Acta Anaesthesiol Scand 2014; ••: ••–••
Printed in Singapore. All rights reserved

ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/aas.12359

Monitoring hypnotic effect and nociception with two EEG-derived indices, qCON and qNOX, during general anaesthesia

E. W. Jensen[1], J. F. Valencia[2], A. López[3], T. Anglada[3], M. Agustí[3], Y. Ramos[4], R. Serra[4], M. Jospin[1], P. Pineda[1] and P. Gambus[4]

[1]*Department ESAII, Centre for Biomedical Engineering Research, UPC BarcelonaTech, Barcelona, Spain,* [3]*Anesthesiology Department, CMA-Section, Barcelona, Spain,* [4]*Anesthesiology Department, SPEC-M Research Group, Hospital Clínic de Barcelona, Barcelona, Spain and* [2]*Department of Electronic Engineering, Universidad de San Buenaventura, Cali, Colombia*

Background: The objective of the present study was to validate the qCON index of hypnotic effect and the qNOX index of nociception. Both indices are derived from the frontal electroencephalogram (EEG) and implemented in the qCON 2000 monitor (Quantium Medical, Barcelona, Spain).

Methods: The study was approved by the local ethics committee, including data from 60 patients scheduled for ambulatory surgery undergoing general anaesthesia with propofol and remifentanil, using TCI. The Bis (Covidien, Boulder, CO, USA) was recorded simultaneously with the qCON. Loss of eyelash reflex [loss of consciousness (LOC)] was recorded, and prediction probability for Bis and qCON was calculated. Movement as a response to noxious stimulation [laryngeal mask airway (LMA) insertion, laryngoscopy and tracheal intubation] was registered. The correlation coefficient between qCON and Bis was calculated. The patients were divided into movers/non-movers as a response to noxious stimulation. A paired *t*-test was used to assess significant difference for qCON and qNOX for movers/non-movers.

Results: The prediction probability (Pk) and the standard error (SE) for qCON and Bis for detecting LOC was 0.92 (0.02) and 0.94 (0.02) respectively (*t*-test, no significant difference). The R between qCON and Bis was 0.85. During the general anaesthesia (Ce propofol > 2 μg/ml, Ce remifentanil > 2 ng/ml), the mean value and standard deviation (SD) for qCON was 45 (8), while for qNOX it was 40 (6). The qNOX pre-stimuli values were significantly different ($P < 0.05$) for movers/non-movers as a response to LMA insertion [62.5 (24.0) vs. 45.5 (24.1)], tracheal intubation [58.7 (21.8) vs. 41.4 (20.9)], laryngoscopy [54.1 (21.4) vs. 41.0 (20.8)]. There were no significant differences in remifentanil or propofol effect-site concentrations for movers vs. non-movers.

Conclusion: The qCON was able to reliably detect LOC during general anaesthesia with propofol and remifentanil. The qNOX showed significant overlap between movers and non-movers, but it was able to predict whether or not the patient would move as a response to noxious stimulation, although the anaesthetic concentrations were similar.

Accepted for publication 21 May 2014

The application of advanced mathematical methods has contributed significantly to the recent advances in monitoring in anaesthesia.[1,2]

Monitoring nociception is presently a modality that has not been completely solved, although a number of different methods have been proposed over the last decade. The proposed monitors can be divided into two groups: those based on analysis of brain signals such as electroencephalogram (EEG) and auditory-evoked potentials (AEP),[3–6] and those based on autonomic nervous system measures such as heart rate variability (HRV)[7] or skin conductance (SC),[8] or combinations of these.[9] There are main differences between the two approaches. HRV and SC are correlated with sympathetic activity and therefore monitors based on these parameters can measure the increase in sympathetic activity. However, this is not necessarily related to pain or nociception because increase in the sympathetic activity can be caused by other factors not related to pain. The brain signal methods based on EEG are typically empirical in their origin as there is not clear consensus of which characteristics of the EEG change during analgesia. The AEP-based methods have the advantage of having an anatomically identifiable origin, but a disadvantage is that the AEP is

a very small electrical signal which in clinical practice is very difficult to record without significant noise levels.

The EEG is a direct measurement of brain activity and from the same recording a measure of hypnotic effect and a measure of pain/nociception can be developed. In the present study, the qCON monitor was used, which defines the qCON index of hypnotic effect and the qNOX index of pain/nociception (Quantium Medical, Barcelona, Spain). The qCON and qNOX indices are based on the combination of different frequency bands that are fed into an Adaptive Neuro Fuzzy Inference System (ANFIS) which generates the output on a 0–99 scale. The qCON and qNOX methods are described in more detail in the Appendix. A vast number of publications have already been made on the validation of hypnotic effect monitor,[10–15] whereas pain/nociception monitors for general anaesthesia are less explored.[16]

Under the hypothesis that EEG could contain information related to the probability of response of the patient to a noxious stimulation as well as being sensitive to changes in opioid concentrations, the objective of the present work was to analyse EEG recorded in patients undergoing surgery under general anaesthesia to find a specific indicator of hypnotic effects and of response to nociceptive stimulation.

