Following tracheal intubation, continuous positive pressure ventilation was commenced with O_2 and air with a minute volume of approximately 100 ml/kg lean mass/min and a frequency of 10-12/min. Anaesthesia was maintained with sevoflurane in oxygen/air, using a fresh gas flow of 1 l/min. At the end of surgery, when closure of the wound was started, the end-tidal (ET) sevoflurane concentration was adjusted to 2%. The adjustment was accomplished by a fresh gas flow of 3 L/min (1.5 L O_2 + 1.5 L air). Thereafter the ET concentration was decreased in 0.5% steps. Following the 0.5% level the administration of sevoflurane ceased. EEG and Entropy were recorded immediately after the target ET sevoflurane concentrations were reached.

EEG recordings

Entropy recordings utilized an Entropy™ Sensor (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland) containing three pre-gelled electrodes placed on the forehead according to the manufacturer's instructions. Two Entropy parameters were assessed. Response Entropy (RE) had an extended frequency range to 47 Hz, and is considered to include both EEG and facial muscle activity. The scale was 0 to 100. State Entropy (SE) on the other hand had a more restricted frequency range to 32 Hz and a scale of 0 to 91. RE was equal to or greater than SE. The values were updated from every few seconds up to 30 s depending on the frequency content of the input signal. The sampling rate was 400 Hz and the epoch length 0.64 s. A variety of artefacts were automatically rejected.

Conventional QEEG analysis utilized the S/5™, M-EEG module, (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland). Transverse frontal and posterior bipolar derivations were used as follows: F8-Fz, Fz-F7, T6-Pz, Pz-T5. In the case of Fz and Pz two electrodes were placed as close as possible at each of these positions because common inputs could not be used. The digitising rate was 100 Hz. For Fourier analysis 12 epochs of 2.5 s each were averaged via the snapshot facility. A Hanning window was applied. The bandpass was 0.5-30 Hz. The results of this analysis included spectral edge frequency 95% (SEF), median frequency (MF), amplitude and the percentage of delta, theta, alpha and beta activity. The relationship of posterior to frontal activity was expressed as a ratio.

The Modified Observer's Assessment of Alertness/Sedation Scale (MOAAS)[7] (Table 1) was applied every 30 to 60 s starting at the sevoflurane 2% ET level after completion of surgery and continuing until the patient achieved a responsive state (MOAAS ≥3).

Table I. Modified Observer's Assessment of Alertness/Sedation Scale (MOAAS)

Response	*Score*
Responds readily to name spoken in normal tone.	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1

The EEG observations were made using the "snapshot" facility, which provided the averaged results of an EEG period of 30 s, immediately after the target ET sevoflurane concentration was reached. The data presented here were obtained at four stages:

1) Pre-anaesthetic wakefulness (state A) when the subjects were fully responsive to verbal commands.
2) At an end-tidal sevoflurane concentration of 2% after the completion of surgery (state B).
3) At a lower sevoflurane concentration of approximately 0.5% ET, when the subject was unresponsive (MOAAS=1) (state C) just prior to the attainment of responsiveness.
4) Upon regaining a responsive state after anaesthesia (state D).

The raw EEG signals were monitored during these post-surgical recordings. In no case was a burst-suppression pattern, which can pose problems for automated analysis, observed.

Statistical analysis

The differences between right- and left-sided conventional QEEG variables were compared by means of paired t-tests. These statistical tests were also used to compare the ability of all the EEG variables to distinguish between: 1) state A and state B, 2) state B and state D, 3) state B and state C, 4) state C and state D, and 5) state A and state D. Since spectral entropy and QEEG parameters were individually of interest, and the comparison of states C versus D of special interest, it was deemed unnecessary to address multiplicity. The variables subjected to further analysis included state and response entropy, SEF, MF, amplitude and those frequency band parameters with p values <0.05.

