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Measurement of surgical stress in anaesthetized children

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Background. The surgical stress index (SSI), derived from a combination of heart rate (HR) and photoplethysmographic amplitude (PPGA) time series, is a novel method for continuous monitoring of intraoperative stress and has been validated in adults. The applicability of SSI and its constituents to monitoring children has not been previously evaluated.

Methods. In this controlled trial, 22 anaesthetized patients, aged 4–17 yr, undergoing strabismus surgery were randomized into two groups, Group LL and Group BSS. Patients in Group LL received topical conjunctival anaesthesia with a 1:1 mixture of lidocaine 2% and levobupivacaine 0.75%, and patients in Group BSS received balanced salt solution.

Results. Endotracheal intubation (n=22) increased median (range) SSI from 39.2 (22.6–55.6) to 53.6 (35.8–63.3) ($P<0.001$), decreased PPGA from 5.62 (2.79–9.69) to 5.27 (2.59–7.54)% ($P=0.001$), and increased the difference of response entropy (RE) and state entropy (SE) of frontal biopotentials (RE−SE) from 3.1 (0.06–9.1) to 5.7 (0.6–9.4) ($P=0.01$). Conventional haemodynamic variables also increased, median (range) HR from 72.9 (56.7–113.8) to 84.2 (60.4–124.8) beats min^{-1} ($P<0.001$), and systolic non-invasive arterial pressure (S-NIBP) from 87 (78–143) to 103 (79–125) ($P=0.007$). When 3 min baseline before surgery was compared with 12 min of surgery, median (range) SSI increased from 43.3 (31.2–58.0) to 49.9 (39.3–57.2) ($P=0.042$) *vs* from 46.6 (26.8–57.8) to 52.1 (31.7–60.1) ($P=0.024$) and PPGA decreased from 6.60 (3.10–8.24) to 5.80 (3.03–7.65)% ($P<0.001$) *vs* from 5.51 (3.25–9.84) to 5.06 (3.08–8.99)% ($P=0.042$), in Groups LL and BSS, respectively, but SSI or other indicators did not differ significantly between the groups.

Conclusions. SSI, PPGA, HR, NIBP, RE, and RE−SE detect autonomic responses to nociceptive stimuli in anaesthetized children undergoing strabismus surgery.

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Neuroendocrine stress caused by pain is a vital reaction in the conscious individual, but may be harmful during surgery on anaesthetized patients.[1] Analgesics reduce the transmission of peripheral nociceptive stimuli to the central nervous system, prevent spinal reflexes, and disrupt the complex pathways in the autonomic nervous system.[2] Responses mediated by the autonomic nervous system on heart rate (HR) and arterial pressure have traditionally considered to indicate nociceptive stress during general anaesthesia. In order to prevent the release of stress hormones and its consequences,[3] a method for real-time monitoring of intraoperative stress would be useful. Grimacing is a universal expression of pain[4] and EMG of the frontal muscles of the face (FEMG) is independent from the stage of consciousness.[5] In addition to predicting movement[6 7] and arousal,[7–9] FEMG assists in the titration of fentanyl during anaesthesia[10 11] and predicts requirements of analgesics after surgery.[12] The state entropy (SE) component of Spectral Entropy™ (GE Healthcare, Helsinki, Finland)[13] monitors the anaesthetic effect on cortical EEG

whereas the response entropy (RE) component reflects activation of the frontal mimic muscles (EMG). RE−SE has been used as an indicator of nociceptive pain.[14] A novel multivariate index, defined as the surgical stress index (SSI),[15–18] based on a combination of the normalized HR and photoplethysmographic amplitude (PPGA),[16] has been found promising in monitoring intraoperative stress. Previous studies have not validated SSI in children or in ophthalmic surgery. The purpose of this study was to compare SSI with the other stress indicators (PPGA, HR, NIBP, RE, and RE−SE) during endotracheal intubation and strabismus surgery in anaesthetized children.

Methods

The local ethics committee of the hospital and the Finnish National Agency for Medicines approved the study. Twenty-two patients undergoing unilateral primary combined rectus muscle surgery under general anaesthesia were included in the study with two ophthalmic surgeons (L.I.L. and A.S.M.) operating on all the patients. Twelve patients had esotropia and they underwent recession of the medial rectus muscle and resection of the lateral rectus muscle. Nine patients with exotropia underwent recession of the lateral rectus muscle and resection of the medial rectus muscle. One patient in Group BSS was operated on because of vertical strabismus.

