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Please cite this article as https://doi.org/10.4097/kja.22002
Different perspectives for monitoring nociception during general anesthesia.

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Running title: Perspectives for nociception monitoring.

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Conflict of interest
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Different perspectives in nociception monitoring

Running title: Perspectives for nociception monitoring
Abstract

A safe anesthesia is achieved by possessing objective methods that estimate the patient’s state along the different phases of the surgery. The patient’s state under anesthesia is characterized by three major aspects linked to the main effects produced by each of the families of anesthetic agents administered: hypnosis, analgesia, and muscular relaxation.
While muscular relaxation assessment, under neuromuscular blocking agents, has a relatively long history of quantification techniques with a high degree of standardization and understanding, such as the train-of-four, the depth of hypnosis estimation, due to the brain complexity, suffers from a lesser degree in both monitoring standardization and interpretation.
The problem of analgesia and nociception monitoring standardization and interpretation increases significantly since more systems get involved, the central nervous system and the autonomic system, which illustrates why currently, there are multiple a priori valid approaches to develop the nociception monitoring from different interpretations and physiological bases of the noxious stimuli processing.
This review describes the main current monitoring technologies available in the daily clinic for estimating the patient’s nociception under general anesthesia.

Keywords: Autonomic neural system; Central neural system; EEG; Heart rate; Nociception; PACU; Plethysmography; Skin conductance; Spinal reflex.
1. Introduction

Monitoring anesthesia

Despite the benefit of widespread use of general anesthetics with patients undergoing surgery, their use has been recognized as a hazardous endeavor with potentially adverse effects [1].

Multi-modal and balanced anesthesia methods refer to all agents and techniques interacting at different components of the anesthesia: from hypnosis and analgesia to muscular relaxation, while maintaining homeostasis and abolishing undesirable autonomic reflexes [1]. For safe anesthesia procedures, it is crucial to possess objective methods that estimate the state of each anesthesia component along the different phases of the surgical context, to provide the practitioner adequate information for deciding the appropriate actions to set the patient’s state to the desired level.

Hypnosis, analgesia, and muscular relaxation depict distinct aspects of the patient’s state, although not fully independent. Even while anesthetic drugs target specifically an anesthesia component, they also might influence the others, either alone or from the interaction with other agents [1-3], Figure 1. For example, the hypnotic effect of propofol is potentiated by μ-agonist opioids, lowering the propofol effect-site concentration needed to reach the loss of consciousness as well as the loss of response to command and pain [4, 5]. Monitoring technologies either for hypnosis and nociception should reflect such synergy to help practitioners to balance anesthesia.

The close relationship between hypnosis and analgesia, commonly synergistic, is symbolized in Figure 1 with a translucent intersection, in contrast to the muscular relaxation liaison regarding the hypnosis and analgesia. Despite hypnotic and analgesic agents promote some muscle relaxation, muscular activity per se has no significant effect on hypnosis and analgesia. Besides the practical benefits of neuromuscular blocking agents (NMBAs) during the surgical procedure, muscular relaxation drawback resides in the suppression of patient movement response hindering hypnotic and analgesia assessment. This effect of muscular relaxation masking the other components assessment is symbolized in Figure 2 with superimposed opaque intersection over the other components.

Neuromuscular monitoring
Muscular relaxation assessment, induced by neuromuscular blocking agents (NMBAs), has a comparatively long history of quantification techniques and a relatively high standard agreement on their use, extensions, and limitations. Neuromuscular monitoring (NMT) becomes crucial every time NMBAs are used, especially to estimate when neuromuscular blockades are sufficiently reversed [6]. Its principle relies essentially on peripheral nerve stimulation-response quantification. Stimulation patterns and measurements can vary from single-twitch to train-of-four, tetanic and post-tetanic counts, and double-burst stimulation. Despite the variety of modalities, all approaches rely on the same principle.

