GE Healthcare

Surgical Plethysmographic Index (SPI) in Anesthesia Practice

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The purpose of this article is to provide answers to the following questions:

1. How does SPI work?
2. What is the information that SPI provides?
3. Which physiological and external factors may affect the SPI values?
4. What are the demonstrated clinical benefits of SPI monitoring?

Answers to these questions were collected from the clinical studies in Table 1 comprising of 35 clinical sites and 1496 patients.
The studies have been performed over the years 2005 - 2012.
The studies followed good clinical practice including ethical board approval and compliance with regulatory requirements for research in human subjects.

SPI is not available for sale in USA and has not been cleared or approved by FDA.

1. HOW DOES SPI WORK?

Painful stimulation causes sympathetic responses of the autonomic nervous system. During a surgical operation, such responses are normally suppressed by analgetic medication. If administration of analgesia is inadequate relative to the level of the stimulation, the patient may show responses such as increased heart rate and peripheral vasoconstriction. SPI derives both these components of information from the plethysmographic signal that is measured by a pulse oximeter. First both the heart rate and the plethysmographic amplitude are normalized in order to decrease inter-patient variability by applying a histogram transformation on the raw time serie data. Then a linear combination of the normalized values is computed as

$$SPI = 100-(0.7*PPGAnorm+0.3*HBInorm),$$

in which PPGAnorm is the normalized plethysmographic pulse wave amplitude and HBInorm the normalized heart beat interval. A detailed description of the method can be found in S1.

2. WHAT IS THE INFORMATION THAT SPI PROVIDES?

Study S1 was the first one to provide evidence of the two main properties of the SPI measurement:

1) SPI values respond to surgical nociceptive stimuli, and

2) SPI responses to stimulation are systematically modulated by analgesic drug concentration

Anesthesia in S1 was delivered using propofol and remifentanil. Since then the relationship of the SPI measurement to surgical stimulus and different types of analgesic medications has been addressed in eleven peer reviewed clinical study publications (S1, S2, S3, S4, S6, S8, S9, S11, S12, S13 and S20). The goal of these trials was to verify that the SPI reacts to the level of analgesic medication and surgical stimuli in a variety of analgesic, anesthetic and surgical regimens. The studies cover different clinical conditions, i.e. include various types of patients, anesthesia, analgesia, medications, and surgery. SPI shows statistically significant responses to surgical stimulation, which is evaluated by comparing the SPI values before and after incision and at known surgical noxious events. SPI also shows statistically significant responses to the changes of the level of analgesia (S1, S3, S4, S6, S11 and S13). In target controlled infusion the analgesic effect has been changed by altering the infusion rate and registering the change in SPI. In other types of analgesic regimen the SPI value has been registered before and after a bolus dose of analgesics.

Additionally, Struys et al (S3) has shown that while SPI is significantly lowered by analgesic medication (Remifentanil), it is not affected by non-analgesic medication (Propofol). This study result is supported by Ojala et al (A2). Ahonen et al (S2) has shown that SPI reflects the nociception-anti-nociception balance in patients receiving beta-blocking agent (Esmolol). Further, in this study the SPI reactivity seems not to be influenced by Esmolol.

The performance of the SPI measurement for assessing the level of nociception and analgesia has been compared to a measurement of skin conductivity by Ledowsky et al (S12). They concluded that Surgical Pleth Index, heart rate and blood pressure, but not the "number of fluctuations in skin conductance" changed in response to changes in level of analgesia by showing significant differences between before and after a bolus of Fentanyl.

It should be noted that SPI measures responses, and therefore it does not provide information of the effect of analgesic drug medication in the absence of stimulation. If there is no stimulation, there are no responses to measure, independently of the level of analgesia.

In summary, SPI provides information of the responses of the patient to ongoing surgical stimulation during general anesthesia and helps to optimize the level of analgesic medication according to the needs of an individual patient.

3. WHICH PHYSIOLOGICAL AND EXTERNAL FACTORS MAY AFFECT THE SPI VALUES?

Surgical Pleth Index reflects a change of the autonomic nervous system balance in body. The increase of the sympathetic activity increases SPI. Potentially, any medication or therapy that affects the sympathetic nervous system balance is reflected in the value of the SPI. The change in the autonomic balance, however, does not necessarily change the reactivity of SPI to analgesic medication or surgical stimulation. In fact, the reactivity is usually maintained, but the interpretation of the absolute SPI level is confounded.

Bonhomme and Hans et al (S15, S18) have studied SPI, HR and mean arterial pressure, MAP, during neurosurgery using standardized noxious stimulus and fluid challenge as interventions. They found that the interpretation of SPI, HR, and MAP is affected by the status of the patient's intravascular blood volume and chronic history of hypertension. Based on the stimulus-response-probability model they suggested that the prediction for the adequate remifentanil level is the best when these factors were taken into account and the parameters were in concord in their prediction.

Mustola et al (S13) showed that Fentanyl boluses during operation decreased SPI and tracheal intubation, skin incision, and surgical stimuli during the procedure increased SPI as they should. SPI reacted consistently in both Sevoflurane and Isoflurane anesthesia. However, they noted that sometimes with poor plethysmographic signal in elderly patients at low blood pressure below MAP 60 mmHg and in the absence of stimulation SPI increased and NIBP decreased. This paradoxical response was reversed by Ethylphenylephrin 2 mg i.v.. Poor signal and weak plethysmographic pulse may thus confound the interpretation of the SPI values.

The study (S10) of Höcker et al investigated the effects of atropine and electric cardiac stimulation (pacemaker) on SPI in the absence of painful stimulation. The increase in HR induced by cardiac pacing or atropine resulted in a considerable increase in SPI without a change of the nociception- anti-nociception balance. They suggested that the absolute level of SPI should be interpreted cautiously in these situations.

Ilies et al (S16) investigated the effect of posture on SPI. The posture of a patient shifts the balance of the autonomic nervous system, and, therefore, has a marked effect on the absolute value, but does not suppress the reactivity of the Surgical Pleth Index.

The study of Ducrocq et al (A7) investigated the effect of ephedrine on SPI. Bolus doses of ephedrine were injected intravenously when systolic arterial pressure values were below 90 mmHg for more than 2 minutes. The study results showed that the ephedrine effect is transient and after 200 sec SPI is not any more influenced by ephedrine bolus. After the short transient the absolute SPI level can again be used as an estimator of the nociception - anti-nociception balance.