Patients aged 4–17 yr of ASA physical status I–II were included in this study. The parents gave written informed consent and, in addition, children aged 15–17 yr gave their written informed consent. Twenty-two consecutive patients were prospectively randomized into two groups using sealed envelopes. Patients randomized to the local anaesthesia group (Group LL) received topical anaesthesia with a 1:1 mixture of lidocaine 2% (Lidocard®, Orion Oyj, Espoo, Finland) and levobupivacaine 0.75% (Chirocaine®, Abbott Scandinavia AB, Solna, Sweden) according to the study plan. Patients in the control group (Group BSS) received balanced salt solution.

Delivery of local anaesthesia

A registered nurse prepared syringes of either local anaesthetic mixture (Group LL) or balanced salt solution (Group BSS) for the patients according to the study group revealed in the consecutive envelopes. The patients, the investigators, and the staff were blinded to the study group. All patients received four topical conjunctival drops of either solution on nine occasions: first, before washing the eye before the operation; second, before incision of the conjunctiva; third, into the conjunctival sac; fourth, before manipulation of the rectus muscle; and fifth, before closure of the conjunctiva. This treatment was repeated for the second operated muscle, that is, 4 drops on an additional four occasions.

Induction of general anaesthesia

No oral premedication was given. The site of venous puncture was anaesthetized with EMLA® cream (AstraZeneca, Espoo, Finland) applied 60 min in advance. One consultant anaesthesiologist (H.K.) induced general anaesthesia using fentanyl 2 μg kg^{-1}, lidocaine 10–30 mg, and propofol 2 mg kg^{-1} i.v. Thereafter, the lungs were ventilated by mask for 6 min using sevoflurane 3–8% in oxygen 4 litre min^{-1} according to its effect on cortical EEG activity as measured by SE (target range 40–60) followed by endotracheal intubation without the use of any neuromuscular blocking agents.

Maintenance of general anaesthesia

An S/5® Anaesthesia Delivery Unit, ADU® (GE Healthcare) was used for volume-controlled ventilation during operation aiming at an $F_{E_{CO_2}}$ of 5.3%. The sevoflurane concentration in fresh gas was adjusted to target SE at range 40–60.[13] When the surgeon performed ophthalmoscopy at the end of the surgery, propacetamol (a prodrug of acetaminophen, Perfalgan®, Bristol-Myers Squibb, Bromma, Sweden) 40 mg kg^{-1} was given for pain prophylaxis to all patients.

Monitoring

In the operating theatre, all patients were continuously monitored with pulse oximetry on the left thumb, photoplethysmographic pulse wave amplitude (PPGA, % of basic absorption), ECG lead II (HR, beats min^{-1}), airway gases (O_2, CO_2, and sevoflurane), ventilation rate from capnometry, and peripheral temperature (°C) of the middle finger tip (S/5 Anaesthesia Monitor of ADU, GE Healthcare). In order to ensure maximal finger pulse amplitude, Ringer's acetate (Baxter Oy, Finland) was infused rapidly to achieve normovolaemia indicated by temperature of the middle finger tip rising over 32°C. The Entropy™ sensor strip was placed contralaterally to the operated eye, so that the recording electrodes (#1 and #3) were placed at the midline of the forehead, above the eyebrows (#3), and laterally as close to the hairline as possible (#1). The ground electrode (#2) was placed where convenient. Non-invasive arterial pressure (S-NIBP, M-NIBP, and D-NIBP, respectively) were recorded every 5 min. A HR of 50 beats min^{-1} or less was defined as bradycardia and was treated by a temporary interruption of surgery. The state of the autonomic nervous system was displayed with a two-dimensional plot of HR *vs* PPGA (ANS spot). Additional fentanyl 1 μg kg^{-1} was administered i.v. to patients exhibiting tachycardic bursts revealed either by the ECG or by ANS spot movement indicating HR increase and PPGA decrease.

A laptop PC running S/5® Collect software (GE Healthcare) registered all the above variables *via* a serial cable and displayed the ANS spot. A plug-in program of the Collect software displayed beat-to-beat PPGA over HR on the laptop PC screen.[15] The SSI was derived from HR

and PPGA time series using a formula given in our previous publication in this journal.[16] Continuous data were converted (K.H.U.) into Windows Excel files, in which variables were presented as means of 10 s intervals. RE−SE was calculated in these worksheets in the post-processing phase.

Power analysis

The power analysis was based on the results of Yli-Hankala and colleagues[19] who compared patients with and without epidural anaesthesia and used increase of SSI after incision of the skin as the primary outcome variable. Assuming similar responses (the groups differed by 20 in ΔSSI and standard deviations were 14.4 and 14.1, respectively) and a power of 0.80, statistical significance at $P<0.05$ would be reached with nine patients in each group.

