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CLINICAL PRACTICE

Assessment of surgical stress during general anaesthesia

M. Huiku[1]*†, K. Uutela[1]†, M. van Gils[2], I. Korhonen[2], M. Kymäläinen[1]†, P. Meriläinen[1]†, M. Paloheimo[1 3]†, M. Rantanen[4]†, P. Takala[1]†, H. Viertiö-Oja[1]† and A. Yli-Hankala[4 5]†

[1]Clinical Research, GE Healthcare Finland Oy, PO Box 900, FI-00031 GE, Helsinki, Finland. [2]VTT, Technical Research Centre of Finland, PO Box 1300, FI-33101 Tampere, Finland. [3]Department of Anaesthesia, ENT and Eye Hospital, Helsinki University Central Hospital, PO Box 340, FI-00029 HUS, Helsinki, Finland. [4]Department of Anaesthesia, Tampere University Hospital, PO Box 2000, FI-33521 Tampere, Finland. [5]Medical School, University of Tampere, FI-33014 Tampere, Finland

**Corresponding author: Clinical Research, GE Healthcare Finland Oy, PO Box 900, FI-00031 GE, Finland. E-mail: matti.huiku@ge.com*

Background. Inadequate analgesia during general anaesthesia may present as undesirable haemodynamic responses. No objective measures of the adequacy of analgesia exist. We aimed at developing a simple numerical measure of the level of surgical stress in an anaesthetized patient.

Methods. Sixty and 12 female patients were included in the development and validation data sets, respectively. All patients had elective surgery with propofol–remifentanil target controlled anaesthesia. Finger photoplethysmography and electrocardiography waveforms were recorded throughout anaesthesia and various waveform parameters were extracted off-line. Total surgical stress (TSS) for a patient was estimated based on stimulus intensity and remifentanil concentration. The surgical stress index (SSI) was developed to correlate with the TSS estimate in the development data set. The performance of SSI was validated within the validation data set during and before surgery, especially at skin incision and during changes of the predicted remifentanil effect-site concentration.

Results. SSI was computed as a combination of normalized heart beat interval (HBI_{norm}) and plethysmographic pulse wave amplitude ($PPGA_{norm}$): $SSI=100-(0.7*PPGA_{norm}+0.3*HBI_{norm})$. SSI increased at skin incision and stayed higher during surgery than before surgery; SSI responded to remifentanil concentration changes and was higher at the lower concentrations of remifentanil.

Conclusions. SSI reacts to surgical nociceptive stimuli and analgesic drug concentration changes during propofol–remifentanil anaesthesia. Further validation studies of SSI are needed to elucidate its usefulness during other anaesthetic and surgical conditions.

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The stress response to surgery is an unconscious response to tissue injury and refers to autonomic, hormonal, and metabolic changes that follow injury or trauma.[1 2] The activation of the sympathetic neural and autonomic humoral pathways causes changes in heart rate, blood pressure, and blood circulation; the elevated levels of catecholamines, and other hormones, mark a sustained stress response.[3–5] Prolonged surgical stress may stimulate biochemical

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reactions throughout the body, which may lead to increased morbidity and delayed postoperative recovery.[6–8]

Sufficient suppression of the pain pathways (antinociception) reduces stress responses during surgery. Stress-free anaesthesia, with measurement-based control of analgesia and hypnosis, should improve postoperative outcome. However, no objective measurements for the level of antinociception exist. Traditionally, a clinician observes heart rate, blood pressure changes, patient movement, and muscle tension to subjectively assess the adequacy of analgesia. Suppression of photoplethysmographic pulse wave amplitude (PPGA), activation of facial muscles, and changes in skin conductivity have also been proposed as indicators of insufficient antinociception.[9–13] A multi-variable approach[9 14] may be needed to reduce the inter-individual variability and improve clinical specificity and sensitivity of the measurement of surgical stress.

Our goal was to develop a simple numerical index suitable for monitoring surgical stress. On the basis of earlier research, the index development was based on evaluation of several variables. We extracted features from common physiological signals that correlate with the level of antinociceptive medication and intensity of nociceptive stimulation during surgery.

Methods

The study was approved by the local institutional review board (Tampere University Hospital, Tampere, Finland), and written informed consent was obtained from all patients. We enrolled 60+12 females (Table 1), ASA status I or II, scheduled for gynaecological or breast surgery under general anaesthesia. Exclusion criteria were known neurological disorders, any medication affecting the central nervous system or heart rate, major cardiac problems, uncontrolled hypertension, history of alcohol or drug abuse, and body mass index over 30 kg m^{-2}.

