

Evaluation of the surgical stress index during spinal and general anaesthesia

C. Ilies*, M. Gruenewald, J. Ludwigs, C. Thee, J. Höcker, R. Hanss, M. Steinfath and B. Bein

Department of Anaesthesiology and Intensive Care Medicine, University-Hospital Schleswig-Holstein, Campus Kiel, Schwanenweg 21, D-24105 Kiel, Germany

* Corresponding author. E-mail: ilies@anaesthesie.uni-kiel.de

Key points

- The surgical stress index (SSI) is not only affected by nociceptive input but also by depth of anaesthesia and sedation.
- Patients under spinal anaesthesia show a higher SSI than under general anaesthesia (GA).
- Changes of the SSI under sedation are not accompanied by changes of heart rate or arterial pressure.
- Assessment of the SSI in patients who are not under GA should take into account the level of sedation.

Background. Although in modern anaesthesia, monitoring depth of anaesthesia and quality of neuromuscular block are routine, monitoring of analgesia still remains challenging. Recently, the surgical stress index (SSI), derived from finger photoplethysmographic signal, was introduced as a surrogate variable reflecting the nociception–antinociception balance. This study aimed at evaluating the SSI in patients undergoing regional anaesthesia either alone or combined with sedation compared with patients undergoing general anaesthesia (GA).

Methods. Seventy-one patients undergoing general ($n=24$) or spinal anaesthesia with ($n=24$) or without sedation ($n=23$) were included. SSI was measured the day before surgery and at defined time points during anaesthesia and surgery and also in the recovery room. SSI was compared with haemodynamic variables like heart rate and systolic arterial pressure.

Results. The SSI was higher in patients undergoing spinal anaesthesia [mean 65, CI (59.3–70.5)] compared with GA [48 (39.9–56.4), $P<0.01$], and baseline [41 (37.3–44.2), $P<0.001$]. During spinal anaesthesia with sedation [44 (36.2–50.9)], it was comparable with the baseline level ($P>0.05$). In comparison with baseline, SSI in the recovery room was higher in patients after GA [59 (48.4–67.9), $P<0.025$] but not after spinal anaesthesia [53 (47.6–60.1), $P>0.05$] or after spinal anaesthesia with sedation [54 (45.8–65.1), $P>0.05$]. Changes of the SSI were not reflected by changes of haemodynamic variables.

Conclusions. In fully awake patients under spinal anaesthesia, the SSI does not reflect the nociception–antinociception balance. This may be due to the influence of mental stress on the sympathetic nervous system. Even light sedation attenuates these influences.

Keywords: analgesia; equipment-monitors; stress; sympathetic nervous system

Accepted for publication: 5 June 2010

Although the definition of general anaesthesia (GA) is still a matter of debate,¹ modern anaesthesia mainly consists of three components: unconsciousness, analgesia, and muscle relaxation. Although neuromuscular monitoring^{2–4} and processed EEG signals for quantifying depth of anaesthesia are well established,^{5–7} measurement of analgesia in unconscious or anaesthetized patients is still challenging. During GA, painful stimulation leads to autonomic, hormonal, and metabolic changes. These changes reflect the nociceptive response. Opioid analgesics affect the nociceptive pathways and provide antinociception. This balance is also affected by the hypnotic agent used, as hypnotics affect the cortical processing of afferent nociceptive stimuli.⁸ Opioid analgesics modify nociceptive stimuli at cortical and subcortical nociceptive pathways.^{9–10} Negative sequelae and impacts on outcome have been shown for inadequate depth of anaesthesia¹¹ and for hormonal, neuroendocrine, and metabolic changes caused

by nociceptive stimuli^{12–13} and also for immunomodulatory changes caused by opioids.¹⁴

The surgical stress index (SSI) was developed as a tool to quantify the physiological reactions caused by nociception during GA and consists of a combined measurement of the central sympathetic influence depicted by the normalized heart beat interval (HBI) and the peripheral sympathetic influence represented by the plethysmographic area under the curve (PPGA). A more detailed description of the underlying algorithm has been published previously.¹⁵ The SSI has not been studied in awake or sedated patients during regional anaesthesia alone. We hypothesized that the SSI is lower in patients during spinal anaesthesia compared with GA due to the complete block of nociceptive stimuli from the surgical site. Furthermore, we suggested that sedation in awake patients affects the SSI due to reduced anxiety during surgical procedures and therefore altered autonomic regulation.

