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Changes in a surgical stress index in response to standardized pain stimuli during propofol–remifentanil infusion

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Background. The surgical stress index (SSI) is based on a sum of the normalized pulse beat interval (PBI) and the pulse wave amplitude (PPGA) time series of the photoplethysmography. As a measure of the nociception–anti-nociception balance in response to a standardized pain stimulus, SSI was compared with EEG changes in state and response entropy (SE and RE), PPGA, and heart rate (HR) during various targeted pseudo-steady-state concentrations of propofol and remifentanil.

Methods. Forty ASA I patients were allocated to one of the four groups to receive a remifentanil step-up/-down effect-compartment target-controlled infusion (Ce_{remi}) of 0, 2, 6, 2, 0 ng ml^{-1}, or 6, 2, 0, 2, 6 ng ml^{-1}, and an effect-compartment target-controlled propofol infusion (Ce_{prop}) to keep the SE between 30 and 50 or 15 and 30, respectively. At each steady-state Ce_{remi}, maximum change in SSI, SE, RE, PPGA, and HR after a noxious stimulus was compared with the baseline value. A correlation and prediction probability (P_K) with Ce_{prop} and Ce_{remi} was measured.

Results. Static and dynamic values of SSI correlated to Ce_{remi} better than SE, RE, HR, and PPGA. SSI was independent of Ce_{prop}, in contrast to SE and RE. The P_K for Ce_{remi} both before and during a noxious stimulus was better with SSI.

Conclusions. SSI appeared to be a better measure of nociception–anti-nociception balance than SE, RE, HR, or PPGA.

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The balancing of nociception–anti-nociception during anaesthesia is important as it may be related to clinical outcome.[1–3] The balance describes the opposing physiological effects of nociceptive stimulation and anti-nociceptive medication.[4] Nociception during anaesthesia results in autonomic, hormonal, and metabolic changes. Conscious pain reactions are absent, but the activation of the sympathetic neural and autonomic humoral pathways results in various physiological changes, such as haemodynamic responses.[5 6] This 'nociceptive cascade' can be blunted by anti-nociceptive drugs such as opioids or local anaesthetics.

Motor response to a noxious stimulus is not a usable measure of nociception–anti-nociception balance, but changes in the autonomic nervous system may be of value. Changes in heart rate (HR) and arterial pressure are used as signs of 'unblocked' nociception during anaesthesia, but their specificity is low.[7 8] Surrogate measures derived from the spontaneous EEG such as the state and response entropy (SE and RE) have been validated as measures of the hypnotic component of anaesthesia,[9] but have limited accuracy for the analgesic component.[10–14] Various measures of the 'status' of the autonomic nervous system during anaesthesia such as HR variability and the variability of the pulse plethysmography amplitude have been studied.[15–19] In an attempt to optimize the accuracy of these measures, various novel multivariable approaches for measuring the nociception–anti-nociception balance were developed based on combinations of information extracted from ECG, photoplethysmography (PPG), and frontal EMG.[4 20] A new multivariate index,[21] defined as the

'surgical stress index' (SSI), based on a sum of the normalized pulse beat interval (PBI) and the pulse wave amplitude (PPGA) time series of the PPG has been developed. In a preliminary study, they found that SSI reacts to nociceptive stimuli and analgesic drug concentration changes during propofol–remifentanil anaesthesia.[21] However, further validation studies are required. Therefore, the aim of this study was to compare the accuracy of the changes in SSI with changes in SE, RE, HR, and PPGA in response to a standardized noxious stimulus during various targeted pseudo-steady-state concentrations of propofol and remifentanil.

Methods

After institutional ethics committee (Ghent University Hospital Ethics' Committee, Ghent, Belgium) approval, written informed consent was obtained from 40 ASA I and II patients, aged 18–65 yr, undergoing urological or gynaecological surgery. Exclusion criteria included weight <70% or >130% of ideal body weight, neurological disorder or any other condition or treatment that could potentially interfere with cardiovascular status or level of consciousness, and a recent use of any concomitant medication. Patients were randomly allocated to one of the four study groups (permuted block randomization, four groups of 10 patients) to receive dedicated propofol and remifentanil infusions.

