DEVELOPMENT OF AN INDEX FOR ASSESSMENT OF NOCICEPTION AT INCISION DURING SURGERY

Mark van Gils*, Ilkka Korhonen*, Markku Rantanen**, Arvi Yli-Hankala**,
Heidi Yppärilä-Wolters*, Matti Huiku***, Minna Kymäläinen***,
Panu Takala***, Kimmo Uutela*** and Hanna Viertiö-Oja***

* VTT Information Technology, Tampere, Finland
** Department of Anaesthesia, Tampere University Hospital, Tampere, Finland
*** GE Healthcare, Helsinki, Finland

Mark.vanGils@vtt.fi

Abstract: Currently no objective direct indicator for nociception in anaesthetised patients exists. We aimed to find an indicator by combining physiological parameters obtained at the moment of skin incision during surgery. 55 females were anaesthetised with propofol–remifentanil target controlled infusions. Propofol was given to maintain a State Entropy of 50. Remifentanil target was randomised to 1, 3, or 5 ng/ml. Electrocardiogram, photoplethysmography (PPG), and EEG spectral entropy were recorded and analysed off-line, starting 60 s before and lasting until 120 s after skin incision. Patient reactions were annotated. Heart rate variability (HRV), PPG signal, and pulse transition time (PTT) related features were derived. Clinical signs, remifentanil levels and estimated intensity of incision were combined into a clinical score (CSSA) associated with probability of nociception. Physiological features were analysed to find a predictor (RN) of CSSA. This was achieved by combining features from HRV, spectral entropy, and PPG. The prediction-probabilty (Pk) of CSSA estimation was 0.74. RN was higher after larger incision (P=0.04), in movers (P=0.02), and in patients with lower remifentanil concentrations (P=0.00001). Concluding, RN seems to adequately monitor the components of analgesia: intensity of noxious stimulus and drug effect, and be related to clinical signs of inadequate analgesia.

Introduction

General anaesthesia consists of three components: hypnosis (suppression of awareness and amnesia), muscle relaxation, and analgesia (suppression of pain, anti-nociception). Well-accepted methods exist for assessing muscle relaxation and the hypnotic component of anaesthesia (e.g., Bispectral Index (BIS) [1] and Spectral Entropy [2]). However, to monitor analgesia, or nociception (the intensity of a sub-cortical reaction of an unconscious patient to a noxious stimulus) during anaesthesia no accepted objective numerical measures exist. Currently, estimation of nociception is commonly based on autonomic reactions, such as hypertension, tachycardia, or sweating and tearing, modelling of plasma concentrations of analgesic drugs or observation of clinical end points, such as movement response to surgery. However, such, typically non-specific, observations are influenced by inter-individual variability and may be insensitive to actual nociception.

The aim of this study was to develop an objective and robust quantitative measure of nociception that can be used in an on-line monitor. As it is known that nociception does activate the sympathetic nervous system, leading to changes in physiological signals, we hypothised that these effects may be used to estimate nociception. From a previous study [3] we learned that no single physiological variable by itself is suitable to solve the problem due existence of other factors than nociception causing variations in the same physiological signals. Also, we obtained from that same study a set of potentially useful feature variables derived from heart rate variability, finger pulse wave form, and electrical brain activity signals.

With the aforementioned set of feature variables as 'building blocks' we set out to find a measure that would reflect nociception associated with a well-defined event. For this we used the first incision of surgery. To provide a yardstick to measure the performance of such a measure we developed a clinical assessment of nociception taking into account: 1) the estimated effect site concentration of analgetic drug; 2) stimulus intensity, and 3) a quantification of clinical observations reflecting signs of stress (movements, coughing etc). These three components were combined to form one number, the CSSA score (Clinical Signs – Stimulus – Analgetic score), which was then used to compare evaluate the performance of the measure of nociception calculated from the recorded physiological data.

This paper describes the data collected, methods used to extract feature variables and select an optimal subset from them. It then describes the multi-variable method developed for calculation of the measure of nociception followed by an assessment of its performance. Discussion and conclusions based on the results finalise this paper.

