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Original Contribution

Cortical, subcortical, brainstem and autonomic responses to nociception under total intravenous anesthesia

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HIGHLIGHTS

- ANI, BIS, HR, NOL, PRD, and qNOX significantly changed after noxious stimulation.
- PRD exhibited the best correlation with varying remifentanil concentrations.
- high PRD was associated with alpha drop and beta arousal in the EEG.

ABSTRACT

Background: Physiological responses to nociception are complex and involve intricate associations between the central, peripheral, and autonomic nervous systems. To optimize intraoperative analgesic titration, several monitoring devices have been developed, each targeting specific physiologic variables. However, existing devices primarily focus on isolated components of the nociceptive response, such as autonomic or cortical activity, without integrating these perspectives comprehensively.

Our aim was to compare the performance of different nociception monitors in response to standardized tetanic stimulation and to investigate the correlation between these monitors' responses and varying concentrations of remifentanil.

Methods: In this study, we evaluated and compared the responses of the Nociception Level index (NOL), Analgesia Nociception Index (ANI), Pupillary Reflex Dilation (PRD) and both raw and processed electroencephalogram (EEG) under varying concentrations of propofol and remifentanil. Standardized tetanic stimuli were administered to patients under general anesthesia with target-controlled infusion of propofol and remifentanil. EEG, PRD, NOL, ANI, heart rate (HR), Bispectral index (BIS), and CONOX monitor indices (qCON and qNOX) were concomitantly recorded.

Results: ANI, BIS, HR, NOL, PRD, and qNOX significantly changed after noxious stimulation. In our dataset, PRD had the strongest correlation with varying remifentanil concentrations, while ANI, NOL, and qNOX did not show significant correlations with remifentanil concentrations. Following a noxious stimulus, the raw EEG in patients with low PRD exhibited a significant increase in power in the high EEG frequencies around 25 Hz and decreased power in frequencies corresponding to the alpha range (8–12 Hz) in the power spectral density.

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Conclusions: PRD, HR, and BIS correlated with varying levels of remifentanil, with PRD exhibiting the strongest correlation. When CE remifentanil are low, noxious stimuli are more likely to dilate the pupil and be detected in the EEG. Considering the complexity of the nociceptive response, integrating multimodal neurophysiologic monitoring with pharmacological data may improve the anesthesiologist's ability to assess on the nociception-antinociception balance. However, further studies are needed to validate these findings and address the study's limitations.

1. Introduction

Personalizing the analgesic component of general anesthesia can improve several clinical outcomes. It reduces intraoperative opioid administration without increasing postoperative pain or opioid consumption. In addition, it shortens extubation time and lowers the incidence of post-operative nausea and vomiting (PONV) [1].

Individualization of the analgesic component can be enhanced using various monitors and indices developed to assess nociception [2]. However, due to the complexity of the nociception process, no single method can evaluate it comprehensively. So far, most solutions have approached this task by measuring the nociception-antinociception balance. Noxious stimuli increase sympathetic activity, decrease parasympathetic tone, or cause changes in cortical activity detectable in the electroencephalogram (EEG) [2,3], whereas opioids have the opposite effect. This can be detected both at a cortical and a subcortical level.

To address this challenge, several nociception monitors have been developed, each targeting different physiological responses associated with nociception. The Nociception Level Index (NOL) comprises a multiparameter nonlinear combination of several autonomic variables acquired through a single finger-mounted probe. The Analgesia Nociception Index (ANI) relies on heart-rate variability (HRV). The qNOX, an index derived from the processed raw EEG, aims to predict the likelihood of movement in response to surgical stimuli in unconscious patients. The Algiscan measures the pupillary diameter and its dilation after applying a standardized noxious stimulus. Although these monitors employ different approaches, they all aim to measure the nociception-antinociception balance.

2. Materials and methods

2.1. Study design and setting

This study was conducted under Institutional Review Board and Ethics in Clinical Research Committee approval (Hospital CLINIC de Barcelona n° HCB/2016/0318v2). Twenty patients scheduled for ambulatory gynecologic and general surgery procedures (surgical hysteroscopy, laparoscopy, and urinary incontinence correction) were included after giving written informed consent.

2.2. Participants

Inclusion criteria were adults scheduled for the specified procedures. Exclusion criteria included prior eye surgery, ocular diseases (other than refraction errors), prescription drugs affecting pupillary size/reflexes, BMI > 35, and intraoperative administration of atropine, ephedrine, or phenylephrine. Four patients were excluded due to the use of atropine (2) and ephedrine (2).

2.3. Objectives

With our study, we aim to compare the performance of different nociception monitors (PRD, ANI, NOL, qNOX, and BIS) in response to standardized tetanic stimulation, investigate the correlation between these monitors' responses and varying concentrations of remifentanil, and further examine the relationship between the most responsive nociception index and raw EEG data.

2.4. Study protocol

Upon arrival to the operating room, routine monitoring was started, including continuous electrocardiogram, pulse oximetry, and non-invasive blood pressure. No premedication or lidocaine was administered. Baseline pupillary light reflex measurements were performed in both eyes to determine if any anomaly or anisocoria was present.

General anesthesia consisted of total intravenous anesthesia with propofol and remifentanil administered using a Target Controlled Infusion (TCI) system (Base Primea docking station, Fresenius Kabi AG, Germany). This protocol is the standard in our institution for ambulatory procedures under general anesthesia as it allows for precise drug titration, fast recovery, and low incidence of PONV.