The aim of the present prospective, controlled, and randomized trial was to evaluate the SSI during (i) GA, (ii) spinal anaesthesia, and (iii) spinal anaesthesia supplemented by conscious sedation during routine surgical procedures.

Methods

The study was registered at clinicaltrials.gov (Identifier: NCT00789438). After approval by the ethics committee of the medical faculty of the Christian-Albrecht-University, Kiel, and written informed consent, 71 patients undergoing elective urological and orthopaedic surgery were included into the study. Surgical procedures were eligible if they could be performed under both general and spinal anaesthesia. Exclusion criteria were age <18 or >80 yr, BMI >35 kg m⁻², emergency cases, cardiac arrhythmias or an implanted pacemaker, and a history of chronic pain. Patients were randomized to one of the three groups. Group 1 (GA, *n*=24) underwent GA, Group 2 (SPA, *n*=24) spinal anaesthesia without sedation, and Group 3 (SPA-S, *n*=23) spinal anaesthesia with sedation. As the ethics committee expressed concerns about randomization to type of anaesthetic procedure itself (spinal anaesthesia vs GA), we asked patients to give consent to both methods. Patients prepared to undergo either type of anaesthesia were randomized to one of the three groups.

The evening before surgery, the patients received dikaliumclorazepate 20 mg orally. Thirty minutes before admission to the operating theatre, midazolam 7.5 mg was given orally. GA was induced with propofol 1.5 mg kg⁻¹ and remifentanyl 0.3 µg kg⁻¹ min⁻¹. Tracheal intubation was facilitated with rocuronium 0.6 mg kg⁻¹. Anaesthesia was maintained with propofol 3–6 mg kg⁻¹ h⁻¹ and remifentanyl 0.1–0.4 µg kg⁻¹ min⁻¹. Ten minutes before the end of surgery, metamizole 1 g was given i.v. Both a laryngeal mask and a tracheal tube were allowed for controlled ventilation of the lungs. In Groups SPA and SPA-S, spinal anaesthesia was performed as follows: after volume preload with 500 ml of hydroxyethyl starch (130/0.4) 6% (Voluven®, Fresenius Kabi, Bad Homburg, Germany), the patients were brought into a sitting position. Local skin infiltration was performed using mepivacaine 20–40 mg. The puncture site was at lumbar level 3/4 or 4/5 using a 24 G, 7 cm Sprotte needle. Plain bupivacaine 10–15 mg was injected after identification of the spinal space. Group SPA did not receive any sedation after premedication, whereas in Group SPA-S, a continuous infusion of propofol 1 mg kg⁻¹ h⁻¹ was started immediately after the spinal puncture and stopped 5 min before the end of the surgical suture aiming at values on the Richmond agitation and sedation scale (RASS) between –1 and –3, indicating sedation grade from light sedation indicated by awakening to voice (–1) to moderate sedation indicated by movement or short eye opening to voice (–3). RASS was tested 5 min before incision and then every 10 min until the end of surgery (suture). We chose this scale because of our clinical experience with it and its reliability in different phases of sedation.^{16 17} Data, including heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressure, oxygen

saturation, and SSI, were recorded using a standard anaesthesia monitor (S/5™, GE Healthcare, Helsinki, Finland).