All patients received an i.v. infusion of crystalloid solution, $2\,ml\,kg^{-1}\,h^{-1}$, to deliver the required drugs and fluids during the study period. Standard vital signs monitoring was used, including cerebral drug effect, and haemodynamic and respiratory monitoring. The cerebral drug effect was continuously monitored using two different spectral entropy measures, SE and RE, derived from the frontal EEG and EMG using three frontal EEG electrodes. Both entropies were calculated using the Entropy™ Module from the S/5 Anaesthesia Monitor (GE Healthcare, Helsinki, Finland). The SE value ranges from 91 to 0 and the RE from 100 to 0. More details can be found elsewhere.[9 11 22] HR and three-lead ECG, pulse oximetry, and capnography were recorded continuously, and non-invasive arterial pressure was recorded intermittently. All data from the monitor were captured electronically using the software program S/5 Collect (GE Healthcare, Helsinki, Finland), which collects numerical and waveform information from selected vital signs. The pulse oximetry waveform data were captured at a rate of 100 Hz and stored on a laptop PC for *post hoc* calculation of the SSI (discussed later). All measures are reported time-synchronized with 10 s interval times. The 'zero' point was the start of the remifentanil administration (Fig. 1).

The patients were randomized into four groups (Table 1). This study design was chosen in order to eliminate the possible time-related changes and to study the possible effect of different propofol effect-site concentrations on the measures. Depending on the group, patients received a dedicated propofol and remifentanil-effect-compartment-controlled infusion. The time line of the study is shown in Figure 1. In Groups 1 and 2, remifentanil was started at an effect-site concentration (Ce_{remi}) of $6\,ng\,ml^{-1}$. At 13 and 20 min, target Ce_{remi} was decreased to 2 and $0\,ng\,ml^{-1}$, respectively. At 27 and 34 min, target Ce_{remi} was increased to 2 and $6\,ng\,ml^{-1}$. In Groups 3 and 4, target remifentanil was set at 0, 2, 6, 2, and 0 ng ml^{-1} at 0, 13, 20, 27, and 34 min, respectively (Fig. 1). Propofol-effect-compartment-controlled infusion was started 2 min after the start of the remifentanil infusion. Initially, the propofol effect-site concentration (Ce_{prop}) was targeted between 3 and $7\,\mu g\,ml^{-1}$ (depending on the study group) in order to reach loss of consciousness and suitable laryngeal mask airway (LMA) insertion conditions as soon as possible (within 2–3 min). Immediately after loss of consciousness, an LMA was inserted in all patients and patients' lungs were ventilated in order to maintain normocapnia. After LMA insertion, the Ce_{prop} was altered in order to reach and maintain an SE between 30 and 50 in Groups 2 and 4 and an SE between 10 and 30 in Groups 1 and 3 (Fig. 1). In order to optimize the SE target range, the investigator was allowed to alter Ce_{prop} up to 6 min after the start of the propofol administration. For the rest of the study, Ce_{prop} was fixed at that concentration.

Propofol[23 24] and remifentanil[25] were administered via a computer-assisted continuous infusion device to a target effect-site concentration [RUGLOOP written by Tom De Smet, MSc (Electronic Engineering) and M.M.R.F. Struys, MD, PhD (Professor in Anesthesia). More information at http://www.anesthesia-uzgent.be] using a three-compartment model enlarged with an effect-site compartment, as described earlier. Ce_{prop} was computed to yield a time to peak effect of 1.6 min after bolus injection. For remifentanil, an age-dependent k_{e0} value of $0.595-0.007\times(\text{age-40})$ min^{-1} was applied.[25] Propofol and remifentanil infusion were administered using an Alaris Asena Infusion Pump. RUGLOOP II steers the pump at infusion rates between 0 and 1200 $ml\,h^{-1}$ via an RS-232 interface. By using this infusion technique, we are able to obtain a steady-state condition for both propofol and remifentanil at every target level after 4 min infusion. Hereby, steady state is defined as the equilibration between the calculated plasma and effect-site concentration of the drug.[26]

Nociception was generated by standardized noxious stimuli at five specific time points (Fig. 1). The applied noxious stimulus was generated using a tetanic stimulus (100 Hz, 60 mA) at the volar forearm level for 30 s.[27] The stimulation electrodes were placed over the ulnar nerve on the volar side of the wrist of the opposite arm from the PPG. Baseline measures were recorded between 30 and 0 s before the noxious stimulus. Changes were recorded from the start of the noxious stimulus until 60 s after the start of the noxious stimulus, called the 'stimulation period'. Each

