ISAP 31st Annual Meeting

2022 Syllabus

October 21st, 2022

JW Marriott New Orleans

614 Canal St., New Orleans, Louisiana

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31st Annual Meeting

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.

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Objectives

After Attending This Program You Should Be Able To:

1. Effectively assess the impact of anesthetic drugs on young brains. Understand the role of neurotoxicity in that process.
2. Obtain insight in the current state of closed loop drug titration in anesthesia.
3. Recapitulate the molecular mechanisms of anesthetic drugs.

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Second Annual Mohamed Naguib Lecture: "The Drug Titration Paradox: Something Obvious Finally Understood" by Talmage Egan, MD, FASA

Generous support provided by Senzime Corporation

ISAP has established the Mohamed Naguib Lecture to honor his many accomplishments, which will be presented at every ISAP Annual Meeting. The Inaugural Lecture was given at the 2021 ISAP Annual Meeting. ISAP has established a fund to endow the Mohamed Naguib Lecture and donations may be made at isaponline.org.

Dr. Naguib's influential work has made significant contributions to the scientific foundation and clinical applications of neuromuscular monitoring and other areas of anesthetic pharmacology. In addition to supporting the Mohamed Naguib Lecture, the ISAP Board has approved Poster Awards of $1,000-1st place, $500-2nd place and $250-3rd place to help support the work of young researchers.

In the world of clinical pharmacology, Dr. Naguib was a renaissance man. As a man of many talents, his influential work has provided direction in many spheres of investigation and discovery. He made significant contributions to the scientific foundation and clinical applications of neuromuscular monitoring. He formed and led a coalition of thought leaders to prepare and disseminate expert consensus guidelines on neuromuscular monitoring. He had substantial interest in the mechanisms of and treatment for neuropathic pain. He led a laboratory that created molecules to treat neuropathic pain. At the time of his passing, he was a principal investigator on a NIH funded multi-center observational study focused on the discovery and validation of a biomarker signature for chemotherapy induced peripheral neuropathic pain.

He was the co-founder of a company that is developing a novel therapy for neuropathic pain and Alzheimer's disease based on his research on the mechanisms of neuroinflammation. For each of these activities, he created a wake of opportunities for many that continue to have a vibrant and productive future. He was a prolific writer. He was the principal author or co-author of 130 peer-reviewed journal articles, 25 book chapters (including the premier Miller's Textbook of Anesthesia) and 150 abstracts.

By way of professional service, for years, he served on the editorial board of numerous anesthesia journals and was influential not only in his reviews but in preparing thought provoking editorials and commentary. He also served for many years in various leadership positions, including President of ISAP.

31st Annual Meeting Schedule

0815 - 1800 US Central Time Zone

0815–0830 **ISAP Welcome Announcements**
Hugo Vereecke, MD, President

0830– 1000 **Session 1 – Anesthesia Related Side Effects**

0830 – 0900 **The Effects of General Anesthesia on Very Young Brain**
Vesna Jevtovic-Todorovic, MD, PhD, MBA, FASA, Chair, Department of Anesthesiology, University of Colorado School of Medicine

0900 – 0930 **Neurosteroid Binding and Action on GABAA Receptors**
Alex S. Evers, MD, Henry E. Mallinckrodt Professor of Anesthesiology, Washington University in St. Louis

0930 – 1000 **Closed-loop Control of Post-operative Hypotension**
Alexandre Joosten, MD, PhD, Associate Professor, Paris Saclay University, Department of Anesthesiology, Intensive Care & Perioperative Medicine, Bicetre & Paul Brousse Hospitals

1000-1015 **Break**

1015 – 1130 **Session 2 – New Therapeutic Strategies in Anesthetic Pharmacology**

1015 – 1045 **Pharmacologic Reversal of General Anesthesia using Competitive Antagonists: Proof of Principle**
Douglas E. Raines, MD, Massachusetts General Hospital Dept. of Anesthesia, Critical Care, and Pain Medicine, and Harvard Medical School

1045 – 1115 **Value of NMM in the Era of Sugammadex**
Manfred Blobner, MD, Professor, Technical University of Munich, School of Medicine, Dept. of Anesthesiology and Intensive Care Medicine and University of Ulm, Medical Faculty, Dept. of Anesthesiology und Intensive Care Medicine

1115 – 1130 **Q & A**

1130 - 1300 **Luncheon – ISAP Business Meeting**

1300 – 1400 **Session 3 - Innovation in Pharmacometrics**

1300 – 1330 **Anaesthetic hysteresis: is it PK, PD or both?**
Alex Proekt, MD, PhD, Associate Professor, Perlman School of Medicine, University of Pennsylvania

1330– 1400 **Pharmacometric approaches to categorical data analysis: an example based on MOAA/S**
Jeroen V. (Vincent) Koomen, PhD, PharmD, Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

1400-1445 **Mohamed Naguib Lecture: The Drug Titration Paradox: Something Obvious Finally Understood.**
Talmage Egan, MD, FASA, Professor and Chair, Department of Anesthesiology, University of Utah School, Salt Lake City, UT, USA

1445-1500 **Break**

1500– 1630 **Moderated Poster Session**

1630-1645 **Break**

1645 – 1730 **Keynote Speaker & Lifetime Achievement Awardee**
"A Life in Anesthetic Pharmacology: Some of What Goes Around Comes Around"
Thomas K. Henthorn, MD, Professor, Department of Anesthesiology, University of Colorado School of Medicine, Adjoint Professor, Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, Anschutz Medical Campus, Aurora, CO, USA

1730 – 1800 **Gathering**

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Abstract Table of Contents

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Remimazolam exposure-response relationship model for sedation depth suggests influence of its main metabolite by competitive antagonism

Presenting Author: Remco Vellinga, M.D[1]
Co-Authors: Michel M.R.F Struys, M.D[1,2]., PhD,Pieter Colin, Pharm D, Phd[1].

[1]Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [2]Department of Anaesthesia and Peri-operative Medicine, Ghent University, Ghent, Belgium.

Background: Remimazolam (Byfavo, Paion), is a benzodiazepine with a sedative effect. Combined with an opioid, for example remifentanil, remimazolam could be useful to induce and maintain general anesthesia. Currently, detailed information about the strength of the interaction between both drugs is lacking. In this study, as a first step towards understanding the remimazolam-remifentanil interaction, we report on the exposure-response relationship for remimazolam for depth of sedation as measured by Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score and the influence of CNS7054, the main metabolite of remimazolam, on this relationship.

