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Influence of nociceptive stimulation on analgesia nociception index (ANI) during propofol–remifentanil anaesthesia

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Editor's key points

- Detecting inadequate analgesia under general anaesthesia can be difficult as pain is a subjective experience.
- Physiological responses to painful stimuli may be used as a surrogate marker of analgesia.
- The analgesia nociception index (ANI) did change in response to noxious stimuli in anaesthetized patients.
- Although the ANI was not useful in predicting inadequate analgesia, it does merit further study.

Background. Measurement of the balance between nociception and anti-nociception during anaesthesia is challenging and not yet clinically established. The Surgical pleth index (SPI), derived from photoplethysmography, was proposed as a surrogate measure of nociception. Recently, the analgesia nociception index (ANI) derived by heart rate (HR) variability was developed. The aim of the present study was to challenge the ability of ANI compared with SPI to detect standardized noxious stimulation during propofol–remifentanil anaesthesia.

Methods. After Ethics approval and informed consent, 25 patients were anaesthetized with propofol [bispectral index (BIS) 30–60]. A laryngeal mask (LMA) was inserted and remifentanil stepwise increased to effect-site concentrations (Ce_{remi}) of 0, 2, and 4 ng ml^{-1}. At each step, tetanic stimulation (STIM) was applied. ANI, SPI, BIS, HR, and mean arterial pressure (MAP) were obtained before and after LMA insertion and each STIM. Analysis was performed using Wilcoxon rank tests and calculation of prediction probabilities (P_K).

Results. ANI and SPI, but not BIS, HR, or MAP, were significantly ($P<0.05$) changed at all examined steps. ANI response to STIM was (median [IQR]) −24 [−12–35], −30 [−20–−40] and −13 [−5–−27] at 0, 2 and 4 ng ml^{-1} Ce_{remi}. However, prediction of movement to STIM was not better than by chance, as P_K values were 0.41 (0.08) for ANI and 0.62 (0.08) for SPI.

Conclusions. The two variables, ANI and SPI, enabled consistent reflection of stimulation during propofol–remifentanil anaesthesia. Nevertheless, ANI and SPI may improve detection but not prediction of a possible inadequate nociception–anti-nociception balance.

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Measurement of the effect of anaesthetic drugs may allow individual titration of anaesthetics leading to a decreased incidence of both over- and underdosage. This may significantly affect the outcome for patients. Processed variables of the electroencephalogram have been suggested for guidance of administration of hypnotics during anaesthesia. However, monitoring nociception, or better the nociceptive–anti-nociceptive balance, during anaesthesia and surgical stimulation has not yet been established. Routinely, administration of analgesics is guided by clinical experience and also somatic or autonomic responses, such as movement, sweating, heart rate (HR), or blood pressure increase. A more reliable quantification of the nociceptive–anti-nociceptive balance has been attempted by analysing reflex pathways, skin vasomotor reflexes, pulse plethysmographic signal, pupillometry, and HR variability.[1] Further, computation of dose-dependent responses was introduced, taking into account the calculated concentrations of both hypnotics and opioids.[2] From a clinical point of view, a feasible measure of adequate anti-nociception would (i) detect a nociceptive–anti-nociceptive misbalance immediately, (ii) allow prediction of a nociceptive response to an upcoming stimulation, and (iii) be easy to install and to interpret (non-invasively).

Recently, promising results of an index based on heart beat interval and pulse wave amplitude of the finger-photoplethysmographic signal (surgical pleth index, SPI) were reported.[3–5] More recently, a new variable called 'analgesia nociception index' (ANI) based on HR variability derived from the standard 5-lead electrocardiogram (ECG) was developed. Whereas ANI has been recently described in patients during laparoscopic surgery and labour,[6 7] a standardized and comparative clinical evaluation during general anaesthesia with changing opioid concentration is missing.

The primary objective of this prospective study was to evaluate the influence of standardized noxious stimulation on ANI at different remifentanil effect site concentrations (Ce_{remi}) during propofol anaesthesia. Secondly, we examined whether ANI is dependent on Ce_{remi} and may enable a prediction of the response to noxious stimulation, such as HR increase or movement. This was to be evaluated in comparison with the previously described SPI.