Methods

Under the approval of the Ethics Committee for Clinical Research of Hospital Clinic de Barcelona (Comité Etico de Investigación Clínica, Hospital Clinic de Barcelona, Villarroel 170, 08036 Barcelona, Spain, protocol number: 2009/4969, approved 23 April 2009) and written informed consent, data was recorded from 60 patients. The surgical patients were scheduled for general anaesthesia with a combination of propofol and remifentanil in the Hospital Clinic of Barcelona. Propofol and remifentanil were infused using a TCI system (Base Primea, Fresenius Vial, Brézins, France).

General anesthesia

The TCI system administered propofol and remifentanil according to the predictions of pharmacokinetic–pharmacodynamic models. In both cases, the TCI was targeting the effect site, applying the Schnider model for propofol (Ce prop)[17,18] and the Minto model for remifentanil (Ce remi).[19,20] The surgeries were ambulatory procedures, including inguinal hernia repair, laparoscopic cholecystectomy, gynecologic laparoscopy and other minor gynecologic procedures. The nociceptive stimulation level was not high, which is usual in this kind of procedures. There were no specific requirements for anesthetic management with regards to preventing movement. It was an observation after stimuli.

The qCON and qNOX indices were continuously recorded. The qCON was recorded to assess the hypnotic effect of the anaesthesia, while the qNOX was recorded to assess the nociception/antinociception balance. The data from the qCON and the qNOX indices were stored in a personal computer with proprietary software, qCON display (Quantium Medical), while the data from the infusion pump and the Bispectral index (Bis, Covidien, CO, USA)[21] were recorded with Rugloop (Demed, Temse, Belgium). The Bis was recorded simultaneously in order to have a reference for the validation of the qCON.

Statistics

A power calculation was based on the following assumptions. We decided to have a power of 0.9 and a level of significance of 0.05. Previous experience showed that the standard deviation (SD) of the qCON is less than 24, and we considered a change of 20 in the transition from awake to anaesthetised as significant, hence the standardised difference was $20/24 = 0.833$. According to Altman,[22] with these conditions the necessary sample size is 60.

The prediction probability (Pk)[23] was used to assess the ability of the Bis, qCON and qNOX to predict the loss of consciousness (LOC) and response to noxious stimulation. The Pk and its standard error (SE) were calculated using the jackknife estimate which has the advantage that the variance can be estimated by the Student's *t*-distribution. We tested for normal distribution using a Lilliefors test before using a Student's *t*-test (paired) to test for significance at $P < 0.05$.

Clinical end points

Loss of eyelash reflex was assessed during the transition from awake to anaesthetised, defining the state of LOC. The values for qCON/Bis awake were the mean qCON/Bis values of 1-min interval immediately before the infusion pumps were started, while the anaesthetised value was the mean taken over the 1-min interval immediately after LOC. The Pk's for Bis and qCON were calculated.

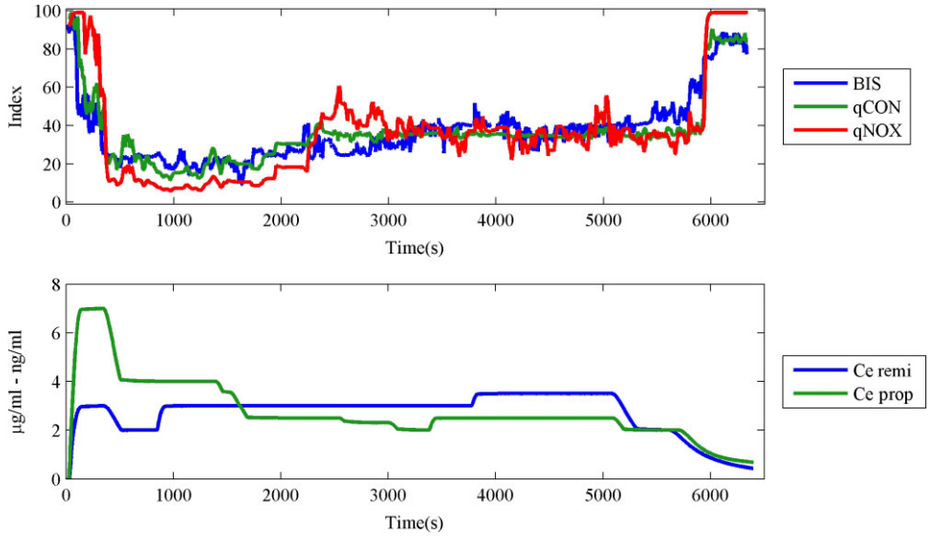

Fig. 1. Example of the three electroencephalogram indices (Bis, qCON and qNOX) and the effect-site concentrations of propofol (Ce prop) and remifentanil (Ce remi).

