

Surgical stress index reflects surgical stress in gynaecological laparoscopic day-case surgery[†]

J. Ahonen^{1*}, R. Jokela¹, K. Uutela² and M. Huiku²

¹Department of Anaesthesia and Intensive Care Medicine, Helsinki University Hospital, Helsinki, Finland.

²GE Healthcare Finland, Helsinki, Finland

*Corresponding author: Department of Anaesthesia and Intensive Care Medicine, Helsinki University Hospital, PO Box 140, FIN-00029 HUS, Finland. E-mail: jouni.ahonen@fimnet.fi

Background. Monitoring of analgesia remains a challenge during general anaesthesia. The surgical stress index (SSI) is derived from the photoplethysmographic waveform amplitude and the heart beat-to-beat interval. We evaluated the ability of SSI to measure surgical stress in patients undergoing gynaecological laparoscopy. Our hypothesis was that while keeping State EntropyTM (SE) at a predetermined level, SSI would be higher in patients receiving a β -blocking agent (esmolol) than in those receiving an opioid (remifentanyl) during laparoscopy.

Methods. Thirty women undergoing gynaecological laparoscopy were assigned randomly to receive esmolol ($n=15$) or remifentanyl ($n=15$). Anaesthesia was induced with propofol and fentanyl and maintained with desflurane and nitrous oxide 50% in oxygen to keep SE at 50(5). The infusion of esmolol or remifentanyl was started before laparoscopy and adjusted to keep the systolic blood pressure at -20 to $+10\%$ from the preoperative value.

Results. During the fentanyl phase, before surgery, both groups behaved similarly, with an increase in SSI after intubation. In the patients receiving esmolol, the SSI reacted to the initial incision ($P<0.05$), and remained high after trocar insertion ($P<0.05$). In patients receiving remifentanyl, it did not react to the initial incision, but increased after trocar insertion ($P<0.05$), and it remained lower both after incision ($P<0.05$) and after trocar insertion ($P<0.05$).

Conclusion. SSI was higher in patients receiving esmolol. The index seems to reflect the level of surgical stress and may help guide the use of opioids during general anaesthesia.

Br J Anaesth 2007; **98**: 456–61

Keywords: adrenergic β -antagonists, esmolol; analgesia, opioid, remifentanyl; monitoring, depth of anaesthesia; surgery, laparoscopy; surgical stress index, nociception

Accepted for publication: January 15, 2007

Pain is a conscious description and in an anaesthetized unconscious patient, the neural response to stressful stimuli, such as laryngoscopy, and surgery is called nociception.¹ In the central nervous system, the nociceptive information activates sympathetic pathways and increases the secretion of pituitary and adrenal hormones.² The increased circulating levels of catecholamines may result in tachycardia and hypertension. Other clinical signs of nociception may include lachrymation, sweating, and movement as a response to surgery.

Monitoring of the nociceptive response to stressful stimuli remains a challenge during general anaesthesia. Direct, clinically relevant, specific indicators of the nociception during general anaesthesia do not exist.³ The surgical stress index (SSI) is derived from the photoplethysmographic waveform amplitude (PPGA) and the heart beat-to-beat interval

(HBI).^{4,5} SSI quantifies the physiological, haemodynamic, and sympathetic stress reactions that occur during general anaesthesia and are caused by nociception. We evaluated the ability of SSI to measure nociception during general anaesthesia in patients undergoing gynaecological laparoscopic day-case surgery. β -Adrenergic antagonists and opioids are likely to stabilize arterial pressure and the heart rate during surgery. However, the action of a β -blocking agent is mainly because of haemodynamic effects whereas the action of an opioid is mainly because of analgesic effects. Our hypothesis

[†]*Declaration of interest.* Dr Ahonen and Dr Jokela have received a data-collecting program from GE Healthcare for their previous study (Valjus, *et al. Acta Anaesthesiol Scand* 2006; **50**: 32–9). Dr Uutela and Dr Huiku are employees of GE Healthcare, Finland. The salaries of the study nurses were paid by GE Healthcare, Finland.

was that while keeping state entropy (SE) and arterial pressure at a predetermined level, SSI would be higher in patients receiving a β -adrenergic antagonists (esmolol) than in those receiving an opioid (remifentanyl) during the surgical procedure.