Methods

After obtaining approval of the institutional review board of the University Hospital Schleswig-Holstein, Campus Kiel, and written informed consent, 25 patients with ASA physical status I or II, age between 18 and 65 years, undergoing elective surgery were enrolled. Patients were not included if they had a history of cardiac arrhythmia, neuromuscular or neurological disease, diabetes mellitus, use of medication or drugs that may affect autonomous regulation (e.g. beta-blocker, clonidine) or were pregnant. All patients were anaesthetized by experienced and certified staff anaesthetists.

Analysed variables were ANI, SPI, bispectral index (BIS), HR, non-invasive mean arterial blood pressure (MAP), and calculated effect site concentrations of anaesthetics.

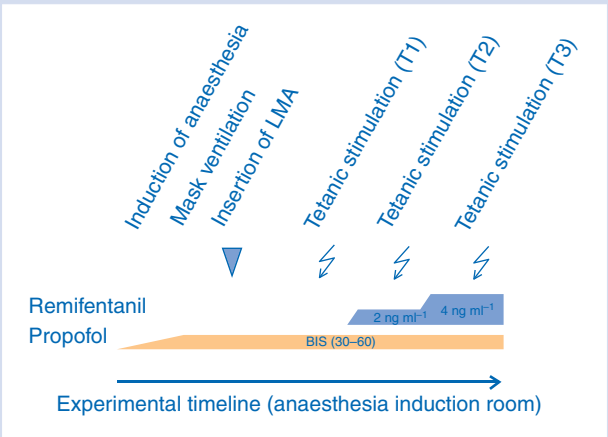

Fig 1 Experimental timeline. The study was performed in the anaesthesia-induction room. For induction of anaesthesia, propofol was administered until loss of consciousness and to achieve a bispectral index (BIS) value range between 30 and 60. The first stimulus was induced by insertion of an LMA, followed by three tetanic stimulations of the forearm at 0, 2, and 4 ng ml^{-1} of remifentanil effect site concentration.

ANI was derived by the CE-certified PhysioDoloris monitor (MetroDoloris, Lille, France), a non-invasive device that takes the online ECG analogue output from the patient monitor (S/5 Monitor, GE-Healthcare, Helsinki, Finland). ANI is calculated from analysis of HR variability, which is based on small beat-to-beat oscillations of the HR and described in detail elsewhere.[8] The calculated values of ANI range from 100 to 0, based on the degree of parasympathetic activation. 100 means a high parasympathetic modulation (low stress level) and 0 means extremely low parasympathetic modulation (high stress level). The PhysioDoloris monitor continuously displays an average measurement of ANI made over the previous 60 s.

SPI (formerly named surgical stress index) is a numerical index for monitoring the anti-nociceptive–nociceptive balance obtained by finger plethysmography reversely ranging between 0 (low stress level) and 100 (high stress level). A value of 50 represents a mean stress level during anaesthesia. SPI was originally developed during propofol–remifentanil anaesthesia in gynaecological patients. A detailed description of SPI, including the algorithm, can be found elsewhere.[3] The finger clip for finger plethysmography was placed on the index finger of the left hand and connected to the anaesthesia monitor, visualizing SPI continuously.

Patients received no premedication before anaesthesia. After arrival in the operating theatre, standard monitoring (non-invasive blood pressure, ECG, pulse oximetry) and venous access via a forearm vein were established. All patients received an i.v. infusion of crystalloids (2–4 ml kg^{-1} h^{-1}) during the entire study period. After preparing the skin of the forehead, the disposable BIS-XP Sensor (Aspect Medical Systems, Newton, MA, USA) was positioned according to the manufacturer's recommendations. The BIS Sensor was connected with the respective M-BIS module of the S/5™ Anaesthesia Monitor (GE-Healthcare, Helsinki, Finland). The EEG was recorded continuously (smoothing rate of 15 s) from induction of anaesthesia until the end of the measuring period.

The study protocol is outlined in Figure 1. Following adequate preoxygenation, anaesthesia was induced with propofol (2 mg kg^{-1}). After loss of the eyelash reflex, mask ventilation was performed followed by insertion of a laryngeal mask (LMA Unique™, LMA Deutschland GmbH, Bonn, Germany), which was defined as the first stimulus. Anaesthesia was maintained with a continuous infusion of propofol to achieve an acceptable level of hypnosis (BIS 30–60). Remifentanil was increased step-by-step via a computer-assisted continuous infusion device (Alaris PK pump, Cardinal Health, Rolle, Switzerland; protocol by Minto, Schnider and Shafer)[9] to a Ce_{remi} of 0–2–4 ng ml^{-1}. A steady-state period of at least 5 min was maintained at each Ce_{remi} before a standardized noxious stimulus was applied via tetanic stimulation (30 s, 60 mA, 50 Hz) above the ulnar side of the wrist using a standard muscle relaxometer (Innervator, Fisher & Paykel Healthcare, Auckland, New Zealand) at the opposite arm from the SPI sensor. Any event of purposeful movement, coughing,