**Hypnosis monitoring**

Hypnosis monitoring has increasingly become widely used since the middle 90’s. Hypnosis assessment technologies rely on EEG analysis; however, it lacks a gold standard definition. Most of the technologies rely on correlating distinct EEG patterns to the agents’ concentrations and qualitative evaluations of the clinical signs under sedation scales such as the OASS. These technologies are more complex than NMT due to the complexity of such estimation. There is a large number of EEG features and algorithms used to define the depth of hypnosis indexes [7, 8], and despite the various estimations alternatives, their concordance is high [9], with enhancements in optimizing the anesthesia drug consumption [10-12], preventing awareness with recall events due to underdoses [13-15] and excessive concentrations (overdoses), improving patients’ outcomes [16-21].

**2. The need of nociception assessment**

The assessment of the analgesia level in the perioperative context refers essentially to the analysis of the physiological neural encoding and processing of noxious stimuli. The goal of monitoring nociception, *(Latin-noci, "harm or injury")*, is to objectively quantify the responses provoked by the surgical stress to the patient to help the maintenance of the nociceptive-anti-nociceptive balance [22, 23].

From the arsenal of anesthetic agents in GA and ICU, opioids play a relevant role in the management of nociception. Their rational use derives in multiple benefits, reducing preoperative pain and anxiety, decreasing somatic and autonomic responses to airway manipulations, improving hemodynamic stability, lowering requirements for inhaled agents, and providing immediate postoperative analgesia [1]. However, opioids are not exempt from adverse effects. Excessive
administration contributes to increasing the frequencies of side-effects such as nausea, vomiting, respiratory depression, opioid-induced hyperalgesia, and the potential for developing opioid addiction [24-27].

3. Anatomy and physiology of nociception in a nutshell

The complexity of nociception processing comes from the multiple complex systems involved in the noxious stimuli experience processing, involving both the Autonomous nervous system (ANS) and the Central nervous system (CNS). Nociception involves four major processes: transduction, transmission, modulation, and perception.

The complexity just starts from the nature of the stimuli, where differences in nociception processing depend on the type of sensory modality involved, mechanical (pressure, pitch), heat, and chemical; with their specific pain receptors or nociceptors. Also with respect to the stimuli location, from cutaneous nerves to visceral or deep musculoskeletal tissues. These differences at the transduction level, in the sensory modalities and locations, influence nociceptive processing and perception.

Focusing on the ascending pain pathway, the nociceptive message, coded in the pattern and frequency of action potentials triggered by different chemicals released by injured cells (e.g. prostaglandins), is transmitted to the spinal cord through the axon of the primary afferent nociceptor (first-order cell). A neuron with the cell body in the dorsal root ganglion with one axon branch out to the periphery and one into the spinal cord, ending near second-order nerve cells in the dorsal horn of the gray matter (substantia gelatinosa) that project over the anterolateral quadrant of the spinal cord to the brain stem and the thalamus. The primary afferent nociceptors release transmitter substances to the spinal terminals (substance P), stimulating second-order pain-transmission cells. Despite, there is a variable relation between nociceptor input and perceived pain intensity, in general, the intensity of the stimuli is proportional to the frequency of the nociception discharges along the ascending pathway. Once nociceptive signaling reaches the thalamus this is projects to widespread areas of the forebrain through 3rd order neurons, from somatosensory cortex, limbic system to frontal cortex.

The nociceptive signal transmission is regulated by the activity transmitted through the descending pathway through the midbrain, crossing the medulla and ending the dorsal horn, projecting by a serotonergic-noradrenergic neuron that inhibits the release of substance-P between the 1st order and 2nd order neurons of the ascending path, and by stimulating a nearby opioid-
interneuron that releases additionally an endogenous opioid (enkephalin) which helps the inhibition of pre- and post-synaptic exchange of substance-P.

