Acta Anaesthesiol Scand 2007; 51: 8–15
Printed in Singapore. All rights reserved

ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2006.01189.x

Comparison of skin conductance with entropy during intubation, tetanic stimulation and emergence from general anaesthesia

A. C. GJERSTAD[1], H. STORM[1], R. HAGEN[2], M. HUIKU[3], E. QVIGSTAD[4] and J. RÆDER[2]
[1]*The Skills Training Centre, National University Hospital, Oslo, Norway,* [2]*Department of Anaesthesiology, Ullevaal University Hospital, Oslo, Norway,* [3]*GE Healthcare, Information Technologies, Helsinki, Finland and* [4]*Department of Gynaecology, Ullevaal University Hospital, Oslo, Norway*

Background: The number of skin conductance fluctuations (NSCF) expresses sympathetic skin nerve activity. The response entropy (RE) measures electromyographic and electroencephalographic activity in the forehead. The state entropy (SE) measures mainly electroencephalographic activity. When the suppression of frontal muscular activity is complete, RE is equal to SE. RE-Δ is defined as SE minus RE. The purposes of this study were to examine whether NSCF and RE-Δ correlate with signs of clinical stress during intubation and tetanic noxious stimulation and to elucidate how rapidly and accurately entropy and NSCF react during emergence from general anaesthesia.

Methods: Twenty women scheduled for gynaecological laparotomy were studied. During intubation in remifentanil and propofol general anaesthesia, NSCF and RE-Δ were correlated with the clinical stress score. After a wash-out period, two series of tetanic stimuli were given, the first with (R+) and the second without (R–) remifentanil infusion. The tetanic pre-stimuli periods were compared with the tetanic post-stimuli periods, and R+ was compared with R–. During emergence, the responses of entropy and skin conductance were related to the time of extubation.

Results: NSCF correlated well with the clinical stress score during intubation ($r^2 = 0.73$, $P < 0.0005$). RE-Δ showed a weaker correlation ($r^2 = 0.33$, $P = 0.007$). During tetanic stimuli, the NSCF pre-stimuli level was lower than the post-stimuli level ($P < 0.001$), and the NSCF R+ response was lower than the NSCF R– response ($P = 0.002$). RE-Δ did not show similar differences. During emergence, RE reacted before NSCF and SE ($P = 0.003$).

Conclusion: NSCF was better than RE-Δ for the measurement of clinical stress during intubation, and was sensitive to tetanic stimuli at different opioid analgesic levels, by contrast with RE-Δ. Both modalities were able to predict emergence at the end of anaesthesia, but RE was more rapid.

Accepted for publication 21 August 2006

Key words: emergence; hypnotic state; intubation; nociception; response entropy; skin conductance; state entropy; tetanic stimuli.

GENERAL anaesthesia involves hypnosis, analgesia and areflexia. Different methods based on the analysis of the electroencephalogram have been developed to monitor the depth of anaesthesia, such as the bispectral index (BIS), auditory evoked potential and state entropy (SE). These methods reveal similar information about the levels of sedation (1, 2), but seem to be related more to the hypnotic state of the patient than to analgesia or the physiological stress induced by noxious stimulation (1, 3). During light or intermediate levels of anaesthesia, frontal electromyographic activity is still present. As the facial muscles are less sensitive than other muscles to the effect of neuromuscular blocking agents, nociceptive stimuli during inadequate anaesthesia may be reflected by an increase in frontal electromyographic activity, even during adequate neuromuscular block (4). Thus, frontal electromyographic contamination in the electroencephalogram may not just be an artefact, but may have the potential to be used as a measure of nociceptive input and adequacy of analgesia. SE mainly involves electroencephalographic signals, whereas the response entropy (RE) is made up of both electroencephalographic and frontal electromyographic activity. When the suppression of frontal muscular activity is complete, RE is equal to

SE. However, RE will be higher than SE in the presence of frontal electromyographic signals, expressed by RE-Δ = SE – RE. The RE response is rapid, with changes in the measured electromyographic/electroencephalographic signal being evident on the monitor in less than 5 s.

The number of skin conductance fluctuations (NSCF) shows the emotional state as reflected in changes in the sympathetic nervous system (5). Activation of the sympathetic nervous system results in filling of the palmar and plantar sweat glands; the skin conductance (SC) increases transiently before the sweat is removed, and then decreases again; an SC fluctuation is therefore observed.