Methods: The study was approved by the Foundation for the Assessment of Ethics of Biomedical Research in Assen, The Netherlands, with reference number NL75782.056.20. The trial was registered at clinicaltrials.gov (NCT04670471). 24 healthy volunteers, stratified by age (3 groups) and sex, were included. Remimazolam was dosed in a step-up and step-down scheme. We used target controlled infusion to target effect side concentrations of 150, 300, 400, 800, 1300, 2000, 1300, 800, 400, 300 and 150 ng. mL^{-1}. Depth of sedation was measured using the MOAA/S. The concentration targets and other features of the trial design were optimized before the trial using clinical trial simulations based on available interim modelling results of remimazolam PK/PD from PAION and Schüttler and colleagues[1]. Arterial samples were drawn at pseudo steady state after a minimum equilibration period of 25 min after target adjustment. The exposure-response relationship was modelled using mixed-effects proportional odds logistic regression (POLR) model in NONMEM.

Results: The POLR model failed to describe our observed data. Most notably, the model did not describe the difference in observed MOAA/s between the step-up and step-down sequence in our trial. Measured concentrations of remimazolam were in close agreement for target concentrations in both sequences. However, the concentration of the CNS7054 accumulated with infusion duration. As a consequence, the CNS7054 : remimazolam ratio increased from 2.9 to 63.4 for the 150 ng.mL-1 target in the step up vs. the step down sequence respectively. A post hoc analysis based on the model proposed by Holford and Sheiner[2] ,that accounts for competitive interaction between two ligands at the same receptor, better fitted our data (ΔOFV of -124). Goodness-of-fit plots showed that the discrepancy in MOAA/S between the step-up and step-down sequence was well predicted when both remimazolam and CNS7054 concentrations were taken into account. The model predicted CNS7054 to be a very weak agonist with a maximum effect on MOAA/S 15-fold lower than remimazolam. At the same time, half of the maximum effect for remimazolam is reached around 210 ng.mL-1 whilst for CNS7054 the IC50 is 10-fold higher at around 2465 ng.mL-1.

Conclusion: We found a significant difference in the depth of sedation for identical effect-site target concentrations between the step-up and step-down sequence. In our study, CNS7054 concentrations accumulated with increasing infusion duration. A model accounting for competitive antagonism between remimazolam and CNS7054 accurately described the higher MOAA/S in the step down vs. the step-up part.

1. Schüttler, J. *et al.* Pharmacokinetics and Pharmacodynamics of Remimazolam (CNS 7056) after Continuous Infusion in Healthy Male VolunteersPart I. Pharmacokinetics and Clinical Pharmacodynamics. *Anesthesiology* **132**, 636–651 (2020).
2. Holford, NHG and Sheiner LB (1982) Kinetics of pharmacologic response. Pharmacol Ther 16:143–166 (1982)

International Society for Anaesthetic Pharmacology (ISAP)
October 21, 2022 – New Orleans, LA

A Multicenter, Randomized, Double-Blinded, Propofol-Controlled, Phase 3 Clinical Study to Evaluate the Efficacy and Safety of HSK3486 Injectable Emulsion for Induction of General Anesthesia in Adults Undergoing Elective Surgery

Presenting Author: Tong J. Gan, MD[1]
Co-Authors: Todd Bertoch, MD[2]; Ashraf S. Habib, MD[3]; Pangke Yan, MD[4]; Rong Zhou, PhD[4]; Yu-Ling Lai, MS[5]; Xiao Liu[4]; William L. Daley, MD, MPH[5]; Adrian W. Gelb, MBChB[6]

[1]Anesthesiology, Critical Care and Pain Medicine Division, University of Texas MD Anderson Cancer Center, Houston, Texas; [2]CenExel JBR, Salt Lake City, Utah; [3]Department of Anesthesiology, Duke University School of Medicine, Durham, North Carolina; [4]Haisco Pharmaceutical Group Co., LTD., Shannan, China; [5]Haisco-USA Pharmaceutical Company, Inc., Bridgewater, New Jersey; [6]Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, California

Background/Introduction: Use of propofol for intravenous (IV) induction of anesthesia can cause significant hypotension,[1,2,3] respiratory depression,[4] and injection-site pain.[5] HSK3486 injectable emulsion is a new chemical entity similar to propofol, having pharmacodynamic characteristics of fast onset and quick, stable recovery. Prior clinical studies have demonstrated HSK3486 to be an effective anesthetic, with a safety profile comparable to propofol but with potentially less cardiopulmonary instability and significantly less injection-site pain.[6,7,8] The primary objective of this study was to demonstrate the non-inferiority of HSK3486 as compared to propofol in successful induction of general anesthesia.

Methods: A total of 255 participants (2:1 ratio: HSK3486 [n=170]; propofol [n=85]) were enrolled in a multicenter, randomized, double-blinded, propofol-controlled, phase 3 clinical study to evaluate the efficacy and safety of HSK3486 for IV induction of general anesthesia in adults undergoing elective surgery with endotracheal intubation.

The primary endpoint was successful induction of anesthesia defined by Modified Observer's Assessment of Awareness/Sedation (MOAA/S ≤1 without >1 top-up doses and no use of rescue drugs; non-inferiority margin of −8%). Key secondary endpoints were (1) proportion of participants with any injection-site pain on the Numerical Rating Scale (NRS ≥1), and (2) proportion of participants with successful induction who maintain desired depth of anesthesia in combination with an inhaled anesthetic, and without significant cardiac and respiratory depression between the time of successful induction to 15 minutes post study drug administration. Safety endpoints included adverse events, vital signs, and injection-site pain.

Results: Two hundred fifty-one participants completed the study and were included in the efficacy and safety analyses (HSK3486 [n=168]; propofol [n=83]).

The success of general anesthesia induction, n (%), was 163 (97.0%) for HSK3486 and 81 (97.6%) for propofol. The treatment difference in the success rate was −0.57% (95% CI, −5.4% to 4.2%). As the lower bound of the 95% CI did not cross the non-inferiority boundary of −8%, the primary endpoint was achieved. HSK3486 was demonstrated to be significantly non-inferior to propofol for successful induction of anesthesia.

Participants with pain scores (NRS ≥1) during injection and induction, n (%), were 30 (18.0%) for HSK3486 and 64 (77.1%) for propofol (P<.0001). Participants who maintained desired depth of anesthesia without significant cardiac and respiratory depression

between the time of successful induction to 15 minutes post study drug administration, n (%), were 76 (45.2%) for HSK3486 and 38 (45.8%) for propofol (*P*=.8867).

Overall study drug–related treatment-emergent adverse events (TEAEs) were 37 patients (22.0%) for HSK3486 and 44 (53.0%) for propofol. Injection-site pain reported as a TEAE related to study drug was 11 (6.5%) for HSK3486 and 36 (43.4%) for propofol.

Conclusions: The study met its primary objective and endpoint, demonstrating noninferiority of HSK3486 compared to propofol for successful induction of anesthesia. HSK3486 was associated with significantly less pain on injection than propofol. The overall incidence of study drug–related TEAEs was numerically higher for participants treated with propofol compared to those treated with HSK3486.