Opioids act on both the brain and spinal cord stimulating the activity of the descending inhibitory pathway, from the midbrain to the dorsal horn. For instance, remifentanil, a $\mu$-receptor agonist [28], modulates the nociceptive transmission and its processing where this receptor is distributed, e.g. in the brain, at the cerebral cortex (upper part of layer V-VI) as well as throughout the spinal cord (primarily confined to laminae I-II, dorsal horn) and peripheral nervous system [29]. This coarse summary of the nociception system skips a much deeper description of the mechanisms involved in nociception processing, from differences in sensory cell types and characteristics, other relevant neurotransmitters and interactions among many other factors [30-32], but we aim to show briefly the physiological basis for the a priori adequacy of the different existing nociception monitoring technology approaches.

It is at the spinal cord, brainstem and thalamus where the nociceptive information communicates to the ANS and CNS. It is important to remark that the different monitoring technologies are not explicitly related to specific direct measurements on certain points of the pain pathway but on the responses elicited to the noxious stimuli on the ANS and CNS, such as heart rate, blood pressure, skin conductance and EEG.

4. Nociception monitoring standpoints

Traditional cardiovascular parameters and clinical signs under some circumstances provide valid clinical criteria of inadequate anaesthesia, for instance, systolic blood pressure 15 mmHg above baseline, heart rate greater than 90 beats/min, besides other autonomic signs such as sweating, flashing or lacrimation, and somatic responses like movements, swallowing, coughing, grimacing, or eye movements [33]. However, these parameters and signs generally have low sensitivity and specificity for nociception since many anaesthetics can bias them (e.g. propofol effect on blood pressure, ephedrine effect on heart rate), as well as other multiple factors involved during the surgical procedure, can difficult their use (e.g. heartbeat absence under cardiopulmonary bypass). Therefore, nociception monitoring technologies are desirable to complement traditional clinical criteria.
Similarly to hypnosis, there is no gold standard to measure nociception due to the multiple complex systems and mechanisms involved [30, 33, 34] with the inherent subject variability. However, coarse but objective approaches to nociception estimation might be valid enough to help the practitioners.

In the following sections, it is described the main features of the available monitoring systems targeting the nociception state inference according to the physiological system targeted: CNS, ANS, Spinal reflex; and their related bio-signals: electroencephalogram, electrocardiogram, electromyogram, plethysmography, pupilometry, skin conductance. The technologies described are:

- **CNS-based monitoring**
  - Conox monitor. qNOX
  - Entropy monitor. Response entropy.

- **ANS-based monitoring**
  - Pupilometry
  - ANI monitor
  - SPI
  - NOL index
  - Skin conductance

- **Spinal reflex-based monitoring**
  - RIII-reflex

### 4.1 CNS-based monitoring

The relevant role of nociception monitoring targeting brain activities is shown from nociceptive-related activations, observed under fMRI that persisted despite abolished clinical responses. Remifentanil dose dependent bold-fMRI signals evoked by noxious stimuli were described in multiple brain regions, especially in frontal areas [35].

While EEG signal information serves to evaluate, in the current modern depth of anesthesia monitor technologies, the patient hypnotic state under GA, multiple studies had shown EEG distinct components modulated by noxious stimuli related information, which can be used to detect stress
situations and help the management of intraoperative analgesic administration: beta and delta arousals, and alpha dropout, among other changes [36-39].

The EEG analysis and interpretation, either in hypnosis and nociception monitoring, may be hampered by EMG presence. Depending on the operative context, EMG presence in EEG may produce a potential bias of the EEG-derived indexes, however modern EEG processing algorithms offer a much better EMG suppression than those implemented in the earlier depth of anaesthesia monitors. It is important under EEG monitoring to interpret the EEG indexes within the EMG presence, as EMG can also be an early indicator of arousal or nociception.

**Entropy monitor. Response entropy index**

The Spectral Entropy monitor (GE Healthcare, Chicago, USA) is a two-index EEG-based monitor. One focuses on describing the hypnosis state (state entropy, SE), and the other evaluates the patient’s response regarding noxious stimuli (response entropy, RE). Essentially, the spectral entropy is computed over the frequency range from 0.8 to 32 Hz to define the SE (EEG-dominant part), and from 0.8 to 47 Hz to define the RE, the latter including the EEG-dominant and EMG-dominant part of the spectrum [40]. The entropy measurements are then scaled into two different unit-less scores; from 0 (very deep anesthesia) to 91 (awake state) for the SE, and from 0 to 100 for the RE.

