Monitoring anesthesia: Optimizing monitoring strategies to reduce adverse effects of anesthetic drugs on ventilation

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Citation

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Title: Monitoring anesthesia: Optimizing monitoring strategies to reduce adverse effects of anesthetic drugs on ventilation
Issue Date: 2020-12-01

CHAPTER 3

Ability of the nociception level, a multiparameter composite of autonomic signals, to detect noxious stimuli during propofol-remifentanil anesthesia

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Introduction

Accurate measurement of nociception during anesthesia remains a challenging task. Nociception, which is defined as the neural process of encoding and processing noxious stimuli (noxious stimuli are actually or potentially tissue damaging events)(1), will elicit behavioral, autonomic and hormonal responses in conscious and unconscious individuals. Detection of behavioral responses during anesthesia is often impossible because of the use of muscle relaxants. Hence, we rely mostly on the autonomic responses to assess the nociception level (NoL) of the patient. Most anesthesia healthcare providers, if not all, use changes in heart rate (HR) and blood pressure as markers of the occurrence of acute nociceptive events. Although these variables may suffice when intense nociceptive stimuli occur, mild and moderate stimuli are often not detected or detected too late(2). In recent years, various indices of nociception have been developed with varying success in actually detecting nociceptive events. These indices derive a numerical value from single variables (such as heart rate variability [HRV], skin conductance, skin vasomotor reflex, the electroencephalogram, pupil diameter) or a combination of signals(3–11). In the current study, we apply a new index of nociception, the NoL index(2). The NoL is a multiparameter nonlinear combination of HR, HRV, amplitude of the finger photoplethysmogram (AP), skin conductance level, fluctuations in skin conductance and their time derivatives, derived from random forest regression. Random forest is an algorithmic modeling approach that enables combining multiple parameters of different origin and discovering their complex nonlinear interactions(12,13). We measured the NoL, HR, and arterial blood pressure during induction of general propofol–remifentanil anesthesia, intubation, and incision. Our aims were to validate the NoL as measured in real time by assessing its ability to detect moderate and intense nociceptive stimuli under different target remifentanil blood concentrations. The NoL was compared with the more commonly used indices of nociception, mean arterial pressure (MAP), and HR.

Materials and Methods

The protocol was performed after obtaining approval from the local Human Ethics Committee Commissie Medische Ethiek, Leiden University Medical Center, Leiden, The Netherlands) and was registered at www.clinicaltrials.gov under number NCT01912118. All patients gave oral and written informed consent before enrolment into the study. The study was performed from July 2013 to June 2014.

Patients
American Society of Anesthesiology class I, II, or III patients (age, 18 to 80 yr) of either sex, scheduled for elective surgery under general anesthesia, were recruited to participate

in the study. Exclusion criteria included inability to give informed consent, pregnancy or lactation, body mass index more than 35 kg/m2, perceived difficult intubation, planned rapid sequence intubation, and use of β-adrenergic receptor antagonists. Preoperative preparation was according to local protocol.

Study Design

In this prospective randomized study, patients received total intravenous anesthesia with propofol and remifentanil. Seventy-two patients were randomly assigned to one of six possible remifentanil target concentrations: 0 (propofol only, n = 12), 1, (n = 12), 2 (n = 12), 3 (n = 12), 4 (n = 12), and 5 (n = 12) ng/ml, using a custom-built remifentanil target controlled infusion pump (Remifusor, University of Glasgow, United Kingdom) programmed with the remifentanil pharmacokinetic dataset published by Minto *et al.*(14). Similarly, propofol was infused using a target-controlled infusion system (Orchestra Base Primea, Fresenius Kabi, The Netherlands) programmed with the propofol pharmacokinetic dataset published by Marsh *et al.*(15). The target was adapted such that before intubation or skin incision the bispectral index (BIS) of the electroencephalogram (BISR VISTA, Covidien, Ireland) was maintained at 45 ± 5 for at least 10 to 15 min. If needed, a muscle relaxant (rocuronium, 0.5 mg/kg) could be given before intubation.

In the protocol, there were two additional study groups (n = 12, BIS, 70; remifentanil, 3 ng/ml; and n = 12, BIS, 30; remifentanil, 3 ng/ml). After enrollment of four subjects in this subprotocol, further inclusion of subjects was stopped because of safety concerns (*e.g.*, possibility of awareness, hemodynamic instability).

Data Collection

A finger probe containing sensors for measurement of the photoplethysmogram, the Galvanic skin response, skin temperature, and three-axis accelerometer was placed on the index finger of the right hand (Medasense Biometrics, Israel)(2,16). The signals from the probe were sampled at 50 Hz and recorded on a laptop computer using the PMD-10X system and software (Medasense Biometrics). All data were processed offline using MATLAB R2011b software (The Mathworks Inc., USA). The following variables were calculated from the finger probe as specified by Ben-Israel *et al.*(2): HR, HRV, AP, skin conductance level, and fluctuations in skin conductance. To measure the noninvasive beat-to-beat blood pressure, an appropriately sized finger cuff was applied to the mid-phalanx of the left index finger, which was connected to a Nexfin monitor (Edwards Lifesciences, USA). Refer the study by Martina *et al.*(17) for an elaborate explanation of the Nexfin system and calculation of blood pressure. The beat-to-beat finger arterial blood pressure was stored on disc for offline analysis. The PMD-10X and the Nexfin systems were time aligned before each study. Data were collected from induction of anesthesia until 3 to 5 min after incision. Specific events occurring during the study (start of induction, patient movement,

intubation, and incision) were logged in the PMD-10X software program enabling a direct link between stimulus and measurements.

