Introducing the NOL-Nociception Level Index® Algorithm

A Technical Overview

Background

The role of anesthesia is to provide optimal conditions during surgery to treat patients, whilst ensuring patient safety and comfort. The components required to achieve this goal when using general anesthesia are hypnosis, analgesia, amnesia, and when indicated, muscle relaxation.

Anesthesia providers use non-invasive monitors to gauge the adequacy of hypnosis, amnesia, and muscle relaxation.

The last remaining component of anesthesia that has no objective, non-invasive monitor available to anesthesia providers, is analgesia (Figure 1).

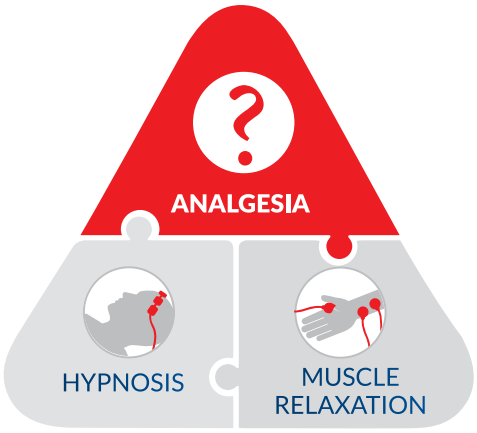


Figure 1: The triad of anaesthesia

Analgesia is the treatment of pain or nociception

Nociception Vs. Pain

The term pain is a conscious perception of actual or potential tissue damage and therefore cannot be used during an unconscious state, such as general anesthesia. The term nociception was introduced and describes the neural process of encoding noxious stimuli. Nociception refers to processing of information by the peripheral (PNS) and central nervous system (CNS) from activation of nociceptors, specific receptors activated by tissue damage. Typically, noxious stimuli activate nociceptors that are present in peripheral structures and transmit information to the spinal cord dorsal horn. From there, the information continues to the brainstem (nucleus caudalis) and ultimately the thalamus and the somatosensory cortex, where the perception of pain is generated (Figure 2).

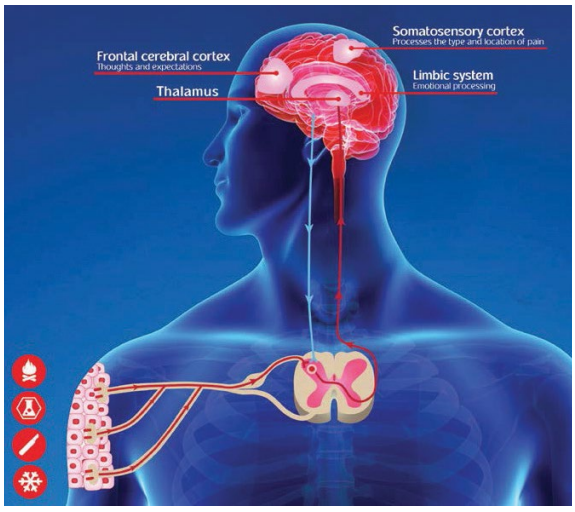


Figure 2: The nociceptive pathway

The importance of nociception monitoring

The adequacy of analgesia in an anesthetized patient is currently assessed using surrogate measures, such as heart rate, blood pressure, tearing, pupillary response, and sweating. These surrogate measures are also influenced by factors not related to pain, such as hypoxia, hypercarbia, hyperthermia, and medications. As a result, treatment of analgesia is highly subjective and variable between providers as they interpret these surrogate measures as signs of adequate analgesia. This subjective interpretation by providers based on training and experience results in wide ranges of opioids being administered to treat moderate to severe surgical pain during the operation. Excessive or insufficient doses of opioids result in the adverse outcomes shown in Figure 3.[1]

Anesthesia practice is evolving to address the need for better nociception management, with efforts to spare and/or substitute opioids, as well as using multimodal analgesia regimens. This underscores the need for a reliable and accurate way to assess the nociceptive/non-nociceptive state of the patient, as a basis for optimizing intraoperative analgesia according to each patient's particular sensitivity and needs.

The characteristics of individual patients, specific procedures, and various analgesia regimens make the titration of analgesics even more challenging.