Movement as a response to laryngeal mask airway (LMA) insertion, laryngoscopy or tracheal intubation was recorded. Movement in the period of 1 min after applying the stimuli was interpreted as the response to each one of the nociceptive stimuli. The patients were classified as movers or non-movers, and the mean value and the SD for the qCON and qNOX were calculated over the 1-min period after the stimulus.

EEG recording

Details of EEG recording, storing and analysis are as follows: The EEG was recorded with the qCON monitor and digitised with 1024-Hz sampling frequency and 16-bit resolution. The EEG was automatically stored in a binary file, while the indices of qCON, qNOX, electromyography (EMG), burst suppression and signal quality index (SQI) were stored in a text file. Data with a SQI < 50 were rejected. The Bis Vista monitor was set to fastest speed, i.e. 10-s smoothing delay in order to ensure that the 0–60 s window was long enough for detecting an increase due to the noxious stimulation.

Results

Correlation to Bis, propofol and remifentanil

The Pk for detection of LOC by the eyelash reflex for qCON and Bis were 0.92 (0.02) and 0.94 (0.02) respectively. There were no significant differences (*t*-test). The mean values for qCON for awake and LOC were 87 (14) and 55 (16) respectively. For the Bis, the values for awake and LOC were 89 (15) and 55 (13).

Figure 1 shows an example of the three EEG indices (Bis, qCON and qNOX) and the effect-site concentrations of propofol and remifentanil.

The data recording started while awake before induction, where the propofol and remifentanil effect-site concentrations were 0. The range of the effect-site concentration was 0–8 µg/ml for propofol and 0–5.3 ng/ml for remifentanil during the general anaesthesia (Ce prop > 2 µg/ml, Ce remi > 2 ng/ml). The mean value for qCON was 45 (8), while for qNOX it was 40 (6).

For further analysis, the data were normalised to obtain a similar number of samples in each state. This gives a more balanced distribution for the statistical analysis. In this case, we have normalised the qCON data, dividing the index value into 10 groups: 0–10, 10–20 . . . 90–100, approximately 5000 samples in each range except the 0–10 and 10–20 ranges, where much fewer samples were recorded. The correlation coefficient between qCON and Bis was R = 0.853.

Figure 2 shows the Bland–Altman plot for (qCON+Bis)/2 vs. (Bis-qCON) containing the 42,000 points recorded from the 60 patients. The bias was –2, while the SD was 12. The dotted lines show the 95% limits of agreement. In a publication by Niedhart et al.,[24] the intra-patient variability of two Bis monitors attached simultaneously to the patient resulted in an SD of 9 in the Bland–Altman plot, which is in a similar range to the SD achieved in the qCON–Bis Bland–Altman plot of the present study.