Statistical analyses

Data are reported as medians (ranges) and compared with Mann–Whitney *U*-test between the groups and Wilcoxon's signed rank test within the groups. Binominal data are given as numbers and percentages and were compared using the χ^2 test or Fisher's exact test. A *P*-value of <0.05 was considered statistically significant. Statistical analyses were performed using SigmaStat®, version 3.5 (Systat Software, Inc., Point Richmond, CA, USA) and graphs were designed based on the same data using SigmaPlot®, version 10 from the same firm.

Our primary outcome measure was acute changes in SSI (and its constituents PPGA and HR) (SE, RE, and NIBP), caused by laryngoscopy and endotracheal intubation and surgery. Baseline data during 3 min period before intubation (T1) and 3 min period after starting to intubate (T2) were compared. Further, a 12 min period from the start of surgery (T4) was compared with the 3 min baseline period (T3) before placing the drapes. The digital raw data of each patient were collected as a mean of 10 s periods. For the 3 min periods of T1, T2, and T3, we took the mean of 18 10 s periods. For the 12 min long T4 interval, we took the mean of 72 10 s samples for each individual. Wilcoxon's test was applied in testing T1 *vs* T2 using data from all 22 patients. Data from the 11 patients within Groups LL and BSS were compared between the time periods T3 and T4 using Wilcoxon's test. The effect of topical anaesthesia on nociceptive stress caused by surgery (during T4) was tested by comparing Groups LL and BSS using the Mann–Whitney *U*-test.

Since the variables often showed rapid transient changes during the time periods of interest (T2 and T4), the maximum change in each individual variable (decrease of PPGA or increase of SSI, HR, NIBP, or RE) was compared with the baseline mean values at T1 and T3 for each patient ($T2_{max}-T1_{mean}$ and $T4_{max}-T3_{mean}$). The criteria for clinical significance were defined as an increase in SSI of 10 units or more ($\Delta SSI \geq +10$ units), a decrease in PPGA of 0.5% units or more ($\Delta PPGA \leq -0.5$% units), an increase in HR of 10 beats min^{-1} or more ($\Delta HR \geq +10$ beats min^{-1}), an increase in systolic arterial pressure of 10 mm Hg or more (ΔS-NIBP$\geq +10$ mm Hg), and an increase in RE of 10 units or more ($\Delta RE \geq +10$ units). Changes of the individual variables from preintubation and presurgical means that exceeded the defined criteria were marked as 1 (positive) or 0 (negative). To determine the relative sensitivities of the variables during intubation and surgery, data were ranked by the sums of positive responses for each variable.

Results

Patient characteristics and the details of general anaesthesia (Table 1) were similar in both groups. The effect of endotracheal intubation (comparisons of T1 with T2) is reported in Table 2. Intubation caused a significant decrease in median PPGA together with a significant increase in SSI, HR, NIBP, RE, and RE−SE in the 22 patients (Table 2 and Fig. 1). Ranking of positive responses of the variables revealed that during intubation, a clinically significant decrease in PPGA occurred in 21/22 (95%) patients, an increase in RE in 19/21 (90%), SSI in 18/22 (82%), HR in 18/22 (82%), and S-NIBP in 11/20 (55%) of patients.

The effect of the start of surgery (period T3 compared with period T4) and comparisons between Group LL and Group BSS over the period of surgery are reported in Table 3 and Figure 2. In Group BSS (n=11), surgery caused a significant increase in SSI and RE−SE, whereas PPGA decreased significantly. In Group LL (n=11), surgery was also associated with a significant increase in SSI and a significant decrease in PPGA, but the increase of RE−SE was not statistically significant. In contrast to intubation, surgery did not increase NIBP or HR significantly. The incidence of positive responses in Groups LL and BSS was not

Table 1 Patient characteristics and management of surgery and anaesthesia. Data are given as mean (range) for age, mean (SD) for weight and height, median (range) or numbers of patients. The groups were comparable with regard to the recorded data

	Group LL	Group BSS
Age (yr)	9.7 (6–17)	9.4 (4–16)
Weight (kg)	38.5 (19.7)	34.4 (15.5)
Height (cm)	141.8 (22.7)	137.4 (23.9)
Male/female	3/8	8/3
ASA I/II	11/0	9/2
Operated eye (right/left) (*n*)	7/4	7/4
Esotropia/exotropia/hypertropia (*n*)	5/6/0	7/3/1
Fentanyl induction ($\mu g\ kg^{-1}$)	2.0 (1.9–2.2)	2.0 (1.9–2.5)
Fentanyl boluses ($\mu g\ kg^{-1}$)	0.9 (0–2.0)	1.0 (0–2.2)
Fentanyl total ($\mu g\ kg^{-1}$)	2.9 (1.9–4.0)	3.0 (2.0–4.4)
Propofol induction ($mg\ kg^{-1}$)	2.0 (1.9–2.4)	2.0 (2.0–2.3)
Sevoflurane ET (%)	2.2 (1.8–2.9)	2.2 (1.3–3.0)
Sevoflurane (min)	53 (38–76)	51 (38–76)
Sevoflurane total dose (min×ET%)	116 (67–174)	120 (53–159)