The additional analysis consisted of the calculation Somers' d_{xy} statistic as the first step in deriving the prediction probability (Pk statistic) as recommended by Smith et al.[8] This provides a yardstick to compare the performance of various EEG variables in distinguishing between different states of arousal and of anaesthesia. A Pk value of 0.5 indicates that the respective EEG parameter predicts the state of hypnosis no better than with a 50:50 chance. Pk values <0.5 indicate that discordance is greater than

Table II. Descriptive statistics for each of the four states of anaesthesia and pairwise comparisons of these states using paired t-tests with p-values, 95% confidence intervals (c.i.) and Pk statistics. State A refers to wakefulness before the surgical procedure, state B to anaesthesia by sevoflurane 2%, state C to anaesthesia by sevoflurane 0.5% and state D to responsiveness after anaesthesia.

EEG Variable	*State*	*Descriptive statistics*				*Pairwise comparisons*			
		Mean	*SD*	*Min.*	*Max.*	*Comparison*	*p-value*	*95% c.i.*	*Pk*
State Entropy	A B C D	85.78 36.93 57.18 82.98	4.38 8.74 14.78 6.37	68 21 26 61	91 62 83 89	A vs B B vs D B vs C C vs D A vs D	<0.001 <0.001 <0.001 <0.001 0.03	45.64 ; 52.06 -49.30 ; -42.80 -24.58 ; -15.92 -30.75 ; -20.85 0.28 ; 5.32	1.00 1.00 0.88 0.95 0.61
Response Entropy	A B C D	95.13 38.65 62.68 93.13	3.25 10.01 16.95 5.52	84 22 34 73	99 63 92 98	A vs B B vs D B vs C C vs D A vs D	<0.001 <0.001 <0.001 <0.001 0.05	53.11 ; 59.84 -57.98 ; -50.97 -28.76 ; -19.29 -35.96 ; -24.94 -0.03 ; 4.03	1.00 1.00 0.89 0.97 0.61
Spectral Edge Frequency (Hz) Frontal	A B C D	13.53 12.24 16.09 20.90	7.77 2.42 3.92 4.63	1.2 6.6 6.6 8.2	28.5 18.0 23.4 28.5	A vs B B vs D B vs C C vs D A vs D	0.34 <0.001 <0.001 <0.001 <0.001	-1.39 ; 3.98 -10.48 ; -7.44 -5.15 ; -2.54 -6.23 ; -3.05 -9.39 ; -3.90	0.52 0.95 0.80 0.79 0.77
Spectral Edge Frequency (Hz) Posterior	A B C D	16.91 10.67 14.52 16.57	3.45 1.96 3.16 4.10	9.4 6.3 8.2 9.0	23.8 15.6 22.3 25.8	A vs B B vs D B vs C C vs D A vs D	<0.001 <0.001 <0.001 0.002 0.59	4.97 ; 7.33 -7.23 ; -4.53 -4.71 ; -2.81 -3.32 ; -0.78 -0.83 ; 1.44	0.93 0.89 0.84 0.64 0.53
Median Frequency Frontal (Hz)	A B C D	2.90 3.45 7.19 7.34	3.25 2.05 4.33 5.67	0.5 0.8 0.4 0.4	12.1 10.2 16.0 18.8	A vs B B vs D B vs C C vs D A vs D	0.36 <0.001 <0.001 0.93 0.001	-1.77 ; 0.66 -5.84 ; -2.27 -5.04 ; -2.44 -2.26 ; 2.08 -6.28 ; 2.23	0.67 0.67 0.74 0.51 0.75