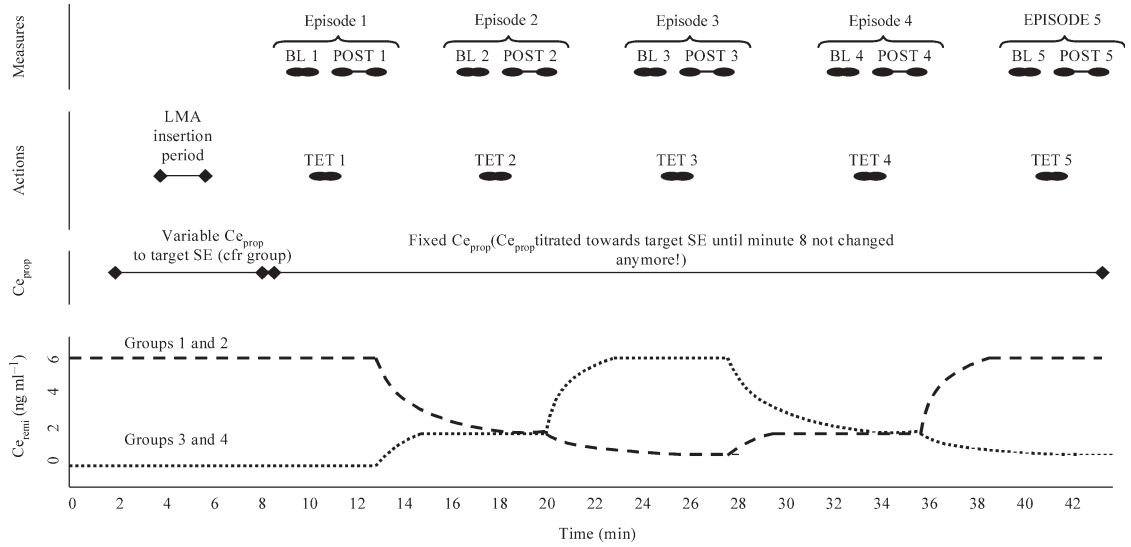

Fig 1 Time course of the study protocol showing induction period, post-induction period for LMA insertion and propofol drug titration (Ce_{prop}) towards the targeted state entropy (SE) value, and the five testing episodes with fixed Ce_{prop}. For each episode, baseline period (BL), stimulation period (TET), and post-stimulation period (POST) are depicted. The lower part of the figure shows the target remifentanil effect-site concentration (Ce_{remi}) for each group.

Table 1 SE target level, target remifentanil effect-site concentration (Ce_{remi}), and patient characteristics for each group

	Group 1	Group 2	Group 3	Group 4
SE target level	10–30	30–50	10–30	30–50
Ce_{remi} (mg ml^{-1})	6–2–0–2–6		0–2–6–2–0	
Gender (female/male)	8/2	9/1	8/2	10/0
Weight (kg)	68 (SD 15)	62 (11)	64 (9)	67 (12)
Height (cm)	160 (33)	168 (8)	168 (7)	169 (8)
Age (yr)	34 (8)	32 (5)	32 (5)	37 (7)

of the five time periods including baseline observations and the stimulation period is defined as an 'episode'. Drug concentrations were not altered until the end of each episode.

During each episode, three different measures for each of SE, RE, HR, PPGA, and SSI were defined:

- (1) $Measure_{baseline}$=mean measure value recorded during the 30 s baseline period before each stimulus.
- (2) $Measure_{max}$=maximum measure value recorded from the start of the stimulus until 60 s after the stimulus (=90 s time frame).
- (3) $Measure_{dif}$=Measure $_{max}$ − $Measure_{baseline}$.

Plethysmography was recorded at a 100 Hz sampling rate throughout the study to calculate SSI *post hoc*. The SSI was calculated for 10 s intervals and time-synchronized with the other measures. The calculation of the SSI is described elsewhere.[21] In brief, the PBI from the pulse plethysmography and the plethysmographic PPGA were automatically detected and the PBI and PPGA time series extracted. The PBI and PPGA are then normalized, called PBI_{norm} and $PPGA_{norm}$, using the individual patient's heart rate and PPGA data history, and the *a priori* PBI and PPGA data distributions obtained by pooling data from a large adult patient group. This normalization procedure adjusts the individual values so that they, after normalization, are in a scale between 0 and 100. As such, the SSI is calculated as:

$$SSI = 100 - (0.33 \times PBI_{norm} + 0.67 \times PPGA_{norm})$$

A value of 100 corresponds to a very high stress level and a value of 0 to a very low stress level.

The level of significance was set at $P<0.05$ unless otherwise reported. For all data sets, a Gaussian distribution was tested using the Kolmogorov–Smirnov test. For Ce_{prop}, Ce_{remi} and $Measure_{baseline}$, $Measure_{max}$, and $Measure_{dif}$, differences within groups between different episodes were tested using repeated measures ANOVA test with *post hoc* analysis. The between-group comparisons for $Measure_{baseline}$, $Measure_{max}$, and $Measure_{dif}$ used one-way ANOVA with *post hoc* test (Tukey). A paired sample *t*-test was used between $Measure_{baseline}$ and $Measure_{max}$ for each episode in all groups.

Spearman correlation between $Measure_{baseline}$, $Measure_{max}$, and $Measure_{dif}$ *vs* Ce_{prop} and Ce_{remi} was studied. To study the combined influence of Ce_{prop} and Ce_{remi} on the SSI, a multiple regression and correlation was carried out using Sigma Plot 2001 (Systat Inc., Point Richmond, CA, USA).