Table. Summary Results

		HSK3486	Propofol
Primary endpoint			
Success of general anesthesia induction, n (%)[a,b]		163 (97.0)	81 (97.6)
Difference of proportions-success rate, %	−0.57		
95% CI, %[c]	(−5.4 to 4.2)		
Key secondary endpoints			
Participants with pain scores (NRS ≥1) during injection and induction, n (%)		30 (18.0)	64 (77.1)
Difference of proportions-pain scores, %	−59.14		
95% CI, %	(−69.9 to −48.4)		
P value	<.0001		
Successful induction, maintaining desired depth of anesthesia, n (%)[d]		76 (45.2)	38 (45.8)
Safety endpoints, n (%)			
Overall study drug–related TEAEs		37 (22.0)	44 (53.0)
Injection-site pain (study drug–related TEAE)		11 (6.5)	36 (43.4)

MOAA/S, Modified Observer's Assessment of Awareness/Sedation; NRS, Numerical Rating Scale; TEAE, treatment-emergent adverse event.
[a] Considered successful if MOAA/S ≤1 and one or less top-up doses required without using any rescue drugs.
[b] Differences in the success rate and CIs are calculated using Farrington-Manning method with the non-inferiority margin of −8%.
[c] HSK3486 is significantly non-inferior to propofol as the lower bound of the 95% CI (−5.4%) does not cross the non-inferiority boundary of −8%.
[d] Maintained desired depth of anesthesia in combination with an inhaled anesthetic without significant cardiac and respiratory depression between the time of successful induction to 15 minutes post study drug administration.

References:
1. Sebel PS, et al. *Anesthesiology*. 1989;71(2):260-277; 2. Chan VW, et al. *J Clin Anesth*. 1996;8(4):317-323; 3. Dundee JW, et al. *Anaesthesia*. 1986;41(5):482-485; 4. Vanlersberghe C, et al. *Handb Exp Pharmacol*. 2008;(182):227-252; 5. Picard P, et al. *Anesth Analg*. 2000;90(4):963-969; 6. Li J, et al. *Basic Clin Pharmacol Toxicol*. 2022;131(2):138-148; 7. Zeng Y, et al. *Eur Rev Med Pharmacol Sci*. 2022;26(4):1114-1124; 8. Luo Z, et al. *CNS Drugs*. 2022;36(3):301-313.

Usefulness of nociception monitors to titrate remifentanil with a stable low noxious stimulation response index (NSRI)

Nele Van Heck, M.D.[1,2], Rik Carette, M.D.[1] ,Jan F.A. Hendrickx, M.D., PhD [1,2,3] , Andre De Wolf, M.D.[4]

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Part of this work was presented at Residents' Graduation Day 2022 Brussels, Belgium, May 2022

Introduction: Opioids blunt autonomic nervous system (ANS) responses to noxious stimuli. Nociception monitors analyze the same ANS responses and thus might prove useful to guide opioid dosing. However, concomitantly administered hypnotics also blunt ANS responses and may thus jeopardize the usefulness of nociception monitors to guide intra-operative opioid dosing. We therefore studied the P_K (prediction probability) of 3 nociception monitors (NOL index, qNOX and SPI) for the prevailing opioid concentration while maintaining the NSRI (noxious stimulus response index) at a low constant value with a range of opioids and inhaled agent combinations.

Methods: After IRB approval, anesthesia was maintained with desflurane in O_2/air and remifentanil (target controlled infusion) in 24 consenting ASA I-II patients undergoing robotic assisted radical prostatectomy. During the dissection phase, the remifentanil effect site concentration (C_e) in each patient was maintained at 1, 3, or 5 ng/mL for 20 min while the end-expired desflurane concentration (F_{ET}) was adjusted to keep the NSRI at 5; the sequence in which each patient received each of the three remifentanil C_e was randomized. After stabilization, during each 20 min study period, the following data were collected: NSRI, NOL Index, SPI, qNOX, and F_{ET}des. For each parameter, the prediction probability (P_K) for C_e remifentanil was calculated.

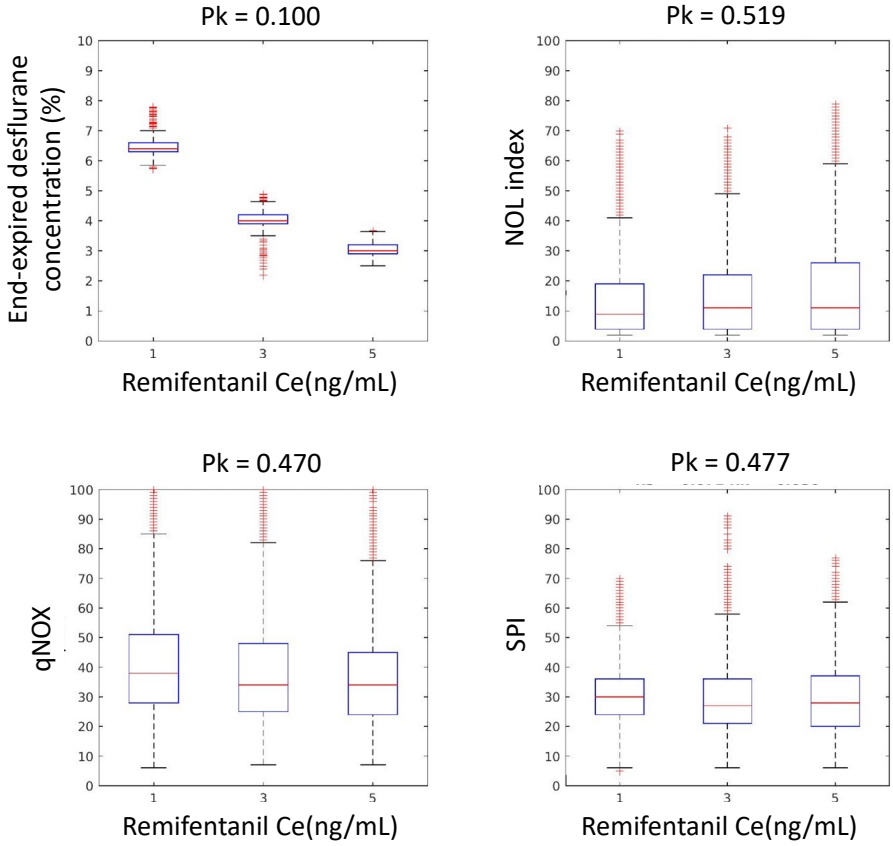
Results: All patients remained hemodynamically stable. Surgery was finished before the last data collection period in 5 patients with a remifentanil C_e = 5 ng/mL, and in 1 patient with a remifentanil C_e = 1 ng/mL. All other data have been included in the data analysis. The prediction probability (P_K) calculated for NOL Index, qNOX and SPI for C_e remifentanil was 0.519, 0.470, and 0.477, respectively.

