International Society
For Anaesthetic
Pharmacology

28th Annual Meeting

2019 Syllabus

Friday, October 18th, 2019

Hilton Orlando • Orlando, FL

6737 W. Washington St., Suite 4210 • Milwaukee, WI 53214
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Mission Statement

The International Society for Anaesthetic Pharmacology (ISAP) is a nonprofit organization with an international membership, which is dedicated to teaching and research about clinical pharmacology in anesthesia, with particular reference to anesthetic drugs.

Accreditation Information

Target Audience
This program is designed for an international audience of general anesthesiologists, pharmacological anesthesiologists, technology anesthesiologists and specialty physicians.

Objectives

After attending this program you should be able to:

1. Describe the influence of anesthesia and anesthetic types on cancer recurrence.
2. Explain how anesthetics alter neuronal activity and learn about pharmacologic reversal of general anesthesia.
3. Discuss experimental analgesic monitoring strategies and drug delivery.

Practice Gaps

- The effects of anesthesia on cancer recurrence are relatively unknown. Anesthetic drug choice and type may play a key role in preventing cancer recurrence.
- Anesthetic effects on neuronal activity are still incompletely understood. Novel agents that facilitate reversal of hypnosis are being developed.
- Improved anesthetic outcomes may be achieved through analgesic monitoring and improved drug delivery.
- A better understanding of the effects of anesthetic agents and surgical stress of glucose homeostasis is necessary.
- Predicting opioid requirements based on patient demographic factors may optimize analgesic therapy of surgical patients.
- Cannabinoids are emerging as a new class of analgesic adjuncts. Understanding their role in pain management and overall anesthetic practice is necessary.
- Potential new approaches to the cannabinoid system for therapeutics.

Acknowledgement of Financial Commercial Support

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No in-kind commercial support was received for this educational activity.

Satisfactory Completion

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Learners must complete an evaluation form to receive a certificate of completion. Your chosen sessions must be attended in their entirety. Partial credit of individual sessions is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

Physicians

In support of improving patient care, this activity has been planned and implemented by Amedco LLC and the International Society of Anaesthetic Pharmacology. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Credit Designation Statement

Amedco LLC designates this live activity for a maximum of 6.75 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Accreditation Statement

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Amedco and the International Society for Anaesthetic Pharmacology. Amedco is accredited by the ACCME to provide continuing medical education for physicians.

Disclosure of Conflict of Interest

The following table of disclosure information is provided to learners and contains the relevant financial relationships that each individual in a position to control the content disclosed to Amedco. All of these relationships were treated as a conflict of interest, and have been resolved. (C7 SCS 6.1--6.2, 6.5)

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Joseph	Foss	NeuroTherapia: Patent Holder
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Hugo	Vereecke	Medasense Inc: Grant for educational project related to NOL monitoring, Quantium Medical Inc: Research Grant Site Principal Investigator

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1. Go to http://isap.cmecertificateonlinecom

2. Click on the "28th Annual Meeting (2019)" link

3. Evaluate the conference

Please print all pages of your certificate for your record.

Questions? Email Certificate@AmedcoEmail.com

28th Annual Meeting Agenda

07:00 – 08:00	Breakfast & Registration
08:00 – 08:10	Welcome ISAP President, Peter Nagele, MD, MSc
08:10 – 08:15	Introduction to the Program Donald Mathews, MD and Jerry Ingrande, MD, MS
08:15 – 09:00	Session 1 – Do Anesthetics Affect Cancer Recurrence?
08:15 – 08:35	Regional Anesthesia and Cancer Recurrence Daniel Sessler, MD
08:35 – 08:55	Systemic Anesthesia and Analgesia and Cancer Recurrence Philipp Lirk, MD, PhD
09:00 – 09:30	Break
09:30 – 10:30	Session 2 – Anesthesia and the Brain: Disrupting Consciousness and Emerging Research on Reversal of Anesthesia
09:30 – 10:00	Personalized Anesthetic Pharmacology Alex Proekt, MD
10:00 – 10:30	The Pharmacology of Anesthetic Reversal Ken Solt, MD
10:30 – 11:30	Session 3 – New Innovations in Analgesic Delivery and Monitoring
10:30 – 11:00	Drug Delivery Technology for Prolonged On-Demand Local Anesthesia Daniel S. Kohane, MD
11:00 – 11:30	Measuring the Nociception-Antinociception Balance: Do We Know What to Expect? Hugo Vereecke, MD, PhD
11:30 – 12:45	Lunch, Business Meeting & Poster Session
12:45 – 13:45	Moderated Poster Discussion
13:45 – 14:45	Session 4 – The Stress of Surgery: Predicting Opioid Requirements and Understanding Anesthetic Effects on Glucose/Insulin Homeostasis
13:45 – 14:15	Predictors of Acute and Long-term Opioid Use in the Postoperative Surgical Patient: From Basic Demographic Data to Pharmacogenomics Rodney A. Gabriel, MD, MAS
14:15 – 14:45	Anesthesia Mellitus: Revisiting the Effects of Volatile Anesthetics and Surgery on Glucose and Insulin Homeostasis William Gabriel Tharp, MD, PhD
14:45 – 15:15	Break
15:15 – 16:15	Session 5 – Anesthetic Applications of Cannabinoids
15:15 – 15:45	Cannabinoids: Therapeutic or Just So Much Smoke? Joseph Foss, MD
15:45 – 16:15	Marijuana and Mechanism of Pain Control Andrew G. Kaufman, MD
16:15 – 16:55	Keynote Speaker & Lifetime Achievement Award Winner: Michel.M.R.F. Struys, MD, PhD, FRCA
16:55 – 17:00	Closing Remarks

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Abstract Table of Contents

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Exhibit Support

MEDASENSE
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Enhanced Microglial Phagocytosis of Glutamatergic Synapses in a Mouse Model of Fragile X Syndrome

Presenting Author: Mohamed Naguib[1]

Co-Authors: Jiang Wu[1], Mark Hocevar[1], Bihua Bie[1]

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Introduction: Fragile X syndrome (FXS) is an inheritable disorder resulting from a mutation of the fragile X mental retardation 1 (*FMR1*) gene on the X chromosome. Patients are generally presented with cognitive disabilities, impaired social and psychiatric behavior, and hypersensitivity and repetitive behavior. The complement system serves as the first line of defense against infection of exogenous pathogens and also clears the cellular debris to protect against autoimmunity. While peripheral circulating complement proteins are mostly synthesized in the liver, many complement proteins are locally produced by the resident neurons or glial cells in the brain. Complement 1q (C1q), which is an initiator of the classical pathway of complement activation and a ligand for C1qRp, a receptor on microglia. C1q-mediated microglial pruning play a pivotal role in the synaptic changes and remodeling in neurodevelopmental disorders. Glutamatergic transmission is impaired in the hippocampal area in mouse ($Fmr^{-/-}$) model of FXS. We hypothesized that C1q-dependent microglial phagocytosis of the hippocampal glutamatergic synapses contributes to the cognitive and psychiatric disorders in FXS.

