Validation of Nociception Monitor – The NoL Index

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Introduction: The physiologic and anesthetic components that remain most challenging to assess are nociception and analgesia. NoL (Nociception Level) is an index of nociception based on a non-linear combination (random forest regression) of heart rate, heart rate variability, photo-plethysmograph wave amplitude, skin conductance, skin conductance fluctuations, and their time derivatives. [1] We evaluated the abilities of NoL and other measures of nociception to discriminate between noxious and non-noxious stimuli, to progressively respond to graded stimuli, and to respond to analgesic administration. Compared measures included heart rate (HR), non invasive blood pressure (NIBP), pulse plethysmograph amplitude (PPGA), and surgical pleth index (SPI).

Materials and Methods: Intraoperative NoL was compared to HR, NIBP, PPGA, and SPI around five specific stimuli in 58 subjects undergoing elective surgery with general anesthesia: tetanic stimulation without analgesia (TET1), tetanic stimulation after 2 µg/kg fentanyl (TET2), intubation (TP1), initial skin incision or trocar insertion (TP2), and a non-noxious period (TNP). The response around TP2 was analyzed at two target plasma concentrations of remifentanil

The Device: The study was conducted using the first generation configuration of PMD device (PMD-100, Figure 1), including: [1] A finger probe containing sensors acquiring nociception-related physiological parameters: photo-plethysmogram (PPG), Galvanic skin response (GSR), skin temperature and a 3D axis accelerometer, connected to [2] a console and a PC.

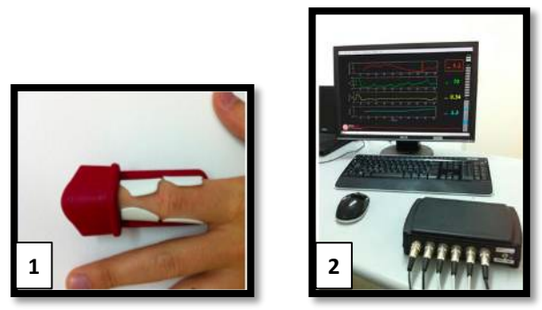


Figure 1: Study device (PMD-100)

Results:

- **NoL responded to noxious stimuli and remained unchanged in response to non-noxious stimuli (Figure 2).**
- **NoL progressively increased in response to increased stimulus intensity, outperforming all other measures which successfully graded only part of the relations (Figure 3).**
- **NoL better discriminated noxious from non-noxious stimuli, with an AUC of 0.93 (95% confidence interval: 0.89–0.97) (Figure 4) and a sensitivity of 87% at a specificity of 84% (Table 1).**
- **NoL was the only measure that reliably reflected two different analgesic concentrations of remi-fentanil during initial skin incision or trocar insertion.**
- **Compared to HR, NoL was less susceptible to remifentanil administration and resulting bradycardia.**
- **Compared to PPGA and SPI, NoL was less susceptible to propofol bolus administration and resulting reduction in systemic vascular resistance.**

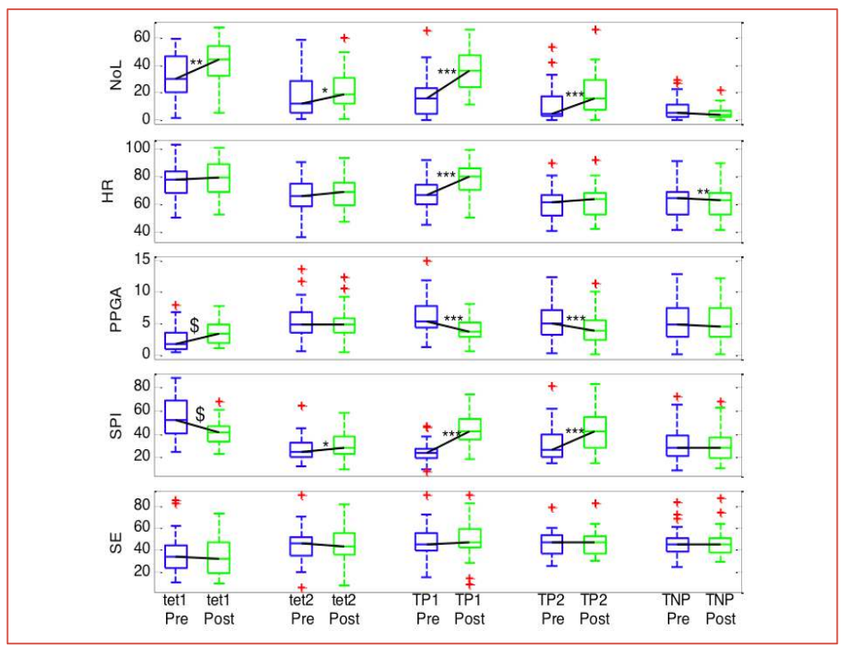


Figure 2: The reaction of individual measures to clinical and experimental stimuli. Wilcoxon Signed-Rank test. *p<0.00625, **p<0.001, ***p<0.0001. Note that NoL, HR, and SPI are expected to increase in response to noxious stimuli while PPGA is expected to decrease. $ denotes significant reaction opposite 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 +.

