Validation of Innovative Techniques for Monitoring Nociception during General Anesthesia

A Clinical Study Using Tetanic and Intracutaneous Electrical Stimulation

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ABSTRACT

Background: This study compares the analgesic indices Analgesia Nociception Index (heart rate variability), Surgical Pleth Index (photoplethysmography), and pupillary dilatation, to heart rate, mean arterial pressure, and bispectral index, with regard to diagnostic accuracy and prediction probability for nociceptive response. The primary endpoint was the correlation between Δ values and the remifentanil dose administered.

Methods: We anesthetized 38 patients with propofol and increasing doses of remifentanil and applied standardized tetanic and intracutaneous electrical painful stimulations on each analgesic level. Baseline and Δ values of the Analgesia Nociception Index, the Surgical Pleth Index, pupillary dilatation, heart rate, mean arterial pressure, and bispectral index and their relation to remifentanil doses were analyzed by receiver operating characteristic curves, prediction probability (P_K), and mixed-model analysis.

Results: Under propofol sedation, sensitivity and specificity of the Analgesia Nociception Index ($P_K = 0.98$), the Surgical Pleth Index ($P_K = 0.87$), and pupillary dilatation ($P_K = 0.98$) for detecting both painful stimulations were high compared to heart rate ($P_K = 0.74$), mean arterial pressure ($P_K = 0.75$), and bispectral index ($P_K = 0.55$). Baseline values had limited prediction probability toward the nociceptive response (Analgesia Nociception Index: $P_K = 0.7$; Surgical Pleth Index: $P_K = 0.63$; pupillary dilatation: $P_K = 0.67$; and bispectral index: $P_K = 0.67$). The remifentanil dose had an effect ($P < 0.001$) on all parameters except for bispectral index ($P = 0.216$).

Conclusions: The Analgesia Nociception Index, the Surgical Pleth Index, and pupillary dilatation are superior in detecting painful stimulations compared to heart rate and mean arterial pressure but had limited predictive value. These effects are attenuated by increasing dosages of remifentanil. Our data confirm that bispectral index is not a marker of analgesia.
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To date, administration of analgesic drugs in general anesthesia is mainly determined by the clinical experience of the anesthesiologist. On the one hand, sufficient analgesic levels are critical to avoid unexpected movements, sympathetic reactions followed by cardiocirculatory complications, and development of pain memory. On the other hand, restriction to the minimum dosage is desirable to avoid opioid-induced hyperalgesia, to avoid drug side effects, and to achieve shorter perioperative treatment periods.[1,2] Opioid dosage is titrated by nocifensive movements and clinical signs of stress-induced activation of the sympathetic system such as an increase in heart rate, blood pressure, lacrimation, and sweating.[3] Still, a monitoring device to specifically reflect the analgesic component of general anesthesia, like electroencephalography-based sedation monitoring for hypnosis, has not been established yet.

In recent years, different monitoring devices estimating the effect of analgesia during unconsciousness became available.[4] Most devices generate an analgesic index from physiologic variables determined by different techniques. According to the manufacturer's specifications, these analgesic indices reflect the balance between nociception

What We Already Know about This Topic

- Analgesic administration is a critical component of anesthetic management
- Physiologic variables alone or in combination are used to measure analgesic status

What This Article Tells Us That Is New

- Changes in the Analgesia Nociception Index and Surgical Pleth Index, as well as pupillary dilatation, were sensitive and specific for painful stimulation
- The bispectral index is sensitive neither to painful stimuli nor to the effects of analgesics and therefore is a poor marker of analgesia

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and antinociception. The Analgesia Nociception Index is an index that can be obtained from the PhysioDoloris monitor (MetroDoloris, France) that measures heart rate variability on a scale from 0 (maximum of nociception) to 100 (complete analgesia). The Surgical Pleth Index was derived from pulse rate and pulse wave amplitude measured with photoplethysmography, obtained from the CARESCAPE B650 monitor (GE Healthcare, Finland), and reflects sympathetic activity on a scale from 1 to 100.[5] Pupil diameter after a noxious event was measured with the portable dynamic videopupillometer AlgiScan (IDMed, France).

Prior validation studies of these devices used tetanic stimulation as a noxious stimulus that is easily reproduced but is not necessarily a specific pain stimulation.[5–10] Furthermore, the accompanying muscular contraction makes the interpretation of the stimulation response difficult. In contrast, the rarely used intracutaneous pain model introduced by Bromm *et al.*[11–13] more than 30 yr ago involves placing an electrode directly in the vicinity of Aδ- and C-fiber terminals on the pulp of the finger, which is why this model is classified as a noxious stimulation directly at the respective receptors. Corresponding stimulation evokes clear pinprick pain in awake patients.

The aim of this study was to compare the three different analgesia monitoring systems, the Analgesia Nociception Index, the Surgical Pleth Index, and pupil diameter, to the clinical parameters heart rate, mean arterial pressure, nocifensive movements, and the bispectral index (BIS monitor; Covidien, USA) under standardized conditions with increasing opioid concentrations. Further, tetanic stimulation was validated as a marker of noxious stimulation. First, we investigated whether the analgesic indices are superior to changes of the clinical parameters with regard to sensitivity and specificity in detection of two different noxious stimuli during general anesthesia. Second, this study evaluated whether the baseline values of the analgesic indices, the clinical parameters, and the bispectral index may serve as a predictor for hemodynamic alteration or nocifensive movements after stimulation. Third, as the primary endpoint of the study, we tested the hypothesis that the effects observed would change with increased infusion rates of remifentanil.

Materials and Methods

This is a single-group assignment interventional clinical study, and data acquisition took place in the operating room. The study protocol was approved by the regional ethics review board of the Medical Council of Hamburg, Germany (reference number PV4543, April 1, 2014) and registered in the ClinicalTrial.gov database (NCT02429960, April 8, 2015). Participating patients gave written informed consent the day before data collection and surgery. Patients consented to a longer duration of anesthesia before the actual start of the surgical procedure for the purpose of analgesia testing.

Patients

Inclusion criteria were American Society of Anesthesiologists physical status I or II, age more than 18 yr, and scheduled for open radical prostatectomy under general anesthesia in combination with spinal anesthesia. Exclusion criteria were preexisting diseases of the sensory system (gout, polyneuropathy, multiple sclerosis, focal neurologic deficiencies, and peripheral arterial obstructive disease), eye diseases, dermal affections of the hands, long-term medication influencing the autonomous nervous system (*e.g.*, β-blockers, atropine, and cardiac glycosides), treatment of chronic pain syndrome, pacemaker, and cardiac arrhythmias.