Methods: *Fmr1* knockout mice ($Fmr^{-/-}$, B6.129P2-$Fmr1^{tm1Cgr}$/J, Jackson Laboratory stock No.: 003025) and C57BL/6 mice were purchased from Jackson Laboratory, regularly maintained and studied at six months old. We investigated whether microglial phagocytosis of glutamatergic synapse existed in $Fmr^{-/-}$ mice. *Whole-cell recordings were performed in brain slices containing* hippocampal CA1 areas.

Results: We noted a substantially increased expression of complement C1q in synaptosomal preparation of hippocampal CA1 in $Fmr^{-/-}$ mice (**Fig. 1a**). We also noted increased localization of postsynaptic density protein 95 (PSD95) immunoreactivity of the lysosomal protein CD68 in microglia (Iba1) (**Fig. 1b**), indicating increased microglial phagocytosis of glutamatergic synapse in the hippocampal CA1 in $Fmr^{-/-}$ mice. In addition, we observed a decreased amplitude and extended inter-event interval of miniature excitatory postsynaptic currents (mEPSCs) of hippocampal CA1 neurons (**Fig. 1c**), indicating altered glutamatergic transmission in $Fmr^{-/-}$ mice.

Conclusions: increased complement C1q-mediated microglial phagocytosis of hippocampal glutamatergic synapses contributes to the cognitive and psychiatric disorders in fragile X syndrome.

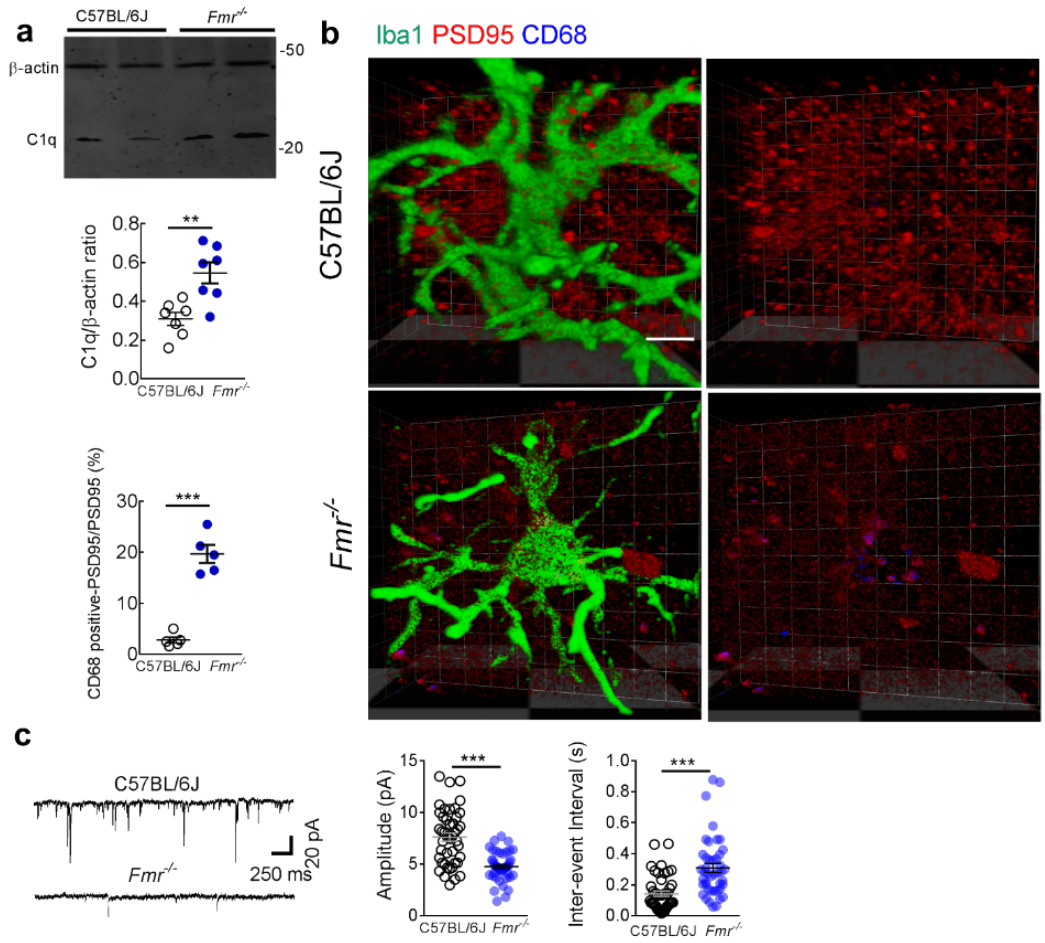


Figure 1. Microglial phagocytosis of glutamatergic synapses in *Fmr*$^{-/-}$ mice. Significantly increased expression of C1q in hippocampal CA1 synaptosomal preparation in *Fmr*$^{-/-}$ mice (**a**, n = 7 mice in each group, t = 3.7, DF = 12, two-tailed P = 0.003). Increased colocalization of PSD95 with the lysosome marker CD68 in microglia (Iba1) in the hippocampal CA1in *Fmr*$^{-/-}$ mice (**b**, n = 5 mice in each group, t = 9.09, DF = 8, two-tailed P<0.0001, scale bar = 10 μm). Right micrographs were presented to show the same microglia in which only the lysosomes (blue) and PSD95 (red) were visualized. Each dot represents the mean value of 4 brain slices of one animal. Decreased the amplitude (**c**, n = 44 neurons in each group, t = 6.26, DF = 86, two-tailed P<0.0001) and increased inter-event interval (**c**, n = 44 neurons in each group, Mann-Whitney U-statistic = 380, two-tailed P <0.0001) of mEPSCs in hippocampal CA1 neurons were observed in *Fmr*$^{-/-}$ mice. Data represent mean ± s.e.m. **P<0.01, ***P<0.001.