Description of the Nociception Level Index

The NoL is based on a nonlinear combination of nociception-related physiologic parameters: HR, HRV (at the 0.15 to 0.4 Hz band power), amplitude of the photoplethysmograph wave, skin conductance level, number of skin conductance fluctuations, and their time derivatives(2). The NoL index was developed to correlate with a reference clinical score of nociception based on the estimated opioid concentration and stimulus strength (*i.e.*, the combined index of stimulus and analgesia [CISA]). A composite parameter was derived from random forest analysis(12,13), a nonlinear regression method, in which the physiologic signals with their derivatives were used as predictor variables and the CISA was used as the observed variable. The estimated multiparameter composite derived from the regression analyses was scaled from 0 to 100 to produce the NoL. The NoL index has been shown to provide a better indication of nociception than each of its component physiologic signals and to their linear combination(2). In the current study, the NoL index was calculated from the extracted signals by the PMD-10X software/hardware system using the algorithm derived from the learning study by Ben-Israel *et al*.(2). The NoL device has not received Food and Drug Administration clearance as yet and is still under investigation.

Data Analysis

Because this study was the first assessment of the NoL in a clinical perioperative setting using total propofol/remifentanil anesthesia, we were uninformed regarding the possible effect sizes of the three stimuli on the NoL. We somewhat arbitrarily set the sample size at 12 subjects per remifentanil treatment level or 72 patients in total, a number very similar to several previous studies linking physiologic signals to nociception(9,11). Statistical and data analyses were performed using MATLAB R2011b software (The Mathworks Inc.). Three distinct stimuli were defined in each patient: a nonnoxious event, incision, and intubation, which were regarded as nonnoxious, moderate noxious, and severe noxious stimuli, respectively(2,18,19). We graded the nociceptive intensity, nonnoxious event > incision > intubation, based on the previous studies that showed that the opioid concentration needed to suppress the autonomic response to intubation exceeds the concentration required to suppress the response to skin incision by a factor of (2.18,19). A nonnoxious event was defined as a 1-min interval within a 5-min window of absence of noxious stimulation; intubation was defined as the time interval around the insertion of the oropharyngeal tube into the trachea and included the preceding laryngoscopy; incision was defined as the time interval around the surgical skin incision. For each stimulus, two parameter values were defined, one before stimulation (before) and one after stimulation (after), which were the average of data before and after the stimulus along a certain

time interval. These time intervals were the first (before) and last (after) 30 s of the 1-min nonnoxious interval for the nonnoxious stimulus and the 30 to 60s before the stimulus (before) and the 10 to 180 s after the stimulus (after) for incision and intubation. Analysis was done on both the absolute MAP, HR, and NoL values and the difference between after and before values (*i.e.*, Δ). In case of use of vasoactive (*e.g.*, ephedrine and phenylephrine) and vagolytic (*e.g.*, atropine) drugs in these time windows, the data were discarded.

Statistical Analysis

The following statistical tests were performed to compare the performance of NoL, ΔNoL, MAP, ΔMAP, HR, and ΔHR:

1) Right-tailed paired *t* test to assess whether the average reaction (Δ) of the three variables to stimulation are significantly greater than 0. Two-tailed unpaired *t* test to assess whether the population values of the variables after stimulation were significantly different from the values obtained before stimulation. In addition, the effect of stimulation on BIS was tested using paired and unpaired *t* tests.

2) Receiver operating characteristic (ROC) curves were constructed to assess the ability of the individual variables (absolute values and Δ) to discriminate between noxious and nonnoxious events. CIs of the area under the ROC curves (AUCs) were calculated using the method suggested by Hanley and McNeil,20 which corrects for the use of correlated data.

3) Repeated measures ANOVA to test the ability of each of the variables to grade noxious stimuli, *i.e.*, to assess whether the variable values increased with an increasing stimulus strength: nonnoxious stimulus < moderate noxious stimulus (incision) < intense noxious stimulus (intubation). In case of a significant main and interaction terms, a Scheffe *post hoc* multiple comparison test was applied to test between pairs nonnoxious stimulus *versus* intubation, nonnoxious stimulus *versus* incision, and incision *versus* intubation.

4) For nonnoxious stimuli and intubation, the Spearman correlation coefficient was calculated to quantify the relation between HR, MAP, NoL, and the remifentanil target concentration. This was done separately for time intervals before and after stimulation. A quadratic polynomial was fitted by least square analysis to the data.

Results

Seventy-two patients participated in the study according to protocol (data from the subprotocol are not considered here). The characteristics of the 72 participating patients are given in Table 1. The complete dataset of one subject was lost because of technical problems. The data from 71 patients were used in the analysis. All patients completed the study without side effects. In about half of the patients, a muscle relaxant was administered before intubation. Before noxious stimulation (intubation/skin incision), BIS values were

on average of 45.0 ± 9.0 (mean ± SD), 45.6 ± 9.9, 47.2 ± 9.1, 42.6 ± 7.4, 44.7 ± 8.0, and 47.0 ± 9.8 in the 0, 1, 2, 3, 4 and 5 ng/ml remifentanil groups, respectively (repeated measures ANOVA: $P > 0.05$; grand mean, 45.5 ± 8.8). Because of technical (*e.g.*, monitor failure), logistic (*e.g.*, change of surgical plan), or other reasons (*e.g.*, hypertension/ hypotension or bradycardia in response to low/high remifentanil requiring the use of vasoactive/vagolytic drugs; lack of annotations) that caused an inadvertent breach of protocol, the datasets missed one of the noxious/nonnoxious stimuli in 20 to 25% of cases. The numbers of excluded events are given in Table 2.

Table 1. Patient characteristics for the six study groups and performed surgical procedures.