The prediction probability (P_K) of specific effect-site concentrations of remifentanil or propofol for a specific $Measure_{baseline}$, $Measure_{max}$, and $Measure_{dif}$ (being SE, RE, HR, PPGA, and SSI) under specific nociceptive conditions was calculated as described by Smith and colleagues.[28 29] A P_K of 1 means a perfect prediction and a P_K of 0.5 means no predictive value. However, values

are dependent on the study design and can only be compared within one study protocol.[30] The jack-knife method was used to compute the standard error of the estimate, based on the assumption that all assessments were independent. Prediction probability was calculated using a custom spreadsheet macro, P_KMACRO.[28 29] The Spearman correlation and P_K value were calculated by pooling the groups to eliminate a possible time effect in the protocol.

An intermediate statistical analysis was done by an independent statistician after 40 patients (10 in each group) to indicate the need for enlarging the groups. The investigators were blinded to this analysis. On the basis of this prospective power analysis, the initial sample size showed statistical significance for SSI (our primary measure).

Results

The groups were similar (Table 1). A significant difference was found for Ce_{prop} between Groups 1 and 2 and between Groups 3 and 4 after titration to SE, but for Ce_{remi} the differences were as per protocol (Table 2).

Analysis of $Measure_{baseline}$ and $Measure_{max}$ for SE, RE, HR, PPG, and SSI for all groups and each episode (Fig. 2) showed that SE target levels at baseline were reached and maintained as required per protocol. Significant differences were found for $SE_{baseline}$ and SE_{max} between Groups 1 and 2 and between Groups 3 and 4. A small increase can be observed during and after stimulation, reaching significance in some of the episodes, but without any clinically significant arousal levels. A similar finding occurred for RE.

For HR, PPG, and SSI, similar mean (SD) results were revealed between Groups 1 and 2 and between Groups 3 and 4, indicating no influence of the hypnotic component of anaesthesia and corresponding propofol concentrations (Fig. 2). HR increased significantly during and after the stimulus in all episodes in Group 2 and in the first two episodes in Groups 3 and 4. PPGA increased in all groups and during all episodes except one. SSI increased significantly in all groups and during all episodes, except at the higher remifentanil concentrations in Group 2.

For each episode, the magnitude of the increase between $Measure_{baseline}$ and $Measure_{max}$ in the individual patient can be clarified by calculating $Measure_{dif}$ (Fig. 3), and there were no significant differences between episodes or groups (between Groups 1 and 2 and between Groups 3 and 4) for SE_{dif} or RE_{dif}, indicating no influence of Ce_{prop} nor Ce_{remi}. Similar to the original data (Fig. 2), no differences were detected for HR_{dif}, $PPGA_{dif}$, and SSI_{dif} between Groups 1 and 2 and between Groups 3 and 4 (Fig. 3). Interpretation of the difference in HR_{dif} within each group during different episodes is difficult due to the inconsistency of the results. No differences for HR_{dif} were found within Group 1. In the other groups, higher HR_{dif} are observed when no remifentanil is administered, but there is a large variability. For $PPGA_{dif}$, lack of significance among episodes within the same group is due to a large variability (large standard deviation). Only in Group 3, was a significant decrease in $PPGA_{dif}$ detected for all episodes compared with episode 1. Within each group, significantly higher SSI_{dif} values were found at no or low remifentanil compared with the higher remifentanil concentrations.

Significant correlation with Ce_{prop} was found for SE, RE, and HR (Table 3). No or poor correlation was found for PPGA and SSI (Table 3). For Ce_{remi}, the overall best correlation was found with the SSI followed by HR. Poor or no correlation was seen with SE, RE, and PPGA.

The P_K analyses on the pooled data from all groups and episodes (Table 4) showed that for Ce_{prop}, only SE, RE, and HR had significant P_K values deviating from 0.5 at $Measure_{baseline}$ and $Measure_{max}$. For Ce_{remi}, SSI showed better P_K values at both $Measure_{baseline}$, $Measure_{max}$, and $Measure_{dif}$ levels compared with SE, RE, HR, and PPGA.

