Influence of different remifentanil concentrations on the performance of the surgical stress index to detect a standardized painful stimulus during sevoflurane anaesthesia

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Background. Although measurement of cerebral hypnotic drug effect and muscle relaxation is common clinical routine during anaesthesia, a reliable measurement of the neurophysiological effects evoked by a painful stimulus is still missing. Recently, the surgical stress index (SSI) has been introduced as a surrogate measure of ‘nociception’. The present study aimed to examine the influence of increasing remifentanil concentrations on the ability of SSI to detect a standardized painful stimulus during sevoflurane anaesthesia.

Methods. Twenty-four patients received incremental or decremental doses of 0, 2, and 4 ng ml⁻¹ remifentanil effect-site concentration (Cₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑ电厂) during 0.7 MAC sevoflurane. Painful tetanic stimulation was applied at least 5 min after changing Cₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑ电厂. SSI, heart rate (HR), response entropy (RE), state entropy (SE), RE–SE difference, and bispectral index (BIS) were obtained in each patient before and after stimulation. Further prediction of an author-defined response to painful stimulus was analysed.

Results. SSI and BIS, but not HR, SE, RE, or RE–SE difference were significantly altered after stimulation. Change in SSI (ΔSSI) was significantly dependent on Cₑₑₑₑₑₑₑₑₑₑₑ电厂, as ΔSSI was [median (inter-quartile range)] 20 (15–31), 10 (1–19), and 3 (1–10) at 0, 2, and 4 ng ml⁻¹ Cₑₑₑₑₑ电厂. In 10 out of 63 cases, SSI detected response to stimulation, not detected by another variable. SSI was unable to predict movement after stimulation as Pₛₚ value is 0.59 (0.09).

Conclusions. The SSI response to tetanic stimulation was dependent on the remifentanil concentration.

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Keywords: anaesthesia, general; anaesthetics volatile, sevoflurane; analgesics opioid, remifentanil; equipment, monitors

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General anaesthesia can be considered as a combination of hypnosis, anti-nociception, and immobility. However, an exact definition of ‘general anaesthesia’ is still under debate. The ability of the central nervous system to respond to a painful stimulus has recently been defined as ‘nociception’ and the potential of analgesic techniques to inhibit this response is called ‘anti-nociception’. A major goal in anaesthesia is to obtain an adequate balance between ‘nociception and anti-nociception’ because a lack of such a balance might result in antagonism of the hypnotic drug effect (arousal), humoral and autonomic stress responses, or involuntary movements. Although monitoring of the cerebral hypnotic drug effect, derived from processed EEG variables and muscle relaxation, has become available for clinical practice, a continuous measure of the neurophysiological effects evoked by a painful stimulus is still missing. Instead, clinical signs like somatic (movement) or autonomic [heart rate (HR) increase, arterial pressure increase, or sweating] responses are used to judge adequacy of analgesia. Efforts to quantify autonomic activation have been made by analysing skin conductance, HR variability, or variability of pulse plethysmography. A bedside quantification of the neurophysiological activation evoked by a painful stimulus may
change drug administration regimens, result in different consumption of anaesthetics,\(^5\) and possibly influence patients’ outcome.

The multivariate surgical stress index (SSI),\(^10\) based on a sum of the photoplethysmographic pulse wave amplitude (PPGA) and the normalized heart beat interval (HBI), has been demonstrated to correlate with surgical stress intensity. SSI showed negative correlation with remifentanil effect-site concentrations (C\(_{\text{remi}}\)) and positive correlation with stimulus intensity during total i.v. anaesthesia with propofol.\(^10\) In contrast to propofol, analgesic properties have been described for the volatile anaesthetic sevoflurane\(^11\) and anaesthetic potency of volatiles are based on response to painful stimulation.\(^12\) Therefore, SSI might be also influenced and results gained from studies during propofol anaesthesia may not be transferred into a balanced anaesthesia setting using sevoflurane.