Aho et al (S4) investigated the effect of hypothermia on SPI. They found that the correlation to core temperature was only 0.022, indicating that mild hypothermia does not affect SPI. Further, the average SPI values were higher during than before surgery and higher with low than high remifentanil levels during surgery. The reactivity of SPI to surgical stimuli and opioid analgesia remained during moderate hypothermia.

Our supplementary studies, not in Table1, revealed that SPI is affected by cardiac arrhythmia, which especially when severe can cause unstable SPI values. In arrhythmia cases SPI should be interpreted cautiously.

SPI algorithm has been developed for finger measurement and cannot be used on other sites such as ear or toe. The change of the SpO2 probe between fingers may also change SPI values, but will maintain the responsiveness of the measurement to stimulation and analgesic medications. As conclusion, after a change of the SpO2 probe site or after removing and re-attaching the probe on the same site, the SPI value may shift to a slightly different level without a change in the nociception-anti-nociception balance.

In most cases the limitations of using SPI are obvious and relate to other than nociception and analgesic medication related changes in the patient's pulse rate or plethysmographic amplitude (R1). Therefore, the interpretation of the SPI values, especially the absolute level of SPI, shall be done in conjunction to other physiological parameters, and therapy forms such as vasoactive and cardiac medications given to a patient.

4. WHAT ARE THE DEMONSTRATED CLINICAL BENEFITS OF SPI MONITORING?

Chen et al. (S14) compared SPI guided analgesia to standard clinical practice and concluded that SPI guided Remifentanil titration resulted in a significant reduction of Remifentanil consumption and less incidences of unwanted events such as hypertension, hypotension, tachycardia and movement during surgery (Figure 1.). Further, SPI showed the highest prediction probability for indicating maximum stimulation during surgery.

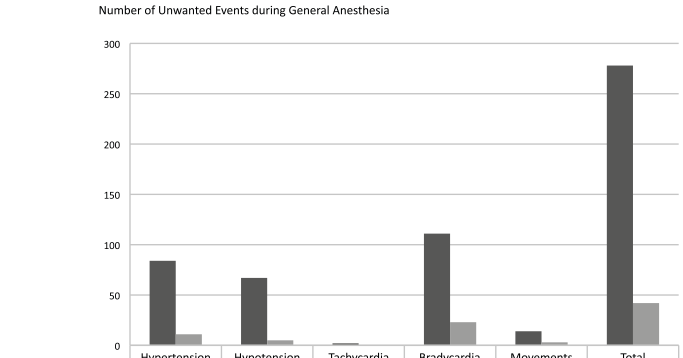

Figure 1. Number of unwanted events during general anesthesia with Propofol and Remifentanil decreased by 85% in the SPI guided anesthesia group in comparison to the standard practice group (Chen et al, Comparison of Surgical Stress Index-guided Analgesia with Standard Clinical practice during Routine General Anesthesia, Anesthesiology 112: 1175-83 (2010).)

Using the same patient population and study set-up Chen et al (S20) also studied the correlation of SPI with the level of stress hormones. They found that in intubation and during surgery the SPI could indicate the predefined specific level of ACTH, cortisol, epinephrine and norepinephrine with an area under ROC curve of 0.85, 0.62, 0.59 and 0.62, respectively. Sensitivity (81%) and specificity (73%) of the SPI to predict ACTH values were highest among the four stress hormones. They conclude that SPI was able to predict ACTH with high sensitivity and specificity.

The study by Bergmann (S17) compared the Propofol and Remifentanil consumption and operation process times between the SPI/Entropy guided anesthesia group and a control group with Entropy and standard clinical parameters in outpatient anesthesia. Both Remifentanil and Propofol consumption was significantly lower in the SPI/Entropy than in the Entropy group ($p<0.05$). The processing times for the opening of eyes and extubation was significantly lower in the SPI/Entropy than in the Entropy group ($p<0.05$). This study and the study by Chen et al (S14) show that the Propofol-Remifentanil anesthesia guided by SPI or SPI and Entropy may have an economic impact on patient care in terms of the consumption of anesthetics and the length of the operation.

In summary, the use of SPI during general anesthesia with Propofol and Remifentanil has been demonstrated to reduce the amount of adverse events, decrease the use of anesthetics, and shorten the time needed for the procedure.

APPENDIX: SUMMARY OF THE CLINICAL STUDIES ON SPI

Clinical evidence for the Surgical Pleth Index, SPI, shown by the studies in Table 1 has been created in a broad range of surgical operations (Figure A1) and in all common types of general anesthesias (Figure A2 and A3). Most of the evaluation studies are for fully anesthetized adults (>=18 yrs) patients during general anesthesia (Figure A4), but SPI has also been evaluated for children and for spinal and local anesthesia with and without sedation, in awake patients in PACU and in chronic pain patients. Both known surgical stimulations and standardized electrical noxious stimulations are used to evaluate the performance of SPI (Figure A5). The usage of SPI for children and awake, sedated and lightly anesthetized patients are out of the intended use patient groups. The effect of certain, potentially confounding, common medications, and artifacts and surgical interventions has been evaluated, as well.

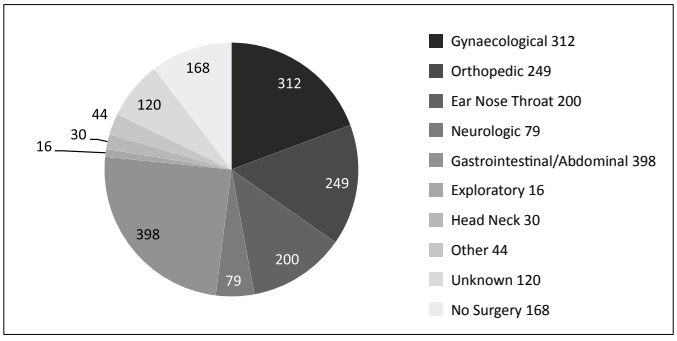

Figure A1. The number of patients in the SPI evaluation studies categorized based on the type of surgery. The total number of clinical cases with SPI is 1496.