chewing, or grimacing during or after stimulation was defined as 'movement'. Stimulation was immediately stopped when movement occurred, and if needed, a 30-mg propofol bolus given as rescue medication (did not cause exclusion of collected data). No visible stimulation response was regarded as 'no movement'. No neuromuscular blocking agents were administered during the entire study period. On the first postoperative day, all patients had a structured interview, and were asked by a blinded anaesthetist if they had any explicit memory or awareness, and the level of satisfaction with the overall procedure was determined using a 0–100 scale (100=totally satisfied).

Statistical analysis

All variables were averaged the minute before stimulation and compared with the peak value within 2 min after the stimulus. Variables before and after stimulation were analysed by Wilcoxon signed-rank test with Bonferroni correction for multiple comparisons using commercially available statistics software (GraphPad Prism 5, Graphpad Software, Inc., San Diego, CA, USA). A *P*-value of <0.05 was considered statistically significant.

Furthermore, averaged data 1 min before stimulation were analysed to reveal whether they were able to predict a stimulus-induced event of an HR response >5 min^{-1} as reported previously[4] or movement. Prediction probabilities (P_K) were calculated using P_KMACRO spread sheets as described by Smith *et al.*[10] A P_K value of 1.0 or 0.0 means a total prediction of the event, whereas 0.5 means no better prediction than flipping a coin. Receiver-operating characteristic was used for calculation of the area under the curve and their respective statistical significance (*P*-value). Sample size was calculated based on published ANI studies to detect a stimulus-induced difference of 15%, with an alpha-error of 0.05 and 90% power.[8]

Results

Twenty-five patients were included in this study. Therefore, data from 25 LMA insertions and a total of 75 noxious tetanic stimulations were finally analysed. Patient characteristic data are presented in Table 1. None of the patients had explicit memory of any event during anaesthesia; overall satisfaction of anaesthesia was median [inter-quartile range;

Table 1 Patient characteristic data of patients and their physical status according to the American Society of Anesthesiologists (ASA). Data are mean (SD/range) or absolute numbers

	Patients ($n=25$)
Gender (f/m)	17/8
Age (years)	44 [24–67]
Height (cm)	169 (10)
Weight (kg)	72 (11)
Body Mass Index	25 (4)
ASA (I/II)	7/18