Using Population Pharmacokinetics to Estimate Chronic and Acute Cannabis Consumption

Presenting Author: Thomas K. Henthorn[1]
Co-Authors: Cristina Sempio[1], Cinnamon Bidwell[3], Marilyn Huestis[4], Uwe Christians[1], Kent Hutchinson[3], Jost Klawitter[1], Susan Mikulich-Gilbertson[2]

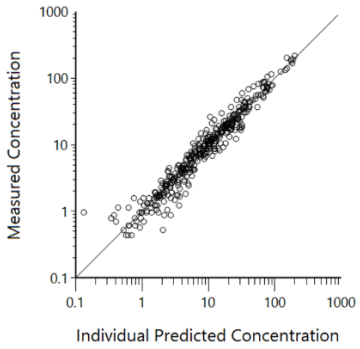
[1]Anesthesiology and [2]Psychiatry, University of Colorado, Aurora, CO; [3]Institute of Cognitive Science, University of Colorado, Boulder, CO; [4]The Lambert Center for the Study of Medicinal Cannabis and Hemp, Thomas Jefferson University, Philadelphia, PA

Introduction: Cannabis for medicinal and recreational use is widespread, increasing and of interest to anesthesiologists. With its current DEA scheduling as a Class 1 substance, scientific inquiry into the effects of THC and other cannabinoids are often limited to observational studies with no clear knowledge of cannabinoid exposure or dose. Two established techniques for estimating cannabis exposure are by the Timeline Follow-Back (TLFB) questionnaire and, rarely, actually weighing the cannabis product used. We have developed a popPK model of THC and two of its metabolites from Phase 1-like THC clinical trial studies. The aim of the current study was to use this popPK model in an observational study to estimate each subject's daily THC exposure as well as the dose consumed at a single uncontrolled cannabis smoking session. We hypothesized that there would be a significant correlation between popPK estimates of exposure or dose and TLFB and weighed cannabis used.

Methods: Thirty-seven regular users of cannabis from a larger study involving psychomotor testing were selected on the basis of indicating smoking as their primary method of consumption. Blood samples were obtained at recruitment, in a mobile lab immediately before smoking in their home, upon returning to the mobile lab and then again one hour later for analysis of THC/metabolites by LC-MS/MS. These data were analyzed with the Bayesian prior from our previous Phase 1-like popPK analysis (Pheonix NMLE, 8.1, Certara, Princeton, NJ). Estimates of elimination and metabolite production clearances were estimated for each subject as well as estimates of (1) daily THC consumption prior to recruitment, (2) daily THC consumption in the interval between recruitment and home-smoking and (3) the dose consumed during the home-smoking event. Linear regression of these latter 3 estimates were compared by linear regression to each subject's TLFB of cannabis use and the weighed amount used at the home-smoking event.

Results: There was a statistically significant correlation between the estimated THC consumed by TLFB and by popPK modeling ($r^2 = 0.56$, $p<0.01$) with a slope of 2.6. Additionally, there was a statistically significant correlation between the estimated THC consumed on a one-time smoking event by weighed cannabis and by popPK modeling ($r^2 = 0.71$, $p<0.01$) with a slope of 0.58.

Conclusions: The current study indicates that, while correlated, TLFB overestimates THC consumption compared to model-derived estimates based on THC and metabolite concentrations. This is consistent with cannabis users titrating to effect, leaving much of the subjects' perceived cannabis consumption (by TLFB) unused. Surprisingly, the current study indicates that estimating a single dose from popPK analysis overestimates the THC consumption compared to the weighed amount smoked. Potential causes to explore in future studies are differences in the assumed and actual duration and timing of smoking to the first blood sample (not measured) as well as important covariates such as the lower BMIs of Colorado versus Maryland subjects.



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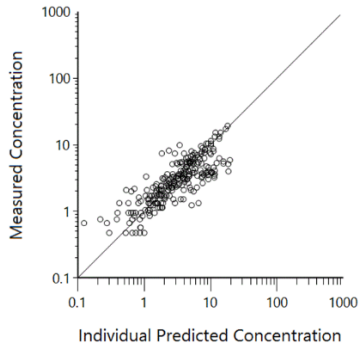

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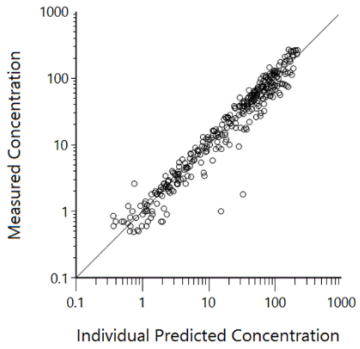

THCCOOH

TCI Lite Administration of Remifentanil Minimizes Coughing Prior to Extubation

Presenting Author: Elie Sarraf[1]
Co-Authors: Max W Breidenstein[2], Donald M. Mathews[2]

[1] Penn State Health Milton S. Hershey Medical Center, Hershey, PA, [2]University of Vermont Larner College of Medicine, Burlington, VT

Background/Introduction: Many techniques have been described to decrease coughing during emergence from anesthesia in an attempt to prevent adverse events such as bleeding and recurrence of hernia following herniorrhaphy. One technique involves the use of remifentanil delivered with a target controlled infusion (TCI) pump. Given the unavailability of TCI specific pumps in the US, we used a previously described *workaround* with a bolus-infusion sequence ("*TCI lite*") that delivers an effective target site concentration of remifentanil (http://bit.ly/2lXH0m8). To demonstrate the clinical effectiveness and safety of *TCI lite*, we conducted a pilot study.

Methods: With IRB approval, ten patients scheduled for inguinal or periumbilical herniorrhaphy were recruited in an unblinded, open-label, pragmatic clinical study. Exclusion criteria included patients with a Lean Body Mass < 20 kg, BMI > 45, presence of pulmonary dysfunction, any allergy to opioids, and patients receiving total intravenous anesthesia. In addition, the anesthesiologist could exclude any patient at any time if there was a concern for patient safety.
A syringe containing remifentanil was placed in a B-Braun Perfusor infusion pump which was programmed with *TCI lite* guidance for a desired remifentanil target concentration of 2.1 ng/mL. Induction and maintenance of anesthesia was performed at the discretion of the anesthesia team. The surgeon was instructed to notify the research team when 5 to 30 minutes remained until the end of the operation. Following the surgeon's notification, the syringe pump was started as programmed. The infusion was stopped when either the patient was extubated or if 15 minutes had elapsed since the end of the procedure. The severity of coughing was recorded on a scale of 0 to 3, with 0 being the absence of cough, and 3 being severe coughing. MATLAB was used to simulate the remifentanil and fentanyl effect site concentration during post-hoc analysis using the Minto and Shafer model respectively.