ISSN: 1727-1983 © 2005 IFMBE

Materials and Methods

Subjects and Protocol. The study was approved by the local ethical committee of Tampere University Hospital and written informed consent was obtained from each patient. Electrocardiography (ECG), photoplethysmography (PPG) and electroencephalography (EEG) for recording of Spectral Entropy [4] were recorded in 55 females during surgery. General anaesthesia was induced and maintained with propofol- remifentanil target controlled infusions (TCI). Depth of hypnosis was targeted to maintain a state entropy (SE) value of 50 (adequate surgical level of hypnosis) [2]. Remifentanil concentration was controlled with a TCI-pump. Target levels of 1, 3 or 5 ng/ml were obtained randomly before the moment of first incision. Once the level remifentanil level was stable skin incision was performed. The exact time of incision was registered on file and a trained research nurse (M.K.) carefully recorded any clinical signs (like coughing, jawing, mouth movements, muscle activity, grimacing, movements of extremities, tearing) and other significant events throughout the surgery.

Data Acquisition. The ECG (sampled at 300 Hz), PPG (sampled at 100 Hz), response entropy (RE) and state entropy (SE) as extracted from 400 Hz EEG [4] were collected and stored using Datex-Ohmeda S/5 Anaesthesia Monitor (Datex-Ohmeda Division, Instrumentarium, Helsinki, Finland; Central® and Wincollect® programs).

Recorded ECG, PPG and Spectral Entropy signals were processed off-line using Matlab® (Matlab, version 6.5, Release 13, The Mathworks Inc, MA, USA).

Parameter Extraction. A signal containing beat-to-beat R-R intervals (RRI) was constructed using automatic detection of R-waves followed by manual correction when necessary. Heart rate variability (HRV) was quantified both in time and frequency domain, and also by Poincaré analysis similarly as reported earlier [3]. The following features were extracted: RRI SD (standard deviation) describing overall HRV, RRI SD1 and RRI SD2 quantifying the fast beat-to-beat and slower short-term characteristics of HRV, respectively, and their ratio (RRI SD1/SD2). Furthermore, regularity of RRI and respiratory sinus arrhythmia (RSA) were estimated [5]. First, epochs of RRI corresponding to each respiratory cycle were extracted. Then, the epochs were interpolated to have equal number of samples (16 samples) in each respiratory cycle. For each respiratory cycle two regularity parameters were computed. The RSA irregularity was calculated by computing the standard deviation (SD) of the difference of two successive RRI epochs. The RRI irregularity ratio was computed as a ratio of HRV non-synchronous and synchronous to respiration. Synchronous RSA component was computed over the last 10 respiratory cycles as the SD of the average of all RRI epochs. The non-synchronous component was calculated as the mean of the SD of the residual (i.e., the difference between the mean of RRI epochs and each single epoch).

The amplitude of the PPG signal and the location of the dicrotic notch were detected automatically, and afterwards visually verified and corrected if needed. Heart-beats with PPG artefacts were excluded from the analysis. For each heart beat, PPG amplitude and vertical PPG notch position were measured, and the corresponding beat-to-beat time-series were constructed. In addition, the PPG amplitude variability was computed using Poincaré analysis and PPG SD1, SD2 and SD1/SD2 were computed, similarly to the RRI signal. Pulse transition time (PTT) was obtained as a time from R-wave from the ECG to the maximum derivative of the PPG waveform.

RE and SE were used as obtained from the monitor, their difference, RE-SE, was calculated as a feature potentially detecting arousal [4].

Features were extracted that represent activity in the periods immediately before incision (60s period) and after (120s period). Both absolute feature values as well as relative values were used. The latter were obtained by dividing the post-incision values by their pre-incision values, except for those variables which may have values close to zero (RE, RE-SE, PPG notch position and PTT) - for those parameters relative values were obtained by subtracting the pre-incision value from post-incision value. In the following relative features are indicated by 'rel' behind their name.