Underdosing of opioids during anesthesia leads to sympathetic activation, manifesting as intraoperative tachycardia, hypertension, and neuroendocrine activation of stress hormones such as cortisol and ACTH. Postoperative adverse events include acute or chronic postoperative pain.[2,3] Opioid overdose may cause intraoperative cardiovascular depression and hypotension, prolonged time to emergence, postoperative respiratory depression,[4] nausea and vomiting,[5] cognitive disturbances, opioid induced hyperalgesia (OIH),[6] urinary retention, and constipation.

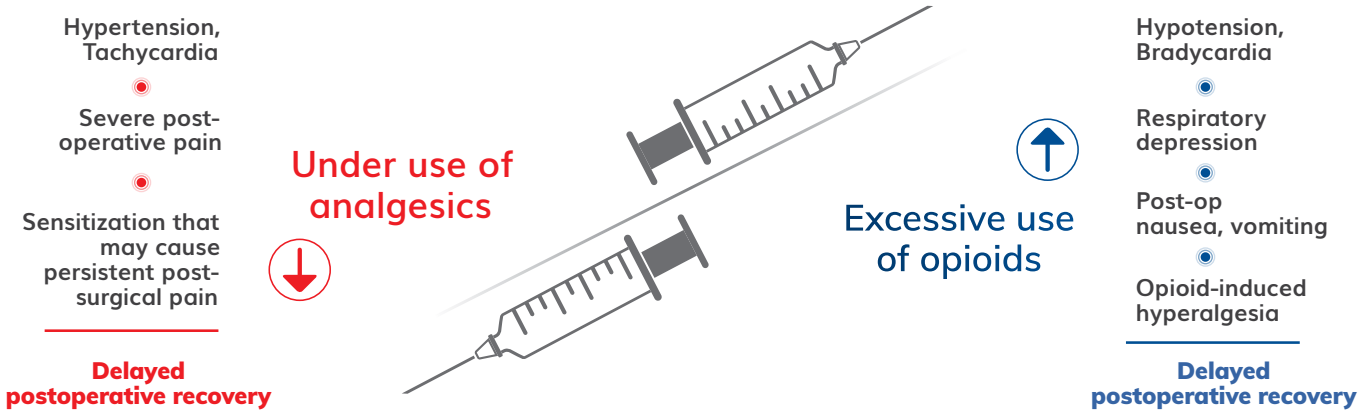


Figure 3: Consequences of insufficient or excessive use of opioids

Setting criteria for a nociception monitor

Developing an objective method of measuring nociception and adequacy of analgesia requires tools that are sensitive and specific to the physiological response to noxious stimuli. They need to be observer-independent and cannot rely on the patient's ability to communicate.

Each patient has a different pain threshold and a different physiological response to the same painful stimulus. Dahan et al present a detailed description of the effect of interpatient variability on opioid dosing and the contribution of a pharmacogenetic effect. After a standard dose of opioid, the inter-patient variability in plasma concentrations and analgesic effect is large (at least 30-fold) and related to various factors including weight-related parameters (lean and fat body mass), organ function (hepatic and renal function), and cardiac output.[7] Furthermore, studies have shown a wide range of analgesic dosing practices across clinicians, depending on their personal beliefs and experiences.[8] Therefore it is vital to monitor each patient's personal response, and personalize the treatment accordingly. There is sufficient evidence in the scientific literature describing the physiological response to nociception to ascertain the following:

1. The activation of nociceptors increases with increasing levels of noxious stimuli.

2. Analgesics block/inhibit the secretion of neurotransmitters after the activation of nociceptors, thereby preventing/attenuating the pain/nociception level.

3. Maintaining the same noxious stimulus while increasing the level of analgesics should result in a decreased level of nociception (and vice versa when decreasing the level of analgesics.

The complexity of the sympathetic nervous system (SNS) response

Activation of the sympathetic nervous system, as a result of multiple stimuli and inputs, leads to a wide range of nociception-related physiological responses (see Figure 4).

Different physiological parameters, representing different systems, may exhibit complex inter-associations and variable response profiles. Consequently, the measurement of intraoperative nociception should integrate multiple physiological parameters in order to reflect the complex nature of pain.[9]

The Nociception Level (NOL) index recognizes the complex nature of this process, and uses a multiparameter composite of autonomic signals, taking into account the effect of anti-nociception (analgesia) agents on board. This is referred to as the nociception/anti-nociception balance (NANB).