Median Frequency Posterior (Hz)	A B C D	7.65 2.79 5.80 6.25	3.09 1.62 3.76 4.03	1.6 0.8 0.4 0.4	11.7 6.3 13.3 15.6	A vs B B vs D B vs C C vs D A vs D	<0.001 <0.001 <0.001 0.52 0.03	3.74 ; 5.98 -4.89 ; -2.12 -4.13 ; - 1.88 -2.19 ; 1.12 0.14 ; 2.91	0.88 0.73 0.72 0.53 0.65
Amplitude Frontal (μV)	A B C D	7.33 21.04 15.42 8.77	5.17 7.66 5.86 4.17	3.1 8.7 6.3 4.4	25.9 38.5 28.7 26.0	A vs B B vs D B vs C C vs D A vs D	<0.001 <0.001 <0.001 <0.001 0.12	-15.98 ; -11.43 10.11 ; 15.23 3.43 ; 7.82 5.16 ; 8.88 -3.27 ; 0.40	0.95 0.95 0.73 0.86 0.71
Amplitude Posterior (μV)	A B C D	6.76 18.15 13.15 9.11	2.98 6.24 4.47 4.37	3.2 1.2 6.1 3.3	14.2 33.6 23.9 25.9	A vs B B vs D B vs C C vs D A vs D	<0.001 <0.001 <0.001 <0.001 <0.001	-13.25 ; -9.53 7.41 ; 10.96 3.16 ; 6.85 2.49 ; 5.62 -3.48 ; -1.05	0.95 0.91 0.76 0.79 0.69
Amplitude Posterior/ Frontal Ratio	A B C D	1.09 0.89 0.89 1.12	0.52 0.23 0.23 0.43	0.3 0.1 0.4 0.3	2.6 1.4 1.5 2.5	A vs B B vs D B vs C C vs D A vs D	0.02 0.002 0.84 0.002 0.94	0.03 ;0.37 -0.37 ;-0.09 -0.09 ;0.08 -0.37 ; -0.10 -0.22 ; 0.20	0.57 0.68 0.51 0.67 0.56
Theta% Frontal	A B C D	7.40 17.75 13.38 8.59	4.75 6.38 10.93 6.94	1.0 8.0 2.0 1.0	17.0 42.0 70.0 30.0	A vs B B vs D B vs C C vs D A vs D	<0.001 <0.001 0.03 0.005 0.54	-12.52 ; -8.18 6.52 ; 12.24 0.36 ; 8.39 1.64 ; 8.47 -3.45 ; 1.82	0.92 0.85 0.76 0.69 0.52
Theta% Posterior/ Frontal Ratio	A B C D	2.10 1.09 1.35 2.24	3.11 0.42 0.64 1.69	0.1 0.3 0.1 0.2	19.0 2.3 3.2 6.2	A vs B B vs D B vs C C vs D A vs D	0.03 <0.001 0.03 0.005 0.08	0.02 ; 2.00 -1.78 ; -0.63 -0.50 ; -0.02 -1.53 ; -0.29 -1.36 ; 0.08	0.54 0.68 0.61 0.61 0.60
Alpha% Posterior/ Frontal Ratio	A B C D	7.03 0.85 1.08 2.49	9.74 0.43 0.59 1.42	0.8 0.3 0.3 0.4	54.0 2.2 3.0 6.4	A vs B B vs D B vs C C vs D A vs D	<0.001 <0.001 0.04 <0.001 0.03	2.97 ; 9.37 -2.14 ; -1.13 -0.45 ; -0.02 -1.88 ; -1.02 0.90 ; 7.92	0.97 0.89 0.64 0.83 0.74
Beta% Frontal	A B C D	10.03 4.75 18.65 32.76	13.49 3.74 17.70 19.36	0.0 1.0 2.0 1.0	48.0 21.0 69.0 80.0	A vs B B vs D B vs C C vs D A vs D	0.02 <0.001 <0.001 <0.001 <0.001	0.75 ; 9.80 -34.99 ; -22.31 -19.45 ; -8.35 -20.68 ; -6.67 -29.52 ; -14.48	0.53 0.95 0.81 0.73 0.86

concordance. A Pk value of 1.0 means that the particular EEG variable perfectly predicts the observed patient's state. In the data analyses Stata Release 8.0 (StataCorp., College Station, TX, USA) statistical software was employed. The median and distribution in quartiles of selected EEG variables are graphically shown in box and whisker plots.

