Tips and tricks to monitor the Nociception-AntiNociception balance

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Summary
Nociception is the physiological response of the autonomic nervous system (ANS) to a noxious stimulus in unconscious patients. Antinociception, on the other hand, consists of the therapeutic components that control this reaction. As both conditions counteract one another, the concept of nociception-antinociception (NAN) balance can be defined as the state of equilibrium between nociception and antinociception. Heart rate and arterial blood pressure changes have traditionally guided anaesthesiologists towards optimal NAN balance, but their sensitivity and specificity are far from perfect. In contemporary medicine, new commercially tools attempt to measure more accurately the ANS tonus. Among them, the Surgical Plethysmographic Index (SPI) is based on pulse wave amplitude and heart beat interval. The Analgesia Nociception Index (ANI) is derived from heart rate variability. Pupil diameter reactivity (PDR) analyses the changes in pupil size. The NoL Index is a multiparameter index which combines pulse rate, HRV, pulse wave amplitude, skin conductance and movement. These SPI, ANI, PDR and Nol indexes are more sensitive to nociception than traditional hemodynamic parameters. They allow clinicians to more precisely titrate opioids, and have been linked to improved hemodynamic stability in ASA 1-2 patients. However, several confounding factors such as cardiovascular drugs or electrocoagulation can impede their interpretation. Their values during non-noxious periods have no predictive ability regarding future events. Moreover, target ranges are not well defined for different patient populations such as children or the elderly patients. Finally, their capacity to measure accurately the NAN balance during opioid free or opioid sparing antinociception remains to be demonstrated. Testing the response to a standard noxious stimulus at a predetermined level of antinociception with a very sensitive NAN index could help to personalize the NAN balance. Future multi centre studies are required to validate the impact of these clinical ANS monitors on the patient outcome.

Keywords: nociception; anesthesia, general; monitoring; analgesia; review

Introduction

Nociception corresponds to the body's unconscious response to a noxious stimulus and is often observed in the anesthetized patient as an increase in the autonomic nervous system's (ANS) tonus[1]. Antinociception, on the other hand, consists of the therapeutic components that control this reaction (e.g., opioid infusion). As both conditions counteract one another, nociception-antinociception (NAN) balance can be defined as the state of equilibrium between nociception and antinociception. Depending on the intensity of either component, each part of the autonomic nervous system tonus can be either activated or inhibited. Currently it is through the degree of activation of the autonomous system that we approach the measurement of this NAN balance.

Traditionally, anesthesiologists administer a loading dose of analgesics based on clinical recommendations and their personal experience followed by titration based on the patient's heart rate and arterial blood pressure responses. However, the sensitivity and specificity of haemodynamic changes are far from perfect. Moreover, this "one-size fits all" approach, however, forces anaesthetists to be one step behind nociception.

On the other side, opioids are the most frequently used antinociceptive agents during general anesthesia, but there is considerable interindividual variability for opioid requirements among patients. Genetic factors[2], age[3] [4] and organ dysfunction[5] alter opioid pharmacodynamics and pharmacokinetics.

Finding the optimal effective dose of opioids or other antinociceptive drugs for each patient to optimize the peroperative NAN balance remains a daily challenge for the anesthesiologist. Goal-directed antinociception using a nociceptive monitor is one logical step to try to optimize the NAN balance.