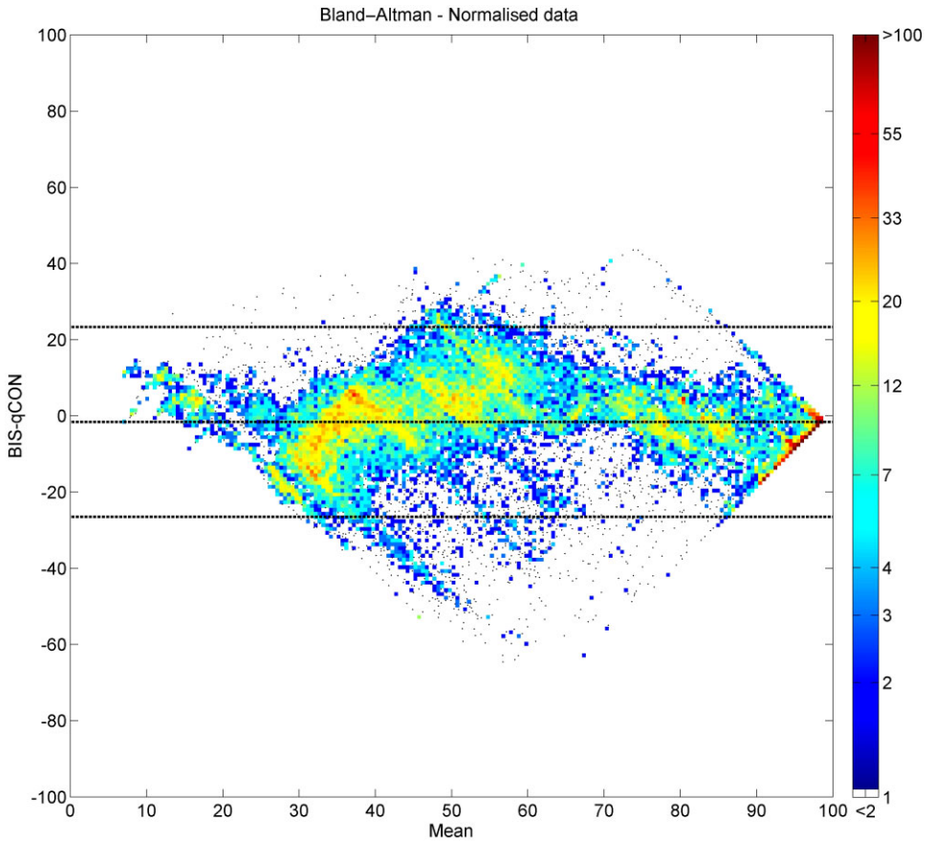

Fig. 2. Bland–Altman plot for (qCON+Bis)/2 vs. (Bis-qCON).

Table 1

qCON prediction of movement as a response to noxious stimulation.

	qCON				
	Start		Final		*t*-test (*P*)
	Mean	SD	Mean	SD	
Laryngoscopy NMOV	44.9	14.7	54.6	19.7	‡
Laryngoscopy MOV	48.1	12.8	57.3	20.1	†
LMA NMOV	47.1	15.3	55.9	18.6	‡
LMA MOV	51.8	13.5	61.1	21.3	†
Tracheal intubation NMOV	45.6	14.6	55.3	19.1	‡
Tracheal intubation MOV	50.8	13.4	59.7	21.7	*

*$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.
LMA, laryngeal mask airway; MOV, movers; NMOV, non-movers.

Movers vs. non-movers

Each patient was classified to the group of movers or non-movers depending on whether they responded to one of the defined stimuli: suture, laryngoscopy, LMA, tracheal intubation or surgical incision.

Tables 1 and 2 show the value immediately before and after stimulation. The values are mean and SD of the qCON and qNOX indices. The non-movers are labelled as 'NMOV', while the patients who moved are labelled as 'MOV'.

The qCON was included to observe whether the same difference between movers and non-movers could be achieved. As for qNOX, this was not the case; the difference between pre-stimuli values for qNOX for movers was significantly larger than those for qCON [17 (20) vs. 5 (12); *t*-test, $P < 0.05$)].

Table 2

qNOX prediction of movement as a response to noxious stimulation.

	qNOX				
	Start		Final		*t*-test (*P*)
	Mean	SD	Mean	SD	
Laryngoscopy NMOV	41.0	20.8	54.0	26.0	‡
Laryngoscopy MOV	54.1	21.4	62.7	28.9	*
LMA NMOV	45.5	24.0	57.0	25.0	‡
LMA MOV	62.5	24.0	70.9	30.1	*
Tracheal intubation NMOV	41.4	20.9	54.3	25.9	‡
Tracheal intubation MOV	58.7	21.8	68.1	29.7	*

*$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.
LMA, laryngeal mask airway; MOV, movers; NMOV, non-movers.