An increase in NSCF can therefore be interpreted as an increase in activity in this part of the sympathetic nervous system (6, 7). The mean SC level decreases while losing consciousness as a result of decreased activity in the sympathetic nervous system and less palmar humidity. During awakening, an increase in the mean SC level is observed as a result of increased activity in the sympathetic nervous system and increased palmar humidity (8). NSCF has been used to evaluate the nociceptive response in pre-term infants (9) and during peri-operative stress (8). NSCF reacts within 2 s after a painful stimulus (9). Haemodynamic variables are often used as an indication of change during stressful inputs, but are also influenced strongly by circulatory changes and cardiovascular-active drugs, and have a low specificity as a sign of adequate or inadequate anaesthesia or sedation (10). NSCF involves acetylcholine transmitters acting on muscarine receptors (11, 12), and is not influenced by hypovoluminous or adrenergic receptor-active agents.

The purposes of this study were to examine whether NSCF and RE-Δ correlate with signs of clinical stress during intubation and tetanic noxious stimulation, and to elucidate how rapidly and accurately entropy and NSCF react during emergence from general anaesthesia.

Methods and subjects

Subjects

The protocol was approved by the regional Ethics Committee for Human Studies, Oslo, Norway. Twenty women, aged 39–56 years, scheduled for gynaecological laparotomy, were enrolled, after having given written informed consent. The patients were ASA group 1 or 2. The exclusion criteria were known contraindications to potential anaesthetic drugs, psychoactive medication, neurological disorder or neuropathy and the use of atropine or other anticholinergics in the pre-operative phase.

Apparatus and software

Skin conductance

NSCF and the mean SC level have been described in detail previously, as has the software program for the sampling and analysis of NSCF and the mean SC level (13, 14). The SC data were measured by a three-electrode system comprising a measuring electrode, a countercurrent electrode and a reference voltage electrode placed on the thenar eminence, the hypothenar eminence and the dorsal side of the hand, respectively. The SC data were stored online using a Dell Latitude D-800 laptop computer (Dell, Round Rock, TX), and were analysed offline by a software analysis package. When analysing the SC data, the program counted the NSCF and mean SC level during a 20-s interval. In order to eliminate electronic noise, the definition of a minimum amplitude was set at 0.020 μS. However, if peaks were observed manually that were not counted with the threshold of 0.020 μS, a threshold of 0.015 μS was used instead.

Entropy

The electroencephalographic signal was collected with a disposable entropy sensor (Datex-Ohmeda Division, GE Healthcare, Helsinki, Finland) composed of self-adhering flexible bands holding three electrodes applied to the forehead. The entropy was measured by two Datex-Ohmeda S/5 Anaesthesia Compact Monitors furnished with M-Entropy, measurement of inspired and expired gases (M-CaiOV), neuromuscular transmission (M-NMT) and haemodynamic measurement modules (M-NESTPR). S/5 Collect was employed for the annotation of the different events using the notes panel. The data record times of the SC variables were synchronized with the S/5 AM clock, and S/5 Collect automatically synchronized the S/5 data with the S/5 monitor. The sampling rate was 400 Hz for SE and RE. All the data were collected with the same laptop as used for the SC variables.

Neuromuscular Train of Four (TOF)-Guard

Two stimulating electrodes were placed above the nervus ulnaris on the wrist of the hand; the mechanosensor was placed from the thumb to the index finger. Noxious stimuli were given manually using a tetanic neuromuscular transmission (NMT) at 50 mA

for 5 s, and then three times for 1 s with a 10-s interval between the stimuli. To test the level of muscle relaxation during surgery, an ordinary TOF-Guard was used. A TOF response in the range 1–2 (1–4 available) was taken as an indication of good surgical relaxation.

Procedure

The patients received 7.5 mg of midazolam orally as pre-medication and pre-operative sedation with propofol and remifentanil. The SC and entropy variables were monitored during different levels of pre-operative sedation and auditory stimulation; these results have been reported previously (15). For the present report, NSCF, RE, SE, blood pressure and heart rate were monitored and stored during intubation, tetanic stimuli, surgery and extubation, together with the clinical stress score (Table 1). One point was given for each clinical stress reaction present, summing these together to yield a total stress score. The clinical stress score was estimated online by observing the patient.

The patients were randomly divided into two groups, each with 10 patients. The target SE was set at SE = 30 for one group and at SE = 60 for the other. The two groups were used to ensure a different level of sedation during tetanic stimuli, and to examine whether different levels of propofol influenced the stress response measured by RE-Δ and NSCF.