Today, almost every component of anesthesia and perioperative medicine can be monitored. Among the pharmacodynamic effects of general anesthesia, the hypnotic component is routinely monitored using frontal electroencephalogram (EEG)-derived indexes[6]. Neuromuscular blockade monitoring using train-of-four count and ratio[7] has become standard care and even minimally invasive hemodynamic monitoring allows clinicians to personalize fluids and inotropes[8]. Unlike many components of anesthesia, however, monitoring the NAN balance remains a challenge and is one of the last components of anesthesia which is not consistently and effectively monitored. If inadequately controlled, it can lead to an increase in blood pressure and heart rate. This can cause cardiac ischemia and heart failure in patients with underlying cardiac disease. These complications are associated with delayed recovery, prolonged hospital length of stay, increased risk of patient institutionalization, and mortality[9]. Ineffective antinociception may also lead to episodes of awareness during general anesthesia following noxious stimulation[10]. The other extreme, opioid or alpha 2 agonists overdose, can cause intraoperative hypotension, decreased organ perfusion, delayed recovery, postoperative hyperalgesia, and increased morbidity[11] [12]. Classical indicators of nociception, such as heart rate and blood pressure changes, however, often force clinicians to be one step behind nociception. Recently, new techniques that measure the ANS response to noxious stimulation during general anesthesia have been developed. These technologies include plethysmographic pulse wave changes in relation to the heart beat interval [14], pupil dilation [15], variability of the heart beat interval over the respiratory cycle [16], and skin conductance [17]. NAN balance monitoring has been shown to be efficient in reducing intraoperative opioid consumption and limiting opioid excess[18] [19]. These indexes are non-invasive and are complementary to monitors of the hypnotic component of anesthesia (e.g., frontal EEG)[20]. The main objective

of this paper was to describe the different technologies, to share our clinical experience and to propose new concepts for a frequently neglected anesthesia component.

Description of most of the available NAN monitors

Surgical Plethysmographic Index

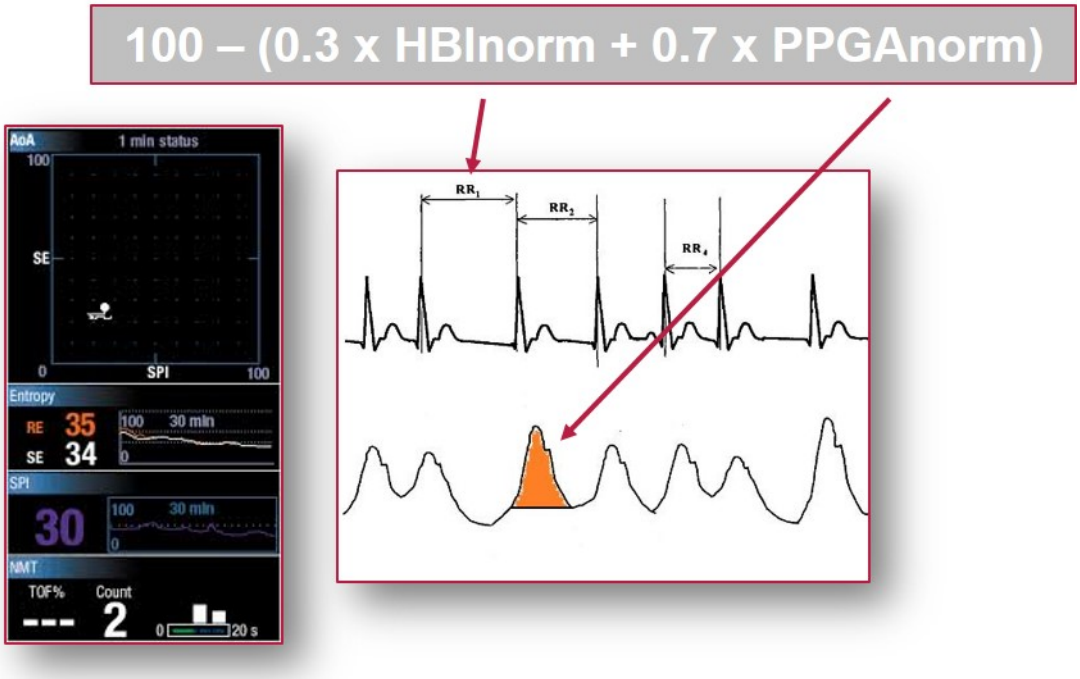
Physiological basis

In 2002, Luginbühl et al. observed that ASA 1-2 patients in whom no pulse wave amplitude changed after a 10 second, 60 mA, 50 Hz tetanic stimulation did not have hemodynamic responses to laryngoscopy and tracheal intubation[21]. Huiku et al. then developed the Surgical Plethysmographic Index (SPI)[14], whose algorithm involves two non-invasive parameters : the pulse wave amplitude and the heart beat interval (Figure 1).