The SSI was computed as follows:

$$\text{SSI} = 100 - (\text{HBI}_{\text{normalized}} \times 0.3 + \text{PPGA}_{\text{normalized}} \times 0.7)$$

The SSI ranges from 0 to 100, and a high value is associated with a high stress level. The range for an optimal SSI has not yet been published, but an SSI of 50 is claimed to reflect a mean stress level. SSI, HR, and arterial pressure were compared between the groups during six defined time points: (i) baseline (BL) data were obtained the day before surgery. The patient was monitored in the supine position at rest and SSI values averaged over 10 min. (ii) Induction (IND) data were collected before induction of GA and in Groups SPA and SPA-S in the supine position before spinal puncture. (iii) Time point 3 was at intubation or insertion of the laryngeal mask (INT) or spinal puncture (SPP). (iv) Time 4 was at skin incision (INC). (v) Time 5 was during surgical suturing (SUT). (iv) Time 6 was 10 min after admission to the recovery room (PACU). At each time point (except baseline), SSI and HR were recorded every 10 s and averaged over 3 min.

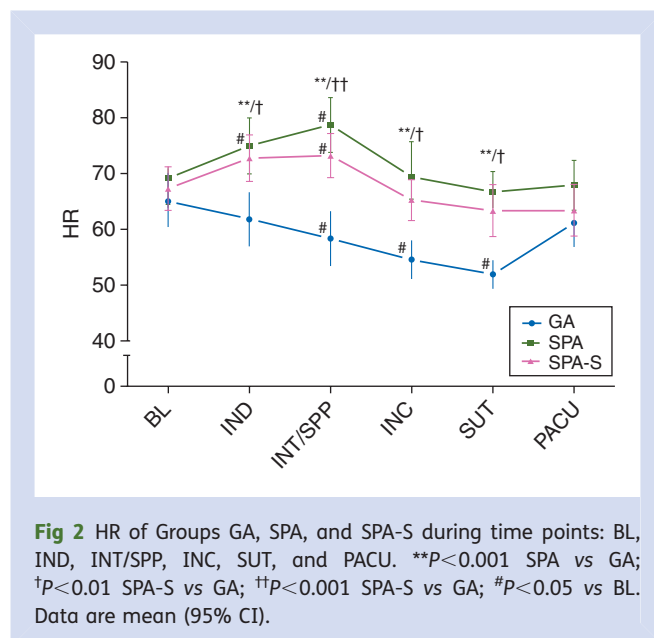
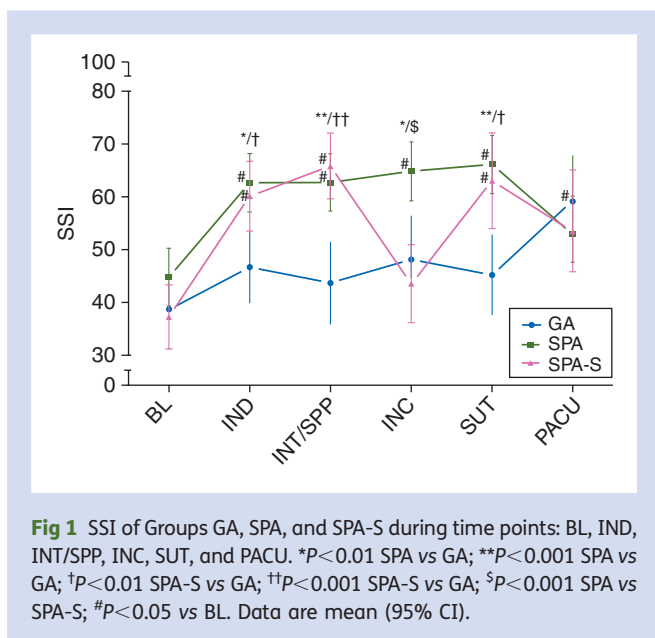
A sample size calculation was performed using the OpenEpi, Version 2, SSMean Software (<http://www.openepi.com/SampleSize/SSMean.htm>). For a confidence interval (two-sided) of 95% (95% CI), a power of 80%, expected mean difference of 15 with a standard deviation of 17, a sample size of 21 patients per group was calculated. Graph Pad Prism software (Version 5.0, Graph Pad Software Inc., San Diego, CA, USA) was used for statistical analysis. For all data sets, a Gaussian distribution was tested using the Kolmogorov–Smirnov test. Changes of arterial pressure and HR were analysed with one-way analysis of variance for repeated measures followed by the Bonferroni correction for multiple comparisons, and SSI values were analysed with Friedman's test followed by Dunn's post-test correction. The level of significance was set at *P*<0.05. Results are expressed as mean (95% CI).