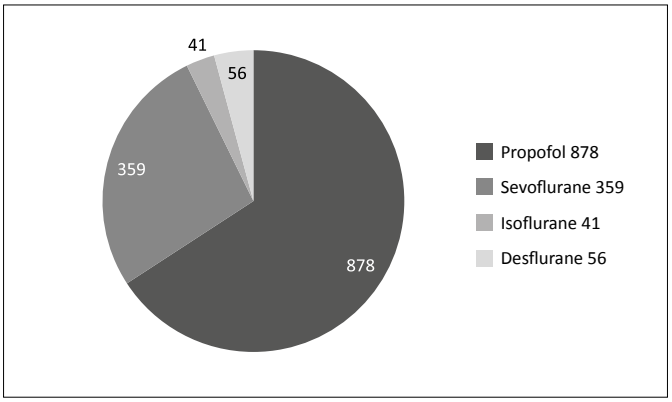

Figure A2. The number of patients in the SPI evaluations categorized by the different types of hypnotic agents.

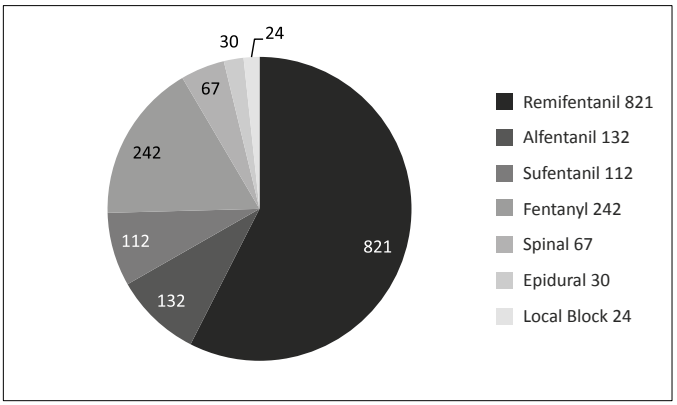

Figure A3. The number of patients in the SPI evaluations categorized by the different types of analgesia.

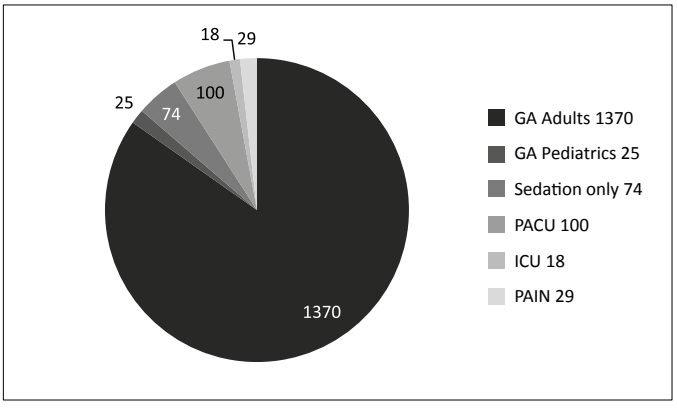

Figure A4. SPI evaluations per patient groups. SPI is intended for fully anesthetized adult patients (GA Adults).

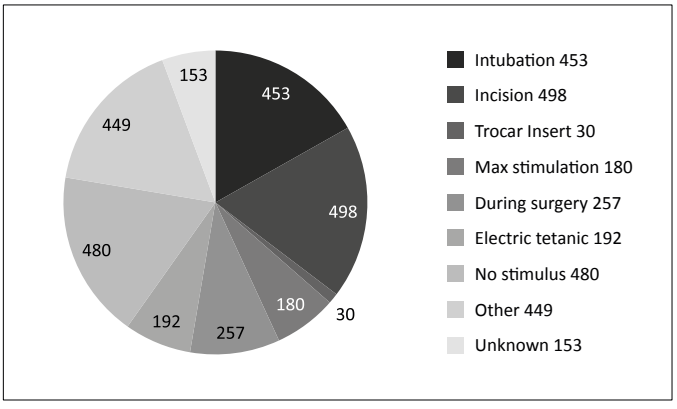

Figure A5. The performance of SPI has been evaluated at broad range of stimulation levels.

Propofol is both fast effecting and almost pure hypnotic agent and remifentanil has a very fast and the shortest time analgesic effect. Therefore, in a propofol-remifentanil anesthesia, the analgesic effect can be investigated separately from the hypnotic effect. Further, both the level of hypnosis and analgesia can be adjusted up and down in short time scales. Therefore, the responses of SPI can be demonstrated in a clear way and the interpretation of the expected effect of the medication is easy.

The inhalational anesthetic agents are typically used with opioids such as fentanyl or alfentanil that have a long lasting and slower effect time. Further, the effect of the inhalational anesthetic agent can be decreased only in relatively long time scales by increasing the ventilation and waiting until the end tidal concentration decreases. The gaseous anesthetic agents also have both hypnotic and analgesic effects in addition that the effects are highly synergistic. Correspondingly, the SPI changes are slower and less clear as they appear on top of the analgesic baseline provided by the inhalational agent alone. Consequently, the SPI responses can be studied between time points, i.e. intervals that are longer and may contain a change in the level of stimulation, which can be very dynamic in some surgical procedures. This smears out the SPI responses and make them more difficult to interpret in terms of the expected change in the balance of the noxious stimulation and analgesic medication.

The total number of patient cases in the studies is 1496. A broad range of surgical operations and all common types of general anesthesia are covered.

SPI has been evaluated for fully anesthetized adults (>=18 yrs) patients during general anesthesia. Both known surgical stimulations and standardized electrical noxious stimulations have been used to evaluate the performance of SPI. The SPI level and responses have been evaluated over wide range of analgesic regimens. SPI has also been evaluated for children during general anesthesia and awake, sedated and lightly anesthetized patients, which are out of the intended use patient groups. The effect of certain, potentially confounding, medications, and artifacts and surgical interventions has been evaluated. Supplementary studies, which are unpublished, have evaluated SPI during cardiac surgeries and are summarized later in this section.

The results show that SPI reflects the nociception - anti-nociception balance during general anesthesia.