SPI = 100 - (0.7 x normalized pulse wave amplitude + 0.3 x normalized heart beat interval)

They demonstrated that SPI was proportional to the intensity of the surgical stimulus and to remifentanil effect-site concentration (Ce)[14].

Figure 1: Surgical Plethysmographic Index, General Electric



Positive Data

Since then, SPI has been shown to increase with surgical stress intensity, to decrease with antinociception depth (e.g., opioid administration[22 23] or loco-regional anesthesia)[24 25], to perform better than traditional hemodynamic parameters[26], and to predict movement in response to noxious stimulation[27]. In a prospective randomized study, Chen et al. compared SPI guided remifentanil TCI with standard care (i.e., titration of remifentanil based on

traditional hemodynamic parameters)[28]. Remifentanil consumption was higher during standard care than in the SPI group (12.3 ± 5.2 and 9.5 ± 3.8 $\mu g.Kg^{-1}.h^{-1}$, respectively). Hemodynamic stability was also better in the SPI group.

In 2017, Ledowski et al. tried to define an SPI target that would be indicative, in children under general anesthesia, of postoperative comfort. Ninety-three 2 to 16 year old patients undergoing sevoflurane-opioid anesthesia were studied. At the end of surgery, SPI was recorded at 6 time points during a 5-minute observation interval before State Entropy EEG reached 60. An SPI value inferior to 40 had a negative predictive value of 87.5% for postoperative pain. They concluded that an SPI value under 40 may be more appropriate than the initially proposed value of 50, especially at the end of anesthesia as this may improve postoperative pain management.

Limitations

This index, however, is not reliable in conscious patients under loco-regional anesthesia for surgery[29] or recovering in the post-anesthesia care unit[30 31]. Although unclear, the lack of reliability of SPI in awake patients may be due to anxiety[29 30]. Another limitation is that the opioid sparing effects described by Chen et al.[28] were not reproduced in adults undergoing combined sufentanil-sevoflurane anesthesia[32] or in children[33]**.** Its interpretation must also be adapted to the clinical context and the risk of artefacts, such as vasoconstriction, hypovolemia[34 35], hypothermia, movement, β-blockade[23], vasoactive amines, and heart pacing[36]. In addition, although it has a correlation with the intraoperative level of activation of the autonomous system, it does not predict postoperative stress hormone response to surgery[37]. To this day there are few data on the interest of SPI in the elderly, in patients suffering from severe systemic disease[38], and in the cardiac surgery patient.

Future Improvements

SPI is a non-invasive measurement of the level of activation of the ANS that is complementary to EEG indexes. Future prospective randomized studies in homogenous populations (e.g., cardiovascular and geriatric patients), are necessary to determine if this monitoring can improve patient outcome.

Pupil Dilation Reflex

Physiological Basis

The pupil dilation reflex (PDR) occurs in awake and anesthetized subjects, but its mechanism depends on the patient's state of consciousness. In awake patients, PDR is mediated through increased sympathetic nervous system tonus[39]. During general anesthesia, however, it is associated with a reduction of the parasympathetic tone[40]. PDR has a very short reaction time of less than one second and peak effect is reached within 1.25 seconds[41]. It then rapidly stops after stimulation.

Positive Data

In 1993, Larson et al. demonstrated that PDR was more sensitive than hemodynamic parameters in detecting a noxious stimulus during general anesthesia[42 43]. During propofol-remifentanil TCI anesthesia, the progressive increase of remifentanil Ce up to 5 $ng.mL^{-1}$ was linked to a decrease in PDR[15]. Moreover, PDR was shown to measure the efficacy of loco-

regional antinociception in patients under general anesthesia[44] and to determine the level of neuraxial blockade[45].