The aim of the present prospective study was to evaluate the influence of noxious stimulation on SSI during sevoflurane anaesthesia and various remifentanil target effect-site concentrations (C\(_{\text{remi}}\)). We hypothesized that, first, during stable sevoflurane concentrations, increasing C\(_{\text{remi}}\) will reduce SSI; secondly, the effect of noxious stimulation on SSI is negatively correlated to C\(_{\text{remi}}\); and thirdly, SSI will enable detection of nociception not indicated by standard monitoring variables. Furthermore, we sought to investigate whether SSI enables prediction of a response to painful stimulation.

**Methods**

After obtaining approval of the institutional review board of the University Hospital Schleswig-Holstein, Campus Kiel, registration of this trial at clinicaltrials.gov (NCT00791791), and written informed consent, 24 patients ASA physical status I or II, aged between 18 and 65 yr, undergoing elective gynaecological laparoscopy were enrolled. Patients were not studied, if they were pregnant, had a history of cardiac arrhythmia, presence of any neuromuscular or neurological disease, and use of CNS-active medication or abuse of alcohol or illicit drugs. Anaesthesia in all patients was performed by an experienced staff anaesthetist.

Patients received no premedication before anaesthesia. After arrival in the operating theatre, standard monitoring, including non-invasive arterial pressure (NIAP; 3 min measuring interval), ECG, pulse oximetry (all measured by S/5\(^\text{TM}\) Anaesthesia Monitor; GE Healthcare, Chalfont, St Giles, UK), and venous access via a forearm vein, was established. Signal from finger plethysmography was additionally transferred to a personal computer calculating, visualizing, and recording the SSI continuously (GE Healthcare, Helsinki, Finland). After preparing the skin of the forehead, two disposable EEG sensors were positioned close to each other, consistent with the manufacturer’s recommendations, and randomly assigned to the left or right side of the forehead. Entropy Sensor (GE Healthcare) and BIS Sensor (BIS Quatro, Aspect Medical Systems, Norwood, MA, USA) were connected with respective M-Entropy (Version 1.0 L-ANE03, Automatic Sensor check ‘on’) and M-BIS (software version 3.12, Automatic Sensor Check ‘on’), smoothing rate of 15 s) modules of S/5\(^\text{TM}\) Anaesthesia Monitor. Bispectral index (BIS), state entropy (SE), and response entropy (RE) were recorded continuously from before induction of anaesthesia until the end of the measuring period. All patients received an i.v. infusion of crystalloid solution (Sterofundin, Braun Melsungen AG, Melsungen, Germany; 2–4 ml kg\(^{-1}\) h\(^{-1}\)) during the entire study period.

An illustration of the study protocol is given in Figure 1. Anaesthesia was induced after preoxygenation via mask induction with sevoflurane (Sevorane\(^\text{®}\), Abbott GmbH, Wiesbaden, Germany) using 5–7 vol% inspiratory gas concentration. After loss of consciousness, a laryngeal mask (LMA Unique\(^\text{™}\), LMA Deutschland GmbH, Bonn, Germany) was inserted. Anaesthesia was maintained using 0.7 MAC sevoflurane in air, so that both an accepted level of hypnosis (BIS and SE <60) and a high rate of movement responses were expected. Spontaneous ventilation was allowed and if needed assisted by pressure support ventilation in order to maintain normocapnia (target end-tidal CO\(_2\): 35–40 mm Hg). Patients were randomized into two groups by using a sealed envelope to eliminate time-related changes of variables (e.g. a change of analysed variables only due to elapsed time of anaesthesia). In Group 1, remifentanil (Ultiva\(^\text{®}\), GlaxoSmithKline GmbH, Munich, Germany) was increased step by step via a computer-assisted continuous infusion device (Alaris PK pump, Cardinal Health, Rolle, Switzerland; protocol by Minto and colleagues\(^13\)) to a C\(_{\text{remi}}\) of 0–2–4 ng ml\(^{-1}\), whereas in Group 2 remifentanil was decreased from 4–2–0 ng ml\(^{-1}\). A steady-state period of at least 5 min was
allowed at each Ce\textsubscript{remi} before a standardized noxious stimulus was applied via tetanic stimulation (30 s, 60 mA, 50 Hz) at the volar forearm using a standard muscle relaxometer (Innervator, Fisher & Paykel Healthcare, Auckland, New Zealand). Stimulation electrodes were placed over the ulnar nerve on the volar side of the wrist at the opposite arm from SSI sensor. Any event of purposeful movement, coughing, chewing, or grimacing after stimulation, was defined as movement (‘movers’). Stimulation was stopped immediately when movement occurred and inspiratory sevoflurane concentration was intermittently raised as rescue medication. Administration of rescue medication did not cause exclusion of collected data. If no subsequent movement after stimulation occurred, response was defined as ‘non-mover’. No neuromuscular blocking drugs were administered during the entire study period. On the first postoperative day, all patients had a structured interview by an independent anaesthetist to investigate if they experienced any explicit memory or awareness. Also, the level of satisfaction with the overall procedure was determined using a 0–100 scale (100, totally satisfied). All questions of the interview are presented in the supplemental section of the manuscript. In case of memory (e.g. intraoperative talk or pain) during the period after induction of anaesthesia until emergence, a professional psychological interview and psychological support were offered according to institutional guidelines.