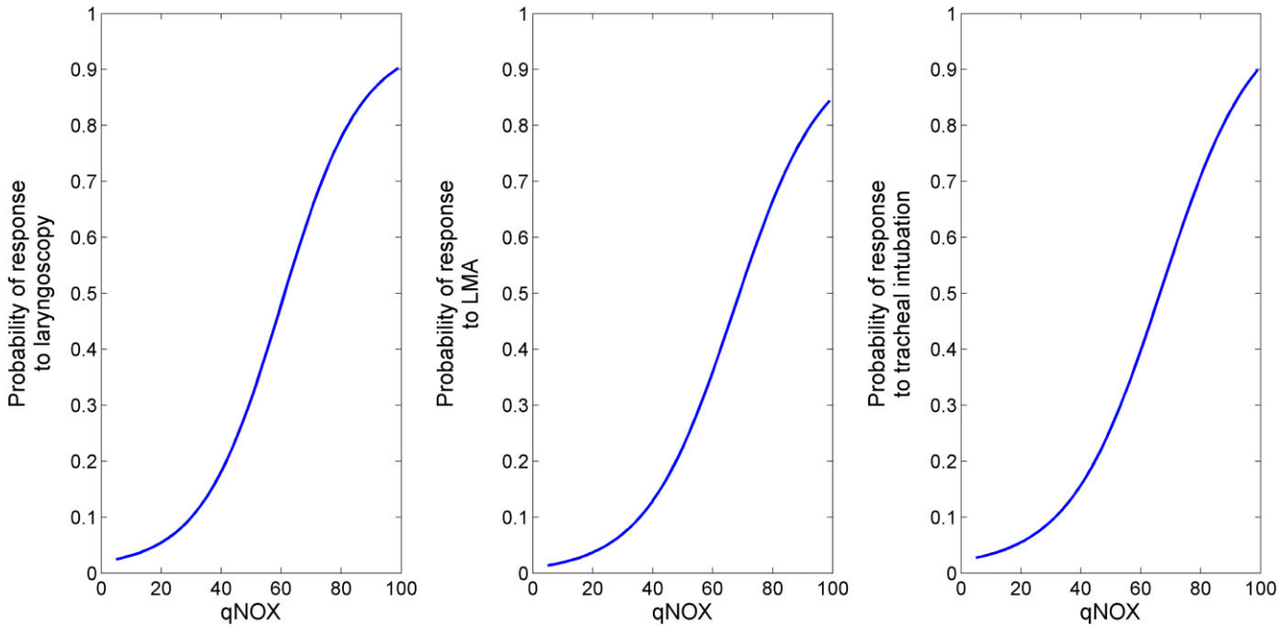

Fig. 3. Logistical regression of the probability of response to laryngoscopy, laryngeal mask airway (LMA) and tracheal intubation.

All 60 patients completed the study, and out of those, 20 patients moved to one or more of the defined stimuli.

Figure 3 shows the logistical regression of the probability of response to laryngoscopy, LMA and tracheal intubation. The qNOX values were pre-stimuli values. Decreasing values of qNOX reduces the probability of response (movement) to a noxious response.

Figure 4 shows that movers had a higher qNOX value after stimulation than the non-movers. The reviewers of this manuscript pointed out that the qNOX differences for movers and non-movers simply could be caused by a lower remifentanil concentration at the moment of movement as a response to noxious stimulation. The Ce remi was 2.96 (1.03) and 2.85 (1.16) ng/ml for non-movers and movers respectively, but there was no significant difference. There was no significant difference in Ce prop either; [NMOV: 3.09(0.54), MOV: 3.09(1.04) µg/ml]. This means that the qNOX was a better predictor than the anaesthetics concentration of response to noxious stimulation.

Discussion

The qCON, as the Bis, is a probability measure, meaning that lower values mean lower probability of being awake. For the qCON, the mean value for loss of eyelash reflex was 55, which means that

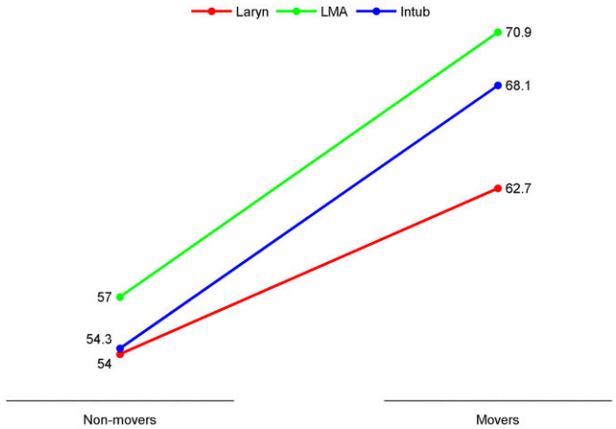

Fig. 4. qNOX value after stimulation for movers and non-movers. Laryn, laryngoscopy; LMA, laryngeal mask airway; Intub, intubation.

patients on average will be asleep below a qCON of 55. The same value was found for the Bis.

The qCON correlated well to the bispectral index during intravenous anaesthesia. Although the qCON and the Bis were not identical, there were a number of samples where differences were observed. The main reason for this is likely to be the difference in update time for the two monitors. As an example, during transition from awake to LOC and vice versa, one monitor may already have dropped to 50 while the other is still at 80, starting the transition to lower values. The algorithms of the two monitors are different, and different artefact rejection methods might play a role as well as the intra-patient variability.[24]

The monitors were not in the exact same position on the forehead of the patient, meaning that one monitor might change to artefact mode while the other is still calculating a valid index, hence creating a difference in update time from what is displayed on the screen.

Both the qCON and the qNOX indices were able to detect movement as a response to noxious stimulation, although the response was larger in the qNOX than in the qCON.

It could be speculated that the reason that the qNOX increases is the direct EEG effect of the noxious stimulation, whereas the qCON rises because of the secondary effect of awakening due to a noxious stimulation.

The logistic regressions show that a qNOX less than 40 means approximately 20% probability of response (defined as movement) to noxious stimuli. In conclusion, the probability of movement is decreasing for lower values of qNOX. The optimal response would be a definite cut-off limit, meaning a sharply rising logistic regression; however, the qNOX has a certain transition where the probability of response decreases, although not at a sharp limit. This behaviour is similar to other monitors of nociception.[25] In earlier monitors, the EMG was often used as an indication of nociception; the qNOX could be considered as an optimised version of an EMG index.

The results of this study showed significant increase in qCON/qNOX as a response to noxious stimulation. It was found that there was a significant difference in the qNOX before and after stimuli both in the mover and the non-mover groups, but the movers had higher qNOX value after stimulation than the non-movers, which does indicate that the movement is related to lighter analgesia.

