

# Preliminary Intraoperative Validation of the Nociception Level Index

## *A Noninvasive Nociception Monitor*

Ruth Edry, M.D., Vasile Recea, M.D., Yuri Dikust, M.D., Daniel I. Sessler, M.D.

### ABSTRACT

**Background:** The nociception level (NoL) index is an index of nociception based on nonlinear combination of heart rate, heart rate variability, photoplethysmograph wave amplitude, skin conductance, skin conductance fluctuations, and their time derivatives. The authors evaluated the abilities of the NoL index and other measures of nociception to discriminate between noxious and nonnoxious stimuli, to progressively respond to graded stimuli, and to respond to opioid administration.

**Methods:** Intraoperative NoL was compared to heart rate, pulse plethysmograph amplitude, noninvasive blood pressure, and the surgical pleth index around five specific stimuli: tetanic stimulation with and without fentanyl analgesia, intubation, first incision/trocar insertion, and a nonnoxious period. The response around first incision was analyzed at two target plasma concentrations of remifentanyl.

**Results:** In 58 patients, the NoL index responded progressively to increased stimulus intensity and remained unchanged in response to nonnoxious stimuli. Compared to other accepted measures of nociception, the NoL index better discriminated noxious from nonnoxious stimuli with an area under the curve of 0.93 (95% CI, 0.89 to 0.97) and a sensitivity of 87% at a specificity of 84%. The NoL index was the only measure that reliably reflected two different analgesic concentrations of remifentanyl during initial skin incision or trocar insertion.

**Conclusions:** The NoL index changes proportionately with patients' response to various clinical and experimental noxious stimuli and discriminates noxious from nonnoxious stimuli with high sensitivity and specificity. The NoL index also responds progressively to increasing stimulus intensity and is appropriately blunted by analgesic administration. The NoL index was superior to other compared measures and appears to accurately characterize nociception during general anesthesia.

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**P**AIN is a conscious response and thus, by definition, cannot be referred to so long as anesthetized surgical patients have an adequate hypnotic level. Nonetheless, anesthetized patients clearly respond to noxious stimuli, and the response appears to be blunted by analgesic administration. A balance between nociceptive and antinociceptive forces can therefore be assumed during anesthesia and surgery. Nociception, which refers to the sympathetic response to surgical and other clinical noxious stimuli during unconsciousness,<sup>1</sup> was defined by the Kyoto Protocol as the neural processes of encoding and processing noxious stimuli, explicitly distinguishing between nociception as a physiologic process and pain (or nociception) as a conscious, subjective phenomenon.<sup>2</sup>

Complete general anesthesia (GA) is the sum of various components including lack of movement, hypnosis, amnesia, control of autonomic responses, and attenuation of the

#### What We Already Know about This Topic

- Objective assessment of nociception in anesthetized patients remains challenging
- Excessive nociception may promote postoperative pain, whereas excessive antinociceptive medications may result in overdosing and related complications

#### What This Article Tells Us That Is New

- The nociception level index, based on an algorithmic combination of multiple physiologic measures, was compared with its underlying measures in anesthetized surgical patients
- Compared to its individual underlying measures, the multiparametric nociception level index was better able to distinguish nonnoxious and graded noxious stimuli, as well as the response to opioids

response to noxious stimulation. Some anesthetic components, such as muscle relaxation and absence of movement, are easy to assess. Similarly, hypnotic state can be estimated

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using processed electroencephalographic signals,<sup>3</sup> but the anesthetic component that remains the most challenging to assess is the nociceptive/antinociceptive state. Typically, intraoperative nociception is estimated from autonomic responses, including hemodynamic stability and clinical signs such as tearing and sweating. Effective antinociception is an important component of balanced anesthesia and appears to enhance postoperative outcomes. The most obvious potential consequence of insufficient intraoperative antinociceptive treatment is excessive postoperative pain, but inadequate treatment may also promote inflammatory, hormonal, and immunologic imbalances.<sup>4–10</sup>

A novel measure of nociception is the nociception level (NoL) index.<sup>11</sup> The NoL index ranges from 0 to 100 and is based on a nonlinear combination of nociception-related physiologic variables, specifically heart rate (HR), heart rate variability at the 0.15- to 0.4-Hz band power, photoplethysmograph wave amplitude (PPGA), skin conductance level, number of skin conductance fluctuations, and their time derivatives.<sup>11</sup> The NoL index estimates the nociceptive/antinociceptive state from these component measures using random forest regression.<sup>12</sup> Previous experimental work on a small number of patients showed that the NoL index is superior to each individual component and to a linear combination of the components.<sup>11</sup> However, it remains unknown whether the NoL index accurately quantifies patients' intraoperative responses to noxious stimuli of varying intensities. We therefore evaluated the ability of the NoL index to discriminate noxious from nonnoxious stimuli, respond to analgesic administration, and progressively increase in response to increasing intensity of noxious stimulation.

## Materials and Methods

The study was approved by our local ethics committee located at Rambam Medical Center, Haifa, Israel (institutional review board #326-12-RMB; principal investigator: R.E.) and registered (ClinicalTrials.gov no.: NCT01762332; registration date: December 23, 2012). Patients were enrolled over a 14-month period between March 2013 and May 2014. We included patients aged 18 to 75 yr having American Society of Anesthesiologists physical status scores 1 to 3 who were scheduled for elective surgery with GA. We excluded patients who were pregnant or lactating, had serious cardiac arrhythmias or neuromuscular disease, abused alcohol or illicit drugs, were cognitively impaired, suffered psychiatric disorders, or were allergic to study drugs.

General anesthesia was induced with 1 mg midazolam and incremental 50 mg propofol boluses until state entropy (SE) (CARESCAPE B650; GE Healthcare, Finland) decreased below 60.<sup>13,14</sup> After induction, but before intubation or surgery, patients were subjected to two tetanic stimulations (60 mA, 100 Hz, 20 s)<sup>15,16</sup> without analgesic administration (TET1) and after a bolus of 2 µg/kg fentanyl (TET2). Intubation (TP1) was facilitated with 1 mg/kg rocuronium, and GA was maintained

with remifentanyl and sevoflurane 1 to 2% in oxygen/air sufficient to maintain entropy (SE) less than 60. Patients were randomly allocated to remifentanyl target plasma concentrations of 2 and 4 ng/ml<sup>17,18</sup> (Minto model; Alaris GH Plus syringe pump, CareFusion; BD-Becton, Dickinson and Company, USA). Sufficient time was allowed to reach steady-state remifentanyl plasma concentrations before skin incision (TP2).

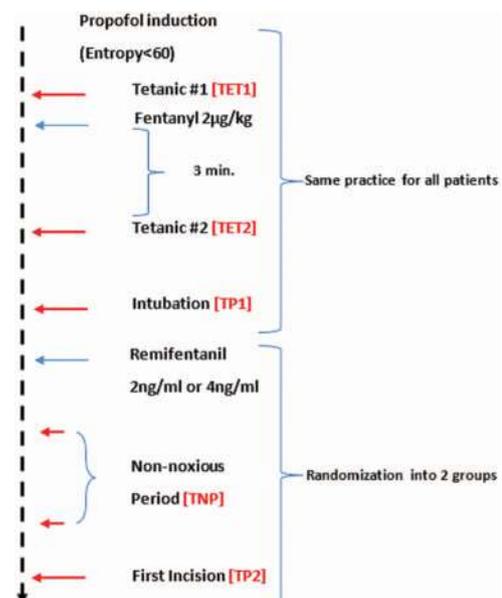
Randomization to remifentanyl concentration groups, 1:1 without stratification, was generated by MATLAB software (Mathworks Inc., USA). A research assistant determined the allocation after informed consent was obtained. The anesthesiologist and patient were blinded to the assigned group. Rescue fentanyl boluses of 50 µg were allowed during surgery at the anesthesiologist's discretion (fig. 1).