Clinical Reference Scoring. Exploratory data analyses were performed to study the relationship between the extracted features and the three different components of nociception. The aim was to thus select those features that would potentially be useful for nociception quantification. To this end the data were classified into groups on the basis of the three components of nociception: remifentanil effect-site concentration during the incision (1, 3, or 5 ng/ml), the size of the incision reflecting stimulus intensity (small incision or large incision), and observed clinical signs of patient reaction to skin incision (non-movers versus movers). The first was estimated using the pharmacokinetic model of Minto et al. [6], the latter two were assessed retrospectively by two anaesthesiologists (M.R. and A.Y-H.). Basic statistic descriptives (numerical and scatter- and box-plots) of the features in the different groups were examined and on the basis of this a set of potentially useful features was processed further.

In order to obtain one single number representing nociception for each case we calculated a score consisting of a summation of values associated with the components: a value in the interval [-4, 0] corresponding to remifentanil concentration 0..6 ng/ml, a value in [0, 4] corresponding to a range from no stimulus to extreme noxious stimulus. and a value in [0,

ISSN: 1727-1983 © 2005 IFMBE

4] mapping the range no clinical signs/observations to clear clinical signs of patient reaction. Adding these 3 values together and adding a constant of value 4 to it leads to a score between 0 and 12, the CSSA score, for which a value of 0 implies no nociception and 12 corresponds with extreme nociception. The aim was thus to develop a method to calculate a measure that would be able to separate recorded data correctly into the three different subgroups as well as have a good correspondence with the CSSA score.

Development of a response index for nociception (RN). A separate estimator was developed for each of the three components of nociception. As the aim of the study was to develop a measure that could be easily calculated in an on-line monitor with limited computing resources we concentrated mainly on rather simple paradigms like linear and logistic regression classifiers. Optimal feature sets were found using the sequential floating forward search (SFFS) method of feature selection [7].

Finally, to obtain one single numerical measure of nociception the outputs of the three estimator modules were linearly combined to come to an estimation of nociception that occurs as a response to skin incision, the response index of nociception (RN). For practical reasons (e.g., in presenting it as a number in an on-line monitoring system) RN was scaled to range from 0 to 100, 0 coinciding with a value of 0 on the CSSA scale and 100 corresponding to a CSSA score of 10 or higher.

Statistical Methods. The performance of the estimator was assessed by the root mean square error (RMSE) and Pearson's correlation coefficient for the module estimating remifentanil level. Prediction probability (Pk) [8] was used as measure of correspondence for the components estimating clinical observations, stimulus intensity and the relation between RN and CSSA. To assess significance of difference in estimator outputs for the different groups Kruskal-Wallis H and Mann-Whitney U test were used.

Results

Exploratory analysis led to a selection of feature variables on the basis of if and how their distributions differed with different patient groups. Figures 1, 2 and 3 shows the distributions for variables that were finally used for estimation of remifentanil concentrations, clinical observation score, and stimulus intensity score respectively.

