Skin conductance monitoring compared with bispectral index® monitoring to assess emergence from general anaesthesia using sevoflurane and remifentanil

T. Ledowski¹ *, M. J. Paech², H. Storm³, R. Jones¹ and S. A. Schug²

¹Department of Anaesthesia and Pain Medicine, Royal Perth Hospital, Perth, Australia. ²School of Medicine and Pharmacology, The University of Western Australia, Perth, Australia. ³The Skills Training Centre, University of Oslo, Norway

*Corresponding author: Department of Anaesthesia and Pain Medicine, Royal Perth Hospital, Wellington Street Campus, Perth WA 6000, Australia. E-mail: thomas.ledowski@health.wa.gov.au

Background. Changes in skin conductance have previously been reported to correlate well with plasma levels of stress hormones and awakening stimuli. In this study, monitoring of skin conductance during emergence from general anaesthesia was compared with the monitoring of bispectral index (BIS).

Methods. Twenty-five patients undergoing minor elective surgery were investigated. The number of fluctuations in mean skin conductance (NFSC), BIS and haemodynamic parameters were recorded simultaneously. The performance of the monitoring devices to predict and distinguish between the clinical states 'steady-state anaesthesia', 'first reaction' and 'extubation' were compared using the method of prediction probability (PÈ) calculation.

Results. Both monitors showed similar performance in distinguishing between 'steady-state anaesthesia' vs 'first reaction' (PÈ, NFSC 0.89; BIS® 0.94) and 'steady-state anaesthesia' vs 'extubation' (PÈ, NFSC 0.96; BIS® 0.96). The response times of the monitors, to indicate the likelihood of 'first reaction', were not significantly different.

Conclusions. NFSC, as a parameter of skin conductance, performed similarly to BIS in patients waking after a general anaesthetic.

Br J Anaesth 2006; 97: 187–91

Keywords: anaesthesia, emergence from; measurement techniques, skin conductance; monitoring, bispectral index

Accepted for publication: April 15, 2006

The correlation of neurophysiological arousal, increased sympathetic tone and changes in electrodermalic properties of the skin have been described by Wallin.¹ An increased activity in subcortical (e.g. brain-stem reticular substance, hypothalamus, amygdala and sympathetic pre-ganglions) and cortical (e.g. prefrontal cortex, orbitofrontal cortex) regions of the brain² ³ finally lead to an increased firing rate of sympathetic, post-ganglionic cholinergic neurons. The resulting increase of sweat gland filling can be measured in terms of skin conductance (SC).⁴

The correlation of SC with perioperative stress has been described more recently by Storm and colleagues.⁵ The same authors demonstrated changes in the mean SC, and in the number of fluctuations within the mean SC per second (NFSC), in patients experiencing either noxious stimuli or during arousal.⁶

The sensitivity and specificity of NFSC regarding the detection of noxious stimuli has been reported to reach 86% when compared with clinical parameters,⁷ but there are no reports about the performance of NFSC monitoring as a tool to indicate arousal after anaesthesia.

As it has been shown that arousal after an anaesthetic correlates with an increase of sympathetic tone measured by heart rate variability (HRV) and stress hormone plasma levels,⁷ we hypothesized that NFSC may be able to detect arousal after general anaesthesia.

The aim of this study was to determine the performance of NFSC during emergence from general anaesthesia and to
compare it with the monitoring of the bispectral index (BIS) as a means of detecting arousal.

**Methods**

After approval by the ethics committee of Royal Perth Hospital, 25 patients undergoing minor elective surgery (minor orthopaedic procedures such as stabilization of single, peripheral fractures, and minor general surgery such as appendectomy, laparoscopic cholecystectomy or hernia repair) gave consent to participate in the trial.

None of the participants received premedication on the day of surgery. The BIS and SC monitors were connected when the patient was positioned on the operating table in a supine position.

BIS monitoring was performed using the BIS® XP A 2000™ monitor (Aspect Medical Systems, Newton, MA, USA) with BIS QUATTRO™ single use electrodes (Aspect Medical Systems, Newton, MA, USA) and a smoothing rate of 15 s. A BIS® value greater than 60 was considered an indicator of light anaesthesia.