Study Design and Data Collection

Preoperative care was performed according to local standards. Upon the patient's arrival in the operation room, an intravenous access and basic monitoring with an electrocardiogram, noninvasive blood pressure, and pulse oximetry were established, and a crystalloid infusion was started. Patients received a single-shot spinal anesthesia with 15 mg bupivacaine. Next, after induction of deep propofol sedation, a laryngeal mask was inserted. Afterward, sedation was maintained by continuous bispectral index-guided propofol infusion with target values of 30 to 50. Patients received continuous noradrenaline administration with a maximum of 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to maintain mean arterial pressure above 65 mmHg.

The baseline measurements took place in a dark and silent room after a stimulus-free interval of 10 min. We recorded heart rate, mean arterial pressure, bispectral index, Analgesia Nociception Index, Surgical Pleth Index, pupil diameter, and the occurrence of nocifensive movements or coughing the minute before noxious stimulation and the peak values during the 120 s after noxious stimulation. The first stimulation was a tetanic stimulation (80 mA, 50 Hz, duration 30 s) above the ulnar side of the wrist using a neuromuscular stimulator (STIMPOD NMS450; Xavant Technology, South Africa). After the values had returned to steady baseline levels for at least 1 min, the second stimulation was an intracutaneous stimulation carried out *via* direct electric nerve provocation (80 mA, 2 Hz, duration of 30 s) applied by a finger probe with a sterile blunt metal spike in the epidermis of the fingertip after disinfection.[11–13]

We carried out the first measurements under propofol sedation only and then started remifentanil with a dose of 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This dose was subsequently increased by steps of 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ up to a maximum dose of 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (fig. 1). After each step, a period of continuous remifentanil infusion of at least 7 min was ensured before the two standardized painful stimuli were reapplied to achieve an approximation to plasma steady state. The changes in the Analgesia Nociception Index, the Surgical Pleth Index, pupil diameter, heart rate, mean arterial pressure, bispectral index, and the occurrence of nocifensive movements or coughing were recorded as described above.

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Analgesia Monitoring Devices

The two analgesic indices, the Surgical Pleth Index and Analgesia Nociception Index, as well as the pupil diameter, were recorded by analgesia monitoring devices commercially available for clinical use.

The Analgesia Nociception Index provides a numerical index between 0 and 100 analyzing the patient's heart-rate variability. R-wave detection allows real-time filtering and identification of the high-frequency component (0.15 to 0.4 Hz), which is only related to the parasympathetic system, *via* online electrocardiogram analog output from the patient monitor. This analyzing method has been described in detail earlier by Jeanne *et al.*[14] Thus, the Analgesia Nociception Index continuously displays the relative parasympathetic tone averaged over the last 68 s. Induction of stress leads to a relative sympathetic outbalance and consecutively to a decrease in the Analgesia Nociception Index.

The Surgical Pleth Index is derived based on information from waveform finger plethysmography. The proprietary algorithm uses changes of the pulse rate in combination with changes of the amplitude of the waveform for calculation of the Surgical Pleth Index. A detailed description of the underlying algorithm has been published by Huiku *et al.*[5] Nociception-antinociception balance is expressed as a numerical index between 0 (total absence of discomfort) and 100 (high stress level) with an increase after noxious stimulation. Thus, the scales of the Analgesia Nociception Index and Surgical Pleth Index are reversed, with nociception leading to an increase in the Surgical Pleth Index and a decrease in the Analgesia Nociception Index. The surgical Pleth Index, like the Analgesia Nociception Index, is visualized continuously on the display of the monitoring device after an initial learning period when placing the special finger probe on a fingertip for the first time.

Pupil diameter was measured continuously 1 min before and the 2 min after noxious stimulation with an infrared portable dynamic videopupillometer. The sampling frequency was 67 Hz (*i.e.*, a pupil diameter recorded every 15 ms) with a precision of 0.05 mm.[8] A special algorithm detects and tracks the pupil from a video recording by holding a camera close to the open eye. The device measures pupillary reflex dilation in millimeters after a nociceptive stimulus mediated by an inhibition of the parasympathetic system.[15]

Statistical Analysis

Based on previous studies, a sample size of 30 evaluable data sets was required to detect a minimal difference of 15% between pre- and poststimulation of the Surgical Pleth Index with a SD of 20%, power of 80%, and a significance level of 0.05.[9,16,17] The power analysis was done without correction for multiple comparisons.

Continuous baseline variables of the patients are expressed as the mean ± SD, categorical variables as category counts and percentages. The continuous outcome variables are the Analgesia Nociception Index, the Surgical Pleth Index, pupil diameter, heart rate, mean arterial pressure, and bispectral index, as well as the differences (Δ values) between their pre- and poststimulation values. The occurrence of hemodynamic changes, defined as an increase in heart rate or blood pressure more than 5 beats/min or 5 mmHg, respectively, or more than 10% of baseline values or the occurrence of nocifensive movements of the patients, was measured as a dichotomous outcome variable.