Patients, premedicated with oral diazepam, were anaesthetized with propofol and remifentanil, and muscle relaxation was achieved with bolus doses of rocuronium or cisatracurium. Propofol and remifentanil were administered as target control infusions (TCI) (Fresenius Orchestra Primea®, France). For propofol, the pharmacokinetic model of Schnider and colleagues,[15] and for remifentanil, the pharmacokinetic model of Minto and colleagues[16] were used. Propofol TCI was adjusted to maintain state entropy (SE)[17] level between 35 and 60, the target being 50.

Table 1 Patient characteristics and anaesthesia. 54 and 12 patients were included in the development and validation data sets, respectively

	Development (n=54)			Validation (n=12)		
	Range	Mean	SD	Range	Mean	SD
Age (yr)	23–66	45	11	21–64	48	12
Height (cm)	155–178	165	5	163–172	166	4
Weight (kg)	50–102	71	13	53–84	68	9
Duration of surgery (min)	30–240	90	46	78–244	148	58
Duration of anaesthesia (min)	53–369	139	55	102–270	182	64
Propofol (μ kg^{-1} min^{-1})	98–216	136	25	137–203	177	22
Mean remif. (ng kg^{-1} min^{-1})	61–205	106	34	93–146	111	17

Development data set

Six from the total of 60 patients were excluded: three due to technical or recording problems, two due to left bundle branch block influencing the heart rate analysis, and one due to large blood and fluid loss making the calculation of anaesthetic drug concentrations uncertain. Patients were allocated randomly to receive remifentanil at three different predicted effect-site concentrations at skin incision: 1, 3, or 5 ng ml^{-1} (18, 14, and 22 patients, respectively). During surgery, the TCI-target level was varied between 1, 3, and 5 ng ml^{-1} in a pre-planned sequence 1-3-5-1- or 1-5-3-1- starting from the randomized target level for incision. The alterations in the predicted remifentanil target level were done by a research nurse with a predetermined interval of 10–20 min at each predicted remifentanil effect-site concentration. If a patient responded to any surgical stimuli at the low concentration of remifentanil, the remifentanil target level was increased to a higher predicted concentration target and the sequence was restarted. As the infusion of propofol was targeted to achieve a fixed SE value in the beginning of operation, only minimal alterations of the predicted propofol effect-site concentration were needed during surgery.

Validation data set

All 12 recruited patients were included in the validation. At intubation, the remifentanil target effect-site concentration was 5 ng ml^{-1}; thereafter, the concentration was lowered so that the predicted effect-site concentration was 0.8 (0.5) ng ml^{-1} remifentanil at skin incision. After skin incision, the remifentanil concentration was varied between the predicted 1 and 5 ng ml^{-1} concentrations in intervals of 10–20 min. After performing the initial adjustment of the predicted propofol effect-site concentration to achieve a target SE=50 at the very early phase of operation, the anesthetist aimed for a constant infusion of propofol during surgery.

Data acquisition and pre-processing

The ECG, photoplethysmography, and EEG waveforms, trends including non-invasive blood pressure (NIBP), and entropy parameters [state entropy (SE) and response entropy (RE)] were monitored and collected using a data acquisition PC (Datex-Ohmeda S/5 Anaesthesia Monitor, S/5 iCentral® Network Workstation and S/5 iCollect data acquisition software, GE Healthcare Finland Oy, Helsinki, Finland).

The ECG and photoplethysmographic signals were analysed off-line: The R-wave peak positions of the ECG and the photoplethysmography pulse peak positions and amplitudes were detected automatically. The R-to-R interval (RRI), heart beat interval (HBI) from the photoplethysmographic waveform and PPGA time series were extracted. The time series were processed by detecting and removing artifacts.

Additional variables included non-invasively measured systolic arterial pressure (NIBP), pulse transit time (PTT) calculated as the delay between ECG R-wave peak and the half height of the photoplethysmography pulse rising slope, and several other parameters quantifying heart rate and PPGA variability, such as a sympatho-vagal ratio of heart rate variability (RRI S/V)[14 18] (for a comprehensive list of tested variables see Supplementary material). For clarity, only the best performing variables are reported here. A trained research nurse noted, using the S/5 iCollect notes template, all drug administration, such as changes of the remifentanil and propofol target concentrations and the total infused drug amounts, and anaesthetic and surgical events, such as intubation, incision, electrocautery, or potentially noxious surgical procedures, throughout anaesthesia. She also noted any clinical signs, such as movement and muscle tension, indicating surgical stress throughout surgery. The S/5 iCollect annotations were automatically time-stamped for maintaining the time synchrony with the physiological parameter data.

Inter-patient variability complicates the interpretation of physiological parameter values as measures of a patient's clinical status. A normalization utilizing a histogram transformation[19] was introduced to decrease the variability in HBI and PPGA (Appendix 1) that is not associated with surgical stress. All normalized variables are in a fixed range, from 0 to 100, in all patients; at all times, the value 50 represents an estimate for the average value of the particular variable in that individual patient.