Results: Data from nine males were included in the analysis. Patient #8 developed laryngospasm following extubation which was determined to be unrelated to the infusion. This, however, led to the exclusion of the patient pending a safety review. Demographics and results are shown in Table 1. Four out of nine patients did not cough and 2/9 had a minor cough. Time to extubation ranged from 7 minutes to more than 19 minutes. Generally, once *TCI lite* was started, heart rate and blood pressure initially decreased and then stabilized without intervention. One patient was given glycopyrrolate for a heart rate of 39 and the anesthesiologist elected to continue the

infusion. Several anesthesiologists commented on the relatively prolonged wakeup time.

Conclusions: Remifentanil administered with *TCI lite* appears to assist in decreasing the incidence and severity of coughing. This technique had an acceptable safety profile and produced results consistent with prior publications. Although a higher target site concentration may be required to further decrease the incidence of coughing, this may result in longer emergence times which may be prohibitive in a fast-paced clinical environment.

Patient	Age	Weight	Height	Total fentanyl	Midazolam	Bolus	Infusion	Total Drug given	TCI_lite Duration	Extubation time	Worst cough	Ec_fentanyl	Ec_remi
#	years	kg	cm	mcg	mg	mcg	mcg/kg/min	mcg	MM:SS	MM:SS	grade	ng/mL	ng/mL
1	60	79	175	100	2	31	0.066	134.58	19:39	08:27	3	0.70	2.06
2	55	86	173	75	2	32	0.064	188.83	28:34	19:16	1	0.19	1.01
3	48	87	183	100	2	32	0.068	190.61	26:46	14:53	1	0.29	2.08
4	63	76	173	50	2	31	0.066	156.18	24:47	09:49	0	0.25	2.10
5	60	97	173	100	2	33	0.056	163.07	23:47	12:40	0	0.27	2.09
6	46	77	188	0	2	31	0.076	188.90	27:00	12:41	2	0.00	2.10
7	78	81	170	50	0	33	0.056	126.91	20:32	08:13	0	0.13	2.08
8	42	86	178	100	2	31	0.070	129.13	16:10	07:16	2	0.54	2.00
10	68	72	169	100	2	30	0.066	210.77	38:01	14:37	0	0.22	2.15

Table 1: Individual demographics and results of the study. *Total drug given* denotes the accumulated remifentanil dose given during the procedure*. TCI lite Duration* is the total duration of the remifentanil infusion. *Extubation time* is the time from anesthetic washout to extubation. Coughing grade is scored as follows: 0=no cough, 1=slight cough, cough without obvious contraction of the abdomen, 2=moderate cough, strong and sudden contraction of the abdomen lasting for less than 5 seconds, 3=severe cough, strong and sudden contraction of the abdomen sustained for more than 5 seconds. Ec_fentanyl and Ec_remi are the estimated effect site concentration of fentanyl and remifentanil at time of extubation.

PI3K/Akt-FoxO3a-p27 Signaling is Involved in Ketamine-Inhibited Proliferation of Rat Fetal Cortical Neural Stem Progenitor Cells

Presenting Author: Chaoxuan Dong[1, 2]
Co-Authors: Ya-lan Li[1], He Tian[1], Cai Nie[1]

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Background/Introduction: Ketamine has been widely used as an anesthetic, sedative or analgesic in pediatric clinical practice and diagnostic procedures. Recent studies indicate that ketamine induces potential developmental neurotoxicity by altering neurogenesis (proliferation and differentiation) of rat fetal cortical neural stem progenitor cells (NSPCs). Previous studies show that ketamine can inhibit the phosphorylation of PI3K/Akt and up-regulate the expression of p27, an inhibitor regulating cell cycle via cyclins, cyclin dependent kinase (CDKs) in rat fetal cortical NSPCs. This study is focused on connecting the PI3K/Akt signaling pathway to the p27 regulated cell cycle of NSPCs exposed to ketamine, investigating intracellular molecular mechanisms of ketamine induced developmental neurotoxicity.

Methods: In this study, rat fetal cortical neural stem progenitor cells are cultured as the *in vitro* model of a developing brain. NSPCs were isolated from embryos of timed-pregnant Sprague-Dawley rats (embryonic day 17). Flow cytometry methods were employed to test how ketamine regulate cell cycle of NSPCs and determine at which cell cycle phase ketamine regulates in rat fetal NSPCs. Western Blots methods are used to detect changes in expression levels of factors of FOXO3a, p27, Akt, and other cell cycle regulators: cyclins and CDKs. Additionally, siRNA, immunoprecipitation (IP) and western-blot methods were used to analyze the role of FOXO3a in the PI3K/Akt-p27 signaling of the NSPCs exposed to ketamine.

Results: The study shows that ketamine mainly inhibits cell cycle of NSPCs at the G1/S check point and up-regulates the expression of p27. Ketamine up-regulated p27 can bind to CDK2, inhibit its kinase activity, and finally arrests the cell cycle of NSPCs. FOXO3a, a downstream factor, acts as a potential connector between the PI3K/Akt signaling and p27.
Ketamine promotes the nuclear translocation of phosphorylated FOXO3a and increases nuclear phosphorylated FOXO3a via the PI3K/Akt signaling. Inhibited levels of FOXO3a using FOXO3a siRNA could decrease the ketamine up-regulated expression of p27 in NSPCs.

Conclusions: This study suggests that PI3K/Akt-FoxO3a-p27-cyclinE/CDK2 as an entire signaling pathway involved in ketamine induced proliferation inhibition in NSPCs, indicating potential intracellular molecular mechanisms of ketamine-induced developmental neurotoxicity in the developing brain.

The effect of ketamine on the qCON and the BIS during propofol anaesthesia

Presenting Author: Joana Cañellas[1]
Co-Authors: Umberto Melia[1], Susana Pacreu[1], J. Fernández-Candil[1], Carmen González[1], Erik W Jensen[1]

[1]Quantium Medical

Background/Introduction: Depth of anaesthesia monitors are in general trustworthy tools to assist anaesthesiologists inducing general anaesthesia (1). These monitors are based on the processing of the electroencephalogram (EEG) to obtain an index, reflecting the clinical state of the patient. However, not all anaesthetics cause the same effects on the EEG, and so under some drugs, such as ketamine, processed EEG monitors can be misleading and provide a resulting index not consistent with the real clinical state of the patient (2). The objective of this study is to validate the qCON index performance during surgical procedures under general anaesthesia with ketamine, as well as to analyse BIS index for comparison.