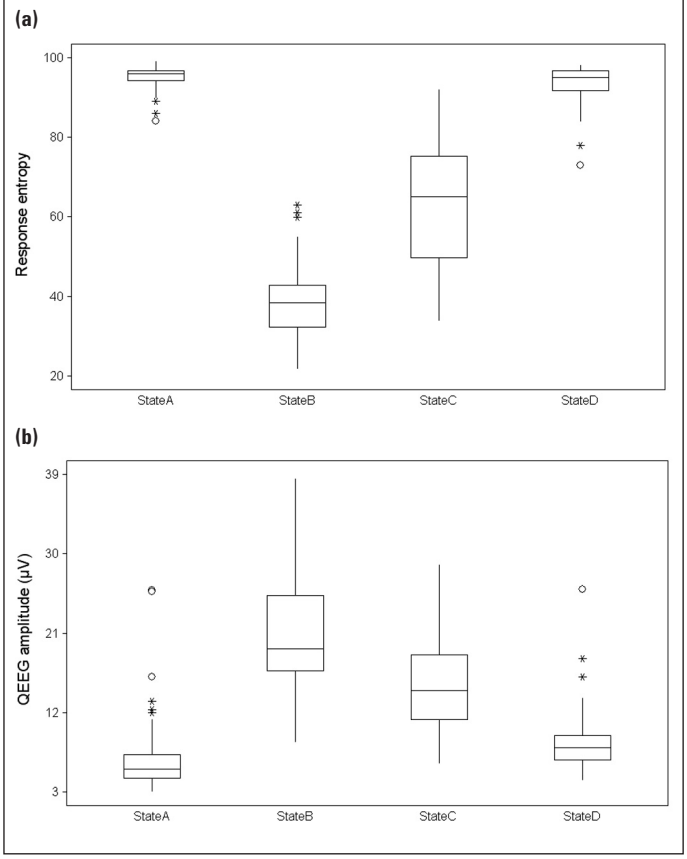
Results

Only left-sided conventional QEEG results are shown here as paired t-tests indicated the absence of consistent left-right differences. The summary statistics, paired t-test and Pk results for the four states appear in Table 2.

Two EEG variables, namely RE from spectral entropy and left frontal amplitude from conventional QEEG are shown graphically in box and whisker plots in Fig.1. Likely outliers were not treated as such since the authors are convinced that these observations are correct.

The overlap of EEG values between states, affecting each of the variables, was most evident in the case of states C and D. To further illustrate the relative ability of spectral entropy compared to conventional QEEG to distinguish between these states, the potential misclassification by these methods was evaluated. Misclassification can be defined as the area or range where unresponsive (state C) subjects may be classified as responsive (state D) on the basis of their EEG scores, i.e. a spectral entropy or QEEG value greater or equal to the observed minimum score in the responsive state. The proportion of misclassified subjects in regard to RE was 28%. Comparable values of misclassification for the conventional QEEG variables, namely posterior SEF and posterior/frontal alpha ratio were both 97%, while misclassification on the basis of frontal amplitude was 92%.

Figure 1. Box and whisker plots of (a) response entropy (RE) and (b) left frontal amplitude from the conventional QEEG, during pre-anaesthetic wakefulness (State A), at an ET sevoflurane concentration of 2% (State B), at a low ET sevoflurane concentration of ~0.5% (State C) and the responsive state after the completion of surgery (State D). * and o denote possible and probable outliers, i.e. values outside the box boundaries by more than 1.5 and 3 times the size of the box, respectively. The box boundaries indicate the 25th and 75th percentiles while the vertical lines represent the total range in the absence of outliers.



Discussion

Putative EEG indicators of the depth of anaesthesia should comply with at least two requirements. Firstly, the comparison of mean values for the different anaesthetic states in question should achieve statistical significance.1 In our study a number of EEG variables complied (paired t-test: $p < 0.05$) in respect of each of four inter-state paired comparisons. These comparisons were pre-anaesthetic wakefulness (state A) versus an ET sevoflurane concentration of 2% (state B), state B versus responsiveness after completion of surgery (state D), State B versus an unresponsive state at a sevoflurane concentration of ~0.5% (state C) and State C versus State D. The successful EEG variables were the spectral entropy measures RE and SE and a number of conventional QEEG values including posterior SEF, frontal and posterior amplitude, frontal percentage theta and beta. In addition, posterior/frontal ratios for amplitude and percentage theta and alpha also achieved statistical significance. Median frequency, which has been used to conduct closed-loop anaesthesia[9], did not fare as well.