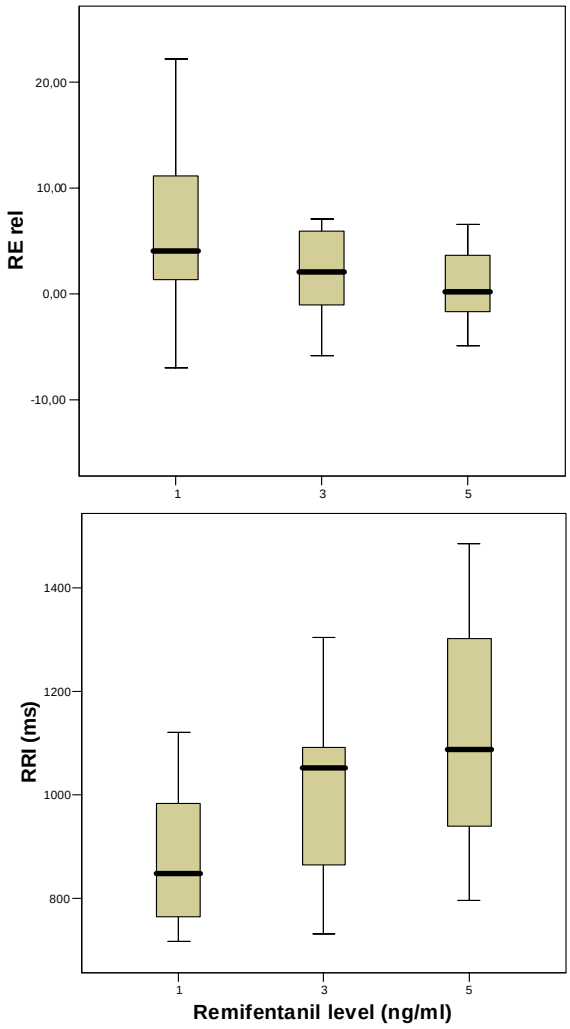

Figure 1: Box-and-whiskers plots depicting different distributions for RE post-incision - RE pre-incision and RRI at skin incision for different levels of remifentanil concentration. Thick lines indicate median, box edges represent 25-75% quartile range and the whiskers indicate the overall range.

ISSN: 1727-1983 © 2005 IFMBE

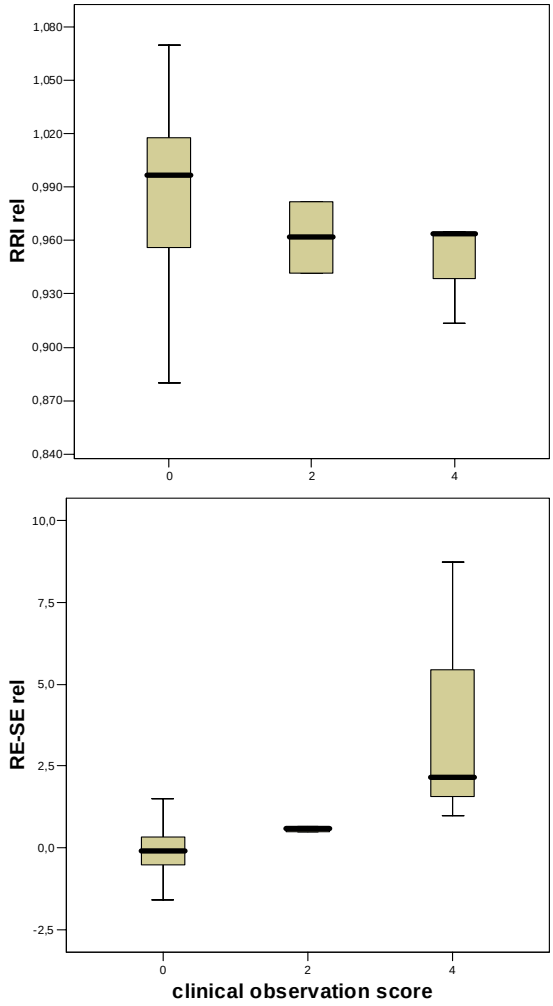

Figure 2: Plots depicting distributions for RE-SE post-incision - pre-incision and RRI post/ pre-incision at incision for different clinical observations scores.

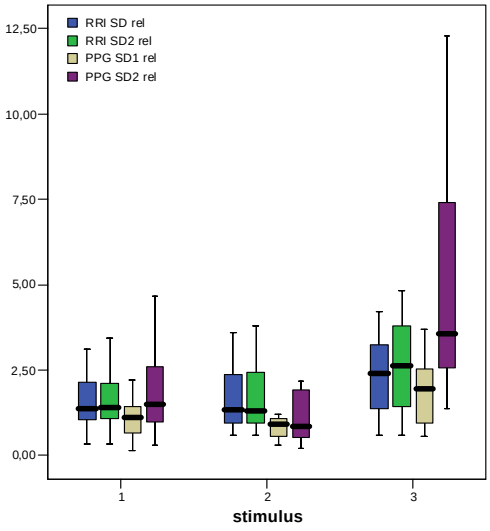

Figure 3: Plots depicting different distributions for relative RRI SD, RRI SD2, PPG SD1 and PPG SD2 at skin incision for different values of the stimulus intensity score.