Methods: The EEG signals, qCON (Conox, Fresenius Kabi, Bad Homburg, Germany) and BIS (Medtronic, Boulder, CO, USA), and anaesthetic agents concentrations were recorded simultaneously from a total of 13 patients scheduled for spine surgeries in Hospital del Mar (Barcelona) undergoing general anaesthesia with ketamine and propofol, after approval of the local IRB and signed informed consent from the patients. Induction was reached with a bolus of propofol (between 40 and 150mg), fentanyl (between 200 and 300mcg) and also rocuronium (40mg), afterwards a bolus of ketamine was administered (between 35 and 50mg). The maintenance was carried out with propofol and ketamine using a target controlled infusion (TCI) system (B. Braun, Sheffield, UK). Clinical signs of loss of consciousness (LOC) such as loss of verbal response, and the drug administration times were recorded during the surgery. The recorded data was divided in the different surgical states: awake, induction, maintenance and recovery. Statistical analysis was carried out in order to compare the index values during awake and maintenance states. Acquired data with either high burst suppression ratio (BSR>10) or low signal quality index (SQI<50) were rejected.

Results: The obtained qCON values indicate that in 30.77% of the surgeries, right after the administration of the ketamine bolus, the index increased over 60 during about 20 minutes. However, in the remaining 69.23% the index reflected an adequate level of sedation during this period of time. During the maintenance state, qCON values were between 40 and 60 for all the patients. Figure 1 represents the ketamine bolus effect on the indexes. Figure 2 represents the boxplots of qCON and BIS for awake and anaesthesia states.

Conclusions: During maintenance, qCON index showed values between 40 and 60 (anaesthesia range) in patients under ketamine and propofol anaesthesia administered by an intravenous TCI system.

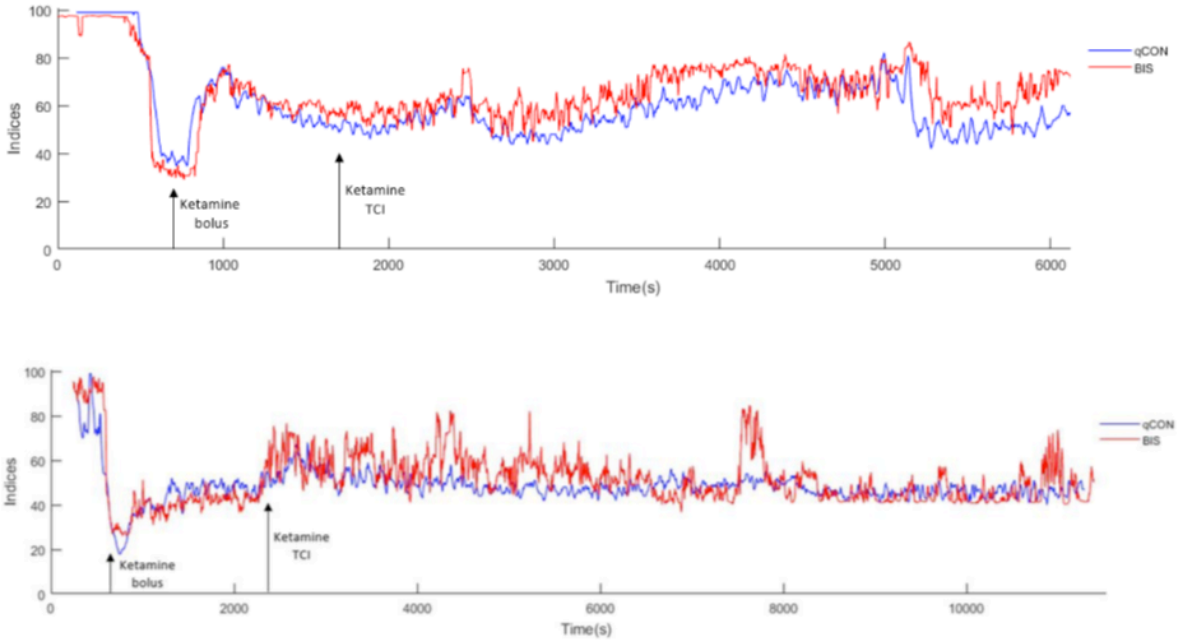

Figure 1. Indices values under the effect of ketamine for two different surgeries