Table 2 Propofol effect-site concentration ($\mu g\,ml^{-1}$) (Ce_{prop}) and remifentanil effect-site concentration ($ng\,ml^{-1}$) (Ce_{remi}) during different episodes. $^*P < 0.05$ for Group 1 *vs* Group 2 and Group 3 *vs* Group 4 during each episode, respectively. †Significant difference within each group between all stimulus episodes, except between 1 and 5. ‡Significant difference between all episodes within each group

	Episode 1	Episode 2	Episode 3	Episode 4	Episode 5
Group 1					
Ce_{prop}	5.4 (1.1)*	5.4 (1.1)*	5.4 (1.1)*	5.4 (1.1)*	5.4 (1.1)*
Ce_{remi}	6.0 (0.0)†	2.4 (0.1)†	1.0 (0.0)†	2.0 (0.0)†	6.0 (0.0)†
Group 2					
Ce_{prop}	3.4 (1.4)*	3.4 (1.4)*	3.4 (1.4)*	3.4 (1.4)*	3.4 (1.4)*
Ce_{remi}	6.0 (0.0)†	2.3 (0.1)†	1.1 (0.1)†	2.0 (0.0)†	6.0 (0.0)†
Group 3					
Ce_{prop}	6.9 (1.4)*	6.9 (1.4)*	6.9 (1.4)*	6.9 (1.4)*	6.9 (1.4)*
Ce_{remi}	0.0 (0.0)‡	2.0 (0.0)‡	6.0 (0.0)‡	2.3 (0.1)‡	1.0 (0.1)‡
Group 4					
Ce_{prop}	5.3 (1.3)*	5.3 (1.3)*	6.9 (1.4)*	6.9 (1.4)*	5.3 (1.3)*
Ce_{remi}	0.0 (0.0)‡	2.0 (0.0)‡	6.0 (0.0)‡	2.3 (0.1)‡	1.0 (0.1)‡

Discussion

The aim of this study was to compare the accuracy of the changes in SSI with changes in SE, RE, HR, and PPGA as a measure of the nociception–anti-nociception balance in response to a standard noxious stimulus during various drug-induced hypnotic and analgesic circumstances. Overall, SSI appeared to be a better measure of this balance than SE, RE, HR, or PPGA, and was not influenced by the hypnotic element of anaesthesia.

As noted, the balance describes the opposing physiological effects of nociceptive stimulation and anti-nociceptive medication.[4] We kept the nociception stable with a specific and standardized noxious stimulus and altered the anti-nociception part by changing the