Under GA with propofol and remifentanil, high values of RE (> 55) before the stimulation increased the risk of motor response. But, lower values did not prevent a response when the opioid concentration was insufficient, despite adequate hypnosis [41].

Entropy-guided anesthesia during propofol-remifentanil GA showed fewer unwanted patient responses than standard practice with a reduction in opioid consumption [42], but there was no differences in recovery, hemodynamic parameters and postoperative outcome.

The difference SE-RE seems to behave as a proxy of the facial electromyography activity which might be useful in the assessment of nociception during surgery [43], and its use for controlling the remifentanil administrations was suggested [44].
**Conox monitor. qNOX index**

Similarly to the Spectral Entropy monitor, the Conox monitor (Fresenius Kabi AG, Bad Homburg, Germany) integrates two EEG-based indexes. The qCON index related to the patient’s level of consciousness and the qNOX index dedicated as a guide to the patient’s probability of response to a noxious stimuli. Similarly to the qCON index, which links with a quadratic model different EEG spectral components to distinct hypnotic aspects (loss of consciousness event, hypnotic concentrations, assessment of alertness/sedation scales); the qNOX index integrates the spectral components into an equivalent model that best predicts the patient response to noxious stimuli. In particular, the different types of airway intubations: laryngoscopy, LMA insertion and tracheal intubation. [45]. The likelihood of movement response to external stimulus is described under a scale ranging from 0 to 100. Recommended values for GA lay between 40-60, where qNOX > 60 corresponds to a high probability of response to external noxious stimuli, and a qNOX < 40 to a low likelihood response occurrence. A qCON and qNOX equal to 0 indicate an isoelectric EEG signal, and consequently a burst suppression ratio of 100%.

For 60 patients, significant increments in the qNOX values pre and post noxious stimuli (LMA insertion, tracheal intubation, and laryngoscopy) occur while remifentanil or propofol effect-site concentrations were found not correlated for movers vs non-movers response [45].

The indexes qCON and qNOX behave differently regarding the detection of loss of consciousness and loss of response to nociceptive stimulation. For 140 patients scheduled for GA with propofol-remifentanil showed that the qCON was able to predict loss of consciousness such as loss of verbal command and eyelash reflex better than qNOX, while the qNOX has a better predictive value for response to the noxious stimulati [46]. Furthermore, in an analysis of the fall and rise times, the qNOX showed a faster increase at the end of the surgery, associated with the hypothesis that a higher probability of response to stimuli might be reached before the recovery of consciousness. Thermoregulatory processes appear essential for the activation of analgesic mechanisms, from a physiological strong negative affiliation between nerve conduction velocity and temperature; apart from significant repercussions on the pharmacological dynamics of the analgesic drugs (decrements in clearance rates with a subsequent increase in the effect-site concentrations). Under the hypothesis that deep hypothermia induces massive effects on the analgesia and hypnosis levels of the patient, 39 patients elective for on-pump coronary artery bypass graft surgery under hypothermia were monitored with the BIS and the Conox monitors.
While the hypnotic indices (BIS, qCON) showed significant but weak correlations with respect to the temperature, the qNOX index showed the strongest correlation [47], not only at population behavior but more importantly regarding each individual patient prediction (linear mixed-effect model for temperature with patient as random factor: $R^2: BIS (0.06, p < 0.05), qCON (0.29, p < 0.001), qNOX (0.74, p < 0.001)$).