Table 2 Endotracheal intubation and stress-related variables [median (range)] during 3 min baseline (T1) and 3 min after starting to intubate (T2) were tested using Wilcoxon's test. The median (range) of the differences for each variable are also given (Delta T2−T1)

	T1 (baseline)	T2 (intubation)	Delta (T2−T1)	*P*-value
SSI	39.2 (22.6–55.6)	53.6 (35.8–63.3)	13.7 (−9.9–37.5)	<0.001
PPGA (%)	5.62 (2.79–9.69)	5.27 (2.59–7.54)	−0.51 (−2.90–1.36)	0.001
HR (beats min^{-1})	72.9 (56.7–113.8)	84.2 (60.4–124.8)	9.6 (−3.3–45.6)	<0.001
S-NIBP (mm Hg)	87 (78–143)	103 (79–125)	13 (−51–27)	0.007
M-NIBP (mm Hg)	62 (54–104)	72 (58–94)	10 (−36–30)	0.001
D-NIBP (mm Hg)	46 (39–82)	56 (42–78)	11 (−30–31)	0.005
SE	39.7 (17.2–57.9)	45.2 (15.9–60.2)	4.89 (−16.07–36.13)	NS
RE	42.0 (19.7–64.1)	50.0 (21.0–66.7)	6.89 (−17.00–37.04)	0.014
RE−SE	3.1 (0.06–9.1)	5.7 (0.6–9.4)	0.91 (−4.05–7.26)	0.01
Sevoflurane ET (%)	3.2 (2.0–5.3)	2.9 (1.5–6.3)	−0.08 (−2.69–1.46)	NS

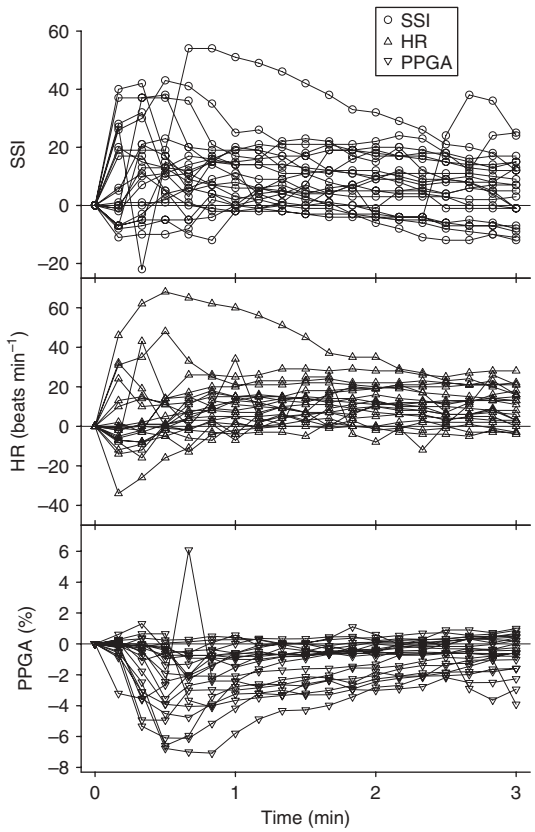

Fig 1 Changes in the SSI, HR, and PPGA over 3 min from the start of endotracheal intubation. Intubation started at time 0. Changes from 'time 0' of each individual (n=22) are depicted.

different, indicating that topical anaesthesia did not alleviate surgical pain stimuli.

Additional fentanyl was administered one to two times to 13 patients, five patients (45%) in Group LL and four (36%) in Group BSS did not receive any rescue fentanyl. During surgery, bradycardia occurred in one patient in Group LL for 200 s duration (at slowest, 48 beats min^{-1}) and in two patients of Group BSS, in one patient for 50 s duration (at slowest, 36 beats min^{-1}) and the other patient for 90 s (at slowest, 44 beats min^{-1}; Fig. 2). The latter patient in Group BSS also had slow HR during the intubation of trachea, that is, 46 beats min^{-1} for 10 s. Another patient of Group BSS was bradycardic during intubation (10 s duration, 47 beats min^{-1}). The pulse beeps during bradycardic episodes produced by the oculocardiac reflex were heard by the surgeons and prompted them to release the muscle. No patient received anticholinergics.