Before intubation, all patients received 4 mg of *cis*-atracurium intravenously. A constant target-controlled infusion (TCI) of 4 μg/ml propofol was given for the SE = 30 group, and of 2 μg/ml propofol for the SE = 60 group. If the target SE values were not reached, propofol TCI adjustments of 0.3 μg/ml were applied. The TCI of remifentanil was 2 ng/ml in both groups. To facilitate intubation, many of the patients received at least one bolus of remifentanil before intubation. The maximum stress score, maximum RE-Δ and maximum NSCF were analysed for 1 min after intubation. After intubation, there was a 4-min delay with the TCI at 2 ng/ml remifentanil before the first tetanic stimulus was conducted (Fig. 1).

Tetanic stimuli were given in two sessions to each patient, with (R+) and without (R–) remifentanil: R+ was given first, with a remifentanil effect site concentration of 2 ng/ml calculated by the TCI pump; this was followed by R–, with the remifentanil target set to zero; a 4-min delay was instituted before a new tetanic stimulus was given, and this was analysed similarly to the first tetanic stimulus. The data were recorded for at least 2 min (Fig. 1). After the two sessions of tetanic stimulation, surgery was started. The maximum response to tetanic stimulation was analysed offline 30 s before and 30 s after the start of the stimulus for RE-Δ and NSCF.

During emergence from anaesthesia after the end of surgery, the mean SC level, NSCF, RE and SE were measured continuously. The same anaesthesiologist extubated all the patients according to regular clinical judgement. The time point at which the tube left the trachea was denoted as T0. T0 was compared with emergence according to entropy measurements and SC. To define whether the patient was emerging from anaesthesia according to the SC variables, we used a mean increase in the SC level of at least 0.1 μS within 20 s, together with at least NSCF = 2 (16). For the entropy measurements, an increase in SE and RE to over 70 or 80 was recognized as emergence. A negative value was given for the first signs of emergence in the monitoring equipment before T0, and a positive value for the first signs of emergence after T0. Registration lasted for 1 min after extubation. The data were analysed offline at the different time points.

Statistical analysis

The maximum NSCF and RE-Δ responses were registered during intubation and analysed offline before correlation with the total stress score. A linear regression analysis was used. The mean of the two pre-stimuli periods was compared with the mean of the two post-stimuli periods using the Wilcoxon non-parametric test. NSCF and RE-Δ responses during R+ were compared with those during R– using the Wilcoxon non-parametric test. To study whether the level of SE influenced the response to tetanic stimuli, R+ and R– in the SE = 60 group were compared with R+ and R– in the SE = 30 group using the Mann–Whitney *U*-test. The time intervals from extubation to emergence for the SC variables, SE and RE were compared using the Wilcoxon non-parametric test.

Table 1

Online stress score. For the clinical stress score, one point of stress was given for each of the reactions; these were summed to give a total stress score. The clinical stress score was estimated online by observing the patient.

Large muscle movement	1
Coughing	1
Eye opening	1
Sweating on the forehead	1
Tears	1
Face muscle reaction	1
Systolic blood pressure >130 mmHg	1