Conclusion: Nociception monitoring becomes useless to titrate opioids when the concomitantly administered hypnotic is adjusted to maintain a low NSRI, presumably because suppression of movement to laryngoscopy also ensures suppression of the sympathetic nervous system response to the noxious stimulus present during intra-abdominal resection of the prostate[1]. Further research may prove (or disprove) a relationship between NSRI and measured nociception by studying nociception monitoring at other (higher) NSRI values.

Reference: 1. Luginbühl M, Schumacher PM, Vuilleumier P, Vereecke H, Heyse B, Bouillon TW, Struys MM (2010) Noxious stimulation response index: a novel anesthetic state index based on hypnotic-opioid interaction. Anesthesiology 112:872-80. https://doi.org/10.1097/ALN.0b013e3181d40368

SPI = Surgical Pleth Index; NOL index = Nociception Level index.

Fig. 1. Prediction probabilities Pk, presented as mean (standard error).



The Application of Alchemical Free Energy Perturbation Calculations to More Robust Correlations of Anesthetic-Protein Binding Energies with Potency

(Ed Bertaccini MD)

Introduction: Currently available intravenous anesthetic agents are associated with profiles of side effects that, while often used advantageously, also produce poorly tolerated and costly physiologic sequelae. This makes the development of a safer anesthetic both a medical and economic imperative.

Modern drug design has been advanced through the evolution of sophisticated computer hardware and software for molecular modeling and computational chemistry. Combining such with the explosion in atomic level coordinate descriptions of relevant drug binding sites (i.e., within the gamma amino butyric acid receptor type A, GABAaR) via methods of cryo-electron microscopy allows for initial drug design to take place more efficiently *in silico*.

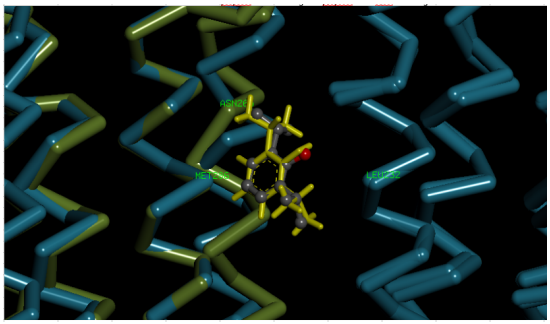
The difficulty with physicochemical calculations of drug-receptor interactions involves the balance between computational speed from approximate calculations versus the more accurate but slower calculations from robust free energy characterizations. However, with the advent of greater computational capabilities a more realistic assessment of drug-receptor interactions involving both enthalpy and entropy can take place utilizing the methods of alchemical free energy perturbation theory (FEP).

Methods For this study, the 6 propofol derivatives from our previous CDocker molecular docking calculations[1-3] (2,6-diisopropylphenol; 2,6-dimethylphenol; phenol; 2,6-diethylphenol; 2-isopropylphenol; 2,6-disecbutylphenol) were combined with the following 5 additional ligands: 4-iodo-2,6-diisopropylphenol; 2-tert-butyl-6-methylphenol; 3,5-diisopropylcatechol; 2,6-diethylphenyl bromide; 3,5-di-tert-butylphenol and their potencies for analysis.[4] All ligands were docked to the propofol binding site in the cryo-electron micrograph coordinates, 6X3T, of the heteromeric GABAaR. Molecular docking and alchemical free energy perturbation calculations were carried out using the preparatory and computational modules for CDocker and FEP methods, respectively, within the Biovia Discovery Studio 2021 software suite (Dassault Systemes, San Diego, CA). Calculations were completed on an HP Z840 workstation running Centos Linux 7 with 256GB of RAM, 40 Intel Xeon CPU cores, and an Nvidia Quadro M6000 graphics card containing 12MB RAM and 3072 GPU cores for GPU-based calculations.

Results: The FEP calculations were completed over the course of several days as opposed to the more approximate CDocker calculations requiring only several hours. While both the CDocker and FEP calculations showed an initial log-linear correlation between their binding energies and ligand potency, the FEP calculations were able to produce a more realistic physical model by including both enthalpic and entropic binding effects as a full assessment of true binding free energy. The correlation was not only more robust for the FEP vs CDocker calculations, but the FEP correlations remained robust when including the 5 additional ligands not previously present in the initial CDocker analyses.

Conclusion: While approximate molecular docking calculations can be implemented for high throughput screens of large ligand databases using grossly favorable characteristics like molecular size and shape, FEP calculations can be used to further assess subtle atomic refinements of favorable core chemical moieties identified from faster search techniques. This may allow more accurate predictions of relative binding affinities and the effectiveness of future modifications to new classes of anesthetics with novel chemical cores while limiting the initial investment in costly *in vitro* and *in vivo* experimentation.

The Application of Alchemical Free Energy Perturbation Calculations to More Robust Correlations of Anesthetic-Protein Binding Energies with Potency
(Ed Bertaccini MD)



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EEG and Sedation Response of Dexmedetomidine during Drug Induced Sleep Endoscopy

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Background/Introduction: Dexmedetomidine has many advantages including limited respiratory depression, analgesia, and decreased emergence delirium, and is one of the anesthetics of choice for drug induced sleep endoscopy (DISE). However, challenges with monitoring sedation levels and prolonged recovery have limited its usage. An improved understanding of dexmedetomidine pharmacokinetics and pharmacodynamics could help overcome these barriers.

Methods: Fifty-one patients received dexmedetomidine sedation with continuous EEG monitoring via SedLine monitoring for DISE. Blood levels of dexmedetomidine and Richmond Agitation-Sedation Scale (RASS) score were assessed at regular intervals throughout the procedure and recovery. We constructed a pharmacokinetic model to determine continuous dexmedetomidine blood concentration. From the SedLine, we extracted the patient state index (PSI), and from the EEG we calculated the spectral edge frequency 95% (SEF95) and the correlation dimension (CD), a type of fractal dimension used to assess the complexity of a system. These metrics were subsequently compared against one another and with the dexmedetomidine concentration.

Results: Our pharmacokinetic model yielded a two-compartment model with volumes of 51.8L and 106.2L, with clearances of 69.5 and 168.9L/hr, respectively, and a time to effect of 9 minutes, similar to prior studies. Based on this model, decreasing RASS score, SEF95, CD, and PSI were all significantly associated with increasing dexmedetomidine concentration ($p < 0.001$, $p = 0.006$, $p < 0.001$, $p < 0.001$ respectively, Figure 1). CD, SEF95 and PSI were superior to the RASS score at capturing the effects of increasing dexmedetomidine concentration and showed significantly relatively preserved power in the 10-15Hz spindle oscillation region, consistent with previous studies. Simulating dexmedetomidine concentration based on titration to target levels derived from CD confirmed adequate sedation seen with commonly used dexmedetomidine infusion dosages.