Fig. 1 illustrates the study protocol, showing the entirety of a single patient's case.

- Algometric responses with varying propofol effect site concentrations

To investigate the interactions between propofol and remifentanil, we employed a criss-cross design. This approach involved varying the concentrations of both drugs to cover a wide range of clinically relevant levels. To achieve this, loss of consciousness was induced by setting the predicted effect-site concentration of propofol between 5 and 8.5 $\mu g \cdot mL^{-1}$ (Ce Propofol - Schnider model [4,5]) [see Fig. 1, first ϟ]. Two minutes after reaching pseudo-steady state equilibrium between predicted plasma and Ce, the first Pupillary Reflex Dilation (PRD) was elicited using the Algiscan® video pupillometer (IDMed, France), which was connected to a set of electrodes placed on the volar surface of the right arm that delivered an electrical stimulus. The stimulus consisted of a 60 mA tetanic stimulus for 5 s, while the pupillary diameter (in mm) was measured 67 times per second. The diameter screen was performed from 3 s before until 5 s after the stimulation. A rubber cup covered the measured eye, and the contralateral eye was taped closed.

- Algometric responses with varying remifentanil effect site concentrations

After the first stimulation, remifentanil infusion was started using the same "criss-cross" design with Ce (Ce remifentanil – Minto model [6,7]) varying between 0.5 and 6 ng/mL [see Fig. 1, second ϟ]. This stimulation was conducted using the same Ce propofol as in the initial measurement. The "criss-cross" approach enabled a combination clinically relevant concentrations of propofol and remifentanil [8]. After two minutes of pseudo-equilibrium, a second PRD was elicited, and the airway was then secured either by placement of a laryngeal mask or by endotracheal intubation. In cases requiring tracheal intubation, 30 mg of rocuronium bromide was administered two minutes before laryngoscopy.

During the maintenance of anesthesia, propofol was titrated using Bispectral Index (BIS) values from the BIS Vista v2.0 (Medtronic, Ireland) and qCON parameters from the CONOX® monitor (Fresenius Kabi, Germany). Remifentanil was adjusted at the anesthesiologist's discretion based on standard practice with vital signs, with the anesthesiologist blinded to the nociception monitors. In the CONOX® monitor, the qNOX index was hidden. PRD was assessed by a researcher whenever active surgical stimulation was absent. All measurements were done at pseudo-equilibrium of propofol and remifentanil, meaning that both Ce and predicted plasma concentrations were the same.

From induction to emergence, PRD from the Algiscan, BIS (including BIS index and raw EEG), CONOX (qCON, qNOX, and raw EEG), Ce remifentanil (in ng/mL) and Ce Propofol (mg/mL) were recorded in real time using Rugloop (Demed, Temse, Belgium), CONOX view (Fresenius Kabi, Germany), and NLViewer (IDMed, France). In addition, heart rate (HR, in bpm), NOL (PMD-200 monitor, V1.5, Medasense, Israel), and ANI (ANI monitor V1, MDoloris, France) were also simultaneously recorded with the highest resolution provided by the monitors.

2.5. Selection of monitors

Although several monitors are available for nociception monitoring, the devices used in this study (Algiscan, ANI, NOL, CONOX, and BIS) were chosen based on their availability and high usage percentage in clinical practice. These monitors cover most of the physiologically relevant variables: ANI and NOL primarily assess autonomic nervous system responses, PRD reflects brainstem activity, and BIS and CONOX capture cortical responses. It is important to note that PRD is limited by its non-continuous nature.

2.6. Data pre-processing

In the 16 patients, a total of 293 nociceptive stimuli were administered, with 73 excluded due to burst suppression (24,9 %), leaving 220 stimuli for analysis. Burst suppression episodes were excluded because of non-stationarity.

For each of the 220 stimuli, baseline values were defined using the mean values between 10 and 20 s before stimulation. Post-stimulation values were defined as the minimum (for ANI, as its value should decrease with noxious stimulus) or maximum (for other variables) values within 60 s after the stimulus. Differences between pre- and post-stimulation values were calculated for all variables and represented by Δ.