Discussion

The results of this study suggest that both SSI and PPGA are sensitive markers of operative stress in children. Endotracheal intubation (T1 *vs* T2) caused significant changes in all of the monitored stress-related variables: SSI, PPGA, HR, NIBP, RE, and RE−SE. Surgery was associated with a significant increase in SSI and decrease in PPGA in both groups, but local anaesthesia appeared to prevent a significant reflex increase of RE−SE in Group LL. However, changes in the stress-related variables did not differ between the groups during the surgery. A safe non-invasive local topical method of anaesthesia was chosen in order to avoid needle-related complications, but the method turned out to be inadequate to alleviate surgical pain stimuli.

Methodological concerns

Surgical procedures were similar regarding pain stimuli, since only primary strabismus operations were included in the study. We failed to mark the exact time of the first conjunctival incision leading to time-dispersion of the responses shown in Figure 2. The variables HR, PPGA, and SSI are based on beat-to-beat intervals (60/HR) and changes in pulse amplitudes. Although the typical responses lasted at least 1–2 min, the averages of 10 s values seen in figures may affect the statistics when comparing groups using mean values over longer time periods within and between the groups. Therefore, we analysed distinct responses detected before (T1) and after (T2) intubation, and during the first 12 min of surgery (T4).

Ranking of the stress markers by the prevalence of positive responses shows that PPGA is the most sensitive variable and HR and SSI are the next most sensitive markers. Marked increases of arterial pressure were the least

Table 3 Comparative data for stress-related variables for the time periods 3 min before surgery (T3) and 12 min after start of surgery (T4). Data from the local anaesthetic (LL) and saline groups (BBS) are shown separately. Wilcoxon's test was used within the groups. *P*-values are shown for the within group comparisons. Comparisons of the variables between the groups using Mann–Whitney *U*-tests (T3, T4, and T4−T3) indicated no statistical significance

	Group LL				Group BSS			
	T3 (baseline)	T4 (surgery)	Delta (T4−T3)	*P*-value	T3 (baseline)	T4 (surgery)	Delta (T4−T3)	*P*-value
SSI	43.3 (31.2–58.0)	49.9 (39.3–57.2)	9.0 (−4.1–12.8)	0.042	46.6 (26.8–57.8)	52.1 (31.7–60.1)	4.8 (−7.2–16.9)	0.024
PPGA (%)	6.60 (3.10–8.24)	5.80 (3.03–7.65)	−0.81 (−1.74–0.07)	<0.001	5.51 (3.25–9.84)	5.06 (3.08–8.99)	−0.20 (−1.51–0.55)	0.042
HR (beats min^{-1})	83.7 (60.8–113.2)	84.2 (60.0–115.5)	0.9 (−5.8–7.5)	NS	82.7 (59.4–112.7)	85.1 (57.2–120.0)	7.0 (−2.8–8.9)	Ns
S-NIBP (mm Hg)	99 (80–109)	98 (86–111)	−0.3 (−11–9)	NS	91 (75–112)	97 (73–114)	1 (−4–10)	NS
M-NIBP (mm Hg)	68 (58–92)	74 (60–81)	2 (−16–8)	NS	69 (50–82)	72 (54–85)	2.5 (−4–8)	NS
D-NIBP (mm Hg)	49 (43–77)	54 (41–66)	0.5 (−16–10)	NS	54 (35–66)	54 (42–70)	3(−7–8.5)	NS
SE	43.7 (2.9–55.2)	40.6 (25.1–59.8)	−0.07 (−7.19–47.59)	NS	37.3 (26.8–53.8)	35.8 (29.2–49.7)	2.72 (−17.99–8.89)	NS
RE	47.1 (3.6–60.9)	46.2 (31.3–62.0)	0.23 (−5.63–58.42)	NS	44.2 (30.2–62.8)	43.1 (38.3–54.1)	5.15 (−18.03–11.23)	NS
RE-SE	3.8 (0.7–8.3)	5.2 (0.9–11.6)	0.09 (−2.26–10.83)	NS	5.6 (1.3–9.1)	8.0 (2.1–10.6)	2.41 (−0.16–3.64)	0.014
Sevoflurane ET (%)	2.7 (2.2–3.2)	2.8 (1.8–3.7)	0.11 (−0.79–0.53)	NS	3.0 (2.3–3.5)	3.0 (1.4–3.3)	0.07 (−1.44–0.42)	NS

sensitive sign of inadequate analgesia both during intubation and during surgery. It should be noted that EMG activity in the upper facial muscles may mimic activity in the EEG frequency band increasing also the SE values, and thus decreasing the RE−SE difference.

Statistical inference hides the large variability and the transient nature of the changes in the stress-related variables as a result of intubation and surgery. There was a large individual spread of pre-intubation (T1) and pre-operative values (T3) in the stress-related variables, which challenged statistical inference. This observation prompted us to also examine the individual positive responses from pre-stimulus values during T2 and T4.