Routine anesthesia monitoring (CARESCAPE B650; GE Healthcare) was supplemented with a pain monitoring device (PMD-100; Medasense, Israel), which generated the NoL index. Measures recorded for comparison were NoL, HR, PPGA, noninvasive blood pressure (NIBP) systolic, and surgical pleth index (SPI). Data were recorded at 5-s intervals by S/5 Collect system (GE Healthcare). All intraoperative caregivers were blinded to remifentanyl target concentration NoL, PPGA, and the SPI.

## Statistical Analysis

Our primary endpoint was that the NoL index does not respond to nonnoxious stimuli and progressively increases in response to increasing intensity of noxious stimuli. Our secondary endpoint was that the NoL index decreases in response to opioid administration.

Tetanic stimuli (TET1, TET2), intubation (TP1), and skin incision/first trocar insertion (TP2) were designated



**Fig. 1.** Study timeline. TET1 = first tetanic stimulus; TET2 = second tetanic stimulus; TNP = nonnoxious period; TP1 = intubation; TP2 = skin incision/first trocar insertion.

as stimuli. A time with no noxious stimulus (time no pain [TNP]) at least 5 min from a noxious stimulus was designated between intubation and initial incision/trocar. Stimuli intensity were *a priori* ordered for analysis purposes based on our experience and published works<sup>1,19,20</sup> as TP1 (moderate to severe) > TP2 (moderate) > TET1 (mild to moderate) > TET2 (mild), and TNP (nonnoxious).

We originally designated a 1-min window before and after stimulation for observing response of measures to events. But early in the study, it became apparent that the time of various clinical stimuli could not be identified within seconds. To be sure that part of the stimulus was not included in the *prestimulus* window, we therefore restricted the analysis to the first 30 s of the designated 1 min before the event (−60 to −30 s). Similarly, we started the *poststimulus* window 10 s after the event annotation and enlarged the window to 80 s.

The original designation for observing the reaction to opioid administration was a 5-min postadministration window. During data analysis, it became apparent that it made better sense to use the same pre- and poststimulus windows used in all other evaluations. To evaluate the response to initial incision/trocar insertion (TP2) under two levels of remifentanyl, we had to define an optimal *postwindow* after TP2 annotation. Trocars are inserted in sequence at the beginning of surgery and cannot be distinguished as independent stimuli. We analyzed our current database of 26 patients who had laparoscopic surgery *post hoc* and found that the first four annotations of trocar insertions lasted between +78 and +646 s after the first trocar annotation (average +238 s, median +170 s). Therefore, a window of +10 to +400 s from the first trocar/skin incision was chosen for analysis (*postlong*). This window was then applied to the entire study population, assuming it to be a good approximation of the time needed for incision of the skin and diathermy separation of the underlying layers in open surgeries as well. Consequently, three values per measure were extracted for comparison, for each stimulus:

1. *Prestimulus*: average value (−60) to (−30) s before stimulus.
2. *Poststimulus*:
  - a. *Post*: average value (+10) to (+80) s after stimulus.
  - b. *Postlong*: average value (+10) to (+400) s (after TP2 only).
3. *Reaction* ( $\Delta$ ): For NoL and SPI (normalized indices), it was calculated as a simple difference as follows:

$$\text{Average}(\text{poststimulus}_i) - \text{Average}(\text{prestimulus}_i)$$

For HR, NIBP, and PPGA, *reaction* ( $\Delta$ ) was normalized as follows:

$$\text{Reaction}_i = \frac{\text{Average}(\text{poststimulus}_i) - \text{Average}(\text{prestimulus}_i)}{\text{Average}(\text{prestimulus}_i)} \cdot 100$$

We expected that HR, NoL, NIBP, and SPI would increase in response to noxious stimulation, and that PPGA would decrease. Statistical analysis was performed using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., USA) and MATLAB R2014a scientific software (Mathworks Inc.). Continuous data are presented as medians and 25th to 75th percentiles. Categorical data are presented as counts and percentages.

The *reaction* of measures after TP1, TP2, TET1, TET2, and TNP was compared by Wilcoxon signed-rank test, and their ability to change proportionately to stimulus intensity was tested by applying a repeated-measures Friedman test for the *reaction* and *post* values after TP1, TP2, and TNP, expecting the relation to be TP1 > TP2 > TNP.<sup>21</sup> In case of statistical significance, a Dunn–Sidak *post hoc* analysis was applied to test the validity of graded relationships, as a nonparametric test for all possible comparisons.

The ability to discriminate between noxious (TP1 and TP2) and nonnoxious (TNP) stimuli was evaluated by receiver operating characteristics curve (ROC) analysis, where the following outcomes (measured by poststimulus values) were considered successful, based on our previous findings<sup>11</sup>: (1) mean sensitivity above 80% at a working point of 84% specificity with at least 70% lower two-sided 95% Clopper–Pearson CI for sensitivity and specificity; (2) a lower CI of area under the curve (AUC) above 0.8. Our statistical plan of analysis treats the repeated measures across the various noxious conditions between subjects as being independent of one another although dependence could be assumed for data extracted from a given subject under various conditions.<sup>22</sup> The within-subject correlation was not removed in the derivation of ROCs since we used an empirical method to plot the ROCs.<sup>23</sup> Conceptually, each data point is compared to all other data points for calculating and drawing the AUC, and therefore, independent assumption between data points holds.

The response to fentanyl administration was tested by comparing pre-TET1 to pre-TET2 values with a Wilcoxon signed-rank test. Bonferroni correction was applied to maintain type 1 error over eight comparisons, that is, post and reaction values of NoL, HR, PPGA, and SPI; the *P* value for significance was therefore  $0.05/8 = 0.00625$ . The ability of measures to reflect two levels of remifentanyl during first skin incision/trocar insertion by postlong TP2 values was compared using Mann–Whitney U tests. After Bonferroni correction for five measures, *P* values of 0.01 or less ( $0.05/5 = 0.01$ ) were considered statistically significant.

Sample size was estimated from preset goals for discrimination between clinical noxious and nonnoxious stimuli of sensitivity above 80% and specificity above 84%. Based on our previous study,<sup>11</sup> at least 100 noxious stimuli were needed to achieve a sensitivity above 80% with 71% lower CI (two-sided 95% Clopper–Pearson CI), and at least 50 nonnoxious stimuli were needed to achieve a specificity of at least 84% with 71% lower CI (two-sided 95% Clopper–Pearson CI).

**Table 1.** Study Patients and Remifentanyl Groups

	All Patients	Patients after Randomization to Two Groups of Remifentanyl TCI		P Value
	Total (N = 58)	Total (N = 22), 2 ng/ml	Total (N = 26), 4 ng/ml	
Age (yr)	46 ± 13 (21–72)	47 ± 13 (21–72)	45 ± 14 (23–68)	0.70
Weight (kg)	83 ± 23 (39–150)	88 ± 28 (55–150)	81 ± 19 (39–132)	0.29
Height (cm)	167 ± 9 (152–185)	167 ± 10 (153–185)	167 ± 9 (152–183)	0.83
BMI (kg/m <sup>2</sup> )	30 ± 7 (17–49)	31 ± 8 (21–49)	29 ± 7 (17–48)	0.24

No difference between two groups in terms of age, weight, height, and body mass index (BMI). Values presented as means ± SDs (min–max). TCI = target-controlled infusion.

Hence, 50 patients, each with two noxious stimuli and one nonnoxious stimulus, were considered sufficient.