Methods

We obtained institutional approval from the local Ethics Committee, permission from the National Agency for Medicines, and also informed written consent from 34 patients undergoing elective gynaecological laparoscopic day-case surgery for endometriosis or an ovarian cyst or both. Using an open-label study design, patients were randomized (sealed envelopes) to receive esmolol or remifentanyl. Exclusion criteria were: age <20 or >65 years; any lung, liver, or renal disease; history of peptic ulcer disease; high blood pressure or the use of a β -adrenergic antagonist; body-mass-index >30; or hypersensitivity to any of the drugs to be used. Four patients were excluded: in one, the procedure was converted to a hysterectomy; in the next, only an operative hysteroscopy was performed; in the third, the pulse oximetry probe had to be moved from the finger tip to the earlobe; and in the fourth, the procedure was cancelled after randomization.

One hour after premedication with diazepam 5 mg orally, anaesthesia was induced with propofol 2–2.5 mg kg⁻¹ and fentanyl 150 μ g. Anaesthesia was maintained with desflurane and nitrous oxide 50% in oxygen with a fresh gas flow of 1 litre min⁻¹ (S/5TM Anaesthesia Delivery Unit, ADUTM, GE Healthcare, Helsinki, Finland). Desflurane was titrated to keep State EntropyTM (SE) at 50(5) (EntropyTM Module, GE Healthcare, Helsinki, Finland).⁶ However, the vaporizer was not turned <2% to avoid any sudden awareness during the anaesthesia. Rocuronium 0.5–0.6 mg kg⁻¹ was given for muscle relaxation. Five minutes after the intubation, tetanic stimulation of the right ulnar nerve was performed for 30 s.

Before the start of surgery, an infusion of esmolol 20 μ g kg⁻¹ min⁻¹ or remifentanyl 0.2 μ g kg⁻¹ min⁻¹ was started and adjusted to keep the systolic pressure at –20 to 10% of the baseline value. When starting and while increasing the infusion rate of esmolol or remifentanyl, a bolus dose of esmolol 20–30 mg or remifentanyl 50 μ g was given. Towards the end of the surgery while removing the trocars, the patients received fentanyl 0.05 mg and the infusion of esmolol or remifentanyl stopped. At the time of the last suture, desflurane and nitrous oxide were turned off. Neostigmine and glycopyrrolate were used to antagonize the muscle paralysis.

In all patients, postoperative nausea and vomiting (PONV) were prevented by a triple-prophylaxis (i.v.) of dexamethasone 5 mg, droperidol 0.75 or 1.0 mg (patients weighing \leq 65 kg, or \geq 66 kg, respectively), and ondansetron 4 mg.⁷ After induction of anaesthesia, all patients received an infusion of paracetamol 1 g and before the end of surgery, they received ketoprofen 100 mg i.v.

We recorded the finger plethysmographic waveform at 100 Hz, heart rate, and the end-tidal concentration of desflurane at intervals of 10 s, and the non-invasive arterial pressure at intervals of 2.5 min on a laptop. The total doses of propofol, esmolol, remifentanyl, and rocuronium were also noted. The requirement for desflurane was determined during the entire anaesthetic and also during surgery by calculating the mean (SD) for the end-tidal desflurane concentration. The systolic arterial pressure and the heart rate were compared by determining the mean (SD) during the entire anaesthetic and surgery. To compare the SE and the Response EntropyTM (RE) recordings between the groups, the mean (SD) for SE and RE were calculated. The SE and the RE values were noted at intervals of 1 min; each value representing the median for three consecutive SE recordings and the corresponding RE values (the values were recorded on a laptop at intervals of 10 s). All the data were collected using the S/5TM Collect program (GE Healthcare, Helsinki, Finland). We also annotated any patient movement during surgery and their association with an eventual increase in the SSI, SE, or RE recording.