Clinical assessment of surgical stress

The development and evaluation of 'awareness monitors' such as BIS[20] or Entropy™ have been based on comparison of the indices to clinical scores for adequacy of the hypnotic component of anaesthesia, such as OAA/S score,[21] or to specific clinical endpoints, for example, loss of response to verbal command. Unfortunately, no such validated clinical scores for stress responses in an anaesthetized patient exist. An objective measure of nociceptive stress response is a function of both the level of stimulation and the drug effect, that is, the balance between nociception and antinociception, whereas BIS and Entropy™ mainly reflect the drug effect. In this study, the nociceptive stimulus and analgesic drug effects were combined linearly to make a simple estimate of the nociceptive–antinociceptive balance, which is used as a surgical stress score.

During the course of surgery, the level of stimulation varies continuously—this requires a constant matching of the analgesic drug concentration to surgical stimulation. The analgesic drug effect-site concentration (Ce_{50}), that is typically needed to reduce patient responses by 50%, reflects the mean level of surgical stimulation in the particular surgical incidence: the higher the nociception, the larger Ce_{50} is needed to suppress the nociceptive response. Pharmacological studies report Ce_{50} or corresponding blood plasma concentrations of analgesics at different surgical incidences.[22–25] The results of these studies were interpreted using the pharmacologic model of Bouillon and colleagues[22] to obtain estimates for the level of surgical stimulation in our study (Appendix 2).

The continuous estimate of the effect-site concentrations of remifentanil (Ce_{remi}) was calculated off-line, based on the annotated infusion rates and the pharmacokinetic model of Minto and colleagues.[16] The calculation was verified by checking that the drug consumption within the model matched the total amount of remifentanil infused during surgery.

The estimate for the total surgical stress (TSS) was calculated as

$$\mathrm{TSS} = \mathrm{PreIntensity} - \frac{\mathrm{Ce_{remi}}}{3\ \mathrm{ng/ml}} \qquad (1)$$

in which PreIntensity is our estimate for the level of stimulation (Appendix 2, Table 2) and Ce_{remi} is the predicted effect-site concentration of remifentanil. The relative weights of the components in TSS were determined so that the clinical range of remifentanil matched to the surgical range of stimulation: the remifentanil Ce=4 ng ml^{-1}

Table 2 Estimation of the level of noxious stimuli during propofol–remifentanil anaesthesia. The studies by Albertin and colleagues[23] and Bouillon and colleagues[22] and by us are for propofol–remifentanil anaesthesia, whereas the study by Ausems and colleagues[25] is for 66% nitrous oxide and alfentanil anaesthesia. [*Subjective estimate; #50 Hz, 50 mA, 30 s on the ulnar nerve. (The tetanic electric stimulus was utilized in a subgroup of 23 patients in the development data set to study the patient responses to an artificial standardized stimulus before surgery. The tetanic stimulus did have only short lasting effects on the patient and was considered not to affect the rest of the data and to have insignificant contribution to the development result. However, it was included in the total surgical stress estimate when applied for the particular patient)]

	Ce_{50} (ng ml^{-1}) (Albertin)	Cp_{50} (ng ml^{-1}) (Ausems)	PreIntensity (Bouillon)	PreIntensity (our study)
Laryngoscopy			0.83	0.83
Laryngoscopy+ intubation	4.6			1.57
Incision (Laparotomy)	2.2	279		1.25
Incision (Laparoscopy)				0.8*
Trocar				1.25*
Laparotomy surgery		309		1.38
Laparoscopy surgery				1.0*
Breast surgery		270		1.21
Intense abdominal exploration				1.5*
Before incision				0.25*
Electric tetanic 30 s				0.8*,#,26

with propofol at about 3 $\mu g\,ml^{-1}$, corresponding to the typical concentration in our study, was estimated to blunt noxious responses for intra-abdominal surgery.[24]

The performance of individual variables was evaluated by calculating the correlation coefficients between the variable and the predicted remifentanil effect-site concentration and stimulus intensity (PreIntensity, Table 2). Different linear combinations of the variables were evaluated by least-squares fit with the TSS estimate as the dependent variable. As no absolute measure of stress level of each patient was available, only the intra-patient variability in the variables and TSS was used. The data from each patient were weighted inversely proportionally to the length of the surgery; each patient thus carried equal effect in the final results.

The performance of the surgical stress index (SSI) was evaluated using Wilcoxon signed rank test and Mann–Whitney test, as appropriate.