4.2 ANS-based monitoring

Pupilometry

Pupillometric assessment of analgesia and nociception rely on portable measuring pupil diameter response systems, under the basis of the pupil constriction and dilation controlled by the sympatho-vagal balance, since both components are innervated into the pupillary muscles [48, 49]. From the different infrared pupilometers used in the assessment of nociception such as ANeurOptics PLR-100 (NeurOptics, Irvine, CA), the Algiscan system (IDMed, Marseille, France) is the unique that has integrated an electrical stimulation unit, which allows to operate easily under four different modes. A first operation mode where changes in pupil size are evaluated regarding noxious stimulus such as incision or electrocautery over a time window of 60 s. A second mode, measuring the diameter changes after 1 second flash of light of 320 lux. And the third and fourth modes, named as Tetanus and PPI modes, correspond to the elicited pupil changes after distinct controlled electrical stimulations applied on the ulnar nerve; differing each mode regarding the stimulation frequency pulse, duration time, and type of amplitude stimulus, constant or variable (rate change 10mA/s to max. 60 mA). In the PPI mode, Algiscan defines an adimensional index ranging from 0 to 10, PPI, where lower values represent lower pupil reactivity, and thus, deeper analgesia, and higher values $PPI > 7$ describes insufficient analgesia.

Pupil diameter reactivity was shown to be correlated with remifentanil effect-site concentrations [50], intraoperative nociception response prediction [51-54], and postoperative pain assessment [55-57]. Pupillometry has shown a faster response to stimuli than heart rate and arterial pressure, and allowed the prediction of the analgesia state previous stimulation [50, 58]. Pupillary dilation after standardized tetanic stimulation was influenced the propofol concentrations under constant 1 ng/mL effect site infusions of remifentanil. Suggesting that pupil reactivity, in this case, stimulus elicited seems to be also influenced by hypnotic level [59]. Further research is needed to evaluate the effects
of hypnotics in pupilometry and other potential confusion factors. Discontinuous measurements with multiple repeated perioperative measurements are the main drawbacks with the additional care of the cornea. Measurements might be biased under neostigmine, pupillary diseases (Horner and Holmes-Adie syndromes, etc.), and blindness. Care must be taken regarding the ambient light conditions.

The ANI monitor

The ANI (MDoloris, Loos, France) evaluates the parasympathetic response reflected on the ECG during GA. This dimensionless index based on the HRV, measures the influence of the parasympathetic system on the cardiac rhythm during the respiration calculated from high-frequency band-pass filtered RR series (between 0.15 and 0.4 Hz). It ranges from 0 (maximal nociception) to 100 (maximal analgesia) [60, 61]. The ANI mean normal values fluctuate around 50-70, where ANI < 30 for longer than 5 min would indicate analgesic underdosing, and ANI > 70 an analgesic overdosing.

ANI has been investigated in both conscious and anesthetized subjects. Boselli et al. in patients under desflurane-remifentanil GA reported that dynamic variations of ANI, instead of ANI static values, showed significant prediction of hemodynamic reactivity [62]. The ANI index, pupilometry and SPI index were superior in detecting painful stimulations than traditional hemodynamic parameters and with performances attenuated by increasing remifentanil dosages. However, baseline values showed significantly lower prediction probabilities toward the nociceptive response [63].

In children, an observational study of 2- to 12-yr-old patients showed changes of ANI index 5 min before and after surgical incision where hemodynamic parameters were found to be of low or of no predictive value for detecting noxious stimuli [64]. Further research with ANI is needed to evaluate its relationship to opioid concentrations as well as its application outside the GA such as regional blocks or conscious sedation. Caution must be taken using the ANI monitor or other ANS-based monitor, since different agents acting on the ANS, such as ephedrine and atropine, bias the index readings [65]. The ANI is not interpretable during around 10 min after ephedrine and 20 min after atropine administration. The latter bias raises concerns on other agents or drugs combinations affecting also ANS such as beta-blockers that need to be studied.
While ANI reflected noxious stimulations during GA anesthesia, its interpretation might become limited by its large interindividual variability and reproducibility [22, 66].

Finally, the ANI index might not be useful during intubation when the patient is under apnea with no respiration.