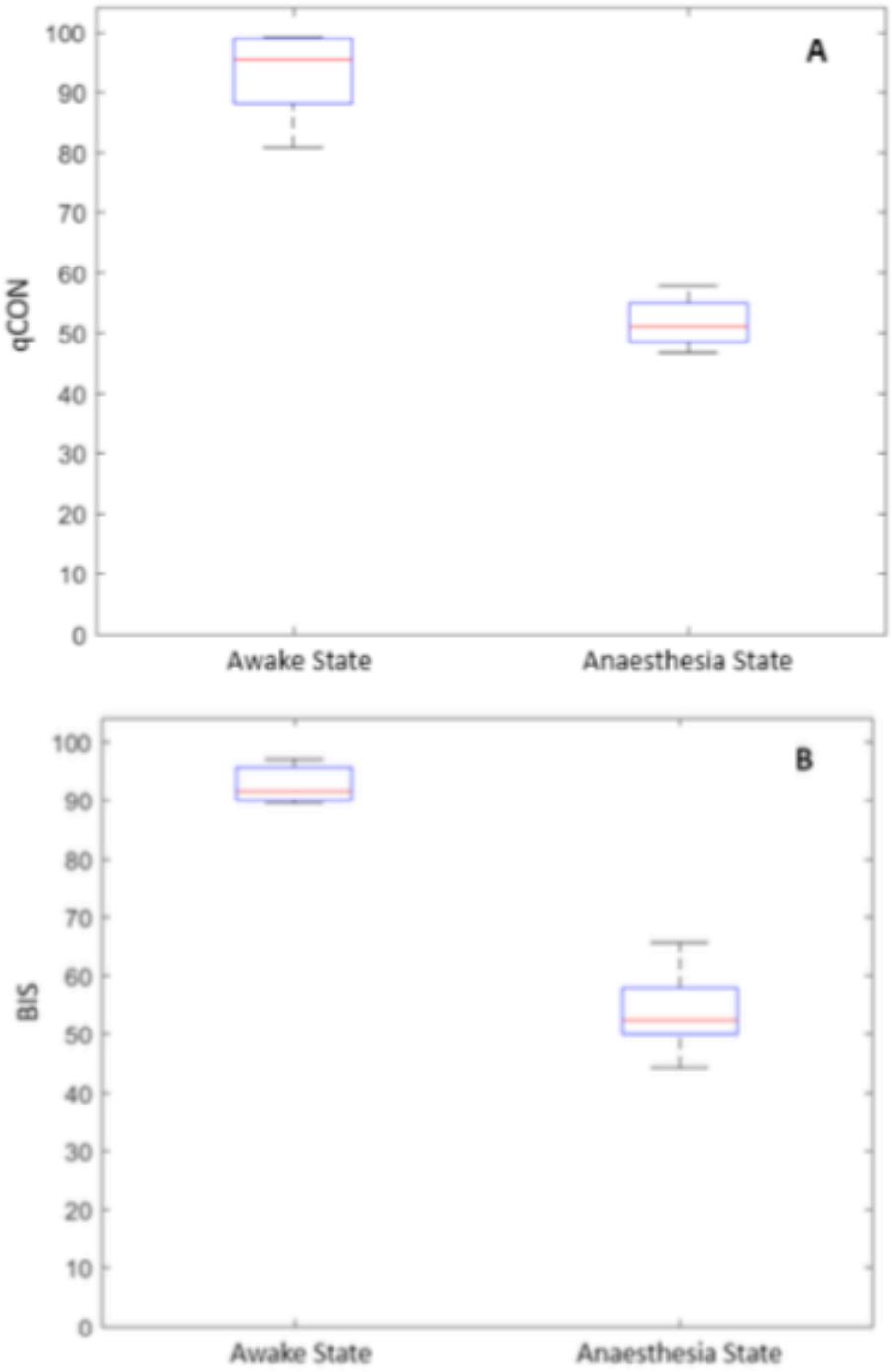

Figure 2. Comparison between awake and anaesthesia state for qCON and BIS indices

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2. WU, C C, MOK, M S, LIN, C S and HAN, S R. EEG-bispectral index changes with ketamine versus thiamylal induction of anesthesia. *Acta anaesthesiologica Sinica*. 2001.

stanpumpR, a PK/PD Simulation Program in the Public Domain

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Background/Introduction: In their comprehensive 2016 review of the history of Target Controlled Infusion (TCI) systems, Struys and colleagues identified software programs that presaged the current commercial TCI systems. Among these are CATIA developed by Schüttler and Schwilden at the University of Bonn, TIAC developed by Ausems and Hug as the University of Leiden, CACI developed by Reves and Alvis at the University of Alabama, CACI II developed by Jacobs and Reves at Duke University, STANPUMP developed by Shafer at Stanford University, STELPUMP developed by Coetzee and Pina at Stellenbosch University, and RUGLOOP developed by De Smet and Struys at the University of Ghent. STANPUMP was placed in the public domain, and the STANPUMP algorithms were incorporated into many commercially available TCI devices. None of these programs were designed to simulation PK/PD models.

Methods: stanpumpR implements many of the same pharmacokinetic models as STANPUMP, with updates for more recently published models based on the openTCI initiative. stanpumpR was written in the R programming language, and deployed using the “shiny” package.

Results: Figure 1 shows a representative output of stanpumpR for a 120-minute anesthetic. stanpumpR has pharmacokinetic models for propofol, remifentanil, fentanyl, alfentanil, sufentanil, morphine, pethidine, hydromorphone, methadone, ketamine, dexmedetomidine, midazolam, etomidate, lidocaine, rocuronium, naloxone, and oxytocin. Models can be adjusted for age, weight, height, and sex, provided the covariate effects are described mathematically. Models can be either time-invariant (the default) or time-variant (e.g., PK changes with the start/stop of cardiopulmonary bypass). Reflecting clinical practice, multiple opioid models can be combined into a single model of opioid drug effect. stanpumpR can also design simple dosing regimens to achieve desired target concentrations at the site of drug effect.

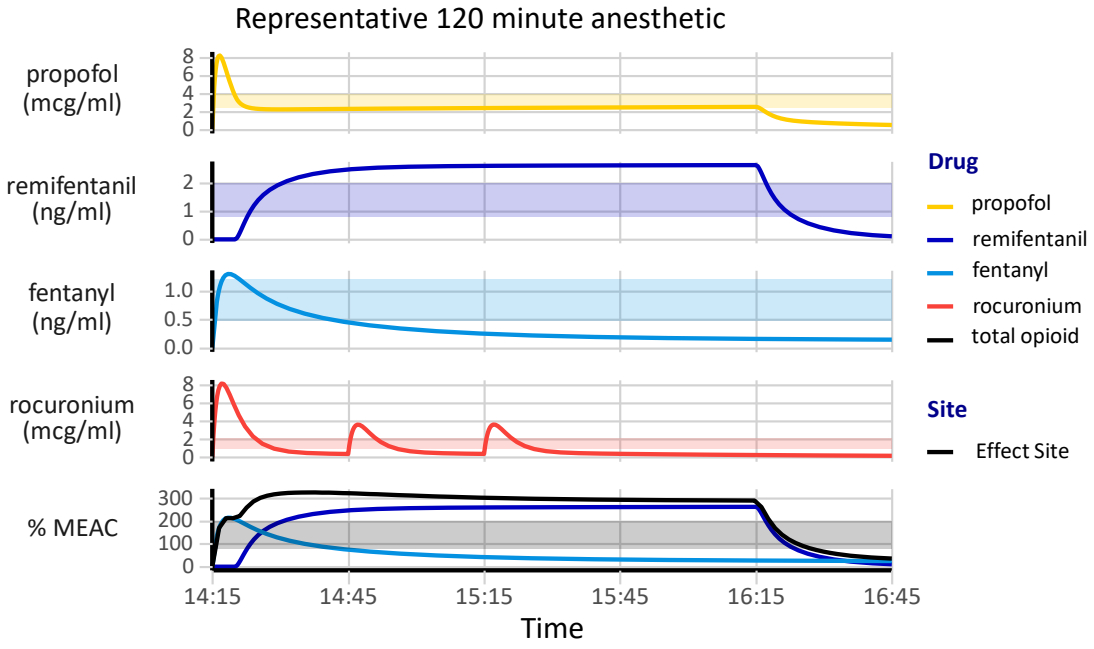
Conclusions: The goal of the original STANPUMP program was to make the results of pharmacokinetic research available to practicing clinicians and clinical investigators, and to test specific hypothesis about how to administer anesthetic drugs (e.g., effect site control). STANPUMP was also created as an open source repository of PK algorithms.

Although very little of the original STANPUMP code was ported to stanpumpR, its underlying philosophy is the same. stanpumpR is open source and freely available (https://github.com/StevenLShafer/stanpumpR), publicly accessible (http://stanpumpr.io), and will remain under development to bring state-of-the-art PK/PD models and concepts to trainees, clinicians, and investigators.