It is probably not possible to separately measure hypnotic and nociceptive effects totally. Effectively, when a patient is under the influence of a strong hypnotic effect, for example a qCON of 20, then the probability of response to noxious stimuli is lower.

The question remains whether two indices are needed to separately assess hypnotic and analgesic effects. More studies should be done in order to answer this question, but if an index of nociception is sufficiently reliable, then it helps the anaesthetist to decide whether to increase the dosing of, for example, propofol or remifentanil.

The qNOX could also be termed an 'arousability measure'. Both the qCON and the qNOX may be affected by the use of muscle relaxants, as has been published with other EEG monitors.[26] During movement, the frontal EMG level may increase, hence causing an increase in the qNOX, which would not have been observed if the patient had been paralysed. In future studies, other markers of nociceptive stimulation, such as increase in blood pressure, heart rate, pulse-plethysmography or skin conduction, should be applied as a validation of the qNOX.

This is, to our knowledge, the first study to validate the qNOX index; more studies are needed to further validate the qNOX.

Conflicts of interest: Erik Weber Jensen, Mathieu Jospin and Patricia Pineda are employees of Quantium Medical. Erik Weber Jensen and Mathieu Jospin hold equity positions. Pedro Gambús is a paid consultant. Quantium Medical is the commercial developer of both indices.

Funding: FIS (Fondo de Investigaciones Sanitarias, Health Department, Government of Spain) grant nos. PI/050072 and PS09/01209.

References

1. Gambús PL, Jensen EW, Jospin M, Borrat X, Martínez Pallí G, Fernández-Candil J, Valencia JF, Barba X, Caminal P, Trocóniz IF. Modeling the effect of propofol and remifentanil combinations for sedation-analgesia in endoscopic procedures using an Adaptive Neuro Fuzzy Inference System (ANFIS). Anesth Analg 2011; 112: 331–9.
2. Borrat X, Trocóniz IF, Valencia JF, Rivadulla S, Sendino O, Llach J, Muñoz J, Castellví-Bel S, Jospin M, Jensen EW, Castells A. Gambús PL. Modeling the influence of the A118G polymorphism in the OPRM1 gene and of noxious stimulation on the synergistic relation between propofol and remifentanil: sedation and analgesia in endoscopic procedures. Anesthesiology 2013; 118: 1395–407.
3. Jensen EW, Lindholm P, Henneberg SW. Autoregressive modeling with exogenous input of middle-latency auditory-evoked potentials to measure rapid changes in depth of anesthesia. Methods Inf Med 1996; 35: 256–60.
4. Henneberg SW, Rosenborg D, Jensen EW, Ahn P, Burgdorff B, Thomsen LL. Preoperative depth of anaesthesia may influence postoperative opioid requirements. Acta Anaesthesiol Scand 2005; 49: 2293–6.
5. Rehberg B, Ryll C, Hadzidiakos D, Dincklage FW, Baars JH. Variability comparison of the composite auditory evoked potential index and the bispectral index during propofol-fentanyl anesthesia. Anesth Analg 2008; 107: 117–24. 2008.
6. Jensen EW, Litvan H, Revuelta M, Rodriguez BE, Caminal P, Martinez P, Vereecke H, Struys MM. Cerebral state index during propofol anesthesia: a comparison with the bispectral index and the A-line ARX index. Anesthesiology 2006; 105: 28–36.
7. Boselli E, Daniela-Ionescu M, Bégou G, Bouvet L, Dabouz R, Magnin C, Allaouchiche B. Prospective observational study of the non-invasive assessment of immediate postoperative pain using the analgesia/nociception index (ANI). Br J Anaesth 2013; 111: 453–9.
8. Storm H. Changes in skin conductance as a tool to monitor nociceptive stimulation and pain. Curr Opin Anaesthesiol 2008; 21: 796–804.
9. Ben-Israel N, Kliger M, Zuckerman G, Katz Y. Edry R. Monitoring the nociception level: a multi-parameter approach. J Clin Monit Comput 2013; 27: 659–68.
10. Lennmarken C, Sandin R. Neuromonitoring for awareness during surgery. Lancet 2004; 363: 1747–8.
11. Vakkuri A, Yli-Hankala A, Sandin R, Mustola S, Høymork S, Nyblom S, Talja P, Sampson T, van Gils M, Viertiö-Oja H. Spectral entropy monitoring is associated with reduced propofol use and faster emergence in propofol–nitrous oxide–alfentanil anesthesia. Anesthesiology 2005; 103: 274–9.
12. Recart A, White PF, Wang A, Gasanova I, Byerly S, Jones SB. Effect of auditory evoked potential index monitoring on anesthetic drug requirements and recovery profile after laparoscopic surgery: a clinical utility study. Anesthesiology 2003; 99: 813–8.
13. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg 2005; 100: 4–10.
14. Bruhn J, Myles PS, Sneyd R, Struys MM. Depth of anaesthesia monitoring: what's available, what's validated and what's next? Br J Anaesth 2006; 97: 85–94.
15. Mashour GA, Shanks A, Tremper KK, Kheterpal S, Turner CR, Ramachandran SK, Picton P, Schueller C, Morris M, Vandervest JC, Lin N, Avidan MS. Prevention of intraoperative awareness with explicit recall in an unselected surgical population: a randomized comparative effectiveness trial. Anesthesiology 2012; 117: 717–25.
16. Migeon A, Desgranges FP, Chassard D, Blaise BJ, De Queiroz M, Stewart A, Cejka JC, Combet S, Rhondali O. Pupillary reflex dilatation and analgesia nociception index monitoring to assess the effectiveness of regional anesthesia in children anesthetised with sevoflurane. Paediatr Anaesth 2013; 23: 1160–5.
17. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ. The influence of age on propofol pharmacodynamics. Anesthesiology 1999; 90: 1502–16.
18. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology 1998; 88: 1170–82.
19. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil: I. Model development. Anesthesiology 1997; 86: 10–23.
20. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil: II. Model application. Anesthesiology 1997; 86: 24–33.
21. Sigl JC, Chamoun NG. An introduction to bispectral analysis for the electroencephalogram. J Clin Monit 1994; 10: 392–404.
22. Altman DG. Practical statistics for medical research. London: Chapman & Hall, 1991.
23. Smith WD, Dutton RC, Smith NT. Measuring the performance of anesthetic depth indicators. Anesthesiology 1996; 84: 38–51.
24. Niedhart DJ, Kaiser HA, Jacobsohn E, Hantler CB, Evers AS, Avidan MS. Intrapatient reproducibility of the BISxp® monitor. Anesthesiology 2006; 104: 242–8.
25. Bonhomme V, Uutela K, Hans G, Maquoi I, Born JD, Brichant JF, Lamy M, Hans P. Comparison of the surgical Pleth Index™ with haemodynamic variables to assess nociception–anti-nociception balance during general anaesthesia. Br J Anaesth 2011; 106: 101–11.
26. Messner M, Beese U, Romstöck J, Dinkel M, Tschaikowsky K. The bispectral index declines during neuromuscular block in fully awake persons. Anesth Analg 2003; 97: 488–91.
27. Jang JSR. ANFIS: Adaptive-Network-Based Fuzzy Inference System. IEEE Trans Syst Man Cybern 1993; 23: 665–85.
28. Takagi T, Sugeno M. Fuzzy identification of systems and its applications to modeling and control. IEEE Trans Syst Man Cybern 1985; 15: 116–32.
29. Sugeno M, Kang GT. Structure identification of fuzzy models. Fuzzy set Syst 1988; 28: 15–33.