Results

The three best candidate variables that correlated with stimulation were the normalized PPGA, $PPGA_{norm}$, the pulse transit time, PTT, and systolic blood pressure, NIBP, whereas with remifentanil the best correlations were obtained for $PPGA_{norm}$, systolic NIBP, and the normalized heart beat interval, HBI_{norm}. The normalized PPGA ($PPGA_{norm}$) correlated best both with the strength of stimulation and predicted remifentanil Ce_{remi} level (Fig. 1A). In a single variable model of surgical stress, $PPGA_{norm}$ explained the TSS, with clearly smaller residual error than any of the other variables. As NIBP is not continuously available during anaesthesia and the pulse transit time is often prone to artifacts with weak signal, a two-variable model was constructed with $PPGA_{norm}$ and HBI_{norm}, which had a positive correlation with remifentanil Ce_{remi} and negative correlation with stimulus intensity. Adding the pulse transit time, response entropy or the sympatho-vagal ratio, RRI S/V, did not improve the performance of the two-variable model, though systolic NIBP, when added as a third variable, somewhat reduced the residual error (Fig. 1B).

The weighting coefficients for the two-variable model were determined based on the least-squares fit with the TSS estimate. The optimization of the combination of HBI_{norm} and $PPGA_{norm}$ resulted in SSI:

$$SSI = 100 - (0.7^{*}PPGA_{norm} + 0.3^{*}HBI_{norm}) \qquad (2)$$

In equation (2), the weighting factors are in ratio 1:0.44 for $PPGA_{norm}$ and HBI_{norm}, respectively; in this representation, the uncertainty of the optimal coefficient of HBI_{norm} varied as 0.44 (0.22) [mean (SD) of the coefficients calculated for each individual subject]. In the expression for SSI, an SSI value close to 100 corresponds to a very high stress level and a value near 0 to a very low stress level. The value of 50 corresponds to the mean stress level.

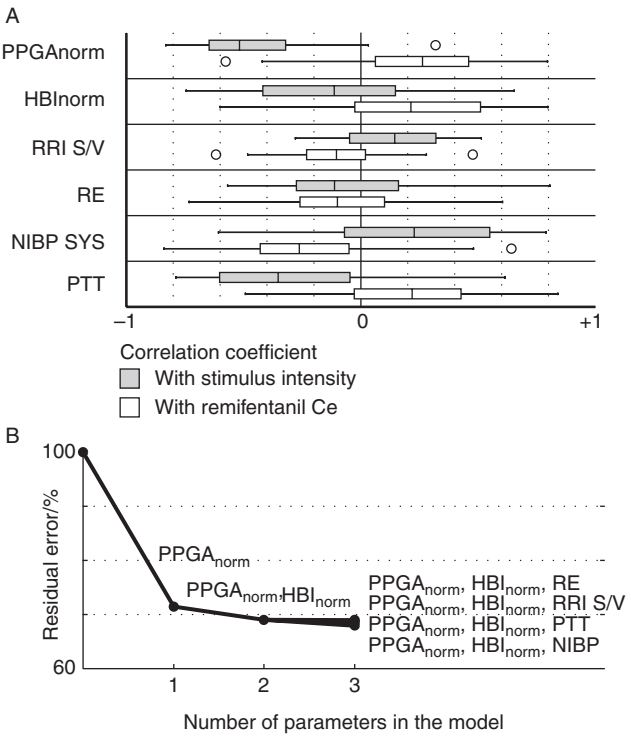

Fig 1 Search of the parameter model for surgical stress. (A) Correlation analysis of the candidate parameters with the predicted remifentanil effect-site concentration (open bars) and severity of stimulation (filled bars). The bars show the median (vertical line), the low and high quartiles (the box), and the minimum and maximum values without outliers (the line ends; open circles for outliers) of the correlation coefficients calculated for each patient. (B) Comparison of different models explaining the total, TSS. The graph shows the decrease in the unexplained variability as more parameters are added. $PPGA_{norm}$, normalized photoplethysmographic pulse amplitude; HBI_{norm}, normalized heart beat interval; RRI S/V, sympatho-vagal ratio of the heart rate variability; RE, response entropy; NIBP SYS, systolic non-invasive blood pressure; PTT, pulse transit time.

During general anaesthesia, SSI correlated positively with the estimated nociceptive stimulus (median Spearman correlation coefficient=0.56, $P<0.0001$) and negatively with the antinociceptive medication (median Spearman correlation coefficient, $r=-0.21$, $P<0.0001$). Median Spearman correlation with the TSS estimate was 0.48 ($P<0.0001$). (All Wilcoxon signed rank.)

SSI increased during incision at each level of the predicted remifentanil concentrations (Fig. 2, Table 3). After incision, SSI increased further, but less with remifentanil 5 $ng\,ml^{-1}$ than with remifentanil 1 and 3 $ng\,ml^{-1}$. The difference between the average SSI during and before surgery was the larger, the lower was the remifentanil effect-site concentration. The results for the development and validation data sets were consistent.