## Results

Seventy-nine consenting patients were enrolled. The trial included a  $\beta$ -blocker arm unrelated to NoL index validation; the 10 patients enrolled to the  $\beta$ -blocker arm were excluded from the validation analysis. Hence, 69 patients remained for analysis, of which 11 were excluded for the following reasons: surgery was postponed in five, technical issues precluded analysis in three, and three were excluded because of protocol deviations. The presented analysis was thus confined to 58 patients, with 37 being men and 21 being women. Twenty-two patients were randomized to the low remifentanyl target-controlled infusion group and 26 to the high remifentanyl target-controlled infusion group. Their demographic and morphometric characteristics were similar (table 1). Various procedures were included: 28 laparoscopic and open abdominal procedures, 17 laparoscopic and open gynecologic procedures, 9 neurosurgical procedures, and 6 plastic or head and neck procedures. For technical and clinical reasons, valid measurements were obtained in 53 patients on average for the first and second tetanic stimulations (TET1 and TET2, respectively), 54 for intubation (TP1), 46 for initial incision/trocar (TP2), and 49 for nonnoxious period (TNP).

### Entropy–SE Analysis

Our *a priori* goal was an intraoperative entropy below 60.<sup>13,14</sup> Among 249 recorded values, entropy was less than 60 in 92%. Entropy generally remained stable before and after stimuli (table 2 and fig. 2), suggesting that hypnosis was the primary determinant of entropy, distinct from nociception/antinociception, which appeared to be the primary determinant of the NoL index and other observed measures of nociception.

### Nociception: Noxious/Nonnoxious Stimuli: Reaction, Discrimination, and Grading

The *reaction* of various measures was evaluated after noxious stimuli (TP1, TP2, TET1, TET2) and nonnoxious period (TNP; table 2 and fig. 2). Compared to HR, PPGA, and SPI, the NoL index was the only measure to

remain essentially unchanged after nonnoxious period and to change progressively in response to increasing noxious stimuli intensity, reaching 36 ( $P < 0.0001$ ) and 44 ( $P < 0.0001$ ) on a 0 to 100 scale after intubation and first tetanic, respectively.

Heart rate changed in the range of 0.2 to 2% ( $P =$  not significant) after skin incision and tetanic stimulations, increasing with statistical significance only after intubation (+17% to 80 beats/min;  $P < 0.0001$ ). PPGA and SPI changed proportionately and with statistical significance after clinical stimuli (intubation, skin incision) and were unchanged around nonnoxious period, but changed opposite to expected after first tetanic. The NoL index, whether by *post* (NoL) or *reaction* value ( $\Delta$ NoL), successfully graded the response to stimuli as expected (intubation > skin incision/trocar > nonnoxious period), outperforming all other observed measures, which only partially generated graded responses to progressively noxious stimuli (fig. 3).

Discrimination between clinical noxious stimuli (intubation, skin incision) and nonnoxious period by various measures, assuming independence between repeated measures,<sup>22</sup> is presented in figure 4. AUC for the NoL index (based on *poststimuli* value) was 0.93 (CI, 0.89 to 0.97) and for  $\Delta$ NoL (based on *reaction* value), it was 0.89 (CI, 0.85 to 0.94), outperforming all other measures. Note that the lower CI for NoL AUC (0.89) exceeded the mean AUCs of all other measures. At a given working point of 84% specificity, the sensitivity achieved by the NoL index (87% [CI, 79 to 93%]) was higher than that of any other tested measure. The sensitivity of  $\Delta$ NoL (80% [CI, 71 to 87%]) exceeded that of any other tested measure except  $\Delta$ SPI (table 3).

### Reflection of Patient's Antinociceptive State

During the nonnoxious period just after anesthesia induction, all measures equally reflected administration of fentanyl, as shown by a statistically significant lower value in the windows preceding second *versus* first tetanic stimulation (*pre*-TET2, *pre*-TET1, respectively). The time before initial skin incision/trocar insertion (*Pre*-TP2) was the second nonnoxious period evaluated. At that point, patients were given one of two doses of remifentanyl. Unsurprisingly, all measures of nociception decreased, regardless of remifentanyl dosage, reflecting the absence of noxious stimuli. For example, NoL values before initial incision/trocar (*pre*-TP2) were 3 and 11,

**Table 2.** Prestimulus, Poststimulus, and Reaction Values (Median [25–75th Percentile]) after Clinical and Experimental Stimuli

	NoL	HR	PPGA	SPI	SE
	Median (25–75%)	Median (25–75%)	Median (25–75%)	Median (25–75%)	Median (25–75%)
TP1 pre	15 (4.2 to 23.1)	67 (60.2 to 74.3)	5.4 (4.3 to 7.7)	24 (19.8 to 27.6)	45 (39 to 55.4)
TP1 post	36 (23.8 to 47)	80 (70 to 85.6)	3.7 (2.9 to 5.1)	42 (35.2 to 52.5)	47 (42.5 to 59.3)
TP1 reaction	21 (10.8 to 30.2)	17% (8 to 26%)	–34% (–45.8 to –13.5%)	20 (10.3 to 25.9)	4 (–2.5 to 7.4)
<i>P</i> value	< 0.0001*	< 0.0001*	< 0.0001*	< 0.0001*	0.009
TP2 pre	5 (2.7 to 17.1)	61 (51.6 to 66.4)	4.9 (3.1 to 7.1)	27 (20.6 to 39.8)	47 (36.5 to 53.5)
TP2 post	15 (7.2 to 29.1)	63 (53 to 68.1)	3.8 (2.3 to 5.5)	42 (28.2 to 54.6)	47 (37 to 52.5)
TP2 reaction	5 (0.6 to 12.9)	2% (–1.4 to 5%)	–18% (–36.1 to –2.6%)	8 (2.6 to 16.9)	0.8 (–1.2 to 2.7)
<i>P</i> value	< 0.0001*	0.01	< 0.0001*	< 0.0001*	0.137
TET1 pre	30 (20 to 46)	78 (68.4 to 83.7)	1.7 (0.9 to 3.5)	52 (40.8 to 68.6)	34 (23.7 to 44.1)
TET1 post	44 (31.8 to 53.8)	79 (68.9 to 88.5)	3.3 (1.8 to 4.9)	42 (33.6 to 46.9)	32 (18.4 to 47.2)
TET1 reaction	9 (–2.5 to 19.6)	0.2% (–5.4 to 8.3%)	78.5% (24.7 to 138.7%)	–14 (–22.1 to –3.3)	–1 (–15.0 to 9.3)
<i>P</i> value	0.0006*	0.286	< 0.0001*†	< 0.0001*†	0.343
TET2 pre	12 (4.9 to 28.4)	66 (58.8 to 74.6)	4.8 (3.5 to 6.7)	25 (20.1 to 32.2)	45 (35.1 to 51.8)
TET2 post	19 (12 to 30.9)	69 (59.2 to 75.1)	4.8 (3.5 to 5.8)	28 (22.5 to 38)	43 (35.7 to 55)
TET2 reaction	6 (–2.4 to 15.8)	2% (–2.6 to 6.4%)	–5% (–18.1 to 10.1%)	2 (–1.4 to 7)	3 (–4.1 to 7.8)
<i>P</i> value	0.0051*	0.34	0.19	0.0025*	0.155
TNP pre	5 (2 to 12)	64 (52 to 69)	5 (3 to 7.5)	28 (21 to 39)	45 (38.5 to 50.3)
TNP post	4 (2.1 to 7.4)	63 (52 to 68)	4.7 (2.9 to 7.6)	28 (19 to 37)	45 (37.7 to 50.4)
TNP reaction	–0.8 (–4.3 to 1.2)	–1% (–2.2 to 0)	–0.25% (–7.4 to 6.6%)	0.16 (–2.3 to 2.3)	1 (–1.6 to 2.5)
<i>P</i> value	0.01	0.0009*	0.92	0.93	0.235

Nociception level (NoL) changed with statistical significance after all noxious stimuli and remained unchanged during nonnoxious period. Other parameters changed with statistical significance after part of the noxious stimuli only. Note the opposite from expected direction of change in surgical pleth index (SPI) and pulse plethysmograph amplitude (PPGA) after first tetanic stimulus (TET1). Note stable state entropy (SE) at all points reflecting adequate sedation, Wilcoxon Signed-rank test.