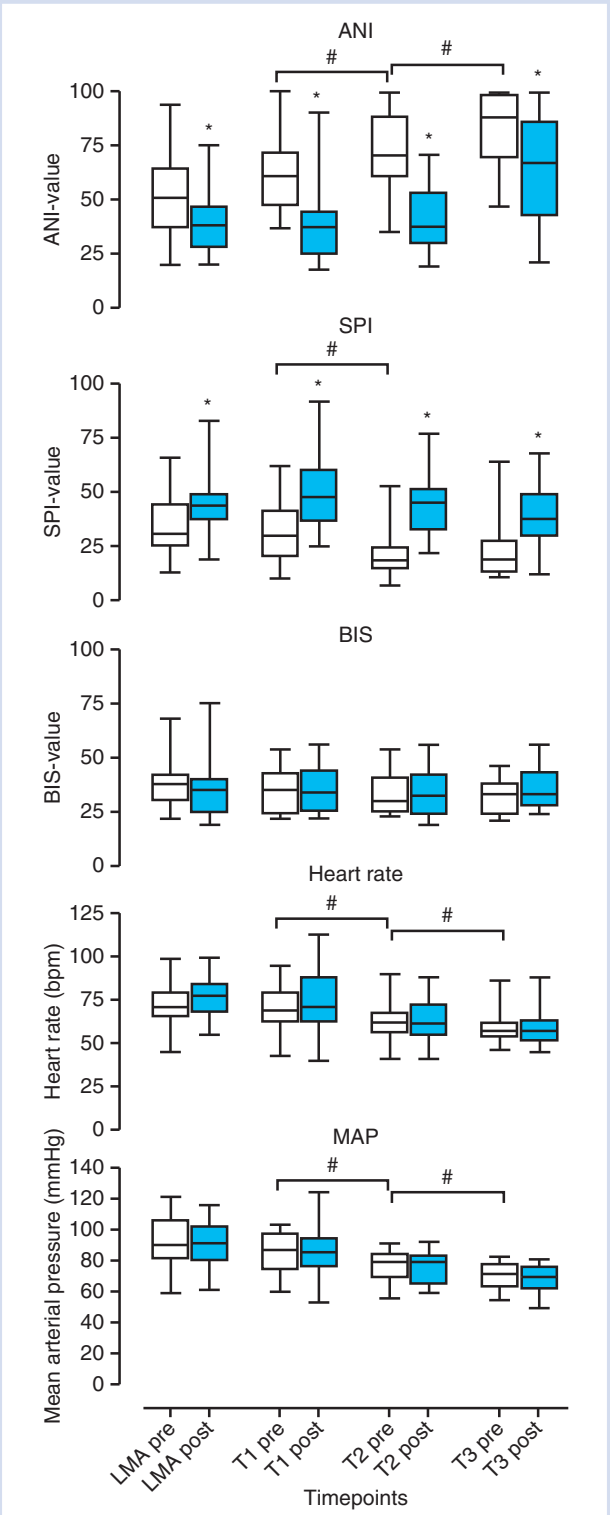

Fig 2 Variables before (white boxes) and after (blue boxes) stimulation by either insertion of an LMA or tetanic stimulations of the forearm at 0, 2, and 4 ng ml^{-1} remifentanil effect site concentration (T1, T2, T3, respectively). Analgesia nociception index (ANI), surgical pleth index (SPI), bispectral index (BIS), HR, and mean arterial pressure (MAP). Data are median, IQR, and range. *$P<0.05$ vs. pre-stimulation value. #$P<0.05$ vs. lower remifentanil concentration

IQR] 97 [86–100]. Twenty-four patients stated that they were willing to participate in a similar study in the future.

With regard to the calculated concentrations of remifentanil, we found that ANI, HR, and MAP, but not SPI and BIS were significantly ($P<0.05$) dependent on tested Ce_{remi} as presented in Figure 2. ANI values before tetanic stimulation were median [IQR] 61 [48–72], 71 [61–88], and 88 [70–98] at 0, 2, and 4 ng ml^{-1} of Ce_{remi}.

Insertions of LMA led to a significant decrease in ANI (from median [IQR] 51 [37–64.5] to 38 [28.5–46.5]; $P<0.03$) and increase in SPI (from 31 [25.5–44] to 44 [37.5–49]; $P<0.01$), induced change in ANI was median [IQR] 12 [7–34] and for SPI 11 [1–22]. BIS remained unchanged (38 [30.5–42] to 35 [25–40]; $P=0.35$). Out of 25 LMA insertions we recorded 12 events of HR response and 6 events of movement.

Tetanic stimulations during 0, 2, and 4 ng ml^{-1} of Ce_{remi} caused consistent changes in ANI and SPI, but not in BIS, HR, or MAP. All examined variables before and after stimulation at the different experimental steps are presented in Figure 2, individual plots of ANI are presented in Figure 3. The response to tetanic stimulation of pooled data, including the resulting differences (Δ-values), are presented in Table 2.

Tetanic stimulation during 0, 2, and 4 ng ml^{-1} Ce_{remi} led to a respective decrease in ANI by median [IQR] 24 [12–35], 30 [20–40], and 13 [5–27; $P<0.05$ vs. stimulation at 0 and 2 ng ml^{-1}], and also SPI increase by 18 [9–30], 23 [10–33], and 17 [8–26]. Out of 25 tetanic stimulations each at Ce_{remi} of 0, 2, and 4 ng ml^{-1}, we detected 9, 5, and 1 events of HR response and 12, 5, and 1 events of movement, respectively. Therefore, stimulation was terminated earlier in the case of movement and reduced mean stimulation time (± SD), which was 18 (12), 26 (8) and 29 (5) s during respective Ce_{remi} of 0, 2, and 4 ng ml^{-1}.

Maximum ANI decrease occurred [mean (SD)] 80 (31), 82 (23), and 79 (26) s after the start of stimulation at respective Ce_{remi} of 0, 2, and 4 ng ml^{-1}.

Predictive power of variables to indicate HR response or movement because of LMA insertion and tetanic stimulation are presented in Table 3, using P_K values. Even though we detected several significant P_K values for HR, MAP, and calculated effect site concentrations, none of the tested variables consistently predicted the response to stimulation.