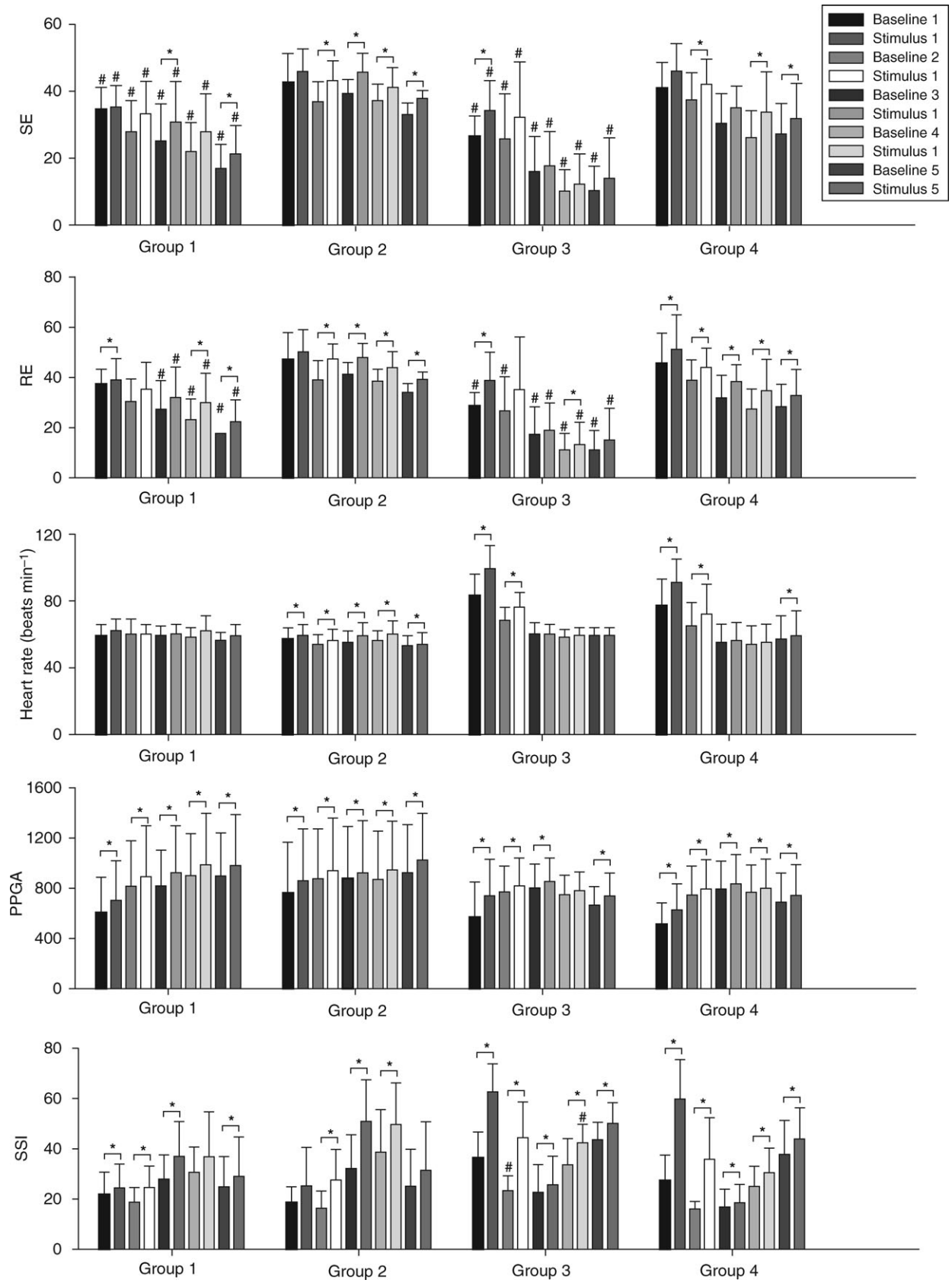

Fig 2 State and response entropy (SE and RE), HR, PPGA, and SSI for the five testing episodes and the four groups. Each episode consists of a baseline value and a maximum value during or post-stimulus. $^{*}P < 0.05$ between baseline and stimulus at specific episode and group. $^{\#}P < 0.05$ for Group 1 *vs* Group 2 and Group 3 *vs* Group 4 at each stimulus, respectively (in between groups).