	REMI 0	REMI 1	REMI 2	REMI 3	REMI 4	REMI 5	ALL
n	12	12	12	12	12	12	72
M/F	6/6	3/9	9/3	4/8	3/9	8/4	33/39
Age (yrs) (range)	43 (20-75)	57 (24-74)	56 (37-69)	55 (21-74)	54 (26-76)	54 (31-73)	54 (20-76)
Height (cm)	176 ± 1	169 ± 6	181 ± 9	171 ± 9	170 ± 9	176 ± 13	174 ± 10
Weight (kg)	81 ± 16	67 ± 12	84 ±15	70 ± 11	69 ± 12	79 ± 16	75 ± 15
BMI	26 ± 5	24 ± 4	26 ± 4	24 ± 3	24 ± 3	26 ± 4	25 ± 4
Heart rate (bpm)*	79 ± 10	74 ± 15	72 ± 15	73 ± 10	70 ± 13	74 ± 18	73 ± 14
MAP (mmHg)*	90 ± 12	99 ± 14	96 ± 14	101 ± 19	96 ± 18	100 ± 10	97 ± 15
ASA 1 (*n*)	7	5	5	5	9	8	39
ASA 2 (*n*)	5	6	7	7	3	4	32
ASA 3 (*n*)	0	1	0	0	0	0	1
General surgery (*n*)	4	4	5	5	4	8	30
Gynecology (*n*)	4	4	2	1	1	4	16
Urology (*n*)	3	2	3	2	1		11
Orthopedics (*n*)	1		1		2		4
ENT (*n*)		1		1	2		4
Neurosurgery (*n*)		1					1
Oral surgery (*n*)			1				1
Plastic surgery (*n*)				3	2		5

All values are represented as mean ± SD or numbers (n), except age, which is represented as median (range).
*Values obtained at patient screening in the preoperative clinic.
ASA = American Society of Anesthesiologists; BMI = Body Mass Index; ENT = ear, nose and throat surgery; F = female; M = male; MAP = mean arterial pressure; REMI = remifentanil target concentration.

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Table 2. Reason for missing or discarded data

	Device	Number of subjects included in the analysis	Number of subjects with missing data
			A / B /C
Non-noxious stimulus	PMD-10X™	63	0 / 0 / 9
	Nexfin device	56	7 / 0 / 9
	BIS monitor	56	7 / 0 / 9
Incision	PMD-10X™	58	1 / 5 / 8
	Nexfin device	53	3 / 5 / 8
	BIS monitor	56	3 / 5 / 8
Intubation	PMD-10X™	67	0 / 2 / 3
	Nexfin device	65	2 / 2 / 3
	BIS monitor	66	1 / 2 / 3

A = technical problems, B = clinical issues (hypotension/hypertension/bradycardia) and
C = lack of annotation; BIS is the bispectral index of the electroencephalogram.

Response to Noxious Events

The effect of nonnoxious stimuli, incision, and intubation on BIS, HR, MAP, and NoL are given in figure 1. Nonnoxious stimuli had no effect on any of the variables when comparing before with after time intervals (mean difference [95% CI]): ΔBIS, −0.1 (−0.9 to 0.7); ΔHR, −0.13/min (−0.7 to 0.3/min); ΔMAP, −0.45 mmHg (−1.9 to 2.1 mmHg); and ΔNoL −1.1 (−3.6 to 2.0). Intubation caused an increase in HR, MAP, and NoL but not BIS: ΔBIS, 1.7 (−3.9 to 6.3; not significant [ns]); ΔHR, 7.0/min (1.4 to 12.0/min; paired t test, $P < 0.001$; unpaired t test, $P < 0.001$); ΔMAP, 13.0 (3.1 to 20; paired t test, $P < 0.001$; unpaired t test, $P < 0.001$); and ΔNoL, 18.0 (7.8 to 29.0; paired t test, $P < 0.001$; unpaired t test, $P < 0.001$). Incision had no effect on BIS and HR but caused increases in MAP and NoL, although, in contrast to MAP, the effects on NoL were significant in both paired and unpaired t tests: ΔBIS, 0.92 (−1.2 to 3.3; ns); ΔHR, 1.3/min (−0.46 to 3.1/min; ns); ΔMAP, 7.9 mmHg (−1.9 to 13.0 mmHg; paired t test, $P < 0.001$; unpaired t test, ns); and ΔNoL, 8.0 (0.4 to 16.0; paired t test, $P < 0.001$; unpaired t test, $P < 0.001$).