SSI is a simple numerical index for surgical stress monitoring obtained by using finger plethysmography and ranging between 0 (very low stress) and 100 (very high stress). A value of 50 represents a mean stress level during anaesthesia. Owing to potentially too broad and ambiguous meaning of the word ‘stress’, SSI will very likely be renamed by the manufacturer to ‘surgical pleth index’. SSI was originally developed during propofol–remifentanil anaesthesia in gynaecological patients. A variety of variables detecting autonomic activation were correlated to the predicted effect-site concentration of remifentanil and stimulus intensity. Then, different linear combinations of these variables were evaluated by least square fit with the estimate of total surgical stress as a dependent variable. SSI finally evolved as a two-variable model including PPGA and HBI, both normalized for inter-patient variability by using histogram transformation. A delay of ~10 s from change in the measured signal to the change in SSI displayed on the monitor is expected due to calculation algorithm of HR and amplitude. The SSI monitor uses a 15 s median filter. A detailed description of SSI, including algorithm for normalization, can be found elsewhere. 10

Statistical analysis

All variables were averaged the minute before stimulation and compared with the peak value within 2 min after the stimulus, and their difference was defined as Δ value. Data comparing variables before and after stimulation were

| Table 1 Patient characteristic data, their physical status according to the ASA, and duration of study period. Group 1 represents patients with increasing remifentanil effect-site concentrations (0–2–4 ng ml\(^{-1}\)), Group 2 represents patients with decreasing remifentanil effect-site concentrations (4–2–0 ng ml\(^{-1}\)). Data are mean (range) or mean (SD), *P<0.05

<table>
<thead>
<tr>
<th>Group 1 (n=11)</th>
<th>Group 2 (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>35 (20–46)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164 (7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63 (12)</td>
</tr>
<tr>
<td>ASA (I/II)</td>
<td>7/4</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>59 (14)</td>
</tr>
</tbody>
</table>

analysed by the Wilcoxon signed-rank test using commercially available statistics software (GraphPad Prism 4, Graphpad Software Inc., San Diego, CA, USA). A P-value of <0.05 was considered statistically significant. Receiver operator characteristics (ROC) analysis was performed to evaluate and visualize whether variables were able to indicate the event of movement. Further, ROC analysis was used to depict threshold values for ΔSSI and ΔHR (peak value after minus average value the minute before the tetanic stimulus) to indicate movement, based on pooled data. Prediction probabilities were calculated to compare the performance of different indicators using \( P_k \)MACRO and \( P_k \)DMACRO spreadsheets as described by Smith and colleagues. 14 Values of variables averaged 1 min before stimulation and Δ values for SSI and HR were used to evaluate predictive power. A \( P_k \) value of 1.0 or 0.0 means a perfect prediction of the event, whereas 0.5 means no better prediction than flipping a coin. Averaged data 1 min before stimulation were analysed to predict a response to painful stimulation as indicated by movement, and also calculated threshold values for ΔSSI and ΔHR or an RE–SE difference ≥5 as reported previously. 15

Results

Twenty-four female patients were included into this study. In three patients, the study could not be completed due to changes in schedule of the operating procedure after inclusion and randomization. Therefore, data of 63 events of painful stimulation in 21 patients were included into the final analysis. Patient characteristic data are illustrated in Table 1. No difference in study groups appeared except for duration of the measuring period. The entropy sensor was attached to the left side in 11 and to the right side in 10 patients (BIS sensor: vice versa). None of the patients had explicit memory of any event during anaesthesia; overall satisfaction was median (inter-quartile range; IQR) 98 (80–100).