Results

Two patients were excluded from the study because of the development of cardiac arrhythmias during surgery (Groups GA and SPA-S, one patient each). Therefore, a total of 414 valid SSI readings (six for each patient) were obtained from 69 patients. Patient characteristics are shown in Table 1. Figure 1 shows the absolute SSI values at the predefined time points and significant differences between the groups and within the group compared with baseline. There was no difference between the groups at baseline. At induction, the SSI did not differ from baseline in Group GA. SSI values in Groups SPA and SPA-S were significantly higher than at baseline (*P*<0.05) and compared with GA (*P*<0.01). In these groups, SSI values were further increased compared with baseline at spinal puncture (*P*<0.05) (corresponding to the event intubation in Group GA) and compared with GA (*P*<0.001), whereas in Group GA, the SSI remained unchanged. Immediately after spinal puncture, propofol

Table 1 Patient characteristics. Data are given as mean (CI), except for age [mean (range)] or absolute numbers

	GA (n=23)	SPA (n=24)	SPA-S (n=22)
Age (yr) (range)	59 (25–80)	61 (18–80)	62 (18–78)
♂/♀ (n)	16/7	19/5	17/5
ASA I/II/III (n)	4/12/7	4/16/4	3/15/4
BMI (kg m ⁻²)	27 (25.5–27.7)	27 (25.5–28.5)	27 (24.6–29.8)
Duration (min)	68 (59–77.7)	74 (61.6–85.4)	89 (74.3–101.4)
Orthopaedics/urology (n)	9/14	8/16	8/14

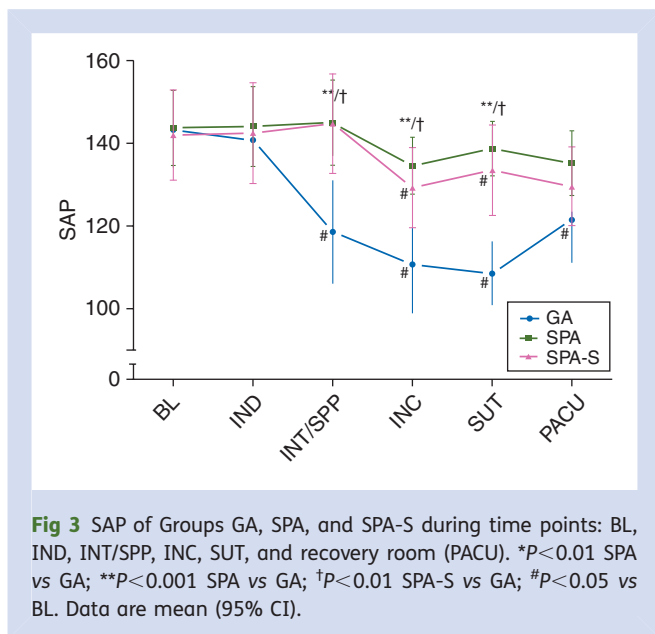


was started with 1 mg kg⁻¹ h⁻¹ in Group SPA-S without giving a bolus. In these patients, RASS values between -1 and -3 were achieved throughout propofol administration. All patients stayed in this predefined range without changing propofol dosage. At incision and after propofol administration, the SSI in Group SPA-S decreased to baseline levels, whereas the SSI in SPA stayed at the level observed at spinal puncture (SPA vs SPA-S at incision, *P*<0.001). There was no significant difference (*P*>0.05) between Groups GA and SPA-S at incision. Five minutes before suture, the propofol infusion was stopped. The SSI in Group GA did not change at time point suture compared with baseline and was significantly lower than in SPA (*P*<0.001) and in SPA-S (*P*<0.01). The SSI in Group SPA-S increased (*P*<0.05) compared with incision and reached a level equal to Group SPA again. Data in PACU were collected 10 min after admission from the operating theatre. Group GA had a significant higher SSI than at baseline (*P*<0.05), whereas in Groups SPA and SPA-S, the SSI was comparable with baseline levels and not significantly different (*P*>0.05) from GA.