The NOL technology focuses on the integrated physiological response to noxious stimuli, rather than a single indicator or individual pain marker.

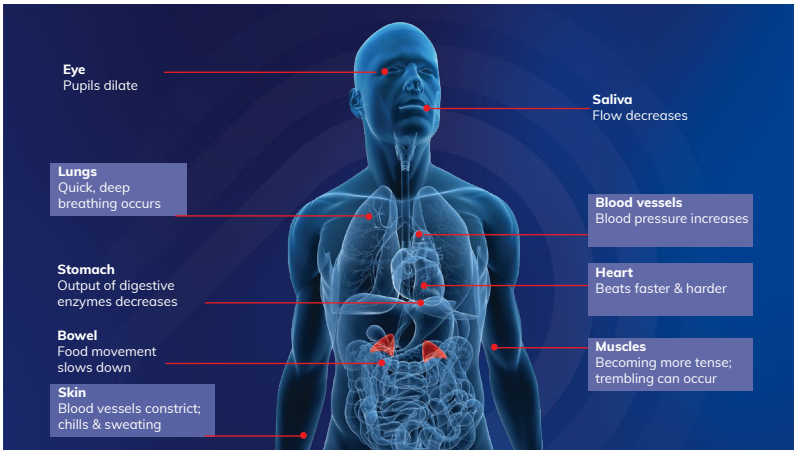


Figure 4: The ANS responses to nociception

The PMD-200™ system with the NOL - Nociception Level Index®

The PMD-200 is a physiological monitor that personalizes analgesic dosing by providing a numeric, non-linear scale of nociceptive response levels, called NOL – the nociception level index. During surgical stimulation under general anesthesia, a NOL value of zero indicates no nociception, and NOL of 100 indicates extreme nociception.

Figure 5: The PMD-200

System components

The PMD-200 system consists of a display and computing unit, a reusable non-invasive finger probe and a single-use sensor.

The proprietary signal acquisition sensor platform (the combination of the finger probe and the single-use sensor) acquires physiological signals. Using advanced algorithms, the system processes and analyses multiple nociception-related physiological parameters and their various derivatives, which correspond with the sympathetic nervous system's response to noxious stimuli.

The finger probe and single-use sensor continuously acquire four physiological signals through the following four sensors (See Figure 6):