Discussion

In this prospective clinical study, ANI enabled consistent detection of standardized noxious stimulation during propofol–remifentanil anaesthesia. ANI values depended on Ce_{remi}, but did not allow the prediction of response to LMA insertion or tetanic stimulation.

During general anaesthesia, there is normally no conscious experience of painful stimulation. Analgesics, and most relevant opioids, are able to attenuate stimulation-induced signal transmission thereby providing nociceptive–anti-nociceptive balance.[11] Currently, administration of analgesics in clinical routine is based on anaesthesiologist's experience and often judged on clinical signs such as movement or unspecific autonomic responses (e.g. tachycardia or sweating). Development of monitoring devices for measurement of the nociceptive–anti-nociceptive balance has focused on reflex pathways and autonomic responses. Spinal cord reflex pathways (e.g. the monosynaptic H-reflex or the polysynaptic R-III reflex) may predict the response to noxious stimulation.[12 13] More complex and centrally mediated reflexes such as the pupillary dilation reflex have also shown to be dependent on opioid concentrations during anaesthesia.[14] However, clinical usefulness is limited because

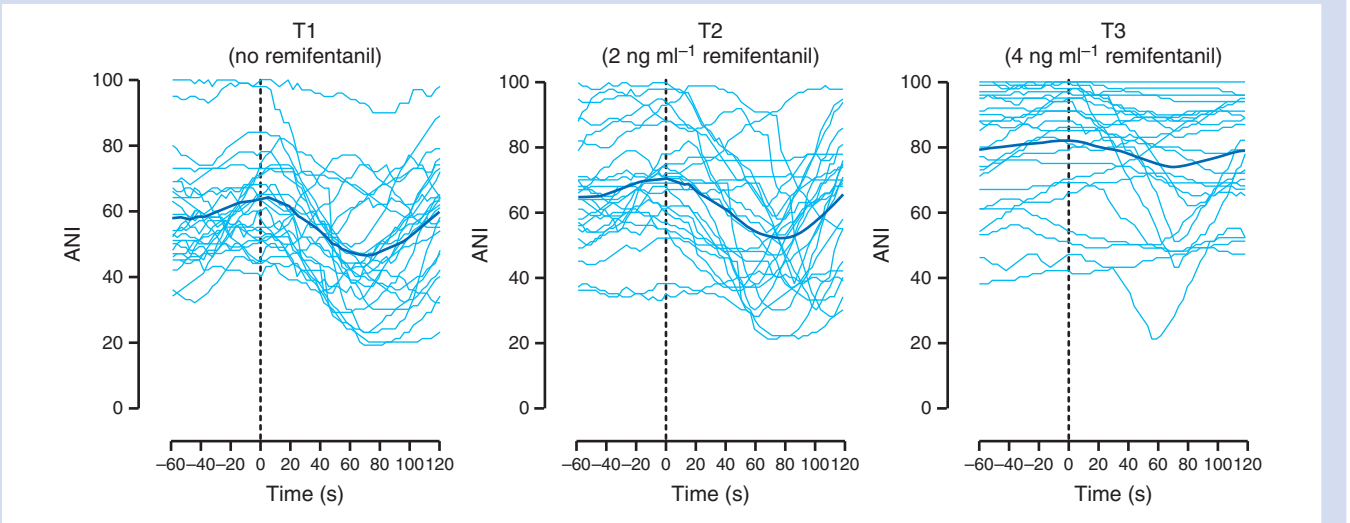

Fig 3 Plots of individual time courses (light blue lines) and mean time course (dark blue lines) of ANI 60 s before and 120 s after tetanic stimulation (dotted line) at different remifentanil effect site concentrations.

Table 2 Pooled data of analgesia nociception index (ANI), surgical pleth index (SPI), bispectral index (BIS), HR, mean blood pressure (MAP) and calculated propofol effect site concentration (Ce_{prop}) in the period (60 s) before tetanic stimulation (pre-stimulation) and peak values (120 s) after tetanic stimulation (post-stimulation). Groups were compared using Wilcoxon signed rank test. $^{**}P<0.001$ *vs* pre-stimulation. Change in variables is presented as △-values in subgroups of patients who moved (movers) or did not move (non-movers) after tetanic stimulation. Data are median (IQR); △-value represents post-stimulation − pre-stimulation difference