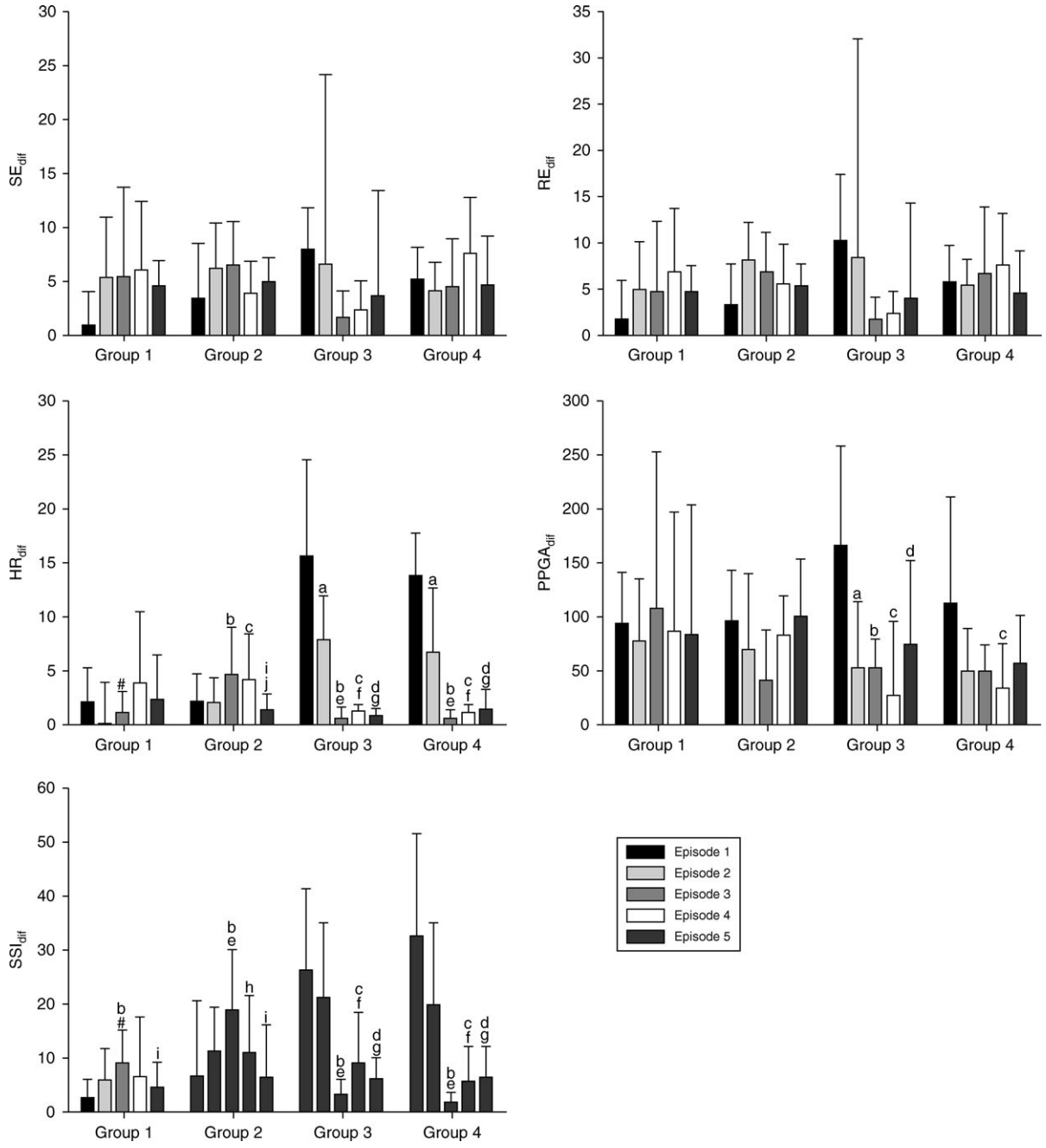

Fig 3 Difference ($Measure_{dif}$) between baseline value and maximum value within each episode for state and response entropy (SE and RE), HR, PPGA, and SSI for the five testing episodes and the four groups. $^{\#}P< 0.05$ for Group 1 *vs* Group 2 and Group 3 *vs* Group 4 at each stimulus, respectively (in between groups). Significance ($P< 0.05$) among different episodes within each group is indicated as: $^{a}1$ *vs* 2; $^{b}1$ *vs* 3; $^{c}1$ *vs* 4; $^{d}1$ *vs* 5; $^{e}2$ *vs* 3; $^{f}2$ *vs* 4; $^{g}2$ *vs* 5; $^{h}3$ *vs* 4; $^{i}3$ *vs* 5; and $^{j}4$ *vs* 5.

concentrations of propofol and remifentanil. However, the possible interaction between the hypnotic and analgesic components of anaesthesia on the nociception–antinociception balance has to be taken into account. Previously, the remifentanil effect-site concentration was accepted as a useful predictor of haemodynamic responsiveness and analgesia to an electrical tetanic stimulus.[19] The applied Ce_{remi} range between 0 and 6 ng ml^{-1} in this study was found previously to blunt autonomic responses to noxious stimuli.[31] We used a tetanic noxious stimulus rather than a 'surgical' standard noxious stimulus such as skin incision. We wished to study the effect of remifentanil in the same patient in order to minimize population variability, and to deliver an identical stimulus during each episode. This could not be done with surgical incisions. An electrical tetanic stimulus offers the advantage that it is reproducible and a 30 s stimulus, as used in this study, is more comparable with a skin incision than a stimulus of 5 s.[27]

Table 3 Spearman's *R* correlation for each measure (SE, RE, HR, PPG, and SSI) at baseline ($Measure_{baseline}$), at the maximum value during and after stimulation ($Measure_{max}$), and for the difference between baseline and maximum value ($Measure_{dif}$) *vs* Ce_{prop} and Ce_{remi} for all groups pooled together. *Significant relationship at the 0.01 level. **Significant relationship at the 0.05 level

	SE	RE	HR	PPG	SSI
$Measure_{baseline}$ *vs* Ce_{prop}	−0.471*	−0.462*	0.376*	0.141**	0.079
$Measure_{max}$ *vs* Ce_{prop}	−0.455**	−0.429*	0.337*	0.141**	0.075
$Measure_{dif}$ *vs* Ce_{prop}	−0.149**	0.178**	0.140**	0.026	0.009
$Measure_{baseline}$ *vs* Ce_{remi}	−0.067	−0.065	−0.306*	0.126	−0.340*
$Measure_{max}$ *vs* Ce_{remi}	−0.139	−0.123	−0.367*	0.147**	−0.550*
$Measure_{dif}$ *vs* Ce_{remi}	−0.162**	−0.145**	−0.433*	−0.073	−0.430*

The Cp_{50} drug concentration to block a response to a tetanic stimulus is close to the Cp_{50} for skin incision.[8 32]

In an attempt to minimize the effect of hypnotic arousal on the autonomic nervous system,[33] we studied two deep levels of anaesthesia, titrated by pre-stimulation spectral entropies between 30 and 50, and between 10 and 30. A small increase in both SE and RE was observed between groups, but this did not result in an arousal reflex and had no correlation or predictive value with Ce_{remi}. A significant correlation and a better P_K were found for $SE_{baseline}$, $RE_{baseline}$, SE_{max}, and RE_{max} with Ce_{prop}. This confirms previous findings that SE and RE monitor the hypnotic component of anaesthesia, but not nociception when no hypnotic arousal is present.[12]

Classically, HR and arterial pressure changes are used to guide opioid administration during anaesthesia.[21] Arterial pressure changes can only be considered as an on-line measure if captured continuously by means of an invasive arterial line. Recently, Seitsonen and colleagues[20] found that HR changes offered some information on adequacy of analgesia at skin incision during sevoflurane anaesthesia, but concluded that information from a number of different sources may be required for accurate monitoring. We included HR as a comparator with the other measures. We found that both $HR_{baseline}$ and HR_{max} were influenced by both Ce_{prop} and $Ce_{remi,}$ but the change in HR was only partially related to $Ce_{remi.}$ Thus, we agree with the previous study but caution that the static values before and during stimulus are less specific as they are influenced by both hypnotics and analgesics, and they show a large variability.