\**P* value < 0.00625 (after Bonferroni correction). †Significant reaction in an unexpected direction.

HR = heart rate; post = poststimulus; pre = prestimulus; TET2 = second tetanic stimulus; TNP = nonnoxious period; TP1 = intubation; TP2 = skin incision/first trocar insertion.

HR values were 61 and 62, and NIBP (systolic) values were 83 and 88 mmHg for the high and low remifentanyl groups, respectively (table 4).

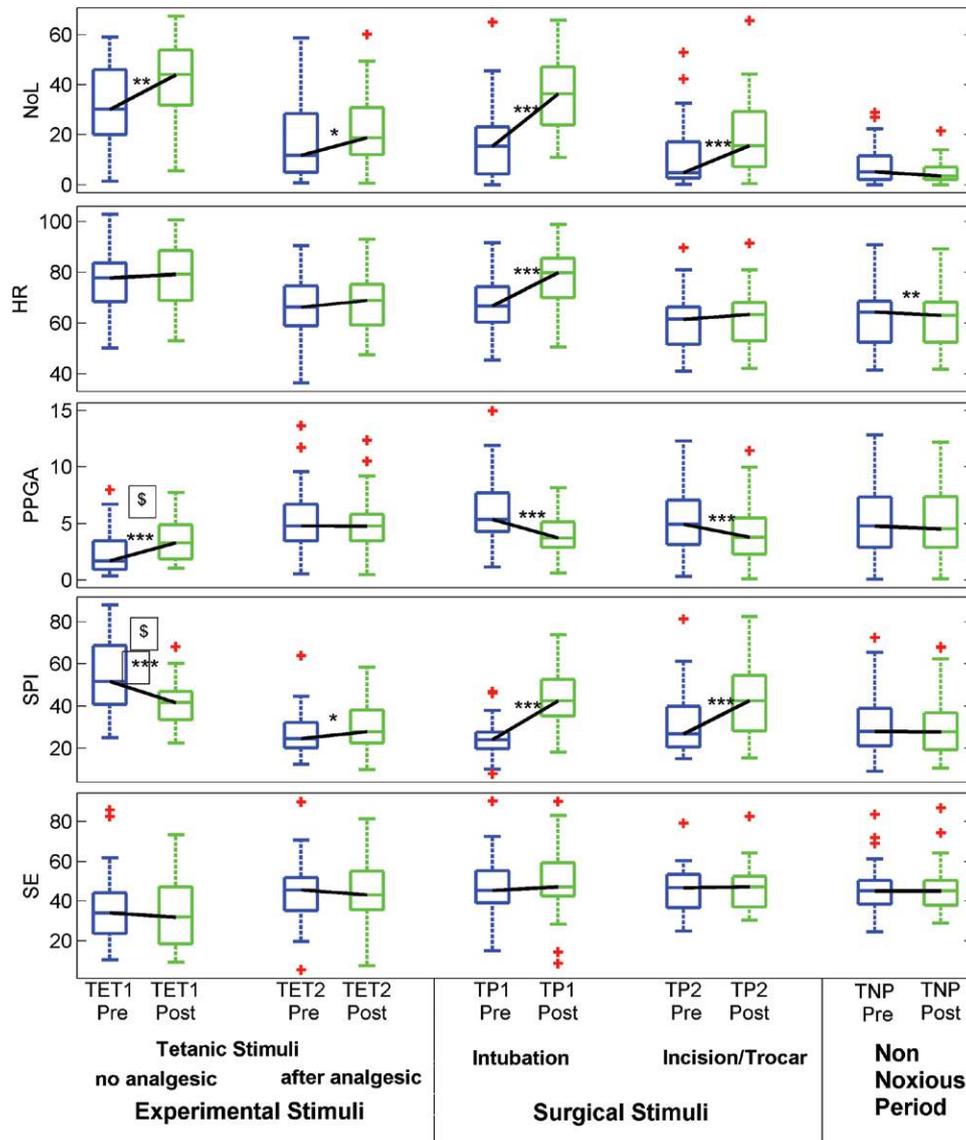
Varying responses to the two remifentanyl doses became apparent only after a noxious stimulus (skin incision, *post-long*TP2). SPI and PPGA, as with NoL, increased significantly after skin incision in the low-dose group, but not in the high-dose group. HR did not increase significantly with either remifentanyl dosage, remaining between 61 and 64 beats/min (table 4). NIBP increased significantly at each dose. This was the only analysis to include NIBP in the model, due to the relatively long window allowing the collection of a sufficient number of data points for a value sampled only every 3 to 5 min. In an unpaired (between-group) comparison of the two remifentanyl doses, the NoL index was the only measure that correctly differentiated between the two remifentanyl analgesic concentrations (*P* = 0.0069; table 4). We note though that HR, NIBP, and NoL responses suggest a low-to-mild nociceptive stimulus, presumably reflecting the fact that patients were given effective doses of remifentanyl in both groups.

Table 5 summarizes study results, as evaluated by the defined primary and secondary endpoints, demonstrating that nociceptive responses during GA were better characterized by the NoL index than by any of the other measures of nociception.

## Discussion

Nociception is the last major anesthetic component lacking a well-validated monitor. We present our preliminary validation study for the NoL index, an index of nociception for surgical patients having GA. Validation of a new nociception index in the absence of an accepted-standard nociception monitor is challenging. We therefore initially analyzed the NoL index's response to clinical and experimental stimuli of varying intensities, expecting the NoL index to change progressively with stimuli's intensity and to discriminate noxious from nonnoxious stimuli. Thereafter, the NoL index was compared to other nociception-related measures to assess their degrees of agreement.

Our results show that the NoL index increased significantly in response to clinical noxious stimuli while remaining essentially unchanged during nonnoxious periods. The NoL index was also better than other tested measures in discriminating noxious (intubation, skin incision) from nonnoxious stimuli. The NoL index was the only measure to increase proportionately with all tested clinical stimuli, correctly grading the response after intubation, skin incision, and nonnoxious period (TP1 > TP2 > TNP), while other measures correctly graded only part of the relations. NoL's response was also appropriately blunted by a bolus of opioids. Moreover, the NoL index differentiated between two remifentanyl doses, both in paired (within patient and