The results showed that these variables may be useful for discerning between the different remifentanil levels, although the variables by themselves alone will not be able to do the job. A linear combination of RRI and relative RE however emerged as suitable estimator for the remifentanil level (remi_est). Similar approaches were used for the estimators for the other components of nociception. For the estimation of stimulus intensity (stim_est) a sigmoid function using the relative RRI SD, RRI SD2, PPG SD1 and PPG SD2 was employed, and the estimation of presence of clinical observation (co_est) was done using a sigmoid function with relative RRI and RE-SE. The reason why for remifentanil level estimation a linear combination is used and for the other components a sigmoid function is that the former exhibits a gradual behaviour whereas latter exhibit a more "on/off" type of non-linear behaviour.

The final configuration of modules and their the way the final RN value is calculated is depicted schematically in Figure 2.

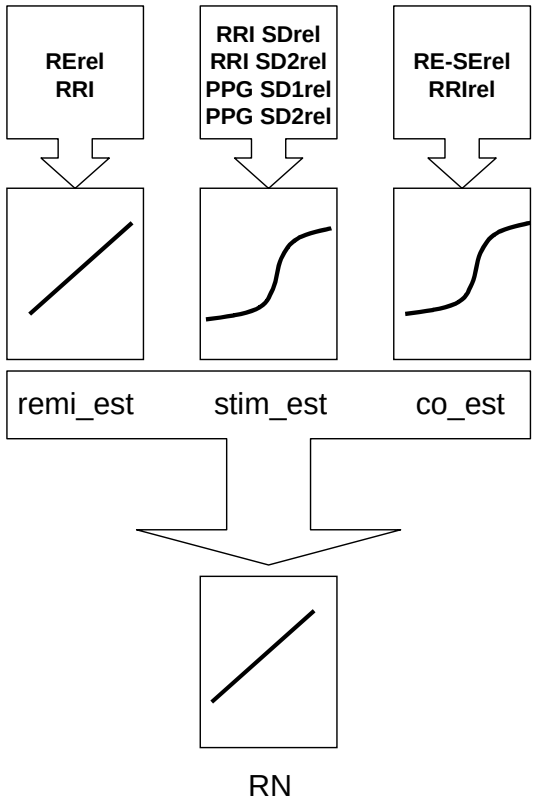

Figure 4: Schematic representation of the method to calculate RN.

The module estimating the remifentanil level performs with a correlation coefficient, r=0.75 ($p = 8 \cdot 10^{-11}$) and an RMSE of 1.1 ng/ml. The correspondence with clinical observation is given as Pk=0.56 (standard error, SE=0.03); and with stimulus intensity Pk=0.57