References

1. Struys MM, De Smet T, Glen JI, Vereecke HE, Absalom AR, Schnider TW. The History of Target-Controlled Infusion. Anesth Analg. 2016;122:56-69.

Figure 1:



Opioid-induced Respiratory Depression On General Care Floors Increases Cost Of Care: Results From The Prodigy Trial

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Introduction: Opioid-induced respiratory depression (OIRD) contributes to increased morbidity and mortality (Anesthesiology 2015; 122:659). The PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY (PRODIGY) trial was performed to derive a risk prediction tool identifying patients at risk of OIRD, identified using continuous capnography and pulse oximetry monitoring. In this prespecified secondary analysis we hypothesized that OIRD also increases cost of care

Methods: Hospital cost or payment data was collected for 865 patients (Figure 1) who received parenteral opioids and underwent continuous capnography and pulse oximetry monitoring (Capnostream™ respiratory monitor, Medtronic) on the general care floor. 9 trial sites in US, Netherlands, Singapore, and Japan provided hospital admission cost per patient. The trial site in France provided diagnosis-related group (DRG) payment data. Costs were converted to US dollars. A propensity weighted generalized linear model was used to determine the impact of OIRD on overall hospital cost per patient. Due to limited sample size, a multi-variable generalized linear model was used for France. Generalized linear models (GLM) were developed to identify factors significantly contributing to US healthcare costs and hospital length of stay.

Results: *Hospital Costs & DRG Payments in Asia and Europe:* Before propensity weighting, the average hospital cost or DRG payment for patients with and without OIRD was not significantly different in Singapore, Japan, Netherlands, or France. After propensity weighting, the average hospital DRG payment was 18% higher for patients in France with OIRD, compared to patients without OIRD (p=0.0268; Table 1).

Hospital Costs in US: Average hospital cost was significantly higher for patients with OIRD ($23,619 vs $19,193 for patients without OIRD; p=0.0001). Average cost for high OIRD risk patients (PRODIGY score), was significantly higher for patients with OIRD ($25,057 vs $18,609 for patients without OIRD, p=0.0087). After propensity weighting, the hospital cost for patients with OIRD was 16% higher compared to patients without OIRD (p=0.0127; Table 1). Predictors of hospital cost: length of stay, occurrence of OIRD, longer length of surgery, and procedure type (Table 2). Predictors of length of stay: OIRD, opioid naivety, use of multiple opioids, male sex, surgery ≥4 h, current smoker, peripheral vascular disease, and sepsis (Table 3). Cost increased exponentially for patients with OIRD as length of stay increased (Figure 2)

Conclusions: OIRD significantly increases both hospital length of stay and hospital cost in the US. Statistical power was limited by smaller sample sizes in Singapore, Japan, Netherlands, and France. Early identification of patients at risk for OIRD holds promise to improve patient safety and outcomes, while reducing cost of care

Figure 1. Patient flow diagram

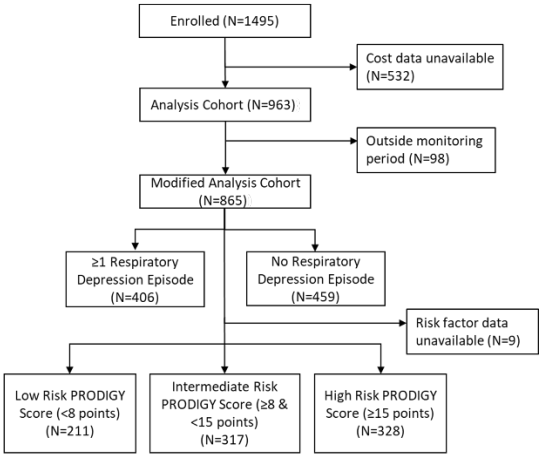

Figure 2. Effect of Length of Stay and OIRD on Overall Cost for US Patients

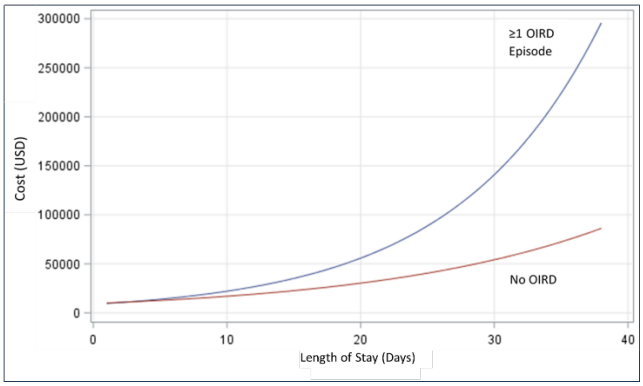

Table 1. Propensity Weighting of Healthcare Cost in Patients with or without OIRD

Market	≥1 OIRD Episode	Patients (N)	Propensity Weighted Cost (Mean ± SD)	Exponentiated Estimate (95% CI)	p-value
United States	No	266	$20,057 ± $13,555	---	
	Yes	142	$23,294 ± $15088	1.16 (1.03 - 1.31)	0.0127
Singapore	No	38	$11,283 ± $2,749	---	
	Yes	61	$10,874 ± $2,198	0.96 (0.89 - 1.04)	0.3666
Japan	No	83	$16,249 ± $5,661	---	
	Yes	130	$16,873 ± $7,100	1.04 (0.93 - 1.16)	0.4892
Netherlands	No	43	$13,704 ± $8,847	---	
	Yes	42	$13,505 ± $9,944	0.99 (0.77 - 1.26)	0.9084
France *(linear model)*	No	23	$7,897	---	
	Yes	25	$9,279	1.18 (1.02 - 1.36)	0.0268

Table 2. GLM of Hospital Cost in US Patients

Characteristic	Exponentiated Estimate	p value
Length of stay	1.06 (1.05-1.07)	<.0001
OIRD	0.92 (0.80-1.06)	0.2705
Length of stay*OIRD	1.04 (1.01 – 1.06)	0.0018
Length of surgery		<.0001
0 hr	0.75 (0.53 – 1.05)	
≥2 - <4 hr vs. <2 hr	1.28 (1.17-1.41)	
>4 hr vs. <2 hr	1.71 (1.51-1.93)	
BMI Class		0.0015
<20	0.82 (0.63-1.06)	
≥20 - <25	---	---
≥25 - <30	0.94 (0.83-1.05)	
≥30 - <35	1 (0.88-1.13)	
≥35	1.19 (1.03-1.38)	
Procedure		<.0001
Bone and joint	1.42 (1.06-1.92)	
Hepatobiliary	1.31 (0.91-1.89)	
Nervous system, skull and spine	1.81 (1.35-2.41)	
Renal and urinary tract	2.07 (0.93-4.58)	
Respiratory tract	1.10 (0.48-2.52)	