TABLE 1. PUBLICATIONS ON THE SPI MEASUREMENT

ID #	Authors	Title	Publication
S1	M. Huiku et al	Assessment of surgical stress during general anaesthesia	Br. J. Anaesth. 98, 447-455 (2007)
S2	J. Ahonen et al	Surgical stress index during gynaecological laparoscopy	Br. J. Anaesth. 98, 456-461 (2007)
S3	M. Struys et al	Changes in a surgical stress index in response to standardized pain stimuli during propofol-remifentanil infusion	Br. J. Anaesth 99, 359-367 (2007)
S4	J. Wennervirta et al	Surgical stress index as a measure of nociception/antinociception balance during general anaesthesia	Acta Anaesthesiol Scand 52, 1038-1045 (2008)
S5	H. Kallio et al	Measurement of surgical stress in anaesthetized children	Br. J. Anaesth 101, 383-389 (2008)
S6	M. Gruenewald et al	Influence of different remifentanil concentrations on the performance of the surgical stress index to detect a standardized painful stimulus during sevoflurane anesthesia	Br. J. Anaesth 103, 586-93 (2009).
S7	T. Ledowski et al	Monitoring of sympathetic tone to assess postoperative pain: skin conductance vs. surgical stress index	Anaesthesia 64, 727-731 (2009).
S8*	C. Ilies et al	Evaluation of the surgical stress index during spinal and general anesthesia	Br. J. Anaesth 105, 533-7 (2010).
S9	M. Paloheimo et al	Autonomic nervous system state: the effect of general anesthesia and bilateral tonsillectomy after unilateral infiltration of lidocaine	Br. J. Anaesth 104, 587-95 (2010).
S10	J. Höcker et al	Surgical stress index in response to pacemaker stimulation or atropine	Br. J. Anaesth 105, 150-4 (2010).
S11	S. Mustola et al	Effect-site concentration of remifentanil attenuating surgical stress index responses to intubation of the trachea	Anaesthesia 65, 581-585 (2010).
S12	T. Ledowski et al	Monitoring of intra-operative nociception: skin conductance and surgical stress index versus stress hormone plasma levels	Anaesthesia 65, 1001-1006 (2010).
S13	S. Mustola et al	Performance of Surgical Stress Index during Sevoflurane-Fentanyl Anesthesia	Anesthesiology Research and Practice 2010, Article ID 810721, 5 pages, (2010).
S14	X. Chen et al	Comparison of Surgical Stress Index-guided Analgesia with Standard General Anesthesia. A Pilot study.	Anesthesiology 112, 1175-83 (2010).
S15	V. Bonhomme et al	Comparison of the Surgical Pleth Index™ with haemodynamic variables to assess nociception-antinociception balance during general anaesthesia	Br. J. Anaesth 105, 101-11 (2011).
S16	C. Ilies et al	The effect of posture and anaesthetic technique on the surgical pleth index	Anaesthesia 67, pp.508-513 (2012).
S17	I. Bergmann et al	Surgical Pleth Index (SPI) reduces propofol and remifentanil consumption and shortens operational process times in outpatient anesthesia	Br. J. Anaesth. 110, 622-8 (2013).
S18	P. Hans et al	Effect of a fluid challenge on the Surgical Pleth Index during stable propofol-remifentanil anaesthesia	Acta Anaesthesiol Scand 56, 787-796 (2012).
S19	K. Hamunen et al	Effect of pain on autonomic nervous system indices derived from photoplethysmography in healthy volunteers	Br. J. Anaesth. 108, 838-44 (2012).
S20	X. Chen et al	Correlation of surgical stress index (SPI) with stress hormones during propofol-remifentanil anaesthesia	The Scientific World Journal, Anesthesiology, Article ID 879158.
R1	I. Korhonen, A. Yli-hankala	Photoplethysmography and nociception	Acta Anaesthesiol Scand 53(8), 975-85 (2009).
A1	K. Uutela et al	A-87: High levels of surgical stress index before movements of anesthetized patients	Europian J. Anaesth. 23, p23 (2006)
A2	N. Ojala et al	A-90: Surgical stress index and entropy provide complementary information of analgesia and hypnosis	European J. Anaesth 23, p23 (2006).
A3	A. Yli-Hankala et al	A-92: Surgical stress index and epidural analgesia	European J. Anaesth. 23, p24 (2006)
A4	A. Aho et al	A1043: Surgical stress index is not influenced by moderate intraoperative hypothermia,	Anesthesiology 105 (2006)
A5	J. Vieri et al	3AP4-5: SSI is sensitive to both sevoflurane and alfentanil during general anaesthesia	European J. Anaesth. 24, p22 (2007).
A6	M. Sorbello et al	A818: Accordance of Surgical stress Index and Clinical Judgement in laparoscopic cholecistectomy	Anesthesiology 107 (2007).
A7	N. Ducrocq et al	3AP7-9: Effect of ephedrine on surgical stress index during anaesthesia	European J. Anaesth. 25, p47 (2008).
A8	M. Gruenewald et al	A674: Effect of Rocuronium Injection and Pre-treatment with Lidocaine on Surgical Pleth Index	ASA Proc. A674 (2010)
A9*	S. Willms et al	1AP6-6: Surgical Pleth index (SPI) guidance vs. Standard practice during sevoflurane-sufentanil anaesthesia: A randomised controlled trial	European J. Anaesth. 28, pp. 21-22 (2011).
A10	M. Bossolasco et al	3AP5-2: Surgical Pleth Index to evaluate analgesia during esophagogastroduodenoscopy (EGD) procedures	European J. Anaesth. 28, p37 (2011).
D1	K. Osten	Effect of standardized noxious stimuli on Surgical Stress Index (SSI) during Sevoflurane-Remifentanil anaesthesia (German)	MD Thesis, Department of Medicine, Christian-Albrechts-University, Kiel (2010).
GE1	M1119248	Test Summary of SPI Clinical Validation Studies	GEHC (2007)
GE2	M1136917	End Report for the Controlled Release for Evaluation (=beta test) of the Surgical Stress Index (SSI) EMEA Q2 – Q4/2007.	GEHC (2007)

*Study is registered in ClinicalTrials.gov. S-8 under NCT00789438 and A-9 under NCT01525537. Refer also to discussion of compliance with www.clinicaltrials.gov at the end of this section.