It should be kept in mind that 66% of SSI is based on PPGA.[16] In our experience, PPGA is decreased in fasted patients with cold fingers. Restricted perfusion allows minimal expression of autonomic responses, although they can still be seen in the HR alone. One drawback in SSI is that it does not indicate whether a change is caused by PPGA or HR.

We routinely monitor middle finger tip temperature as an indicator of peripheral perfusion.[20] Peripheral perfusion can be improved by liberal infusion of isotonic salt solution. Volumes of up to hundreds of millilitres may be required to cause physiological redistribution of blood flow. Fingers are well perfused when the finger tip temperature increases above 32ºC and the drip can be slowed down in this fully perfused state.

Comparison with previous work

In this study, stress due to intubation appeared to be alleviated more than in an otherwise similar previous study[21] in 62 children (average age 6 yr) receiving fentanyl 2 $\mu g\ kg^{-1}$ and propofol 2.5 $mg\ kg^{-1}$. For example, HR changed by 15% *vs* 26% and systolic arterial pressure changed by 18% *vs* 33% in the present and previous study, respectively.[21]

Rantanen and colleagues[14] investigated the relationship between nociception and RE−SE during general anaesthesia. They found the mean (SD) RE−SE increased by 2.61 (3.49) units at incision in patients who moved in response to the surgical stimulus (n=5), whereas no RE−SE response was seen in non-movers who had a change in RE−SE of −0.05 (1.62) (n=50), suggesting facial activation in moving patients. In the study by Rantanen and colleagues, skin incision caused a mean increase in RE−SE of 0.307 (3.025) in patients receiving remifentanil infused to a target concentration of 1 $ng\ ml^{-1}$, whereas the change in RE−SE in patients receiving a target concentration of 5 $ng\ ml^{-1}$ was −0.232 (0.723). In the present study, endotracheal intubation caused a median increase in RE−SE of 0.91 (30%) (n=22). Start of surgery (incision of conjunctiva and preparation of the muscle) caused a 2.4 (43%) increase in RE−SE in Group BSS, but no significant change in Group LL. Rantanen and colleagues[14] administered rocuronium 40 mg to all patients. In our study, since no neuromuscular blocking agents were used, RE, reflecting upper facial mimic muscle