Comparing the three different stimuli (*i.e.*, assuming nonnoxious event ≠ incision ≠ intubation), a significant main and interaction effect was observed for HR, MAP, and NoL after (but not before) stimulation and Δs: HR $F(2,96) = 9.4$, $P < 0.001$; ΔHR $F(2,96) = 27$, $P < 0.0001$); MAP $F(2,80) = 28$, $P < 0.001$; ΔMAP $F(2,80) = 19$, $P < 0.0001$; NoL $F(2,96) = 23$, $P < 0.0001$; ΔNoL $F(2,96) = 46$, $P < 0.0001$. *Post hoc* analysis showed that only NoL (after stimulation) and ΔNoL graded the level of noxious intensity with nonnoxious NoL < incision NoL < intubation NoL. HR after stimulation and ΔHR could not differentiate between nonnoxious stimuli and incision ($P = 0.24$). ΔMAP could not discriminate between incision and intubation ($P = 0.07$). See also Supplemental Digital Content 1, tables 1 and 2, http://links.lww.com/ALN/B170.
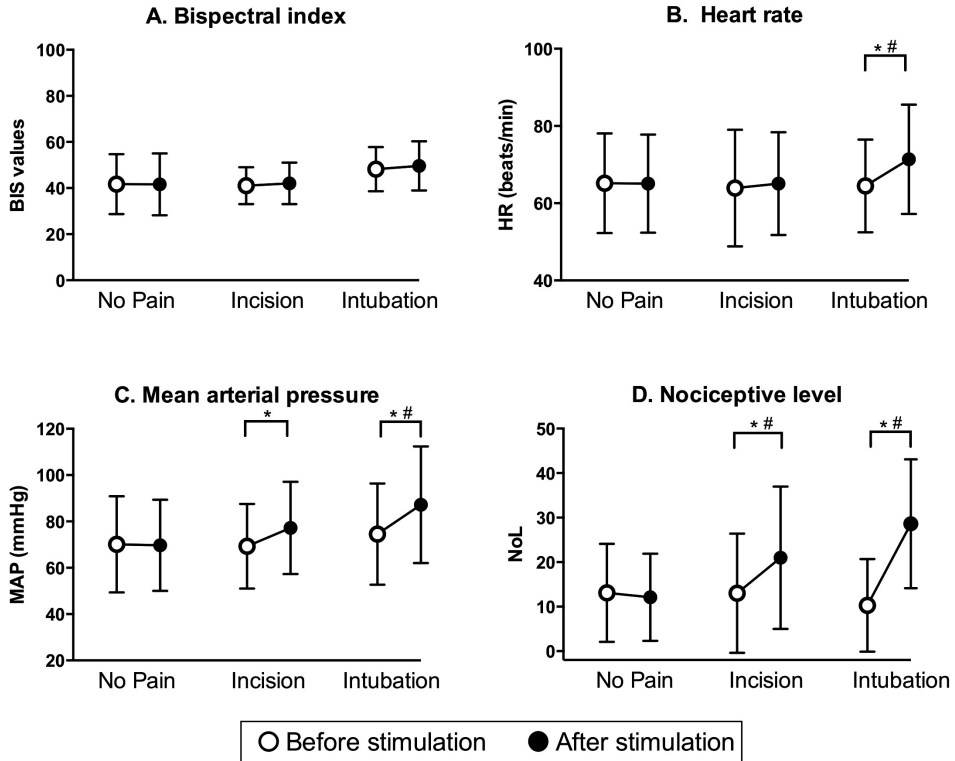
Figure 1. Bispectral Index (BIS)(**A**), heart rate (HR)(**B**), mean arterial pressure (MAP)(**C**) and nociceptive level (NoL)(**D**) before and after noxious stimulation for nonnociceptive conditions, incision and intubation. *Paired t test, p < 0.001. Open symbol = before stimulation; closed symbol = after stimulation.

The ROC curves, calculated (n = 71) for HR, MAP, and NoL (all after stimulation), and ΔHR, ΔMAP, and ΔNoL, are shown in figures 2 and 3. ROC areas under the curve sensitivity values at a specificity of 75% are given in table 3. ΔNoL outperformed all other variables in ability to discriminate between noxious (intubation or incision) and nonnoxious events with an AUC of 0.95 (95% CI, 0.91 to 0.99). The ΔNoL AUC was significantly larger compared with all other variables (P = 0.0003 $vs.$ ΔHR; P <0.0001 $vs.$ ΔMAP; P < 0.0001 $vs.$ HR; P = 0.00004 $vs.$ MAP). Moreover, NoL after stimulation outperformed MAP and HR in classifying noxious stimuli (AUC, 0.82; 95% CI, 0.75 to 0.89, P = 0.001 $vs.$ HR; P = 0.035 $vs.$ MAP). The NoL outperformed HR and MAP and ΔNoL outperformed ΔHR and ΔMAP in terms of sensitivity, specificity, and positive and negative predictive values for the detection of noxious stimuli (table 3). For NoL a cutoff value between noxious and nonnoxious stimuli of 16 yielded a specificity and sensitivity of 80 and 73%.
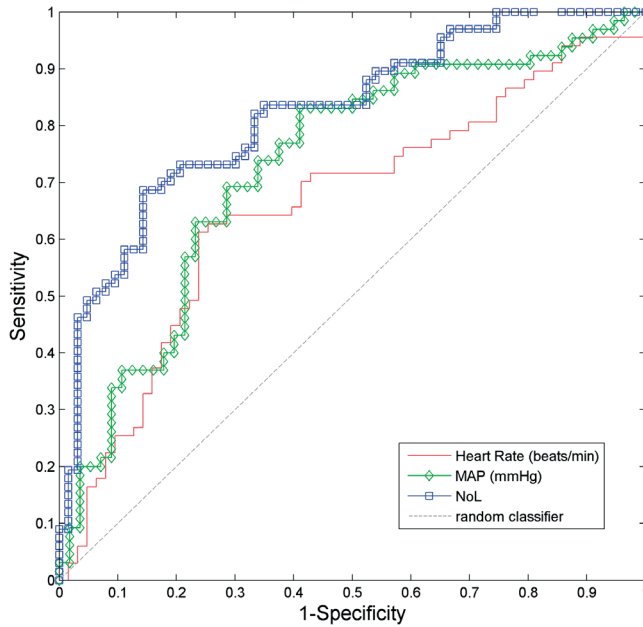
Figure 2. Discrimination between nociceptive (incision and intubation) and nonnociceptive stimuli: receiver operating curves of heart rate, mean arterial pressure (MAP) and the composite parameter, the nociceptive level (NoL).
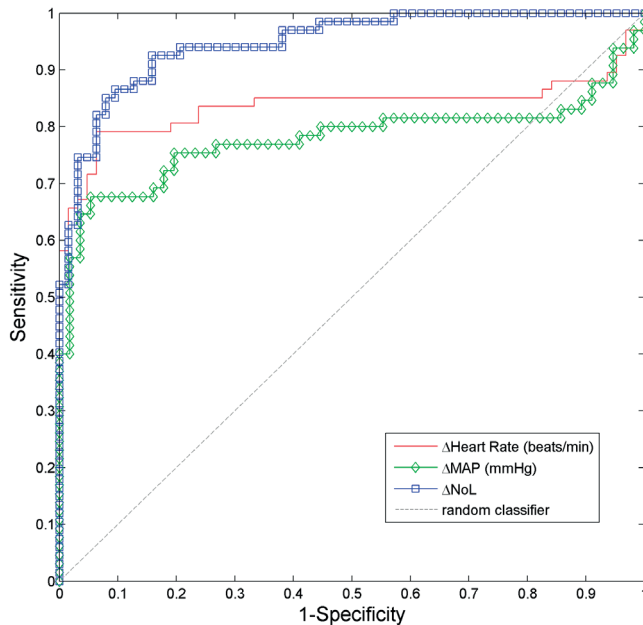