During surgery, the average level of SSI was high when the remifentanil concentration was low and vice versa

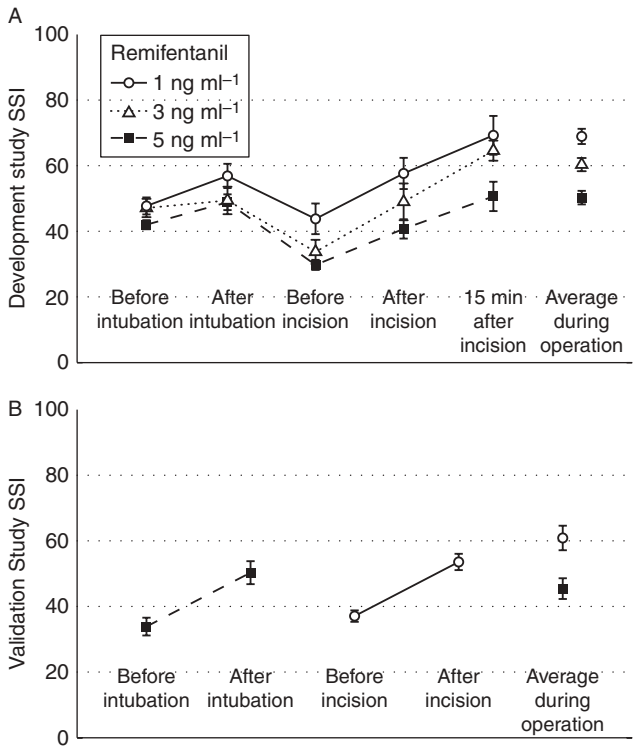

Fig 2 SSI during general anaesthesia in all patients [mean (SE)]. The effect-site target concentration of remifentanil (Ce) was cycled between 1, 3, and 5 ng ml^{-1} in the development set, and between 1 and 5 ng ml^{-1} in the validation set for each patient during surgery. Therefore, the SSI average data over the surgery at each remifentanil target level include data segments from each patient; the other SSI data include data only from a certain subgroup of patients.

(Fig. 2). SSI systematically decreased with increasing remifentanil concentration during surgery (Table 4). The baseline values of SSI before incision depended less on the remifentanil level. During surgery, the difference of SSI between 1 and 5 ng ml^{-1} was similar in the validation and development data sets.

When SSI is displayed with the raw variables, heart rate and photoplethysmography pulse amplitude, and the calculated remifentanil Ce_{remi} concentrations for one patient from the validation set, it increased during intubation and incision (Fig. 3). A low predicted remifentanil concentration was associated with a high SSI value and vice versa. The SSI changes followed the pattern of the photoplethysmographic signal, whereas this was less obvious for the raw heart rate signal.

Table 3 Effect of stimulation on SSI. Differences between the mean SSI values after and before certain anaesthesia and surgical events (SE, the standard error for the differences of the mean SSI values) at the predicted remifentanil effect-site concentrations 1, 3, and 5 ng ml^{-1}. (*P<0.05, **P<0.01, ****P<0.0001, all Mann–Whitney)

	Remifentanil (ng ml^{-1})				
	Development			Validation	
	1	3	5	1	5
After intubation–before intubation	9 (5)	2 (5)	7 (3)*	NA	16 (4)**
After incision–before incision	14 (7)*	15 (7)*	11 (3)**	17 (3)****	NA
During surgery–before surgery	28 (3)****	26 (3)****	18 (2)****	24 (4)****	6 (4)

Table 4 Effect of remifentanil on SSI. Differences of the mean SSI values between the predicted remifentanil effect-site concentrations 1, 3, and 5 ng ml^{-1} (SE, the standard error for the differences of the mean SSI values) at certain anaesthesia and surgical events. The SSI difference is calculated between the mean SSI at a lower level minus the mean SSI at a higher level of the predicted remifentanil effect-site concentration. (*P<0.05, **P< 0.01, ***P<0.001, ****P<0.0001, all Mann–Whitney)

	Remifentanil (ng ml^{-1})			
	Development			Validation
	1 *vs* 3	3 *vs* 5	1 *vs* 5	1 *vs* 5
Average before incision	6 (3)*	2 (2)	9 (2)***	−3 (3)*
Before incision	10 (6)	4 (4)	14 (5)*	NA
After incision	9 (7)	8 (6)	17 (6)**	NA
During surgery	9 (3)**	10 (3)***	19 (3)****	15 (5)**

Discussion

Heart rate and photoplethysmographic pulse wave amplitude proved the most useful non-invasive sources of information for a surgical patient's analgesic state. We developed a SSI combining these variables into a single number between 0 and 100. The index estimates surgical stress on a patient undergoing gynaecological or breast surgery during propofol–remifentanil anaesthesia. SSI is high when noxious stimulation is high and the remifentanil concentration is inadequate; SSI is low when the remifentanil concentration is high or the stimulation is low.