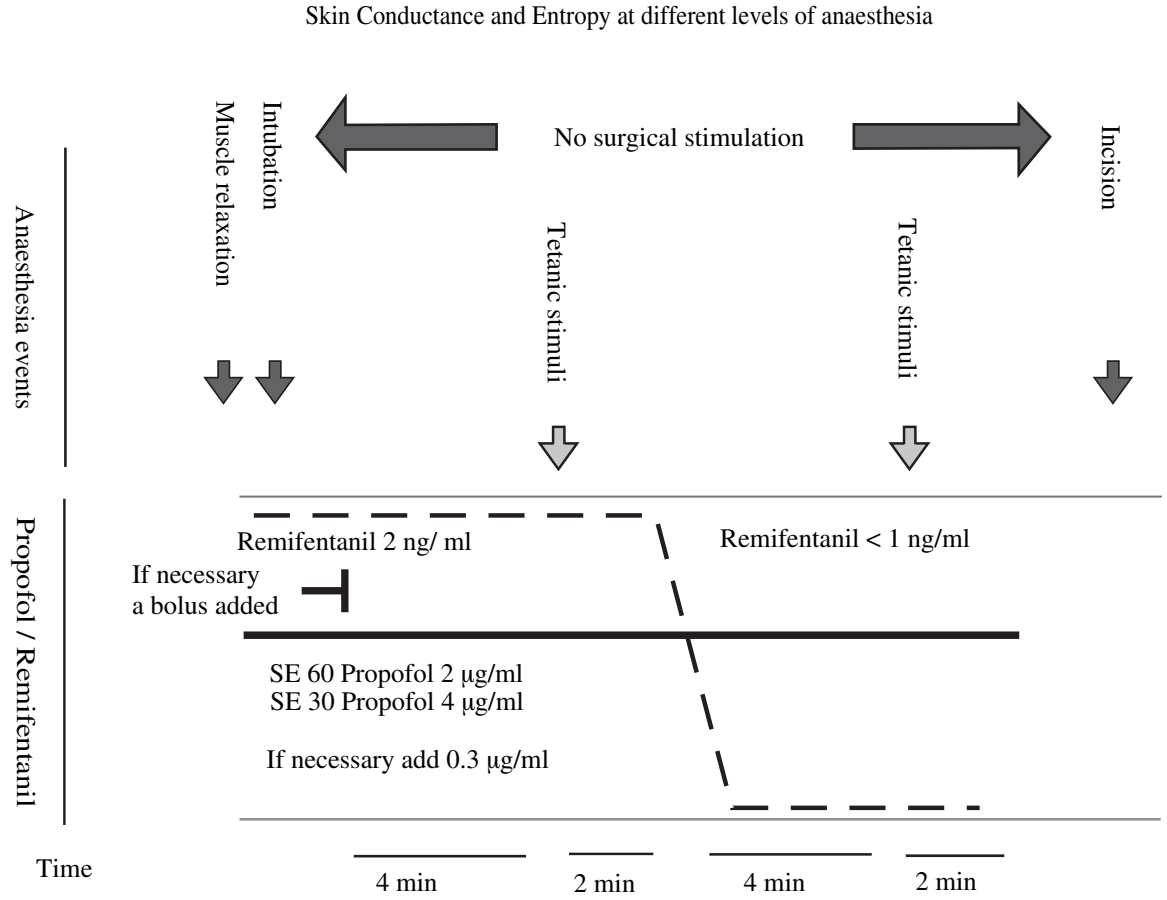

Fig. 1. Before intubation, the patients were randomly divided into two different groups targeting for different levels of sedation: state entropy (SE) = 60 and SE = 30. The SE = 60 group was given propofol at a target-controlled infusion (TCI) of 2 µg/ml; 0.3 µg/ml was added if necessary, together with remifentanil at a TCI of 2 ng/ml (a bolus of remifentanil was added if necessary during intubation). The SE = 30 group was given propofol at a TCI of 4 µg/ml; 0.3 µg/ml was added if necessary, together with remifentanil at a TCI of 2 ng/ml (a bolus of remifentanil was added if necessary during intubation). After intubation, the patients were maintained at the two different levels of sedation, SE = 30 and SE = 60; remifentanil was maintained at 2 ng/ml for 4 min before skin conductance and entropy responses to tetanic stimulation were measured at different levels of analgesia.

These data are described as the median and range, with the 25% and 75% quartiles added for the data during emergence. All P values are given with the numerical values. All the tests were performed using SPSS 12.0 (SPSS Inc., Chicago, IL). The level of statistically significant values was $P < 0.05$. $P > 0.05$ was characterized as not significant (NS). Owing to the controversy concerning the Bonferroni method, the data are shown without Bonferroni correction (17).

Results

Nine of the 20 patients reacted to intubation according to the criteria in the clinical stress score, having a clinical stress score different from zero. NSCF increased from zero in all of these nine patients and in two others, with significant correlation found between the observed and measured stress responses in the full group of 20 patients ($r^2 = 0.73$, $P < 0.0005$) (Fig. 2). RE-Δ increased by > 10 in five of these nine patients and in two others. RE-Δ also correlated with the stress score in the full patient group ($r^2 = 0.33$, $P = 0.007$). Fifteen patients had an SE index below 70 during intubation; four of these had a positive clinical stress response score. In these 15 patients, the stress score correlated with the NSCF and RE-Δ responses. Six of the 15 patients, including the four with a positive stress score, showed an increase in NSCF ($r^2 = 0.72$, $P < 0.0005$), and four of the 15 patients, including two with a positive stress score, showed an increase in RE-Δ ($r^2 = 0.34$, $P = 0.02$).