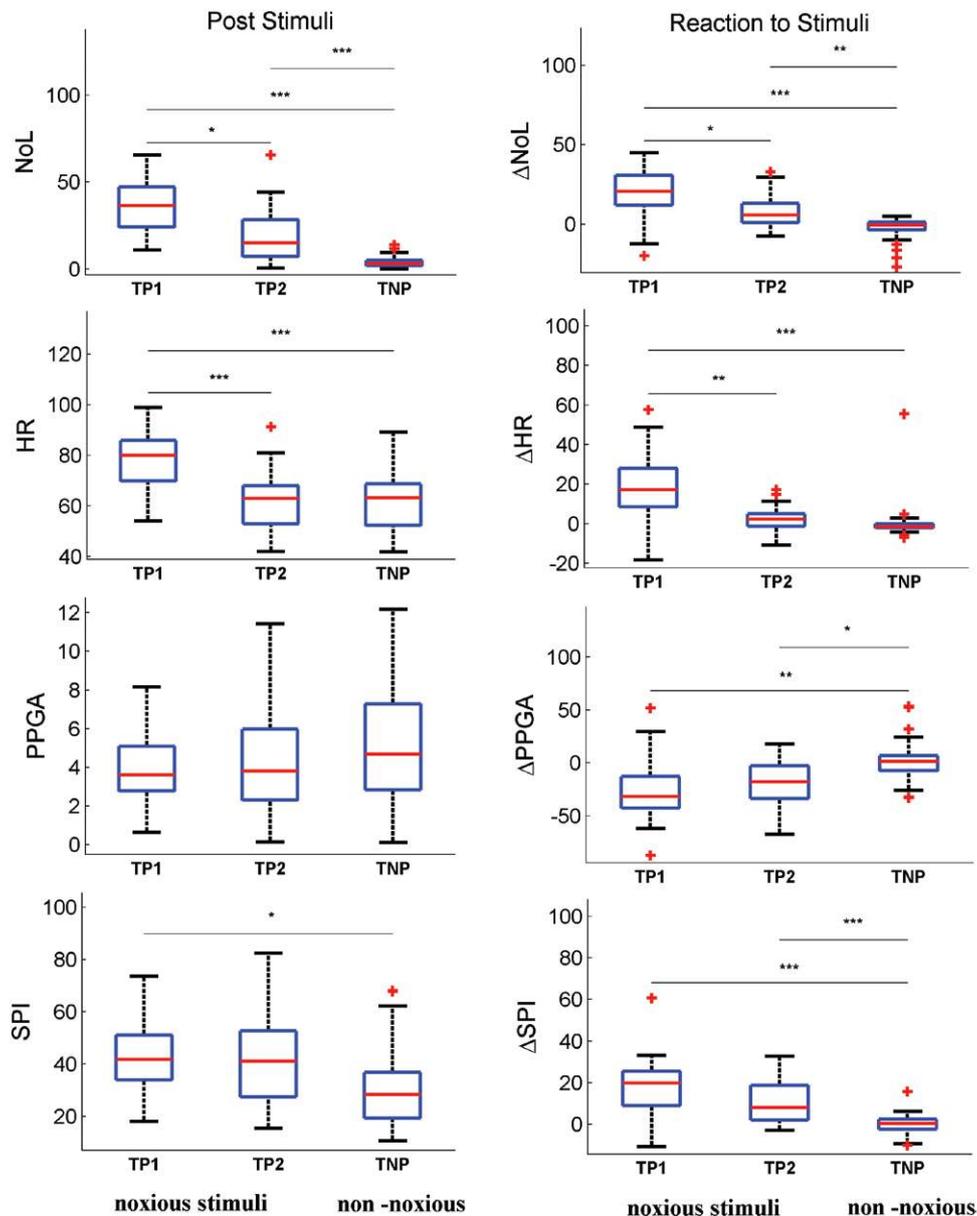
**Fig. 2.** The reaction of individual measures to clinical and experimental stimuli. Nociception level (NoL) changed with statistical significance after all noxious stimuli and remained unchanged during nonnoxious period. Heart rate (HR) changed with statistical significance after intubation only. Note the opposite from expected direction of change in surgical pleth index (SPI) and pulse plethysmograph amplitude (PPGA) after 1st tetanic stimulus (TET1). Note stable state entropy (SE) at all points reflecting adequate sedation. Wilcoxon signed-rank test. \* $P < 0.00625$ , \*\* $P < 0.001$ , \*\*\* $P < 0.0001$ . \$Significant reaction opposite to expected direction. For each box: central mark = median; edges of box = 25, 75 percentiles; whiskers extend to the most extreme data points; outliers are plotted individually by +. post = poststimulus; pre = prestimulus TET2 = second tetanic stimulus; TNP = nonnoxious period; TP1 = intubation; TP2 = skin incision/first trocar insertion.

dose) and unpaired (within groups) analyses, demonstrating its sensitivity.

Methodologically, our analysis is based on the average values of measures in the windows before and after the stimuli. Both the duration of the window and the selected response descriptor influence interpretation. For example, maximum stimulus response may be substantial, but lasts only a brief period. In contrast, a smaller but sustained response might be clinically more important. Results thus usually differ when analysis is characterized as maximum or average, and the average clearly also depends on the window

duration. Others have compared average prestimuli values to the maximum value within the poststimuli window, which overestimates changes.<sup>15,16,24</sup> Our approach, evaluating the average response within each window, seems more likely to provide clinically relevant assessments of patient response.

We included clinical and experimental noxious stimuli in the study. Obviously, our patients were given analgesic agents before intubation, incision, and clinical stimuli; therefore, all responses to those stimuli were attenuated. Moreover, all clinical stimulations inevitably differed in location,

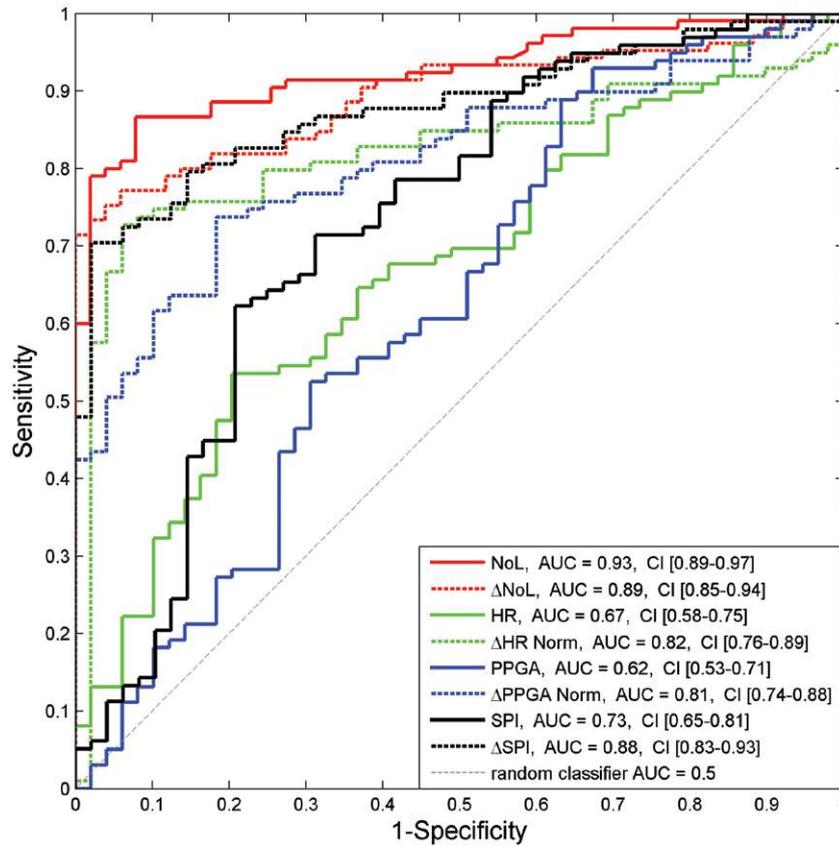


**Fig. 3.** Grading the response to intubation, skin incision/first trocar insertion, and nonnoxious period by post and reaction ( $\Delta$ ) values. The nociception level (NoL) index, whether by post (NoL) or reaction value ( $\Delta$ NoL), successfully graded the response to stimuli as expected (TP1 > TP2 > TNP) outperforming all other tested measures, which only partially generated graded responses to progressively noxious stimuli. For each box: central mark = median; edges of box = 25, 75%; whiskers extend to the most extreme data points; outliers are plotted individually by +. \* $P < 0.00625$ , \*\* $P < 0.001$ , \*\*\* $P < 0.0001$ . HR = heart rate; PPGA = pulse plethysmograph amplitude; SPI = surgical pleth index; TNP = nonnoxious period; TP1 = intubation; TP2 = skin incision/first trocar insertion.

duration, intensity, and time and were operator dependent. To overcome lack of standardization among clinical stimuli, an experimental noxious stimulus was included in the study protocol as a standardized, repeatable stimulus—tetanic stimulation.<sup>15,16</sup> The tetanic stimulation was repeated twice, with and without fentanyl, with the hypothesis that the measured response to the same stimulus with opioids will be attenuated compared to that with no analgesic. Compared to HR, PPGA, and SPI, NoL's *reaction* after the tetanic stimulations was the only one to change in the expected direction

after both noxious stimuli and be consistent with the antinociceptive state of the patient.