SSI was determined before and after tracheal intubation, tetanic stimulation, surgical incision, and trocar insertion. Measures for subsequent analysis of SSI were recorded on a laptop independently by a study nurse while the anaesthesiologist and the nurse anaesthetist took care of the patient. In addition, the average values during 2–12, 12–22, and 22–32 min after the trocar insertion were determined. SSI was calculated using only plethysmographic waveform information.⁸ PPGA and HBI were extracted off-line. In order to reduce the patient-to-patient variability in the HBI and PPGA time series, we subjected the raw variable data to normalization, which transformed HBI and PPGA to the same normalized value range (0–100) and value distribution in each patient. The normalization was based on a histogram transformation commonly used for image contrast enhancement.⁸ The normalized HBI and PPGA were combined to a SSI:^{4–5}

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

Results are expressed as mean (SD). SSI values between the groups were compared with a multivariate repeated measures test (type III sum of squares) and if the groups differed, SSI values at different phases of the operation were compared with two-tailed Wilcoxon sign-rank test or Mann–Whitney rank sum test. Patient characteristics and other variables were compared using the two samples, two-tailed Student's *t*-test assuming unequal variances.

Results

Patient characteristics in the 15 women receiving esmolol and the 15 receiving remifentanyl did not differ significantly (Table 1). The length of surgery and that of

Table 1 Preoperative characteristics, surgical data, and perioperative medication in patients undergoing gynaecological laparoscopic day-case surgery [mean (SD) or number (n)]. E'DES_{tot}, end-tidal concentration of desflurane during entire anaesthesia; E'DES_{surgery}, end-tidal concentration of desflurane during surgery; Propofol, induction dose of propofol; Esmolol_{time}, total dose of esmolol in proportion to time; Remifentanil_{time}, total dose of remifentanil in proportion to time. *Significantly different from the remifentanil group ($P<0.05$)

	Esmolol (n=15)	Remifentanil (n=16)
Age (yr)	32 (6)	34 (8)
Weight (kg)	65 (9)	67 (8)
Endometriosis/dermoid/else (n)	6/4/5	11/3/2
Duration of operation (min)	69 (28)	89 (37)
Duration of anaesthesia (min)	93 (31)	114 (40)
Time to awakening (min)	5 (2)	5 (2)
Time to extubation (min)	5 (2)	5 (2)
Desflurane (E'DES _{tot})	2.9 (0.4)*	2.5 (0.5)
Desflurane (E'DES _{surgery})	3.3 (0.5)*	2.6 (0.7)
Propofol (mg kg ⁻¹)	2.9 (0.3)	2.8 (0.4)
Esmolol _{time} (µg kg ⁻¹ min ⁻¹)	42.6 (35.5)	—
Remifentanil _{time} (µg kg ⁻¹ min ⁻¹)	—	0.09 (0.03)
Rocuronium (mg kg ⁻¹)	0.9 (0.3)	0.9 (0.2)

anaesthesia did not differ significantly, nor did the time to awakening or tracheal extubation (Table 1).

A multivariate repeated measures test showed that there was a significant difference between the data from the two groups ($P<0.001$) (Fig. 1). During the fentanyl phase before surgery, both groups behaved similarly with an increase in SSI after intubation (Fig. 1). The tetanic stimulation caused only a transient response with SSI, which returned to baseline quickly. In patients receiving esmolol, SSI reacted to the initial incision ($P<0.05$), and remained high after trocar insertion ($P<0.05$). However, in patients receiving remifentanil, SSI did not significantly react to the initial incision, but increased after trocar insertion ($P<0.05$). SSI remained significantly lower in patients receiving remifentanil both after incision ($P<0.05$) and

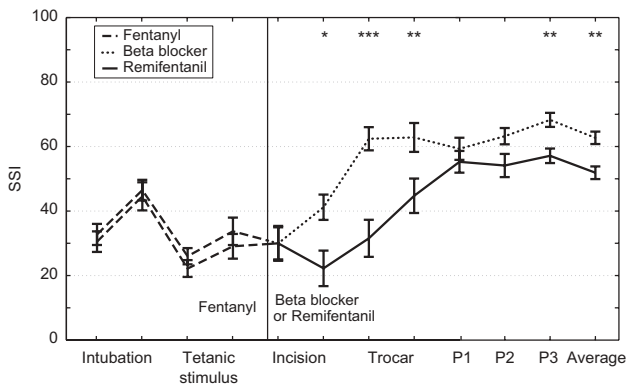


Fig 1 SSI recordings (mean SEM) during anaesthesia and surgery in patients receiving esmolol or remifentanil as a part of their general anaesthesia. P1, P2, and P3 represent average values during 2–12, 12–22, and 22–32 min after trocar insertion, respectively. * $P<0.05$, ** $P<0.01$, and *** $P<0.001$.