	All pre-stimulation ($n=75$)	All post-stimulation ($n=75$)	Movers △-value ($n=57$)	Non-movers △-value ($n=18$)
ANI	70 (58–90)	43 (32–61)**	−18 (−27 to −10)	−25 (−38 to −11)
SPI	22 (15–30)	45 (32–54)**	17 (5 to 20)	19 (8 to 30)
BIS	32 (25–40)	33 (27–43)]	1 (−1 to 3)	2 (−1 to 6)
HR (bpm)	63 (55–69)	62 (55–74)	1 (−2 to 6)	0 (−2 to 3)
MAP (mm Hg)	77 (69–85)	76 (67–83)	−2 (−8 to 2)	0 (−3 to 1)
Ce_{prop} (μg ml^{-1})	4 (3–5)	n.a.	4 (4 to 6)	4 (3 to 5)

Table 3 Prediction probability (P_K) for variables averaged 60 s before the tetanic stimulation and peak values within 120 s after LMA airway (LMA) insertion and tetanic stimulus of the forearm (30 s, 60 mA, 50 Hz) for analgesia nociception index (ANI), surgical pleth index (SPI), HR, mean arterial pressure (MAP), bispectral index (BIS) and effect site concentration of propofol (Ce_{prop}) and remifentanil (Ce_{remi}). Variables were tested to predict an increase in HR (△HR >5 bpm) or detection of movement. n.a., not applicable. Data are P_K-values (standard error) (*P*-value)

	LMA—insertion		Tetanic stimulation	
	HR response (12/25)	Movement (6/25)	HR response (15/75)	Movement (18/75)
ANI	0.66 (0.12) ($P=0.18$)	0.52 (0.14) ($P=0.84$)	0.38 (0.09) ($P=0.06$)	0.41 (0.08) ($P=0.13$)
SPI	0.32 (0.12) ($P=0.13$)	0.50 (0.15) ($P=0.97$)	0.60 (0.09) ($P=0.37$)	0.62 (0.08) ($P=0.12$)
BIS	0.40 (0.12) ($P=0.38$)	0.29 (0.13) ($P=0.14$)	0.34 (0.09) ($P=0.08$)	0.45 (0.08) ($P=0.32$)
HR	0.30 (0.11) ($P=0.10$)	0.58 (0.12) ($P=0.59$)	0.81 (0.06) ($P<0.01$)	0.63 (0.08) ($P=0.15$)
MAP	0.53 (0.12) ($P=0.79$)	0.49 (0.15) ($P=0.95$)	0.72 (0.08) ($P<0.02$)	0.70 (0.07) ($P<0.05$)
Ce_{prop}	0.60 (0.12) ($P=0.38$)	0.50 (0.16) ($P=0.97$)	0.76 (0.06) ($P<0.01$)	0.73 (0.06) ($P<0.01$)
Ce_{remi}	n.a.	n.a.	0.34 (0.08) ($P<0.02$)	0.29 (0.08) ($P<0.01$)

they are difficult to obtain or cannot be measured continuously. Therefore, variables are being developed which use the clinically available standard anaesthesia monitoring such as ECG recordings (ANI) or pulse plethysmographic signal (SPI). During stable anaesthesia, the variation of heart beat interval is small and mainly influenced by respiratory sinus arrhythmia, whereas variability increases after stimulation.[15] The high-frequency component (HF) of the HR variability reflects parasympathetic modulation of the heart, which can be measured by filtering the beat-to-beat series in the HF domain [0.15–0.5 Hz]. As nociception increases, the parasympathetic tone decreases in response to the increased sympathetic activity, which in turn leads to a decrease of ANI.[8]

In the present study, only ANI and SPI, but not BIS, HR, or MAP, consistently detected stimulations induced by LMA insertion and tetanic stimulation. Consequently, these variables may add clinically important information regarding the present nociceptive–anti-nociceptive balance. We detected significant decreases of ANI during all tested Ce_{remi}, which were significantly attenuated during a remifentanil plasma concentration of 4 ng ml^{-1}. Similarly, it has been described that stimulation-induced change of the HF component during 'adequate' analgesia is attenuated in comparison with 'inadequate' or 'light' analgesia.[8] The developers have recently described that ANI is influenced by tetanic stimulation, trocar insertion, and pneumoperitoneum during anaesthesia, but did not examine change in ANI values nor different opioid concentrations.[7]