1. Photoplethysmograph (PPG)
2. Galvanic Skin Response (GSR)
3. Peripheral Temperature (Temp)
4. Accelerometer (ACC)

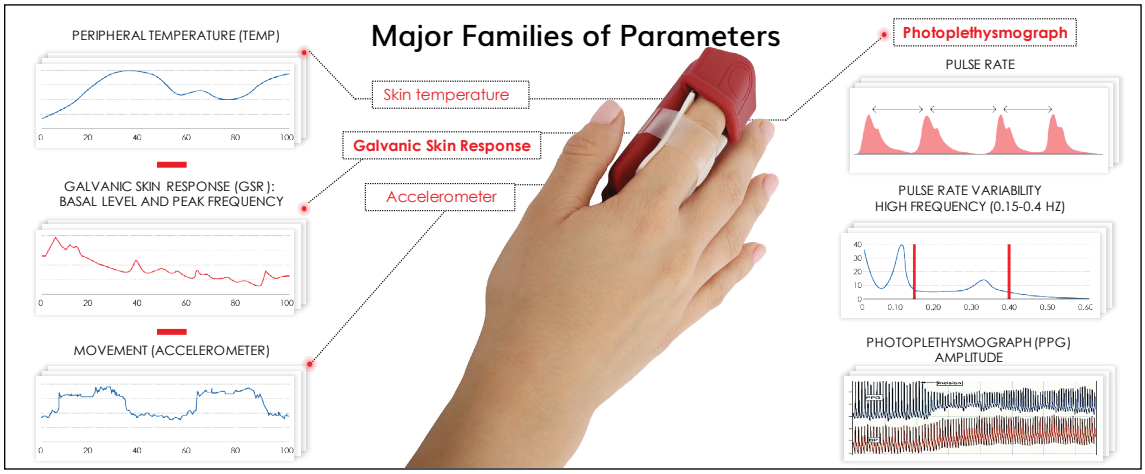


Figure 6: Illustration of the signals and parameters extracted from the sensors

From these four signals the NOL algorithm extracts and analyses nociception-related physiological parameters and derivatives: pulse rate, pulse rate variability, pulse wave amplitude, skin conductance level, peripheral temperature, movement, and their various derivatives. Then a patient's specific nociception signature is established and continuously monitored. Peripheral temperature and movement serve as guardrails supporting algorithm validity and do not contribute directly to the algorithm calculation.

NOL algorithm development

The NOL algorithm was developed using a supervised machine learning method called Random Forest.
The Random Forest algorithm, introduced by Breiman in 2001, is a powerful method that makes a prediction by aggregating results from an ensemble of randomized regression trees (Figure 7).
The algorithm was trained on thousands of data points from the four sensors to characterize nociception patterns in terms of physiological response, interactions, and correlations between different variables, including multiple mathematical derivatives. A training database comprising multiple examples of input and output pairs was constructed. The database contains dozens of annotated NOL data sets from elective surgeries conducted under general anesthesia in adult patients. The NOL algorithm input values were a set of features from the four signals associated with the response of the sympathetic nervous system to noxious responses and non-noxious states, and the output values were nociception levels, as graded by clinicians, for different noxious stimuli of various intensities. Standard Pk/Pd models were used to calculate the effect site concentration of opioid based on the dosing. A clinical score, named the Combined Index of Stimulus and Analgesia (CISA), was derived from the clinician estimated stimulus level during surgery and the effect of the analgesic drugs.

The stimulus intensity level ($Stim_{intensity}$) represents the clinician graded intensity of the surgical event and is a number between 0 and 10.

Subtracted from the stimulus intensity is the normalized measure of the effect of analgesic drugs ($-ß \cdot ce_{opioids}$). The size of this effect at each point in time during the surgery is derived from the pharmacokinetic and pharmacodynamic model of the opioid dosing scheme (Minto et. al. for remifentanil and Shafer et al. for fentanyl).[10,11]

$$CISA = Stim_{intensity} - ß \cdot ce_{opioids} + Y$$

Thus the CISA score is higher for more intense and noxious stimuli but is reduced by the magnitude of the analgesic (opioid) given during the case. To maintain a positive CISA value, an offset 'Y' was added.

The training phase of the Random Forest model captures the pattern that best describes the response of all parameters and derivatives to the different levels of noxious stimulation (CISA levels). The Random Forest model output is then transformed into the NOL index, a non-linear integer scale with a range of 0-100 in which 0 represents the absence of nociceptive response and 100 represents an extreme nociceptive response.

Machine learning algorithms, such as Random Forest can use either 'supervised' (or 'labeled') learning, or 'unsupervised' learning. The stimulus intensity during each case used in training the algorithm was 'labeled' by trained clinicians. Therefore, the NOL algorithm does not use 'unsupervised' learning.