After identifying the PRD as the most reactive parameter to varying

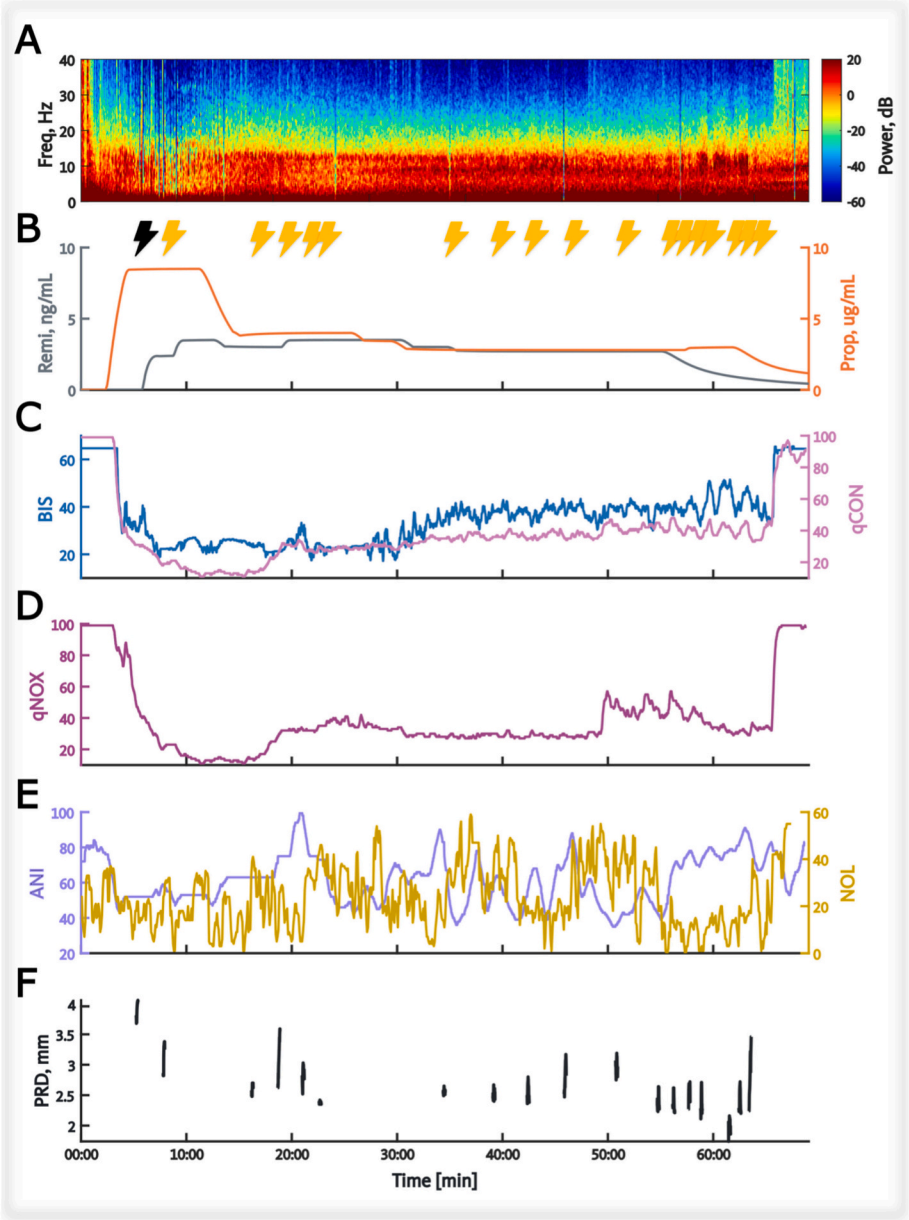

Fig. 1. Example of a complete patient case illustrating the study protocol. The lightning symbols indicate periods of 5-s, 60 mA tetanic stimulation. The black lightning symbol represents stimulation under propofol only, while the subsequent lightning symbols denote stimulation under varying concentrations of propofol and remifentanil. The figure also displays the density spectral arrays of the EEG, Ce of propofol and remifentanil as well as trends of the processed parameters.

remifentanil concentrations in our data, as demonstrated in the Results, we stratified the patients into two categories based on their percent-PRD change (%PRD). For each stimulus, we calculated this percentage using the ratio between the maximum and the baseline pupillary diameter. The 220 events were then divided into two different groups: low PRD (lPRD) – events in which the percentage of pupillary dilation after the stimuli was less than 10 %, and high PRD (hPRD) – events in which the percentage of pupillary dilation after the stimuli was higher or equal to 10 %. The cutoff was chosen based on a value that could divide our sample into two groups similar in number. Additionally, the 10 % marks the threshold of the second dilation of the PRD which is highly sensitive to the depressant effects of opioids [9].

To evaluate changes in the EEG resulting from the noxious stimulus, we compared the power spectral density (PSD) derived from 20 to 10 s before the stimulus versus the PSD from 20 to 30 s after the stimulus. EEG recordings used in the analysis were collected with the CONOX or BIS monitors from frontal electrodes with 1024 and 128 Hz sampling rates, respectively. Because of different recording setups, we decided to z-score the EEG to correct for possible differences in EEG amplitude before analysis. Then, we calculated the PSD with the MATLAB *pwelch* function (MATLAB R2017b, The MathWorks, Natick, MA, USA) using default settings. The frequency resolution was 1 Hz. Because each patient received multiple stimuli, we used the median of the pre- or post-stimulus PSD for further analysis.

2.7. Statistical analysis

Graphical analysis of data preceded statistical inference.

The Shapiro-Wilk test was used to determine if the data were normally distributed. Differences between lPRD and hPRD were evaluated with a multivariate analysis of variance (MANOVA) using SPSS (IBM version 24.0 II, USA). Data are presented as mean ± standard deviation (SD) or median (min-max) unless stated otherwise. A p-value of $p < 0.05$ was considered statistically significant.

To compare the pre and post-stimulus PSDs, we calculated the effect size Hedge's g for dependent data together with 10 k-fold bootstrapped 95 % confidence intervals (CI). We considered 95 % CI's not containing 0 as significant on a $p < 0.05$ level. Therefore, we used the MATLAB-based MES toolbox [10]. We only described a significant effect if we found significant differences in two neighboring frequencies to adjust for multiple comparisons, similar to previous approaches [11,12].

3. Results

3.1. Demographics

Sixteen patients (11 female and 5 male) were included in the study, with a median age of 39 (19–79) years. The mean weight was 63.5 (46–86) kg, and the mean height was 163 (149–178) cm. Male patients had significantly higher BMI than female patients ($p < 0,05$). Ce of propofol and remifentanil at each measurement are present in Supplementary Fig. 1 and Supplementary Fig. 2. There was no statistically significant difference in the concentrations of propofol or remifentanil between patients who received rocuronium and those who did not ($p > 0.05$).