ISSN: 1727-1983 © 2005 IFMBE

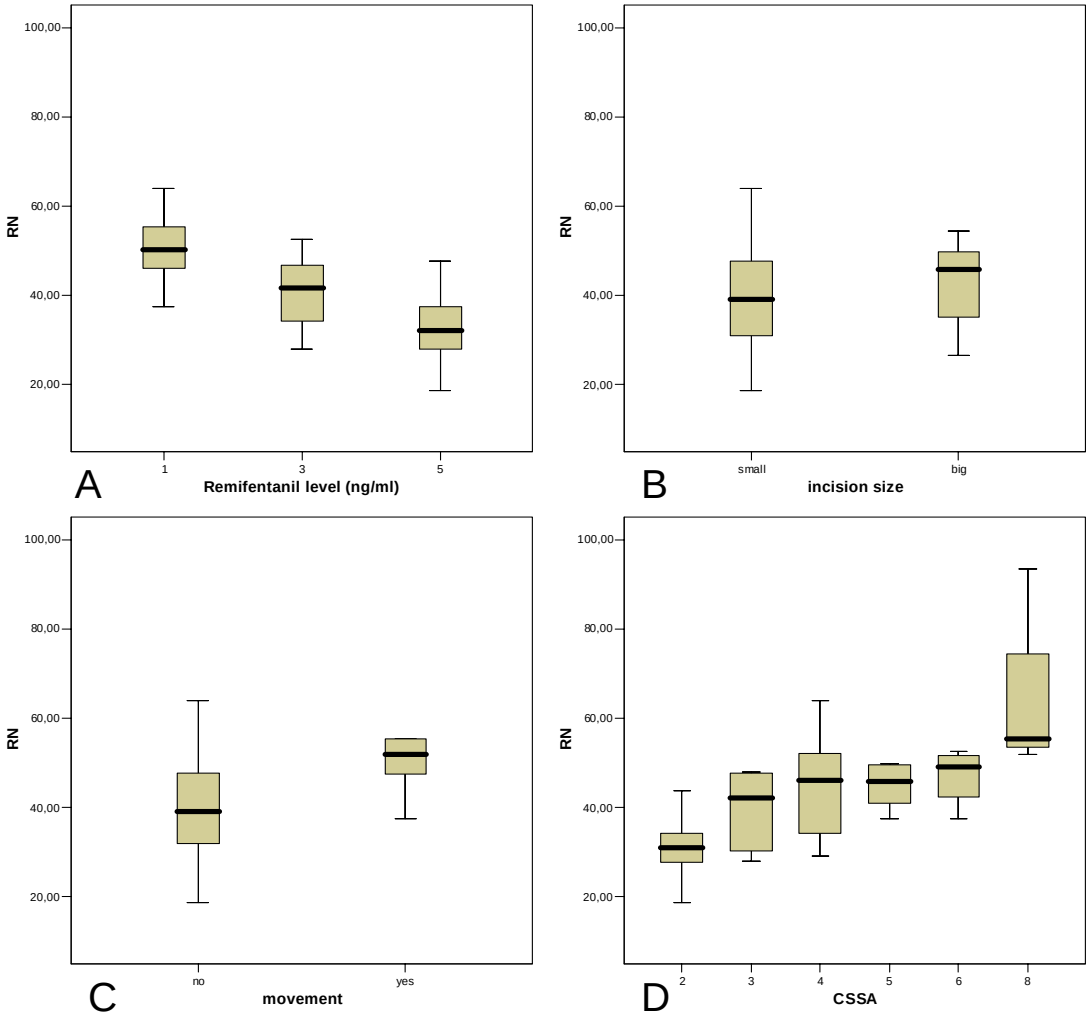

Figure 5: Distributions of RN for a) different remifentanil levels, b) different incision sizes, c) movement yes or no, and d) different CSSA scores.

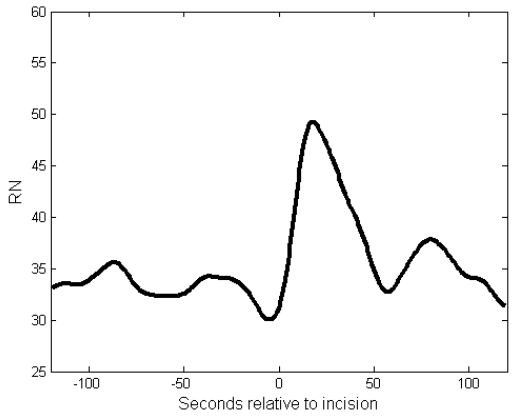

Figure 6: Example of behaviour of RN in a period starting 2 minutes before skin incision and ending 2 minutes after it. At incision, clinical observation score is 0, stimulus intensity score is 3, and remifentanil concentration is 3 ng/ml, resulting in CSSA score of 5.

(SE=0.04). The Pk for the CSSA estimation is 0.74 (SE=0.03). RN was significantly higher in low doses of remifentanil as compared to higher doses (p=0.00001). Patients with clear signs of nociception had significantly higher RN values than others (p=0.04), and those undergoing a small-size incision had smaller RN than those undergoing a larger size incision (p=0.02). RN's behaviour is depicted graphically in Figures 5 and 6.

Discussion

A multi-variate modular algorithm to estimate nociception at the time of skin incision was developed. The modular approach provides a more robust, easy maintainable and tuneable, and intuitive implementation as compared to one in which the final index would be estimated directly in one step. The algorithm displays a bigger response after a bigger than a small incision, differentiates the movers from non-movers, and changes gradually and consistently with varying concentrations of remifentanil. Thus, the algorithm seems to adequately monitor the crucial components of analgesia, i.e. the intensity of noxious stimulus and drug effect, and also

ISSN: 1727-1983 © 2005 IFMBE

to reflect presence or absence of clinical signs (movement).