SSI awake was median (IQR) 69 (53–78) and 36 (27–47) at loss of consciousness (P<0.05). The adjusted end-tidal sevoflurane concentration was 1.6 (0.1) vol%, corresponding to an individual MAC of 0.7. Normocapnia was achieved throughout the entire experimental period and
mean $\text{E}_\text{CO}_2$ was 41 (3) mm Hg. In the groups receiving $\text{Ce}_{\text{remi}}$ at 0, 2, and 4 ng ml$^{-1}$, a number of 21, 14, and 2 patients remained spontaneously breathing, whereas, respectively, 0, 7, and 19 patients needed positive pressure ventilation.

Figure 2 demonstrates examined variables at each $\text{Ce}_{\text{remi}}$ before and after stimulation. SSI and HR, measured before stimulation, were significantly ($P<0.05$) reduced at $\text{Ce}_{\text{remi}}$ of 2 ng ml$^{-1}$ compared with sevoflurane anaesthesia alone. No further change of SSI and HR was recorded at $\text{Ce}_{\text{remi}}$ of 4 ng ml$^{-1}$.

Painful stimulation resulted in a consistent increase in SSI, which depended on $\text{Ce}_{\text{remi}}$. During $\text{Ce}_{\text{remi}}$ of 0, 2, and 4 ng ml$^{-1}$, painful stimulation increased SSI significantly by median (IQR) 20 (15–31), 10 (1–19), and 3 (1–10) ($P<0.05$, compared with lower $\text{Ce}_{\text{remi}}$). HR, SE, RE, and RE–SE difference were not consistently changed after stimulation.

Tetanic stimulation was more often indicated by SSI than any other examined variable. During 0, 2, and 4 ng ml$^{-1}$ of $\text{Ce}_{\text{remi}}$, stimulation resulted in 17, 3, and 0 cases in movement, in 19, 11, and 6 patients in a $\Delta\text{SSI} \geq 10$, and in 5, 3, and 0 patients in a cerebral arousal detected by an increase in BIS or SE above the recommended threshold of 60 for adequate hypnosis. Movement led to immediate interruption of tetanic stimulation after a mean stimulation time (SD) of 13 (7) s, and therefore significant shorter stimulation period than in non-movers ($P<0.01$). Table 2 presents pooled data of variables before and after stimulation and also $\Delta$ values comparing movers vs non-movers. $\Delta\text{SSI}$, $\Delta\text{HR}$, $\Delta\text{RE}$, and $\Delta\text{RE–SE}$ difference were significantly different in movers and non-movers. SSI showed fast onset after noxious stimulation with peak values occurring 17 s after start of the stimulus. The time course of SSI 60 s before and 120 s after tetanic stimulation is plotted for movers and non-movers in Figure 3.

Regarding pooled data, movement was indicated with an area under the curve of 0.84 for $\Delta\text{SSI}$ and 0.73 for $\Delta\text{HR}$. The optimal threshold value given by ROC analysis was 10 for $\Delta\text{SSI}$: an SSI value of $\geq 10$ predicts movement with a sensitivity of 95% and a specificity of 69%. This threshold value was $\geq 5$ for HR (sensitivity: 50%; specificity: 84%). ROC curves of $\Delta\text{SSI}$ and $\Delta\text{HR}$ are given in Supplementary Figure S1. Further $\Delta\text{SSI}$ is plotted against $\Delta\text{HR}$ in Supplementary Figure S2. In 16 out of 63 cases, SSI indicated stress response that was not indicated by HR increase. In 10 out of these 16 stimulations, patients did not show movement. Predictive power of variables using pooled data is presented in Table 3 using $P_k$ values. Only $\text{Ce}_{\text{remi}}$ and HR values before stimulation showed a predictive power regarding movement, a $\Delta\text{SSI} \geq 10$ and $\Delta\text{HR} \geq 10$ after stimulation. SSI, SE, RE, RE–SE difference, and BIS before stimulation had no predictive power. The ‘sevoflurane only’ subgroup was further analysed and results are presented in Supplementary Table S1.
Discussion

In this prospective randomized study, SSI enabled detection of standardized noxious stimulation at three different remifentanil concentrations during sevoflurane anaesthesia. Detection of stimulation response was more frequent using SSI than any other variable studied. \( \Delta SSI \) was negatively correlated with \( C_{\text{remi}} \). However, prediction of stimulation response, like movement, was better using \( C_{\text{remi}} \) and HR than SSI.