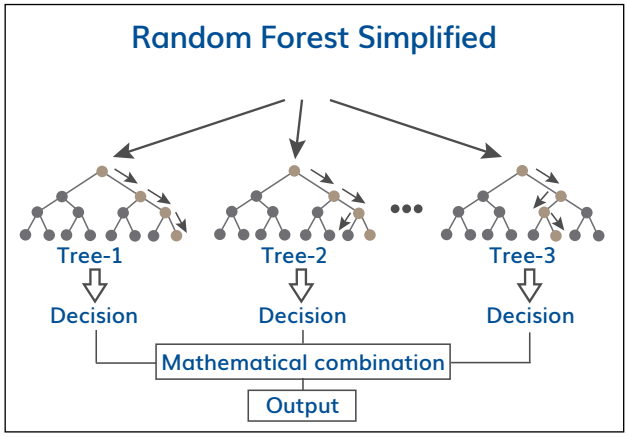


Figure 7: Random Forest Model

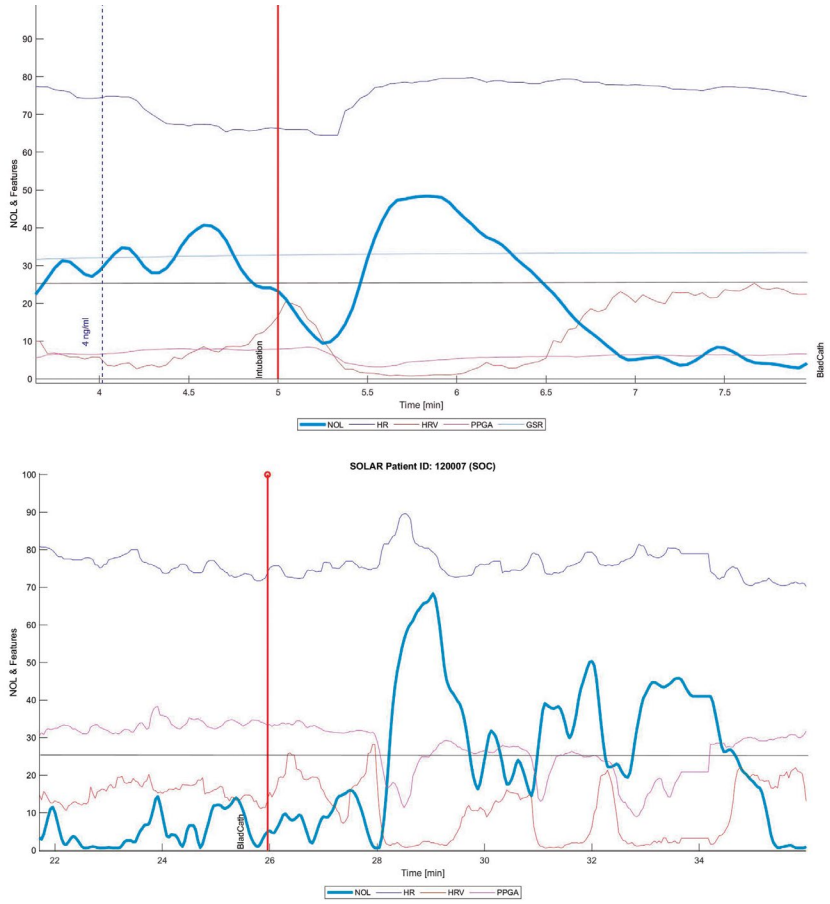
Personalized monitoring with NOL

NOL is a continuous, adaptive and objective measure of the nociception/anti-nociception balance that is personalized to the patient.

Although the model is locked, the algorithm personalizes the nociception index to the individual patient by implementing an adaptive weighting mechanism between the static model and the patient's unique physiologic responses during the surgical procedure. Initially, the extracted physiological features of the patient are normalized to a pre-loaded database of tens of thousands of data points. As more data is gathered for the currently monitored patient, the influence of the pre-loaded population data decreases and the weighting of the patient's unique physiological response increases, and thus the NOL output is personalized to the patient.

This personalization confers benefits in clinical practice as patients vary widely in their response to nociceptive stimuli and analgesia. NOL does not just treat the 'average' patient, since there is wide interpatient variability associated with both the response to the nociceptive stimulus and to the analgesia. By using a personalized measure, NOL can be used to objectively assess patients with extreme responses (outliers) who do not match the typical population models on which drug dose response curves are based, and therefore treat outlier cases that require less or more analgesia than would be predicted.

The examples in Figure 8 demonstrate the individualization and learning characteristics of the NOL algorithm, in the case of inter-patient differences in resting HR levels. For Patient A, who has a resting HR of around 70 bpm, a heart rate of 80 bpm is considered above their normal range, and therefore indicates nociception, as seen by the peak in NOL at minute 5.5. For Patient B, who's resting heart is around 80 bpm, only when their heart rate reaches 90bpm does NOL increase above 25 and indicate nociception (at minute 28).



Patient A

Patient B

Figure 8: Patient A and Patient B NOL and features

Algorithm verification & validation

After completion of training, verification and validation was conducted using datasets that were separate from the training dataset. The two verification and validation datasets were taken from nine clinical trials conducted in adult patients undergoing elective major abdominal surgery under general anesthesia in multiple geographic locations representing a diverse dataset intended to ensure adequate challenging of the algorithm in a wide variety of clinical settings.