A shortcoming of our study design, measuring noninvasive blood pressure every 3 to 5 min, precluded the comparison between NoL and blood pressure. However, Martini *et al.*<sup>25</sup> recently tested the pain monitoring device compared to a continuous noninvasive measurement of blood pressure. They calculated an AUC of 0.95 for  $\Delta$ NoL, which was superior to the AUC of 0.78 calculated for change in mean arterial pressure ( $P < 0.001$ ). Also, under nonnociceptive conditions,



**Fig. 4.** Receiver operating characteristics curve analysis: discrimination of noxious stimuli (TP1 + TP2) from nonnoxious period. Nociception level (NoL) and  $\Delta$ NoL outperformed all other measures. *Dashed lines* for reaction ( $\Delta$ ) values; *Solid lines* for post-values. Heart rate (HR) and pulse plethysmograph amplitude (PPGA) reaction values are normalized (norm). AUC = area under the curve; SPI = surgical pleth index; TP1 = intubation; TP2 = skin incision/first trocar insertion.

**Table 3.** Sensitivity for Detecting Noxious Events at 84% Specificity

Parameter/Index	Sensitivity (%)	95% CI
NoL	87	77–92%
HR	37	28–47%
PPGA	21	14–30%
SPI	43	33–53%
$\Delta$ NoL	80	71–87%
$\Delta$ HR	76	66–84%
$\Delta$ PPGA	64	54–73%
$\Delta$ SPI	80	71–87%

Nociception level (NoL) achieved the highest sensitivity both in absolute values and reaction ( $\Delta$ ) values.

HR = heart rate; PPGA = pulse plethysmograph amplitude; SPI = surgical pleth index.

remifentanyl had no effect on NoL, in contrast to mean arterial pressure, which decreased as a function of dose.

Several factors explain why the NoL index proved more responsive to clinical and experimental stimuli than other measures. First, the vasodilating effect of propofol and loss of consciousness, affecting vessels' diameter, increase pulse amplitude to the point where PPGA ceases to correlate with noxious stimulation.<sup>26</sup> SPI largely depends on PPGA

(67%),<sup>19,26</sup> making it susceptible to the effect of propofol administered for anesthesia induction. A close look at the trend of PPGA (fig. 5A blue line) shows a steep rise after propofol administration, followed by a small descent after first tetanic stimulation (TET1), too small to change the direction of the slope. In comparison, the trend of measures around intubation (TP1) is shown (fig. 5B). Note the steep descent of PPGA when no propofol boluses were administered before the noxious stimulus. These results reveal possible limitations of PPGA and PPGA-based SPI as nociception monitors, especially in anesthetized patients who are subject to various external factors including pharmacologic and thermoregulatory influences on arteriovenous shunt perfusion.<sup>27</sup>

Second, the NoL index performed better than HR, which was the only measure that did not change significantly in response to initial skin incision/trocar insertion. This may be attributed to a remifentanyl-induced dose-dependent bradycardia that prevented progressive HR response with stimulus intensity.<sup>28,29</sup> In fact, HR responses to all noxious stimuli except intubation were marginal, resulting in a low AUC of 0.67.

Nociception level was superior to all other tested measures in discriminating noxious from nonnoxious stimuli, both as an absolute value after the stimulus, and comparing

**Table 4.** Reflection of Different Doses of Remifentanil during Nonnoxious (*Pre-TP2*) and Noxious (*Postlong TP2, Reaction*) Periods

Parameter	Remifentanil Group ng/ml	TP2 <i>Pre</i> Median (25–75%)	Pre <i>P</i> Value Comparison 2 vs. 4		TP2 <i>Reaction</i> ( <i>Postshort</i> ) Median (25–75%)	Comparison 2 vs. 4 <i>Postlong</i> <i>P</i> Value (Mann–Whitney)	Pre vs. Post within Dose <i>P</i> Value (Wilcoxon Signed-rank test)
			<i>P</i> Value (Mann–Whitney)	Median (25–75%)			
NoL (abs)	2	11 (3 to 17.7)	0.0654	22 (12.8 to 31.2)	5 (1.2 to 15)	0.0069	0.0027
	4	3 (2.2 to 8.6)		11 (4.9 to 18.9)			
HR (beats/min, %)	2	62 (54.6 to 68.9)	0.6819	64 (54.7 to 71.3)	3% (–0.7 to 6.5%)	0.27	0.073
	4	61 (51 to 66.4)		63 (52.2 to 66.8)			
PPGA (abs, %)	2	4 (1.8 to 6.6)	0.4579	4 (1.2 to 5.2)	–25% (–103.2 to –7.4%)	0.13	0.0009
	4	5 (3.1 to 7.6)		4 (2.8 to 7.1)			
SPI (abs)	2	36 (23.3 to 48.2)	0.0988	49 (30.6 to 62.7)	8 (2.3 to 22.5)	0.027	0.001
	4	25 (19.8 to 35.1)		33 (23 to 44.5)			
NIBP (mmHg, %)	2	88 (84.3 to 96)	0.5693	104 (92.7 to 108.8)	10% (4.2 to 15.7%)	0.16	0.0003
	4	83 (74 to 101.8)		93 (83.1 to 102)			

Nociception level (NoL) was the only measure to significantly differ as a function of remifentanil dose. NoL, surgical pleth index (SPI), and pulse plethysmograph amplitude (PPGA) increased significantly after skin incision in the low-dose group, but not in the high-dose group. Statistical significance after Bonferroni corrections: *P* < 0.00625 for *pre-TP2* comparison; *P* < 0.01 for *postlongTP2* comparison.

HR = heart rate; NIBP = noninvasive blood pressure; post = poststimulus; pre = prestimulus; TP2 = skin incision/first trocar insertion.

**Table 5.** Performance of Parameters and Indices by Study Endpoints.

Efficacy Endpoint	Success Criterion	NoL	HR	PPGA	SPI
Primary endpoint 1: response to stimuli (reaction, Δ)					
TP1	<i>P</i> < 0.00625	1	1	1	1
TP2	<i>P</i> < 0.00625	1	0	1	1
TNP	Not significant	1	0	1	1
TET1	<i>P</i> < 0.00625	1	0	–1	–1
TET2	<i>P</i> < 0.00625	1	0	0	1
Primary endpoint 2: discriminating noxious from nonnoxious stimuli					
ROC analysis	Median <i>poststimulus</i> analysis—AUC > 0.8	1	0	0	0
	Sensitivity > 80% (lower CI > 71%), for specificity of 84% (lower CI > 71%)	1	0	0	0
	<i>Reaction</i> analysis—AUC > 0.8	1	1	1	1
Secondary end point 1: grading response to stimuli of different intensities					
TET1-TET2 (post)	TET1 > TET2, <i>P</i> < 0.00625	1	1	1	1
TET1-TET2 (Δ)	TET1 > TET2, <i>P</i> < 0.00625	0	0	–1	–1
TP1-TP2-TNP (post)	TP1 > TP2 > TNP, <i>P</i> < 0.00625	1	0	0	0
TP1-TP2-TNP (Δ)	TP1 > TP2 > TNP, <i>P</i> < 0.00625	1	0	0	0
Secondary end point 2: reflecting different basal states of analgesia					
Nonnoxious period with and without fentanyl	<i>Pre-TET1</i> > <i>pre-TET2</i> , <i>P</i> < 0.00625	1	1	1	1
Noxious period with two levels of remifentanil	<i>Postlong TP2</i> : 2 ng/ml > 4 ng/ml, <i>P</i> < 0.01	1	0	0	0
	<i>Reaction long TP2</i> (Δ): 2 ng/ml > 4 ng/ml, <i>P</i> < 0.01	1	0	1	1