Table 2 Pooled data of SSI, HR, NIAP\(_{\text{sys}}\), SE, RE, BIS in the period (60 s) before tetanic stimulation (pre-stimulation) and peak values (120 s) after tetanic stimulation (post-stimulation). Data are median (IQR) and mean (SD); Groups were compared using the Wilcoxon signed-rank test or paired \( t \)-test. *\( P<0.01 \), **\( P<0.001 \) vs pre-stimulation. Change in variables is presented as \( \Delta \) values (post-stimulation–pre-stimulation difference) in subgroups where movement occurred after tetanic stimulation (mover) and no movement occurred after tetanic stimulation (non-mover). \( \Delta \) Values were compared using the Mann–Whitney \( U \)-test or unpaired \( t \)-test, *\( P<0.01 \), **\( P<0.001 \) vs mover

<table>
<thead>
<tr>
<th></th>
<th>All pre-stimulation (n=63)</th>
<th>All post-stimulation (n=63)</th>
<th>Movers ( \Delta ) value (n=20)</th>
<th>Non-movers ( \Delta ) value (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSI (n=63)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats min(^{-1}))</td>
<td>56 (8)</td>
<td>61 (15)**</td>
<td>11 (10)</td>
<td>3 (7)**</td>
</tr>
<tr>
<td>NIAP(_{\text{sys}}) (mm Hg)</td>
<td>91 (13)</td>
<td>91 (10)</td>
<td>0 (9)</td>
<td>0 (8)</td>
</tr>
<tr>
<td>SE</td>
<td>41 (31–51)</td>
<td>42 (35–53)*</td>
<td>5 (0–11)</td>
<td>2 (–2 to 5)</td>
</tr>
<tr>
<td>RE</td>
<td>41 (33–52)</td>
<td>45 (37–55)**</td>
<td>7 (2–14)</td>
<td>2 (–1 to 5)*</td>
</tr>
<tr>
<td>RE–SE</td>
<td>1 (0–2)</td>
<td>1 (0–3)</td>
<td>2 (0–7)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>BIS</td>
<td>39 (32–49)</td>
<td>43 (35–53)**</td>
<td>3 (0–11)</td>
<td>1 (–1 to 5)</td>
</tr>
</tbody>
</table>

Fig 3 Time response of SSI and HR. Individual (grey) and averaged (black) time response of SSI 60 s before and 120 s after tetanic stimulation (dotted line) in patients who moved (\( \lambda \)) and did not move (\( \sigma \)) due to painful tetanic stimulation.
Only few studies are available that assessed the ability of SSI to monitor the surgical stress response. Huiku and colleagues have first described this variable and its development during propofol–remifentanil anaesthesia. SSI, a combination of normalized PPGA and normalized HBI, was found to best reflect remifentanil concentration and the effect of various noxious stimuli and was therefore introduced to measure the nociception–anti-nociception balance. Struys and colleagues have studied the effect of noxious stimulation on SSI during differing hypnotic drug effect induced by propofol and various analgesia levels by changing remifentanil effect-site concentrations. SSI was not affected by propofol but by remifentanil concentration, which was likely, since SSI was developed based on remifentanil concentration. Nonetheless, an evaluation of SSI during anaesthesia using a volatile anaesthetic like sevoflurane is still missing. The present study indicates that SSI is a better detector of noxious stimulation than HR, RE, SE, RE–SE difference, and BIS during sevoflurane–remifentanil anaesthesia. Only SSI and BIS were consistently influenced by the standard stimulus during the examined concentrations of remifentanil. However, in contrast to SSI, the effect on BIS was too small to gain clinical relevance as median ΔBIS was only 2 in patients with remifentanil effect-site concentration of 0 ng ml\(^{-1}\). On the other hand, noxious stimulation in eight of 63 cases resulted in cerebral arousal as detected by an increase in SE or BIS above the recommended level of 60. Therefore, monitoring both, hypnosis and nociception, may help to guide balanced anaesthesia by separately adjusting anaesthetics. None of our patients reported any event of explicit awareness, and satisfaction with anaesthetic procedure was comparable with previous studies.