Address
Erik Weber Jensen
Department ESAII, Centre for Biomedical Engineering Research
08034 Barcelona
Spain
e-mail: erikweberjensen@gmail.com

Appendix

The qCON and qNOX were developed using an empirical approach. The qNOX algorithm was developed using a database of 450 patients undergoing

endoscopy sedated with propofol and remifentanil, 80 patients in general anaesthesia with sevoflurane, 10 patients anaesthetised with desflurane, and 50 awake volunteers, a total of 590 patients. The qCON was developed from the same database, but additionally 520 patients from total intravenous anaesthesia, sevoflurane, desflurane and isoflurane were included in the training.

ANFIS

The mathematical model used for the development of both qCON and qNOX were the Adaptive Neuro Fuzzy Inference System (ANFIS). This model is described briefly in this paragraph.

ANFIS is a hybrid of an artificial neural network and a fuzzy logic system, and was developed by Jang in 1993.[27] It represents a Sugeno-type fuzzy system in a special five-layer feed-forward network architecture where the inputs are not counted as a layer. The first-order Sugeno fuzzy model was originally proposed by Takagi and Sugeno in 1985[28] and further elaborated by Sugeno and Kang in 1988.[29]

Standard learning procedures from neural network theory are applied in ANFIS. Backpropagation is used to learn the antecedent parameters, i.e. the membership functions; least squares estimation is used to determine the coefficients of the linear combinations in the rules' consequents. An epoch in the learning procedure has two passes. In the first pass, the forward pass, the input patterns are propagated, and the optimal consequent parameters are estimated by an iterative least mean squares (LMS) procedure, while the antecedent parameters are fixed for the current cycle through the training set. In the second pass, the backward pass, the patterns are propagated again, and in this pass backpropagation is used to modify the antecedent parameters, while the consequent parameters remain fixed. This procedure is then iterated through the desired number of epochs. If the antecedent parameters are initially chosen appropriately, based on expert knowledge, then one training epoch will be sufficient. This is because the LMS algorithm determines the optimal consequent parameters in one pass, and if the antecedents do not change significantly by use of the gradient descent method, neither will the LMS calculation of the consequents lead to another result through successive epochs.