Figure 3. Receiver operating curves of the hemodynamic Δ signals and the Δ nociceptive level (ΔNoL). MAP = mean arterial pressure.

Table 3. AUC, Sensitivity, PPV and NPV of the NoL, ΔNoL, HR, ΔHR, MAP and ΔMAP at a Specificity of 75%.

Variable	AUC (95% CI)	Sensitivity(%)	Specificity(%)	PPV (%)	NPV(%)
HR	0.66 (0.56-0.75)	63	75	72	65
MAP	0.73 (0.64-0.81)	63	75	75	64
NoL	0.82 (0.75-0.89)[*]	73	75	75	72
ΔHR	0.84 (0.77-0.91)	84	75	78	81
ΔMAP	0.78 (0.70-0.86)	75	75	78	72
ΔNoL	0.95 (0.91-0.99)[#]	94	75	80	92
Random classifier	0.50	25	75	50	50

Statistical test was performed according to Hanley and McNeil[20]. NoL, MAP and HR given were obtained after noxious stimulation.
*p = 0.001 vs HR. p = 0.036 vs MAP.
# p = 0.0003 *vs.* ΔHR; p < 0.001 *vs.* ΔMAP; p = 0.0001 *vs.* ΔNoL; p < 0.0001 *vs.* HR; p < 0.0001 *vs.* MAP.
AUC = area under the receiver operating characteristics curve; HR = heart rate; MAP = mean arterial pressure; NoL = nociceptive level; NPV = negative predictive value; PPV = positive predictive value.

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Response to Intubation under Different Remifentanil Target Concentrations

The effects of increasing concentrations of remifentanil on HR (n = 57), MAP (n = 50), and NoL (n = 57) before and after noxious stimulation are shown in figures 4 to 6. The NoL before and after nonnoxious stimulation showed no significant correlation with the remifentanil concentration (rS = −0.047 and 0.024, *P* > 0.05; fig. 4, A and B). The before and after intubation NoL values showed a significant Spearman correlation with rS = −0.3, *P* < 0.05 (before, fig. 4C) and rS = −0.51, *P* < 0.001; after, fig. 4D). The analysis indicates that with increasing remifentanil concentrations, the NoL response to intubation decreases significantly with the smallest response observed at a remifentanil target concentration of 5 ng/ml (fig. 4D). HR before and after nonnoxious stimulation and intubation decreased significantly with increasing remifentanil concentrations (*P* < 0.01; fig. 5, A–D). A similar observation was made for MAP before and after nonnoxious stimulation and intubation (*P* < 0.05; fig. 6, A–D).
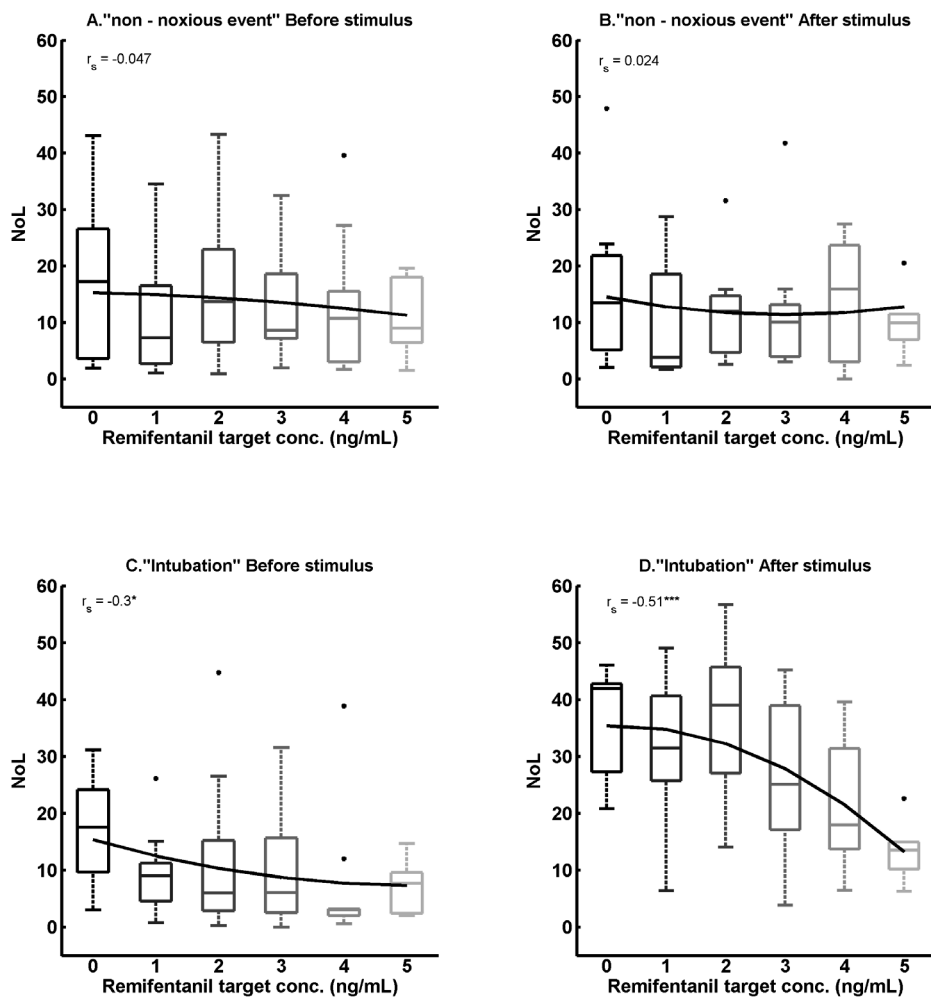
Figure 4. Boxplot of the effect of remifentanil on nociception level (NoL) before (**A**) and after (**B**) noxious stimulation for nonnociceptive conditions and before (**C**) and after (**D**) noxious stimulation for intubation. Boxplots represent the median and 25th and 75th percentiles, and the *whiskers* extend to the most extreme data points; outliers are plotted individually (*block dots*). The Spearman correlation is given (rS), with *P < 0.05 and ***P < 0.001. A quadratic polynomial is fitted to the data to guide the eye.