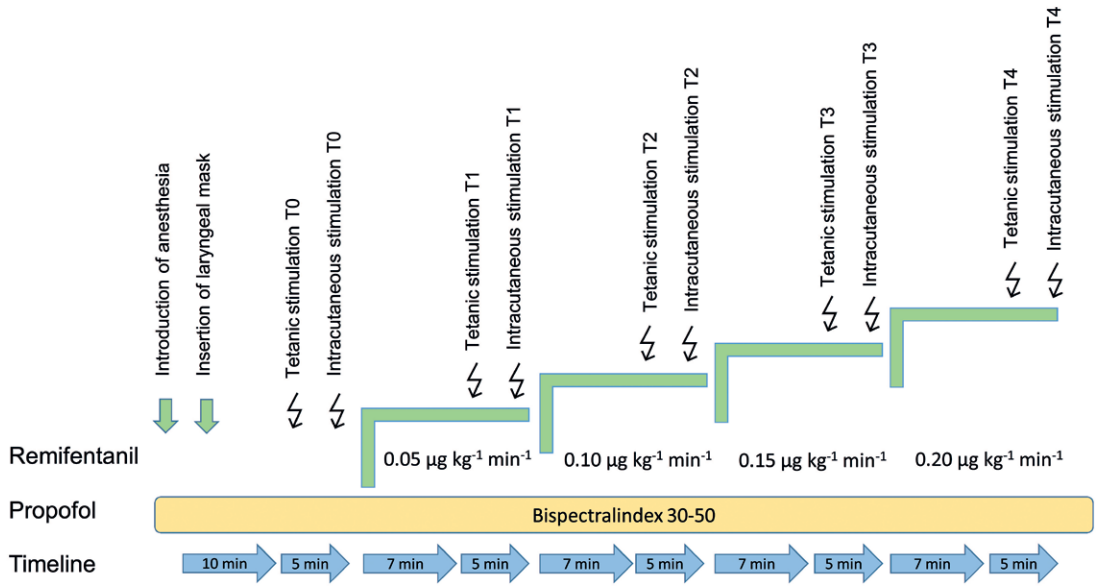

Fig. 1. Study protocol. After induction of anesthesia with propofol, a laryngeal mask was inserted. Anesthesia was maintained bispectral index–guided throughout the whole study period. The first pair of stimuli was applied after an equilibration period of about 10 min, followed by repetitive measurements of the same noxious events on four different steps of infused remifentanil (0.05 µg · kg^{-1} · min^{-1} up to 0.2 µg · kg^{-1} · min^{-1}).

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We recorded the baseline values of the Analgesia Nociception Index (ANI), the Surgical Pleth Index (SPI), pupil diameter (PD), heart rate (HR), mean arterial pressure, and bispectral index (BIS), before noxious stimulation (prestimulation) and maximum/minimum in the following 2 min after noxious stimulation (poststimulation), as well as the difference between pre- and poststimulation values (Δ). These Δ values (ΔANI, ΔSPI, ΔPD, ΔHR, ΔMAP, and ΔBIS) over time, *i.e.*, across treatment steps, are graphically displayed for each patient. The data were checked by histograms and box plots for normal distribution. ΔPD, ΔHR, and ΔBIS were ln-transformed before further analyses (ΔPD′ = ln[ΔPD + 0.03], ΔHR′ = ln[ΔHR + 15], ΔBIS′ = ln[ΔBIS + 50]; the constants 0.03, 15, and 50 ensured that the values to be transformed were more than 0) to minimize skewness and heteroscedasticity. We then performed one-sample *t* tests of the Δ values against a test value of 0 for each stimulus and treatment step. Receiver operating characteristics (ROC) curves and the associated areas under the curves (AUC) were computed to characterize the sensitivity and specificity of the Analgesia Nociception Index, the Surgical Pleth Index, pupil diameter, heart rate, mean arterial pressure, and bispectral index in detecting a standardized noxious stimulation at different remifentanil doses.[18] The asymptotic 95% CI of each AUC was calculated, as well as the asymptotic *P* value under the null hypothesis that the true AUC = 0.5.

Additionally, we calculated prediction probabilities, sensitivity, and specificity for a specific optimal threshold g to detect a noxious stimulation and to assess the ability of "prestimulation" values of the Analgesia Nociception Index, the Surgical Pleth Index, pupil diameter, and bispectral index to predict hemodynamic reactivity or nocifensive movements after the standardized noxious stimulation. Prediction probabilities (P_K) were determined by using the PK Tool as described by Jordan *et al.*[19] The PK Tool is a further development of the P_KMACRO spread sheet implemented beforehand by Smith *et al.*[20] for assessment of indicators of the level of anesthesia. P_K quantifies the association between clinically observed analgesic depth (reaction to painful stimuli) and the classifier values of analgesic monitoring. Although the AUC of ROC curves was introduced to assess a predictor of dichotomous classes (*e.g.*, consciousness and unconsciousness in anesthesia), P_K is intended for polytomous patient states (*i.e.*, more than two analgesic levels) and can be considered as a generalization of the AUC.[19] AUC and P_K values range between 0.5 and 1 with a result of 1 representing a perfect separation and prediction of the clinically observed levels of analgesia, whereas a result of 0.5 reflects mere chance. The best cutoff (reported as optimal threshold g) is the value with the maximum sum of sensitivity and specificity of the analgesic indices.[19] P_K values were calculated without accounting for repeated measures in the same individual.

The Δ values, respectively ln-transformed Δ values, were further subjected to mixed-model analyses. We specified a model with random intercepts for patients, a variance components covariance structure, and remifentanil doses considered as repeated measures within patient and stimulus. Fixed effects were stimulus, remifentanil dose, and their interaction term (remifentanil dose × stimulus type). The model computations were baseline-adjusted with prestimulus values for each remifentanil dose–stimulus type combination. Baseline-adjusted marginal means with 95% CI were computed for the Δ values of all stimulus-by-remifentanil dose combinations, followed by Bonferroni-adjusted multiple pairwise *t* test comparisons of means. The marginal means and 95% CI were back-transformed into the original scales if applicable.

Statistical analyses were performed using the SPSS statistical software package 23.0 (IBM SPSS Statistics Inc., USA), GraphPad Prism 5 (GraphPad Inc., USA), and PK Tool 1.2 (PK Tool; Department of Anesthesiology, Klinikum rechts der Isar, Technical University, Munich, Germany). Two-tailed *P* values less than 0.05 were considered significant.

Results

We initially included 46 white, European patients, who all gave informed consent, scheduled for elective open radical prostatectomy between April 4, 2015, and August 20, 2015. From these 46 patients, nine had to be excluded before entering the study protocol due to organizational or clinical issues (seven patients did not undergo surgery on the initially appointed time, and two patients required tracheal intubation with muscle relaxation), leaving 37 patients for data analysis. In these 37 patients, we recorded values before and after tetanic stimulation with the five different levels of remifentanil infusion, leading to 185 Δ values with tetanic stimulation. Due to a temporary technical failure of the intracutaneous stimulation method in eight of the 37 patients, we recorded values before and after intracutaneous stimulation in only 29 patients, leading to 145 Δ values with tetanic stimulation with a total of 330 Δ values. Patient characteristics are shown in table 1. The mean patient temperature measured by a nasal probe after induction of general anesthesia was 35.7 ± 0.4°C. None of the patients reported memory of events or stimulation during general anesthesia.