The second and more demanding requirement is that there should not be overlap between the EEG values for the different anaesthetic or arousal levels in question.[1] In this respect RE and SE were clearly superior to the conventional QEEG parameters. RE was the only measure where no overlap of values occurred between states A and B as well as between states B and D.

The overlap of EEG values was most evident in the case of states C and D, where each of the variables assessed was affected. This was not unexpected since these states were relatively close to each other, both in terms of time and in anaesthetic concentration. These two states spanned the period of recovery of responsiveness at the end of anaesthesia. While the potential misclassification of subjects on the basis of RE was 28%, conventional QEEG measures fared far worse with misclassification >90%. The performance of the posterior/frontal relationships might improve when using more sophisticated strategies such as the topographical techniques of Gugino et al.[6]

Currently, the predictive probability (Pk) statistic is being widely used to evaluate and compare the ability of EEG variables to discriminate between states of anaesthesia independent of cut-off points.[8] Our Pk values were closely comparable to those of Vakkuri et al.[2] who used 50% O_2 in N_2O as carrier gas for sevoflurane. In our series the Pk values of RE and SE were ≥0.95 for each state of arousal, a performance that none of the conventional QEEG parameters could match. In fact, in the discrimination between states C and D, the Pk values of several conventional QEEG parameters fell below the 0.70 cut-off of relative effectiveness[10] including posterior SEF, frontal and posterior MF, frontal percentage theta and the percentage theta posterior/frontal ratio.

Some of our SE values in pre-surgical wakefulness were lower than the range reported by Anderson and Jakobsson[4] using the same type of spectral entropy monitor. The lowest SE value in our series was 68, with a corresponding RE value of 84. We were unable to detect any particular abnormality in those raw EEG

traces. This particular subject's corresponding SE and RE values in the post-anaesthetic responsive state (State D) were 89 and 98. This trend was atypical because the mean RE and SE results for State D were statistically significantly lower than for State A. While premedication with midazolam 7.5 mg may be too low a dose to affect the EEG[11], in our experience distinct drowsiness can ensue.

During recovery from anaesthesia, unexpectedly high EEG entropy values may predict responsiveness in a behaviourally unresponsive subject.[12] In our series 4/40 subjects had RE scores ≥ 90 in the low sevoflurane concentration, unresponsive state C. On the other hand, potentially misleadingly low values in the responsive state D also occurred in our series, e.g. two RE values were lower than 80, namely 78 and 73. These latter findings are compatible with the common observation that patients may regain conscious awareness, during recovery from anaesthesia, at a lower level of wakefulness than that prevailing in the pre-induction phase when they are alert and anxious and ready to respond to simple commands.[6]

The practical superiority of spectral entropy over conventional QEEG in this on-line monitoring situation had a lot to do with the stability of the display and the relative simplicity of interpretation based on the guidelines of the manufacturer. Conventional QEEG parameters had little or no defence against a range of artefacts, and required time to return to stable displays following high voltage disturbances. In contrast, spectral entropy incorporates seemingly effective algorithms to combat artefacts. This advantage, shared by BIS, may be of considerable importance.[13] Furthermore, optimal classification of state by conventional QEEG parameters is likely to depend on each patient serving as his/her own control. In this respect, artefacts, such as eye movements, pose special challenges, especially when using frontal montages in the responsive state. Nevertheless, improvements in the monitoring of conventional QEEG parameters may prove to be beneficial because of their possible usefulness during monitoring for brain ischaemia.[14] It is in this area where entropy has also shown some potential.[15]

Spectral entropy has shown promising initial results in distinguishing the conscious from unconscious states in respect of sevoflurane, propofol and thiopental anaesthesia.[2,5] The challenge of other classes of anaesthetic agents, including the opioids, remains to be addressed.