Table 2 Systolic arterial pressure, heart rate, State EntropyTM, and Response EntropyTM recordings during entire anaesthetic and during surgery in patients undergoing gynaecological laparoscopic day-case surgery [mean (SD)]

	Esmolol (n=15)	Remifentanil (n=15)
During entire anaesthetic		
Systolic arterial pressure (mm Hg)	107 (10)	109 (6)
Heart rate (beats min ⁻¹)	62 (7)	63 (7)
State Entropy TM	41 (6)	39 (5)
Response Entropy TM	42 (6)	39 (5)
During surgery		
Systolic arterial pressure (mm Hg)	108 (10)	111 (6)
Heart rate (beats min ⁻¹)	61 (6)	62 (8)
State Entropy TM	40 (7)	38 (6)
Response Entropy TM	41 (7)	38 (6)

after trocar insertion ($P<0.05$). Thereafter, the difference was statistically significant during 22–32 min, but not during 2–12 or 12–22 min (Fig. 1).

The systolic arterial pressure and heart rate (Table 2, Fig. 2) did not differ significantly between the groups. The requirement for desflurane (Table 1, Fig. 2) was significantly higher in patients receiving esmolol during the entire anaesthetic ($P=0.048$) and especially during surgery ($P=0.008$), whereas no significant differences were detected in SE (Fig. 3) or RE recordings (Table 2). Two patients receiving esmolol moved during the procedure interfering with surgery, whereas no one in the remifentanil group moved. The patient movements were associated with high SSI levels while the SE and RE remained at a low level (Fig. 4). The dose of rocuronium was similar in both groups (Table 1).

Discussion

In our patients undergoing gynaecological laparoscopic day-case surgery, SSI was significantly higher in patients receiving esmolol instead of remifentanil during surgery. Furthermore, the use of a β -adrenergic antagonist instead of an opioid resulted in a significantly higher requirement for the volatile anaesthetic to reach the targeted SE level.

Esmolol is a short-acting β -adrenergic antagonist having little sedative effect, but no analgesic activity or local anaesthetic property.^{9,10} However, it has been shown to reduce the intra-operative need for an inhalation agent and fentanyl, decrease the haemodynamic response, and to reduce morphine consumption for the first day after abdominal hysterectomy.¹¹ The specific mechanism by which esmolol may potentiate the analgesic effects of an opioid or an inhalation anaesthetic remains controversial. Both esmolol¹² and remifentanil¹³ reduce the heart rate, but the impact of esmolol on the intra-operative heart beat-to-beat variability has not been studied. In spite of the induction dose of fentanyl in our patients receiving esmolol, SSI remained significantly higher in these patients compared with those receiving remifentanil.

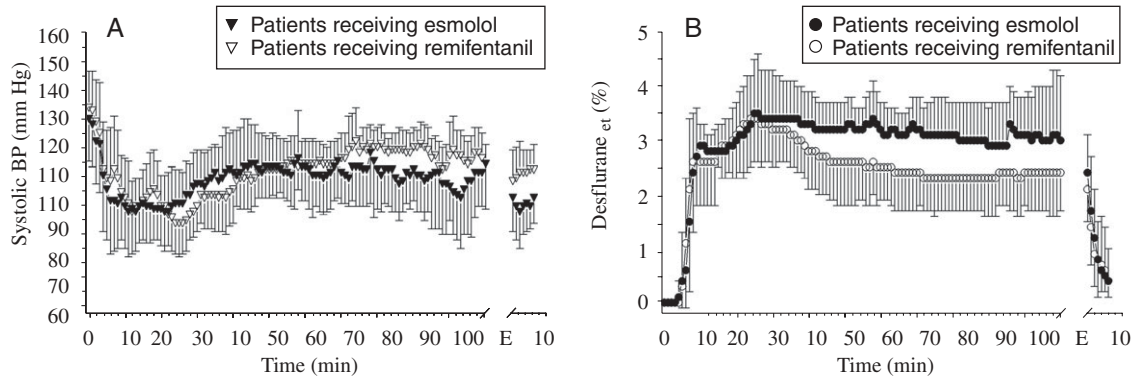


Fig 2 (A) Systolic blood pressure [mean (SD)] recordings in patients receiving esmolol or remifentanyl as a part of their general anaesthesia. E=end of the anaesthesia. (B) End-tidal (e_t) desflurane concentrations [mean (SD)] in patients receiving esmolol or remifentanyl as a part of their general anaesthesia. E=end of the anaesthesia.