Test Quality for the Detection of Noxious Events under Propofol and Opioid Infusion

Under propofol sedation, sensitivity and specificity in ROC curves of the Analgesia Nociception Index (AUC = 0.97 and 0.99), the Surgical Pleth Index (AUC = 0.86 and 0.90), and pupil diameter (AUC = 1.00 and 0.96) for detecting tetanic and intracutaneous painful stimuli were high compared to heart rate, mean arterial pressure, and bispectral index (AUC = 0.75 and 0.74, 0.74 and 0.76, and 0.53 and 0.58; fig. 2, A and B). With the start of the remifentanil administration, AUCs decreased with increasing opioid infusion. Still, with propofol sedation and remifentanil 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, sensitivity and specificity of the Analgesia Nociception Index (AUC = 0.82

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Table 1. Patient Characteristics

Patient Characteristics	Values
Age, yr	62 ± 6
Height, cm	179 ± 5
Weight, kg	84 ± 10
BMI, kg/m^2	26 ± 3
ASA physical status class	
I	8 (22)
II	29 (78)
Preoperative medication	
Cardiovascular	9 (24)
Metabolic	8 (22)
Others	7 (19)
None	18 (49)

Data are expressed as mean ± SD for continuous data and counts (percentages) for categorical data.

ASA = American Society of Anesthesiologists; BMI = body mass index.

and 0.80), the Surgical Pleth Index (AUC = 0.73 and 0.84), and pupil diameter (AUC = 0.63 and 0.68) for detecting both painful stimuli were higher compared to heart rate, mean arterial pressure, and bispectral index (AUC = 0.52 and 0.51, 0.48 and 0.48, and 0.52 and 0.60; fig. 2, C–F). Numerical values of all time points are displayed in table 1 in Supplemental Digital Content 1 (http://links.lww.com/ALN/B453, which is a table listing the area under the curve of the receiver operating characteristics curves for the detection of noxious events).

Table 2 displays the sensitivity and specificity of the different parameters regarding the detection of a standardized painful stimulus under exclusive propofol sedation, *i.e.*, without simultaneous influence of remifentanil. The closer the P_K values are to 1.0 or 0.0, the better is the detection of the event, whereas 0.5 means mere chance.[15] P_K values for the two analgesic indices, Analgesia Nociception Index and Surgical Pleth Index, and pupil diameter (P_K = 0.98, 0.87, and 0.98, respectively) almost reached the optimum value of 1.0. The clinical parameters heart rate and mean arterial pressure (P_K = 0.74 and 0.75) were lower, whereas bispectral index (P_K = 0.55) was close to the random classifier. The best cutoff values for the tested parameters were Analgesia Nociception Index g = 38, Surgical Pleth Index g = 51, and pupil diameter g = 2.83 mm.

Test Quality for the Prediction of Hemodynamic Response or Nocifensive Movements

Hemodynamic response or nocifensive movements occurred in many patients under propofol sedation only, but the frequency declined with the onset of remifentanil infusion (table 2 in Supplemental Digital Content 2, http://links.lww.com/ALN/B454, which is a table showing the occurrence of hemodynamic response or movements). Table 3 depicts the calculated prediction probability of the two analgesic indices, pupil diameter, and bispectral index toward hemodynamic response and/or movements. None of the parameters showed P_K values higher than 0.7 (Analgesia Nociception Index: P_K = 0.7; Surgical Pleth Index: P_K = 0.63; pupil diameter: P_K = 0.67; and bispectral index: P_K = 0.67).

Association of Δ Values with the Opioid Infusion Rate

Mean values before (pre) and after (post) stimulation, as well as the resulting difference (Δ) including *P* values for the significance of changes, are shown for all measurement time points in table 4. The *P* values for the additive main effects of remifentanil dose, stimulus type, and the interaction effect of remifentanil dose × stimulus type, as resulting from mixed-model analyses, are shown in figure 3. We found a significant dose effect on Δ values of the Analgesia Nociception Index, the Surgical Pleth Index, pupil diameter, heart rate, and mean arterial pressure ($P < 0.001$) but not on bispectral index ($P = 0.216$). In addition, table 3 in Supplemental Digital Content 3 (http://links.lww.com/ALN/B455) shows Bonferroni-adjusted *P* values for multiple pairwise comparisons of remifentanil doses by stimulus type. Figures 1 and 2 in Supplemental Digital Content 4 (http://links.lww.com/ALN/B456) and 5 (http://links.lww.com/ALN/B457) depict individual course of Δ values for each patient over the study period.

Discussion

The main finding of this study is that the two analgesic indices, the Analgesia Nociception Index and the Surgical Pleth Index, as well as pupil diameter, are superior in detecting strictly standardized painful stimuli under sedation on all different analgesic levels compared to clinical signs. Bispectral index, as a parameter of sedation, was confirmed to be no marker of the analgesic level. On the contrary, baseline values of those parameters failed in predicting reaction, defined as hemodynamic responses or nocifensive movements, to noxious stimuli. Moreover, this study revealed that the often-used and easily applicable tetanic stimulation is a comparable noxious event to the direct intracutaneous stimulation of pain fibers. As expected, reactions to both stimuli diminished with increasing remifentanil dosages. All parameters except for bispectral index correlated with the dosage of infused opioid. The mixed-model approach adjusted for within-patient effects due to repeated measurements of individual reactions to noxious stimulation.

To date, determining the optimal dosage of analgesics in unconsciousness still remains challenging. So far, analgesics are initially calculated considering patient-related factors (*e.g.*, age, codiseases) and determinants of planned surgical procedures (*e.g.*, duration, nociceptive intensity). In the further course of surgery, opioids are titrated by clinical signs of pain caused by activation of the autonomic nervous system. On the one hand, overdosage leads to longer[21] and less-comfortable recovery periods[22] and accumulation of side effects and may cause opioid-induced hyperalgesia.[1,2] On the other hand, sufficient analgesia is desirable to reduce the release of stress hormones,[23] to avoid nocifensive movements, and to achieve more hemodynamic stability.[24] Because individual quantification of pain during general anesthesia is not