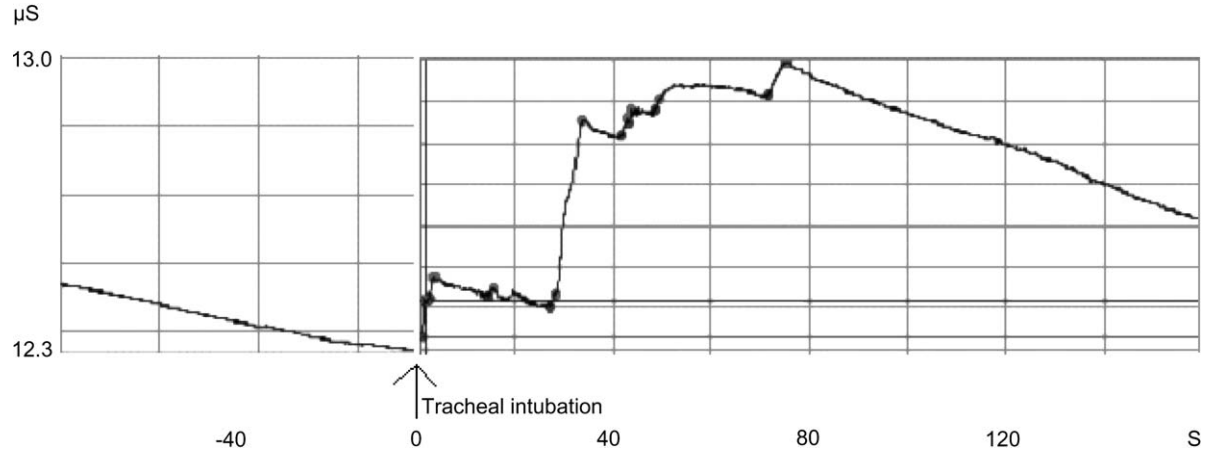

Fig. 2. Skin conductance variables changed during endotracheal intubation. This patient moved her arms and coughed. The response entropy (RE) was then 97 and the state entropy (SE) was 87.

There was no response during tetanic stimulation, as judged by the clinical stress score. However, 16 of the 20 patients reacted to tetanic stimulation according to NSCF, and showed an NSCF pre-stimuli level that was significantly lower than the post-stimuli level ($P < 0.001$) (Fig. 3, Table 2). The RE-Δ pre-stimuli level was no different from the post-stimuli level (NS) (Table 2). All of these 16 patients reacted to tetanic stimulation during R–, but only nine during R+. The NSCF response during R– was significantly greater than that during R+, with 14 patients having a higher NSCF value during R–than during R+ ($P = 0.002$). The RE-Δ responses did not differ between R+ and R– (Table 2). NSCF showed a non-significant tendency to be higher during both R+ and R– in the SE = 60 group than in the SE = 30 group (Table 3). The *post hoc* power test showed that, to find a possible statistical significance of the observed difference, another 20 patients needed to be studied (Table 3).

During emergence, SC responded similarly to SE = 70 and SE = 80. However, RE = 70 and RE = 80 were reached significantly more rapidly than changes in SC variables, with $P = 0.002$ and $P = 0.03$, respectively (Table 4, Fig. 4). In one case, the SC variables did not increase within 1 min after extubation. In this case, SE = 70, SE = 80, RE = 70 and RE = 80 showed emergence at 278, 252, 288 and 270 s before extubation, respectively. In another case, SE = 70, SE = 80 and RE = 80 were not reached within 1 min after extubation, and RE = 70 was reached within 58 s after extubation. In this case, the SC variables showed emergence 2 s before extubation.

The SC variables indicated signs of emergence before RE = 70 in three patients. Signs of emergence before extubation (T0) were present in 80%, 80%,

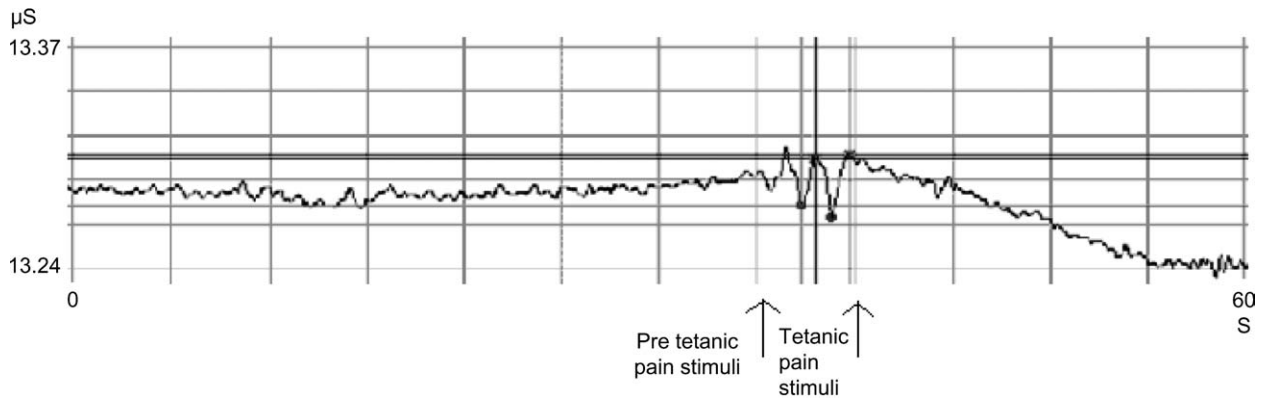

Fig. 3. Skin conductance variables before, during and after tetanic stimulation.