**Pletismography-based monitoring**

The SPI (GE Healthcare, Helsinki, Finland) basis relies on the plethysmography pulse-wave changes provoked by noxious a stimulus; a sympathetic response on the peripheral vasoconstriction and cardiac autonomic tone. The SPI index is computed as the normalized heartbeat interval ($HBI_{norm}$) and plethysmographic pulse wave amplitude ($PPGA_{norm}$): $SPI = 100 - (0.7 \times PPGA_{norm} + 0.3 \times HBI_{norm})$ [67]. This unitless score ranges from 0 to 100, where lower values indicate deeper analgesia. An index of SPI> 50 is considered inadequate analgesia.

The SPI index responded to remifentanil concentration changes and was higher at the lower concentrations of remifentanil. The SPI reacts to surgical nociceptive stimuli and analgesic drug concentration changes during propofol–remifentanil anaesthesia, where the SPI increased at skin incision and stayed higher during surgery than before surgery [67]. SPI guided anesthesia has been reported to result in lower opioid [68] and propofol [16] consumption with more stable hemodynamic, lower incidence of unwanted events short times to patient arousal.

The physiological basis of the SPI index is not generally valid, since the SPI index is not interpretable in the postoperative pain assessment in conscious subjects [69]. Furthermore, due to the biosignal used the index might be significantly biased by agents acting on the hemodynamic as well as inotropic and chronotropic agents among other factors. Surprisingly, SPI does not appear to be valid in children where SPI guided analgesia led to less fentanyl consumption but more postoperative agitation and higher analgesic requirements than conventional practice [70]. This may be due to both blood vessel distensibility and baseline increased heart rates in children versus adults, suggesting the need of a redefinition of the index for children or might suggest that opioids levels used in standard practice in children are closer to the minimum acceptable concentration threshold than the adults. And then a larger margin of agents consumption reduction is possible in adults but not completely related to the nociception but to the influence of the effect of the anesthetic agents on the hemodynamic variables. In that sense, neither skin conductance nor SPI monitoring reliably
predicted changes in stress hormones (adrenaline, noradrenaline, adrenocorticotropic hormone, and cortisol) levels in plasma throughout the intraoperative period [71].

**The NOL index**

The PMD100 Monitor with the NOL index (Medasense Biometrics, Ramat Gan, Israel) is a score integrating different parameters from multiple biosignals. Reported as a function of HR (HRV(at the 0.15 to 0.4 Hz band power)), plethysmograph wave amplitude, and skin conductance [72, 73]. All biosignals are collected with a finger probe placed on the index finger of the right hand containing photoplethysmographic and galvanic skin sensors as well as a skin temperature sensor, and a three-axis accelerometer. NOL is a unitless index, updated every 5 seconds, and ranging from 0 to 100, where lower values indicate lower sympathetic activation, deeper analgesia, and recommended values laying within 10-25 for maintenance. NOL index has been reported under GA to have a higher intraoperative sensitivity and specificity than HR and MAP predicting responses to noxious stimuli, e.g intubation, incision, and tetanic stimulation [73, 74]. NOL level-guided analgesia during major abdominal surgery was reported to result in a 30% less remifentanil consumption [75]. Peri-stimulus changes of NOL has been reported to correlate with remifentanil dosage [76]. In abdominal surgery under fentanyl/sevoflurane, despite the non-significant differences in fentanyl and morphine consumption after surgery, there was an improvement in the postoperative pain scores in the NOL-guided group with respect to the standard HR- and MAP-guided fentanyl administration [77]. However, in this study no clear differences can be observed between the NOL values during NOL-guided and the standard care (Fig.2, [77]), since essentially all lay within and below the recommended maintenance values of 10-25. This suggests that NOL scale definition is does not offer the best dynamics for NOL guided administration, since the recommended value range (10-25) is narrow and far from being centered with respect to the whole dynamic range (0-100). NOL scale should be enhanced to offer a larger sensitivity and dynamics.