3.2. Effect of noxious stimulation on the measured variables

All processed indices and the heart rate significantly ($p < 0.01$) changed with the application of the standardized electrical noxious stimulation. Fig. 2 shows the box plots of the relative change for each parameter after the tetanic stimulation. The range of each variable influences the magnitude of the percentage of change.

3.3. Remifentanil effect on parameter response

The parameter that correlated best with changes in remifentanil concentration and showed a significant regression slope was the PRD (rho = −0.27). qNOX (rho = −0.05), NOL (rho = 0.02), and ANI (rho = −0.03) percentages of change showed lower correlation coefficients and the regression analyses did not reveal a significant change with varying remifentanil levels. Fig. 3 presents the plots of the relative change of each parameter at the respective remifentanil concentration.

3.4. Power spectral density analysis

We used the PRD (shown to correlate best with remifentanil concentrations in our sample) as a pharmacodynamic endpoint to investigate possible helpful information in the raw EEG under different levels of nociception-antinociception balance. We divided the 220 recorded stimulation events into two groups according to the dilation threshold of 10 % [9]. 109 cases were classified as low PRD (lPRD), and 111 were high PRD (hPRD). We found no significant change in the PSD of the lPRD group following the noxious stimulation. For the hPRD stimuli, we observed a significant increase in power in the high EEG frequencies around 25 Hz. We further observed a frequency decrease corresponding to the alpha range (8–12 Hz). Fig. 4 presents the PSD before and after the

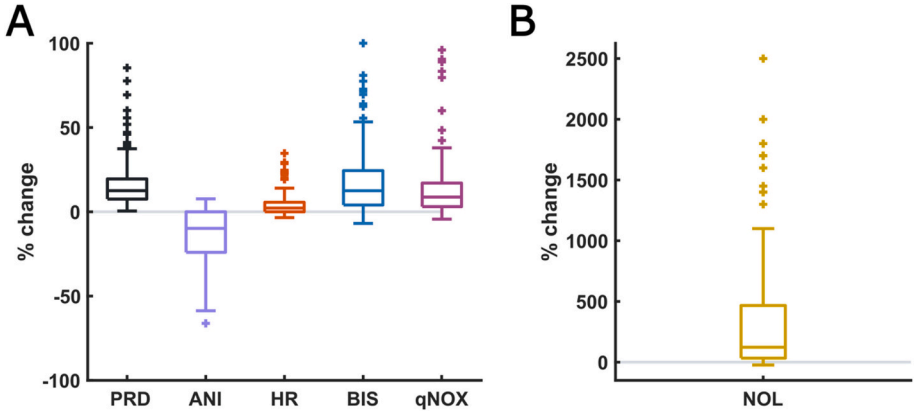

Fig. 2. Relative change in parameter from before to after the stimulation in the 220 segments. The NOL is presented separately because of the different scale.
A. PRD, ANI, heart rate (HR), BIS, and qNOX significantly ($p < 0.01$) changed after the stimulation.
B. NOL significantly ($p < 0.01$) changed after the stimulation
The dots indicate outliers as detected by MATLAB's boxplot function. The function defines points as outliers.