Table 2

Skin conductance and entropy during tetanic stimulation. During tetanic stimulation, the mean of the two tetanic pre-stimuli periods was compared with the mean of the two tetanic post-stimuli periods, and the responses during tetanic stimulation with remifentanil (R+) were compared with those during tetanic stimulation without remifentanil (R–).

	Median	Range	25–75% percentiles	*P* values
Mean pre NSCF level	0.0	0.0–0.03	0.0–0.0	
Mean post NSCF level	0.04	0.0–0.2	0.03–0.09	0.001
Mean pre RE-Δ level	2.0	0.5–11.0	0.63–2.5	
Mean post RE-Δ level	1.5	−0.5–4.5	1.0–2.0	0.442
NSCF R+	0.0	0.0–0.15	0.0–0.05	
NSCF R–	0.05	0.0–0.4	0.05–0.1	0.002
RE-Δ R+	1.0	−2.0–8.0	1.0–2.0	
RE-Δ R–	1.0	0.0–5.0	1.0–3.0	0.28

NSCF, number of skin conductance fluctuations; RE-Δ, SE – RE.

80%, 95% and 90% for the SC variables, SE = 70, SE = 80, RE = 70 and RE = 80, respectively.

Two patients showed values of emergence (SE > 65 and RE > 80) during surgery that lasted for 30 min and 35 min, respectively, without any other signs of stress or awakening or change in the SC variables. In both of these cases, the propofol doses were increased, just in case, but with no resulting reduction in RE and SE.

Discussion

This study evaluated the RE-Δ and NSCF responses to tracheal intubation stress and noxious stimuli during general anaesthesia. Moreover, the responses of SE, RE and SC variables during emergence were studied. During tracheal intubation, NSCF showed a significant positive correlation with the clinical stress score. This correlation was also maintained in patients in a deeper anaesthetic state, as judged by low SE values, making NSCF useful even in patients in deeper levels of anaesthesia. RE-Δ showed a less pronounced correlation with the clinical stress score during tracheal intubation. Seitsonen et al. (18) found that RE-Δ measured the responses to skin incision. The method used as a stress score was movement only. In our patients, movement was also followed by high levels of RE and SE (SE > 65). The movement response, in general, may therefore be a sign of a wake-up situation, and more sensitive measurement modalities may be beneficial to detect stress at an earlier stage.

Although parts of the clinical stress score (movement) and electromyographic signals may be abolished by neuromuscular blockers, the dose of blocking agent in our study was low and both the stress score and RE-Δ were still sensitive to intubation stimuli. Messner et al. (19) showed that, in fully awake subjects, succinylcholine injection resulted in a profound decrease in BIS values to the range defined as clinical anaesthesia. They interpreted this as the electromyographic signal being an important part of BIS (SW version 3.31). Messner et al. did not expose their subjects to noxious stimuli.

In our study, NSCF was more sensitive than RE-Δ and the clinical stress score to noxious tetanic stimulation. During concomitant analgesic infusion (i.e. remifentanil), the stress response from tetanic stimulation was further reduced according to NSCF, whereas SE, RE and RE-Δ were still unresponsive (Table 3). This may indicate that NSCF is a more sensitive detector of subclinical stress than the other monitoring indices. Furthermore, NSCF may be used to monitor the opioid analgesic effect in the unconscious patient, as the response was decreased when opioid was added to propofol-based general anaesthesia during standardized noxious stimulation. Alternatively, electroencephalographic bicoherence has previously been found to be sensitive to noxious stimulation. Noxious stimulation decreased the peak heights of electroencephalographic bicoherence,

Table 3

Response of the number of skin conductance fluctuations (NSCF) during tetanic stimulation with (R+) and without (R–) remifentanil in the state entropy (SE) = 30 and SE = 60 groups.

Group (mean, range)	NSCF, R+ (mean, range)	NSCF, R– (mean, range)
SE = 30 (37.4, 21–50)	0.015 (0.05–0.10)	0.05 (0.0–0.15)
SE = 60 (52, 41–64)	0.04 (0.0–0.15)	0.11 (0.0–0.3)

Table 4

Skin conductance and entropy during emergence after surgery. During emergence after surgery, skin conductance (SC) was compared with response entropy (RE) and state entropy (SE). Median, range and 25% and 75% percentiles are given in seconds from the extubation time point. Negative values are before extubation and positive values are within 60 s after extubation. One patient did not reach emergence according to SC within 60 s after extubation, and another patient did not reach emergence according to SE = 70, SE = 80 and RE = 80 within 60 s after extubation.