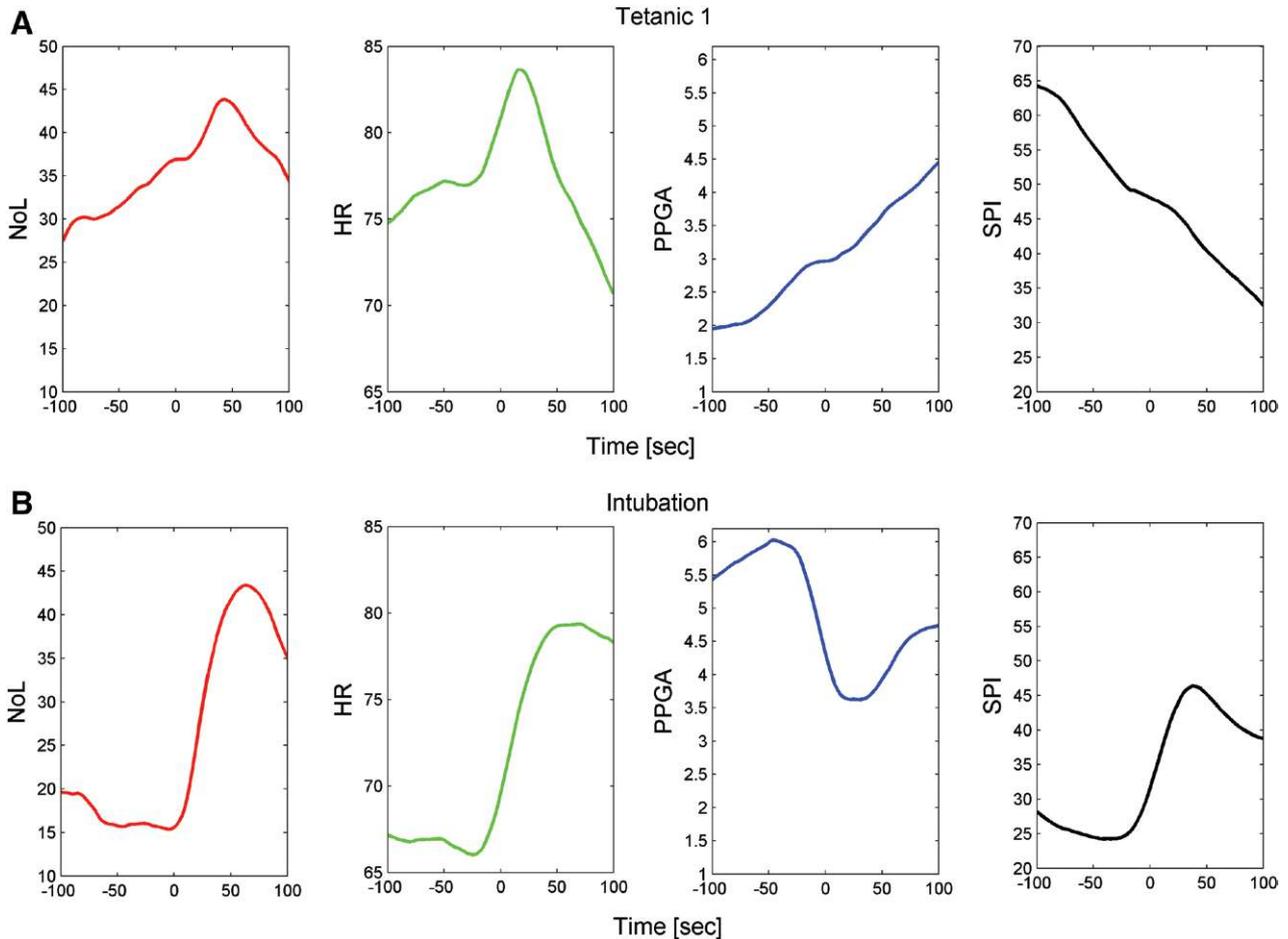
[1] indicates statistical significance in the expected direction, hence successfully meeting criterion requirements; [0] indicates the no statistical significance, hence failure to successfully meet criterion requirements. [–1] indicates the statistical significance in the opposite direction to that defined by study endpoint, hence failure to successfully meet criterion requirements.

abs = absolute value; AUC = area under the curve; HR = heart rate; NoL = nociception level; post = poststimulus; PPGA = pulse plethysmograph amplitude; pre = prestimulus; ROC = receiver operating characteristic curves; SPI = surgical pleth index; TET1 = first tetanic stimulus; TET2 = second tetanic stimulus; TNP = nonnoxious period; TP1 = intubation; TP2 = skin incision/first trocar insertion.

the change in values around stimulus (ΔNoL). Interestingly, although the AUC for all parameters was higher for the change compared to the absolute value, the reverse was true for the NoL index. We believe this difference to result from

the fact that the NoL index includes not only nociception-related parameters, but also their time derivatives.

The NoL algorithm was first introduced based on an analysis in which the patient data set was used for NoL's algorithm



**Fig. 5.** Trend over time. Nociception level (NoL) (*red*), heart rate (HR) (*green*), pulse plethysmograph amplitude (PPGA) (*blue*), and surgical pleth index (SPI) (*black*). Time 0s indicates annotation of stimulus: (A) tetanic 1 and (B) intubation.

development as well as evaluation.<sup>11</sup> These preliminary results showed that the NoL index better discriminates noxious from nonnoxious stimuli compared to single measures (AUC, 0.97 *vs.* 0.56 to 0.74, respectively).<sup>11</sup> Although a five-fold cross-validation method<sup>30</sup> was used, there remained a potential for bias. In the current study, the NoL index was calculated using the same closed algorithm on a new patient data set. Its performance remained high, validating the index algorithm.

As part of this initial validation of the NoL index, we included in this study a larger variety of procedures compared to the primary initiation study,<sup>11</sup> with NoL validity being maintained. Nonetheless, all procedures were conducted with GA. The NoL index has yet to be evaluated under other important settings including regional anesthesia, combined regional anesthesia and GA, local analgesia, and sedation.

This study compared the NoL index to other accepted measures of nociception, including HR, PPGA, and SPI, and found it to be largely superior to them. Other methods for the assessment of nociception are currently under development. It is not the scope of this article to compare the various methods. However, a recent review<sup>31</sup> of novel developments in pain assessment scans the different methods and outlines the difficulties in this field of research. Striving for objective assessment, these new

methods are based on physiologic systems such as the autonomic nervous system, central nervous system electrical activity, and biomarkers, among others, and these are influenced by various pharmacologic, pathophysiologic, and psychologic factors involved in the processing of pain. This review concluded that composite algorithms like the one used by the NoL index may be a promising future avenue.<sup>31</sup>

The importance of our results, along with two previously published works about this novel index,<sup>11,25</sup> is their encouraging findings, which suggests that it can monitor measures' trends accurately. Although the NoL index relies on various physiologic measures, it was largely unaffected by mechanisms hindering proportionate changes in various single measures. In agreement with Cowen *et al.*,<sup>31</sup> these results demonstrate the strength of multiparametric approaches and algorithms that incorporate multiple time derivatives and the value of advanced statistical methods in combining diverse inputs. Trending of physiologic parameters has always been the basis for medical management and a prerequisite in order to influence patient outcome. This article presents an effective index for trending the nociceptive state of the anesthetized patient. Once in clinical practice, large-scale studies will be able to reveal the influence of nociception/antinociception monitoring on patient outcome.