The SC monitoring was achieved using the MEDSTORM AS 2005 monitor (Medstorm Innovations, Oslo, Norway) with three single use Ag/AgCl paediatric ECG electrodes (NEOTRODE®, ConMed Corp., Utica, NY, USA) attached to the palmar surface of the hand. The exosomatic electrodermal activity was measured in terms of conductance, which was preferred to resistance because of the parallel nature of the electric polarization and conductance in the skin. The equipment used an alternating current of 88 Hz, which was high enough to reduce the requirements for low electrode polarizability, but low enough to ensure minimal influence from layers of the skin other than the stratum corneum. An applied voltage of 50 mV (highest density 2.5 µA) and a 3-electrode system (measuring, counter and reference electrodes) were used for unipolar measurement with a constant voltage applied to the stratum corneum beneath the measuring electrode. The method has been described as not being disturbed by light movements or changes of the room temperature. The monitor was connected to a laptop computer via a standard serial port connection to see and process the obtained data using a software program developed by Asbjørn Frennings and Hanne Storm and modified for the purpose of the study by Asbjørn Frennings and Thomas Ledowski. The mean SC was given in microsiemens (µS) with a refreshing rate of 1 s. The software was able to define valleys and troughs to determine the amplitude of fluctuations within the mean SC and from this count NFSC. To reduce the electronic noise the minimum amplitude was set at 0.02 µS. According to the study by Storm and coworkers, an increase in the mean SC of >0.1 µS from baseline and/or a NFSC of >0.1 s⁻¹ in a period of 15 s might be counted as a significant change and indicates an increase in the sympathetic outflow/arousal. Based on our pilot study (T.L., unpublished observations, data on file) to look for SC changes during awakening, we opted to use only a change of the NFSC of >0.1 s⁻¹ in a period of 15 s for the purpose of this trial, as our experience suggested the changes in the derivate of the mean SC were not sufficiently sensitive to indicate arousal.

Anaesthesia was induced with propofol 2 mg kg⁻¹ and remifentanil 0.5 µg kg⁻¹ min⁻¹. Muscle relaxation was achieved with rocuronium 0.6 mg kg⁻¹ and, after full recovery, no reversal agents were given at the end of surgery. After placement of the airway device, either a tracheal tube or a laryngeal mask, anaesthesia was maintained using sevoflurane and remifentanil, as clinically appropriate. Ten minutes before the anticipated end of surgery, the remifentanil infusion was stopped and fentanyl was given in a dose considered appropriate for postoperative analgesia (dose range 0–150 µg). Sevoflurane was ceased at the end of surgery. At the time of stopping the remifentanil infusion, a stopwatch was started and blood pressure, heart rate, BIS, NFSC and a clinical score of depth of sedation, the observer alertness assessment scale (OAA/S) were recorded every 2 min and at defined time points (‘first clinical reaction’, ‘extubation’). The times from cessation of remifentanil and sevoflurane to the first BIS value >60 and NFSC >0.1 s⁻¹, and from a BIS >60 and NFSC >0.1 s⁻¹ to the time of first clinical reaction (defined as any reaction of the patient that would clinically indicate a light anaesthesia, like coughing, movement or eye opening) and extubation were recorded. The patients were extubated as soon as they were considered clinically suitable and showed a minimum OAA/S of 3 points.

**Statistical analysis**

The accuracy to distinguish between the anaesthetic states of ‘steady state’ vs ‘first clinical reaction’ and ‘steady state’ vs ‘extubation’ were analysed with the prediction probability (PK). This method has previously been described by Smith and colleagues and recently published to compare the performance of BIS® and NARCOpTREN® monitoring by Schmidt and colleagues. For the calculation of the PK values a custom spreadsheet macro (PKMACRO) as described by Smith and colleagues was used. A second spreadsheet (PKDMACRO) was used to compute the r-value for a comparison between PK values of the different monitors.

The standard error of the estimate was computed by the jackknife method. A PK value of 1 means a 100% correct prediction of a certain clinical state by a specific monitor, whereas a value of 0.5 represents only a 50:50 chance.

Correlation of NFSC and BIS were estimated using the Spearman rank correlation coefficient (p). The probability for first reaction (OAA/S>0) compared with steady-state anaesthesia was calculated for certain values of BIS and NFSC.

**Results**

The data of 25 patients [5 female, 20 male; mean age (range): 35 (18–65) yr; mean weight (SD): 85 (17) kg;
mean height: (SD) 174 (9) cm; 14 ASA I, 11 ASA II) were included in the analysis.

A laryngeal mask was used as was an airway device in 14 patients and a tracheal tube in 11 patients.

Fentanyl was given in a mean dose of 70 μg (0–150 μg) at the time the remifentanil infusion [0.24 (0.15) μg kg⁻¹ min⁻¹ [mean (SD)]] was stopped.