TABLE 2: SUMMARY OF THE STUDY RESULTS

Study	Study site (Sponsor)	No. of patients	Exclusion criteria	Type of surgery	Pharmaceutical Regimen	Hypothesis	Results
S1	Tampere University Hospital, Tampere, Finland (GE Healthcare Finland Oy, GEHC)	72	Neurological disorders, medication affecting the CNS or HR, major cardiac problems, uncontrolled hypertension, alcohol or drug abuse, BMI > 30	Gynae-cological and breast surgery	Propofol - Remifentanil	Development study.	SPI was significantly ($p<0.05$) different after vs. before incision, during vs. before surgery and low (1 ng/ml) vs. high (5 ng/ml) Remifentanil concentration.
S2	Helsinki University Hospital, Helsinki, Finland (GEHC)	30	Age<20 or >65 years, any lung, liver, or renal disease, history of peptic ulcer disease, BMI > 30, hypersensitivity to any of the drugs used	Gynae-cological laparo-scopic surgery	Desflurane/N2O - Remifentanil	At Entropy and arterial pressure at a predetermine-ed level SPI would be higher in patients receiving Esmolol than in those receiving Remifentanil during the surgical procedure.	SPI reacted to surgical incision and was higher in patients receiving Esmolol ($p<0.05$). In patient receiving Remifentanil SPI did not react to incision and maintained a lower level throughout surgery ($p<0.05$). SPI seems to reflect the level of nociception and may help to guide the use of opioids. SPI reactivity seems not to be influenced by Esmolol. Main results are presented in Fig. 1.
S3	Ghent University Hospital, Ghent, Belgium (GEHC)	40	Weight <70% or >130% of ideal body weight, neurological disorder, any condition that interferes with cardiovascular status or level of consciousness, recent use of any concomitant medication	Urologic-al or gynaec-ological surgery	Propofol - Remifentanil	Not stated.	Static and dynamic values of SPI correlated to the Remifentanil concentration ($p<0.01$) better than Entropy, heart rate and plethysmographic amplitude. SPI was independent of the Propofol concentration. The prediction probability for the concentration of Remifentanil both before and during the noxious stimulus was better for SPI.
S4	Helsinki University Hospital, Helsinki, Finland (GEHC)	26	BMI >35, untreated hypertension, any medication affecting the CNS, a history of neurological or a connective tissue disease, diabetes, history of alcohol or drug abuse	Shoulder Surgery	Desflurane - Alfentanil with or without Mepivacaine Local Block	SPI is lower in patients who received interscalene plexus block before surgery compared with patients who did not receive a block. A diminished need of opioids in the plexus group would indicate effective anti-nociception.	SPI reacted to surgical incision and was higher in the control group (no local block) compared with the plexus block group patients ($p<0.005$). Alfentanil bolus decreased SPI in the control group. The total cumulative need for Alfentanil was higher in the control group than in the plexus block group ($p<0.008$). Tetanic stimulation increased SPI significantly only among the patients with plexus block not covering the site of the stimulation ($p<0.05$).
S5	Helsinki University Hospital, Helsinki, Finland (GEHC)	22	None	Unilateral primary combined rectus muscle surgery	Sevoflurane with or without local anesthesia	Not stated.	Pediatric patients. All parameters, SPI, PPGA, HR, NIBP, RE, and RE-SE detected autonomic responses to nociception in children undergoing strabismus surgery. Endotracheal intubation caused significant changes in all parameters (For SPI $p<0.001$).
S6	University Hospital Schleswig-Holstein, Kiel, Germany (The site)	24	Pregnancy, history of cardiac arrhytmia, neuromuscular or neurological disease, use of CNS-active medication, alcohol or illicit drug abuse	Gynaecological laparoscopic surgery	Sevoflurane - Remifentanil	During stable Sevoflurane concentration increasing Remifentanil concentration decreases SPI. Secondly, the effect of noxious stimulation is negatively correlated with Remifentanil concentration. Thirdly, SPI will enable detection of nociception not indicated by standard monitoring parameters.	SPI and BIS, but not HR and Entropy, were significantly altered after stimulation. Change in SPI was significantly dependent on Remifentanil concentration. In 10 out of 63 cases, SPI detected response to stimulation, not detected by another variable. Main results are presented in Fig. 2.

Study	Study site (Sponsor)	No. of patients	Exclusion criteria	Type of surgery	Pharmaceutical Regimen	Hypothesis	Results
S7	University of Western Australia, Perth, Australia (The site)	100	Age <18 or >85 years, autonomic neuropathy, pacemaker, anticholinergic drugs, beta-blockers, ketamine or clonidine, regional anesthesia, post-operative analgesia by continuous infusion	Post-operative Pain	Fentanyl	SPI could reflect changes in sympathetic tone in awake patients and hence reflect states of pain with reaonable accuracy.	Both number of fluctuations in skin conductance per second and SPI identified timepoints with moderate to severe pain with only moderate sensitivity and specificity. Mainresults are presented in tables 1 and 2.
S8	University Hospital Schleswig-Holstein, Kiel, Germany (The site)	71	Age <18 or >80 years, BMI >35, emergency cases, cardiac arrhytmias, pacemaker, history of chronic pain	Urological or orthopedic surgery	General anesthesia with propofol and remifentanil or spinal anesthesia with or without propofol sedation	SPI is lower in patients during spinal anesthesia compared with general anesthesia. Sedation in awake patients affects SPI due to reduced anciety during surgical procedures.	Patients under spinal anesthesia show a higher SPI than under general anesthesia. SPI is not only affected by nociceptive input but also by the level of sedation. Assessment of SPI in patients who are not under general anesthesia should take into account the level of sedation. In fully awake patients under spinal anesthesia SPI is influeced by mental stress. Even light sedation attenuates these influences. Main results are presented in Figs. 1-3.
S9	Helsinki University Hospital, Helsinki, Finland (GEHC)	12	Age <18 or >65 years, CNS disease, cardiovascular disease, ANS disease, drugs affecting the ANS, the CNS or cardiovascular system, alcohol or drug abuse	Bilateral tonsillectomy	Propofol/ Sevoflurane - Fentanyl	Not stated.	All autonomic signs including SPI indicated statistically significant sympathetic activation during saline-infiltrated tonsillectomies when compared with lidocaine-infiltrated sides. Main results are presented in Table 2.
S10	University Hospital Schleswig-Holstein, Kiel, Germany (The site)	18	Emergency surgery, history of severe arrhytmia, perioperative beta-blockers, neurological disease, postoperative HR <50 or >80 and norepinephrine infusion >0.1 ug/ kg/min	ASA III ICU patients	Propofol	Not stated.	The increase in HR induced by cardiac pacing or atropine resulted in a considerable increase in SPI without a change of the nociception- anti-nociception balance. Re-calibration of SPI decreased SPI during cardiac pacing, but had no effect after atropine administration. main results are presented in Figs. 1 and 2.
S11	South Carelia Central Hospital, Lappeenranta, Finland (GEHC)	30	Cardiac arrhythmia, neurological disorder, medication affecting the CNS, history of algohol or drug abuse	Laparoscopy/- tomy and Neck/ Shoulder Surgery	Propofol - Remifentanil	Not stated.	SPI worked well as a response parameter in the probit analysis. Mean effect-site concentrations of Remifentanil were 2.13 ng/ ml and 3.05 ng/ml in deep and normal groups (p=0.034). The 50% response probability levels for SPI were 2.34 and 3.17 ng/ml in the deep and normal groups, respectively. Main result is presented in Fig. 2.
S12	University of Western Australia, Perth, Australia (The site)	20	Age <18 years, incapability to consent, medication with sympathomimetic, sympatholytic or anticholinergic drugs, pacemaker, hypersensitivity to any of the used drugs, medication interacting with the assessment of stress hormone plasma levels	Abdominal, Maxillo Facial, and Orthopedic Surgery	Sevoflurane - Fentanyl	Not stated.	SPI (but not NFSC) changed significantly with increasing depth of analgesia after a bolus doses of fentanyl (p<0.001). Neither SPI nor NFSC accurately reflected the time course of stress hormone changes. Main results are presented in Fig. 1.