	SC (n = 19)	SE 70 (n = 19)	SE 80 (n = 19)	RE 70 (n = 20)	RE 80 (n = 19)
Median	−14	−24	−9	−50	−33
Range	−63 to +27	−278 to +2	−252 to +7	−288 to +58	−270 to +1
25−75% percentiles	−27 to −7	−55 to −12	−38 to −4	−78 to −23	−69 to −12
P value		0.2	0.9	0.002	0.03

and this effect was counteracted by fentanyl analgesia (20).

A method is needed to measure the level of analgesia during general anaesthesia. Without analgesia, the high concentrations of hypnotic anaesthetics required to prevent patient reaction during surgery would delay post-operative recovery from anaesthesia. Hypnotic anaesthetics are generally unable to fully suppress brain responses to noxious stimulation at clinical doses (21, 22).

RE, SE and SC variables predicted emergence, with RE being the most rapid predictor. During emergence after surgery, RE = 70 was reached significantly more rapidly than changes in the SC variables ($P = 0.002$). However, there are individual variations. One patient showed a good prediction of emergence according to the entropy parameters, with the SC parameters delayed. In another patient, the situation was reversed, with SC as the better predictive modality.

RE and the SC variables thus seem to provide supplementary information to each other during emergence, possibly because they act by different physiological mechanisms. A faster indication of emergence from anaesthesia has been reported previously with RE than with SE and BIS (23). The finding that RE indicates emergence earlier than SE and BIS can partly be explained by the different lengths of the time windows applied in the evaluations of the indicators (24). The high frequencies associated with frontal electromyographic activity are obtained from a window of less than 2 s in the RE computations, providing practically instantaneous information. For SE, most data are obtained from a 15-s window. For BIS, the length of the smoothing window is 15 s, which is the fastest alternative provided by the BIS monitor (23).

In conclusion, the results show that NSCF is better than RE-Δ for the prediction of clinical stress during intubation. By contrast with RE-Δ, NSCF is also responsive to tetanic stimulation, with an attenuated response when opioid analgesia is added to propofol anaesthesia. During emergence from anaesthesia, RE responds before the SC variables, but both modes of monitoring can predict emergence in the majority of cases.

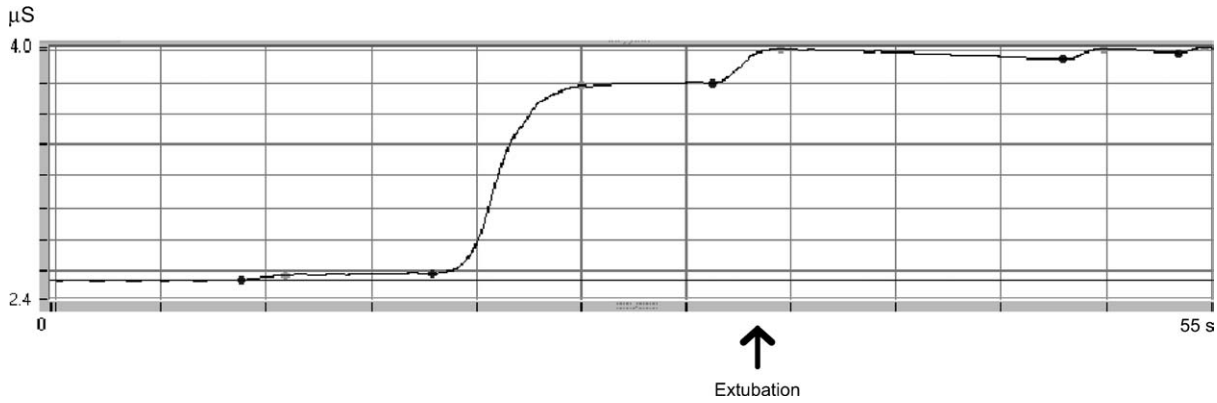

Fig. 4. Skin conductance variables during emergence after surgery under general anaesthesia.