Sabourdin et al. studied 50 women undergoing major gynecologic surgery to determine if a goal-directed strategy guided by PDR was feasible[46]. In the pupil group, pupillary changes (i.e., diameter change to noxious stimulation before incision) guided remifentanil Ce titration every 5 minutes. If dilation was greater than 30%, remifentanil Ce was increased by 0.5 $ng.mL^{-1}$. If dilation was between 5 and 30%, remifentanil Ce was not modified. If the diameter remained within 5% of baseline, remifentanil Ce was decreased by 0.5 $ng.mL^{-1}$. In the control group, remifentanil TCI was left to the discretion of the anesthesiologist and pupil diameter was measured every 5 minutes by an independent investigator. The lower limit of remifentanil Ce was 1 $ng.mL^{-1}$. Their results indicated that PDR-guided intraoperative antinociception was associated with decreased intraoperative remifentanil and postoperative morphine consumption.

PDR therefore is a non-invasive index which has been shown to reflect the intra-operative level of opioid concentration. It performs better at assessing level of activation of the autonomous system than hemodynamic parameters[26] and is useful during the immediate postoperative period to assess pain[47]. PDR seems to be complementary to the EEG indices at guiding opioid agent administration.

Limitations

PDR shows promise in guiding antinociception during general anesthesia, but studies are limited in size and target patient populations. PDR is altered in the elderly[48], diabetic patients[49], and those suffering from ocular disease[50]. Additionally, it does not allow continuous monitoring due to obvious anatomical limitations. Coupling PDR with a continuous monitor, such as SPI, could possibly improve the clinician's capacity to guide opioid administration.

Future Improvements

In order to determine the impact of PDR-guided antinociception on patient outcome, studies with larger samples are necessary. Future large scale randomized controlled trials will determine if its large implementation is feasible and if it has an impact on patient outcome. One available pupilometer (Algiscan and MAP Station, IDMed, Marseille, France, www.idmed.fr) incorporates an electrical stimulator and can apply tetanic stimulations at the wrist (Figure 2), which may be useful in determining the patient's antinociceptive requirements to a standard noxious stimulus. Studies on the interest of PDR monitoring to quantify the dose of non-opioid antinociceptive drugs such as alpha agonists and ketamine are also warranted.

Figure 2*:* Pupillometer Algiscan, Idmed

AlgiScan®

Algésimètre Pupillaire

Heart rate variability

Physiological Basis

Heart rate variability (HRV) is a physiological characteristic of young healthy subjects. It requires sinus rhythm and corresponds to a variable time interval between each electrocardiographic QRS wave. HRV decreases during brain death[51], myocardial infarction[52], and diabetic dysautonomia[53]. The spectral analysis by Fourier transformation of HRV yields a power peak in the low frequency range (0.04 to 0.15 Hz), which corresponds to the modulation of heart rate by the autonomic nervous system. The power peak observed in a higher frequency range (0.15 to 0.40 Hz) corresponds to the modulation of heart rate by the parasympathetic tone and is linked to the respiratory cycle. Each respiratory cycle is accompanied by a transient reduction in parasympathetic activity that yields a transitory increase in heart rate with a shorter heart beat interval. The Analgesia Nociception Index (ANI) (MDoloris Medical Systems, Loos, France, www.metrodoloris.com) (Figure 3) is derived from the area under the curve of heart beat interval variation as compared to the mean interval[16] and is calculated as follows:

$$ANI = 100 * [(5.1*AUCmin_{nu} + 1.2) / 12.8]$$

($AUCmin_{nu}$ corresponds to the normalized minimal Area Under Curve)

This index is independent from heart and respiratory rates and essentially reflects parasympathetic tonus. In case of pain, stress, anxiety, noxious stimulation or insufficient analgesia/antinociception, the amplitude of HRV decreases and leads to a concomitant ANI decrease.