The initiation of pneumoperitoneum increases plasma catecholamine concentrations.¹⁴ This may be, in part, because of chemoreceptor activation and enhanced sympathetic outflow caused by soluble carbon dioxide. In a previous study, esmolol was more effective than alfentanil alone to prevent haemodynamic responses to pneumoperitoneum leading to the conclusion that the heart rate and blood pressure responses were not only because of painful stimuli.¹⁵ We have shown, however, that in spite of high doses of esmolol, remifentanyl is more effective in

obtaining the haemodynamic response to pneumoperitoneum.¹⁶ Thus, irrespective of the mechanisms, the phenomenon may be linked to the nociception.

The surgical injury results in profound changes in neural, endocrine, and metabolic systems and also alterations in organ functions, which may result in complications impeding recovery. There is some evidence of the association between the attenuated surgical stress response and improved overall postoperative outcome, but further studies are needed to separate those responses, which should be suppressed or enhanced, and those that should be left unaltered.² Therefore, monitoring of nociception may turn out to be important in evaluating different strategies to control the intra-operative stress response and their association with patient outcome.

The surgical stress response is related to the magnitude of surgical injury, and the lower morbidity rates are observed after minor surgical interventions.² Although SSI was able to detect a significant difference when using a

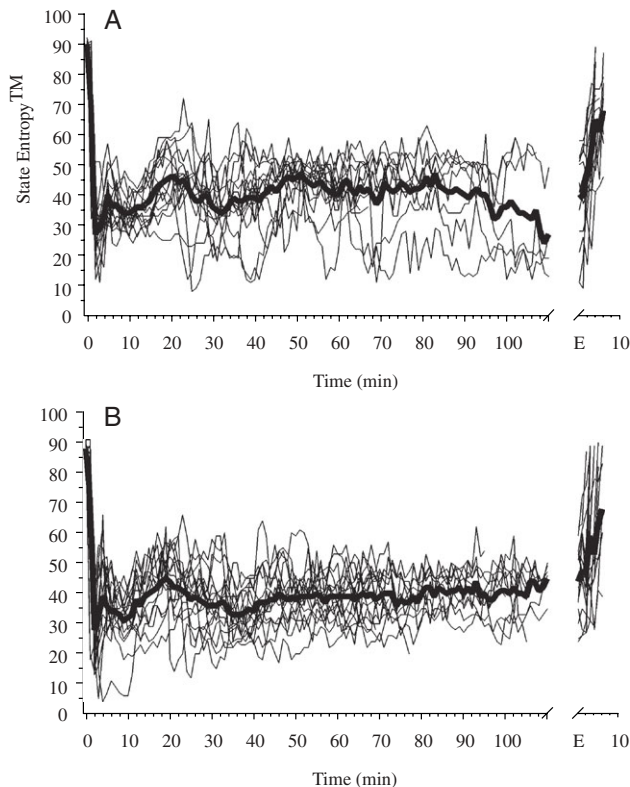


Fig 3 Individual (thin lines) and mean (thick line) State EntropyTM recordings in patients receiving esmolol (A) or remifentanyl (B) as a part of their general anaesthesia. E=end of the anaesthesia.