We recorded the maximum decrease in ANI ~80 s after the stimulus occurred, thus markedly later as reported for SPI.[4] This is probably the result of the prolonged calculation time period, a possible drawback of the ANI method. We can confirm the existing results with regard to SPI monitoring, where a significant increase as a result of noxious stimulation was detected in various anaesthesia settings before.[3 4 16] Nevertheless, it must be considered that ANI and SPI are measures of the sympathetic response to nociceptive input. Therefore, many confounders of the sympathetic tone have to be taken into account. Actual data report possible effects of intravascular volume status,[17] posture,[18] medication,[17 19] and different level of consciousness.[20]

Stimulation response was not detected by BIS. It has been reported that processed EEG variables reflecting the hypnotic state may only show small changes after stimulation, unless a hypnotic arousal occurs.[21] However, the BIS index also

contains facial electromyographic signals. A very recent work has shown that a composite index (CVI) derived from BIS variability and the facial electromyogram may reflect inadequate anti-nociception during anaesthesia.[22]

In this study, we further found that ANI, HR, and MAP were dependent on Ce_{remi}. To our best knowledge, this is the first study of ANI during a controlled and standardized anaesthesia regimen with increasing remifentanil concentrations. Previously, Luginbühl *et al*. have described the effect of different hypnotic and analgesic states on HR variability and shown that HF may be dependent on remifentanil concentration,[23] which is in accordance with our findings. However, we recorded a large inter-individual variability in pre-stimulation ANI values, which may be associated with reduced sensitivity and specificity to depict an adequate threshold of the analgesic component during anaesthesia. Similar to a previous study during sevoflurane–remifentanil anaesthesia, SPI depended on remifentanil concentration from 0 to 2 ng ml^{-1}, but not further on.[4] Concerning the dependency of HR and MAP on remifentanil concentrations, it is well known that increasing remifentanil concentrations have significant effects on haemodynamics.[24]

Additionally, we sought to examine whether a vegetative or somatic response to noxious stimulation can be predicted. None of the tested variables showed a consistent and clinically suitable prediction of the response to either LMA insertion or tetanic stimulation. In contrast to prediction of loss of consciousness, where P_K-values of 0.99 have been reported for BIS,[25] comparable prediction of nociception–anti-nociception balance has not yet been possible. We hypothesize that nociception–anti-nociception balance during the measurement period is most likely adequate, and then the additional noxious stimulation causes a sudden nociceptive input.

Nevertheless, we detected significant P_K-values for HR, MAP and calculated effect site concentrations of the anaesthetics propofol and remifentanil. This is consistent with our previous results during sevoflurane–remifentanil anaesthesia and likely reflects the anaesthetic drug effect.[4] It further emphasizes the potential of using the hypnotic–opioid interaction for evaluation of nociceptive balance as proposed by others.[2]

Some limitations of the present study should be noted. First, the study was performed in the anaesthesia induction room before the start of surgery and ANI was not evaluated during a specific surgical procedure. Therefore, values were recorded during steady-state conditions without any other type of stimulation apart from tetanic stimulation and LMA insertion. It is conceivable that activation and suppression of the autonomic system differs during surgery with permanent painful stimulation. Secondly, the maximum value of the measured variables in patients moving was probably underestimated because of termination of stimulation and application of rescue medication immediately upon movement. Thirdly, we excluded a considerable number of patients who are on concomitant medications such as beta-blockers and who may impair the predictive power of variables that are based on changes in HR. More studies are needed to prove the effect of monitoring ANI for evaluation of nociceptive balance, anaesthetic drug consumption, emergence, and postoperative morbidity before drawing conclusions for the clinical benefit.

In conclusion, ANI monitoring based on the HF component of HR variability and SPI monitoring derived by finger photoplethysmography consistently indicated nociceptive response during propofol–remifentanil anaesthesia and therefore provided additional information about nociceptive–anti-nociceptive balance. However, these variables did not enable prediction of the vegetative or somatic response to a noxious stimulus. Further investigations are needed to evaluate these variables during other anaesthesia regimen and to answer the question whether their monitoring will provide beneficial effects to the patients.

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Declaration of interest

B.B. has received honoraria for consulting and giving lectures from GE Healthcare, the manufacturer of the SPI module.