Study	Study site (Sponsor)	No. of patients	Exclusion criteria	Type of surgery	Pharmaceutical Regimen	Hypothesis	Results
S13	South Carelia Central Hospital, Lappeenranta, Finland (GEHC)	40	Cardiac arrhythmia, neurological disorder, medication affecting the CNS, history of algohol or drug abuse		Thiopentone - Fentanyl/ Sevoflurane - Fentanyl or Isoflurane - Fentanyl	Not stated.	Fentanyl bolus (2 ug/kg), given 5 minutes before tracheal intubation, did not block totally the increase of SPI. Fentanyl boluses during procedure decreased SPI, indicating that increased analgesia decreases SPI ($p<0.01$). Tracheal intubation and skin incision increased SPI, indicating that nociception increases SPI ($p<0.001$). SPI reacted consistently in both Sevoflurane and Isoflurane groups. Sometimes in elderly patients at low blood pressure in the absence of stimulation SPI increased and reported poor signal while NIBP decreased. When Ethylphenylephrin 2 mg was given iv., NIBP increased and SPI decreased. Main results are presented in Fig. 1 and Table 2.
S14	University Hospital Schleswig-Holstein, Kiel, Germany (The site)	80	CNS disease, chronic use of psychoactive medication, abuse of alcohol or illicit drugs, significant cardiovascular, renal, hepatic, or endocrinologic disorders, hemodynamic status being considered as "unwanted event" already at baseline	Ear-nose-throat Surgery	Propofol - Remifentanil	First, SPI guided remifentanil administration results in more stable hemodynamics, less consumption of Remifentanil, and shorter recovery times. Seconly, SPI may react well to the intensity of stimuli such as intubation and painful manipulation during surgery.	Remifentanil consumption was lower in the SPI group than in the control group (9.5 ug/kg vs. 12.3 ug/kg; $p<0.05$). The number of unwanted events was less in the SPI group (84) than in the control group (556); $p < 0.01$. The authors conclude that SPI guided anesthesia resulted in lower Remifentanil consumption, more stable hemodynamics, and a lower incidence of unwanted events. The time fractions of SPI values between 20 and 50 were significantly higher in the SPI group than in the control group ($p<0.01$). For indicating the state of intubation and the state of maximum stimulation during surgery the Pk value of SPI was the highest ($p<0.01$) among variables SPI, BIS, MAP, and HR. The main results are presented in Figs. 1 and 2 and in Tables 3, 4, and 5.
S15	CHU Liege, Liege, Belgium (The site)	33	Age <18 or >80 years, impaired cardiac function, diabetes	Intracranial neurosurgery	Propofol - Remifentanil	Not stated.	SPI, HR, and MAP are of comparable value at gauging the noxious stimulation- Ce-Remifentanil balance. Their interpretation is improved by taking into account of intravascular volume, treatment for chronic high arterial pressure, and concordance between their predictions. Main results are presented in Fig. 2 and Table 2 and 4.
S16	University Hospital Schleswig-Holstein, Kiel, Germany (The site)	60	Age <18 or >80 years, emergency surgery, cardiac arrhythmia, pacemaker, history of chronic pain		General anesthesia with propofol and remifentanil or spinal anesthesia with or without propofol sedation or healthy awake volunteers.	The changing of patient position would affect the SPI value and these effects would differ depending on the anesthetic technique being used.	Change in posture has marked effect on SPI which lasts for at least 45 minutes. The effect of posture should be considered when interpreting the displayed values. Main results are presented in Figs. 1 and 4, and Table 2.
S17	University of Göttingen Medical School, Göttingen, Germany (The site)	170	Intended position change during surgery and cardiac arrhythmias, age <18 or >75 years, ASA > III	Orthopedic Surgery	Propofol - Remifentanil	The combination of SPI and Entropy monitoring reduces the consumption of Propofol and Remifentanil and allows recovery times to be shorter compared with Entropy monitoring alone.	Both Remifentanil ($p=0.006$) and Propofol ($p<0.001$) consumption was significantly lower in the SPI/ Entropy than in the Entropy group. The processing times for the opening of eyes and extubation was significantly lower in the SPI/ Entropy than in the Entropy group ($p<0.001$). The main results are presented in Table 2.