References

1. Struys MM, Jensen EW, Smith W et al. Performance of the ARX-derived auditory evoked potential index as an indicator of anesthetic depth. *Anesthesiology* 2002; **96** (4): 803–16.
2. Schmidt GN, Bischoff P, Standl T, Hellstern A, Teuber O, Schulte Esch J. Comparative evaluation of the Datex-Ohmeda S/5 Entropy Module and the Bispectral Index Monitor during propofol–remifentanil anesthesia. *Anesthesiology* 2004; **101** (6): 1283–90.
3. Vanluchene AL, Struys MM, Heyse BE, Mortier EP. Spectral entropy measurement of patient responsiveness during propofol and remifentanil. A comparison with the bispectral index. *Br J Anaesth* 2004; **93** (5): 645–54.
4. Paloheimo M. Quantitative surface electromyography (qEMG): applications in anaesthesiology and critical care. *Acta Anaesthesiol Scand Suppl* 1990; **93**: 1–83.
5. Edelberg R. Electrical properties of the skin. In: Brown, CC, ed. *Methods in Psychophysiology.* Baltimore: Williams & Wilkins, 1967: 1–53.
6. Lidberg L, Wallin G. Sympathetic skin nerve discharges in relation to amplitude of skin resistance responses. *Psychophysiology* 1981; **18** (3): 268–70.
7. Bini G, Hagbarth KE, Hynninen P, Wallin BG. Thermoregulatory and rhythm-generating mechanisms governing the sudomotor and vasoconstrictor outflow in human cutaneous nerves. *J Physiol* 1980; **306**: 537–52.
8. Storm H, Myre K, Rostrup M, Stokland O, Lien MD, Ræder X. Skin conductance correlates with perioperative stress. *Acta Anaesthesiol Scand* 2002; **46**: 887–95.
9. Storm H. Skin conductance and the stress response from heel stick in preterm. *Infants Arch Dis Child Fetal Neonatal Ed* 2000; **83**: F143–7.
10. Wessel DL. Hemodynamic responses to perioperative pain and stress in infants. *Crit Care Med* 1993; **21**: 361–2.
11. Hagbarth KE, Hallin RG, Hongell A, Torebjørk HE, Wallin BG. General characteristics of sympathetic activity in human skin nerves. *Acta Physiol Scand* 1972; **84**: 164–76.
12. Wallin BG, Sundløf G, Delius W. The effect of carotid sinus nerve stimulations on muscle and skin nerve sympathetic activity in man. *Plügers Arch* 1975; **358**: 101–10.
13. Grimnes S. Pathways of ionic flow through human skin in vivo. *Acta Derm Venereol* 1984; **64**: 93–8.
14. Storm H, Fremming A, Ødegaard S, Martinsen ØG, Mørkrid L. The development of a software program for analyzing spontaneous and externally elicited skin conductance changes in infants and adults. *Clin Neurophysiol* 2000; **111**: 1889–98.
15. Gjerstad AC, Storm H, Hagen R, Huiku M, Quigstad E, Raeder J. Skin conductance or entropy for detection of non-noxious stimulation during different clinical levels of sedation. *Acta Anaesthesiol Scand* 2007; **51**: 1–7.
16. Storm H, Shafiei M, Myre K, Ræder J. Palmar skin conductance compared to a developed stress score and to noxious and awakening stimuli on patients in anaesthesia. *Acta Anaesthesiol Scand* 2005; **49**: 798–803.
17. Perneger T. What's wrong with Bonferroni adjustments. *Br Med J* 1998; **316**: 1236–8.
18. Seitsonen ER, Korhonen IK, van Gils MJ et al. EEG spectral entropy, heart rate, photoplethysmography and motor responses to skin incision during sevoflurane anaesthesia. *Acta Anaesthesiol Scand* 2005; **49**: 284–92.
19. 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.
20. Hagihira S, Takashina M, Mori T, Ueyama H, Mashimo T. Electroencephalographic bicoherence is sensitive to noxious stimuli during isoflurane or sevoflurane anesthesia. *Anesthesiology* 2004; **100** (4): 818–25.
21. Segawa H, Mori K, Murakawa M et al. Isoflurane and sevoflurane augment norepinephrine responses to surgical noxious stimulation in humans. *Anesthesiology* 1998; **89**: 1407–13.
22. Zbinden AM, Petersen-Felix S, Thomson DA. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia: hemodynamic responses. *Anesthesiology* 1994; **80**: 261–7.
23. Vakkuri A, Yli-Hankala A, Talja P 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** (2): 145–53.
24. Viertô-Oja H, Maja V, Sârkela M et al. Description of the Entropy™ algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. *Acta Anaesthesiol Scand* 2004; **48**: 154–61.

Address:
Ann Christin Gjerstad
The Skills Training Centre
National University Hospital
Oslo
Norway
e-mail: acg@online.no