The role of temperature and particularly accelerometry in the PMD100 Monitor is not clear, if they act as side parameters or they modulate the NOL index. Furthermore, research with the NOL index under other important settings including regional anesthesia, combined regional anesthesia and local analgesia, as well as sedation, are needed.
Skin conductance

The SC algesimeter (Med-Storm, Oslo, Norway) system monitors the skin galvanic response as a proxy for the SNS activity, where increments in sympathetic activity result in the following filling of the palmar and plantar sweat glands. The SC measurements rely on the sympathetic terminals encircling sweat glands which are innervated by postganglionic sympathetic neurons, which are connected to preganglionic neurons projected from the sweat nucleus of the hypothalamus [78]. The SC algesimeter measures micro-fluctuations in skin conductance measured in PPS from a delivered micro-current on palmar and plantar areas. The SC increases transiently before the sweat is removed, decreases again with the sweat, and the consequent fluctuation is therefore observed. SC is commonly measured in the hand for adults and in the feet for neonates. Accordingly to the manufacturers, the PPS parameter should be interpreted regarding the VAS as: PPS within (0-0.07) no pain, (0.13-0.21) no pain or VAS less than 40, (0.26) patient is active and VAS around 40-50, PPS(0.33) patient probably in pain with VAS around 60-80, and PPS(0.40-0.7) indicating patient probably in pain with VAS within 80-100.

Perioperative correlations to nociception stimuli were reported [79, 80], while skin conductance, measured as PPS, showed moderate sensitivity and specificity in identified timepoints with moderate to severe pain defined from hormone plasma levels [71].

Skin conductance did not reliably predict changes in stress hormone plasma levels throughout the intra-operative period [71]. Clinically relevant benefits from the use of skin conductance are unclear which might rely on the biosignal nature, potential confounding effects or the selected characterization used to describe this biosignal (i.e. PPS). Despite manufacturer considerations, from a physiological basis, that skin conductance monitoring advantages not being influenced by temperature (22- 42 \( ^\circ \)C), general hypoxia, hypo- and hyper-volume, beta-blockers, epinephrines, among other factors [69, 79], further research is needed to confirm such statements.

4.3 Spinal reflex-based monitoring

RIII-reflex monitor

The RIII-reflex (NFR) threshold system (Dolosys GmbH, Berlin, Germany) describes the electrical intensity needed to elicit a spinal polysynaptic withdrawal reflex quantified by changes in the electromyographic activity, as a proxy of the analgesia level [81]. The electrical stimulus is applied
on the sural nerve and its effect is measured on the biceps femoris muscle electromyography. The amount of current needed raises with the analgesia [82-84]. This has been used also in studies of central sensitization and chronic pain [85]. Under propofol/remifentanil GA the RRIII threshold increases with remifentanil [83], with a higher predictive power of patient movement to noxious stimulus responses such as laryngeal mask airway insertion and skin incision that other index such as BIS, NSRI or CVI [84].

The NFR depends on sex, age and weight (obesity), and distinct physiologic factors [81]. Its limitations lay on the degree of the neuromuscular block, the skin impedance as well as peripherical nerve alterations and muscular diseases.

5. Discussions

On the intraoperative prediction of pain at PACU.

Lately, several research studies aimed to evaluate the performance of different nociception monitoring index values at a single punctual time during the intraoperative period, mainly at arousal before extubation to predict Post-operatives pain (POP) on PACU arrival. Evaluating the pain scores such as the NRS around 5-10 min after extubation. In this review, this specific research was not included in each individual description of each nociception index. The essential reason relies on multiple contradictory results, and in our humble opinion, the ground arguments against such research approach.