Study	Study site (Sponsor)	No. of patients	Exclusion criteria	Type of surgery	Pharmaceutical Regimen	Hypothesis	Results
S18	CHU Liege, Liege, Belgium (The site)	33	Age <18 or >80 years, impaired cardiac function, diabetes	Neurosurgery	Propofol - Remifentanil	A alteration of the intravascular volume status could affect SPI in the absense of any change in the nocicption-antinociception balance.	SPI response to FC was variable: SPI did not change in 16, increased in 12, and decreased in 3 patients. SPI tended to show no response in normovolemic patients, a decrease in hypovolemia, and an increase at higher Propofol concentrations. The overall response to FC remained small, in average +6 units from +1 min to the peak response at +8-9 min after FC. The main results are presented in Fig. 2 and Table 2.
S19	Helsinki University Hospital, Helsinki, Finland (The site)	29	History of chronic disease, prescription medications	NA	NA	Not stated.	All three stimuli changed PPGA, HR, and SPI values significantly from their respective baseline values ($p<0.001$ for all). CPT-induced pain, but not heat stimulus induced pain, correlated with the magnitude of the respective changes of the calculated indices. The main results are presented in Table 1.
S20	University Hospital Schleswig-Holstein, Kiel, Germany (The site)	80	History of CNS disease, chronic use of psychoactive medication, abuse of alcohol or illicit drugs, significant cardiovascular, renal, hepatic or endocrinologic disorders	Ear-nose-throat Surgery	Propofol - Remifentanil	SPI has a different performance at different states of consciousness and SPI has a better correlation with stress hormones than arterial blood pressure, heart rate or the BIS.	The correlation coefficients between the SPI values and the four stress hormones were low (<0.3) at the awake baseline, whereas at the three other time points under general anesthesia were between 0.3 and 0.5. The SPI could indicate the specific level of ACTH, cortisol, epinephrine and norepinephrine with an area under the ROC curve of 0.85, 0.62, 0.59 and 0.62, respectively. Sensitivity (81%) and specificity (73%) of the SPI to predict ACTH values were highest among the four stress hormones. the main results are presented in Fig. 2 and Table 3.
R1	NA	NA		NA	NA	NA	Specificity of the PPG monitoring. As PPG pulse amplitude is a parameter in SPI, SPI is influenced whenever PPG is altered. Medications and artifacts that affect PPG potentially affect the SPI values.
A1	Tampere University Hospital, Tampere, Finland (GEHC)	55		Abdominal surgeries	Propofol - Remifentanil	The changes in the balance between the level of analgesia and average level of noxious stimulation might increase both stress level and probability of movements.	There were significantly ($p<0.05$) more high SPI values with the patients that moved than the ones that did not. However, SPI could not infallibly predict the patient movement.
A2	Tampere University Hospital, Tampere, Finland (GEHC)	33	Age <18 or >65 years, BMI >30, neurological disorders, history of head injury, major cardiac disease, uncontrolled hypertension, thyroid disease, history of alcohol or drug abuse, medication affecting central or peripheral nervous system, smoking, hypovolemia or hypothermia during operation, and drug change too close to the incision	Laparotomy surgeries	Propofol - Remifentanil	Not stated.	SPI during surgery was significantly higher than before surgery, while the Propofol level did not significantly affect SPI. Propofol alters significantly SE, but not SPI. SPI and entropy provide complementary information on the level of analgesia and hypnosis and may thus help balancing the hypnotic and antinociceptive medications.

Study	Study site (Sponsor)	No. of patients	Exclusion criteria	Type of surgery	Pharmaceutical Regimen	Hypothesis	Results
A3	Tampere University Hospital, Tampere, Finland (GEHC)	30	Age <18 or >65 yr, BMI >30, known neurological disorders, history of head injury, disease of thyreoidea, any medication seriously affecting HR, central nervous system or peripheral nervous system, major cardiac problems, uncontrolled hypertension, and history of alcohol or drug abuse, contraindication to epidural analgesia	Abdominal surgeries	Sevoflurane - Sufentanil - Nitrous Oxide	Epidurally administered Ropivacaine, given before surgery, is associated with lower intraoperative SPI values than eipdurally given saline in adult patients undergoing open abdominal surgery in Sevoflurane-Sufentanil-Nitrous Oxide anesthesia.	Epidural block was associated with low SPI values after skin incision (p=0.0322). However, the significant difference disappeared after about 20 minutes, and, thereafter, the index values did not differ between the groups. Low SPI values indicated adequate level of analgesia in the both groups.
A4	Tampere University Hospital, Tampere, Finland (GEHC)	16	Age <18 or >65 yr, BMI >30, known neurological disorders, history of head injury, any medication seriously affecting central nervous system, major cardiac disorders, uncontrolled hypertension, and history of substance abuse	Laparatomy surgeries	Propofol - Remifentanil	Not stated.	During 162+-55 min of surgery, the core temperature of the patients decreased from 36.01+-0.36 to 35.46+-0.51 C minimum. For the patients, the average SPI values were higher during than before surgery and higher with low than high Remifentanil levels during surgery (both p<0.05). The difference in SPI between high and low Remifentanil levels remained during surgery. The correlation to core temperature was 0.022. The reactivity of SPI to surgical stimuli and opioid analgesia remained during moderate hypothermia.
A5	Tampere University Hospital, Tampere, Finland (GEHC)	72	Age <18 or > 80. ASA IV and V patients.	Abdominal surgeries	Sevoflurane - Alfentanil / Propofol - Alfentanil	A change in Sevoflurane and Alfentanil concentration would cause the SPI value to change, both drugs possessing analgesic qualities.	Increases of Alfentanil and Sevoflurane concentrations were associated with sustained decreases in SPI. With Alfentanil the decrease was abrupt, while Sevoflurane caused a smooth decrease in SPI (p<0.05). The result suggest that SPI behaves as an indicator of nociceptive - antinociceptive balance.
A6	Policlinoco University Hospital Catania, Catania, Italy (The site)	30	ASA III-V patients.	Laparoscopic cholecistectomy	Sevoflurane - Fentanyl	Not stated.	For total amount of pre-determined surgical time points (150) 75.3% of decisions (113) were in coincidence. The highest concordance degree was found for the gallbladder extraction. SPI showed a good correlation with clinical judgement of an expert anesthesiologist for analgesic titration.
A7	Centre Hospitalier Universitaire de Nancy, Vandouvre-les-Nancy, France (GEHC)	10		resynchronization therapy	Propofol - Remifentanil	SPI could be influenced by factors other than nociception-antinociception balance, namely vasoactive drugs such as ephedrine.	Before incision median SPI values were 35 and 32 (NS) before and 200 sec after ephedrine injections (17), respectively. After incision SPI values were 48 and 42 (NS) before and 200 sec after ephedrine injections (10), respectively. The study suggest that under the conditions of the study SPI is not influenced by ephedrine and may be used as an estimator of the nociception - anti-nociception balance.
A8	University Hospital Schleswig-Holstein, Kiel, Germany (The site)	20	ASA III-V patients.		Sevoflurane - Remifentanil	Not stated.	SPI before injection of Rocuronium was 18.5+-4.8 (P) and 17.4+-7.3 (L) and increased in both groups significantly to 28.5+-5.2 (P, p<0.01) and 26.1 +-7.0 (L, p<0.01). SPI is significantly altered after injection of Rocuronium indicating a nociceptive response.