Figure 5. Boxplot of the effect of remifentanil on heart rate before (**A**) and after (**B**) noxious stimulation for nonnociceptive conditions and before (**C**) and after (**D**) noxious stimulation for intubation. Boxplots represent the median and 25th and 75th percentiles, and the *whiskers* extend to the most extreme data points; outliers are plotted individually (*black dots*). The Spearman correlation is given (rS), with **$P < 0.01$ and ***$P < 0.001$. A quadratic polynomial is fitted to the data to guide the eye.
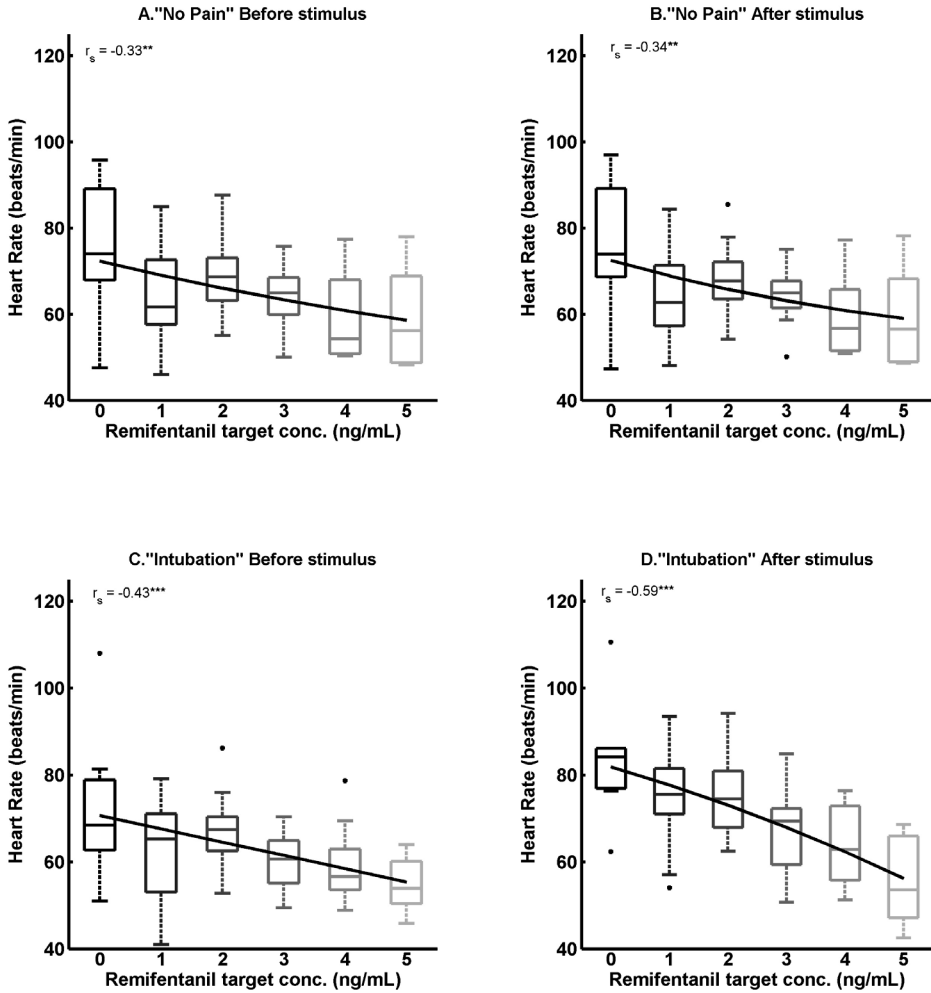
Figure 6. Boxplot of the effect of remifentanil on mean arterial pressure (MAP) before (**A**) and after (**B**) noxious stimulation for nonnociceptive conditions and before (**C**) and after (**D**) noxious stimulation for intubation. Boxplots represent the median and 25th and 75th percentiles, and the *whiskers* extend to the most extreme data points; outliers are plotted individually (*black dots*). The Spearman correlation is given (rS) with *$P < 0.05$ and ***$P < 0.001$. A quadratic polynomial is fitted to the data to guide the eye.
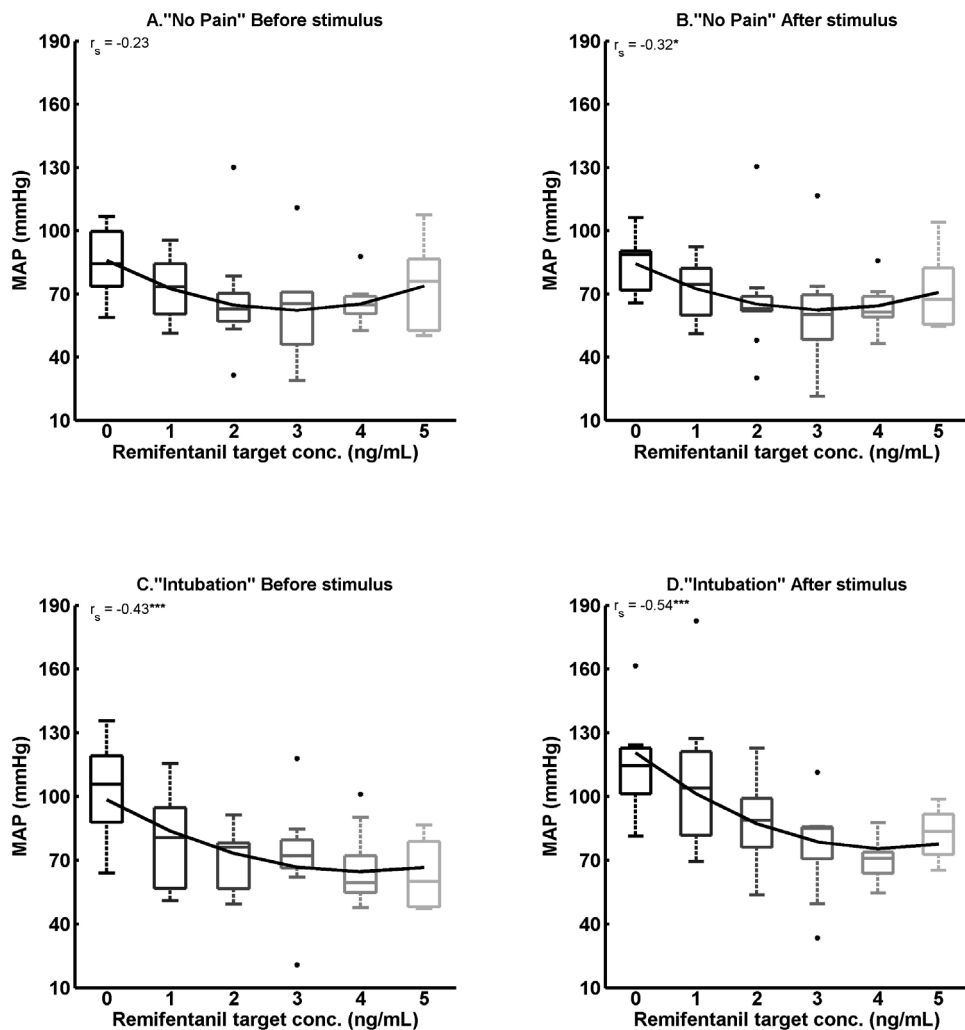
Discussion