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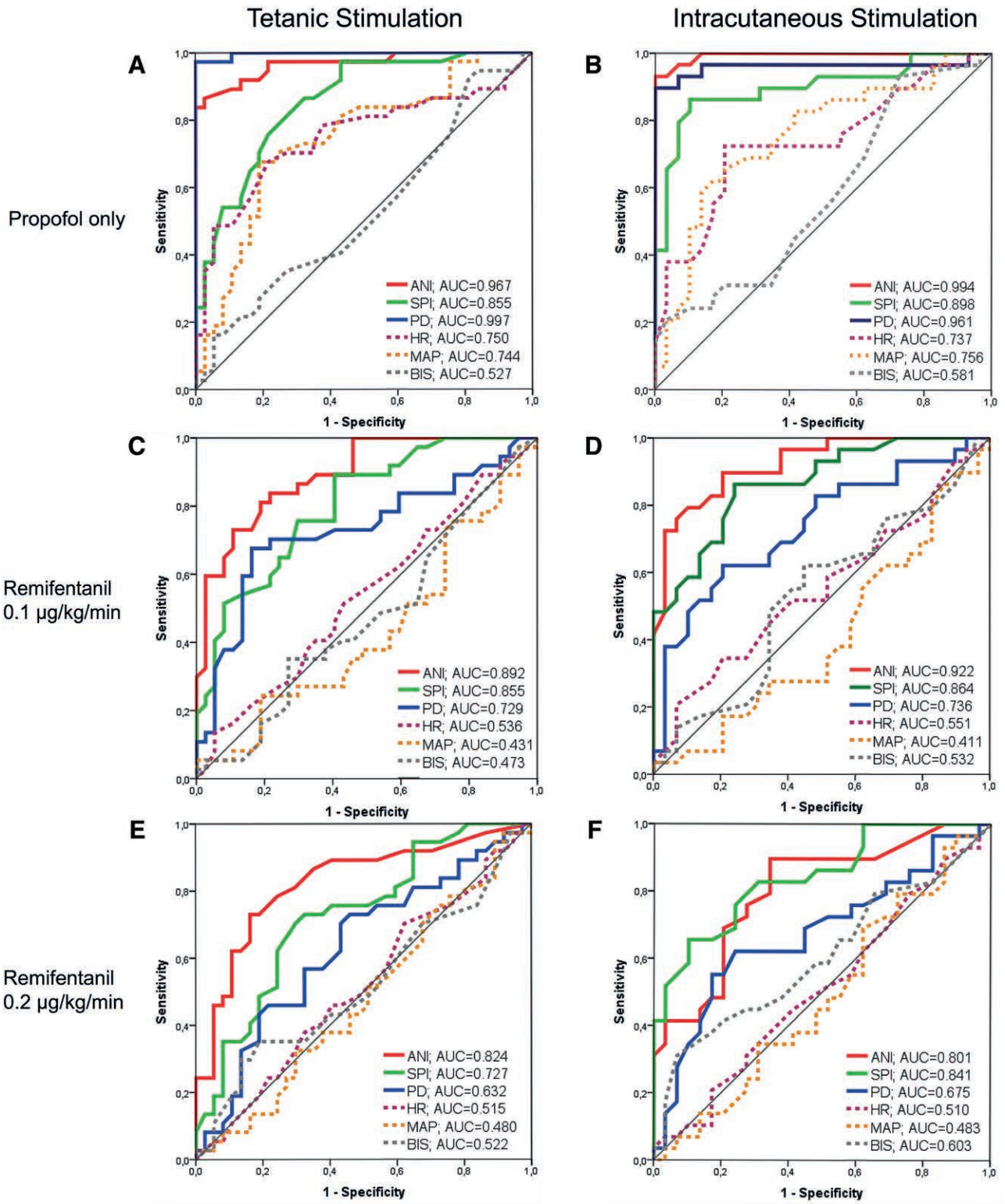

Fig. 2. Comparative receiver operating characteristic (ROC) curves of the two indices Analgesia Nociception Index (ANI) and Surgical Pleth Index (SPI), as well as pupil diameter (PD), displayed directly next to the clinical parameters heart rate (HR) and mean arterial blood pressure (MAP) and the parameter of hypnosis bispectral index (BIS) for the reaction toward noxious stimulation. (*A*, *B*) Measurements with propofol only (no infused analgesic). (*C*, *D*) Remifentanil infusion at 0.1 µg · kg^{-1} · min^{-1}. (*E*, *F*) Remifentanil infusion at 0.2 µg · kg^{-1} · min^{-1}. The *left column* (*A*, *C*, *E*) shows the area under the curve (AUC) from the ROC curves for tetanic stimulation, whereas the *right column* (*B*, *D*, *F*) shows ROC curves for intracutaneous stimulation.

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Table 2. Sensitivity and Specificity in Detecting a Standardized Painful Stimulus without Opioid Administration

Variable	P_K (95% CI)*	Threshold g†	Sensitivity, %	Specificity, %
ANI	0.98 (0.96, 1.00)	38	87.9	98.5
SPI	0.87 (0.80, 0.93)	51	74.2	86.4
PD	0.98 (0.95, 1.00)	2.83	93.9	100
HR	0.74 (0.65, 0.82)	69	71.2	71.2
MAP	0.75 (0.66, 0.83)	81	65.2	81.8
BIS	0.55 (0.50, 0.65)	36	19.7	92.4

*Prediction probability with 95% CI for predicting hemodynamic response (defined as an increase in heart rate or blood pressure > 5 beats/min or > 5 mmHg, respectively, or > 10%) and/or movements. †Optimum of sensitivity and specificity to detect a noxious stimulation (intracutaneous or tetanic; n_{total} = 330).

ANI = Analgesia Nociception Index; BIS = bispectral index; HR = heart rate; MAP = mean arterial blood pressure; PD = pupil diameter; P_K = prediction probability; SPI = Surgical Pleth Index; Threshold g = optimum of sensitivity and specificity.

Table 3. Prognostic Power in Predicting Hemodynamic Response or Movements

Variable	P_K (95% CI)*	Threshold g†	Sensitivity, %	Specificity, %
ANI	0.70 (0.64, 0.76)	92	20.6	46.8
SPI	0.63 (0.56, 0.70)	29	70.1	57.5
PD	0.67 (0.60, 0.74)	2.1	45.4	87.1
BIS	0.67 (0.57, 0.70)	26	34.0	42.1

*Prediction probability with 95% CI for predicting hemodynamic response (defined as an increase in heart rate or blood pressure > 5 beats/min or > 5 mmHg, respectively, or > 10%) and/or movements. †Optimum of sensitivity and specificity to detect a noxious stimulation (intracutaneous or tetanic; n_{total} = 330).