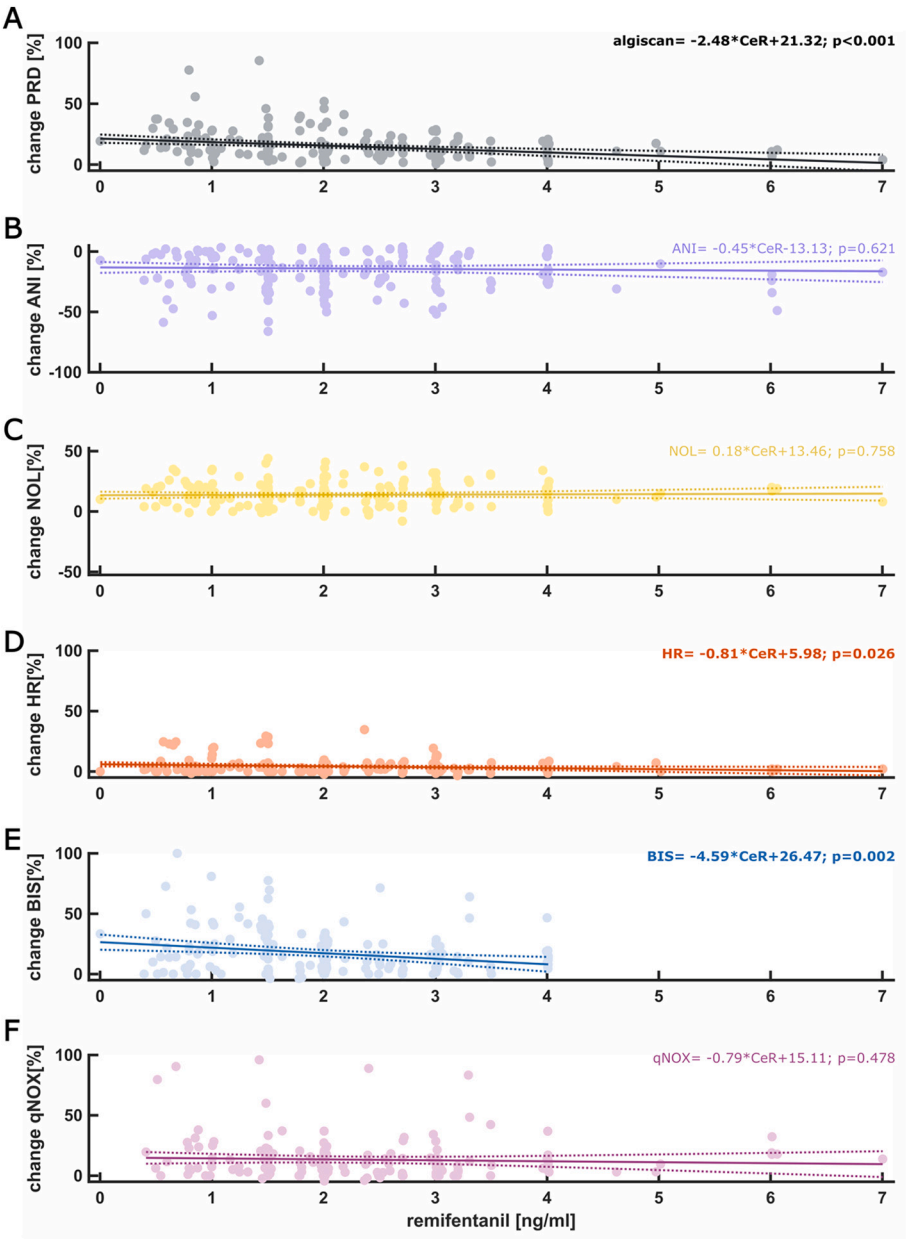

Fig. 3. Relative change of each parameter at the respective remifentanil concentration and their linear regression model equation.

stimulation for the lPRD, the hPRD, and the combined groups.

4. Discussion

Using various approaches, we studied the cortical, subcortical, brainstem, and autonomic responses to standardized electric noxious stimulation. ANI, BIS, heart rate, NOL, PRD, and qNOX all showed significant changes following noxious stimulation. Among these, PRD exhibited the strongest correlation with Ce remifentanil, while ANI, NOL, and qNOX did not show a significant change with Ce remifentanil and only low correlation coefficients.

The rationale behind monitoring the activity of the autonomic nervous system (ANS) to infer the balance between nociception and antinociception is undisputable. This approach captures the intricate interactions among several regions, including the insular and anterior cingulate cortices, amygdala, hypothalamus, midbrain periaqueductal gray matter (PAG), parabrachial nucleus in the pons, medulla, nucleus of the solitary tract, ventrolateral reticular formation and raphe nuclei [13]. These regions process visceral and nociceptive inputs, subsequently generating autonomic responses via pathways to preganglionic sympathetic and parasympathetic neurons [14]. Notably, the PAG and hypothalamus play pivotal roles as intermediaries between the ANS and nociceptive inputs. The PAG integrates localized cutaneous nociceptive signals from the dorsal horns and less localized inputs from somatic, visceral, or muscular sources. Activation of the dorsal or ventral PAG can lead to either sympathetic responses like fight-or-flight or parasympathetic responses such as hypotension, bradycardia, and immobility [14]. Utilizing this understanding, of how nociceptive inputs can evoke different responses in the subcortical and brainstem region, various physiological variables have been transformed into the indices we studied to gauge the nociception/antinociception balance. The ANI reflects parasympathetic activity by analyzing HRV, targeting pathways involving the nucleus of the solitary tract and hypothalamus, which modulate vagal tone in response to nociceptive inputs [15]. In addition to HRV, the NOL, also depends on vasoconstriction and skin conductance changes which are influence by the PAG and rostral ventromedial