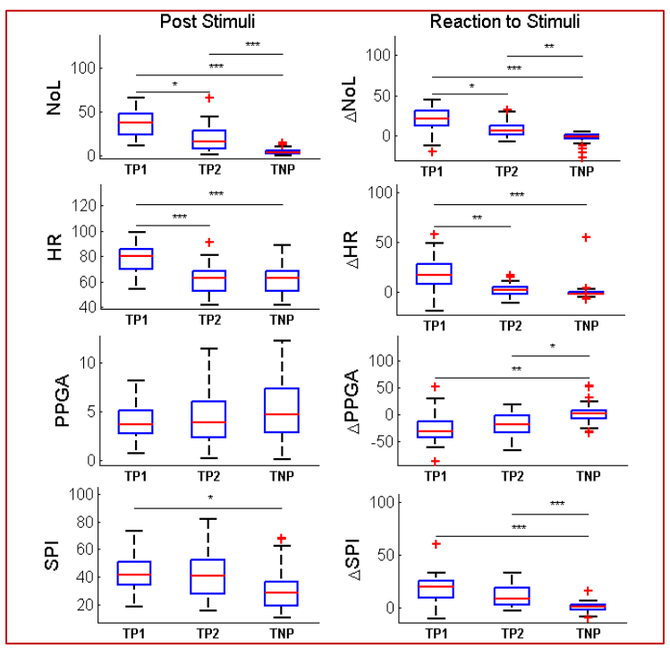
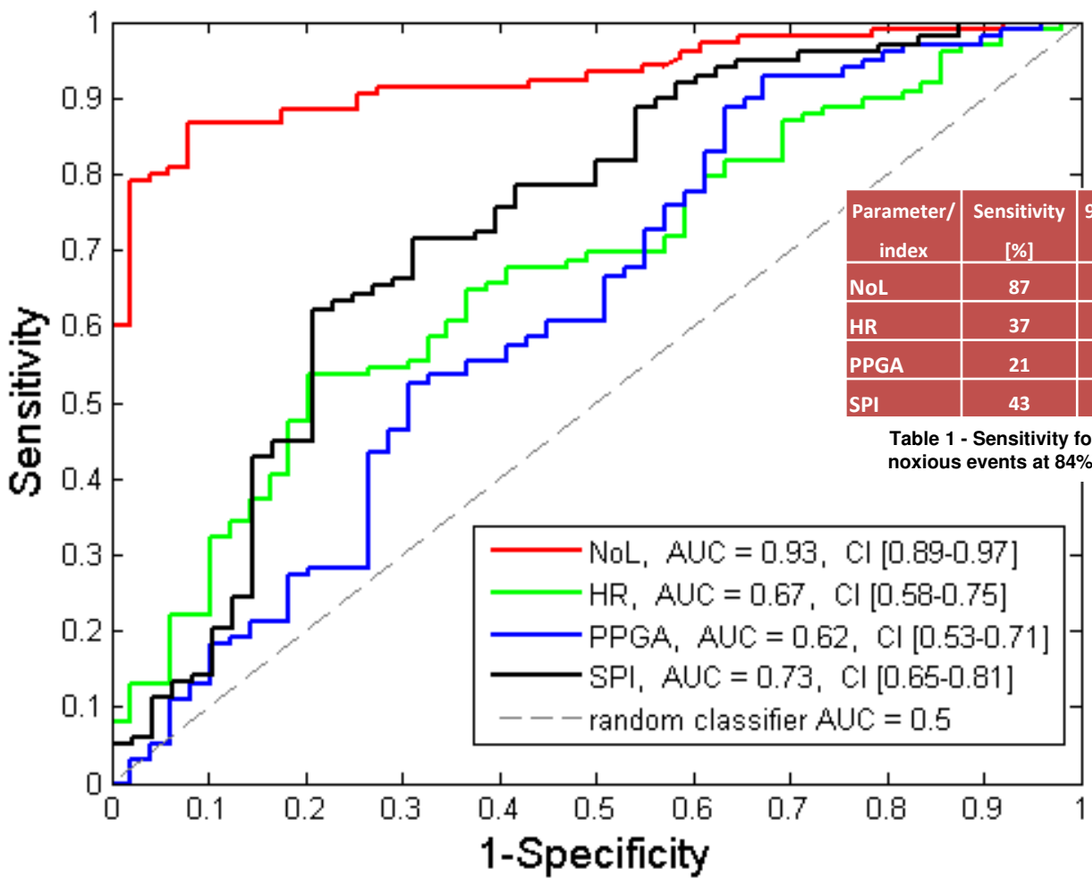


Figure 3: Grading the response to clinical stimuli TP1, TP2, TNP by *post* and *reaction* (Δ) values. For each box: central mark=median; edges of box=25, 75%; whiskers extend to the most extreme data points; outliers are plotted individually by +. *p<0.00625, **p<0.001, ***p<0.0001.



Parameter/ index	Sensitivity [%]	95% Confidence interval
NoL	87	[77%, 92%]
HR	37	[28%, 47%]
PPGA	21	[14%, 30%]
SPI	43	[33%, 53%]

Table 1 - Sensitivity for detecting noxious events at 84% specificity

Figure 4: ROC analysis: Discrimination of noxious stimuli (TP1 + TP2) from non-noxious period (TNP). HR and PPGA *reaction* values are normalized (norm).

CONCLUSIONS: Study results validate the performance of the NoL index, demonstrating its ability to correctly **identify and grade the response** to clinical and experimental noxious stimuli and to **discriminate between noxious and non-noxious stimuli** with **high sensitivity and specificity**. Moreover, NoL index correctly **reflected the analgesic state of the patient**. Compared to four other measures of nociception, NoL index was superior and seems more adapted for representing nociception in patients with general anesthesia.

References: 1. Ben-Israel N, Kliger M, Zuckerman G, Katz Y, Edry R: Monitoring the nociception level: A multi-parameter approach. J Clin Monitor Comput 2013; 27(6):659–68.