Figure 2 shows the HR of all groups during the predefined time points and significant differences between the groups and within the group compared with baseline. In Group GA,

patients showed a decrease during the surgical procedure, which reached significance level (*P*<0.05) at intubation, incision, and suture. There was no difference between baseline and PACU. In Groups SPA and SPA-S, HR showed a comparable pattern. HR increased from baseline to spinal puncture and decreased during incision, suture, and in PACU. Group GA showed a significant decrease in HR at induction, intubation, incision, and suture (*P*<0.001) compared with patients in Group SPA. The difference between Groups GA and SPA-S was significantly lower at induction (*P*<0.01), intubation/spinal puncture (*P*<0.001), incision (*P*<0.01), and suture (*P*<0.01). HR values at baseline and PACU were similar in all groups.

Figure 3 shows the SAP in all groups at the predefined time points and significant differences between the groups and within the group compared with baseline. In Group GA, the SAP decreased after induction and reached significance level (*P*<0.05) at intubation, incision, suture, and PACU compared with baseline. There was no difference in SAP between Groups SPA and SPA-S. Compared with Group GA, the SAP in Group SPA was significantly higher at intubation/spinal puncture (*P*<0.001), incision (*P*<0.01), and suture (*P*<0.001). The differences between Groups GA and SPA-S were significantly



different at intubation/spinal puncture ($P < 0.01$), incision ($P < 0.01$), and suture ($P < 0.01$).

Discussion

Main findings of our prospective, controlled, and randomized trial are as follows: (i) the SSI in patients under spinal anaesthesia is affected by conscious sedation, (ii) compared with patients under GA, the SSI under spinal anaesthesia is lower in PACU compared with baseline, (iii) changes of the SSI are not reflected by HR or SAP, (iv) SSI is higher than baseline during spinal anaesthesia despite complete blockade of nociceptive input.

Data on SSI performance so far are primarily based on measurements during GA with defined application of antinociceptive drugs or defined depth of anaesthesia levels. Therefore, in these studies, the influence of consciousness on the SSI was negligible. During the first study by Huiku and colleagues,¹⁵ the SSI showed a correlation to nociceptive stimuli and remifentanyl effect-site concentrations under GA. Struys and colleagues¹⁸ could show that the SSI was only minimally influenced by alterations of the propofol effect-site concentration, whereas SSI values were strongly dependent on the remifentanyl effect-site concentration. The SSI has also been shown to be superior for the detection of intraoperative painful stimuli compared with standard surrogate variables such as HR, state (SE) and response entropy (RE), or the PPGA.¹⁸ Ahonen and colleagues¹⁹ described the properties of the SSI dependent on an esmolol or remifentanyl infusion. Skin incision under esmolol infusion led to an increase in the SSI by 12%, whereas during remifentanyl infusion, no increase in the SSI was observed. According to their results, an increase in the SSI is only attenuated by analgesics but not by β -blocking agents causing a suppression of the sympathetic response.

The first trial evaluating SSI in children during strabismus surgery under GA found the SSI and PPGA capable in

detecting nociceptive stimuli caused by intubation or surgery in this patient group.²⁰ Our group previously investigated the SSI under sevoflurane and remifentanyl anaesthesia with predefined effect-site concentrations of remifentanyl. Only SSI and BIS in contrast to HR, SE, RE, and the RE-SE difference were influenced by a noxious stimulus.²¹ None of the tested variables could predict a nociceptive event, but SSI was capable of detecting noxious stimuli. A delta SSI of 10 was identified as the threshold value to predict movement and hence may indicate an inadequate analgesic application, especially when neuromuscular blocking agents are used.