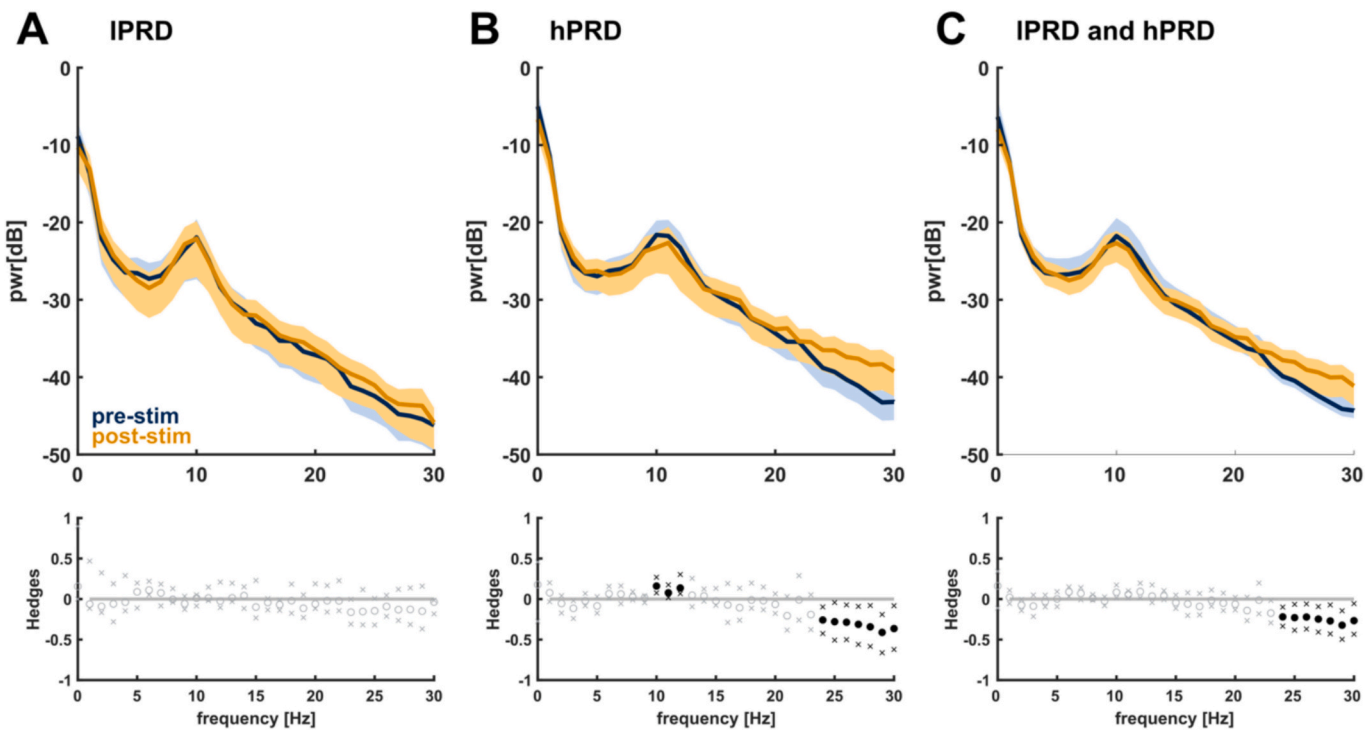

Fig. 4. Stimulus-induced relative change in the PSD of the z-scored EEG for A) lPRD, B) hPRD, and C) both groups. The solid lines present the average, and the shaded areas represent the SEM. Black dots in the Hedge's g graph indicate an effect with the 95 % confidence interval excluding 0.

medulla (RVM) [16]. The PRD in anesthetized patients is primarily mediated through the inhibition of the Edinger–Westphal (EW), with additional modulation involving the PAG [17].

In addition to the subcortical, brainstem and autonomic responses previously mentioned, we studied EEG-derived variables. We used PRD as a pharmacodynamic indicator of the nociception-antinociception balance for each stimulation to reduce the previously observed inter-patient variability response to the same Ce remifentanil [18,19]. This allowed us to study the raw EEG in groups with similar pharmacodynamic conditions. Doing so, we found a stronger pattern indicative of beta-arousal phenomena in the hPRD group compared to when all the segments were analyzed (lPRD + hPRD). This beta-arousal induced by noxious stimulation causes the EEG to shift towards a pattern with lower voltage and higher-frequency components [20]. In addition, we also found changes compatible with alpha dropout in the hPRD group. The alpha dropout, characterized by a loss of alpha power, has also been described following noxious stimulation under general anesthesia [21]. These changes in the EEG may well explain the changes observed in the processed indices. The BIS has a component, i.e., the beta-ratio, that focuses on changes in the EEG power in the beta-band and low-gamma-band of the EEG [22]. A reverse engineering approach of the BIS revealed that the index extracts most information from the low-gamma-band range of the EEG [23]. The qNOX also seems to be driven, at least in part, by changes in the beta-band and low-gamma-band [24]. The observed alpha-dropout phenomenon may not contribute to the index increase as it does not seem to be uniformly interpreted by the monitoring systems [25]. As age can influence the intraoperative (processed) EEG information, we only evaluated the rate of change for the included parameters.

The commercially available nociception monitors based on the autonomic nervous system yielded different results in our study. NOL demonstrated a significant increase in values after noxious stimulation. However, the amplitude of the change did not correlate with varying levels of remifentanil. ANI significantly decreased after noxious stimulation, but the amplitude of change did not correlate with remifentanil levels. The PRD significantly changed after the standardized noxious stimuli and was the parameter that best correlated with varying remifentanil concentrations. This correlation with remifentanil has been previously demonstrated for the index provided by Algiscan, the Pupillary Pain Index (PPI) [26].

Based on our data, PRD demonstrated consistent responsiveness to standardized noxious stimulus, indicating its potential as a measure of nociception and as a pharmacodynamic indicator of remifentanil effect. This finding is corroborated by the literature, as the amount of opioids administered and the intensity of the nociceptive stimulation experienced by the patient can influence the pupillary diameter. Additionally, opioids have been shown to produce a dose-related depression of PRD in response to noxious stimuli [27]. Due to this dual dependence on opioid dose and nociceptive intensity, pupillary diameter reflects a balance between nociception and antinociception. In a previous publication we have proposed that the EW neuronal firing rates represent a surrogate measure of the firing rates of supraspinal neurons that possess descending inhibitory projections from the RVM to the spinal cord. Although we believe that this theory is possibly valid, it is based upon rodent experiments and would be difficult to prove in humans [28]. Previous publications have demonstrated that maintaining a small pupil during total intravenous anesthesia is associated with an acceptable degree of antinociception [29,30].

There are several limitations in our study. It has a small sample size which prevents the generalization of our findings. Additionally, we employed a 60 mA tetanic stimulation for 5 s as noxious stimulus, which differs from surgical stimulation (direct trauma of peripheral nervous fibers, heat and acidosis). However, it has been demonstrated that tetanic stimulation, which is frequently used and easily applicable, is a valid and reproducible stimulus [31]. Furthermore, and although not entirely physiological, electrical stimulation, when administered as a near supramaximal stimulus, has been shown to effectively substitute for conventional forms of stimulation [32]. However, this approach does not apply to neuropathic pain as its cortical manifestations differ, and opioids are not effective in this context.