Table 3. GLM of Length of Stay in US Patients

Characteristic	Wald Chi-Square	Pr > Chi Square
≥1 OIRD Episode	8.60	0.0034
Male	8.03	0.0046
Opioid Naive	18.21	<.0001
Number of Opioids		
>1 - <4	42.85	<.0001
≥4	71.93	<.0001
Length of surgery (h)		
≥2 - <4	3.79	0.0516
≥4	5.08	0.0242
Current smoker	9.13	0.0025
Peripheral Vascular Disease	6.57	0.0104
Sepsis	90.27	<.0001

Conox EEG indices outperform ECG parameters in anaesthesia and nociception monitoring

Andrea Hortal, Umberto Melia, Pedro Gambús, Carmen González, Erik W Jensen

Background/Introduction: Monitoring nociception under general anesthesia is an area of research that is currently being explored using a wide variety of methods, aiming at ensuring that patients do not feel pain during surgery, minimizing postoperative stays and optimizing patient comfort. This study compares the performance of hemodynamic parameters and EEG based indices on their ability to reflect loss of consciousness and nociception.

Methods: The EEG based indices qCON and qNOX (Conox, Fresenius Kabi, Bad Homburg, Germany) and the hemodynamic signals ECG and ICG (qCO, Quantium Medical, Barcelona, Spain) were recorded simultaneously from a total of 58 patients scheduled for gynaecological surgeries in Hospital CLÍNIC (Barcelona) undergoing general anaesthesia with remifentanil and propofol using a target controlled infusion (TCI) system, after approval of the local IRB and signed informed consent from the patients. Clinical signs of loss of consciousness (LOC), such as loss of verbal response, and nociceptive stimuli such as LMA insertion or incision were recorded during the surgery.

The study was divided in two parts, one based on depth of anaesthesia and one based on nociception. In both cases, the parameters considered for analysis heart rate (HR), the high frequency component of heart rate variability (HF), cardiac output (CO) and RR Shannon entropy, together with qCON for depth of anesthesia monitoring and qNOX for nociception.
For the analysis of depth of anesthesia, the mean values of all the parameters during awake, anesthesia and recovery states were evaluated and compared through the prediction probability (pk) statistic. Regarding the nociception component, index values were compared before and after a stimulus during surgery, considering the presence or absence of movement response after the stimulus. In this case, 20-second windows have been collected before and after the stimuli. Prediction probability (Pk) was calculated to compare index values for movers and non-movers.

Results: The evolution of the indices is validated by the Pk-value that is shown in *Table 1* for the different states of anesthesia and in *Table 2* for the responses to stimuli. In the first case, the index that reveals more information to differentiate the patient's state of anesthesia is the qCON (Figure 1), followed by RR Shannon Entropy and the CO. On the other side, *Figure 2* represents the most important index to detect a patient's response to pain after a stimulus, the qNOX, presenting a higher Pk than all the hemodynamic indices proposed.

Conclusions: EEG based indices showed a better ability to detect LOC (qCON index) and predict reactions to nociceptive stimulation (qNOX). Those results suggest that EEG monitoring outperforms ECG parameters in anesthesia monitoring, both in terms of anesthetic depth and nociception.

Variable	*qCON*	*HR*	*HF*	*CO*	*RR Entropy*
Pk	0.955	0.650	0.658	0.661	0.799

Table 1. Pk values obtained for LOC analysis

Variable	*qNOX*	*HR*	*HF*	*CO*	*RR Entropy*
Pk before stim	0.621	0.588	0.474	0.620	0.580
Pk after stim	0.685	0.589	0.490	0.663	0.592

Table 2. Pk values obtained for nociception analysis

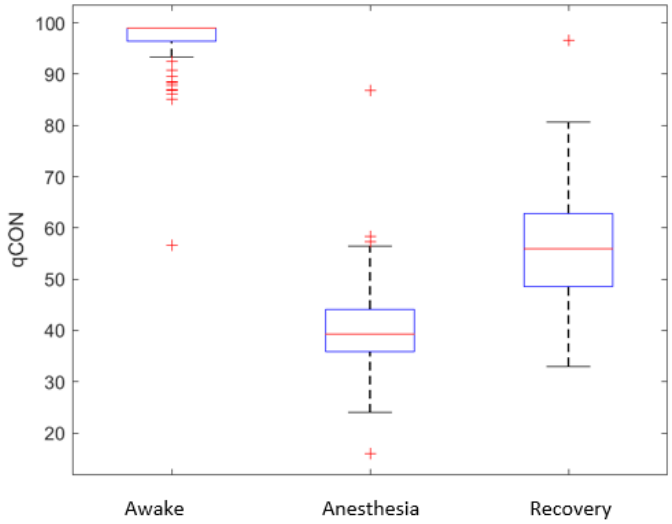

Figure 1. Boxplot showing qCON performance in depth of anaesthesia monitoring

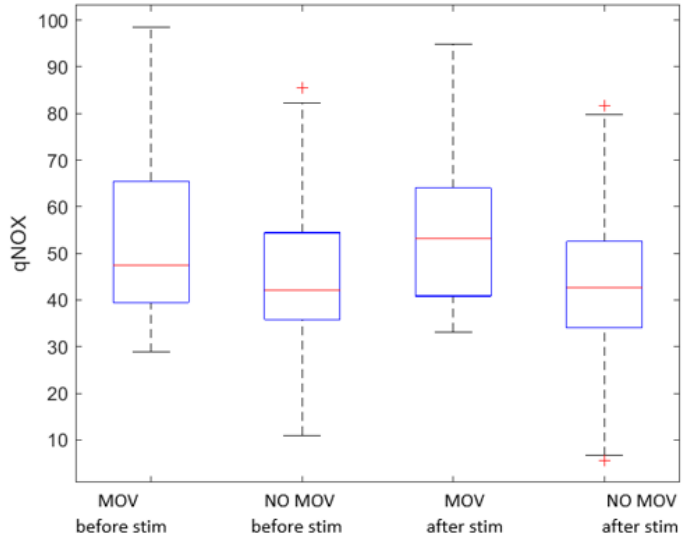

Figure 2. Boxplot showing qNOX performance in nociception monitoring