At present, only one study has evaluated the SSI during regional anaesthesia. Patients with an interscalene plexus block combined with GA maintained by desflurane and alfentanil undergoing shoulder surgery had lower SSI values and lower additional alfentanil consumption compared with patients under GA with desflurane and alfentanil alone. The SSI also showed better performance in detecting nociceptive stimuli compared with HR, arterial pressure, or RE.²² The first study which investigated the SSI in awake patients was performed by Ledowski and colleagues.²³ The SSI was able to discriminate between moderate and severe pain, indicated by the numerical rating scale higher or lower than 5, in patients on the PACU. The sensitivity and specificity of the SSI in the detection of a pain score NRS > 3 , however, was weak. It was concluded that the performance of the SSI in awake patients might be improved by adapting its algorithm and normalize it to a data set based on awake subjects.

If the SSI only reflects the nociception-antinociception balance in awake patients, there should be no difference under spinal anaesthesia compared with baseline measurement, except for the time point the spinal puncture is performed. In contrast, the SSI of patients under spinal anaesthesia in our study was higher compared with baseline and with the group under GA during the whole time in the operating theatre. To reveal the effect of mental stress on the SSI, we studied the effect of a light sedation in Group SPA-S. With propofol $1 \text{ mg kg}^{-1} \text{ h}^{-1}$, patients were awake, slightly sedated (all patients between RASS -1 and -3), and spontaneous breathing but apparently protected from the environmental input from the operating theatre. During this period, the SSI reached baseline levels. Another issue emphasizing the effects of mental stress is the low SSI levels at the PACU. In this comfortable environment (at least compared with the operating theatre), the SSI reached baseline levels in patients after spinal anaesthesia, indicating low pain levels compared with patients under GA without sensory block. Patients after GA showed significantly higher SSI levels at PACU compared with baseline. As post-operative pain after GA is also modulated by an interindividually different contribution of mental stress, these findings might explain the weak sensitivity and specificity of the SSI in discriminating between pain levels indicated by the NRS described by Ledowski and colleagues.²³ In contrast to our study, all patients received GA and mainly underwent orthopaedic surgery, what probably resulted in higher pain and

also stress levels. The index of the SSI is normalized using a collective of patients under GA at a defined depth of anaesthesia. The environmental stress in awake patients is not recognized and may bias the SSI. Nevertheless, despite the influence of stress in awake patients, postoperative nociceptive input is also reflected as indicated by the lower SSI levels of patients under spinal anaesthesia at the PACU. A correlation of the SSI with HR and arterial pressure or propofol concentration was not present. The period between incision and suture lasted between 48 and 118 min (Table 1), a period during which the SSI showed no major changes (data not shown). The SSI is processed from an algorithm comprising the normalized HBI and the photoplethysmographic pulse wave amplitude. These variables reflect the sympathetic influence on the heart and on the peripheral vessels. In awake patients, mental stress is likely to affect the sympathetic tone and therefore might influence SSI readings. Some limitations of our study should be noted. Different types of surgery were enrolled. The urological patients primarily underwent transurethral prostatectomy, where no high nociceptive input is expected. A higher number of patients undergoing orthopaedic surgery with higher nociceptive input might have resulted in clearer differences between spinal anaesthesia and GA.

We conclude that changes of the sympathetic activity, independent from their origin, somatic or not, impact the SSI. The SSI reacts on a changing autonomic tone, for example, changing levels of sedation as shown in our study. When using the SSI for guidance of analgesia, clinicians should be aware of these confounders and rather rely on relative changes of the SSI than on absolute values.

Conflict of interest

None declared.

Funding

The current study was supported by departmental funding only. No extramural financial support was provided for this study. All physicians involved in this study were staff members of the Department of Anaesthesiology and Intensive Care Medicine, University-Hospital Schleswig-Holstein, Campus Kiel, Germany. There was no payment depending on the results of the study nor was there any additional financial support for one of the team members. Monitoring, equipment, and medication used within the study were those routinely used for anaesthesia in our hospital. The SSI software was supplied by GE Healthcare, Helsinki, Finland. Neither was loan of the software dependent on the results of the study nor were objectives, conduction, or publication under supervision of the company.