ANI = Analgesia Nociception Index; BIS = bispectral index; PD = pupil diameter; P_K = prediction probability; SPI = Surgical Pleth Index; Threshold g = optimum of sensitivity and specificity.

possible due to unconsciousness of the patient, visualizing the balance between nociception and antinociception is the underlying mechanism for assessment of reaction to a painful stimulus in different monitoring systems. Whereas monitoring of depth of hypnosis by electroencephalography monitoring is nowadays more and more daily clinical routine, measurement of nociception is still not standardized. Different monitoring techniques have been developed to more accurately quantify the current status of nociception and antinociception balance as an index value and have been tested by standardized, reproducible noxious stimuli. Because no proper direct comparison between different monitoring methods has existed so far, until today it remained unclear which one of the indices is the most useful in clinical practice.[25]

For the two analgesic indices, the Analgesia Nociception Index and the Surgical Pleth Index, and pupil diameter, previous studies showed that changes in the nociception antinociception balance caused by a noxious stimulus were detectable by the different techniques.[6,7,10,26,27] The current study reinforces these findings (table 4). Furthermore, this effect is preserved on different analgesic levels (fig. 2). Additionally, indices were superior in detecting both painful stimuli under sedation compared to clinical signs even on higher rates of infused opioids. Clinical signs as markers of vegetative response, in contrast, have been repetitively reported as being unspecific and insensitive. They are affected by many confounders (autonomic, hormonal, or metabolic changes) and may differ individually.[28,29] Accordingly, with the start of infusion of opioids (even in a very low dosage of 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$) a strong stimulus could not be detected by changes in mean arterial pressure or heart rate anymore. Likewise, bispectral index, as a marker of sedation and therefore functioning as a negative control, did not correlate with noxious stimulation and was therefore confirmed to be no indicator of the analgesic level (table 2). This is also in line with the results of previous studies.[17]

Noxious stimulation during surgery occurs in many different ways, such as the direct trauma of peripheral nervous fibers, heat (*e.g.*, by coagulation), or acidosis (tissue hypoxia). Generation of a stimulus with reproducible intensity is a prerequisite for judgment in how far techniques of pain evaluation are reliable. Recent studies often used tetanic stimulation with good reproducibility. It remains unclear how far a muscular contraction is comparable to direct stimulation of pain fibers. Therefore, studies extended the investigation of indices after tetanic stimulation to events such as skin incision and intubation.[10] Obviously, this leads to a loss in comparability and reproducibility. Hence, we use Bromm's pain model, which evokes clear pinprick pain as noxious stimulation directly at the respective receptors of Aδ- and C-fiber terminals.[11] Due to the good neurophysiologic evaluation of this model revealing neuroanatomic locations of noxious sensations, it can be considered a proven model of pain.[12] In addition, this model was validated in awake patients, and pain-evoked potentials correlated with the patient's indication of painful stimulation.[13] In the current study, both tetanic and intracutaneous stimulation led to changes of analgesic parameters and clinical signs to a similar extent (fig. 2). This strengthens the assumption that tetanic stimulation is a valid and reproducible stimulus, although pain fibers are not directly activated.

Further, it would be clinically very helpful to be able to anticipate whether an upcoming noxious event would cause a painful sensation. Therefore, we investigated how far baseline values of the two indices, as well as pupil diameter and bispectral index, may serve as predictors for hemodynamic alterations or nocifensive movements after a noxious stimulation. None of the parameters allowed this prediction (table 3). On the one hand, previous studies showed that high baseline values, indicating a shift toward high nociceptive status before stimulation, were associated with reaction to a following surgical stimulus.[30,31] More recent studies, on the other hand, found that Δ values, but not the baseline values before noxious stimulation, had a predictive value for reactions.[9,10,32,33] However, predicting the response to a surgical stimulation during