The investigated response times ‘Cessation of remifentanil to first BIS >60/NFSC >0.1 s⁻¹’, ‘Cessation of sevoflurane to first BIS >60/NFSC >0.1 s⁻¹ to first clinical reaction’ and ‘First BIS >60/NFSC >0.1 s⁻¹ to extinction’ were not significantly different (Table 1). There was no significant difference between patients with a laryngeal mask or a tracheal tube. The amount of fentanyl given did not significantly affect the response times.

BIS showed a higher $P_K$ value than NFSC regarding the differentiation between ‘steady-state anaesthesia’ and ‘first clinical reaction’ and both monitors were identical regarding ‘steady-state anaesthesia’ and ‘extubation’ (Table 2). Both BIS and NFSC were able to distinguish the investigated clinical stages with a higher $P_K$ than the classic haemodynamic parameters of heart rate and blood pressure (Table 2). However, only the difference of $P_K$ values of BIS and heart rate for distinguishing ‘steady-state anaesthesia’ from ‘extubation’ reached the level of statistical significance ($P<0.05$).

We investigated the correlation between the achieved points in the OAA/S scale at the time of ‘first reaction’ and ‘extubation’ and the BIS and NFSC readings at these times. The only statistically significant correlation ($r=0.404; P<0.05$) was found between NFSC and the OAA/S scale at the time of extubation ($P<0.05$).

A significant correlation could be found between BIS and NFSC values at the time of ‘first clinical reaction’ ($p=0.541; P<0.01$).

The probability of an OAA/S scale value of >0 as a function of BIS and NFSC at all 317 readings was calculated and is shown in Figure 1.

**Discussion**

This investigation demonstrates that the monitoring of SC, represented by the monitoring of fluctuations in the mean level of SC per second, was able to predict a first clinical reaction of the patient, when emerging from steady-state anaesthesia with sevoflurane and remifentanil, with a slightly lower accuracy than BIS. The performance of BIS and NFSC was identical in differentiating the clinical state ‘extubation’ from that of ‘steady-state anaesthesia’.

Both, NFSC and BIS, showed higher $P_K$ values (significant for BIS vs heart rate, see Table 2) than the classic haemodynamic parameters said to be associated with light anaesthesia, namely blood pressure and heart rate. However, the parameter blood pressure distinguished ‘steady-state anaesthesia’ from ‘extubation’, with a $P_K$ value higher than 0.9.

| Table 1 | Response times of bispectral index (BIS) and SC (represented by the number of fluctuations per seconds, NFSC). n=25 |

<table>
<thead>
<tr>
<th>Response times (s)</th>
<th>Percentiles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Cessation remifentanil to BIS &gt;60</td>
<td>420</td>
</tr>
<tr>
<td>Cessation remifentanil to NFSC &gt;0.1 s⁻¹</td>
<td>399</td>
</tr>
<tr>
<td>Cessation sevoflurane to BIS &gt;60</td>
<td>270</td>
</tr>
<tr>
<td>Cessation sevoflurane to NFSC &gt;0.1 s⁻¹</td>
<td>236</td>
</tr>
<tr>
<td>BIS &gt;60 to 1st clinical reaction</td>
<td>420</td>
</tr>
<tr>
<td>NFSC &gt;0.1 s⁻¹ to 1st clinical reaction</td>
<td>441</td>
</tr>
<tr>
<td>BIS &gt;60 to extubation</td>
<td>510</td>
</tr>
<tr>
<td>NFSC &gt;0.1 s⁻¹ to extubation</td>
<td>534</td>
</tr>
</tbody>
</table>

| Table 2 | Prediction probability ($P_K$) and standard error (SE) for mean arterial blood pressure (MAP), heart rate (HR), bispectral index (BIS) and skin conductance (SC). $P_K$ of 1 means a correct prediction in 100%, $P_K$ 0.5 means that a parameter predicts a condition correctly only with a 50:50 chance. * Statistically significant $P<0.05$ |

<table>
<thead>
<tr>
<th>Steady state vs 1st clinical reaction</th>
<th>Steady state vs extubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_K$</td>
<td>SE</td>
</tr>
<tr>
<td>BIS</td>
<td>0.94</td>
</tr>
<tr>
<td>SC</td>
<td>0.89</td>
</tr>
<tr>
<td>MAP</td>
<td>0.85</td>
</tr>
<tr>
<td>HR</td>
<td>0.81</td>
</tr>
</tbody>
</table>

The fact that changes of SC do not only reflect changes in subcortical, but also in cortical areas (e.g. the medial prefrontal lobe and the visual cortex) may explain the similar performance of NFSC and BIS at specific endpoints. However, changes of SC have been correlated with an increased activity of a high number of different areas of the brain, such as the cerebellum, lingual gyrus or right posterior cingulate and it remains unclear, where exactly a change in anaesthetic depth provokes an increased brain activity leading to a change of NFSC. This reflects the unsolved discussion about what depth of anaesthesia really means and how and where it should ideally be assessed.