qCON

The qCON algorithm was developed using four EEG spectral ratios and the burst suppression. The electroencephalogram (EEG) spectral ratios were fed into an ANFIS. A reference scale was developed based on the Observer Assessment of Alertness and Sedation (OAAS) scale and the Ramsay scale. The effect-site concentrations of propofol and remifentanil and the end-tidal concentration of the volatile gases were used as consistency controls, i.e. data where the OAAS or Ramsay level was indicating a different state (awake vs. anaesthetised) than what was expected from the anaesthetic concentrations were rejected and not used in the training of the model. The ANFIS model was trained using the spectral ratios as input while the reference clinical scale was the output. The final step was adding the burst suppression (BS) as the major parameter to indicate deep anaesthesia. When BS occurs, the clinical signs of responsiveness have already been suppressed. The qCON scale from a range below 25 relies solely on the BS ratio (BSR). The BSR is the percentage of near isoelectric EEG in a window of 30 s. Both suppression and bursts should have a duration of more than 1 s in order to add up to the final BS count, detected by a maximum-likelihood algorithm. The frequency ratios are calculated every second, thus the qCON is updated every second. An exponential moving average has been applied in order to smoothen rapid transitions, therefore the 50% update time of the qCON is 5 s, assuming no artefacts in the EEG. The frequency ratios were defined in Equation (1):

$$Frequency_n = 20 \times \log \frac{E_n}{E_{tot}} \quad (1)$$

Where

$$E_{tot} = E(1\text{–}44\ \text{Hz})$$

$$E_1 = E(4\text{–}8\ \text{Hz})$$

$$E_2 = E(8\text{–}13\ \text{Hz})$$

$$E_3 = E(11\text{–}22\ \text{Hz})$$

$$E_4 = E(33\text{–}44\ \text{Hz})$$

qNOX

As it was the case with the qCON, the qNOX was developed by fitting the EEG to a reference scale. The reference was composed of the Ramsay levels 5 and 6. Those were assessed by applying nailbed pressure, and if the patient removed his hand, then this was interpreted as a response to noxious stimulation. The OAAS levels 1 and 0 were used as well to generate

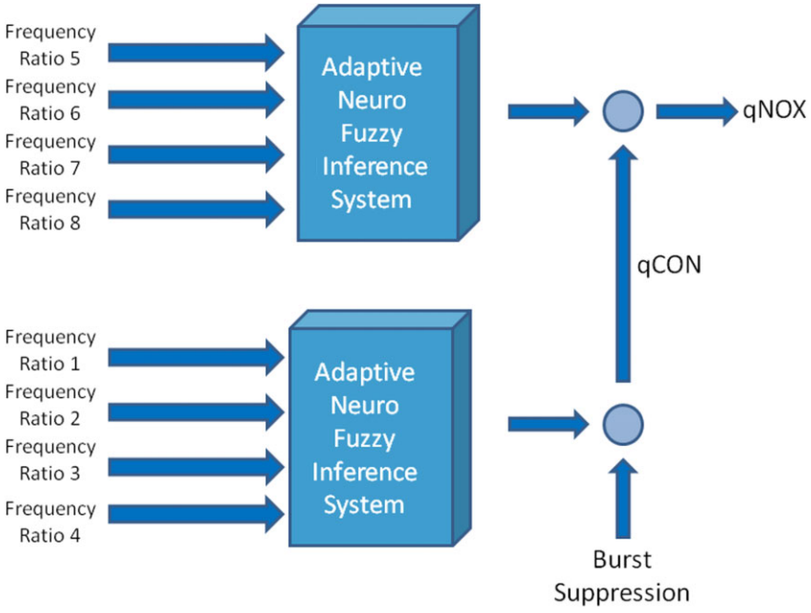

Fig. 5. Diagram of the qCON and qNOX indices.

the reference scale. The base of the qNOX was the four frequency ratios, ranging from 1 to 44 Hz. The qNOX was compensated with the qCON; if the qCON is below 25, then it is assumed that the patient is in very deep anaesthesia that response to noxious stimulation is unlikely. The qNOX uses Equation (1) as qCON, the denominator is the same E_{tot}, but the four frequency ratios are different, defined as:

$$E_5 = E(1\text{–}4\ \text{Hz})$$

$$E_6 = E(8\text{–}13\ \text{Hz})$$

$$E_7 = E(13\text{–}44\ \text{Hz})$$

$$E_8 = E(30\text{–}44\ \text{Hz})$$

Figure 5 shows the diagram of the qCON and qNOX indices.