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Table 4. Δ Values

Remifentanil Dose, μg · kg^{-1} · min^{-1}	Variable	Mean (95% CI) Pre Value	Post Value	Δ*	*P* Value†
Tetanic stimulation (n = 37)					
0 (Propofol only)	ANI	67 (61, 73)	25 (21, 29)	−42 (−48, −36)	< 0.001
	SPI	37 (32, 42)	60 (55, 65)	23 (19, 26)	< 0.001
	PD	2.2 (2.0, 2.3)	5.7 (5.3, 6.1)	3.3 (2.9, 3.7)	< 0.001
	HR	64 (60, 67)	73 (69, 78)	8 (6, 11)	< 0.001
	MAP	77 (74, 80)	85 (82, 88)	8 (7,10)	< 0.001
	BIS	26 (24, 28)	28 (25, 30)	1 (0, 3)	0.105
0.05	ANI	86 (8, 90)	42 (36, 48)	−44 (−50, −38)	< 0.001
	SPI	29 (25, 32)	53 (47, 58)	24 (20, 28)	< 0.001
	PD	1.9 (1.8, 2.0)	2.5 (2.3, 2.7)	0.4 (0.3, 0.6)	< 0.001
	HR	56 (53, 59)	60 (56, 63)	3 (2, 5)	< 0.001
	MAP	81 (77, 85)	79 (76, 83)	−2 (−3, −0.1)	0.044
	BIS	27 (25, 29)	30 (2, −33)	2 (0, 5)	0.058
0.1	ANI	88 (84, 92)	60 (54, 66)	−28 (−33, −24)	< 0.001
	SPI	30 (27, 34)	46 (41, 51)	16 (12, 20)	< 0.001
	PD	1.9 (1.8, 2.0)	2.1 (2.0, 2.2)	0.2 (0.1, 0.2)	< 0.001
	HR	53 (51, 56)	54 (51, 57)	0.5 (−0.4, 1.4)	0.325
	MAP	78 (74, 81)	76 (72, 79)	−2 (−4, 0)	0.031
	BIS	31 (28, 34)	30 (27, 33)	−1 (−1, 3)	0.508
0.15	ANI	90 (87, 93)	72 (66, 78)	−18 (−22, −13)	< 0.001
	SPI	29 (25, 33)	43 (37, 48)	14 (9, 18)	< 0.001
	PD	1.8 (1.7, 1.9)	2.0 (1.9, 2.1)	0.1 (0.1, 0.2)	< 0.001
	HR	51 (48, 53)	52 (49, 54)	1 (−0.1, 1)	0.091
	MAP	74 (71, 78)	73 (70, 77)	−1 (−3, 1)	0.248
	BIS	31 (28, 33)	30 (27, 32)	−1 (−3, 0)	0.153
0.2	ANI	92 (89, 95)	72 (66, 79)	−20 (−24, −15)	< 0.001
	SPI	31 (27, 35)	42 (37, 47)	11 (8, 15)	< 0.001
	PD	1.9 (1.8, 2.0)	2.0 (1.9, 2.1)	0,1 (0.1, 0.1)	< 0.001
	HR	49 (47, 52)	50 (48, 52)	0 (−0, 1)	0.078
	MAP	74 (70, 78)	74 (70, 77)	−1 (−2, 0)	0.222
	BIS	30 (28, 33)	31 (29, 34)	1 (0, 2)	0.208
Intracutaneous stimulation (n = 29)					
0 (Propofol only)	ANI	75 (69, 81)	26 (22, 30)	−48 (−54, −43)	< 0.001
	SPI	35 (30, 40)	68 (61, 75)	33 (28, 38)	< 0.001
	PD	2.15 (2.0, 2.3)	4.97 (4.5, 5.4)	2.3 (1.7, 3.1)	< 0.001
	HR	63 (59, 66)	72 (68, 77)	8 (6, 11)	< 0.001
	MAP	77 (73, 80)	86 (82, 90)	9 (5, 13)	< 0.001
	BIS	27 (25, 29)	30 (27, 34)	2 (1, 5)	0.138
0.05	ANI	84 (79, 88)	35 (30, 40)	−49 (−55, −43)	< 0.001
	SPI	29 (25, 33)	63 (57, 69)	34 (30, 38)	< 0.001
	PD	1.9 (1.8, 2.0)	2.3 (2.2, 2.5)	0.4 (0.3, 0.5)	< 0.001
	HR	57 (54, 60)	61 (57, 64)	3.8 (2.4, 5.2)	< 0.001
	MAP	81 (76, 85)	79 (75, 83)	−1 (−4, −1)	0.269
	BIS	33 (29, 36)	33 (30, 36)	0 (−2, 3)	0.716
0.1	ANI	87 (82, 91)	54 (47, 60)	−33 (−40, −26)	< 0.001
	SPI	30 (25, 34)	55 (48, 62)	25 (20, 30)	< 0.001
	PD	1.9 (1.8, 2.0)	2.1 (2.0, 2.2)	0.2 (0.2, 0.3)	< 0.001
	HR	54 (51, 57)	55 (52, 58)	0 (0, 2)	0.224
	MAP	78 (74, 82)	75 (71, 79)	−3 (−5, −1)	0.003
	BIS	33 (30, 37)	35 (31, 39)	2 (0, 4)	0.126
0.15	ANI	88 (83, 93)	65 (58, 71)	−24 (−29, −18)	< 0.001
	SPI	31 (26, 36)	51 (45, 58)	20 (16, 25)	< 0.001
	PD	1.8 (1.7, 2.0)	2.0 (1.9, 2.1)	0.1 (0.1, 0.2)	< 0.001
	HR	51 (49, 54)	52 (49, 54)	1 (0, 1)	0.019
	MAP	74 (70, 78)	73 (69, 78)	−1 (−3, 1)	0.424
	BIS	32 (29, 34)	34 (30, 37)	1 (−1, 3)	0.249

(*Continued*)

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Table 4. (Continued)

Remifentanil Dose, μg · kg^{-1} · min^{-1}	Variable	Mean (95% CI) Pre Value	Post Value	Δ*	*P* Value†
0.2	ANI	91 (86, 95)	73 (66, 80)	−18 (−23, −13)	< 0.001
	SPI	30 (26, 34)	50 (44, 57)	20 (16, 24)	< 0.001
	PD	1.9 (1.8, 1.9)	2.0 (1.9, 2.0)	0.1 (0.1, 0.1)	< 0.001
	HR	50 (48, 53)	50 (48, 53)	0 (0, 0)	0.548
	MAP	74 (69, 78)	73 (69, 76)	−1 (−2, 1)	0.270
	BIS	31 (28, 34)	34 (31, 38)	3 (1, 5)	0.003

Shown are the Analgesia Nociception Index (ANI), Surgical Pleth Index (SPI), pupil diameter (PD), heart rate (HR), mean arterial blood pressure (MAP), and bispectral index (BIS) values before and after the two standardized tetanic (n = 37 patients) and intracutaneous (n = 29 patients) noxious stimulations. The results are expressed as means (95% CI) and are based on back-transformed values, if applicable.

*Δ is the difference between the value before the standardized noxious test (pre value) and the value after the standardized noxious test (post value) of each variable. †*P* values are derived from a one-sample *t* test and indicate whether the Δ values are significantly different from 0.

general anesthesia becomes possible with intermittent testing of the patient's nociception with painful stimulations. So far, the clinical utility seems to be limited to situations in which the anesthesiologist is able and willing to administer a routine pain stimulus at regular intervals to evaluate the Δ values in the chosen analgesia monitoring. For example, measuring pupil diameter has been previously proven to be of clinical use for the prediction of the patient's reactions.[27]

The observed effects of all indices changed by administration of opioids. Δ values decreased by an increase of analgesics except for bispectral index (fig. 3), which is in line with previous studies.[6,9,15] However, this study detected differences between the indices by direct comparison (fig. 2). The Analgesia Nociception Index showed the highest sensitivity in detecting tetanic stimulation on all remifentanil levels. Although the Analgesia Nociception Index and pupil diameter did not detect intracutaneous stimulation as reliably during high doses of infused opioid, compared to no or low doses of infused opioid, the Surgical Pleth Index detected intracutaneous stimulation with consistent power also with higher dosages of infused opioid. The pupil diameter was the index with the highest sensitivity and specificity in detecting stimuli under propofol sedation only (table 2). However, there was an extinction beginning already at intermediate dosage of opioids, which could be revealed by mixed-model analysis. Due to individual factors and limitations of the different measuring methods, there is no general superiority of one of the monitoring methods. Although pupil diameter seems to be the most sensitive and specific indicator for noxious events under light analgesia, the Analgesia Nociception Index and the Surgical Pleth Index also display reliably analgesic status on higher levels of infused opioids. Bispectral index clearly was not associated with the presence or absence of analgesic medication in general anesthesia and should therefore not be used to decide on the application of analgesic medication.