An easy to perform clinical score, like the OAA/S, is cost-effective and has been validated for depth of sedation assessment. Though such a scale could be appropriate for unparalysed, anaesthetized patients, there are reports of intraoperatively undetected awareness even in unparalysed patients. The value of the classic haemodynamic parameters is controversial. Schmidt and colleagues comparing the performance of BIS and Narcotrend monitoring, found that the parameter ‘blood pressure’ performed as well as in our trial. They concluded that the increase in blood pressure towards the end of surgery was more likely to reflect the fading of cardio-depressant effects of the anaesthetic drugs than to reflect arousal. The fact that intraoperative awareness can be indicated by increased sympathetic tone has resulted in the investigation of monitoring of sympathovagal balance, such as the assessment of HRV. Currently there does not appear to be a device for HRV monitoring that
fulfils the criteria for suitable online, in-theatre monitoring, because the minimal sampling rate for HRV data is several minutes.

The concept of using changes in the electrogalvanic activity of the skin for the purpose of assessment of sympathetic activity, and related to that, sedation was raised almost 40 yr ago by Nisbet and coworkers\textsuperscript{16} and reinvestigated by Goddard\textsuperscript{17} in 1982. Storm and colleagues\textsuperscript{5} recently demonstrated a significant correlation of SC with perioperative plasma levels of stress hormones. The same group compared a clinical stress score and noxious and awakening stimuli with the readings of the palmar SC from these patients.\textsuperscript{5} The authors concluded that, in particular, the parameter NFSC, or a combination of that value with the increase in mean level of SC, might be a useful tool for depth of anaesthesia assessment.\textsuperscript{6} They suggested it had the potential to distinguish a state in which either the depth of anaesthesia or the analgesic state was inadequate. In our study, we used only the parameter of NFSC to represent SC and to compare it with BIS. For this reason we are unable to comment on the value of a combination of different SC parameters.

Using a modified software version we were able to generate a monitor that was as easy to read in the operating room as BIS (with only one value of the NFSC on the screen). We were able to demonstrate the similar performance of NFSC and BIS in distinguishing between ‘steady-state anaesthesia’ and ‘first clinical reaction’ or ‘extubation’, respectively. To our knowledge, this is the first study that compares these two monitors and therefore it is premature to draw conclusions about the value of NFSC in anaesthesia. The fast refreshing rate of 1 s might have contributed to the good performance of NFSC, as BIS readings in contrast, are known to represent the clinical state with a delay of approximately 30 s.\textsuperscript{18} Hence, a BIS software with a faster sampling rate may well perform better, especially with regard to the investigated response times. Despite this we found BIS performed very well in distinguishing ‘steady-state anaesthesia’ from a ‘first clinical reaction’ ($P_k$ 0.94). Schmidt and coworkers\textsuperscript{10} found BIS achieved only a $P_k$ of 0.79 in describing the same clinical states. However, the different monitor we used (the BIS XP A 2000\textsuperscript{TM}, monitor compared with a BIS A-1000\textsuperscript{TM} monitor) or the different anaesthetic technique (in this study sevoflurane and remifentanil compared with propofol and remifentanil by Schmidt and coworkers\textsuperscript{10}) might at least partially explain the different results.

In this study, we found similar changes in NFSC and BIS during the investigated states of anaesthesia. The response times indicating arousal were not significantly different between the monitors. Both monitors showed higher $P_k$ values than the haemodynamic parameters for distinguishing different clinical states during emergence from a balanced general anaesthetic.

Acknowledgements

Financial support: This study was funded by the Department of Anaesthesia and Pain Medicine, Royal Perth Hospital. Each monitor was a research bound loan device from the manufacturers: Device for Skin Conductance by Medstorn Innovation, Oslo, Norway; Bispectral Index\textsuperscript{R} Monitor by Aspect Medical Systems Inc., Natick, USA.

References

9 Smith WD, Dutton RC, Smith NT. Measuring the performance of anesthetic depth indicators. Anesthesiology 1996; 84: 38–51
18 Jensen EW, Litvan H. Rapid extraction of mid-latency auditory-evoked potentials (letter). Anesthesiology 2001; 94: 718