In this validation study, the NoL, a novel multidimensional parameter, was used to detect nociceptive events during propofol–remifentanil anesthesia. The variables that make up the NoL cover both sympathetic and parasympathetic activities of the autonomous nervous system.(21) The main observations from our study are that 1) the NoL is able to detect intense noxious stimulation (intubation) and moderate nociceptive stimuli (incision). In this respect, the NoL outperformed the standard variables (HR and MAP) that were sensitive to intubation but to a lesser extent to incision. Furthermore, as based on the AUC of the ROC, the NoL was best in differentiating noxious from nonnoxious stimuli; and 2) the NoL was significantly correlated with the target remifentanil concentration after noxious stimulation. Similar observations were made for HR and MAP; however, in contrast to HR and MAP, the NoL was not affected by nonnoxious events.

Various previous studies have relied on single signals to assess nociception during surgery(3–11,22). For example, indices from the high-frequency component of HRV were used to evaluate surgical nociception and analgesia during anesthesia and to predict postoperative pain based on the measurements before extubation(3,22). Another example is the measurement of changes in skin conductance, which is based on the sympathetically induced secretion of sweat, which increases skin conductance(4). This response (*i.e.*, nociceptionrelated sweating) is unrelated to hemodynamic changes. All single indices aimed at detecting nociception share that they are surrogate markers of the autonomic nervous system and show a large within- and between-subject variability(2,23). Another approach in detecting nociception during surgery is the use of multiparameter indices(8–10). Several studies show that a multiparameter approach yields greater sensitivity and specificity in discriminating between noxious and nonnoxious stimuli than the single-signal approach(2,11,16). Examples of multiparameter indices are the Surgical Pleth or Stress Index (which combines HR and AP)(9), the response index of nociception (which combines parameters from the electroencephalographic and hemodynamic signals)(11), and the composite variability index (which combines the variability of the forehead electromyogram and BIS of the electroencephalogram)(11).

In the current study, we applied the multiparameter NoL to assess nociceptive responses at three levels of increasing nociceptive intensity. The NoL showed a remifentanil dose-independent increase in noxious response from −1.1 (nonnoxious stimulus) to 8.0 (incision) and 18.0 (intubation), with significant increases (Δ signal) occurring for incision and intubation (fig. 1). This contrasts with the two other variables that were tested, the commonly used HR and MAP, which on a population level did show significant increases at intense stimulation but not at moderate noxious stimulation. The ROC curves (figs. 2 and 3; table 2) showed that of all tested Δ signals, ΔNoL was best at differentiating