A limitation of our study is the exclusion of events with burst suppression from our analysis. As mentioned in the methods, we could not

analyze the burst suppression EEG due to non-stationarity. Hence, we cannot make any statement about possible EEG changes induced by noxious stimulation during burst suppression. The stimulus-induced EEG reaction during burst suppression should be investigated with other methods in a subsequent study. Additionally, the number of burst-suppression segments could have been reduced if an alternative induction approach was implemented. As we intended to acquire measurements in the absence of opioids, high concentrations of propofol had to be administered to induce unconsciousness. Furthermore, the induction was performed using a TCI system, which administers the bolus at a fast infusion rate. This method may affect how propofol induces unconsciousness, as "bottom-up" mechanisms will predominate [33]. Besides the burst-suppression segments that were excluded, the initial high dose of propofol may affect the subsequent oscillations and influence our results.

Another limitation of our study is that, due to the clinical nature of our setup, several combinations of propofol and remifentanil concentrations were not covered in our criss-cross design and there was a difference in the intensity of background stimulation, as measurements were performed before, during or after the surgical procedure.

Future studies should include larger and more balanced samples to evaluate potential gender and age related differences in nociceptive responses and anesthetic effects, which may contribute to more personalized and effective patient care. Moreover, research should further investigate the correlation between PRD and the effect-site concentration of remifentanil needed to suppress cortical activation in response to standardized tetanic stimulation. The observed correlation between PRD and Ce remifentanil suggests that other factors might contribute to its variability and should also be explored. Finally, post-operative pain outcomes should be explored to determine how specific intraoperative patterns relate with distinct pain trajectories.

In summary, our exploratory study demonstrates that different nociception monitors respond variably to standardized noxious stimulation under general anesthesia with propofol and remifentanil. Among the indices studied, PRD showed the strongest correlation with remifentanil concentration, suggesting it may be a sensitive measure of the nociception-antinociception balance during general anesthesia. Furthermore, when noxious stimulation surpassed the antinociceptive effect of remifentanil, we observed cortical EEG changes characterized by alpha-dropout and beta-arousal.

CRediT authorship contribution statement

Sérgio Vide: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Matthias Kreuzer:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Ana Ferreira:** Writing – original draft, Methodology, Formal analysis, Data curation. **Mafalda Couto:** Data curation. **Mercè Agustí:** Visualization, Resources. **Sebastian Jaramillo:** Formal analysis. **Gerhard Schneider:** Validation, Supervision, Resources, Methodology. **Paul S. García:** Supervision, Methodology, Conceptualization. **Fernando Abelha:** Writing – review & editing, Investigation. **Pedro Amorim:** Validation, Supervision, Conceptualization. **Iñaki Trocóniz:** Methodology, Investigation, Formal analysis. **Merlin Larson:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization. **Pedro Gambús:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2025.111825.

References

[1] Ma D, Ma J, Chen H, Mu D, Kong H, Yu L. Nociception monitors vs. standard practice for titration of opioid administration in general anesthesia: a meta-analysis of randomized controlled trials. Front Med (Lausanne) 2022:9. https://doi.org/10.3389/fmed.2022.963185.
[2] Ledowski T. Objective monitoring of nociception: a review of current commercial solutions. Br J Anaesth 2019;123(2):e312–21. https://doi.org/10.1016/j.bja.2019.03.024.
[3] García PS, Kreuzer M, Hight D, Sleigh JW. Effects of noxious stimulation on the electroencephalogram during general anaesthesia: a narrative review and approach to analgesic titration. Br J Anaesth 2021;126(2):445–57. https://doi.org/10.1016/j.bja.2020.10.036.
[4] Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. Anesthesiology 1999;90(6):1502–16. https://doi.org/10.1097/00000542-199906000-00003.
[5] Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology 1998;88(5):1170–82. https://doi.org/10.1097/00000542-199805000-00006.
[6] Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II Model application. Anesthesiology 1997;86(1):24–33. https://doi.org/10.1097/00000542-199701000-00005.
[7] Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I Model development. Anesthesiology 1997;86(1):10–23. https://doi.org/10.1097/00000542-199701000-00004.
[8] Short TG, Ho TY, Minto CF, Schnider TW, Shafer SL. Efficient trial design for eliciting a pharmacokinetic-pharmacodynamic model-based response surface describing the interaction between two intravenous anesthetic drugs. Anesthesiology 2002;96(2):400–8. https://doi.org/10.1097/00000542-200202000-00027.
[9] Larson MD, Berry PD, May J, Bjorksten A, Sessler DI. Latency of pupillary reflex dilation during general anesthesia. J Appl Physiol 2004;97(2):725–30. https://doi.org/10.1152/japplphysiol.00098.2004.
[10] Hentschke H, Stüttgen MC. Computation of measures of effect size for neuroscience data sets. Eur J Neurosci 2011;34(12):1887–94. https://doi.org/10.1111/j.1460-9568.2011.07902.x.
[11] Akeju O, Westover MB, Pavone KJ, et al. Effects of sevoflurane and propofol on frontal electroencephalogram power and coherence. Anesthesiology 2014;121(5):990–8. https://doi.org/10.1097/ALN.0000000000000436.
[12] Kreuzer M, Stern MA, Hight D, et al. Spectral and entropic features are altered by age in the electroencephalogram in patients under sevoflurane anesthesia. Anesthesiology 2020;132(5):1003–16. https://doi.org/10.1097/ALN.0000000000003182.
[13] Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc 1993;68(10):988–1001.
[14] Benarroch EE. Pain-autonomic interactions. Neurol Sci 2006;27(Suppl. 2):130–3. https://doi.org/10.1007/s10072-006-0587-x.
[15] Boscan P, Pickering AE, Paton JFR. The nucleus of the solitary tract: an integrating station for nociceptive and cardiorespiratory afferents. Exp Physiol 2002;87(2):259–66. https://doi.org/10.1113/eph8702353.
[16] Ruffinazzi M, Dusi V. Central nervous system Management of Autonomic Cardiovascular Control. In: Govoni S, Politi P, Vanoli E, editors. Brain and heart dynamics. Springer International Publishing; 2020. p. 1–27. https://doi.org/10.1007/978-3-319-90305-7_65-1.
[17] Larson MD, Behrends M. Portable infrared pupillometry: a review. Anesth Analg 2015;120(6):1242–53. https://doi.org/10.1213/ANE.0000000000000314.
[18] Vide S, Castro A, Antunes P, et al. Pharmacodynamic modelling of the effect of remifentanil using the pupillary pain index. J Clin Monit Comput 2020;34(2):319–24. https://doi.org/10.1007/s10877-019-00323-x.
[19] Barvais L, Engelman E, Eba JM, Coussaert E, Cantraine F, Kenny GN. Effect site concentrations of remifentanil and pupil response to noxious stimulation. Br J Anaesth 2003;91(3):347–52. https://doi.org/10.1093/bja/aeg178.
[20] Hagihira S, Takashina M, Mori T, Ueyama H, Mashimo T. Electroencephalographic bicoherence is sensitive to noxious stimuli during isoflurane or sevoflurane