In current anaesthesia practice, no objective measurements for nociception or surgical stress exist. We developed SSI to indicate the analgesic state of a patient. Ideally, the state index could both follow the slow changes of the antinociceptive drug level or severity of surgical stimulation and respond to sudden acute stimuli. This approach is challenging, because it requires knowledge of the real level of surgical stress over the whole surgery, and because the index should have a fixed scaling such as 0–100, to discriminate between insufficient and sufficient analgesia. Further, the patient-to-patient variability of the index values should be small. We resolved the first challenge by developing a clinical estimate for the TSS which combines the effect of remifentanil concentration with an estimate of the severity of nociceptive stimuli during and before surgery. Through a normalization process, we eliminated most of the inter-patient variability and set the index values into a fixed scale, between 0 and 100.

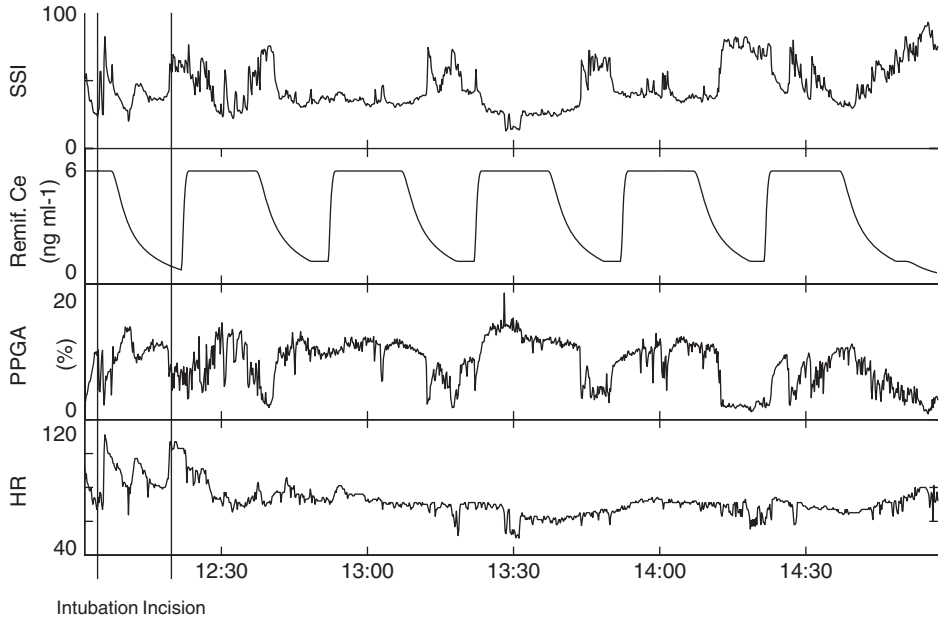

Fig 3 SSI, the remifentanil concentration, raw PPGA, and heart rate during general anaesthesia. Time (hh:mm) is on the *x*-axis. Intubation at remifentanil 5 ng ml^{-1} was done at 12:07 and incision at remifentanil less than 1 ng ml^{-1} at 12:20. The propofol infusion was kept constant during the whole operation. HR, heart rate; PPGA, photoplethysmographic pulse amplitude; Remif. Ce, effect-site concentration of remifentanil; SSI, surgical stress index.

Instead of directly optimizing the index with the full set of candidate variables to the TSS estimate during surgery, the candidate variables were first evaluated against the two basic components of the TSS (Fig. 1). A suitable candidate was expected to react to the changes of the level of surgical stimulation and the suppression effect of the antinociceptive drug for the majority of the subjects. Further, the index should be available and computable in a standard anaesthesia monitor. Promising candidate variable sets were selected based on these expectations. The optimization of SSI to the surgical stress reference, TSS, was done first within a two-variable model including the two most suitable candidates and then within a three-variable model. With this approach, we were able to develop SSI to a simple clinical index including only the most significant physiological variables for surgical stress.

The model for the TSS was chosen to reflect the balance between nociception (stimuli) and antinociception (drug effect) and to indicate their opposite effects on surgical stress. Surgical stress increases with increasing stimulation and decreases with increasing analgesia. SSI was developed to have the same essential features of the balance between nociception and antinociception as the estimate for the TSS. In our approach the TSS [equation (1)] is not required to be an optimal or complete model for surgical stress. We aimed to sufficiently develop an index, which can subsequently be tested in other clinical studies and clinical use.

SSI does not use EEG derived information, although EEG has been shown to be prone to substantial changes in association with nociceptive stimuli.[26] In our analyses, including EEG and frontal electromyogram-related response entropy (RE) did not significantly improve the performance of SSI, as their reactions are typically short-lasting and transient in nature. Further studies have indicated that the EEG-derived SE and RE are complementary variables to SSI and that a change in SE or RE does not imply a simultaneous change in SSI, and vice versa.[27] The lack of a strong correlation between the indices of hypnosis and antinociception would allow for good clinical decision support for controlling balanced anaesthesia. This should, however, be further studied and confirmed with other clinical setups and drugs.