Conclusions: Our in-depth analysis of dexmedetomidine use for procedural sedation confirms previous pharmacokinetic models and spectral changes seen with dexmedetomidine. Changes in brain state with increasing dexmedetomidine were better captured by the complex EEG metrics, such as PSI and CD, as compared to the RASS score and SEF95. EEG metrics that capture complexity have the potential to improve our assessment of sedation with dexmedetomidine.

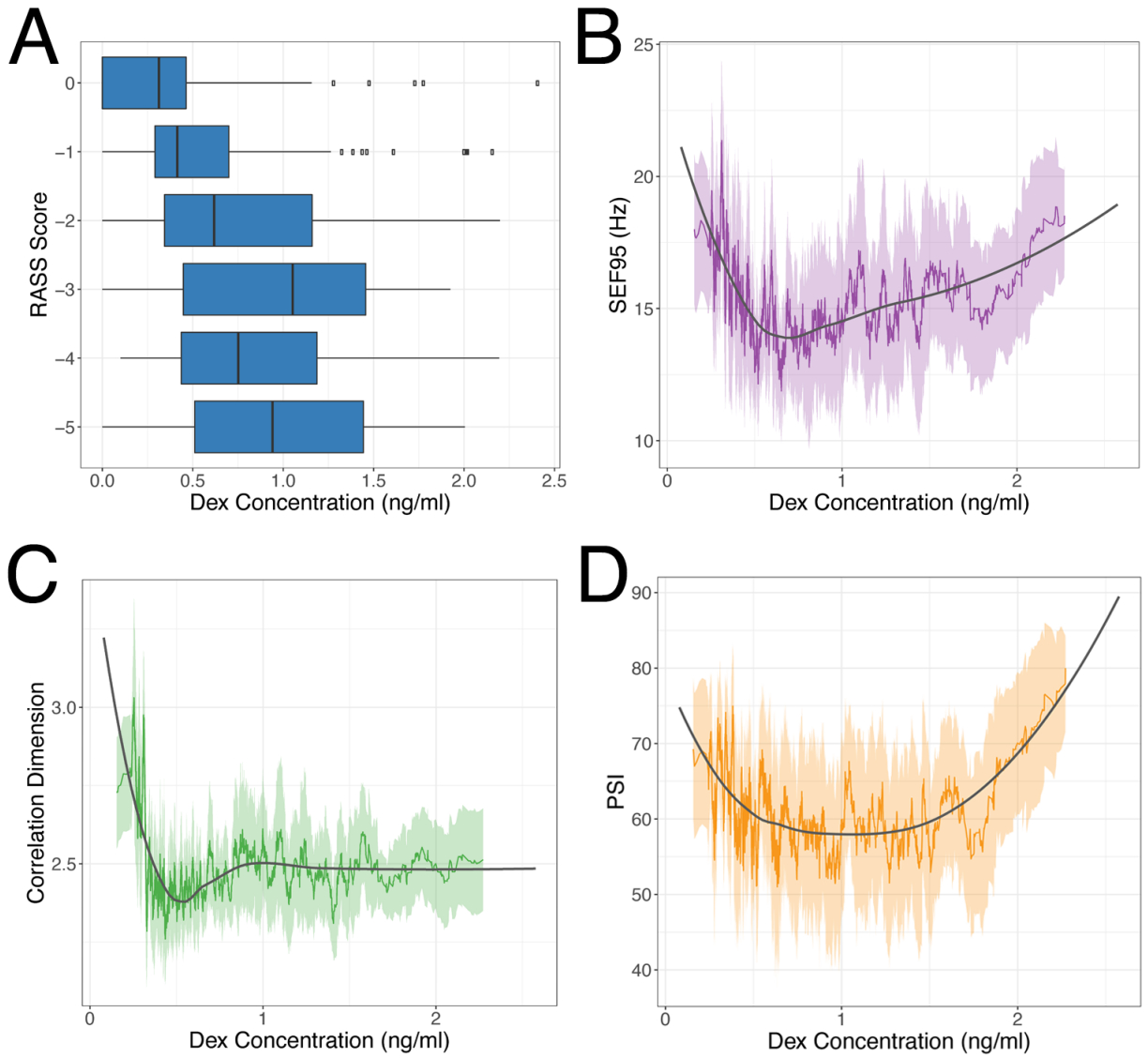

Figure 1. RASS score (A), SEF95 (B), CD (C), and PSI (D) versus dexmedetomidine (dex) concentration. SEF95, CD, and PSI are depicted as rolling mean in the colored solid line, the standard deviation in the shaded area, with local polynomial regression (loess) fitting shown in black.

Title: Performance of the qCON index in infants during sevoflurane general anesthesia

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Introduction

Infants are known to present EEG differences when compared to other pediatric patients or to adult patients, due to the immaturity of their brain. This poses a challenge to the application of depth of anesthesia indices when used in newborns and infants up to 2 or 3 years old. Hence, in this work, the ability of the qCON index (Conox, Fresenius Kabi, Germany) to reflect depth of anesthesia in infants, despite of their specificity, is assessed, as well as the performance of the index using data from different EEG channels.

Methods

Data from 10 pediatric patients undergoing sevoflurane anesthesia were collected. EEG signals were recorded with the microEEG® device (Bio-signal Group, USA), with electrodes placed following the 10-20 standard. Signals were resampled and rescaled to be afterwards replayed by the Conox.

Each recording was divided in three stages: Awake (before the anesthetic agent starts to be administered), Under Anesthesia (from start of induction to stop of sevoflurane) and Anesthesia Recovery (until the end of the recording). For each channel, statistical differences in the qCON index between consecutive patient states were computed. The normality of the qCON data was assessed through a Kolmogorov-Smirnov test, followed by a student t-test or Mann-Whitney as appropriate, depending on the data distribution. Statistical significance was defined as $p< 0.05$, and Bonferroni correction considered. Moreover, the probability of the qCON index to predict loss of consciousness was calculated by means of the Pk statistic. Data with low signal quality (SQI < 75) were excluded from analysis.

Results

Data from 10 infants (1 female) with average age of 312.5 days (46 – 540 days), weight of 8.41 kg (2.69 – 11.7 kg) and ASA I to III were analyzed. Statistically significative differences between consecutive anesthesia stages were found for all channels except for O1. The best results ($p<0.00005$) were obtained in the frontal and temporal channels (F3, F4, T5 and T6). As an example, the values obtained for F3 are shown in Figure 1. The Pk values were showed a good prediction of loss of consciousness in all channels ($pk \geq 0.85$) with some frontal and temporal channels presenting a perfect prediction ($Pk=1$): F3, F4, T5 and T6.

The qCON values during Under Anesthesia were consistently lower than values obtained for the Awake and Anesthesia Recovery states. However, some of the values obtained during the Under Anesthesia state were higher than the ones usually recommended for the qCON index (40 – 60 interval). Similar findings were reported for other depth of anesthesia indices [1], in which a negative correlation

between age and Beta power was found, causing the consciousness index to be higher compared to values expected in adults.