References

- Eger EI II, Sonner JM. Anaesthesia defined (gentlemen, this is no humbug). *Best Pract Res Clin Anaesthesiol* 2006; **20**: 23–9
- Kopman AF. Neuromuscular monitoring: old issues, new controversies. *J Crit Care* 2009; **24**: 11–20
- Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarization: a meta-analysis. *Br J Anaesth* 2007; **98**: 302–16
- Fuchs-Buder T, Schreiber JU, Meistelman C. Monitoring neuromuscular block: an update. *Anaesthesia* 2009; **64**: 82–9
- Myles PS, Leslie K, McNeil J, Forbes A, Chan MT. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. *Lancet* 2004; **363**: 1757–63
- Punjasawadwong Y, Boonjeungmonkol N, Phongchiewboon A. Bispectral index for improving anaesthetic delivery and postoperative recovery. *Cochrane Database Syst Rev* 2007: CD003843
- Bruhn J, Myles PS, Sneyd R, Struys MM. Depth of anaesthesia monitoring: what's available, what's validated, and what's next? *Br J Anaesth* 2006; **97**: 85–94
- Hofbauer RK, Fiset P, Plourde G, Backman SB, Bushnell MC. Dose-dependent effects of propofol on the central processing of thermal pain. *Anesthesiology* 2004; **100**: 386–94
- Wagner KJ, Sprenger T, Kochs EF, Tolle TR, Valet M, Willoch F. Imaging human cerebral pain modulation by dose-dependent opioid analgesia: a positron emission tomography activation study using remifentanyl. *Anesthesiology* 2007; **106**: 548–56
- Becerra L, Harter K, Gonzalez RG, Borsook D. Functional magnetic resonance imaging measures of the effects of morphine on central nervous system circuitry in opioid-naïve healthy volunteers. *Anesth Analg* 2006; **103**: 208–16
- Monk TG. Processed EEG and patient outcome. *Best Pract Res Clin Anaesthesiol* 2006; **20**: 221–8
- Desborough JP. The stress response to trauma and surgery. *Br J Anaesth* 2000; **85**: 109–17
- Weissman C. The metabolic response to stress: an overview and update. *Anesthesiology* 1990; **73**: 308–27
- Sacerdote P. Opioid-induced immunosuppression. *Curr Opin Support Palliat Care* 2008; **2**: 14–8
- Huiku M, Uutela K, van Gils M, et al. Assessment of surgical stress during general anaesthesia. *Br J Anaesth* 2007; **98**: 447–55
- Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *J Am Med Assoc* 2003; **289**: 2983–91
- Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; **166**: 1338–44
- Struys MM, Vanpeteghem C, Huiku M, Uutela K, Blyeaert NB, Mortier EP. Changes in a surgical stress index in response to standardized pain stimuli during propofol–remifentanyl infusion. *Br J Anaesth* 2007; **99**: 359–67
- 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
- Kallio H, Lindberg LI, Majander AS, Uutela KH, Niskanen ML, Paloheimo MP. Measurement of surgical stress in anaesthetized children. *Br J Anaesth* 2008; **101**: 383–9
- Gruenewald M, Meybohm P, Ilies C, et al. Influence of different remifentanyl concentrations on the performance of the surgical stress index to detect a standardized painful stimulus during sevoflurane anaesthesia. *Br J Anaesth* 2009; **103**: 586–93
- Wennervirta J, Hynynen M, Koivusalo AM, Uutela K, Huiku M, Vakkuri A. Surgical stress index as a measure of nociception/antinociception balance during general anaesthesia. *Acta Anaesthesiol Scand* 2008; **52**: 1038–45
- Ledowski T, Ang B, Schmarbeck T, Rhodes J. Monitoring of sympathetic tone to assess postoperative pain: skin conductance vs surgical stress index. *Anaesthesia* 2009; **64**: 727–31