Our results were based on a limited and relatively homogeneous population of ASA I and II class female subjects during propofol–remifentanil anaesthesia. Elderly patients or patients with cardiovascular or neurological diseases were not included. The validation data set was rather small and similar to the development set. Therefore, SSI should be further validated in a wide variety of anaesthesia and surgery and in many different patient groups.

In conclusion, we propose a simple measure for the level of surgical stress during general anaesthesia. It uses only continuous cardiovascular variables, heart rate, and PPGA, which are pre-processed by normalization. The index, SSI, was developed with data collected during propofol–remifentanil anaesthesia. The incidents and stimuli generally expected to increase nociceptive input, such as skin incision, increase SSI. The factors that normally increase the antinociceptive effects, such as increasing analgesia, produce a decrease of SSI. Further validation studies are needed to elucidate its feasibility to monitor

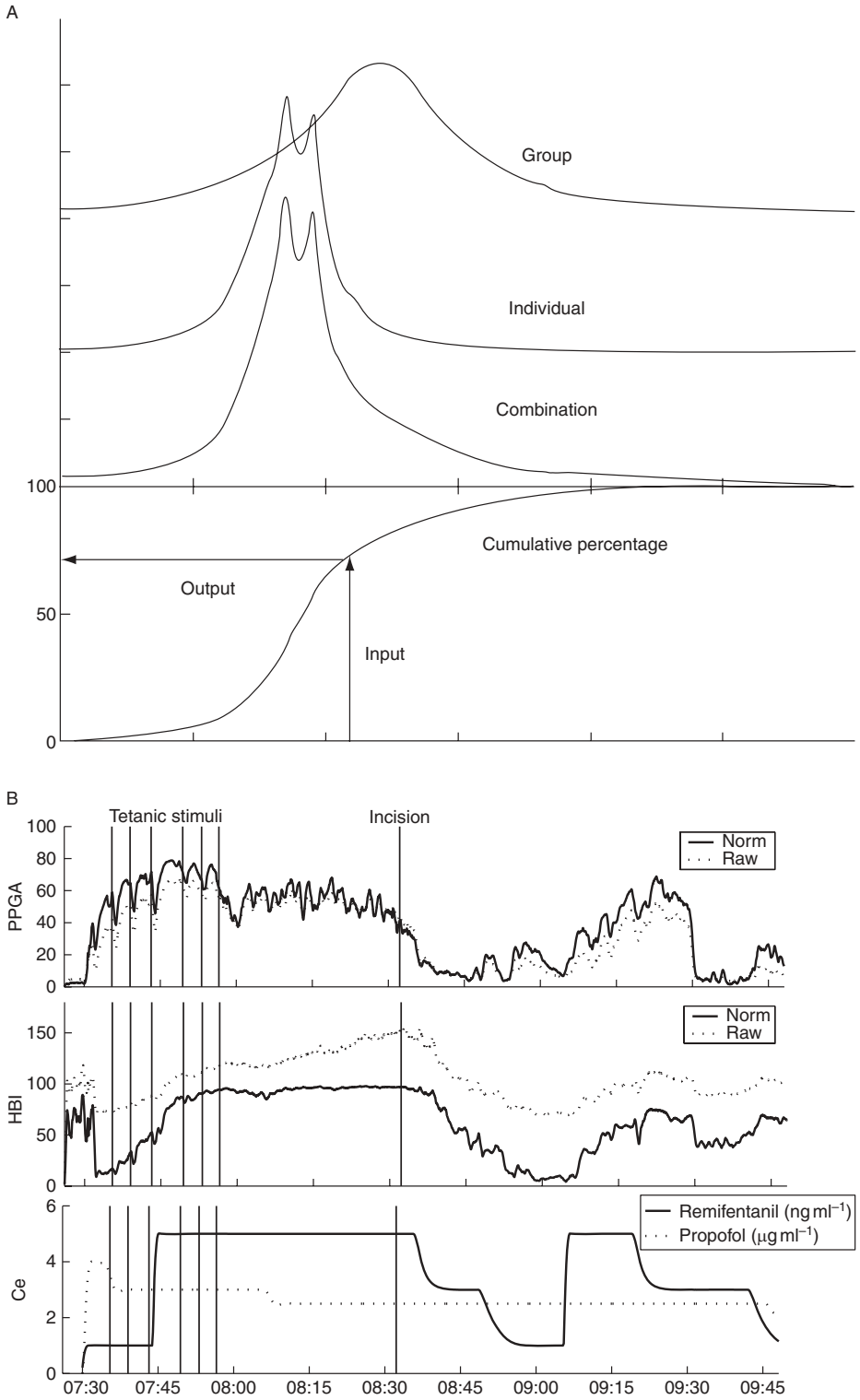

Fig 4 Normalization transformation. (A) Transformation function. The *x*-scale, referring to the input value of the parameter, either HBI or PPGA, is arbitrary. The upper plot represents the histogram of the input parameter values for the *a priori* (group) average data, the second plot shows the histogram of individual patient data, and the third plot depicts a combination of these two. The normalization transformation function, the cumulative distribution, is presented in the bottom plot. The input value is first mapped onto the transformation curve and from there to the percentage output, as shown by the arrows. (B) An example of the normalization. The transformation from the original raw PPGA to the normalized PPGA ($PPGA_{norm}$) and from the original HBI to the normalized HBI (HBI_{norm}) are shown for one patient during general anaesthesia. The responses to electric tetanic stimuli (50 mA, 50 Hz, 30 s on the ulnar nerve) and skin incision are indicated by vertical lines. The predicted remifentanil and propofol effect-site concentrations are plotted in the bottom plot.

surgical stress in different patient groups, during different types of anaesthesia, in the presence of drugs affecting the autonomic nervous system, and in other clinical conditions.

Supplementary material

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

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Appendix 1

Description of the normalization used in SSI

The normalization of the individual patient data is based on the histogram transformation.[19] If the distribution of a parameter, such as PPGA, is known, the transformation of a parameter returns the percentage of the measured values smaller than or equal to the transformed value. Thus, regardless of the distribution of the original parameter, the normalized value is uniformly distributed between 0% and 100%.

In image processing, the distribution used for the histogram transformation can be taken from the original image. A clinical index has to be calculated on-line and can only use data that were measured earlier than the value that is to be transformed. We made two adjustments to the conventional histogram transformation to facilitate on-line use. First, we used *a priori* knowledge of the distribution of the parameter values in a large patient group. Initially, the transformation is calculated using the group distribution only. When data are collected during anaesthesia, we combine the group distribution and the individual distribution and use the combination in the transformation (Fig. 4). The weight of the individual transformation increases as more data are collected; when 5 min or more data are collected the weight of the individual distribution is fixed to 70%.