Study	Study site (Sponsor)	No. of patients	Exclusion criteria	Type of surgery	Pharmaceutical Regimen	Hypothesis	Results
A9	University Hospital Schleswig-Holstein, Kiel, Germany (The site)	82	ASA III-V patients.	Trauma or gynaecological laparoscopic surgery	Sevoflurane - Sufentanil	Not stated.	Sufentanil consumption was 5,84 ng/kg/min in the SPI group and 6.62 ng/kg/min in the control group (p=0.18). The number of hypotensive events (p=0.25), hypertensive events (p=0.13) and unwanted intraoperative events such as movement, coughing or unwanted spontaneous breathing(p=0.89) were lower in the SPI group than in the control group, but not significantly different. Recovery times (suture to extubation) were slightly (9%) shorter in the SPI group (p=0.55).
A10	Azienda Ospedaliera S. Croce e Carle, Cuneo, Italy	30	None mentioned.	Esophagogastro-duodenoscopy	Propofol - Remifentanil	Not stated.	Group P had a higher mean SPI [74.9 (50-96)] than Group RP [72.8 (35-89)] (p<0.05). SPI seems to be useful during EGD sedation procedure.
D1	University Hospital Schleswig-Holstein, Kiel, Germany	21	Age <18 or >65 years, pregnancy, emergency case, neurologic disease, Chronic CNS medication, alcohol or drug abuse, expected difficult intubation	Before surgical procedure	Sevoflurane - Remifentanil	1. SPI is not influenced by Sevoflurane anesthesia. 2.1. SPI can detect noxious stimuli during Sevoflurane anesthesia. The change of SPI is dependent on the Remifentanil concentration. 2.2. SPI can detect the noxious stimulation responses better than HR, BIS, SE, RE, and the RE-SE diffrence. 3. SPI can predict movements caused by noxious electric stimulation.	Only SPI and BIS, but not HR, SE, RE, RE-SE, changed significantly after the noxious stimulus. The change of SPI depended on the Remifentanil concentration being 20 (15-30), 10 (1-19), and 3 (1-10) for Remifentanil EC 0, 2, and 4 ng/ml, respectively. The change of BIS had no clinical relevance. Fot 10 of 63 tetanic stimuli SPI was the only parameter that detected the noxious stimulus. However, the SPI value could not predict the patient movement (Pk-value 0.59+-0.09). In the ROC analysis for the delta-SPI and delta-HR, DSPI and DHR had AUC 0.84 and 0.73, respectively. The sensitivity and specificity for detection of movement was 95% and 69% for DSPI and 50% and 84% for DHR, respectively.
GE1	Tampere University Hospital, Tampere, Finland; South Carelia Central Hospital, Lappeenranta, Finland (GEHC)	74		Abdominal surgeries	i. Sevoflurane - Fentanyl; ii. Isoflurane - Fentanyl; iii. Sevoflurane - Alfentanil; iv. Propofol - Alfentanil	Not stated.	For all the four anesthesia types i-iv, there were (a) statistically significant SPI decreases after opioid administration (p<0.05), and (b) statistically significant SPI increases when the level of noxious stimulation increased during the surgery (p<0.01). The Pk statistics for the SPI levels predicting the drug levels were 0.62-0.76. The Pk statistics for the SPI levels predicting the expected noxious stimulation levels were 0.62-0.89.

Study	Study site (Sponsor)	No. of patients	Exclusion criteria	Type of surgery	Pharmaceutical Regimen	Hypothesis	Results
GE2	**Belgium:** CHR Citadelle Liège: Prof Hans; Erasme Brussels: Prof Barvais **France:** Bordeaux University Hospital: Dr. Karine Nouette-Gaulain Lille University Hospital: Prof Le Beuffe; Institut Gustave Roussy (IGR): Dr Billard; Nancy: Prof Dan Langrois **Great Britain:** Addenbrooks: (Dr Tony Absolam); Edinburgh: (Dr Keith Kelly and Dr Duncan Douglas); St Mary's: (Dr Sanjay Gautama Sanjay) **Italy:** A.O. San Luigi Gonzaga, Orbassano, Torino: Prof. Tempia; A.O. Luigi Sacco di Milano: Prof. Raimondi, Dr. Castelli; A.O.U. Careggi, Firenze: Prof. De Gaudio; A.O. Vittorio Emanuele II – Catania:Prof. Mangiameli and Dr. Sorbello **Spain:** Hospital "La Milagrosa", Madrid: Dr. Ricardo Martín-Larrauri; Hospital Germans Trias y Pujol, Badalona Barcelona: Dr Jaume Canet; Cartagena, Murcia: Prof Gómez **Holland:** Mesos Medical Centre Utrecht: Dr. Jaap de Vries; Spaarne Hospital Hoofddorp: Dr.Martijn Mertens; Canisius Wilhelmina Hospital Nijmegen: Dr.Wil Gerritsen (GEHC)	153		153 different surgeries	Various anesthetic regimens with medications given pre- or intraoperatively: Beta blockers, Sedative-hypnotics, Dissociative anesthetics, Reanimation anesthesthetics, Opiods, Combined anesthetic analgesics, Muscle relaxants, Morphine derivitives , Alpha-2 adrenergic agonists, Local anesthetics, Analgesics, Opioid analgesics.	NA	The end-users were asked to fill out feedback forms (147 returned) related to the beta testing. Two key questions about the parameter elicited that: 90% felt SSI (SPI) was clinically acceptable as a parameter. 96% felt SSI (SPI) worked 'well to excellent' during/after nociceptive (="painful") stimuli. In conclusion, the SSI (SPI) algorithm functions as planned and in a clinically acceptable, relevant way. The SSI (SPI) was seen as easy to use. The SSI (SPI) beta tests were also successful in terms of amounts of feedback received and active involvement of the sites.

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