Figure 3: Analgesia Nociception Index, Metrodoloris

Positive Data

ANI variations have been shown to perform better at detecting nociception than traditional hemodynamic parameters and BIS values in both adults[26] [54] and children[55]. In 2017, Chanques et al. recorded the Behavioral Pain Scale (BPS) and ANI before, during and after routine care procedures in critically ill non-comatose patients[56]. ANI showed a negative significant correlation with the BPS and an ANI threshold of 43 had a negative predictive value of 90% for significant pain. Despite these findings, there is still room for improvement. A better approach to using ANI may be to analyze dynamic variations of ANI as a function of time. These measures have been shown to perform better than the static ANI value for

assessing the risk of movement in response to stimulation[27] [57]. ANI may be helpful in predicting[58] and assessing[59] [60] pain during the immediate recovery period, but there have been conflicting results on its ability to guide preemptive opioid administration for postoperative pain[61] [62]. Nevertheless, ANI has been shown to reduce intraoperative opioid consumption, for example during bariatric surgery[63].

Limitations

Despite its strengths, several factors may interfere with this index, such pharmacological interventions (e.g., atropine), cardiac arrhythmia, slow or irregular respiratory frequency, and apnea. Electrocautery, which is often used at the beginning of surgery, when nociception is high, may cause artifacts and impede ANI calculation. In addition, some results are conflicting regarding its inability to predict the occurrence of movement in response to stimulation[54], or inconclusive regarding the benefit of ANI-guided antinociception on patient outcome.

Future Improvements

Future large scale randomized controlled trials in homogenous populations are needed to determine the impact of guiding antinociception with ANI on patient outcome. Furthermore, opioid-sparing agents such as dexmedetomidine or ketamine should be investigated to determine their impact on this monitor and the potential to guide antinociception with ANI during opioid-sparing and opioid free anesthesia.

Nociception Level Index: Combining Multiple Parameters

Physiological Basis

The Nociception Level (NoL) index (Medasense Biometrics, Ramat Gan, Israel) (Figure 4) uses a multi-parametric approach to quantify nociception. A non-invasive finger probe, equipped with a single use electrode, records four nociceptive-related physiological parameters: pulse rate, high frequency (0.15-0.4 Hz) pulse rate variability, amplitude of the photoplethysmographic signal, and the galvanic skin response (GSR). GSR is a measure of skin conductance and takes into account the baseline level and the frequency of conductance peaks. A composite algorithm, which is not publicly available, analyses the data and outputs the NoL index, a dimensionless value that ranges from 0 (no nociception) to 100 (extreme nociception). It is individually calibrated and provides continuous and real time monitoring. The PMD-200 monitor has an internal test system that assesses the signal quality, and informs the user in case of poor signal quality.

Figure 4: NOL index PMD 200, Medasense

Positive Data

The available NoL Index studies have focused on opioid-based antinociception. In their prospective randomized controlled trial in patients undergoing low-to-moderate risk abdominal surgery, Meijer et al. showed that NoL Index-guided antinociception not only decreased opioid requirements, but also led to a decrease in the number of low blood pressure episodes[19]. As intraoperative hypotension is linked to poor perioperative outcome[64 66], larger studies may be able to demonstrate the benefits of guiding antinociception with the NoL Index on patient outcome. In our department, we compared two groups of 24 patients scheduled for cardiovascular surgery with TCI anesthesia and goal-directed hemodynamic management. Patients were randomized either to NOL-guidance with remifentanil titrated to maintain the NOL index between 10 and 25 or to remifentanil adjusted per clinical responses with the NOL blinded. Slightly less remifentanil was given to patients randomized to NOL guidance (0.11 ± 0.03 vs. 0.13 ± 0.03 $\mu g\ kg^{-1}\ min^{1}$, $p=0.0034$) but no significant difference in intraoperative hemodynamics, doses of norepinephrine and infused fluids, was observed between groups.

Limitations

Although integrating multiple parameters may increase the monitor's capacity of detecting the autonomic response to nociception, it may also hinder its precision, a major limitation is that each parameter can be responsible for different false positives. For example, the slightly bradycardic effect of a phenylephrine bolus has been shown to decrease NoL index value[67]. Other drugs that modify heart rate, such as ephedrine, atropine, or glycopyrrolate could change the NoL index value and consequently give a false sense of the patient's nociceptive response. The effects from diathermia or electrocautery, which can affect conductance signals, also limit its use during surgery. In case of a diathermy effect on the finger probe signal quality, the NoL becomes unavailable to the user, and its trend display is interrupted for the length of the interference. Once the interference is over, the NoL is recalculated, and displayed again after 20 seconds. The considerable length of time with loss of signal can have important implications and limit the use of this monitor during surgery. In addition, the NoL index can be affected by changes in the patient's position during surgery. In the event of patient repositioning, a transient change in NoL index can occur. This change fades within 1-2 minutes, following the patient's physiological adjustment to the new position. If the patient is laying on the side, it is recommended to connect the finger probe to the hand below the heart. Despite these limitations, several studies have shown that the NoL index discriminates between noxious and non-noxious stimuli and outperforms other parameters in that respect[17 68 69].