All verification and validation tests met their acceptance criteria and NOL demonstrated high levels of sensitivity and specificity for noxious stimulation at a threshold of 25.

Clinical validation

Following the development of the NOL index, validation studies were performed to assess its ability to detect the ANS response to noxious stimuli and to changes in analgesics dosage.

The results from the Martini et al.,[12] Stöckle et al.,[13] and Edry et al.[14] validation studies, demonstrate NOL's performance in the intraoperative care setting during general anesthesia, in common regimens such as inhalational anesthesia, TIVA and general anesthesia combined with regional anesthesia.

The NOL index reliably measures the changes in the nociceptive response at different remifentanil concentrations[12]

N=71; ASA I – III; Ages 18-80; BIS target 45+/-5; Elective surgery under general anesthesia

NOL demonstrated clinically relevant correlation with the analgesic state of the subject.

The NOL index remains unaffected under non-noxious conditions, regardless of remifentanil concentration, and decreases for the same noxious stimulus with increasing remifentanil concentrations.

This analysis indicates that the NOL is a reliable measure of nociception and is not affected by the hemodynamic effects of remifentanil (Figure 9).

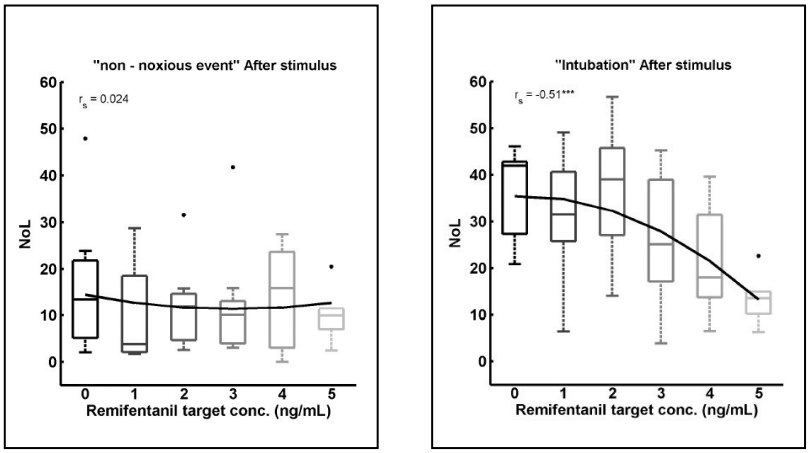


Figure 9: NOL values against increasing remifentanil concentrations

Superiority of the NOL index in detecting and distinguishing between various noxious stimuli, compared to commonly used parameters[12]

N=71; ASA I – III; Ages 18-80; BIS target 45+/-5; Elective surgery under general anesthesia

In the analysis testing the response of NOL, BIS, HR and MAP to different noxious stimuli and non-noxious periods, (Figure 10) NOL demonstrated clinically relevant grading of noxious stimuli as expected by the intensity of a stimulus, significantly changing after intubation and incision, while showing no significant change during the non-noxious period.

NOL correctly graded the level of nociceptive reaction: non-noxious stimulus NOL < incision NOL < intubation NOL ($p < 0.05$).

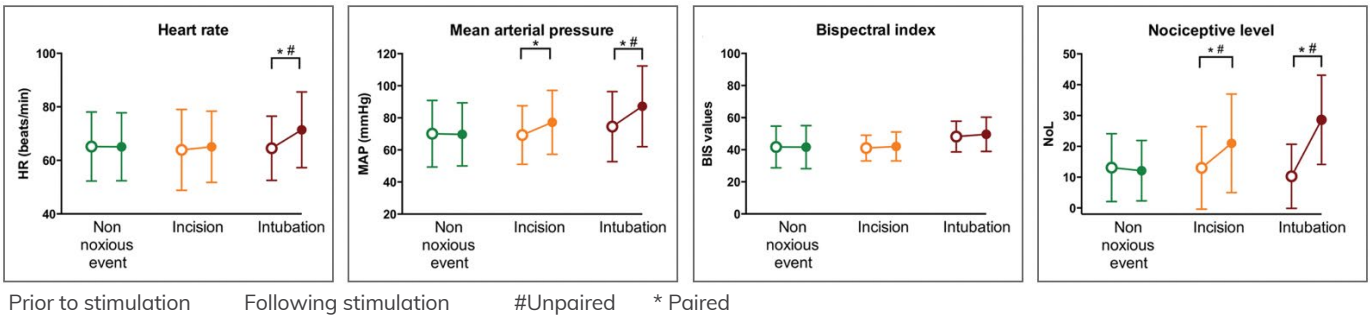


Figure 10: Different parameters ability to distinguish between various noxious stimuli