Induction of anaesthesia by sevoflurane induced a significant decrease in SSI. This seems counterintuitive as previous studies reported no influence of hypnotic drug effect on SSI. However, a reduction of SSI induced solely by the analgesic drug effect of sevoflurane seems unlikely. According to the manufacturer, SSI is not suitable for detection of stress response and nociception during the awake state but only during general anaesthesia, most probably since during the awake state many variables apart from nociceptive pathways may influence both PPGA and HBI. Consequently, during transition from the awake to the unconscious state, significant change of SSI is likely, as observed in the present study. We believe that hypnotic drug effect also affects SSI, but predominantly during transition to unconsciousness, and further studies comparing effects of different concentrations of sevoflurane are needed.

During anaesthesia with sevoflurane, SSI significantly decreased after remifentanil administration. However, an increase in \(C_{\text{remi}}\) from 2 to 4 ng ml\(^{-1}\) did not further reduce SSI. In contrast, ΔSSI is significantly dependent on \(C_{\text{remi}}\), with highest values without remifentanil and lowest values at 4 ng ml\(^{-1}\). Thus, we suggest that the stimulation induced nociceptive response was reduced during higher remifentanil concentrations.

In the present study, SSI enabled a more frequent detection than any other examined variable, for example, 16 cases of painful stimulation were indicated by SSI and not detected by HR. In 10 of these 16 cases, no movement as another indicator of inadequate anaesthesia occurred. Thus, SSI may allow displaying a response to painful stimulation by structuring PPGA and HBI into a simple numerical index.

In the present study, ΔSSI of 10 was found to be the threshold for movement. Consequently, if SSI increases by 10 or more during surgical stimulation, inadequate analgesia may be reasonable to assume. Movement in response to surgical stimulation is an unambiguous clinical endpoint and usually considered as the ultimate indicator of inadequate analgesia. However, these data do not allow the conclusion that a ΔSSI ≥10 will be clinically relevant and affect patients’ outcome. Possibly, a recommended range of SSI values as known for processed EEG variables will be more relevant. Therefore, upcoming studies need to prove the clinical application of measuring SSI.

We further evaluated the predictive power of variables using prediction probability by Smith and colleagues. Shafer and Stanski have defined anesthetic depth as the probability of non-response to stimulation. Regarding variables obtained before stimulation, only \(C_{\text{remi}}, \text{NIAP}_{\text{sys}},\) and HR but not SSI showed predictive power concerning a defined response, like movement, after stimulation. These findings were expected for \(C_{\text{remi}}\), as increasing remifentanil concentration reduces MAC. Regarding the predictive power of HR and NIAP\(_{\text{sys}}\), we suggest that HR and NIAP\(_{\text{sys}}\) were most probably reduced by increasing \(C_{\text{remi}}\). Because in this setting, painful stimulation was applied during a period without other stimulation, HR and NIAP\(_{\text{sys}}\) reduction may indicate opioid reduced MAC. In a previous study, HR was not associated with immobility during sevoflurane anaesthesia without supplemental opioids. We could confirm these findings by observing no better \(P_K\) values for HR compared with SSI in the ‘sevoflurane only’ subgroup. It is not surprising that SSI has no predictive power, as