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References

1 Guignard B. Monitoring analgesia. *Best Pract Res Clin Anaesthesiol* 2006; **20**: 161–80

2 Luginbuhl M, Schumacher PM, Vuilleumier P, *et al.* Noxious stimulation response index: a novel anesthetic state index based on hypnotic-opioid interaction. *Anesthesiology* 2010; **112**: 872–80

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

4 Gruenewald M, Meybohm P, Ilies C, *et al.* Influence of different remifentanil 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

5 Chen X, Thee C, Gruenewald M, *et al.* Comparison of surgical stress index-guided analgesia with standard clinical practice during routine general anesthesia: a pilot study. *Anesthesiology* 2010; **112**: 1175–83

6 Le Guen M, Jeanne M, Sievert K, *et al.* The analgesia nociception index: a pilot study to evaluation of a new pain parameter during labor. *Int J Obstet Anesth* 2012; **21**: 146–51

7 Jeanne M, Clement C, De Jonckheere J, Logier R, Tavernier B. Variations of the analgesia nociception index during general anaesthesia for laparoscopic abdominal surgery. *J Clin Monit Comput* 2012; **26**: 289–94

8 Jeanne M, Logier R, De Jonckheere J, Tavernier B. Validation of a graphic measurement of heart rate variability to assess analgesia/nociception balance during general anesthesia. *Conf Proc IEEE Eng Med Biol Soc* 2009; **2009**: 1840–3

9 Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. *Anesthesiology* 1997; **86**: 24–33

10 Smith WD, Dutton RC, Smith NT. Measuring the performance of anesthetic depth indicators. *Anesthesiology* 1996; **84**: 38–51

11 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

12 Rehberg B, Grunewald M, Baars J, *et al.* Monitoring of immobility to noxious stimulation during sevoflurane anesthesia using the spinal H-reflex. *Anesthesiology* 2004; **100**: 44–50

13 von Dincklage F, Correll C, Schneider MH, Rehberg B, Baars JH. Utility of nociceptive flexion reflex threshold, bispectral index, composite variability index and noxious stimulation response index as measures for nociception during general anaesthesia. *Anaesthesia* 2012; **67**: 899–905

14 Larson MD, Kurz A, Sessler DI, *et al.* Alfentanil blocks reflex pupillary dilation in response to noxious stimulation but does not diminish the light reflex. *Anesthesiology* 1997; **87**: 849–55

15 Logier R, Jeanne M, Tavernier B, De Jonckheere J. Pain/analgesia evaluation using heart rate variability analysis. *Conf Proc IEEE Eng Med Biol Soc* 2006; **1**: 4303–6

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

17 Bonhomme V, Uutela K, Hans G, *et al.* Comparison of the surgical pleth index with haemodynamic variables to assess nociception–anti-nociception balance during general anaesthesia. *Br J Anaesth* 2011; **106**: 101–11

18 Ilies C, Ludwigs J, Gruenewald M, *et al.* The effect of posture and anaesthetic technique on the surgical pleth index. *Anaesthesia* 2012; **67**: 508–13

19 Hocker J, Broch O, Grasner JT, *et al.* Surgical stress index in response to pacemaker stimulation or atropine. *Br J Anaesth* 2010; **105**: 150–4

20 Ilies C, Gruenewald M, Ludwigs J, *et al.* Evaluation of the surgical stress index during spinal and general anaesthesia. *Br J Anaesth* 2010; **105**: 533–7

21 Vanluchene AL, Struys MM, Heyse BE, Mortier EP. Spectral entropy measurement of patient responsiveness during propofol and remifentanil. A comparison with the bispectral index. *Br J Anaesth* 2004; **93**: 645–54

22 Mathews DM, Clark L, Johansen J, Matute E, Seshagiri CV. Increases in electroencephalogram and electromyogram variability are associated with an increased incidence of intraoperative somatic response. *Anesth Analg* 2012; **114**: 759–70

23 Luginbuhl M, Ypparila-Wolters H, Rufenacht M, Petersen-Felix S, Korhonen I. Heart rate variability does not discriminate between different levels of haemodynamic responsiveness during surgical anaesthesia. *Br J Anaesth* 2007; **98**: 728–36

24 Guignard B, Menigaux C, Dupont X, Fletcher D, Chauvin M. The effect of remifentanil on the bispectral index change and hemodynamic responses after orotracheal intubation. *Anesth Analg* 2000; **90**: 161–7

25 Kreuer S, Bruhn J, Larsen R, Hoepstein M, Wilhelm W. Comparison of Alaris AEP index and bispectral index during propofol–remifentanil anaesthesia. *Br J Anaesth* 2003; **91**: 336–40

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