We also presented a new reference score for the assessment of severity of nociception in an anaesthetised patient, the CSSA score. Here we assume that the three elements which are used to assess the probability of actual nociception at a given time instant (clinical signs, intensity of the stimulus, and level of analgetic drug), are separate additive factors, whose contributions are of equal importance. This score was then used as a clinical reference in the development of the RN. The score was developed heuristically; using our clinical knowledge and judgement - we do not claim that the score would provide an unambiguous evaluation of the actual nociception of the patient. However, it still provides some reasonable clinical reference and as such may be used as a reference while developing methods.

The Pk or RN for CSSA estimation was 0.74, which may appear as a relatively low value as compared to Pk values for awareness monitors such as BIS or Entropy, which are typically well above 0.90 for comparison with e.g. the OAA/S score [9]. A reason for this may be that the CSSA score is less exactly defined as clinical references used for awareness monitors (e.g., OAA/S score or clinical endpoints). The contributions of different components in the score were defined to our best knowledge but still somewhat arbitrarily, and as a result the scale is may not necessarily be fully monotonous. The high and low CSSA values are undoubtedly associated with high and low probability of nociception, respectively, but close values in the mid-range of the scale may not always be correctly ranked in each individual patient and situation (e.g., a value of 5 does not necessarily differ significantly from value 6). As a result, when this scale is used as a reference, high values for Pk are beyond reach. In addition, the CSSA distribution in our data was not very wide, having heavy presentation at few low levels of CSSA, this further degrades possibilities for reaching a high Pk. Therefore, we think that the Pk value of 0.74 is acceptable.

The data used in development of RN were collected during propofol-remifentanil anaesthesia in relatively healthy persons. Performance of the model with other drug combinations remains to be tested in further prospective studies.

Conclusions

A modular algorithm was developed to estimate nociception at time of incision. The modular approach provides a robust, easy maintainable, and intuitive implementation as compared to one in which the final estimation would be done in one step. Recordings are currently being performed to evaluate the algorithm's behaviour on a wider group of patients.

References

[1] GLASS P.S., BLOOM M., KEARSE L. et al. (1997): 'Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers', *Anesthesiology,* **86**, pp. 836-847

[2] VAKKURI A., YLI-HANKALA A., TALJA P. et al. (2004): 'Time-frequency balanced spectral entropy as a measure of anesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anesthesia', *Acta Anaesthesiology Scandinavica,* **48**, pp. 145-153

[3] SEITSONEN E, KORHONEN I., VAN GILS M. et al. (2005): 'EEG Spectral Entropy, Heart Rate, Photoplethysmography And Motor Responses To Skin Incision During Sevoflurane Anaesthesia', *Acta Anaesthesiologica Scandinavica,* **49**, pp. 284-292

[4] VIERTIÖ-OJA H., MAJA V., SÄRKELÄ M. et al. (2004): 'Description of the Entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module', *Acta Anaesthesiologica Scandinavica,* **48**, pp. 154-61

[5] HUIKU M., VAN GILS M., KORHONEN I. et al. (2005): 'Measurement of surgical stress using heart rate and plethysmographic pulse wave amplitude variability', Proc. of the 3rd European Medical & Biological Engineering Conference (EMBEC 2005), Prague, Czech Republic.

[6] MINTO C.F., SCHNIDER T.W. and SHAFER S.L. (1997): 'Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application', *Anesthesiology,* **86**, pp. 24-33

[7] PUDIL P., NOVOVICOVA J. and KITTLER J. (1994): 'Floating Search Methods In Feature Selection', *Pattern Recognition Letters*, **15**, pp. 1119-1125

[8] SMITH W.D., DUTTON R.C. and TY SMITH N. (1996): 'Measuring the performance of anesthetic depth indicators', *Anesthesiology,* **84**, pp. 38-51

[9] CHERNIK, D.A., GILLINGS, D., LAINE, H. et al. (1990): 'Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam', *Journal of Clinical Psychopharmacology*, **10**, pp. 244-251

ISSN: 1727-1983 © 2005 IFMBE