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## Competing Interests

Drs. Edry and Sessler serve on an advisory board for Medasense, Ramat Yishai, Israel, and have an equity interest in the company. Medasense is the developer of the nociception level index. The other authors declare no competing interests.

## Reproducible Science

Full protocol available from Dr. Edry: ruedry@gmail.com. Raw data available from Dr. Edry: ruedry@gmail.com.

## Correspondence

Address correspondence to Dr. Edry: Anesthesiology Department, Rambam Medical Centre, The Ruth and Bruce Rappaport Faculty of Medicine, Technion Institute of Technology, 8th Aliya Street, Yaad 20155, Israel. ruedry@gmail.com. This article may be accessed for personal use at no charge through the Journal Web site, [www.anesthesiology.org](http://www.anesthesiology.org).

## References

- Rantanen M, Yli-Hankala A, van Gils M, Yppärilä-Wolters H, Takala P, Huiku M, Kymäläinen M, Seitsonen E, Korhonen I: Novel multiparameter approach for measurement of nociception at skin incision during general anaesthesia. *Br J Anaesth* 2006; 96:367–76
- Loeser JD, Treede RD: The Kyoto protocol of IASP basic pain terminology. *Pain* 2008; 137:473–7
- Le Guen M, Liu N, Bourgeois E, Chazot T, Sessler DI, Rouby JJ, Fischler M: Automated sedation outperforms manual administration of propofol and remifentanyl in critically ill patients with deep sedation: A randomized phase II trial. *Intensive Care Med* 2013; 39:454–62
- Salo M: Effects of anaesthesia and surgery on the immune response. *Acta Anaesthesiol Scand* 1992; 36:201–20
- Libby P: Inflammation in atherosclerosis. *Nature* 2002; 420:868–74
- Vallejo R, Hord ED, Barna SA, Santiago-Palma J, Ahmed S: Perioperative immunosuppression in cancer patients. *J Environ Pathol Toxicol Oncol* 2003; 22:139–46
- Tsuchiya Y, Sawada S, Yoshioka I, Ohashi Y, Matsuo M, Harimaya Y, Tsukada K, Saiki I: Increased surgical stress promotes tumor metastasis. *Surgery* 2003; 133:547–55
- Page GG, Ben-Eliyahu S: The immune-suppressive nature of pain. *Semin Oncol Nurs* 1997; 13:10–5
- Crozier TA, Müller JE, Quittkat D, Sydow M, Wuttke W, Kettler D: Effect of anaesthesia on the cytokine responses to abdominal surgery. *Br J Anaesth* 1994; 72:280–5
- Corsi M, Mariconti P, Calvillo L, Falchi M, Tiengo M, Ferrero ME: Influence of inhalational, neuroleptic and local anaesthesia on lymphocyte subset distribution. *Int J Tissue React* 1995; 17:211–7
- Ben-Israel N, Kliger M, Zuckerman G, Katz Y, Edry R: Monitoring the nociception level: A multi-parameter approach. *J Clin Monit Comput* 2013; 27:659–68
- Breiman L: Random forests. *Mach Learn* 2001; 45:5–32
- Blake DW, Hogg MN, Hackman CH, Pang J, Bjorksten AR: Induction of anaesthesia with sevoflurane, preprogrammed propofol infusion or combined sevoflurane/propofol for laryngeal mask insertion: Cardiovascular, movement and EEG bispectral index responses. *Anaesth Intensive Care* 1998; 26:360–5
- Aho AJ, Yli-Hankala A, Lyytikäinen LP, Jääntti V: Facial muscle activity, Response Entropy, and State Entropy indices during noxious stimuli in propofol-nitrous oxide or propofol-nitrous oxide-remifentanyl anaesthesia without neuromuscular block. *Br J Anaesth* 2009; 102:227–33
- Ellerkmann RK, Grass A, Hoefft A, Soehle M: The response of the composite variability index to a standardized noxious stimulus during propofol-remifentanyl anaesthesia. *Anesth Analg* 2013; 116:580–8
- Gruenewald M, Meybohm P, Ilies C, Höcker J, Hanss R, Scholz J, Bein B: Influence of different remifentanyl concentrations on the performance of the surgical stress index to detect a standardized painful stimulus during sevoflurane anaesthesia. *Br J Anaesth* 2009; 103:586–93
- Ferreira DA, Nunes CS, Antunes L, Lobo F, Amorim P: Practical aspects of the use of target controlled infusion with remifentanyl in neurosurgical patients: Predicted cerebral concentrations at intubation, incision and extubation. *Acta Anaesthesiol Belg* 2006; 57:265–70
- Do WS, Kim TK, Kim HK, Kim CH: The EC(50) of remifentanyl to minimize the cardiovascular changes during head holder pinning in neurosurgery. *Korean J Anesthesiol* 2012; 63:327–33
- Huiku M, Uutela K, van Gils M, Korhonen I, Kymäläinen M, Meriläinen P, Paloheimo M, Rantanen M, Takala P, Viertiö-Oja H, Yli-Hankala A: Assessment of surgical stress during general anaesthesia. *Br J Anaesth* 2007; 98:447–55
- Gelb AW, Leslie K, Stanski DR, Shafer SL: Monitoring the depth of anaesthesia, Miller's Anaesthesia, 7th edition. Edited by Miller RD. Philadelphia, Churchill Livingstone, 2010, p 1234
- Kazama T, Ikeda K, Morita K: Reduction by fentanyl of the Cp50 values of propofol and hemodynamic responses to various noxious stimuli. *ANESTHESIOLOGY* 1997; 87:213–27
- Liu H, Wu T: Estimating the area under a receiver operating characteristic curve for repeated measures design. *J Stat Softw* 2003; 8:1–18
- Hanley JA, McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; 143:29–36
- Struys MM, Vanpeteghem C, Huiku M, Uutela K, Blyeaert NB, Mortier EP: Changes in a surgical stress index in response to standardized pain stimuli during propofol-remifentanyl infusion. *Br J Anaesth* 2007; 99:359–67
- Martini CH, Boon M, Broens SJ, Hekkelman EF, Oudhoff LA, Buddeke AW, Dahan A: Ability of the nociception level, a multiparameter composite of autonomic signals, to detect noxious stimuli during propofol-remifentanyl anaesthesia. *ANESTHESIOLOGY* 2015; 123:524–34
- Korhonen I, Yli-Hankala A: Photoplethysmography and nociception. *Acta Anaesthesiol Scand* 2009; 53:975–85
- Kurz A, Xiong J, Sessler DI, Dechert M, Noyes K, Belani K: Desflurane reduces the gain of thermoregulatory arteriovenous shunt vasoconstriction in humans. *ANESTHESIOLOGY* 1995; 83:1212–9
- Masjedi M, Zand F, Kazemi AP, Hoseinipour A: Prophylactic effect of ephedrine to reduce hemodynamic changes associated with anaesthesia induction with propofol and remifentanyl. *J Anaesthesiol Clin Pharmacol* 2014; 30:217–21
- Komatsu R, Turan AM, Orhan-Sungur M, McGuire J, Radke OC, Apfel CC: Remifentanyl for general anaesthesia: A systematic review. *Anaesthesia* 2007; 62:1266–80
- Hastie T, Tibshirani R, Friedman J: The Elements of Statistical Learning: Data Mining, Inference and Prediction, 2nd edition. New York: Springer, 2009
- Cowen R, Stasiowska MK, Laycock H, Bantel C: Assessing pain objectively: The use of physiological markers. *Anaesthesia* 2015; 70:828–47