Conclusions

Despite of the specificities of the EEG signals in infants, the qCON index was able to distinguish between awake and anesthetized states both in induction and emergence of anesthesia. Furthermore, it showed a good performance in the prediction of loss of consciousness. All EEG channels provided good results, with frontal and temporal areas presenting the highest prediction and lowest p-values. The data suggest that a single channel is enough for depth of anesthesia monitoring in these patients and that the optimal channel is in the frontal or temporal area.

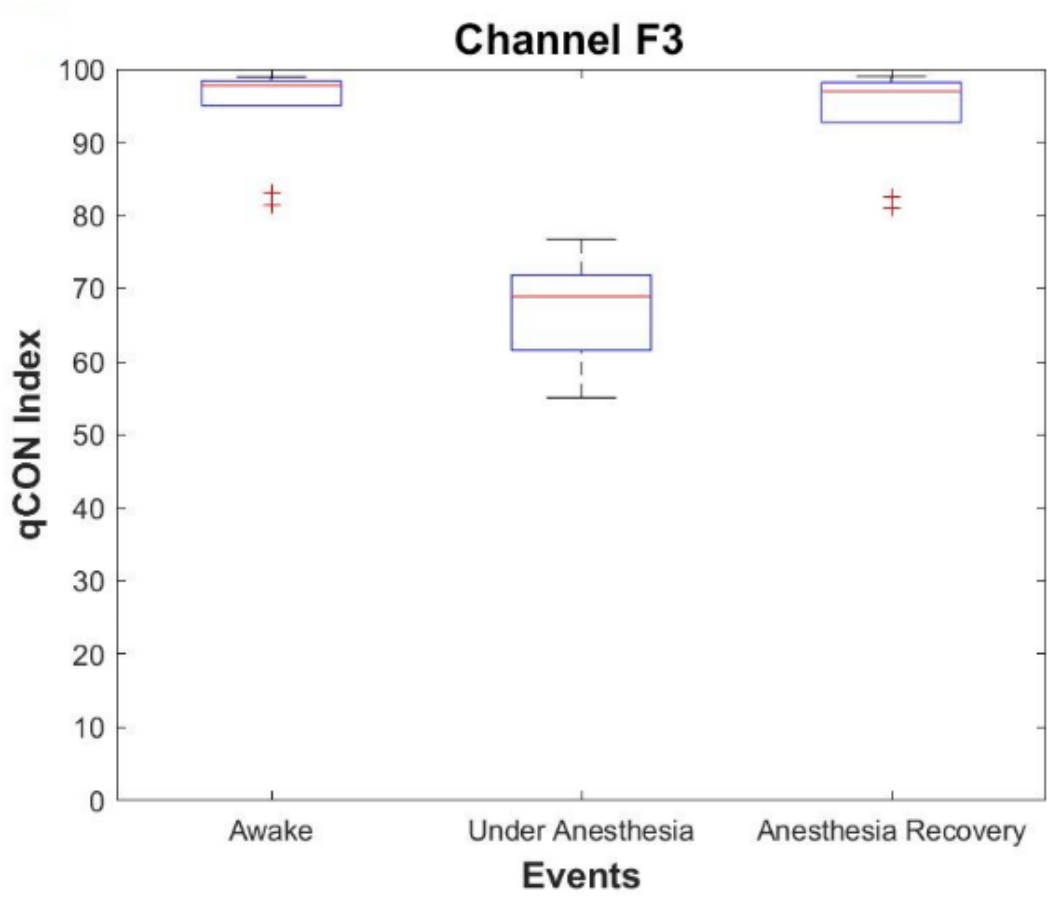

Figure 1: Boxplot of qCON index values in the three stages.

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Assessment of the effect of sevoflurane and dexmedetomidine on the BIS and qCON indices.

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Co-Authors: Carmen González Pijuan[1], Montserrat Vallverdú-Ferrer[2], Erik Weber Jensen[1], Alexander F. Friend[3], Max W. Breidenstein[3], Denis J. Nuñez[3], Catherine M. Christenson MD[3]

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Background/Introduction: Monitoring of the hypnotic effect and nociceptive balance during general anaesthesia is ever-changing with the inclusion of new drugs in the operating theatre [1]. The administration of analgesic and hypnotic drugs causes a decrease in consciousness and nociception, and the different methods developed over the last decades to monitor them might not be precise in the new scenarios set by the newer general anaesthesia practices.

Methods: Forty-two patients scheduled for surgical procedures under general anaesthesia were included in the study. Propofol was used as the induction hypnotic agent and anaesthesia was maintained with sevoflurane. Out of the 42 patients, there were 10 patients given dexmedetomidine in small doses (4mcg to 10mcg) as an anxiolytic [2]. To assess the performance of the indices of hypnotic effect qCON and BIS under general anesthesia combined with dexmedetomidine, the prediction probability Pk between the indices and the sevoflurane MAC was assessed. The MAC was split in three groups to assess the performance of both indices in different stages of depth of anaesthesia.

Results: The qCON and the BIS decreased when the MAC of sevoflurane increased for all the patients, with or without dexmedetomidine (Figure 1). The ability of qCON index to predict MAC for qCON was Pk = 0.131 (0.042) whereas for BIS was Pk = 0.151 (0.053) for the patients with dexmedetomidine, and Pk = 0.173 (0.029), Pk = 0.129 (0.025) for qCON and BIS respectively for the patients without dexmedetomidine. The prediction probability between qCON and BIS for the patients with dexmedetomidine was Pk = 0.8842 (0.035).

Conclusions: These results indicate that both the qCON and the BIS predicted the hypnotic effect of sevoflurane with or without the presence of dexmedetomidine, when administered as an anxiolytic. More studies should be done to establish the effect of larger doses of dexmedetomidine on the qCON index.