The NOL index correlates with increased dosage of analgesics[13]

Standardized painful stimuli were applied to patients under general anesthesia, while each patient received increasing remifentanil doses.

The magnitude of the NOL index response to a standardized nociceptive stimulus decreases with higher doses of remifentanil (Figure 11).

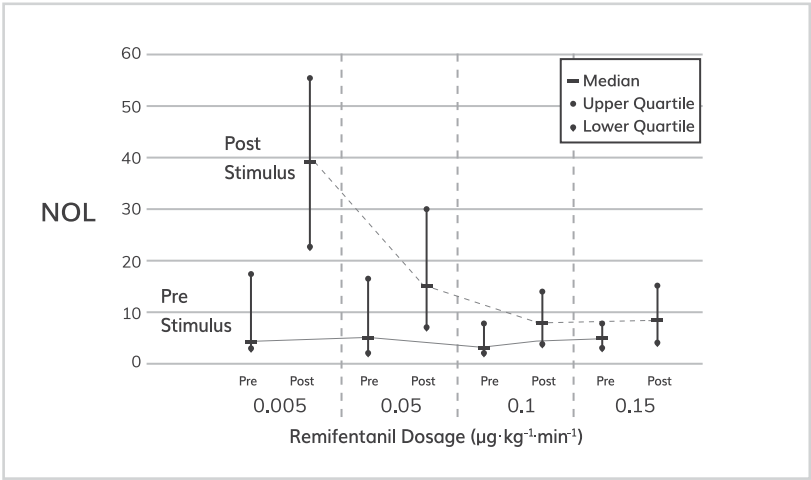


Figure 11: NOL response to higher doses of remifentanil

The NOL index outperforms single parameters in routine use for nociception[14]

N=58; ASA I – III; Ages 18-75; Entropy target <60; Elective surgery under general anesthesia

The multiparameter NOL index demonstrated high levels of sensitivity and specificity outperforming single parameters in routine use (HR, PPGA and surgical pleth index (SPI,GE) for nociception assessment in the operating room (Figure 12). NOL reached an AUC of 0.93, outperforming all the other parameters.

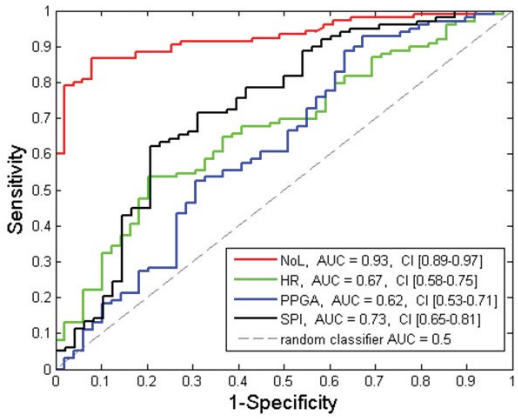


Figure 12: ROC curve of NOL against single parameters

The NOL index performs consistently in different patient cohorts

A large-scale validation study was performed in a cohort of 447 patients including sub group analysis for age, sex, BMI, analgesia regimen ASA status and anesthesia regimen in order to demonstrate the generalizability of the performance of the NOL index in multiple cohorts including different anesthetic and analgesic techniques distinguishing between non-nociceptive and nociceptive events with high levels of sensitivity and specificity in all cohorts (Figure 13).[15]