For example, Boselli et al. [61], under inhalation GA with remifentanil, reported excellent predictions of pain 10 min ahead in PACU from a single ANI index measurement index before extubation, with 86% sensitivity and 92% specificity to discriminate between patients with NRS≤3 and NRS>3. However, very different results were reported under sevoflurane-fentanyl anesthesia, when comparable single pre-extubation ANI measurement did not reflect different states of acute postoperative pain under the same NRS scale at 5 min post-intubation intervals in PACU [86]. Similarly, for pre-extubation SPI values (SPI>30), it was reported to predict postoperative NRS assessments with sensitivity/specificity of 50% and 89.7%, respectively [87]. However, in a posterior study, it was reported that despite the best SPI sensitivity/specificity to predict moderate-to-severe pain in PACU achieved for SPI values around 30, its predictive accuracy was overall poorer [23].
Furthermore, the severity of postoperative pain significantly influences skin conductance. Using cut-off values, PPS may prove a useful tool for pain assessment in the postoperative period [88, 89]. However, it is difficult to link such predictions when skin conductance did not reliably predict changes, for instance, in stress hormone plasma levels throughout the intra-operative period [71]. A contradiction between an index insensitive behavior under short-term prediction with respect to longer term predictions.

An extreme situation of single value POP prediction, with a longer prediction horizon, is recently reported [90], where only low NOL index values after skin incision significantly excluded moderate-severe pain at PACU, with a negative predictive value of 83%, while other intraoperative NOL values, including the end of the surgery, showed no significant prediction. Result that conceptually invalidates all post-incision NOL estimations, with low sensitivity to detect a potential pain subjacent problem found at the incision event, that emerge later at PACU. Such a result contradicts the forecasting principle, where the more ahead is the forecasting, the more uncertainty.

Independently of the research type (surgery, anesthesia, nociception index, etc.), PACU pain assessment prediction from single perioperative values seems unrealistic. Some of the main arguments are:

**Monitoring reflects only time local conditions.** Any monitoring system aims to accurately estimate continuously the system (patient) state, to be able to track its changes. In fact, while keeping the estimation power, the faster the better. If the system state varies, the monitor must reflex such variations, making previous single estimations outdated. The validity of single estimations last as long as the system remains unchanged, being the system transitions the need for newer updates. In our opinion, patient state transition from intraoperative period to PACU is pretty short in time and large in the changed state magnitude, invalidating single short-term estimations.

**Lack of trends.** From previous argument, any statistical forecasting method requires a minimum of consecutive measurements, at least few historical samples to pick up some sort of trends for short-term prediction, and for longer-term predictions and more complex systems and transitions the historical data needs to be larger (Box and Jenkins, 1976). In general, the longer is the prediction horizon the larger information is required.

**Lack of concomitant factor analysis.** The Patient’s pain perception at PACU might depend on multiple factors, from patient’s demographic and historical data, to surgery type, duration, etc.
Factors not included in the statistical analysis of mentioned papers, additionally to a lack of control groups and statistical post-hoc techniques for better noise levels assessments.

6. Conclusions

The latest development of better monitoring technologies for the different aspects of the patient’s state under anesthesia, has led to novel methods which focus on monitoring nociception. The nociception monitors can either be based on ANS or CNS parameters, however CNS based methods focus on the cortex and subcortex of the brain which is the target organ for the analgesics therefore in the future CNS monitoring is likely to be the prevalent method for monitoring of analgesia and nociception during general anaesthesia.

Conflict of interest

P.M.V works as research consultant for Quantium Medical. E.W.J is co-owner and CEO of Quantium Medical and works at Fresenius Kabi.

Bibliography


Figure 1. General anesthesia components relationship scheme. The close relationship between hypnosis and analgesia, commonly synergetic, is symbolized with a translucent intersection. However, the muscular relaxation undesired effect of masking and hindering the hypnosis and analgesia assessment is symbolized with and opaque color covering a complete observation (assessment) of the other two components.
**Figure 2.** Simplified illustration of the general pathway of nociception. Anterolateral ascending spinothalamic nociceptive transmission path (black line) and descending modulatory path (blue line). Action locations of the nociception processes: transduction, transmission, modulation, and perception, and most noteworthy related substances.