Future Improvements

NoL technology is non-invasive, and may be more reactive to nociception than other indicators of the sympathetic response. Similarly to other nociception monitors, its placement at the beginning of the procedure is not time consuming. Theoretically, it could be influenced by different confounding factors, such as a low intravascular volume status, the administration of vasoactive agents, atropine or a pacemaker. An important next step in its improvement would be the isolation of the NoL index signal from artefacts such as electrocautery. In addition, like most other monitors, its impact has been mainly evaluated during opioid-based anesthesia. The effect of opioid sparing strategies and opioid-free antinociception on this monitor should be tested in future randomized controlled trials.

Other ways of assessing the NAN balance

Aside from the above-mentioned monitors, a few other systems that attempt to measure nociception are commercially available. The Cardean index (Alpha-2, Lyon, France, www.alpha2.fr) monitors the cardiac baroreflex, which is inhibited during nociception [70–72]. The EDDI software, previously known as Custos (University of Auckland, New Zealand) continuously records several parameters from the standard anesthesia monitor and detects concordance of changes over time to suggest a diagnosis. When an increase in blood pressure and tachycardia occur simultaneously with a reduction in pulse amplitude, it alerts the clinician of a possible sympathetic response to stimulation[73]. Custos alerts are not necessarily concordant with changes in other indexes of the NAN balance, and the system still needs clinical validation[74]. The Algesimeter (Med-Storm, Norway, www.med-storm.com) measures skin conductance alone and has been shown to measure NAN balance[37]. Since it does not measure hemodynamic response to nociception, it is not affected by variations in heart rate due to pharmaceutical or physiological confounders. It shows good correlation with postoperative pain levels[75] and is efficient at testing loco-regional blocks during general anesthesia[76].

Technologies that assess NAN balance by focusing on other components of nociceptive response than the ANS are pharmacodynamic modeling[77], detection of a motor response to stimulation[78], and measurement of the cerebral cortex arousal[79–82]. The latter two are commercially available. The detection of a motor response to stimulation (Pain Tracker, www.dolosys.de; Response Entropy, RE, M-Entropy; GE Healthcare Helsinki, Finland) is strongly affected by the administration of muscle relaxants during anesthesia and consequently has major limitations[83]. The qNOX index (Conox monitor, Fresenius Kabi, Germany, www.fresenius-kabi.com; Quantum Medical, Spain, www.quantiummedical.com) seems to reflect NAN balance[84], but is still the object of relatively few studies. This is also true for the Cortical Input index (BAR monitor, Cortical Dynamics, Australia, www.corticaldynamics.com)[85].

Discussion

Despite the abundance of the available technologies, the ideal nociceptive monitor does not exist. An ideal monitor would allow clinicians to optimize and personalize antinociception avoiding excessive or inadequate analgesia. This would improve intraoperative hemodynamic stability, limit the stress response to surgery, and decrease the risk of toxicity. In addition, it should quickly detect nociception, determine its intensity and predict pain at recovery. Contemporary monitors unfortunately are far from ideal and have several limitations. Firstly, although part of the nociceptive response consists in autonomic response, its physiology involves cortical activation which is ignored by most monitors. Secondly, antinociception using ketamine or central α_2-agonists has not been demonstrated to be adequately monitored using all the proposed NAN indexes. Thirdly, confounding factors such as electrocautery or hemodynamic changes often influence these monitors. Furthermore, the classical indicators of nociception (i.e., heart rate and blood pressure changes), should be integrated into such systems. From our personal experience, there are several key clinical principles to optimize the use nociceptive monitors:

1) The absolute value of available NAN balance indexes obtained during periods of no stimulation have limited to no predictive ability. The index change after a noxious stimulus, however, has the potential to guide antinociception strategies.
2) Although NAN indexes responses to noxious stimulation are more sensitive indicators than traditional hemodynamic parameters alone, one must keep in mind that their values can be strongly influenced by many cardiovascular drugs and by the interaction between anti-nociceptive and hypnotic anesthetic agents. Opioid-sparing strategies may require higher doses of hypnotic agents, which could be associated with burst suppression and postoperative cognitive dysfunction[62]. NAN indexes variations must always be interpreted according to the simultaneous measured EEG index.
3) Physiologically appropriate NAN index ranges for nociception may vary depending on the patient (e.g., children, the morbidly obese, those suffering from cardiovascular disease, and the elderly).
4) One promising recent approach to personalize the NAN balance is to quantify each patient's response to a standard noxious stimulus. Three studies have tried to validate this concept.
    a. Funcke et al. applied a standardized electrical cutaneous stimulation to 38 anesthetized patients and recorded heart rate, mean arterial blood pressure, ANI, SPI, PDR, and BIS values at varying remifentanil doses[26]. The baseline values of ANI, SPI and PDR had limited predictive ability regarding the response to stimulation, but their gradient following standardized stimulation were correlated with the remifentanil concentration. This correlation was greater than that of classical hemodynamic parameters (e.g., heart rate and mean arterial blood pressure). The authors proposed that an intermittent noxious stimulation could test the patient's nociceptive responsiveness and predict the required remifentanil Ce to control hemodynamic reaction to surgery.
    b. In a prospective randomized two-center controlled study, the capacity of a SPI patient's response to a calibrated noxious stimulus to guide remifentanil antinociception was compared to standard practice with fixed remifentanil concentrations[20]. Investigators applied a100 Hz, 60 mA, 30-second electrical tetanic stimulation superficial to the ulnar nerve at the wrist during a steady-state remifentanil-propofol TCI (i.e., remifentanil Ce of 3 $ng.mL^{-1}$ and a propofol Ce required to maintain BIS at 40). Before laryngoscopy or surgical incision, remifentanil Ce was adjusted based on the SPI gradient to stimulation in the SPI guided group, while it was set at a fixed 4 $ng.mL^{-1}$ concentration in the control group. The primary endpoint was the absence of hemodynamic response to tracheal intubation or surgical incision. The performance of SPI guided antinociception, however, was not superior to the control group. There were two major limitations in this study. The thresholds of remifentanil Ce as a function of SPI change during tetanic stimulation were arbitrarily chosen and the remifentanil Ce for skin incision inn the control group was high (4 $ng.mL^{-1}$)
    c. Recently, Perrin et al. have tried to predict personalised remifentanil effect site concentration for haemodynamic stability at skin incision, using the NOL Index in a prospective calibration and validation study[86]. During a no-touch

period in patients under steady-state TCI propofol remifentanil anaesthesia, the NOL index change to a tetanic stimulus under remifentanil at 4 ng/ml has been demonstrated to be useful to personalise remifentanil Ce for the start of surgery and ensure stable haemodynamics. This study introduces the concept of predicting personalised antinociception for surgical incision. Further work is needed to better define the type of standardized stimulus used and the relationship between its nociceptive effects and the required antinociception for different levels of surgical stimulation. For such an approach, the NoL multiparameter index looks to be quite efficient.

Conclusion

Personalizing antinociception remains a challenge in perioperative medicine. Many NAN monitors are helpful for the titration of opioid drugs, improving the haemodynamic stability in some study conditions, but there is still a lack of evidence on their impact on patient outcome. Testing the response to a standard noxious stimulus at a predetermined level of antinociception with a very sensitive NAN index could help to personalize the NAN balance. Future multi centre studies are required to validate this concept in different types of high-risk populations such as elderly frail patients, using both NAN and EEG monitors.

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