In conclusion, in the on-line monitoring situation, spectral entropy provided distinct advantages for the assessment of the state of anaesthesia compared to conventional QEEG as provided by the M-ENTROPY and M-EEG modules.

Acknowledgements

The electrode arrays for the spectral entropy recordings were donated by Datex-Ohmeda. Karlien Fourie and Charlotte Kleingeld provided invaluable assistance with the EEG recordings and data gathering.

References

1. *Drummond JC. Monitoring depth of anesthesia: with emphasis on the application of the bispectral index and the middle latency auditory evoked response to the prevention of recall. Anesthesiology 2000; 93: 876-882.*
2. *Vakkuri A, Yli-Hankala A, Talja P, Mustola S, Tolvanen-Laakso H, Sampson T, et al. Time-frequency balanced spectral Entropy as a measure of anesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia. Acta Anaesthesiol Scand 2004; 48: 145-153.*
3. *Rampil IJ. A primer for EEG signal processing in anesthesia. Anesthesiology 1998; 89 980-1002.*
4. *Anderson RE, Jakobsson JG. Entropy of EEG during anaesthetic induction: a comparative study with propofol or nitrous oxide as sole agent. Br J Anaesth 2004; 92: 167-170.*
5. *Vanluchene AL, Vereecke H, Thas O, Mortier EP, Shafer SL, Struys MM. Spectral entropy as an electroencephalographic measure of anesthetic drug effect: a comparison with bispectral index and processed midlatency auditory evoked response. Anesthesiology 2004; 101: 34-42.*
6. *Gugino LD, Chabot RJ, Prichep LS, John ER, Formanek V, Aglio LS. Quantitative EEG changes associated with loss and return of consciousness in healthy adult volunteers anaesthetized with propofol or sevoflurane. Br J Anaesth 2001; 87: 421-428.*
7. *Kearse LA, Rosow C, Zaslavsky A, Connors P, Dershwitz M, Denman W. Bispectral analysis of the electroencephalogram predicts conscious processing of information during propofol sedation and hypnosis. Anesthesiology 1998;88:25-34.*
8. *Smith WD, Dutton RC, Ty Smith N. Measuring the performance of anesthetic depth indicators. Anesthesiology 1996; 84: 38-51.*
9. *Schwilden H, Schüttler J, Stoeckel H, Closed-loop feedback control of methohexital anesthesia by quantitative EEG analysis in humans. Anesthesiology 1987; 67: 341-347.*
10. *Schneider G, Gelb AW, Schmeller B, Tschakert R, Kochs E. Detection of awareness in surgical patients with EEG-based indices–bispectral index and patient state index. Br J Anaesth 2003; 91: 329-335.*
11. *Bruhn J, Ropcke H, Hoeft A. Approximate Entropy as an electroencephalographic measure of anesthetic drug effect during desflurane anesthesia. Anesthesiology 2000; 92: 715-726.*
12. *Muncaster AR, Sleigh JW, Williams M. Changes in consciousness, conceptual memory, and quantitative electroencephalographical measures during recovery from sevoflurane- and remifentanil-based anesthesia. Anesth Analg 2003; 96: 720-725.*
13. *Miller A, Sleigh JW, Barnard J, Steyn-Ross DA. Does bispectral analysis of the electroencephalogram add anything but complexity? Br J Anaesth 2004; 92: 8-13.*
14. *Visser GH, Wieneke GH, Van Huffelen AC. Carotid endarterectomy monitoring: patterns of spectral EEG changes due to carotid artery clamping. Clin Neurophysiol 1999; 110: 286-294.*
15. *Bezerianos A, Tong S, Thakor N. Time-dependent entropy estimation of EEG rhythm changes following brain ischemia. Ann Biomed Eng 2003; 31: 221-232.*