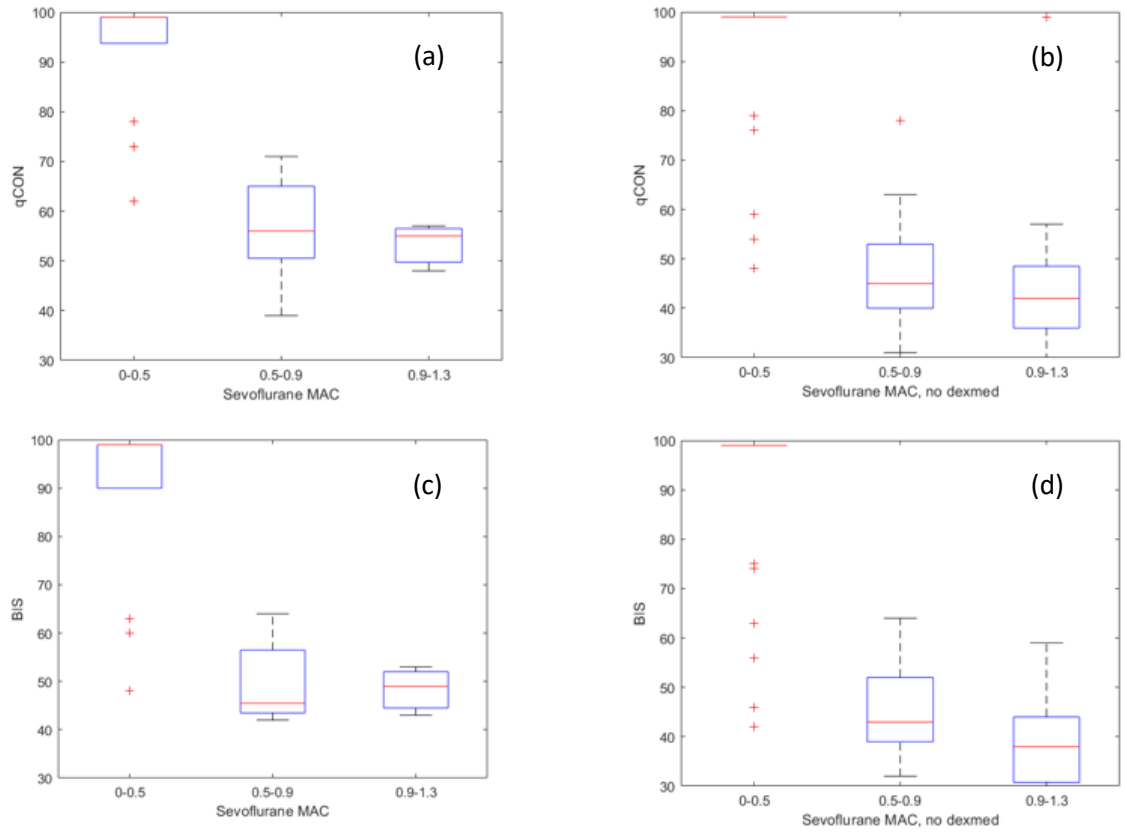

Figure 1: Boxplot of qCON (a, b) and BIS (c, d) data as a function of sevoflurane MAC for patients receiving (a, c) and not receiving (b,d) dexmedetomidine boluses.

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A NOVEL INDEX OF NOCICEPTION DERIVED FROM HEART RATE VARIABILITY PARAMETERS

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Background/Introduction: Monitoring the nociception/anti-nociception balance during general anaesthesia can be a valuable tool in the operating room. But a unified consensus is not yet defined with a number of different methods being proposed over the last decade. These methods can be grouped into those based on analysis of cerebral activity such as the electroencephalogram (EEG) and Auditory Evoked Potentials (AEP) [1-4] and those based on the activity of the autonomic nervous system e.g. through heart rate variability (HRV) [5] or skin conductance [6] and the combination of both methods [7]. For those based on HRV there is a focus on the high frequency component of HRV which is closely related to parasympathetic activity [8,9]. However, some studies show that the sympathetic system, the activity of which modulates the low frequency component of HRV (LF), can also reflect nociception [10-12]. The aim of this paper is to compare a HRV based nociception index that takes into account both parasympathetic and sympathetic modulation and compare it to one only based on parasympathetic modulation, using as reference a more a nociception index derived from the EEG, the qNOX (Conox, Quantium Medical).

Methods: Two EEG channels and one electrocardiogram (ECG) channel were recorded with the CoreSysOne monitor (Fig. 1) at a sampling frequency of 1024 Hz. The recordings were performed at Hospital Teknon (Barcelona) after Institutional Review Boards (IRB) approval. Fifteen adult patients scheduled for elective major abdominal surgery were anaesthetized with Total Intravenous Anaesthesia (TIVA). From the EEG channels, a nociception index was derived. The parameters extracted from the ECG for the index that accounts for sympathetic modulation where the number of times successive heartbeat intervals exceed 50ms (PNN50), the division between LF and HF (LF/HF) and the heart rate(HR). For the index that doesn't take it into account, LF/HF was replaced for HF. The new HRV based nociception indexes were obtained using these parameters and a linear model. These nociception indexes can reach values from 0 to 100. The results were then cross validated.

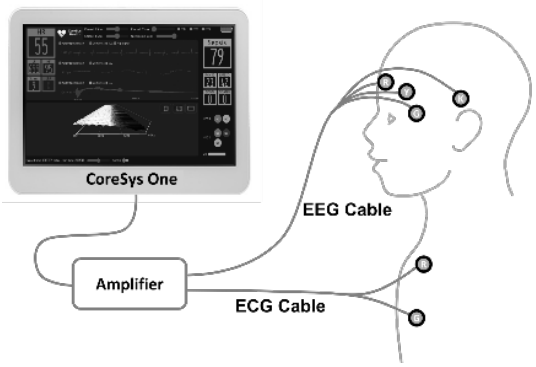

Figure 1 CoreSys One monitor with the position of the EEG/ ECG electrodes.

Results: Figure 2 shows the 3 nociception indexes predicted on subject 2.