between noxious and nonnoxious stimuli (AUC, 0.95). Similar observations were made for NoL (AUC, 0.82) relative to HR (0.66) and MAP (0.73). Cutoff values of 16 for NoL yielded an acceptable sensitivity of 73% with specificity of 80% and could be interpreted as a cutoff for discriminating noxious from nonnoxious stimuli. Furthermore, when testing the effect of multiple target concentrations of remifentanil, the NoL, in contrast to HR and MAP, remained unaffected under nonnociceptive conditions. This indicates that the NoL was a more reliable measure of nociception *per se*, whereas HR and MAP are additionally affected by the hemodynamic effects of remifentanil (figs. 4–6). Treister *et al*.(16) studied the same index response to three intensities of noxious stimulation in awake volunteers. Although none of the signals that make up the NoL were able to discriminate between the different noxious intensities, they observed, in agreement with our findings, that the combination of parameters (*i.e.*, the NoL) was able to differentiate between pain and no pain and also between all three noxious intensities. This indicates that the NoL performs equally well in the awake and anesthetized individuals. Interestingly, single indices, such as HRV, perform better under conditions of general anesthesia than the awake state(24). Also in chronic pain patients, the ability to obtain objective and accurate measures of pain and nociception, next to subjective self-reports (that are often colored by a variety of biopsychosocial factors), is important(21). To assess the ability of the NoL to track nociception in patients with chronic pain, Ben-Israel *et al*.(25) studied patients with chronic radicular pain treated with spinal cord stimulation (SCS). The NoL values were in accordance with the efficacy of the SCS treatment as presented a correlation between reported pain score while turning the SCS device on and off. This indicates that the multivariate NoL may be used as an objective measurement of pain in patients with chronic pain and evaluate the efficacy of treatment.

The NoL is based on the advanced statistical and machine learning techniques to combine multiple signals into a single composite index. Machine learning methods rely on the concept that a specific algorithm that connects input to output can be trained to discover their optimal relationship. In our case, the link between input and output was established in a previous learn study, where the input were the records of physiologic signals collected during surgery under general anesthesia and the output the CISA, which is the linear combination of stimulus intensity and estimated analgesic plasma concentration(2). A detailed description of the CISA can be found in Ref. 2. The different autonomic variables that make up the NoL representldifferent underlying systems, which have nontrivial nonlinear interactions. Adding their time derivatives to the equation (which is done to increase the ability to obtain a more reliable estimate of nociception) introduces an additional level of complexity by significantly enlarging the number of variables and creating additional nonlinear dependencies. Machine learning was performed using random forest regression analysis, a technique that is able to handle a large number of predictors to discover the optimal algorithm combining input to output, without the need

for an *a priori* specification of a stochastic data model (*i.e.*, the created algorithmic model treats the data mechanisms as unknown)(12,13). Random forest regression is applied in different areas of science and engineering such as the identification of the smallest possible set of genes that can still achieve a good predictive outcome in clinical tests, prediction of protein interactions, and forecasting murderous conduct by individuals on probation or parole(26–28).

An important issue is whether continuous measurement of nociception during surgery and treatment of signs of increased nociception will improve patient outcome. Chen *et al*.9 addressed this issue by studying the effect of surgical stress index–guided propofol–remifentanil anesthesia in patients undergoing elective ear, nose, and throat surgery. Compared with standard of practice, nociception-guided anesthesia reduced remifentanil consumption and unwanted movement and hemodynamic events. Parker *et al*.(29) showed that the catecholamine (stress) response during anesthesia and emergence, in patients undergoing lower extremity revascularization, contributed to the development of postoperative hypertension and possibly also to the occurrence of thrombotic events. Similarly, also anesthesia with overdoses in anesthetic and opioid delivery may be associated with a poor outcome(30,31). Cumulatively these data suggest that the prevention of overdosing or underdosing of opioid and anesthetic drug delivery by continuous monitoring of nociception (and possibly also indices from the electroencephalogram) may result in a more stable nociceptive condition with beneficiary effects on outcome. Evidently, further studies are needed to fully understand the complexities of anesthetic monitoring and outcome.

The current study has some limitations:
1) The level of anesthetic depth as measured by the BIS was fixed to values ranging between 40 and 50. Therefore, we remain unaware of the influence of variations in anesthetic depth at multiple target opioid concentrations on the NoL. Assuming a synergistic effect of remifentanil and propofol on nociception,32 we expect some effect of propofol on the NoL. Our subprotocol was intended to study this issue but was not completed. Data were collected in four patients (two at BIS 30 and two at BIS 70). The analysis of these data suggests no dependency on BIS value on the effect of intubation on the NoL (data not shown). Evidently, this issue requires further study.
2) Each subject only received one dose level of remifentanil. This precluded the assessment of the intraindividual variance in the response to remifentanil.
3) We used a finger cuff system (Nexfin) to noninvasively measure the beat-to-beat blood pressure rather than invasive blood pressure. This finger cuff technique is reliable(17), and Nexfin MAP measurements were second to the NoL in ability to detect nociceptive responses (fig. 2). Possibly adding the beat-to-beat MAP to the NoL algorithm would further improve the accuracy of the NoL.

4) We performed our studies in 72 patients. Because of technical, logistic, or other issues, nonnoxious, incision, and intubation events were obtained on average in 60 (83%) subjects. This may have affected the outcome of the study. Given the fact that the NoL performed as expected from results of previous studies, the loss of data did not affect the power of our study with respect to the NoL(2,16). Conversely, the loss of data may have caused the inability of MAP to detect moderate nociceptive stimuli (fig. 1).

5) Finally, we excluded patients on β-adrenergic-blocking drugs. Because β-adrenergic blockers and other vasoactive drugs affect the autonomic system at multiple sites, their effect on the accuracy of the NoL requires further study.

In conclusion, we applied a novel multidimensional index, the NoL, to detect nociception during conditions of no, moderate, and intense noxious stimulation in surgical patients under propofol–remifentanil anesthesia. We observed that compared with HR and MAP, the index was best at differentiating nociceptive from nonnociceptive conditions. In additionally, in contrast to MAP and HR, the NoL remained unaffected by the hemodynamic effects of increasing concentrations of remifentanil.

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