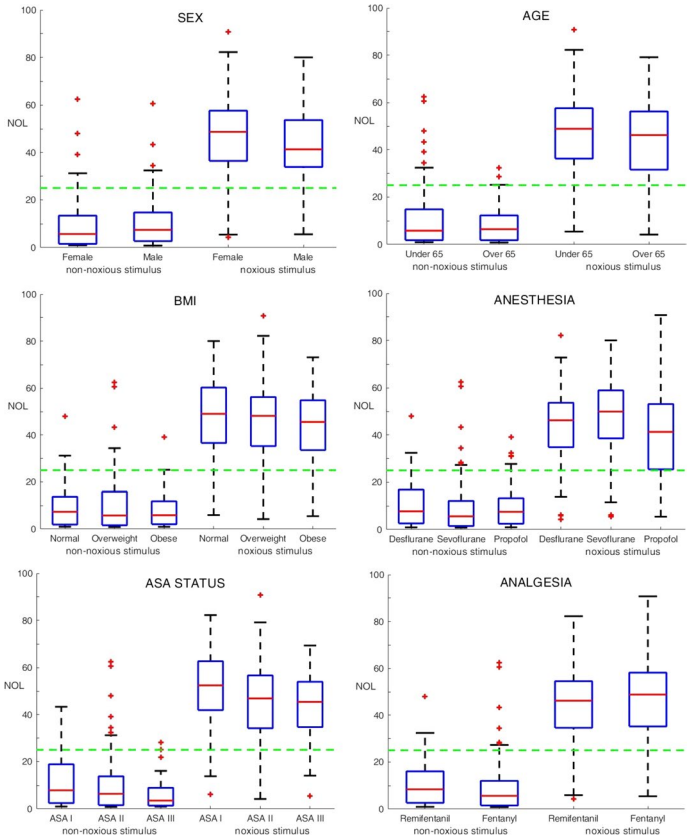
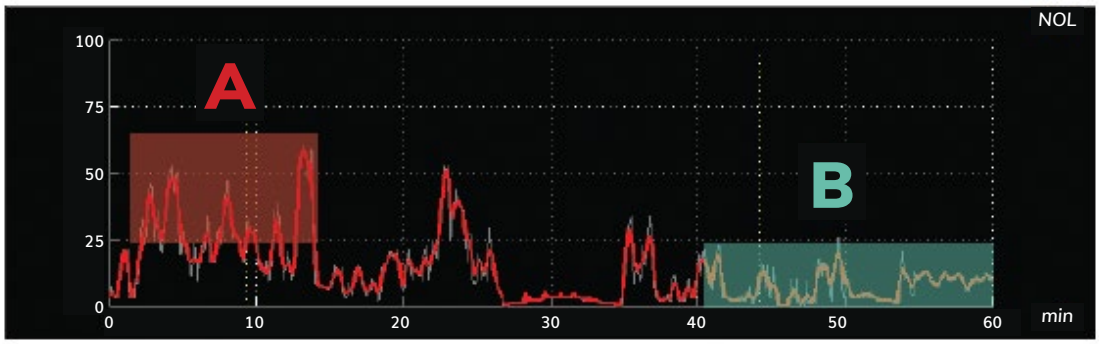


Figure 13: Performance of NOL in different patient cohorts

Clinical implementation

Clinical evidence suggests the following guidelines for procedures under general anesthesia:[12, 16, 17, 18]

- NOL above 25 for more than one minute may indicate the patient requires additional analgesic therapy. Higher values indicate a stronger nociceptive response.
- NOL between 0–25 represents an appropriately suppressed physiological response to noxious stimuli and suggests adequate analgesia.
- When using IV analgesia (not combined with regional analgesia/blocks), NOL < 10 under surgical stimulation, for 1-2 minutes, may indicate excessive analgesia.
- The NOL index cannot anticipate noxious stimuli and thus a minimal level of analgesics should always be maintained.



Clinical Benefits

Controlled studies have shown that NOL guided intraoperative analgesia resulted in a reduction of remifentanil requirement and greater hemodynamic stability when used during target controlled total intravenous anesthesia[16] and in a reduction in post operative pain scores and lower levels of stress hormones when used during a fentanyl/sevoflurane general anesthesia regimen.[17,19] A full list of publications and further clinical resources may be found at www.medasense.com.

Future directions

The clinical benefits of NOL guided analgesia in different settings continue to be evaluated in multiple clinical studies worldwide. Medasense is continuing to design, develop and validate product solutions for nociception and pain monitoring to address clinical needs throughout the continuum of care.

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info@medasense.com

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