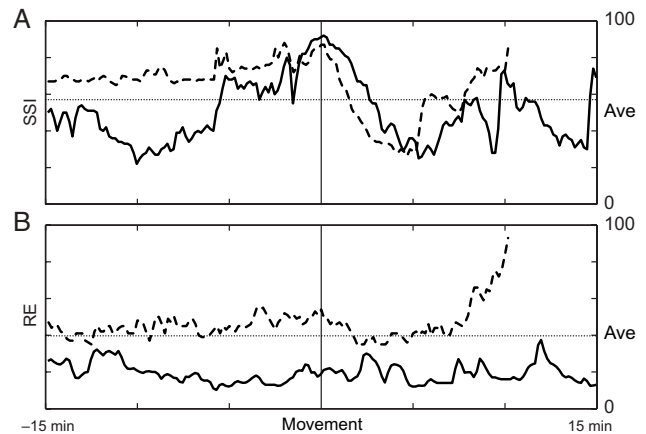


Fig 4 SSI (A) and RE (B) recordings 15 min before and 15 min after the movement in two patients receiving esmolol. The horizontal dotted lines represent the average levels during the operation in all patients. In one of the patients (dashed line), surgery ended soon after the movement and the patient was woken up, reflected in increasing RE and SSI values.

β -adrenergic antagonist instead of an opioid, the use of SSI may be more important in major surgery to evaluate the efficacy of different intra-operative anti-nociception strategies, such as neuraxial blockade, and different analgesic and anaesthetic techniques to reduce postoperative complications, to shorten the patient recovery, and increase patient well-being. However, there are no previous data linking the manipulation of intra-operative pulse wave amplitude or heart beat-to-beat variability to improved patient outcome.

The type and length of surgery may be important when evaluating the need for an analgesia monitor. In a previous study with women undergoing laparoscopic tubal ligation, esmolol and remifentanyl infusions were similarly effective in maintaining haemodynamic stability.¹⁸ Despite induction dose of fentanyl, however, the need for esmolol was higher in the present study, probably reflecting the type and length of surgery. It is plausible that the administration of paracetamol had no impact on the intensity of the intra-operative nociception as it reaches the maximum effect in 30–60 min.

There are some limitations in our study. We used an open-label study design. The systolic pressure did not, however, differ significantly between the groups and the information for SSI was gathered on a laptop by a study nurse not taking part in the anaesthesia teamwork. One patient was excluded as the pulse oximetry probe had to be moved from the finger tip to the earlobe. As the mechanisms of vasoconstriction may differ in the earlobe and the finger,¹⁹ SSI may work differently based on the location of the pulse oximetry probe. Autonomic changes related to awakening may interfere with SSI recordings. Accordingly, towards the end of anaesthesia, SSI increased more markedly in some of the patients receiving remifentanyl compared with those receiving esmolol, while all patients were pain-free on awakening.

The level of SE was low in several patients in both groups. However, we did not allow the desflurane vaporizer to go <2% to avoid any risk of sudden awareness. During abdominal surgery with desflurane–nitrous oxide–remifentanyl anaesthesia, the desflurane requirement was between 2 and 3%,²⁰ which is close to both the MAC–awake value (i.e. 2.6% in oxygen),²¹ and also to the MAC–incision value when combined with nitrous oxide (i.e. 2.8–4% depending on age).²² In the present study, the information of SSI was not used to guide the administration of the anaesthetics. The EEG-derived measures of hypnosis are not able to predict any changes in the level of the surgical stress, and there are several reports on a sudden increase in these measures during low levels of hypnotic administration.²³ The level of hypnosis was very similar in both groups.

In conclusion, we have shown that, in spite of the induction dose of fentanyl, SSI was significantly higher in our patients receiving esmolol than in those receiving remifentanyl. The index seems to reflect the level of

surgical stress and may help guide the use of opioids during general anaesthesia and evaluate the efficacy of different intra-operative anti-nociception strategies on patient outcome.

Acknowledgements

We thank Minna Kymäläinen and Jari Järvinen for collecting the data and all the staff of the operating theatre for their great aid during the study.