<table>
<thead>
<tr>
<th>Movement</th>
<th>ΔSSI ≥10</th>
<th>ΔHR ≥5</th>
<th>RE–SE &gt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSI</td>
<td>0.59 (0.09)</td>
<td>0.50 (0.08)</td>
<td>0.54 (0.08)</td>
</tr>
<tr>
<td>ΔSSI</td>
<td>0.84 (0.06)*</td>
<td>NA</td>
<td>0.92 (0.03)*</td>
</tr>
<tr>
<td>HR</td>
<td>0.72 (0.07)*</td>
<td>0.84 (0.05)*</td>
<td>0.83 (0.06)*</td>
</tr>
<tr>
<td>ΔHR</td>
<td>0.73 (0.07)*</td>
<td>0.85 (0.05)*</td>
<td>NA</td>
</tr>
<tr>
<td>NIAP(_{\text{sys}})</td>
<td>0.79 (0.06)*</td>
<td>0.78 (0.06)*</td>
<td>0.63 (0.08)</td>
</tr>
<tr>
<td>(C_{\text{remi}})</td>
<td>0.93 (0.03)*</td>
<td>0.77 (0.06)*</td>
<td>0.79 (0.05)*</td>
</tr>
<tr>
<td>SE</td>
<td>0.48 (0.08)</td>
<td>0.47 (0.07)</td>
<td>0.53 (0.09)</td>
</tr>
<tr>
<td>RE</td>
<td>0.48 (0.08)</td>
<td>0.48 (0.08)</td>
<td>0.54 (0.08)</td>
</tr>
<tr>
<td>BIS</td>
<td>0.44 (0.08)</td>
<td>0.47 (0.08)</td>
<td>0.56 (0.07)</td>
</tr>
</tbody>
</table>

Table 3 Prediction probability (\(P_K\)) for variables averaged 60 s before the tetanic stimulation and Δ values (post-stimulation–pre-stimulation difference) for SSI, HR, NIAP\(_{\text{sys}},\) \(C_{\text{remi}},\) RE, SE, BIS. Data are \(P_K\) values (\(\times\)). *\(P<0.05\) compared with SSI. Variables were tested to predict an increase in SSI (ΔSSI ≥10) or HR (ΔHR ≥5), an RE–SE difference >5 or movement after noxious tetanic stimulation.
values are obtained during a period of no stimulation. Nociception–anti-nociception balance during this period is most likely adequate, and misbalance results as the effect of noxious stimulation. Therefore, ΔSSI was tested and showed predictive power ($P_K=0.84$) for movement. If a monitor is able to adequately detect such misbalance, the physician can react promptly by adjusting drug administration. Recently, Wennervirta and colleagues$^{15}$ described similar $P_K$ values for ΔSSI in a small subgroup of 10 patients during desflurane–alfentanil anaesthesia. Thus, SSI can help to detect nociception, but does not provide a true predictive value of adequate analgesia for a future painful event.

An ideal anaesthesia monitoring tool should meet different requirements. It should be non-invasive and provide continuous measurement, should be easy to apply and to interpret, fast reacting with high robustness to artifacts, useful in a large patient population, and should have high sensibility and sensitivity. As an important advantage, SSI reacts promptly after start of the stimulus. Further, it is easy to install and by displaying a single number easy to interpret. On the other hand, SSI will only work in patients without cardiac arrhythmia, and therefore its usability is impeded in a relevant group of patients.$^{23}$ Also, photoplethysmographic waveform might be influenced during haemorrhage or administration of vasopressors. Recent reports, however, have shown that β-blocker therapy does not hamper the use of SSI.$^{16}$

Our study has some limitations. Only women were included. Previous studies have shown a possible role of gender concerning anaesthesia requirement.$^{24}$ Peak effect on measured variables in some patients who moved may have been underestimated, due to application of rescue medication and significant shorter tetanic stimulation. Arterial pressure was only measured intermittently using a 3 min interval, and therefore the 30 s of painful stimulation did not affect NIAP. When continuously measured, arterial pressure may respond well to painful stimulation. Further, the study did not assess any outcome variables of patients monitored with SSI. As mentioned earlier, it still has to be tested whether SSI is useful as a tool for titrating drugs and affect anaesthetic drug consumption, emergence, or postoperative morbidity.

In conclusion, SSI measured by finger photoplethysmography enabled detection of painful stimulation that may have not been detected by standard monitoring devices during sevoflurane–remifentanil anaesthesia. SSI was reduced by remifentanil administration and SSI response to noxious stimulation depended on remifentanil effect-site concentration. However, SSI before noxious stimulation did not enable prediction of movement or ΔSSI after stimulation.

**Supplementary material**

Supplementary material is available at *British Journal of Anaesthesia* online.

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