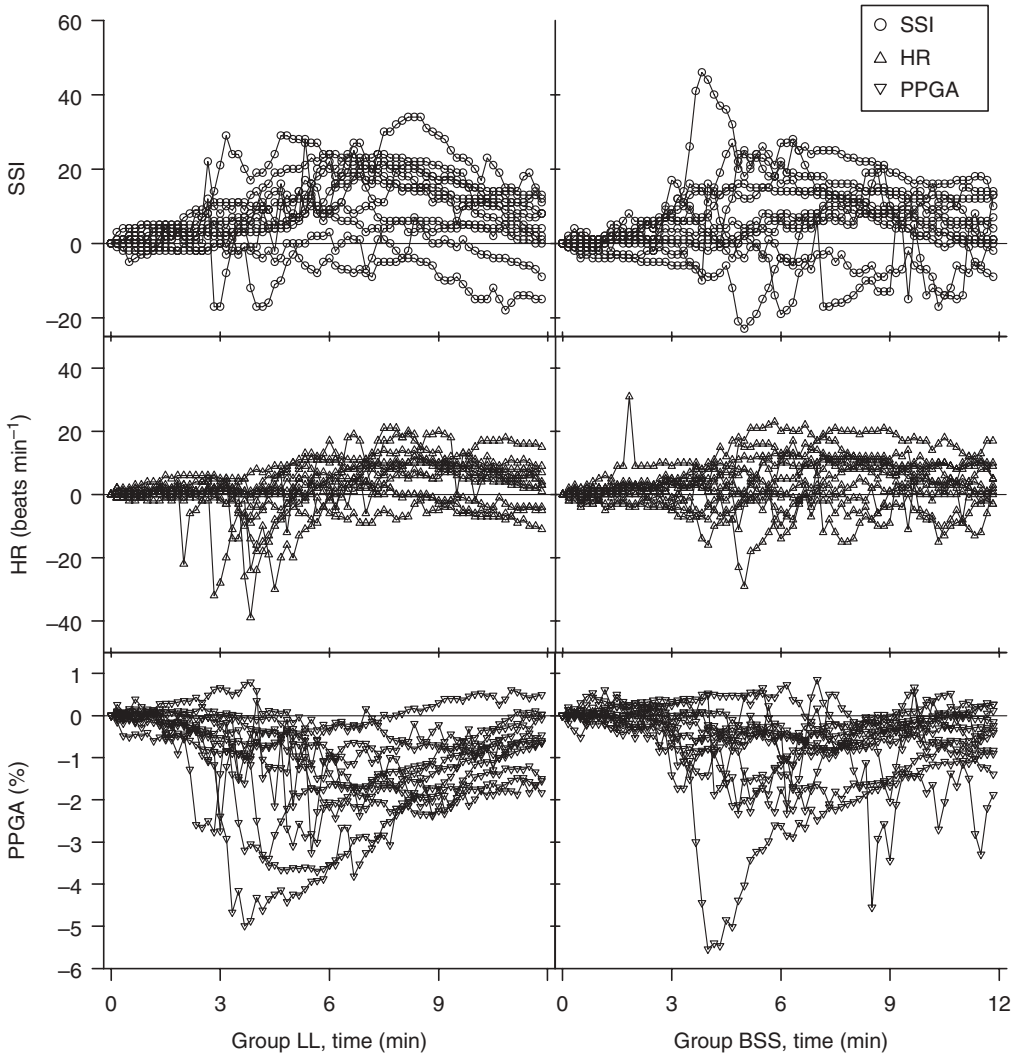

Fig 2 Changes in the SSI, HR, and PPGA over 12 min from the start of surgery. Data from the local anaesthetic (LL) and saline groups (BBS) are shown separately. Surgery started at time 0. Changes from 'time 0' of each individual (n=11) are depicted.

activation, remained sensitive to nociceptive stimuli also in patients without visible movement.[8]

In the present study, the change in SSI in response to endotracheal intubation and surgery was similar to that seen in the three previous studies.[16–18] In a remifentanil–propofol target control study,[16] differences in SSI correlated directly with the dose of remifentanil, but the dose of propofol had no impact on SSI. As effect-site concentrations of remifentanil increased (1, 3, and 5 ng ml^{-1}), the mean change in SSI was 9, 2, and 7 units during intubation and 28, 26, and 18 units during surgery.[16] In our paediatric study, we found an increase of SSI (ΔSSI) of 13.7 and 6.9 units caused by intubation and surgery, respectively.

In another study,[17] a remifentanil infusion was compared with a beta-blocker (esmolol) in 30 adult females. Exact SSI values or changes of SSI were not reported, but graphical data reported from this study suggest an increase of about 11% units as a result of intubation and about 12% units at incision in the group receiving beta-blockers. Surgical incision increased SSI in the esmolol group (insufficient prevention of sympathetic responses), but was not associated with an increase of SSI in the remifentanil group (sufficient analgesia).[17]

Huiku and colleagues,[16] also Struys and colleagues,[18] showed that SSI does not appear to be affected by the depth of anaesthesia.[18] They used a 30 s tetanic stimulation without any use of analgesics.[18] (A 30 s tetanic stimulation has been demonstrated to be comparable with stress from skin incision.)[22] Increasing predicted effect-site concentration of propofol from 5.3 to 6.9 μg ml^{-1} had minimal impact on SSI (ΔSSI decreased only from 32 to 25).[18] Furthermore, SSI identified tetanic stimuli more accurately compared with SE, RE, HR, or PPGA.[18]

The autonomic nervous system is fully developed at birth[23] as is the control of facial mimic muscles as we all have seen in newborn babies. The applicability of SE for monitoring hypnosis in children over 1 yr old has been tested, and shown to correlate with BIS values.[24 25] The

youngest children in our study were 4 yr old and well within the specified functionality of the Entropy Module™ (User's Manual, GE Medical, Helsinki, Finland). When neuromuscular blocking agents are avoided, RE stays some 6–10 units above SE down to around SE=25 (unpublished observation), whereas in deeper anaesthesia, the facial muscle activity decreases and RE−SE flattens.

Implications: theoretical, clinical, or both

SSI and RE−SE have not previously been tested in children. Our results in children during general anaesthesia without neuromuscular block are in agreement with four prior studies in adults.[14 16–18] SSI is not yet available commercially, but HR, PPGA, and RE−SE can be followed on monitor screens and by audible pulse beeps. The stress marker which was found to be the most sensitive in this study, PPGA, is awaiting wide clinical use. Display of the slow plethysmographic pulse waveform is already a commercially available feature, and indicates the same changes in autonomic nervous system responses as the ANS spot.[15]

Conclusion

All the stress indicators (SSI, PPGA, HR, NIBP, RE, and RE−SE) which were available in this randomized, controlled, and double-blinded trial succeeded in detecting the nociceptive stimulus caused by intubation and strabismus surgery in anaesthetized children.