References

- 1 Yaksh TL. An introductory perspective on the study of nociception and its modulation. In: Yaksh TL, Lynch C III, Zapol WM, Mace M, Biebuyck JF, Saidman LJ eds. *Anesthesia—Biologic Foundations*. Philadelphia: Lippincott–Raven Publishers, 1998; 471–82
- 2 Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* 1997; **78**: 606–17
- 3 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
- 4 Huiku M, Kymäläinen M, Uutela K, Korhonen J, Yli-Hankala A. A novel index of nociception correlates with remifentanyl concentrations and responds to surgical incision in general anaesthesia. *Anesthesiology* 2005; **103**: A67
- 5 Huiku M, Uutela K, van Gils M, et al. Assessment of surgical stress during general anaesthesia. *Br J Anaesth* **98**: 447–55
- 6 Vakkuri A, Yli-Hankala A, Talja P, et al. Time-frequency balanced spectral entropy as a measure of anaesthetic drug effect in central nervous system during sevoflurane, propofol, and thiopental anaesthesia. *Acta Anaesthesiol Scand* 2004; **48**: 145–53
- 7 Apfel CC, Korttila K, Abdalla M, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med* 2004; **350**: 2441–51
- 8 Gonzales R, Woods R, eds. *Digital Image Processing*. USA: Addison Wesley Publishing Company, 1992; 173–80
- 9 Gorczynski RJ. Basic pharmacology of esmolol. *Am J Cardiol* 1985; **56**: 3F–13F
- 10 Angaran DM, Schultz NJ, Tschida VH. Esmolol hydrochloride: an ultrashort-acting, beta-adrenergic blocking agent. *Clin Pharm* 1986; **5**: 288–303
- 11 Chia YY, Chan MH, Ko NH, Liu K. Role of β -blockade in anaesthesia and postoperative pain management after hysterectomy. *Br J Anaesth* 2004; **93**: 799–805
- 12 Gold JI, Sacks DJ, Grosnoff DB, Herrington C, Skillman CA. Use of esmolol during anaesthesia to treat tachycardia and hypertension. *Anesth Analg* 1989; **68**: 101–4
- 13 Mouren S, De Winter G, Guerrero SP, Baillard C, Bertrand M, Coriat P. The continuous recording of blood pressure in patients undergoing carotid surgery under remifentanyl versus sufentanil anaesthesia. *Anesth Analg* 2001; **93**: 1402–9
- 14 Mikami O, Kawakita S, Fujise K, Shingu K, Takahashi H, Matsuda T. Catecholamine release caused by carbon dioxide insufflation during laparoscopic surgery. *J Urol* 1996; **155**: 1368–71
- 15 Koivusalo A-M, Scheinin M, Tikkanen I, et al. Effects of esmolol on haemodynamic response to CO₂ pneumoperitoneum for laparoscopic surgery. *Acta Anaesthesiol Scand* 1998; **42**: 510–7
- 16 Valjus M, Ahonen J, Jokela R, Korttila K. Response Entropy is not more sensitive than State Entropy in distinguishing the use of

- esmolol instead of remifentanyl in patients undergoing gynaecological laparoscopy. *Acta Anaesthesiol Scand* 2006; **50**: 32–9
- 17** Ochroch EA, Gottschalk A, Augostides J, et al. Long-term pain and activity during recovery from major thoracotomy using thoracic epidural analgesia. *Anesthesiology* 2002; **97**: 1234–44
- 18** Coloma M, Chiu JW, White PF, Armbruster SC. The use of esmolol as an alternative to remifentanyl during desflurane anesthesia for fast-track outpatient gynecologic laparoscopic surgery. *Anesth Analg* 2001; **92**: 352–7
- 19** Aymen A, Awad M, Ashraf M, et al. Different responses of ear and finger pulse oximeter wave form to cold pressor test. *Anesth Analg* 2001; **92**: 1483–86
- 20** Billard V, Servin F, Guignard B, et al. Desflurane-remifentanyl-nitrous oxide anaesthesia for abdominal surgery: optimal concentrations and recovery features. *Acta Anaesthesiol Scand* 2004; **48**: 355–64
- 21** Chortkoff BS, Eger EI II, Crankshaw DP, Gonsowski CT, Dutton RC, Ionescu P. Concentrations of desflurane and propofol that suppress response to command in humans. *Anesth Analg* 1995; **81**: 737–43
- 22** Rampil IJ, Lockhart SH, Zwass MS, et al. Clinical characteristics of desflurane in surgical patients: minimum alveolar concentration. *Anesthesiology* 1991; **74**: 429–33
- 23** Hoymork SC, Raeder J, Grimsmo B, Steen PA. Bispectral index, serum drug concentrations and emergence associated with individually adjusted target-controlled infusions of remifentanyl and propofol for laparoscopic surgery. *Br J Anaesth* 2003; **91**: 773–80