Pulse wave amplitude (PPGA) time series of the PPG were also studied. Previously, Luginbuhl and colleagues[19] found that titanic-induced PPG variation, induced by a 5 s, 60 mA electrical tetanic stimulus, did not reflect haemodynamic responsiveness and hence the analgesic state. Wide interpatient variability and the brief electrical stimulus (5 s) used may explain this difference.[27] We also found an increase in PPGA at stimulus between groups and during some episodes, but this was not significantly different due to large variability. This also resulted in a lack of correlation and non-significant P_K values for all PPGA measures and suggests that PPGA changes in response to noxious stimulus are not specific enough for monitoring the nociception–anti-nociception balance.

In an attempt to deal with the lack of specificity and in order to reduce interpatient variability,[4 20] Huiku and colleagues developed the multivariate SSI. In a preliminary validation study, they found that the SSI was accurate to measure the nociception–anti-nociception balance during surgical anaesthesia, defined as surgical stress, in response to skin incision and surgery during propofol–remifentanil anaesthesia. However, in the preliminary study, standardized noxious stimuli could not be applied during surgery, and randomization to eliminate a possible time component was not possible. In our study, these limitations were avoided. Both $SSI_{baseline}$ and SSI_{max} changed between low and high concentrations of remifentanil (Fig. 2). An increase in SSI in response to a tetanic stimulus was seen in all groups depending on the Ce_{remi} (Fig. 3). In contrast, no clinically significant differences were found between Groups 1 and 2 or Groups 3 and 4, indicating no relationship with adequacy of the hypnotic component of anaesthesia before the stimulus. This is also confirmed by the significant correlation between $SSI_{baseline}$, SSI_{max}, and SSI_{dif} with Ce_{remi}. There was also no correlation of $SSI_{baseline}$, SSI_{max}, and SSI_{dif} with Ce_{prop}, making this variable independent of the hypnotic component of anaesthesia. We also found better P_K values and correlations with Ce_{remi} for SSI compared with SE, RE, HR, and PPGA. For HR, the correlation and P_K with Ce_{remi} are not that much lower than for SSI, but HR and changes in HR were also influenced by the hypnotic component of anaesthesia, so SSI may be more specific for nociception. The static values at baseline and the maximum response to stimulation for SSI appear to be an accurate monitor of response to a tetanic stimulus. One could

Table 4 Prediction probability [mean (SE)] for each measure (SE, RE, HR, PPG, and SSI) at baseline ($Measure_{baseline}$), at the maximum value during and after stimulation ($Measure_{max}$), and for the difference between baseline and maximum value ($Measure_{dif}$) *vs* Ce_{prop} and Ce_{remi} for all groups pooled together

	SE	RE	HR	PPG	SSI
$Measure_{baseline}$ *vs* Ce_{prop}	0.66 (0.02)	0.66 (0.02)	0.63 (0.02)	0.54 (0.02)	0.53 (0.03)
$Measure_{max}$ *vs* Ce_{prop}	0.66 (0.02)	0.65 (0.02)	0.61 (0.02)	0.54 (0.02)	0.52 (0.02)
$Measure_{dif}$ *vs* Ce_{prop}	0.55 (0.02)	0.56 (0.02)	0.51 (0.02)	0.51 (0.03)	0.52 (0.02)
$Measure_{baseline}$ *vs* Ce_{remi}	0.52 (0.02)	0.52 (0.02)	0.61 (0.03)	0.56 (0.02)	0.64 (0.02)
$Measure_{max}$ *vs* Ce_{remi}	0.55 (0.02)	0.54 (0.02)	0.63 (0.03)	0.55 (0.02)	0.72 (0.02)
$Measure_{dif}$ *vs* Ce_{remi}	0.55 (0.02)	0.55 (0.02)	0.64 (0.02)	0.53 (0.02)	0.66 (0.02)

hypothesize that a lower adrenergic tone caused by remifentanil might be the origin of these findings, but this has to be confirmed in further research. The absolute values of P_K are lower than that observed in other published applications such as monitoring the adequacy of the hypnotic component of anaesthesia, but these P_K values are only comparable with one other study protocol.[30]

In conclusion, SSI appeared to be a better measure of the autonomic response to a tetanic noxious stimulus than SE, RE, HR, or PPGA during specific hypnotic and analgesic conditions. Both static and dynamic values were significantly correlated with Ce_{remi}, but neither correlation nor predictive values was found between SSI and Ce_{prop}. Under these conditions, SSI may be a useful measure of the nociception–anti-nociception balance during anaesthesia.

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