References

1 Roizen MF, Horrigan RW, Frazer BM. Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision—MAC BAR. *Anesthesiology* 1981; **54**: 390–8

2 Urban BW. Current assessment of targets and theories of anaesthesia. *Br J Anaesth* 2002; **89**: 167–83

3 Oddby-Muhrbeck E, Eksborg S, Helander A, *et al*. Blood-borne factors possibly associated with post-operative nausea and vomiting: an explorative study in women after breast cancer surgery. *Acta Anaesthesiol Scand* 2005; **49**: 1346–54

4 Prkachin KM. The consistency of facial expressions of pain: a comparison across modalities. *Pain* 1992; **51**: 297–306

5 Edmonds HL Jr, Couture LJ, Stolzy SL, Paloheimo M. Quantitative surface electromyography in anesthesia and critical care. *Int J Clin Monit Comput* 1986; **3**: 135–45

6 Yli-Hankala A, Edmonds HL Jr, Heine MF, Strickland T Jr, Tsueda K. Auditory steady-state response, upper facial EMG, EEG and heart rate as predictors of movement during isoflurane–nitrous oxide anaesthesia. *Br J Anaesth* 1994; **73**: 174–9

7 Dutton RC, Smith WD, Bennett HL, Archer S, Smith NT. Craniofacial electromyogram activation response: another indicator of anesthetic depth. *J Clin Monit Comput* 1998; **14**: 5–17

8 Paloheimo M. Quantitative surface electromyography (qEMG): applications in anaesthesiology and critical care. *Acta Anaesthesiol Scand Suppl* 1990; **93**: 1–83

9 Tammisto T, Toikka O. Spontaneous EMG activity for detection of arousal during general anaesthesia—comparison between recordings from frontal and neck musculature. *Eur J Anaesthesiol* 1991; **8**: 109–14

10 Edmonds HL Jr, Couture LJ, Paloheimo MP, Rigor BM Sr. Objective assessment of opioid action by facial muscle surface electromyography (SEMG). *Prog Neuropsychopharmacol Biol Psychiatry* 1988; **12**: 727–38

11 Mathews DM, Cirullo PM, Struys MMRF, *et al*. Feasibility study for the administration of remifentanil based on the difference between response entropy and state entropy. *Br J Anaesth* 2007; **98**: 785–91

12 Shander A, Qin F, Bennett H. Prediction of postoperative analgesic requirements by facial electromyography during simultaneous BIS monitoring. *J Clin Anesth* 2001; **13**: 78

13 Viertiö-Oja H, Maja V, Särkelä M, *et al*. Description of the Entropy™; algorithm as applied in the Datex-Ohmeda S/5™; Entropy Module. *Acta Anaesthesiol Scand* 2004; **48**: 154–61

14 Rantanen M, Yli-Hankala A, van Gils M, *et al*. Novel multiparameter approach for measurement of nociception at skin incision during general anaesthesia. *Br J Anaesth* 2006; **96**: 367–76

15 Paloheimo MPJ, Penttinen M. ANS-spot and autonomic nervous system stability during general anaesthesia—a new pain indicator. *Br J Anaesth* 2004; **93**: 489P–90

16 Huiku M, Uutela K, van Gils M, *et al*. Assessment of surgical stress during general anaesthesia. *Br J Anaesth* 2007; **98**: 447–55

17 Ahonen J, Jokela R, Uutela K, Huiku M. Surgical stress index reflects surgical stress in gynaecological laparoscopic day-case surgery. *Br J Anaesth* 2007; **98**: 456–61

18 Struys MMRF, Vanpeteghem C, Huiku M, *et al*. Changes in a surgical stress index in response to standardized pain stimuli during propofol–remifentanil infusion. *Br J Anaesth* 2007; **99**: 359–67

19 Yli-Hankala A, Rantanen M, Uutela K, *et al*. Surgical stress index and epidural analgesia. *Eur J Anaesthesiol Suppl* 2006; **23**: 24 (A-92)

20 Lima AP, Beelen P, Bakker J. Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. *Crit Care Med* 2002; **30**: 1210–3

21 Xue FS, Liao X, Liu KP, *et al*. The circulatory responses to tracheal intubation in children: a comparison of the oral and nasal routes. *Anaesthesia* 2007; **62**: 220–6

22 Rantanen M, Yppärilä-Wolters H, van Gils M, *et al*. Tetanic stimulus of ulnar nerve as a predictor of heart rate response to skin incision in propofol–remifentanil anaesthesia. *Br J Anaesth* 2007; **99**: 509–13

23 Hill CE. Development of the autonomic nervous system. In: Robertson D, Biaggioni I, Burnstock G, Low PA, eds. *Primer on the Autonomic Nervous System*. USA: Elsevier Academic Press, 2004; 3–5

24 Davidson AJ, Kim MJ, Sangolt GK. Entropy and bispectral index during anaesthesia in children. *Anaesth Intensive Care* 2004; **32**: 485–93

25 Klockars JGM, Hiller A, Ranta S, *et al*. Spectral Entropy as a measure of hypnosis in children. *Anesthesiology* 2006; **104**: 708–17