Given the limitations of a clinical study, one has to consider the artificial, stimulus-reduced setting (dark and silent room). Confounders such as noise, light, or other sensoric stimuli had been reduced to a very low level. Hereby, and by the study protocol with defined points in time for documentation of values, false-positive events were potentially eliminated. Furthermore, only American Society of Anesthesiologists physical status class I and II patients participated in this study. This led to an automatic exclusion of patients with frequent comorbidities and complex combinations of medication in their medical history. In addition, relevance for opioid consumption and perioperative periods remains unclear. Although there is some evidence that consumption of analgesics, hypnotics, and the time to extubation can be reduced by analgesia index-guided anesthesia,[21] reduction in postoperative pain and long-term benefits, such as shorter stay in recovery room and reduction in postoperative opioid consumption, have not been observed.[17,21,34,35] However, intraoperative stress-hormone levels correlated with the Surgical Pleth Index.[23]

In conclusion, using one of the three parameters, the Analgesia Nociception Index, the Surgical Pleth Index, and pupil diameter, in anesthetized patients helped to visualize the current balance between nociception and antinociception. The changes observed are attenuated by increasing dosages of remifentanil. Moreover, tetanic stimulation is validated as a noxious stimulation that is equivalent to the intracutaneous pain model by Bromm *et al.* and can be used in future studies on analgesia during general anesthesia. This might help to improve the application of opioids to the dose needed. Because a prediction of reaction to surgical stimulation from baseline values is not possible, intermittent stimulation to test the patient's responsiveness seems reasonable and may increase the diagnostic value of the monitoring methods.

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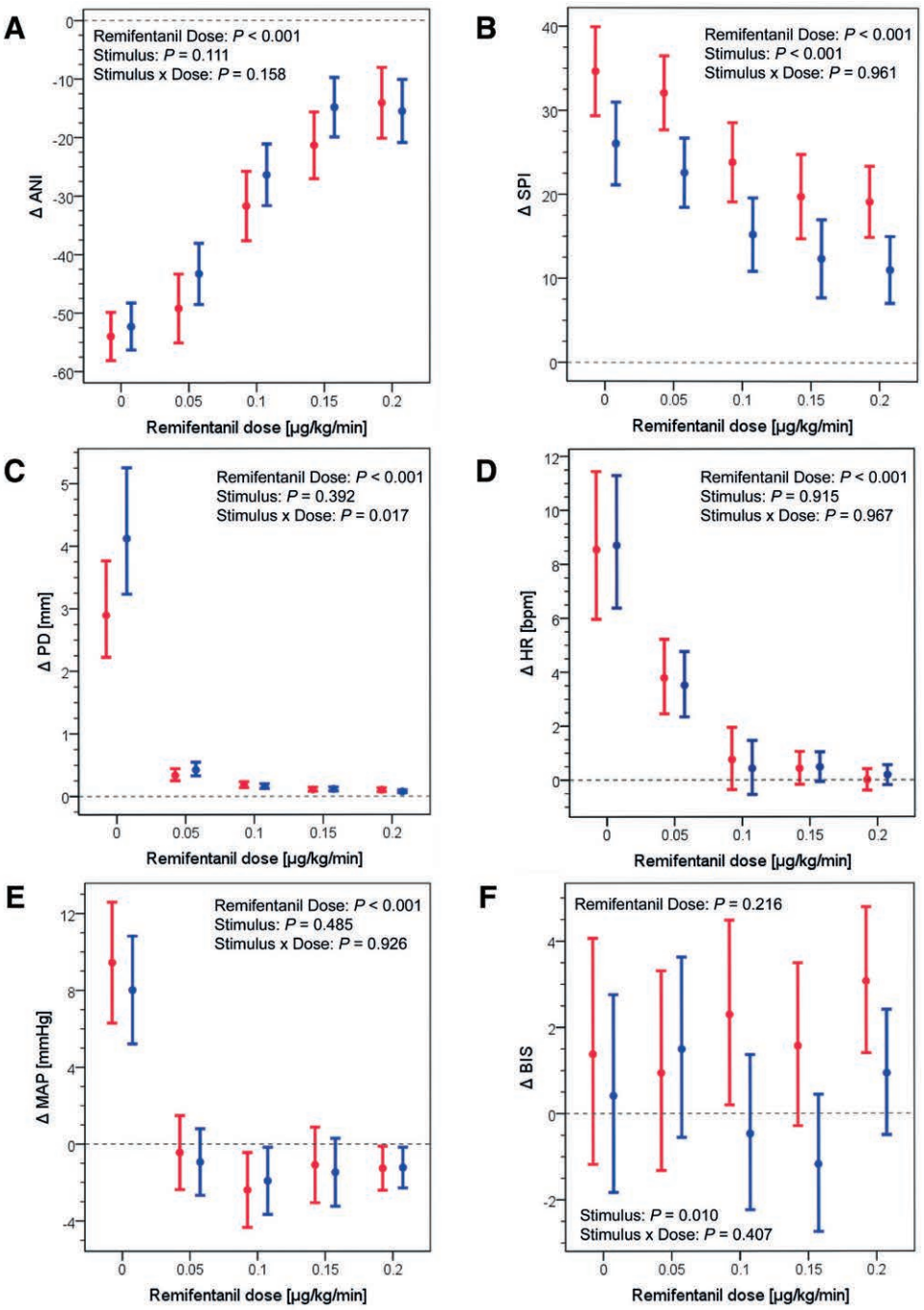

Fig. 3. Baseline-adjusted marginal means with 95% CI of the Δ values of all stimulus-by-remifentanil dose combinations as determined by mixed models. Values for differences in pupil diameter (ΔPD), heart rate (ΔHR), and bispectral index (ΔBIS) are based on back-transformation as: ΔPD = e(ΔPD′) + 3.50656, ΔHR = e(ΔHR′) − 2.70805, and ΔBIS = e(ΔBIS′) − 3.91202 (see Materials and Methods for transformation of variables). *Red bars* indicate tetanic stimulation, and *blue bars* indicate intracutaneous stimulation. *P* values are for the additive main effects of remifentanil dose, stimulus type, and the interaction effect of remifentanil dose × stimulus type. ANI = Analgesia Nociception Index; MAP = mean arterial blood pressure; SPI = Surgical Pleth Index.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: s.funcke@uke.de. Raw data available at: s.funcke@uke.de.

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