Second, as the shape and width of the distribution are difficult to estimate without an excessive amount of data, we modelled the distributions as a normal distribution with a pre-defined standard deviation. When new parameter values are measured, the mean of the distribution is defined as the mean of the measured data, but the standard deviation is fixed. The fixed standard deviation is defined by calculating the standard deviation for each patient in the development data set and using the average of standard deviations of individual patients in the validation data set.

Appendix 2

Estimation of surgical stimulation during anaesthesia

The afferent nociceptive pain pathway transmits the nociceptive input impulses from the site of tissue injury to the brain for higher order processing.[28] The nociceptive input signal is blunted by the opioid drug affecting the ascending pain pathways. In the pharmacologic model by Bouillon and colleagues[22] the modulation of the intensity of noxious stimulation by an antinociceptive drug is described by a relationship:

$$\text{PostIntensity} = \text{PreIntensity} * \left[1 - \frac{\text{Ce}_{\text{remi}}^{\gamma}}{\text{Ce}_{\text{remi}}^{\gamma} + (\text{C}_{50} * \text{PreIntensity})^{\gamma}}\right] \quad (3)$$

in which PreIntensity is the intensity of the afferent noxious stimulus; PostIntensity is the intensity of the nociceptive stimulus after attenuation by the antinociceptive drug; Ce_{remi} is the effect-site concentration of the drug; C_{50}, defined at PreIntensity=1, is the drug concentration associated with 50% blunting of the PreIntensity; and γ is the steepness of the drug concentration *vs* response relation. In the approach by Bouillon and colleagues, PostIntensity is projected to the cortex, in which the probability of non-responsiveness is defined with another sigmoid function describing the effect of the hypnotic drug concentration. The parameters of equation (3) in the Bouillon model were Ce_{50}=71.01 ng ml^{-1} remifentanil and $\gamma = 0.72$. PreIntensity for laryngoscopy was 0.83.[22]

We employed our annotations of surgical events and the above model to estimate the pre-opioid noxious stimulation, that is, PreIntensity. We first took the complete pharmacologic model from Bouillon and colleagues including equation (3) and the synergistic effects of propofol on the patient responses. Then, based on the ratio of the effect-site concentrations of remifentanil at propofol concentration of 3.4 μg ml^{-1} to block responses to laryngoscopy and abdominal skin incision and intubation,[23] we calculated the PreIntensities 1.25 and 1.57 for incision and intubation, respectively (Table 2). We scaled the PreIntensity for laparatomy and breast surgery using the data of Ausems and colleagues.[25] The intensity of tetanic stimulation and laparoscopic skin incision[14 29] was defined equal to laryngoscopy without intubation. We graded the level of stimulation in insertion of trocars, laparoscopic surgery, and intense laparotomic abdominal exploration as 0.8, 1, and 1.5, respectively. For the period before surgery, we set a baseline stimulation level equal to 0.25, representing the stimulation caused by the tracheal tube without active surgical stimulation.

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