anesthesia. Anesthesiology 2004;100(4):818–25. https://doi.org/10.1097/00000542-200404000-00011.
[21] Hight DF, Gaskell AL, Kreuzer M, Voss LJ, García PS, Sleigh JW. Transient electroencephalographic alpha power loss during maintenance of general anaesthesia. Br J Anaesth 2019;122(5):635–42. https://doi.org/10.1016/j.bja.2018.11.029.
[22] Rampil IJ. A primer for EEG signal processing in anesthesia. Anesthesiology 1998;89(4):980–1002. https://doi.org/10.1097/00000542-199810000-00023.
[23] Connor CW. Open reimplementation of the BIS algorithms for depth of anesthesia. Anesth Analg 2022;135(4):855–64. https://doi.org/10.1213/ANE.0000000000006119.
[24] Jensen EW, Valencia JF, López A, et al. Monitoring hypnotic effect and nociception with two EEG-derived indices, qCON and qNOX, during general anaesthesia. Acta Anaesthesiol Scand 2014;58(8):933–41. https://doi.org/10.1111/aas.12359.
[25] Weyer C, Prötzl E, Kinateder T, et al. The strength of alpha oscillations in the electroencephalogram differently affects algorithms used for anesthesia monitoring. Anesth Analg 2021;133(6):1577–87. https://doi.org/10.1213/ANE.0000000000005704.
[26] Vide S, Castro A, Antunes P, et al. Pharmacodynamic modelling of the effect of remifentanil using the pupillary pain index. J Clin Monit Comput 2019. https://doi.org/10.1007/s10877-019-00323-x. Published online.
[27] Larson MD, Kurz A, Sessler D. Alfentanil blocks reflex pupillary dilation in response to noxious stimulation but does not diminish the light reflex. Anesthesiology 1997;87:849–55.
[28] Fields H. State-dependent opioid control of pain. Nat Rev Neurosci 2004;5(7):565–75. https://doi.org/10.1038/nrn1431.
[29] Sabourdin N, Barrois J, Louvet N, et al. Pupillometry-guided intraoperative remifentanil administration versus standard practice influences opioid use: a randomized study. Anesthesiology 2017;127(2):284–92. https://doi.org/10.1097/ALN.0000000000001705.
[30] Guglielminotti J, Grillot N, Paule M, et al. Prediction of movement to surgical stimulation by the pupillary dilatation reflex amplitude evoked by a standardized noxious test. Anesthesiology 2015;122(5):985–93. https://doi.org/10.1097/ALN.0000000000000624.
[31] Funcke S, Sauerlaender S, Pinnschmidt HO, et al. Validation of innovative techniques for monitoring nociception during general anesthesia. Anesthesiology 2017;127(2):272–83. https://doi.org/10.1097/ALN.0000000000001670.
[32] Laster MJ, Liu J, Eger EI, Taheri S. Electrical stimulation as a substitute for the tail clamp in the determination of minimum alveolar concentration. Anesth Analg 1993;76(6):1310–2. https://doi.org/10.1213/00000539-199376060-00021.
[33] Sepúlveda P, Cortinez LI, Irani M, et al. Differential frontal alpha oscillations and mechanisms underlying loss of consciousness: a comparison between slow and fast propofol infusion rates. Anaesthesia 2020;75(2):196–201. https://doi.org/10.1111/anae.14885.

Glossary

ANI: Analgesia Nociception index
ANS: Autonomic Nervous System
BIS: Bispectral index
BMI: Body Mass Index
CI: Confidence Intervals
EEG: Electroencephalogram
EW: Edinger-Westphal
HRV: Heart-Rate Variability
hPRD: High Pupillary Reflex Dilation
lPRD: Low Pupillary Reflex Dilation
NOL: Nociception Level Index
PONV: Post-operative nausea and vomiting
PSD: Power Spectral Density
Ce: Predicted effect-site concentration
PRD: Pupillary Reflex Dilation
RVM: Rostral Ventromedial Medulla
TCI: Target Controlled Infusion