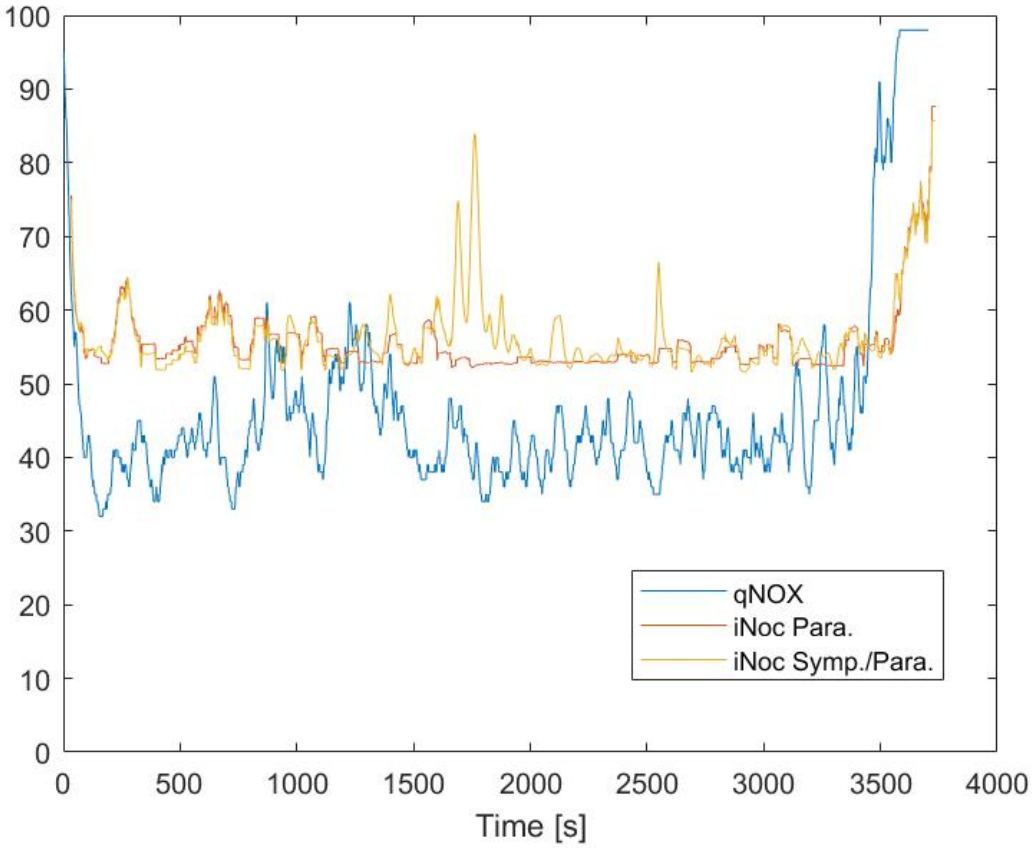

Figure 2 Evolution of the Nociception indexes for Subject 2

Table 1 shows the root mean squared error between the indexes calculated through HRV and the one calculated through EEG for all the cross validations.

Table 1 RMSE for each nociception index

	RMSE	MdAPE
Model using LF/HF	18.03 (13.72-21.42)	0.257 (0.212-0.318)
Model using HF	17.38 (13.89-21.82)	0.267 (0.214-0.324)

[a] *Median Value (Q1-Q3)*

Conclusions: There was no significant difference between the two HRV derived indices of nociception.

Both of them are relatively similar to the one calculated through EEG. The similarity between the HRV derived indexes and the difference with the one derived from EEG does not give significant evidence about the validity of accounting for sympathetic activity yet. More studies with a larger population and different models are needed.

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An update on twenty-one years fresh gas flow data.

Presenting author R Ross Kennedy [1,2]

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Introduction
There has been interest in the economical and efficient use of inhalational agents for many years. In the past the primary focus was on the financial and possibly the theoretical aspects of reducing vapor consumption. More recently the environmental benefits of maximising the efficiency of vapor delivery have come to the fore.

Fresh gas flow (FGF) rates are a useful surrogate for vapor consumption. We have sampled and reported our FGF data from Christchurch Hospital in Aotearoa - New Zealand at intervals since 2001. Our data sets cover the entire case and do not exclude the induction, or pre-surgical period which we suggest can account for a significant proportion of vapor consumption (1)

Aims
This poster updates our FGF data series and includes. We also explore outliers in the 2022 data to identify areas for further refinement of our volatile use and incorporate data on TIVA use over recent years.

Methods
Prior to 2018 a variety of methods were used to collect our data (1). Since 2018 we have used a production version of Insights from Ge HealthCare. More recent data has been downloaded from a production version of GE Insights and analysed using R and R studio. Data for 2022 are from 20 of 25 OR, including dedicated pediatric, neurosurgical and cardiac rooms and cover the period through to the end of July.

Results
We have data for almost 6000 cases from the first seven months of 2022. The proportion of cases using sevoflurane each month is between 35% & 45%. The time weighted mean FGF for these cases is 789ml/min. No use of desflurane has been recorded for more than eight months, (2021 6 cases, 2020: 14 cases). The mean sevoflurane use for 2022 is 13.2ml, with a median [IQR] of 11.2 [7.0 -17.2]ml for an average (mean) CO2e footprint of 2.6kg / case.
The median duration of initial high flow period was 1.0 min {upper quartile 3.3min, 90th centile 6.0}min. The median FGF during this period was 6.0 {6.0, 8.0} l/min with a FGF ≥6l/min in 65% of cases. Provisional analysis suggests FGF is lower in acute rooms out of hours than during the day when these rooms are more likely to have resident staff.

Conclusions
We now have a FGF data series extending back 21 years, with the last four years documented in increasing detail. Our overall FGF, and thus volatile use, remains very low despite the increasing

use of TIVA in our hospital. Although the duration of the initial high flow period is generally brief, the initial FGF is still 6l/min in 2/3 cases and over 8l/min in 10% suggesting direction for further improvement. There is a suggestion that, despite the increasing use of TIVA, our trainees are very efficient with the use of sevoflurane.

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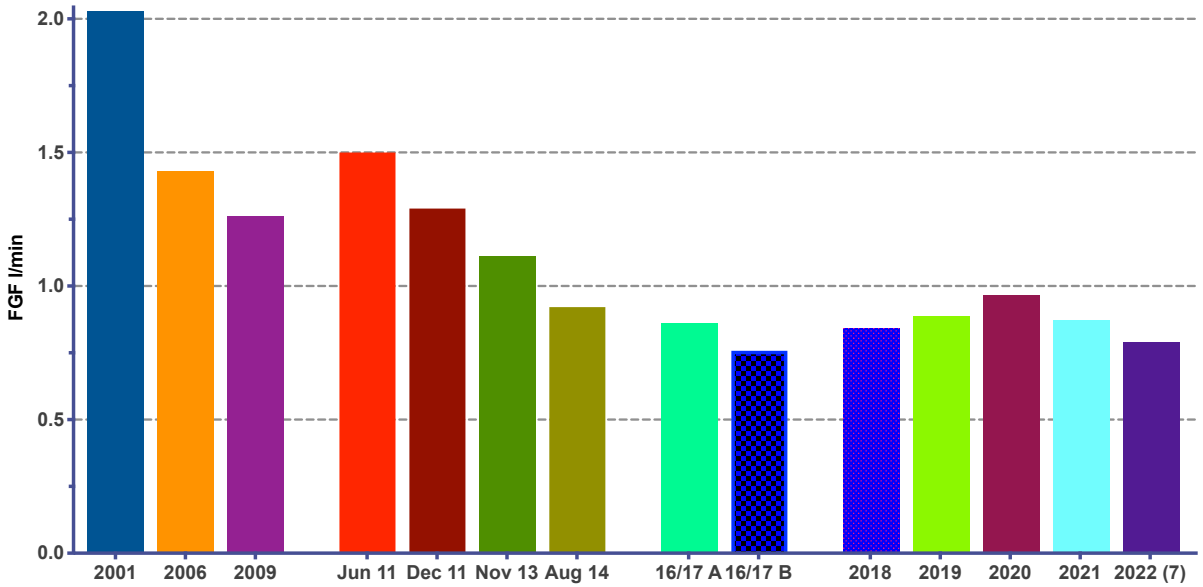

Figure: Mean time weighted FGF during sevoflurane anesthesia 2001 – 2022. Data prior to 2010 from Datex ADU. GE Aisys with automated vapor control introduced 2010. Data for 2016 from Insights devolvement project. 2018 onwards commercial version of GE Insights.